大学共同利用機関法人

自然科学研究機構

基礎生物学研究所

外部点検評価報告書
第一部

2007

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はじめに

平成１９年度の自然科学研究機構基礎生物学研究所の外部点検評価報告書をお送りします。

基礎生物学研究所は昭和 52 年に創設され、平成１９年６月１日に創立３０周年記念の会をおこないました。３つの研究部門と一つの研究施設および技術課という陣容で始まった研究所は、２０研究部門と１１研究室および３つの研究施設を持つ組織に成長し、細胞生物学・発生生物学・神経生物学の三大分野に加え、進化多様性・環境生物学・理論生物学等の新たな研究分野において、大学共同利用と研究の新たな展開を図っています。平成１６年より大学共同利用機関法人・自然科学研究機構が発足してその一員となりました。

勝木元也前所長の任期満了退任に伴って、平成１９年４月１日に私が所長に就任しました。研究所の運営について貴重な助言をいただいている運営会議の外部委員はほぼ全委員が任期満了となるために新たな委員に就任して頂きましたが、平成１９年度の所内の運営体制や研究所の諸事業はほぼ前年通りに継続することにしました。平成１９年度の運営交付金および外部資金はほぼ前年と同額となり、活発な先端生物学研究を推進するとともに、共同利用研究・国際連携・新領域の開拓・若手研究者の育成などの業務も順調に伸展しました。

平成１９年度におこなった主要な事業としては、ほぼ十年ぶりに研究所のすべての研究室主宰者に対して、外国人を含む多数の研究者に依頼して外部評価を実施したことと、複数の教授および独立准教授ポストについての新たな人事選考を開始したことが挙げられます。在職１０年を迎えた３名の教授についての業績の評価もおこないました。外部評価の実施状況と結果はこの冊子（報告書第一部）に、在職１０年の教授の業績評価は別冊（報告書第二部）に掲載しました。人事選考はこれまでの空きポストと退職予定職員のポストである４名の教授職と１名の独立准教授職について公募したもので、研究所の将来を見据えて、現在慎重に選考を進めているところです。また、前年度から申請していた研究所の耐震工事費用が認められ、研究所の南側部分の工事がおこなわれました。平成２０年度は中央部分の耐震工事をおこなう予定です。

研究所の活動を分かり易い形で社会と研究者コミュニティにお知らせする努力も進めています。研究所を紹介するパンフレットを新たに作成し、創設３０周年記念事業の一つとして写真集「研究を支えるいきものたち」を刊行しました。いずれも好評をいただいています。パンフレットは別冊に綴じ込みました。写真集は研究所のホームページで見ることもできます。

この報告書をご一読いただき、基礎生物学研究所の運営と活動についてのご意見ならびにご支援を頂ければ誠にありがたく存じます。

平成２０年５月

基礎生物学研究所

所長　岡田清孝

沿　　革

昭和37年頃から生物学研究者の間に研究所設立の要望が高まり，関連学会(日本動物学会，日本植物学会等)を中心に種々検討がなされた。

昭和 41 年 5 月　日本学術会議は , 第 46 回総会において , 生物研究所 (仮称) 並びに生物科学研究交流センター (仮称) の設立について内閣総理大臣に勧告した。

昭和 48 年 10 月　学術審議会は , 分子科学研究所 , 基礎生物学研究所 (仮称) 及び生理学研究所 (仮称) を緊急に設立すべき旨 , 文部大臣に報告した。

昭和 50 年 4 月　昭和 50 年度予算に岡崎基礎総合研究所 (仮称) 調査費が計上された。

昭和 50 年 5 月　事務次官裁定により , 岡崎基礎総合研究所 (仮称) 調査会議設置。

昭和 50 年 12 月　岡崎基礎総合研究所 (仮称) 調査会議から文部大臣に報告が行われた。

昭和 51 年 5 月　昭和 51 年度予算に分子科学研究所調査室経費が計上され ,5 月 10 日 , 文部大臣裁定により分子科学研究所に調査室 (定員 5 人) 及び岡崎総合研究機構調査会議設置。

昭和 51 年 6 月　岡崎総合研究機構調査会議においては , 昭和 50 年度の岡崎基礎総合研究所 (仮称) 調査会議の報告を踏まえ , 岡崎地区における総合研究機構はさしあたり基礎生物学及び生理学の 2 研究所より構成することとし , その具体的事項について調査検討した。

昭和 52 年 5 月　生物科学総合研究機構 (基礎生物学研究所 , 生理学研究所) 創設。
国立学校設置法の一部を改正する法律 (昭和 52 年法律第 29 号) の施行により生物科学総合研究機構創設。
機構に基礎生物学研究所及び生理学研究所設置。基礎生物学研究所創設と同時に 3 研究系 , 3 研究部門 , 1 研究施設及び技術課設置。
細胞生物学研究系 (細胞機構研究部門)
発生生物学研究系 (生殖研究部門)
制御機構研究系 (情報制御研究部門)
培養育成研究施設
技術課

昭和 53 年 4 月　分子科学研究所の管理部が管理局となり , 生物科学総合研究機構の事務を併せ処理することとなった。3 研究部門設置。
細胞生物学研究系 (細胞融合研究部門)
発生生物学研究系 (細胞分化研究部門)
制御機構研究系 (感覚情報処理研究部門)

昭和 54 年 4 月　3 研究部門及び 1 研究施設設置。
細胞生物学研究系
(細胞内エネルギー変換機構研究部門)
制御機構研究系
(計時機構研究部門 , 行動制御研究部門)
アイソトープ実験施設

昭和 55 年 4 月　細胞生物学研究系に細胞情報研究部門設置。

昭和 56 年 4 月　岡崎国立共同研究機構創設。
国立学校設置法の一部を改正する法律 (昭和 56 年法律第 23 号) の施行により , 分子科学研究所及

び生物科学総合研究機構 (基礎生物学研究所 , 生理学研究所) は , 昭和 56 年 4 月 14 日をもって総合化され , 3 研究所は岡崎国立共同研究機構として一体的に運営。
細胞生物学研究系に細胞増殖研究部門設置。

昭和 57 年 4 月　発生生物学研究系に形態形成研究部門設置。

昭和 58 年 4 月　発生生物学研究系に発生生物学研究部門設置。

昭和 63 年 4 月　制御機構研究系に遺伝子発現統御研究部門設置。

昭和 63 年 10 月　総合研究大学院大学が創設。
基礎生物学研究所に同大学生命科学研究科分子生物機構論専攻が置かれる。

平 成 元 年 5 月　遺伝子発現統御研究部門が廃止され , 形質統御実験施設 (遺伝子発現統御第一研究部門 , 遺伝子発現統御第二研究部門) 設置。

平成 4 年 4 月　形質統御実験施設に種分化機構第一研究部門設置。

平成 8 年 5 月　形質統御実験施設に種分化機構第二研究部門設置。

平成 10 年 5 月　形質転換生物研究施設設置。

平成 11 年 4 月　生命環境科学研究センター設置。

平成 12 年 4 月　アイソトープ実験施設 , 生命環境科学研究センター廃止。
共通研究施設として , 統合バイオサイエンスセンター , 計算科学研究センター , 動物実験センター , アイソトープ実験センター設置。

平成 13 年 4 月　情報生物学研究センター設置。

平成 16 年 4 月　大学共同利用機関法人自然科学研究機構創設。
国立大学法人法の施行により , 国立天文台 , 核融合科学研究所 , 基礎生物学研究所 , 生理学研究所及び分子科学研究所が統合再編され , 大学共同利用機関法人自然科学研究機構となった。岡崎国立共同研究機構管理局が大学共同利用機関法人自然科学研究機構岡崎統合事務センターとなった。
3 研究系の廃止とともに研究部門名を変更し , 新たに研究室を設けた。

平成 17 年 4 月　連携・広報企画運営戦略室設置。

概　　要

基礎生物学研究所は大学における学術研究の発展に資するため，基礎生物学に関する総合研究を行うことを目的として設置された。生物現象の基礎的事項の究明を目標とし，動物・植物を対象に，生物の基本単位である細胞の構造・働き・増殖・分化，器官の形成，外界からの刺激に対する生体の反応・制御等について総合的研究を行う。

組織の概要

設置形態

国立大学法人法 (平成 15 年法律第 112 号) の制定により，大学共同利用機関法人自然科学研究機構が創設され，基礎生物学研究所は他の４研究所とともに自然科学研究機構の一員となった。

運営組織

自然科学研究機構に，経営，教育研究及び機構運営に関する重要事項を審議するため経営協議会，教育研究評議会及び機構会議を置く。また，研究所に，研究教育職員の人事等研究所の運営に関する重要事項で，所長が必要と認めるものについて所長の諮問に応じる運営会議を置く。

事務組織

研究所の事務は，自然科学研究機構岡崎統合事務センターが処理する。

研究組織

19 研究部門，10 研究室，2 研究施設及び 1 研究センターと技術課を置いている。全国の大学の教員その他の者で，研究所の目的たる研究と同一の研究に従事する者の利用に供するとともに共同研究を行う。

研究体制の概要

基礎生物学研究所における研究体制

昨年 (平成 16 年 4 月)，大学共同利用機関が法人化されたのを機会に，基礎生物学研究所および統合バイオサイエンスセンターの基礎生物学関連研究領域における研究体制の大幅な見直しを行った。その目的は，基礎生物学研究所における基盤研究を一層充実させることにあり，そのために研究部門を再編成するとともに，新たに研究室を設けた。このうち「研究部門」については，従来どおりの教授のリーダーシップの下に基盤研究を推進する研究グループである。その名称については現在の基礎生物学分野を考慮しつつ，実際の研究活動を反映したものに改めた。一方，「研究室」は，主に施設やセンターなどに所属する個々の研究者から構成される比較的小さな研究グループである。研究部門と研究室は研究単位であり，いわば研究の現場である。それらの研究活動の実績と現状は「研究活動」の項に述べてある。

22 研究部門と 11 研究室とをさらに 7 研究領域に分類したが，これらは中期計画のなかで，今後さらに強化，発展させる必要があると判断された基盤研究領域と一致する。

上記の研究体制見直しによる基盤研究の充実と，新しい分野の創成に対してそれぞれの研究者が自由に変更できる柔軟な研究協力体制の構築は，研究所をあげての新たな研究プロジェクト創設のための堅固な基盤となる。国際的に重要かつ緊急に進展させる必要のある基礎生物学のプロジェクトについて，研究領域，部門，室の枠を越えた研究プロジェクトを実施する。

共同利用

全国の大学の教員その他の者で，研究所が目的とする研究に従事する者には施設の利用を供するとともに研究所の教員との共同利用研究を行う。

●重点共同利用研究

生物学の基盤研究をさらに強化発展させ，独創的で世界を先導する研究を創成し，発展させるため，他の研究機関の研究者と所内の教授，助教授が共同して行う複数のグループからなる総合研究。

●モデル生物・技術開発共同利用研究

生物学研究に有用な新しいモデル生物の確立および解析技術開発に向けて，他研究機関の研究者あるいは所内の研究者が，基礎生物学研究所の施設 (培養育成研究施設，形質転換生物研究施設，情報生物学研究センター，分析室) および岡崎共通研究施設アイソトープ実験センターと共同して行う研究。

●個別共同利用研究

他の研究機関の研究者が所内の教授，助教授と協力して行う個別プロジェクト研究。

●共同利用実験

大型スペクトログラフを使用して，本研究所が設定した実験課題について行う実験・研究。昭和 56 年度から開始している。

●研究会

基礎生物学及びその関連分野での緊急かつ重要なプロジェクトについて現状分析を行うと共に，将来の具体的研究計画を討議し，研究推進する比較的少人数の研究討論集会。

●施設利用

研究所の施設は個別に利用するもので，分析室については，平成 8 年度からその有する機器をより有効に活用するため，公募による利用の申し込みを受け付けている。

以上の共同利用研究 (重点共同利用研究, 個別共同利用研究) 及び研究会並びに, 共同利用実験, 施設利用は年 1 回, 研究課題を公募している。なお，平成 17 年度から従来のグループ共同研究，個別共同研究，研究会，大型スペクトログラフ共同利用実験，形質統御実験施設共同利用実験，環境耐性植物共同利用実験と細分化していたものを，新たに重点共同利用研究を設けるとともに，個別共同利用研究，研究会，大型スペクトログラフ共同利用実験に整理統合している。

総合研究大学院大学

総合研究大学院大学に参加し，同大学と緊密な連携・協力の下に，国立遺伝学研究所及び生理学研究所とともに生命科学研究科を組織し，基礎生物学専攻を担当し教育研究を行う。

同大学は，学部を持たない大学院大学である。平成元年度から後期 3 年の博士課程のみで発足した。平成 16 年度からは後期 3 年の博士課程に加えて 5 年一貫制の博士課程を併設し，大学院教育の充実を図っている。

大学院教育協力

大学共同利用機関として, 広く基礎生物学及びこれに関連する分野における研究者の共同利用に供されるとともに, 研究者の養成に関しては，国・公・私立大学の要請に応じてそれらの大学に所属する大学院学生を「特別共同利用研究員」として受け入れ，併せて研究指導を行い大学院教育の協力を行っている。

国際交流

基礎生物学分野の国際的な学術交流を活発化するため，研究者の交流や国際シンポジウム等を開催している。

●国際共同研究

自然科学研究機構の共同研究協定に基づき，基礎生物学研究所と EMBL との合同シンポジウムによる質の高い情報交換や，大学院生を含めた研究者交流を行っている。また，共同研究の中核をなすバイオイメージングにおいては，EMBL で新しく開発された顕微鏡システム（SPIM）を基礎生物学研究所に導入するなどの技術交流も盛んに行っている。

●国際研究拠点

日本学術振興会先端研究拠点事業 (課題 : アフリカツメガエル・ニシツメガエルを用いた機能ゲノム学の推進) を始めとした，基礎生物学分野の国際研究拠点としての事業を積極的に行っている。

●基礎生物学研究所コンファレンス (NIBB Conference)

平成 9 年度まで特定研究経費により，国際研究集会として「基礎生物学研究所コンファレンス」を毎年開催して 40 回に及んだ。しかし特定研究が平成 9 年度限りで打切られたため，平成 10 年度からは国際シンポジウム (COE) 及びリーダーシップ支援経費を活用して,「基礎生物学研究所コンファレンス」を継続している。すでにこの線に沿って 13 回のコンファレンスが国内外多数の研究者の参加を得て行われている。

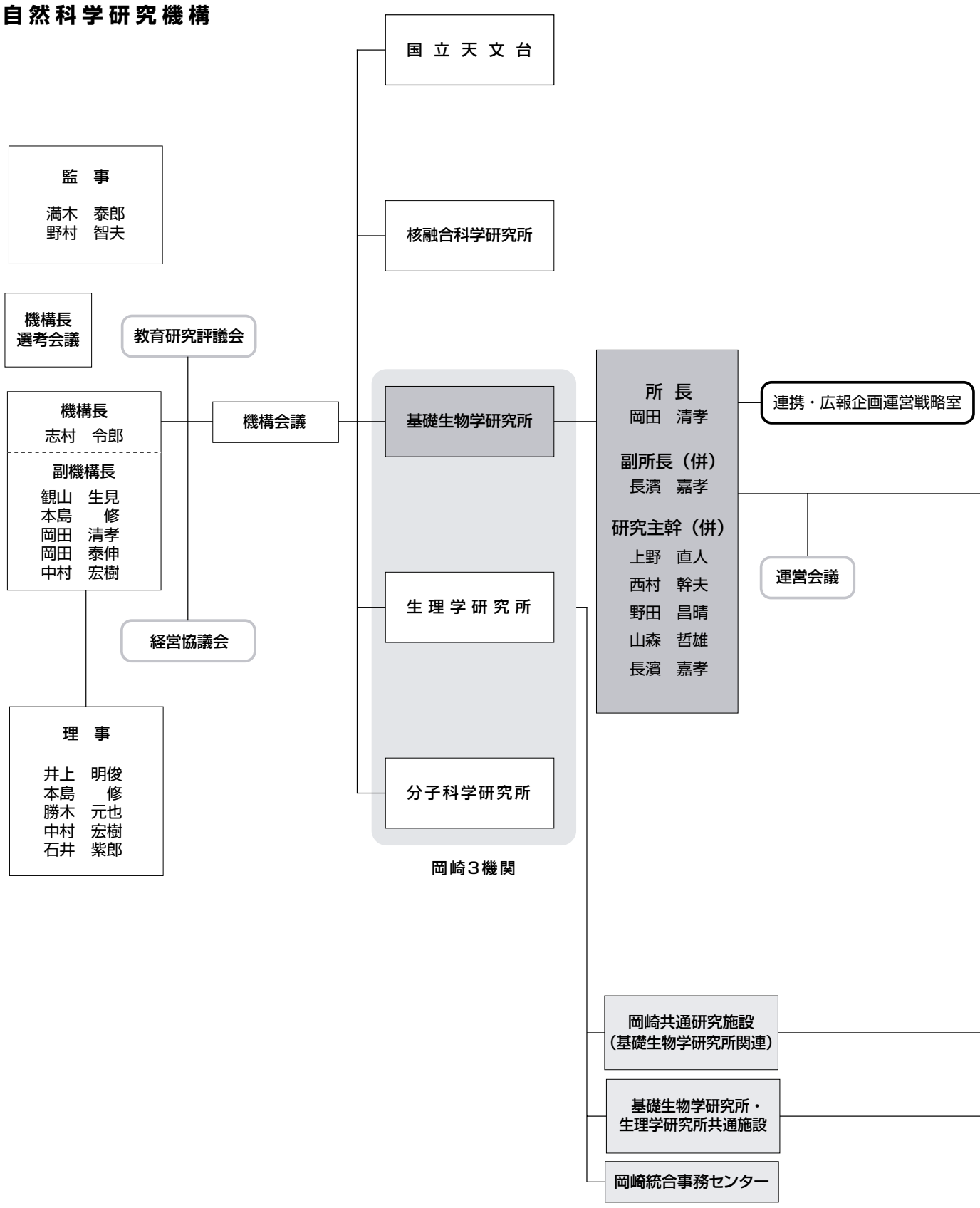
●生物学国際高等コンファレンス (Okazaki Biology Conferences)

現代の生物学は，分子生物学的な還元的な方法論に依拠しながら，大きな発展を遂げてきた。しかしながら，さらなる生物学の発展には，新しい研究課題としての問題発掘が必須である。

我が国の基礎生物学を先導する基礎生物学研究所では，生物学コミュニティの大きな組織の一つである生物科学学会連合に意見を聞きながら，今後生物学が進むべき新たな研究分野の国際的コミュニティを形成するため，先導的な国際研究集会を開催することを提唱してきた。

生物科学学会連合の推薦を受けて，基礎生物学研究所は，平成 15 年度から国内外の第一線級の研究者の参加を得て生物学国際高等コンファレンス (OBC)(http://obc.nibb.ac.jp/) を主催している。第 1 回 OBC は，平成 16 年 1 月に「絶滅の生物学 (The Biology of Extinction)」と題して開催され，国外からの招待者 40 数名を含め 70 数名の参加者のもとに活発な発表，討論が行われた。OBC に関しては，Nature 誌が本コンファレンス直後に News Article “Extinction meeting kicks off Japan's plans for networking (February 5，2004)”として取り上げるなど，国内外からの期待はきわめて大きい。平成 16 年 9 月には，第 2 回「地球圏微生物学 (Terra Microbiology)」，平成 18 年 3 月には第 3 回「絶滅の生物学 2（The Biology of Extinction 2)」，平成 18 年 9 月には第 4 回「地球圏微生物学 2」，平成 19 年 3 月には第 5 回「種分化と適応：モデル生物の生体ゲノミクスとその展望」が開催された。

自然科学研究機構組織図



研究部門・研究室

細胞生物学領域	■	高次細胞機構研究部門	西村　幹夫
	■	分子細胞生物学研究部門	大隅　良典
	■	細胞増殖研究部門＊	酒巻　和弘
	■	細胞構造研究室	小川　和男
	■	細胞社会学研究室	濱田　義雄
発生生物学領域	■	生殖生物学研究部門	長濱　嘉孝
	■	性差生物学研究部門	諸橋憲一郎(九大)
	■	形態形成研究部門	上野　直人
	■	発生遺伝学研究部門	小林　悟
	■	分子発生学研究部門	高田　慎治
	■	生殖遺伝学研究室	田中　実
神経生物学領域	■	統合神経生物学研究部門	野田　昌晴
	■	脳生物学研究部門	山森　哲雄
	■	行動生物学研究部門＊	森　裕司
	■	神経生理学研究室	渡辺　英治
	■	神経生化学研究室	笹岡　俊邦
進化多様性生物学領域	■	分子遺伝学研究部門	飯田　滋
	■	ゲノム動態研究部門	堀内　嵩
	■	生物進化研究部門	長谷部光泰
	■	構造多様性研究室	児玉　隆治
	■	バイオリソース研究室	成瀬　清
環境生物学領域	■	分子環境生物学研究部門	井口　泰泉
	■	植物発生遺伝学研究部門＊	塚谷　裕一
	■	光情報研究部門＊	和田　正三
	■	光環境学研究室	渡辺　正勝
理論生物学領域	■	理論生物学研究部門	望月　敦史
	■	ゲノム情報研究室	内山　郁夫
イメージングサイエンス研究領域	■	発生ダイナミクス研究部門＊	宮脇　敦史
	■	時空間制御研究室	野中　茂紀

＊客員研究部門

研究施設

- 培養育成研究施設
  - 細胞器官培養室
  - 人工気象室
  - 実験圃場
  - 下等真核細胞培養室
  - 大型スペクトログラフ室
  - 電子計算機室
- 形質転換生物研究施設
- 情報生物学研究センター
- 技術課

- 岡崎統合バイオサイエンスセンター
  - ■ 時系列生命現象領域Ⅰ・発生遺伝
  - ■ 時系列生命現象領域Ⅱ・分子発生
  - ■ 生命環境研究領域Ⅰ・生命環境
  - ■ 生命環境研究領域Ⅱ・植物発生
- 計算科学研究センター
- 動物実験センター
- アイソトープ実験センター

- ■ 分析室
- ■ 洗滌室
- ■ 廃棄物処理室
- ■ 電子顕微鏡室
- ■ 機器研究試作室

名誉教授

太田　行人
岡田　節人
江口　吾朗
竹内　郁夫
鈴木　義昭
毛利　秀雄
勝木　元也

名誉技官

服部　宏之

配　置　図

施　設	面積 (m²)
① 実験研究棟	11,077
A 大型スペクトログラフ室	
B 動物実験センター (水生動物室)	
② 形質統御実験棟	2,575
③ 共通施設棟 Ⅰ	3,080
(アイソトープ実験センター，分析室，電子顕微鏡室)	
④ 共通施設棟Ⅱ	612
(形質転換生物研究施設の一部，機器研究試作室)	
⑤ 動物実験センター (陸生動物室)	3,184
⑥ 実験廃液処理施設	–
⑦ 実験圃場 (管理棟・温室)	200

施　設	面積 (m²)
⑧ 山手 1 号館 A	4,674
(動物実験センターの一部 , アイソトープ実験センターの一部)	
⑨ 山手 1 号館 B (形質転換生物研究施設)	2,303
⑩ 山手 2 号館	8,453
(統合バイオサイエンスセンターの一部,	
計算科学研究センターの一部，生理学研究所の一部)	

施　設	面積 (m²)
⑪ 山手 3 号館	10,757
(基礎生物学研究所の一部 , 生理学研究所の一部 ,	
分子科学研究所の一部 , 統合バイオサイエンスセンターの一部)	
⑫ 山手 4 号館	3,813
(分子スケールナノサイエンスセンター)	
⑬ 山手 5 号館 (核磁気共鳴装置による実験施設)	664
⑭ 高圧配電施設	440
⑮ 実験排水処理施設	111

総合研究大学院大学

設立の目的

総合研究大学院大学は、全国の大学研究者の共同研究推進について中心的役割を果たしている大学共同利用機関との緊密な連携・協力の下に、その優れた人材と研究環境を基盤として博士課程の研究教育を行い、新しい学問分野を開拓すると共に、それぞれの専門分野において学術研究の新しい流れに先導的に対応することができる幅広い視野を持つ、創造性豊かな研究者を養成することを目的とする。本学は、全国で初めての学部を持たない博士後期課程の大学院だけの大学として創設されたが、平成 16 年度に生命科学研究科に 5 年一貫制博士課程が先行導入され、平成 18 年度には他 3 研究科（物理科学、高エネルギー加速器科学・複合科学研究科）にも続いて導入された。

基礎生物学専攻

基礎生物学研究所は、国立遺伝学研究所および生理学研究所と共に生命科学研究科を組織し、分子生物機構論専攻を担当してきたが、平成 17 年 4 月から基礎生物学専攻に名称変更した。本専攻は、分子生物学を基盤として動植物に関わる基本的、かつ高次な生物現象を分子レベルまで掘り下げて解析する高度な研究者の養成を行う。そのため生体物質の物理化学的解析手法や遺伝子操作を含む細胞工学・遺伝子工学的手法を総合して、細胞生物学、発生生物学、制御生物学、形質発現学などにわたる高次な生物現象の解析を中心に高度な教育研究を行う。なお、本専攻を終了した者に授与する学位は博士で、付記する専攻分野は「理学」となる。ただし、基礎生物学に係る学術的分野を主な内容とする論文については、「学術」となる。

沿革

1982（昭 57）年

6 月　国立大学共同利用機関所長懇談会が「国立大学共同利用機関における大学院の設置について」を要望

1986（昭 61）年

4 月　国立大学共同利用機関所長懇談会が「大学院問題に関するワーキング・グループ」で検基づき「総合研究大学院大学の基本構想について」を取りまとめ
岡崎国立共同研究機構に総合研究大学院創設準備調査室及び同創設準備調査委員会を設置

1987（昭 62）年

3 月　総合研究大学院創設準備調査委員会が「総合研究大学院の基本構想」を取りまとめ

5 月　岡崎国立共同研究機構に総合研究大学院創設準備室及び同創設準備委員会を設置

7 月　総合研究大学院創設準備委員会が「総合研究大学院大学（仮称）の創設準備について一中間まとめ一」を取りまとめ

1988（昭 63）年

4 月　岡崎国立共同研究機構に総合研究大学院大学創設準備室及び同創設準備委員会を設置

5 月　本学の設置を規定した「国立学校設置法の一部を改正する法律（昭和 63 年法律第 67 号）」が公布、施行

9 月　総合研究大学院大学創設準備委員会が「総合研究大学院大学の創設準備について」を取りまとめ

10 月　総合研究大学院大学開学
大学本部は東京工業大学長津田キャンパス内に設置
数物科学研究科
・統計科学専攻　・加速器科学専攻
・放射光科学専攻 ・構造分子科学専攻
・機能分子科学専攻
生命科学研究科
・遺伝学専攻 ・分子生物機構論専攻
・生理科学専攻
(学生受入は平成元年 4 月)
初代学長に長倉三郎（理学博士）就任

1989（平元）年

4月　文化科学研究科（地域文化学専攻、比較文化学専攻）を設置
3研究科学生受入

1991（平3）年

4月　教育研究交流センター設置

1992（平4）年

4月　文化科学研究科に国際日本研究専攻、数物科学研究科に天文科学専攻及び核融合科学専攻設置、学生受入

1993（平5）年

4月　数物科学研究科に極域科学専攻設置、学生受入

1994（平6）年

2月　神奈川県の斡旋により、三浦郡葉山町に本部用地（27,000㎡）を㈱三井不動産から寄附により取得

3月　葉山キャンパスにおいて本部共通棟（4,205㎡）着工

6月　教育研究情報資料センター設置

1995（平7）年

2月　大学本部は葉山キャンパスに移転、本部共通棟竣功

4月　2代学長に廣田榮治（理学博士）就任

1997（平9）年

4月　先導科学研究科（生命体科学専攻）を設置（学生受入は平成11年4月）

1998（平10）年

4月　先導科学研究科に光科学専攻設置（学生受入は平成11年4月）
数物科学研究科放射光科学専攻を物質構造科学専攻に名称変更

9月　葉山キャンパスにおいて先導科学研究科棟（3,060㎡）着工

1999（平11）年

4月　文化科学研究科に日本歴史研究専攻、数物科学研究科に素粒子原子核専攻設置、学生受入　先導科学研究科学生受入

6月　先導科学研究科棟竣功

2000（平13）年

4月　3代学長に小平桂一（理学博士）就任
文化科学研究科にメディア社会文化専攻設置、学生受入

7月　葉山キャンパスにおいて図書館棟（1,427㎡）着工

2002（平14）年

2月　図書館棟竣功

4月　数物科学研究科に情報学専攻設置、学生受入

2003（平15）年

4月　文化科学研究科に日本文学研究専攻、数物科学研究科に宇宙科学専攻設置、学生受入

10月　本学の国立大学法人への移行を規定した「国立大学法人法（平成15年法律第112号）」が公布、施行（適用は平成16年4月1日）

2004（平16）年

4月　国立大学法人総合研究大学院大学発足
学長に小平桂一（理学博士）就任
数物科学研究科を物理科学研究科（構造分子科学専攻、機能分子科学専攻、天文科学専攻、核融合科学専攻、宇宙科学専攻）、高エネルギー加速器科学研究科（加速器科学専攻、物質構造科学専攻、素粒子原子核専攻）、複合科学研究科（統計科学専攻、極域科学専攻、情報学専攻）の3研究科に改組、数物科学研究科を廃止
生命科学研究科を博士後期課程から博士後期課程を併設した5年一貫性博士課程に改組、学生受入
教育研究交流センター及び教育研究情報資料センターを統合し、葉山高等研究センターに改組

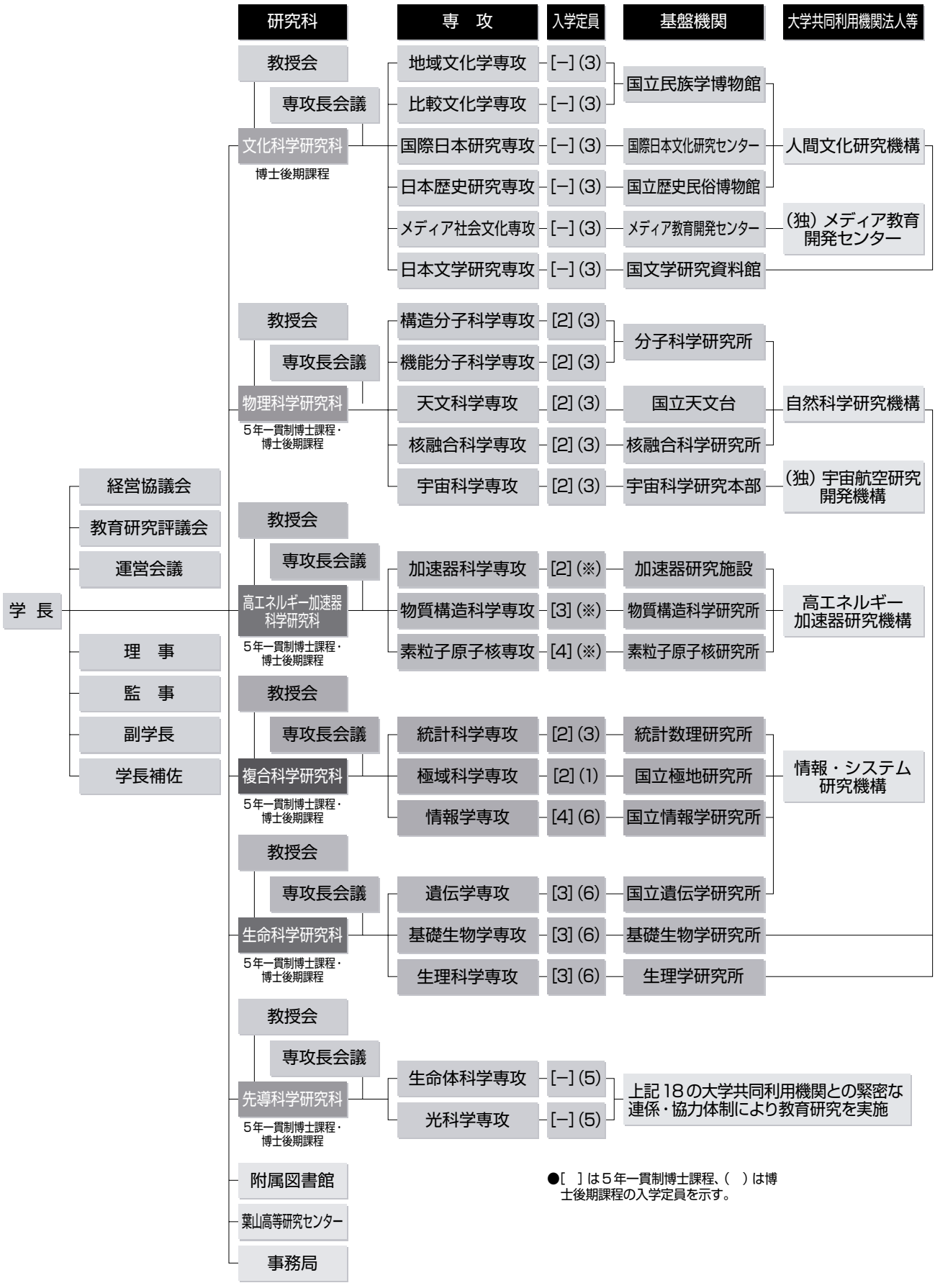
2005（平17）年

4月　生命科学研究科分子生物機構論専攻を基礎生物学専攻に名称変更

2006（平18）年

4月　物理科学研究科、高エネルギー加速器科学研究科、複合科学研究科を博士後期課程から博士後期課程を併設した5年一貫性博士課程に改組、学生受入

総合研究大学院大学組織図



予算の推移

（単位：千円）

区分	人件費	物件費	計
平成 9 年度	705,378	820,206	1,525,584
平成 10 年度	716,159	927,008	1,643,167
平成 11 年度	758,753	1,074,543	1,833,296
平成 12 年度	681,290	889,000	1,570,290
平成 13 年度	713,232	1,119,557	1,832,789
平成 14 年度	645,126	888,904	1,534,030
平成 15 年度	661,474	834,445	1,495,919
平成 16 年度	793,750	797,773	1,591,523

区分（＊）	運営交付金			計	外部資金		計
	人件費	物件費	施設費		科学研究費補助金	その他の外部資金	
平成 17 年度	807,534	819,038	1,657,171	3,283,743	695,600	329,980	1,025,580
平成 18 年度	857,827	845,637	3,339	1,706,803	523,840	286,438	810,278
平成 19 年度	863,017	875,702	564,592	2,303,311	759,260	361,607	1,120,867

定員の推移

19.4.1

区分	所長	教授	助教授（†）	助手（†）	小計	技官（＊）	計
平成 9 年度	1	11 (6)	12 (6)	37	61 (12)	32	93 (12)
平成 10 年度	1	11 (6)	12 (6)	37	61 (12)	31	92 (12)
平成 11 年度	1	13 (7)	16 (7)	40	70 (14)	33	103 (14)
平成 12 年度	1	14 (7)	15 (6)	36	66 (13)	32	98 (13)
平成 13 年度	1	15 (7)	17 (6)	35	68 (13)	31	99 (13)
平成 14 年度	1	15 (7)	19 (6)	35	70 (13)	29	99 (13)
平成 15 年度	1	15 (7)	19 (6)	35	70 (13)	28	98 (13)
平成 16 年度	1	14 (5)	15 (3)	35	65 (8)	27	92 (8)
平成 17 年度	1	13 (4)	14 (3)	32	60 (7)	27	87 (7)
平成 18 年度	1	13 (6)	14 (3)	31	59 (9)	26	85 (9)
平成 19 年度	1	12 (6)	12 (3)	31	56 (9)	26	82 (9)

（ ）内は客員で，外数

平成 12 年度以降は，基礎生物学研究所関連の岡崎共通研究施設定員を含む。ただし，平成 16 年度の法人化以降は，現員

（†）平成 19 年度からは，助教授は准教授に，助手は助教に変更

（＊）平成 16 年度からは，技官の名称は技術職員に変更

１．教員外部評価

基礎生物学研究所は昭和 52 年に創設され、平成 19 年 6 月 1 日に創設 30 周年を迎えた。これを機に、同年 11 月末から 12 月中旬にかけて研究所のすべての研究室主宰者 24 名（教授 14 名、准教授 10 名）に対して、外国人 5 人を含む 15 名の研究者に依頼して、この 10 年間における外部評価を面接により実施した（教員外部評価）。なお、平成 9 年以降に赴任した教員については赴任して以降の研究活動を評価の対象とした。また同時に、この 10 年間に研究所が行った各種事業についても忌憚のないご意見や提言をいただいた（研究所事業評価）。

研究所で行われている研究を、１）細胞生物学、２）発生生物学、３）生殖・環境生物学、４）神経生物学、５）進化多様性、の 5 つの領域に分け、それぞれのグループについて 3 人の研究者（うち 1 名は外国人）に評価を依頼した。

外部評価委員

１）細胞生物学領域： Nam-Hai Chua（Rockefeller University, USA）、岩渕雅樹（岡山県生物科学総合研究所）、中野明彦（東京大学）

２）発生生物学領域： Richard Behringer（University of Texas, USA）、濱田博司（大阪大学）、黒岩　厚（名古屋大学）

３）生殖・環境生物学領域： Peter Koopman（University of Queensland, Australia）、星　元紀（放送大学）、佐藤英明（東北大学）

４）神経生物学領域： Gail Mandel（Vollum Institute, Oregon Health & Science University, USA）、小幡邦彦（理化学研究所）、藤沢　肇（名古屋大学名誉教授）

５）進化多様性領域： George Coupland（Max-Planck Institute, Germany）、柴岡弘郎（大阪大学名誉教授）、神谷 律（東京大学）

評価は各グループ 2 日間にわたる面接により行われた。予め、この 10 年間に研究所が実施した事業の内容、及び各教員の研究活動（研究内容の概要、略歴、業績リスト、学会での活動等）をまとめた英文資料を基礎生物学研究所の要覧、年報等とともに評価委員に送付した。面接にあたっては、教員それぞれが研究内容についてスライド等を使用して 1 時間ほど説明し、その後に評価委員が質問した。教員の面接が終了後、研究所が実施した各種事業などについて評価委員と所長、副所長とが質疑応答を行った。面接終了後、評価委員には各研究室、施設を視察いただいた。

１） 細胞生物学領域

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Professor Mikio Nishimura has been working on biogenesis and functional organization/differentiation of plant organelles with a particular focus on vacuoles, ER bodies and peroxisomes. The achievements of his group are most prominent in the field of peroxisome biogenesis, which is now collaborated with the young associate professor, Makoto Hayashi, and is therefore commented in more detail in the next section. The studies on vacuoles and ER bodies are in collaboration with Professor Ikuko Hara-Nishimura, who used to be the associate professor of this group and now has established her own group in Kyoto University.

Briefly, Nishimura's group discovered a Golgi-independent transport pathway for a set of seed storage proteins, which is unique to the plant kingdom. They have identified many components involved in transport and processing of these proteins, including vacuolar sorting receptors (VSR) and vacuolar processing enzymes (VPE). VPE turned out to possess a caspase activity being involved in programmed cell death, which was the first molecular identification in plants. They also found novel structures derived from the endoplasmic reticulum and named them ER bodies. Genes involved in the formation of ER bodies are now being identified and studied. Nishimura's work on peroxisomes is outstanding and has already received worldwide appreciation. Molecular mechanisms of biogenesis, transition during plant development, and their regulations have been extensively studied. This group has also extended a research activity on molecular chaperones and is currently studying functions of Hsp90.

To summarize, Nishimura's group has made and continues to make great achievements in the field of plant organelles, which are of top quality. They are now trying to incorporate new methodologies such as live imaging and omics research, which will be very promising in the future.

（和訳）

西村 幹夫教授は植物のオルガネラの機能的組織化／分化のバイオジェネシスに関して研究してきており、とりわけ液胞、ER ボディ、ペルオキシソームを重点的に調べている。教授の研究グループの業績は、ペルオキシソームのバイオジェネシスの分野で極めて目覚ましく、この分野の研究は、現在では若い林　誠准教授と共同して行われているので、より詳細には、次のセクションで検討する。液胞と ER ボディに関する研究は、西村いくことの共同研究によるものである。彼女はかつては、このグループの准教授であったが、現在では、京都大学に自身の研究室を作っている。

簡潔に述べると、西村グループは、一連の種子貯蔵タンパク質を輸送するゴルジ体非依存的な輸送経路を発見した。これは、植物界にユニークなものである。彼らは、液胞輸

送レセプター(VSR)や液胞プロセシング酵素(VPE)を含む、種子貯蔵タンパク質の輸送と処理に関与している多くのコンポーネントを同定した。VPE には、プログラム細胞死に関与している caspase 活性があることがわかった。これは、植物で caspase 様の分子を最初に発見したものであった。彼らはまた、小胞体由来の新規構造を見つけ、ER ボディと名付けた。ER ボディの形成に関与している遺伝子が現在同定され、研究が進められている。ペルオキシソームに関する西村の研究は、傑出したもので、世界的な賞賛をすでに得ている。バイオジェネシス、植物発生中のトランジションならびにそれらの制御の分子機序について広範な研究が進められてきている。このグループはまた、研究活動を分子シャペロンに広げており、現在 Hsp90 の機能について調べている。

以上まとめると、西村グループは、植物オルガネラの領域で偉大な業績をあげ、現在でも進めつつあり、これはトップレベルの研究である。現在では、ライブイメージング法や omics 研究などの新たな研究法も取り込もうとしており、これらは今後極めて有望であると思われる。

研究業績：

1) Research articles in peer reviewed journals

1. Esaka, M., Yamada, N., Kitabayashi, M., Setoguchi, Y., Tsugeki, R., Kondo, M., and Nishimura, M. (1997). cDNA cloning and differential gene expression of three catalases in pumpkin. Plant Mol. Biol. *33*, 141-155.
2. Hatano, K., Shimada, T., Hiraiwa, N., Nishimura, M., and Hara-Nishimura, I. (1997). A rapid increase in the level of binding protein (BiP) is accompanied by synthesis and degradation of storage proteins in pumpkin cotyledons. Plant Cell Physiol. *38*, 344-351.
3. Inoue, K., Wada, Y., Nishimura, M., and Hara-Nishimura, I. (1997). Heterologous expression and subcellular localization of pumpkin seed tonoplast intrinsic (TIP) in yeast cells. Plant Cell Physiol.*38*, 366-370.
4. Mano, S., Hayashi, M., Kondo, M., and Nishimura, M. (1997). Hydroxypyruvate reductase with a carboxy-terminal targeting signal to microbodies is expressed in *Arabidopsis*. Plant Cell Physiol. *38*, 449-455.
5. Hiraiwa, N., Kondo, M., Nishimura, M., and Hara-Nishimura, I. (1997). An aspartic proteinase is involved in the breakdown of polypeptides of storage proteins in protein-storage vacuoles of plants. Eur. J. Biochem. *246*, 133-141.
6. Hayashi, M., Aoki, M., Kondo, M., and Nishimura, M. (1997). Changes in targeting efficiencies of proteins to plant microbodies caused by amino acid substitution in the carboxy-terminal tripeptide. Plant Cell Physiol. *38*, 759-768.
7. Mano, S., Yamaguchi, K., Hayashi, M., and Nishimura, M. (1997). Stromal and thylakoid-bound ascorbate peroxidases are produced by alternative splicing in pumpkin. FEBS Lett. *413*, 21-26.
8. Minami, Y., Takao, H., Kanafugi, T., Miura, K., Kondo, K., Hara-Nishimura, I., Nishimura,

M., and Matsubara, H. (1997). β-glucosidase in the Indigo plant: intracellular localization and tissue specific expression in leaves. Plant Cell Physiol. *38*, 1069-1074.
9. Hiraiwa, N., Nishimura, M., and Hara-Nishimura, I. (1997). Expression and activation of the vacuolar processing enzyme in *Saccharomyces cerevisiae*. Plant J. *12*, 819-829.
10. Nii, N., Yamaguchi, K., and Nishimura, M. (1997). Changes in carbohydrate and ribulose bisphosphate carboxylase contents in peach leaves after applications of different amounts of nitrogen fertilizer. J. Jap. Soc. Hort. Sci. *66*, 505-511.
11. Sato, M. H., Nakamura, N., Ohsumi, Y., Kouchi, H., Kondo, M., Hara-Nishimura, I., Nishimura, M., and Wada, Y. (1997). The *AtVAM3* encodes a syntaxin-related molecule implicated in the vacuolar assembly in *Arabidopsis thaliana*. J. Biol. Chem. *272*, 24530-24535.
12. Nozue, M., Yamada, K., Nakamura, T., Kubo, H., Kondo, M., and Nishimura, M. (1997). Expression of a vacuolar protein (VP24) in anthocyanin-producing cells of sweet potato in suspension culture. Plant Physiol. *115*, 1065-1072.
13. Shimada, T., Kuroyanagi, M., Nishimura, M., and Hara-Nishimura, I. (1997). A pumpkin 72-kDa membrane protein of precursor accumulating vesicles has characteristics for a vacuolar sorting receptor. Plant Cell Physiol. *38*, 1414-1420.
14. Kato, A., Takeda-Yoshikawa, Y., Hayashi, M., Kondo, M., Hara-Nishimura, I., and Nishimura, M. (1998). Glyoxysomal malate dehydrogenase in pumpkin: cloning of a cDNA and functional analysis of its presequence. Plant Cell Physiol. *39*, 186-195.
15. Hayashi, M., Toriyama, K., Kondo, M., and Nishimura, M. (1998). 2,4-Dichlorophenoxybutyric acid-resistant mutants of *Arabidopsis* have defects on glyoxysomal β-oxidation. Plant Cell *10*, 183-195.
16. Hayashi, H., De Bellis, L., Yamaguchi, K., Kato, A., Hayashi, M., and Nishimura, M. (1998). Molecular characterization of a glyoxysomal long-chain acyl-CoA oxidase that is synthesized as a precursor of higher molecular mass in pumpkin. J. Biol. Chem. *273*, 8301-8307.
17. Hara-Nishimura, I., Shimada, Y., Hatano, K., Takeuchi, Y., and Nishimura, M. (1998). Transport of storage proteins to protein-storage vacuoles is mediated by large precursor-accumulating vesicles. Plant Cell *10*, 825-836.
18. Yamada, K., Shimada, T., Kondo, M., Nishimura, M., and I. Hara-Nishimura, I. (1999). Multiple functional proteins are produced by cleaving Asn-Gln bonds of a single precursor protein by vacuolar processing enzyme. J. Biol. Chem. *274*, 2563-2570.
19. Hayashi, M., Toriyama, K., Kondo, M., Hara-Nishimura, I., and Nishimura, M. (1999). Induction of precursor-accumulating vesicles by expression of chimeric genes consisting of pumpkin 2S albumin and phosphinothricin acetyltransferase. Plant Cell Physiol. *40*, 263-272.
20. Mano, S., Hayashi, M., and Nishimura, M. (1999). Light regulates alternative splicing of hydroxypyruvate reductase in pumpkin. Plant J. *17*, 309-320.
21. Koumoto, Y., Shimada, T., Kondo, M., Takao, T., Shimonishi, Y., Hara-Nishimura, I., and Nishimura, M. (1999). Chloroplast Cpn20 forms a tetrameric structure in *Arabidopsis thaliana*. Plant J. *17*, 467-477.
22. Hiraiwa, N., Nishimura, M., and Hara-Nishimura, I. (1999). Vacuolar processing enzyme is

activated self-catalytically by sequential removal of the C-terminal and N-terminal propeptides. FEBS Lett. *447*, 213-216.
23. Hayashi, H., De Bellis, L., Ciurli, A., Kondo, M., Hayashi, M, and Nishimura, M. (1999). A novel oxidase that catalyzes oxidation of short-chain acyl CoA in plant peroxisomes. J. Biol. Chem. *274*, 12715-12721.
24. Kato, A., Hayashi, M., and Nishimura, M. (1999). Oligomeric proteins containing N-terminal targeting signals are imported into peroxisomes in transgenic *Arabidopsis*. Plant Cell Physiol. *40*, 586-591.
25. Kinoshita, T., Yamada, K., Hiraiwa, N., Kondo, M., Nishimura, M., and Hara-Nishimura, I. (1999). Vacuolar processing enzyme is up-regulated in the lytic vacuoles of vegetative tissues during senescence and under various stressed conditions. Plant J. *19*, 43-53.
26. Miyagishima, S., Itoh, R., Toda, K., Kuroiwa, H., Nishimura, M., and Kuroiwa, T. (1999). Microbody proliferation and segregation cycle in the single microbody-alga *Cyanidioschyzon merolae*. Planta *208*, 326-336.
27. De Bellis L., Giuntini, P., Hayashi, H., Hayashi, M., and Nishimura, M. (1999). Purification and characterization of pumpkin long-chain acyl-CoA oxidase. Physiol. Plant *106*, 170-176.
28. Takemoto, D., Hayashi, M., Doke, N., Nishimura, M., and Kawakita, K. (1999). Molecular cloning of a defense-response-related cytochrome P450 gene from tobacco using a fungal elicitor. Plant Cell Physiol. *40*, 1232-1242.
29. Ali, K., Nii, N., Yamaguchi, K., and Nishimura, M. (1999). Levels of nonstructural carbohydrate in leaves and roots and some characteristics of chloroplasts after application of different amounts of nitrogen fertilizer to peach seedlings. J. Jap. Soc. Hort. Sci. *68*, 739-745.
30. Minami, Y., Nishimura, O., Hara-Nishimura, I., Nishimura, M., and Matsubara, H. (1999). Tissue and intracellular localization of indican and the purification and characterization of indican synthase from Indigo plants. Plant Cell Physiol. *41*, 218-225.
31. Takemoto, D., Hayashi, M., Doke, N, Nishimura, M., and Kawakita, K. (2000). Isolation of gene for EIR, an elicitor inducible receptor like protein, from tobacco by differential display. Plant Cell Physiol. *41*, 458-464.
32. De Bellis, L., Gonzali, S., Alpi, A., Hayashi, H., Hayashi, M., and Nishimura, M. (2000). Purification and characterization of a novel pumpkin short-chain acyl-CoA oxidase which structure resembles acyl-CoA dehydrogenase. Plant Physiol. *123*, 327-334.
33. Mitsuhashi, N., T. Shimada, T., Mano, S., Nishimura, M., and Hara-Nishimura, I. (2000). Characterization of organelles in the vacuolar-sorting pathway by visualization with GFP in tobacco BY-2 cells. Plant Cell Physiol. *41*, 993-1001.
34. Hayashi, M., Nito, K., Toriyama-Kato, K., Kondo, M., Yamaya, T., and Nishimura, M. (2000). AtPex14 maintains peroxisomal functions by determining protein targeting to three kinds of plant peroxisomes. EMBO J. *19*, 5701-5710.
35. Yamaguchi, K., and Nishimura, M. (2000). Reduction to below threshold levels of glycolate oxidase activities in transgenic tobacco enhances photoinhibition during irradiation. Plant Cell Physiol. *41*, 1397-1406.
36. Xu, W., Moriya, K., Yamada, K., Nishimura, M., Shioiri, H., Kojima, M., and Nozue, M.

(2000). Detection and characterization of a 36-kDa peptide in C-terminal region of a 24-kDa vacuolar protein (VP24) precursor in anthocyanin-producing sweet potato cells in suspension culture. Plant Sci. *160*, 121-128.

37. Nito, K., Yamaguchi, K., Kondo, M., Hayashi, M., and Nishimura, M. (2001). Pumpkin peroxisomal ascorbate peroxidase is localized on peroxisomal membranes and unknown membranous structures. Plant Cell Physiol. *42*, 20-27.
38. Hayashi, Y., Hayashi, M., Hayashi, H., Hara-Nishimura, I., and Nishimura, M. (2001). Direct interaction between glyoxysomes and lipid bodies in etiolated cotyledons of *Arabidopsis thaliana ped1* mutant. Protoplasma *218*, 83-94.
39. Fukao, Y., Hayashi, Y., Mano, S., Hayashi, M., and Nishimura, M. (2001). Developmental analysis of a putative ATP/ADP carrier protein localized on glyoxysomal membranes during the peroxisome transition in pumpkin. Plant Cell Physiol. *42*, 835-841.
40. Minamikawa, T., Toyooka, K., Okamoto, T., Hara-Nishimura, I., and Nishimura, M. (2001). Degradation of ribulose 1,5-bisphosphate carboxylase/oxygenase by vacuolar enzymes of senescing French bean leaves: Immunocytochemical and ultrastructural observations. Protoplasma *218*, 144-153.
41. Koumoto, K., Shimada, T., Kondo, M., Hara-Nishimura, I., and Nishimura, M. (2001). Chloroplasts have a novel Cpn10 in addition to Cpn20 as co-chaperonins in *Arabidopsisthaliana*. J. Biol. Chem. *276*, 29688-29694.
42. Mitsuhashi, N., Hayashi, Y., Koumoto, Y., Shimada, T., Fukasawa-Akada, T., Nishimura, M., and Hara-Nishimura, I. (2001). A novel membrane protein of protein bodies that is transported to protein-storage vacuoles via precursor-accumulating vesicles. Plant Cell *13*, 2361-2372.
43. Hayashi, Y., Yamada, K., Shimada, T., Matsushima, R., Nishizawa, N.K., Nishimura, M., and Hara-Nishimura, I. (2001). A proteinase-storing body that prepares for cell death or stresses in the epidermal cells of *Arabidopsis*. Plant Cell Physiol. *42*, 894-899.
44. Yamada, K., Matsushima, R., Nishimura, M., and Hara-Nishimura, I. (2001). A unique cysteine protease with a granulin domain that slowly matures in the vacuoles of senescing *Arabidopsis* leaves. Plant Physiol. *127*, 1626-1634.
45. Tanaka, H., Onouchi, H., Kondo, M., Hara-Nishimura, I., Nishimura, M., Machida, C., and Machida, Y. (2001). A subtilisin-like serine protease is required for epidermal surface formation in *Arabidopsis* embryos and juvenile plants. Development *128*, 4681-4689.
46. Xu, W., Morita, K., Yamada, K., Kondo, M., Nishimura, M., Shioiri, H., Kojima, M., and Nozue, M. (2001). Expression and localization of a 36-kDa vacuolar protein (VP24) precursor in anthocyanin-producing sweet potato cells in suspension culture. Plant Biotechnol. *18*, 203-208.
47. Hayashi, M., Nito, K., Takei-Hoshi, R., Yagi, M., Kondo, M., Suenaga, A., Yamaya, T., and Nishimura, M. (2002), Ped 3p is a peroxisomal ATP-binding cassete transporter that might supply substrate for fatty acid β-oxidation. Plant Cell Physiol. *43*, 1-11.
48. Kuroyanagi, M., Nishimura, M., and Hara-Nishimura, I. （2002）. Activation of Arabidopsis vacuolar processing enzyme by self-catalytic removal of an auto-inhibitory domain of the C-terminal propeptide. Plant Cell Physiol. *43*, 143-151.
49. Kimura, Y., Matsuno, S., Tsurusaki, S., Kimura, M., Hara-Nishimura, I., and Nishimura, M.

(2002). Subcellular localization of endo-b-N-acetylglucosaminidase and high-mannose type free N-glycans in plant cell. Biochim. Biophys. Acta *1570*, 38-46.

50. Watanabe, E., Shimada, T., Kuroyanagi, M., Nishimura, M., and Hara-Nishimura, I. (2002). Calcium-mediated association of a putative vacuolar sorting receptor PV72 with a propeptide of 2S albumin. J. Biol. Chem. *277*, 8708-8715.
51. Mano, S., Nakamori, C., Hayashi, M., Kato, A., Kondo, M., and Nishimura, M. (2002). Distribution and characterization of peroxisomes in *Arabidopsis* by visualization with GFP: Dynamic morphology and actin dependent movement. Plant Cell Physiol. *43*, 331-341.
52. Nito, K., Hayashi, M., and Nishimura, M. (2002). Direct interaction and determination of binding domains among peroxisomal import factors in *Arabidopsis thaliana*. Plant Cell Physiol. *43*, 355-366.
53. Fukao, Y., Hayashi, M., and Nishimura, M. (2002). Proteomic analysis of leaf peroxisomes in greening cotyledons of *Arabidopsis thaliana.* Plant Cell Physiol. *43*, 689-686.
54. Shimada, T., Watanabe, E., Tamura, K., Hayashi, Y., Nishimura, M., and Hara-Nishimura, I. (2002). A vacuolar-sorting receptor on the membrane of the PAC vesicles that accumulate precursors of seed storage proteins. Plant Cell Physiol. *43*, 1086-1095.
55. Maser, P., Eckerman, B., Vaidyanathan, R., Fairbairn, D.J., Kubo, M., Yamagami, M., Yamaguchi, K., Nishimura, M., Uozumi, N., Robertson, W., Sussman, M., and Schroeder, J.I. (2002). Altered shoot/root Na^+ distribution and bifurcating salt sensitivity in *Arabidopsis* by genetic disruption of the Na^+ transporter *AtHKT1*. FEBS Lett. *531*, 157-161.
56. Hayashi, H., De Bellis, L., Kato, A., Hayashi, Y., Nito, K., Hayashi, M., Hara-Nishimura, I., and Nishimura, M. (2002). Molecular characterization of an Arabidopsis acyl-CoA synthetase localized on glyoxysomal membranes. Plant Physiol. *130*, 2019-2026.
57. Kamigaki, A., Mano, S., Terauchi, K., Nishi, Y., Tachibe-Kinoshita, Y., Kondo, M., Nito, K., Hayashi, M., Nishimura, M., and Esaka, M. (2003). Identification of peroxisomal targeting signal of pumpkin catalase and the binding analysis with PTS1 receptor. Plant J. *33*, 161-175.
58. Matsushima, R., Kondo, M., Nishimura, M., and Hara-Nishimura, I. (2003). A novel ER-derived compartment, the ER body, selectively accumulates a β-glucosidase with an ER retention signal in *Arabidopsis*. Plant J. *33*, 493-502.
59. Ono, K., Kondo, M., Osafune, T., Miyatake, K., Inui, H., Kitaoka, S., Nishimura, M., and Nakano, Y. (2003). Presence of glyoxylate cycle enzymes in the mitochondria of *Euglena gracilis.* J. Eukaryo. Microbiol. *50*, 92-96.
60. Kurisu, M., Morita, M., Kashiwayama, Y., Yokota, S., Hayashi, H., Sakai, Y., Ohkuma, S., Nishimura, M., and Imanaka, T. (2003). Existence of catalase-less peroxisomes in Sf21 insect cells. Biochem. Biophys. Res. Commun. *306*, 169-176.
61. Shirahama-Noda, K., Yamamoto, A., Sugihara, K., Hashimoto, N., Asano, M., Nishimura, M., and Hara-Nishimura, I. (2003). Biosynthetic processing of cathepsins and lysosomal degradation in asparaginylendopeptidase-deficient mice. J. Biol. Chem. *278*, 33194-33199.
62. Matsushima, R., Hayashi, Y., Yamada, K., Shimada, T., Nishimura, M., and Hara-Nishimura, I. (2003). The ER body, a novel endoplasmic reticulum-derived structure in *Arabidopsis*. Plant Cell Physiol. *47*, 661-666.

63. Tamura, K., Shimada, T., Ono, E., Tanaka, Y., Nagatani, A., Higashi, S., Watanabe, M., Nishimura, M., and Hara-Nishimura, I. (2003). Why green fluorescent fusion proteins have not been observed in the vacuoles of higher plant? Plant J. *35*, 545-555.
64. Shimada, T., Yamada, K., Kataoka, M., Nakaune, S., Koumoto, Y., Kuroyanagi, M., Tabata, S., Kato, T., Shinozaki, K., Seki, M., Kobayashi, M., Kondo, M., Nishimura, M., and Hara-Nishimura, I. (2003). Vacuolar processing enzymes are required for proper processing of seed storage proteins in *Arabidopsis thaliana*. J. Biol. Chem. *278*, 32292-32299.
65. Okamoto, T., Shimada, T., Hara-Nishimura, I., Nishimura, M., and Minamikawa, T. (2003). C-terminal KDEL sequence of a KDEL-tailed cysteine protease (sulfhydryl-endopeptidase) is involved in formation of KEDL vesicle and in efficient vacuolar transport of sulfhydryl-endopeptidase. Plant Physiol. *132*, 1892-1900.
66. Fukao, Y., Hayashi, M., Hara-Nishimura, I., and Nishimura, M. (2003). Novel glyoxysomal protein kinase, GPK1, identified by proteomic analysis of glyoxysomes in etiolated cotyledons of *Arabidopsis thaliana*. Plant Cell Physiol. *44*, 1002-1012.
67. Yamamoto, Y., Nishimura, M., Hara-Nishimura, I., and Noguchi, T. (2003). Behavior of vacuoles during pollen development and maturation in *Arabidopsis thaliana*. Plant Cell Physiol. *44*, 1192-1201.
68. Shimada, T., Fuji, K., Kondo, M., Nishimura, M., and Hara-Nishimura, I. (2003). A vacuolar sorting receptor for seed storage proteins in *Arabidopsis thaliana.* Proc. Natl. Acad. Sci. USA *100*, 16095-16100.
69. Kamada, T., Nito, K., Hayashi, H., Mano, S., Hayashi, M., and Nishimura, M. (2003). Functional differentiation of peroxisomes revealed by expression profiles of peroxisomal genes in *Arabidopsis thaliana*. Plant Cell Physiol. *44*, 1275-1289.
70. Watanabe, E., Shimada, S., Tamura, K., Matsushima, R., Koumoto, Y., Nishimura, M., and Hara-Nishimura, I. (2004). An ER-localized form of PV72, a seed-specific vacuolar sorting receptor, interferes the transport of an NPIR-containing proteinase in *Arabidopsis* leaves. Plant Cell Physiol. *45*, 9-17.
71. Yamada, K., Nishimura, M., and Hara-Nishimura, I. (2004). The slow wound-response of VPE is regulated by endogenous salicylic acid in Arabidopsis. Planta *218*, 599-605.
72. Mano, S., Nakamori, C., Kondo, M., Hayashi, M., and Nishimura, M. (2004). An *Arabidopsis* dynamin-related protein, DRP3A, controls both peroxisomal and mitochondrial division. Plant J. *38*, 487-498.
73. Matsushima, R., Fukao, Y., Nishimura, M., and Hara-Nishimura, I. (2004). *NAI* 1 gene that encodes a basic-helix-loop-type transcription factor that regulates the formation of a novel ER-derived structure, the ER body. Plant Cell *15*, 1536-1549.
74. Hatsugai, N., Kuroyanagi, M., Yamada, K., Meshi, T., Tsuda, S., Kondo, K., Nishimura, M., and Hara-Nishimura, I. (2004). A plant vacuolar protease, VPE, mediates virus-induced hypersensitive cell death. Science *305*, 855-858.
75. Usami, T., Mochizuki, N., Kondo, M., Nishimura, M., and Nagatani, A. (2004). Cryptochromes and phytochromes synergetically regulate the *Arabidopsis* root greening under blue light. Plant Cell Physiol. *45*, 1798-1808.
76. Yamada, K., Fuji, K., Shimada, T., Nishimura, M., and Hara-Nishimura, I. (2005). Endosomal proteases facilitate for the fusion of endosomes with vacuoles at the step of the

endocytotic pathway. Plant J. *41*, 888-898.
77. Nakaune, S., Yamada, K., Kondo, M., Kato, T., Tabata, A., Nishimura, M., and Hara-Nishimura, I. (2005). A vacuolar processing enzyme, δVPE, involved in seed coat formation at the early stage of seed development. Plant Cell *17*, 876-887.
78. Hayashi, M., Nito, K., Yagi, M., Kamada, T., and Nishimura, M. (2005). Differential contribution of two peroxisomal protein receptors to the maintenance of peroxisomal functions in Arabidopsis. J. Biol. Chem. *280*, 14829-14835.
79. Yoshida, K., Kawachi, M., Mori, M., Maeshima, M., Kondo, M., Nishimura, M., and Kondo, T. (2005). The involvement of tonoplast proton pumps and $Na^+(K^+)/H^+$ exchangers in the change of petal color during flower-opening of morning glory, *Ipomoea tricolor* cv. Heavenly Blue. Plant Cell Physiol. *46*, 407-415.
80. Hashimoto,K., Igarashi, H., Mano, S., Nishimura, M., Shimmen, T., and Yokota, E. (2005). Peroxisomal localization of a myosin XI isoform in *Arabidopsis thaliana*. Plant Cell Physiol. *46*, 782-789.
81. Maehr, R., Hang, H.C., Mintern, J.D., Kim, Y-M., Cuvillier, A., Nishimura, M., Yamada, K., Shirahama-Noda, K., Hara-Nishimura, I., and Ploegh, H.L. (2005). Asparagine endopeptidase is not essential for class II MHC antigen presentation but is required for processing of Cathepsin L in mice. J. Immunol. *174*, 7066-7074.
82. Tamura, I., Shimada, T., Kondo, M., Nishimura, M., and Hara-Nishimura, I. (2005). Katamari1/Murus3 is a novel Golgi membrane protein that is required for endomembrane organization in Arabidopsis. Plant Cell *17*, 1764-1776.
83. Kuroyanagi, M., Yamada, K., Hatsugai, N., Kondo, M., Tazawa, M., Nishimura, M., and Hara-Nishimura, I. (2005). Vacuolar processing enzyme is essential for microtoxin-induced cell death in *Arabidopsis thaliana*. J. Biol. Chem. *280*, 32914-32920.
84. Afitlhile, M.M., Fukushige, H., Nishimura, M., and Hildebrand, D. (2005). A defect in glyoxysomal fatty acid β-oxidation reduces jasmonic acid accumulation in Arabidopsis. Plant Physiol. Biochem. *43*, 603-609.
85. Ueda, H., Nishiyama, C., Shimada, T., Koumoto, Y., Yayashi, Y., Kondo, M., Takahashi, T., Ohtomo, I., Nishimura, M., and Hara-Nishimura, I. (2006). AtVAM3 is required for normal specification of idioblasts, myrosin cells. Plant Cell Physiol. *47*, 164-175.
86. Mano. S., Nakamori, C., Nito, K., Kondo, M., and Nishimura, M. (2006). The Arabidopsis *pex12* and *pex13* mutants are defective in both PTS1- and PTS2- dependent transport to peroxisomes. Plant J. *47*, 1187-1194.
87. Shimada, T., Koumoto, Y., Li, I., Yamazaki, M., Kondo, M., Nishimura, M., and Hara-Nishimura, I. (2006). AtVPS29, a Putative component of a retromer complex, is required for the efficient sorting of seed storage proteins. Plant Cell Physiol. *47*, 1187-1194.
88. Li L., Shimada, T., Takahashi, H., Ueda, H., Fukao, Y., Kondo, M., Nishimura, M., and Hara-Nishimura, I. (2006). MAIGO2 is involved in exit of seed storage proteins from the endoplasmic reticulum in *Arabidopsis thaliana.* Plant Cell *18*, 3535-3547.
89. Morita, Y., Arai, H., Sugimoto, T., Takeuchi, K., Yamane, T., Maeda, T., Yamamoto, Y., Nishi, K., Asano, M., Shirahama-Noda, K., Nishimura, M., Uzu, T., Hara-Nishimura, I., Koya, D., Kashiwagi, A., and Ohkubo, I. (2007). Legumain/asparaginyl endopeptidase

controls extracellular matrix remodeling through the degradation of fibronectin in mouse renal proximal tubular cells. FEBS Lett. *581*, 1417-1424.
90. Nito, K., Kamigaki, A., Kondo, M., Yagi, M., Hayashi, M., and Nishimura, M. (2007). Functional identification of *Arabidopsis* peroxisome biogenesis factors proposed from analysis of knockdown mutants. Plant Cell Physiol. *48*, 763-774.
91. Kobayashi, K., Kondo, M., Nishimura, M., and Ohta, H. (2007). Galactolipid synthesis on chloroplast inner envelope is essential for proper thylakoid biogenesis, photosynthesis and embryogenesis. Proc. Natl. Acad. Sci, USA *104*, 17216-17221.
92. Yamada, K., Fukazawa, M., Hayashi, M., Suzuki, I., and Nishimura, M. (2007). HSP90 regulates the heat shock response in *Arabidopsis thaliana* that is responsible for heat adaptation. J. Biol. Chem. *282*, 37794-37804.

2) Invited reviews, book chapters

1. Nishimura, M. (1998). Molecular chaperones and temperature stress. Stress Responses of Photosynthesis Organisms: Molecular Mechanisms and Molecular Regulations, Edited by K. Satoh and N. Murata, Elsevier, pp. 83-92.
2. Nishimura, M., Hayashi, M., Toriyama, K., Kato, A., Mano, S., Yamaguchi, K., Kondo, K., and Hayashi, H. (1998). Microbody defective mutants of Arabidopsis. J. Plant Res. *111*, 329-332.
3. Hara-Nishimura, I., Kinoshita, T., Hiraiwa, N., and Nishimura, M. (1998). Vacuolar processing enzymes in protein-storage vacuoles and lytic vacuoles. J. Plant Physiol. *152*, 668-674.
4. Mano, S., Hayashi, M., and Nishimura, M. (2000). A leaf-peroxisomal protein, hydroxypyruvate reductase, is produced by light-regulated alternative splicing. Cell Biochem. Biophys. *32*, 147-154.
5. Kato, A., Hayashi, M., Kondo, M., and Nishimura, M. (2000). Transport of peroxisomal proteins that are synthesized as large precursors in plants. Cell Biochem. Biophys. *32*, 269-275.
6. Hayashi, M., Toriyama, K., Kondo, M., Kato, A., Mano, S., De Bellis, L., Hayashi-Ishimaru, Y., Yamaguchi, K., Hayashi, H., and Nishimura, M. (2000). Functional transformation of plant peroxisomes. Cell Biochem. Biophys. *32*, 295-304.
7. Hayashi, M., and Nishimura, M. (2002). Genetic approaches to understand plant peroxisomes. Plant peroxisomes, Edited by A. Baker and I. Graham, Kluwer pp. 273-303.
8. Nishimura, M. (2002). Molecular mechanisms of reviersible transformation of organelles in differentiation of higher plant cells. 4 Organism Constructing Mechanisms (Reproduction and Development) pp. 13-14.
9. Matsushima, R., Hayashi, Y., Yamada, K., Shimada, T., Nishimura, M., and Hara-Nishimura, I. (2003). The ER body, a novel endoplasmic reticulum-derived structure in *Arabidopsis*. Plant Cell Physiol. *44*, 661-666.
10. Hayashi, M., and Nishimura, M. (2003). Entering a new era of research on plant peroxisomes. Cri. Rev. Plant Sci. *6*, 577-582.

11. Hara-Nishimura, I., Matsushima, R., Shimada, T., and Nishimura, M. (2004). Diversity and functions of ER-derived compartments in plants: Are these compartments specific to plant cells? Plant Physiol. *136*, 3435-3439.
12. Yamada, K., Shimada, T., Nishimura, M., and Hara-Nishimura, I. (2005). A VPE family supporting various vacuolar functions in plants. Physiol. Plant. *123*, 369-375.
13. Mano, S., and Nishimura, M. (2005). Plant peroxisomes. Vitamin and Hormones *72*, 111-154, Flsevier Sci. Press.
14. Hara-Nishimura, I., Hatsugai, N., Nakaune, S., Kuroyanagi, M., and Nishimura, M. (2005). Vacuolar processing enzyme: an executor of plant cell death. Curr. Opin. Plant Biol. *8*, 404-408.
15. Hatsugai, N., Kuroyanagi, M., Nishimura, M., and Hara-Nishimura, I. (2006). The cellular suicide strategy of plants: Vacuole-mediated cell death. Apoptosis *11*, 905-911.
16. Hayashi, M., and Nishimura, M. (2006). *Arabidopsis thaliana*-A model organism to study plant peroxisomes. Biophys. Biochim. Acta *1763*, 1382-1391.
17. Kuroyanagi, M., Hatsugai, N., Nishimura, M., and Hara-Nishimura, I. (2007). Vacuolar processing enzyme, a key molecule in both pathogen-induced and phytotoxin induced cell death in higher plants. Mol. Plant Microbe Interact. *5*, 208-214.

大隅良典
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Professor Ohsumi is the world-recognized pioneer in the field of molecular mechanisms of autophagy. He discovered the bulk protein degradation system in yeast vacuoles in late 1980's all by himself, and demonstrated that it was due to autophagy. He then moved on to isolation of yeast mutants defective in autophagy, now called *atg* mutants, together with young students, which enabled them to open up a completely new exciting world. Since then, the achievements of Ohsumi's group are more than amazing. They include the state-of-the-art demonstration of membrane dynamics by electron and light microscopy and identification of many novel molecular mechanisms of autophagic machinery such as kinase cascades, ubiquitin-like conjugation systems and lipid processing. For these brilliant achievements, Ohsumi received Fujiwara Award in 2005, the Japan Academy Award in 2006, and the Science Award from the Botanical Society of Japan in 2007. Nobody would doubt that he has contributed most in the world to elucidate the importance and wonder of autophagy.

Now many researchers are interested in a variety of aspects in and around the field of autophagy. From the viewpoint of mechanisms of authophagy, the largest question that remains to be answered is from where the autophagosomes is generated at the beginning. Other people are curious about the physiological significance of autophagy in development, morphogenesis, and some aspects of diseases. Ohsumi's group has always been producing important clues to solve these problems. NIBB must be honored to have the research group of such high originality and quality.

One concern of the evaluation committee is how these outstanding activities of the Ohsumi group can be succeeded by young generations, when Ohsumi retires two years from now. Encouragement of young researchers to become independent to continue these activities should be seriously considered. Every effort should be made to identify/recruit capable young researcher(s) (perhaps an outstanding research associate or post-doc in the current laboratory) to continue the project.

（和訳）

大隅教授は、オートファジーの分子機序の領域の世界が認める先駆者である。教授は1980 年代の終わりに、一人で、酵母の液胞内に多量のタンパク質を分解するシステムが存在することを発見し、これがオートファジーによるものであることを示した。その後、オートファジーが不能な酵母の突然変異株を単離し（現在では *atg* 変異と呼ばれている）、そのことが、彼らが全く新しい世界を開くのを可能にした。それ以降、大隅グループの業績は、極めて目覚ましいものである。そのような業績としては、電子顕微鏡ならびに光学顕微鏡による膜ダイナミクスの見事な実証、およびキナーゼカスケードやユビキチン様の結合システムならびに脂質処理などのオートファジーに関与するマシ

ナリーの多くの新たな分子機序を同定したことがあげられる。このような輝かしい業績により、大隅は、2005 年藤原賞、2006 年日本学士院賞、2007 年日本植物学会学術賞を受賞した。オートファジーの重要性と不思議の解明に世界で最も貢献した人であることを誰もが認めるであろう。

現在では多くの研究者が、オートファジー内外の様々な側面に関心を示している。オートファジーの機序に関する観点からは、まだ解明されていない最大の疑問は、オートファゴソームが最初にどこで作られるかという点である。また、発生や形態形成、ある種の疾病におけるオートファジーの生理的重要性について関心を寄せている。大隅グループは、これらの問題を解決する重要な鍵を常に見つけてきた。基礎生物学研究所はこのような高いオリジナリティーとクオリティーを持った研究グループを抱えていることを名誉なこととしなければならない。

外部評価委員会が懸念することの一つは、大隅教授が 2 年後に退官する際に、このような大隅グループの傑出した活動を若い世代にどのように継承していくかである。若手研究者に、独立してこれらの研究活動を継続できるようになるよう奨励することを真剣に検討する必要がある。プロジェクトを継続できる能力の高い若手研究者（おそらくは、現在の研究室にいる傑出した准教授やポストドク）を見つけ採用することにあらゆる努力を尽くす必要がある。

研究業績：

1) Research articles in peer reviewed journals

1. Nakamura, N., Matsuura, A., Wada, Y., and Ohsumi, Y. (1997). Acidification of vacuoles is required for autophagic degradation in the yeast, *Saccharomyces cerevisiae.* J. Biochem. (Tokyo) *121*, 338-344.
2. Funakoshi, T., Matsuura, A., Noda, T., and Ohsumi, Y. (1997). Analyses of *APG13* gene involved in autophagy in yeast, *Saccharomyces cerevisiae.* Gene *192*, 207-213.
3. Matsuura, A., Tsukada, M., Wada, Y., and Ohsumi, Y. (1997). Apg1p, a novel protein kinase required for the autophagic process in *Saccharomyces cerevisiae.* Gene *192*, 245-250.
4. Scott, S.V., Baba, M., Ohsumi, Y., and Klionsky, D.J. (1977). Aminopeptidase I is targeted to the vacuole by a nonclassical vescicular mechanism. J. Cell Biol. *138*, 37-44.
5. Nakamura, N., Hirata, A., Ohsumi, Y., and Wada, Y. (1997). Vam2/Vps41p and Vam6/Vps39p are components of a protein complex on the vacuolar membranes and involved in the vacuolar assembly in the yeast *Saccharomyces cerevisiae.* J. Biol. Chem. *272*, 11344-11349.
6. Wada, Y., Nakamura, N., Ohsumi, Y., and Hirata, A. (1997). Vam3p, a new member of syntaxin related protein, is required for vacuolar assembly in the yeast *Saccharomyces cerevisiae.* J. Cell Sci. *110*, 1299-1306.
7. Baba, M., Osumi, M., Scott, S.V., Klionsky, D.J., and Ohsumi, Y. (1997). Two distinct

pathways for targeting proteins from the cytoplasm to the vacuole/lysosome. J. Cell Biol. *139*, 1687-1695.
8. Shirahama, K., Noda, T., and Ohsumi, Y. (1997). Mutational analysis of Csc1/Vps4p: involvement of endosome in regulation of the autophagy in yeast. Cell Struc. Func. *22*, 501-509.
9. Noda, T., and Ohsumi, Y. (1998). Tor, a phosphatidylinositol kinase homologue, controls autophagy in yeast. J. Biol. Chem. *273*, 3963-3966.
10. Kametaka, S., Okano, T., Ohsumi, M., and Ohsumi, Y. (1998). Apg14p and Apg6/Vps30p form a protein complex essential for autophagy in the yeast, *Saccharomyces cerevisiae*. J. Biol. Chem. *273*, 22284-22291.
11. Mizushima, N., Noda, T., Yoshimori, T., Tanaka, T., Ishii, T., George, M.D. Klionsky, D.J., Ohsumi, M., and Ohsumi, Y. (1998). A protein conjugation system essential for autophagy. Nature *395*, 395-398.
12. Mizushima, N., Sugita, H., Yoshimori, T., and Ohsumi, Y. (1998). A new protein conjugation system in human. The counterpart of the yeast Apg12p conjugation sytem essential for autophagy. J. Biol. Chem. *273*, 33889-33892.
13. Tanida, I., Mizushima, N., Kiyooka, M. Ohsumi, M., Ueno, T., Ohsumi, Y., and Kominami, E. (1999). Apg7p/Cvt2p: A novel protein-activating enzyme essential for autophagy. Mol. Cell Biol. *10*, 1367-1379.
14. Mizushima, N., Noda, T., and Ohsumi Y. (1999). Apg16p is required for the function of the Apg12p-Apg5p conjugate in the yeast autophagic pathway. EMBO J. *18*, 3888-3896.
15. Shintani, T., Mizushima, N., Ogawa, Y., Matsuura, A., Noda, T., and Ohsumi Y. (1999). Apg10p, a novel protein-conjugating enzyme essential for autophagy in yeast. EMBO J. *18*, 5234-5241.
16. Kirisako, T., Baba, M., Ishihara, N., Miyazawa, K., Ohsumi, M., Yoshimori, T., Noda, T., and Ohsumi, Y. (1999). Formation process of autophagosome is traced with Apg8/Aut7p in yeast. J. Cell Biol. *147*, 435-446.
17. Yabe, I., Horiuchi, K., Nakahara, K., Hiyama, T., Yamanaka, T., Wang, P. C., Toda, K., Hirata, A., Ohsumi, Y., Hirata, R., Anraku, Y., and Kusaka, I. (1999). Patch clamp studies on V-type ATPase of vacuolar membrane of haploid *Saccharomyces cerevisiae*. Preparation and utilization of giant cell containing a giant vacuole. J. Biol. Chem. *274*, 34903-34910.
18. Yoshimori, T., Yamagata, F., Yamamoto, A., Mizushima, N., Kabeya, Y., Nara, A., Ishido, M., Ohashi, M., Ohsumi, M., and Ohsumi, Y. (2000). The mouse SKD1, a homologue of yeast Vps4p, is required for normal endosomal trafficking and morphology in mammalian cells. Mol. Biol. Cell *11*, 747-763.
19. George, M,D., Baba, M., Scott, S.V., Mizushima, N., Garrison, B.S., Ohsumi, Y., and Klionsky, D.J. (2000). Apg5p functions in the sequestration step in the cytoplasm-to-vacuole targeting and macroautophagy pathways. Mol. Biol. Cell *11*, 969-982.
20. Noda, T., Kim. J., Huang, W-P., Baba, M., Tokunaga, C., Ohsumi, Y., and Klionsky, D.J. (2000). Apg9p/Cvt7p is an integral membrane protein required for transport vesicle formation in the Cvt and autophagy pathways. J. Cell Biol. *148*, 465-480.
21. Furukawa, K., Mizushima, N., Noda, T., and Ohsumi, Y. (2000). A protein conjugation system in yeast with homology to biosyntheic enzyme reaction of prokaryotes. J. Biol.

Chem. *275*, 7462-7465.
22. Scott, S.V., Nice, III, D.C., Nau, J.J., Weisman, L.S., Kamada, Y., Keizer-Gunnink, I., Funakoshi, T., Veenhuis, M., Ohsumi, Y., and Klionsky, D.J. (2000). Apg13p and Vac8p are part of a complex of phosphoproteins that are required for cytoplasm to vacuole targeting. J. Biol. Chem. *275*, 25840-25849.
23. Kamada, Y., Funakoshi, T., Shintani, T., Nagano, K., Ohsumi, M., and Ohsumi, Y. (2000). Tor-mediated induction of autophagy via an Apg1 protein kinase complex. J. Cell Biol. *150*, 1507-1513.
24. Kirisako, T., Ichimura, Y., Okada, H., Kabeya, Y., Mizushima, N., Yoshimori, T., Ohsumi, M., Noda, T., and Ohsumi, Y. (2000). The reversible modification regulates the membrane-binding state of Apg8/Aut7 essential for autophagy and the cytoplasm to vacuole targeting pathway. J. Cell Biol. *151*, 263-276.
25. Kabeya, Y., Mizushima, N., Ueno, T., Yamamoto, A., Kirisako, T., Noda, T., Kominami, E., Ohsumi, Y., and Yoshimori, T. (2000). LC3, a mammalian homologue of yeast Apg8p is localized in autophagosome membranes after processing. EMBO J. *19*, 5720-5728.
26. Grote, E., Baba, M., Ohsumi, Y., and Novick, P.J. (2000). Geranylgeranylated SNAREs are dominant inhibitors of membrane fusion. J. Cell Biol. *151*, 453-466.
27. Ichimura, Y., Kirisako, T., Takao, T., Satomi, Y., Shimonishi, Y., Ishihara, N., Mizushima, N., Tanida, I., Kominami, E., Ohsumi, M., Noda, T., and Ohsumi, Y. (2000). A ubiquitin-like system mediates protein lipidation. Nature *408*, 488-492.
28. Kihara, A., Noda, T., Ishihara, N., and Ohsumi, Y. (2001). Two distinct Vps34 phosphatidylinositol 3-kinase complexes function in autophagy and carboxypeptidase Y sorting in *Saccharomyces cerevisiae*. J. Cell Biol. *152*, 519-530.
29. Kihara, A., Kabeya, Y., Ohsumi, Y., and Yoshimori, T. (2001). Beclin-phsophatidylinositol 3-kinase complex functions at the trans-Golgi network. EMBO Report *2*, 330-335.
30. Mizushima, N., Yamamoto, A., Hatano, M., Kobayashi, Y., Kabeya, Y., Suzuki, K., Tokuhisa, T., Ohsumi, Y., and Yoshimori, T. (2001). Dissection of autophagosome formation using Apg5-deficient mouse embryonic stem cells. J. Cell Biol. *152*, 657-668.
31. Komatsu, M., Tanida, I., Ueno, T., Ohsumi, M., Ohsumi, Y., and Kominami, E. (2001). The C-terminal region of an Apg7p/Cvt2p is required for homodimerization and is essential for its E1 activity and E1-E2 complex formation. J. Biol. Chem. *276*, 9846-9854.
32. Kim, J., Kamada, Y., Stromhaug, P.E., Guan, J., Hefner-Gravink, A., Baba, M., Scott, S.V., Ohsumi, Y., Dunn, Jr., W.A., and Klionsky, D.J. (2001). Cvt9/Gsa9 functions in sequestering selective cytosolic cargo destined for the vacuole. J. Cell Biol. *153*, 381-396.
33. Shintani, T., Suzuki, K., Kamada, Y., Noda, T., and Ohsumi, Y. (2001). Apg2p functions in autophagosome formation on the perivacuolar structure. J. Biol. Chem. *276*, 30452-30460.
34. Ishihara, N., Hamasaki, M., Yokota, S., Suzuki, K., Kamada, Y., Kihara, A., Yoshimori, T., Noda, T., and Ohsumi, Y. (2001). Autophagosome requires specific early Sec proteins for its formation and NSF/SNARE for vacuolar fusion. Mol. Biol. Cell *12*, 3690-3702.
35. Suzuki, K., Kirisako, T., Kamada, Y., Mizushima, N., Noda, T., and Ohsumi, Y. (2001). The pre-autophagosomal structure organized by concerted functions of *APG* genes is essential for autophagosome formation. EMBO J. *20*, 5971-5981.
36. Nara, A., Mizushima, N., Yamamoto, A, Kabeya, Y., Ohsumi, Y., and Yoshimori, T. (2002).

SKD1 AAA ATPase-dependent endosomal transport is involved in autolysosome formation. Cell Struc. Func. *27*, 29-37.
37. Kuma, A., Mizushima, N., Ishihara, N., and Ohsumi, Y. (2002). Formation of the approximately 350-kDa Apg12-Apg5, Apg16 multimeric complex, mediated by Apg16 oligomerization, is essential for autophagy in yeast. J. Biol. Chem. *277*, 18619-18625.
38. Hanaoka, H., Noda, T., Shirano, Y., Kato, T., Hayashi, H., Shibata, D., Tabata, S., and Ohsumi, Y. (2002). Leaf senescence and starvation-induced chlorosis are accelerated by the disruption of an Arabidopsis autophagy gene. Plant Physiol. *129*, 1181-1193.
39. Suzuki, T., Nakagawa, M., Yoshikawa, A., Sasagawa, N., Yoshimori, T., Ohsumi, Y., Nishino, I., Ishiura, S., and Nonaka, I. (2002). The first molecular evidence that autophagy relates rimmed vacuole formation in chloroquine myopathy. J. Biochem. (Tokyo) *131*, 647-651.
40. Mizushima, N., Yoshimori, T., and Ohsumi, Y. (2002). Mouse Apg10 as an Apg12-conjugating enzyme: analysis by the conjugation-mediated yeast two-hybrid method. FEBS lett. *532*, 450-454.
41. Suzuki, K., Kamada, Y., and Ohsumi, Y. (2002). Studies of cargo delivery to the vacuole mediated by autophagosomes in *Saccharomyces cerevisiae*. Dev. Cell *3*, 815-824.
42. Hamasaki, M., Noda, T., and Ohsumi, Y. (2003). The early secretory pathway contributes to autophagy in yeast. Cell Struct. Funct. *28*, 49-54.
43. Mizushima, N., Kuma, A., Kobayashi, Y., Yamamoto, A., Matsubae, M., Takao, T., Natsume, T., Ohsumi, Y., and Yoshimori, T. (2003). Mouse Apg16L, a novel WD-repeat protein, targets to the sutophagic isolation membrane with the Apg12-Apg5 conjugate. J. Cell Sci. *116*, 1679-1688.
44. Klionsky D. J,, Cregg, J. M,, Dunn, W. A. Jr., Emr, S. D., Sakai, Y., Sandoval, I. V., Sibirny, A., Subramani, S., Thumm, M., Veenhuis, M., and Ohsumi, Y. (2003). A unified nomenclature for yeast autophagy-related genes. Dev. Cell *5*, 539-545.
45. Qu, X., Yu, J., Bhagat, G., Furuya,N., Hibshoosh, H., Troxel, A., Rosen, J., Eskelinen, E.L., Mizushima, N., Ohsumi, Y., Cattoretti, G., and Levine, B. (2003). Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. J. Clin. Invest. *112*, 1809-1820.
46. Sugawara, K., Suzuki, N. N., Fujioka, Y., Mizushima, N., Ohsumi, Y., and Inagaki, F. (2003). Crystallization and preliminary X-ray analyses of LC3-I. Acta Crys. D. *59*, 1464-1465.
47. Mukaiyama, H., Baba, M., Osumi, M., Aoyagi, S., Kato, N., Ohsumi, Y., and Sakai, Y. (2004).Modification of a ubiquitin-like protein Paz2 conducted micropexophagy through formation of a novel membrane structure. Mol. Biol. Cell *15*, 58-70.
48. Mizushima, N,, Yamamoto, A., Matsui, M., Yoshimori, T., and Ohsumi, Y. (2004). In vivo analysis of autophagy in response to nutrient starvation using transgenic mice expressing a fluorescent autophagosome marker. Mol. Biol. Cell *15*, 1101-1111.
49. Kabeya, Y., Mizushima, N., Yamamoto, A., Oshitani-Okamoto, S., Ohsumi, Y., and Yoshimori, T. (2004). LC3, GABARAP and GATE16 localize to autophagosomal membrane depending on form-II formation. J. Cell Sci. *117*, 2805-2812.
50. Onodera, J., and Ohsumi, Y. (2004). Ald6p is a preferred target for autophagy in the yeast,

Saccharomyces cerevisiae. J.Biol. Chem. *279*, 16071-16076.
51. Sugawara, K., Suzuki, N. N. Fujioka, Y., Mizushima, N., Ohsumi, Y., and Inagaki, F. (2004). The crystal structure of microtubule-associated protein light chain 3, a mammalian homologue of *Saccharomyces cerevisiae* Atg8. Genes Cells *9*, 611-618.
52. Okazaki, H., Ono, B., Ohsumi, Y., and Ohsumi, M. (2004). *apg15-1*, a UGA mutant allele in the *Saccharomyces cerevisiae APG16* gene, and its suppression by a cytoplasmic factor. Biosci. Biotechnol. Biochem. *68*, 1541-1548.
53. Suzuki, K., Noda, T., and Ohsumi, Y. (2004). Interrelationships among Atg proteins during autophagy in *Saccharomyces cerevisiae.* Yeast *21*, 1057-1065.
54. Ichimura,Y., Imamura,Y., Emoto, K., Umeda, M., Noda, T., and Ohsumi,Y. (2004). In vivo and in vitro reconstitution of Atg8 conjugation essential for autophagy. J. Biol. Chem. *279*, 40584-40592.
55. Yoshimoto, K., Hanaoka, H., Sato, S., Kato, T., Tabata, S., Noda, T., and Ohsumi, Y. (2004). Processing of *ATG8*s, ubiquitin-like proteins, and their deconjugation by *ATG4*s are essential for plant autophagy. Plant Cell *16*, 2967-2983.
56. Kuma, A., Hatano, M., Matsui, M., Yamamoto, A., Nakaya, H., Yoshimori, T., Ohsumi, Y., Tokuhisa, T., and Mizushima, N. (2004). The role of autophagy during the early neonatal starvation period. Nature *432*, 1032-1036.
57. Hamasaki, M., Noda, T., Baba, M., and Ohsumi, Y. (2005). Starvation triggers the delivery of the endoplasmic reticulum to the vacuole via autophagy in yeast. Traffic *6*, 56-65.
58. Ano, Y., Hattori, T., Oku, M., Mukaiyama, H., Baba, M., Ohsumi, Y., Kato, N., and Sakai, Y. (2005). A sorting nexin PpAtg24 regulates vacuolar membrane dynamics during pexophagy via binding to phosphatidylinositol-3-phosphate. Mol. Biol. Cell *16*, 446-457.
59. Shimazu. M., Sekito, T., Akiyama, K., Ohsumi, Y., and Kakinuma, Y. (2005). A family of basic amino acid transporters of the vacuolar membrane from *Saccharomyces cerevisiae*. J. Biol. Chem. *280*, 4851-4857.
60. Kabeya, Y., Kamada, Y., Baba, M., Takikawa, H., Sasaki, M., and Ohsumi, Y. (2005). Atg17 functions in cooperation with Atg1 and Atg13 in yeast autophagy. Mol. Biol. Cell *16*, 2544-2553.
61. Komatsu, M., Waguri, S., Ueno, T., Iwata, J., Murata, S., Tanida, I., Ezaki, J., Mizushima, N., Ohsumi, Y., Uchiyama, Y., Kominami. E., Tanaka, K., and Chiba, T. (2005). Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice. J. Cell Biol. *169*, 425-434.
62. Hanada, T., and Ohsumi, Y. (2005). Structure-function relationship of Atg12, a ubiquitin-like modifier essential for autophagy. Autophagy *1*, 110-118.
63. Suzuki, N. N., Yoshimoto, K., Fujioka, Y., Ohsumi, Y., and Inagaki, F. (2005). The crystal structure of plant ATG12 and its biological implication in autophagy. Autophagy *1*, 119-126.
64. Pyo, J.O., Jang, M.H., Kwon, Y.K., Lee, H.J., Jun, J.I., Woo, H.N., Cho, D.H., Choi, B., Lee, H., Kim, J.H., Mizushima, N., Ohsumi, Y., and Jung, Y.K. (2005). Essential roles of Atg5 and FADD in autophagic cell death: dissection of autophagic cell death into vacuole formation and cell death. J. Biol. Chem. *280*, 20722-20729.
65. Kamada, Y., Fujioka, Y., Suzuki, N.N., Inagaki, F., Wullschleger, S., Loewith, R., Hall, M.,N., and Ohsumi, Y. (2005). Tor2 directly phosphorylates the AGC kinase Ypk2 to

regulate actin polarization. Mol. Cell Biol. *25*, 7239-7248.
66. Sugawara , K., Suzuki, N. N., Fujioka, Y., Mizushima, N., Ohsumi, Y., and Inagaki, F. (2005). Structural basis for the specificity and catalysis of human Atg4B responsible for mammalian autophagy. J. Biol. Chem. *280*, 40058-40065.
67. Onodera, J., and Ohsumi, Y. (2005). Autophagy is required for maintenance of amino acids levels and protein synthesis under nitrogen starvation. J. Biol. Chem. *280*, 31582-31586.
68. Kawamata, T., Kamada, Y., Suzuki, K., Kuboshima, N., Akimatsu, H., Ota, S., Ohsumi, M., and Ohsumi, Y. (2005). Characterization of a novel autophagy-specific gene, ATG29. Biochem. Biophys. Res. Commun. *338*, 1884-1889.
69. Matsui, M., Yamamoto, A., Kuma, A., Ohsumi, Y., and Mizushima, N. (2006). Organelle degradation during the lens and erythroid differentiation is independent of autophagy. Biochem. Biophys. Res. Comm. *339*, 485-489
70. Obara, K., Sekito, T., and Ohsumi, Y. (2006). Assortment of phosphatidylinositol 3-kinase complexes --Atg14p directs association of complex I to the pre-autophagosomal structure in *Saccharomyces cerevisiae*. Mol. Biol. Cell *17*, 1527-1539.
71. Amar, N., Lustig, G., Ichimura, Y., Ohsumi, Y., and Elazar, Z. (2006). Two newly identified sites in the ubiquitin-like protein Atg8 are essential for autophagy. EMBO Report *7*, 635-642.
72. Matsushita, M., Suzuki, N. N., Fujioka, Y., Ohsumi, Y., and Inagaki, F. (2006). Expression, purification and crystallization of the Atg5-Atg16 complex essential for autophagy. Acta Crystallograph. Sect. F. Struct. Biol. Cryst. Commun. *62*, 1021-1023.
73. Yamada, Y., Suzuki, N. N., Fujioka. Y., Ichimura, Y., Ohsumi, Y., and Inagaki, F. (2006). Crystallization and preliminary X-ray analysis of Atg3. Acta Crystallograph, Sect. F. Struct. Biol. Cryst. Commun. *62*, 1016-1017.
74. Inoue, Y., Suzuki, T., Hattori, M., Yoshimoto, K., Ohsumi, Y., and Moriyasu, Y. (2006). AtATG genes, homologs of yeast autophagy genes, are involved in constitutive autophagy in Arabidopsis root tip cells. Plant Cell Physiol. *47*, 1641-1652.
75. Kabeya, Y., Kawamata, T., Suzuki, K., and Ohsumi, Y. (2007). Cis1/Atg31 is required for autophagosome formation in *Saccharomyces cerevisiae*. Biochem. Biophys. Res. Comm. *356*, 405-410.
76. Fujiki, Y., Yoshimoto, K., and Ohsumi, Y. (2007). An Arabidopsis homolog of Yeast *ATG6/VPS30* is essential for pollen germination. Plant Physiology *143*, 1132-1139.
77. Yamada, Y., Suzuki, N., N., Hanada, T., Ichimura, Y., Kumeta, H., Fujioka, Y., Ohsumi, Y., and Inagaki, F. (2007). The crystal structure of *Atg3*, an autophagy-related ubiquitin carrier protein (E2) enzyme that mediates Atg8 lipidation. J. Biol. Chem. *282*, 8036-8043.
78. Adachi, W., Suzuki, N., N., Fujioka, Y., Suzuki, K., Ohsumi, Y., and Inagaki, F. (2007). Crystallization of *Saccharomyces cerevisiae* aminopeptidase 1, the major cargo protein of the Cvt pathway. Acta Crystallograph, Sect. F. Struct.Biol. Cryst. Commun. *63*, 200-203.
79. Satoo, K., Suzuki, N., N., Fujioka, Y., Mizushima, N., Ohsumi, Y., and Inagaki, F. (2007). Crystallization and preliminary crystallographic analysis of human Atg4B-LC3 complex. Acta Crystallograph, Sect. F. Struct. Biol. Cryst. Commun. *63*, 99-102.
80. Matsushita, M., Suzuki, N., N., Obara, K., Fujioka,Y., Ohsumi, Y., and Inagaki, F. (2007). Structure of Atg5-Atg16, a complex essential for autophagy. J. Biol. Chem. *282*, 6763-6772.

81. Suzuki, K., Kubota, Y., Sekito, T., and Ohsumi, Y. (2007). Hierarchy of Atg proteins In pre-autophagsomal structure organization. Genes Cells *12*, 209-218.
82. Yamaguti, M., Suzuki, N., N., Fujioka, Y., Ohsumi, Y., and Inagaki, F. (2007). Crystallization and preliminary X-ray analysis of Atg10. Acta Crystallograph. Sect. F. Struct. Biol. Cryst. Commun. *63*, 443-445.
83. Nakatogawa, H., Ichimura, Y., and Ohsumi Y. (2007). Atg8, a ubiquitin-like protein required for autophagosome formation, mediates membrane tethering and hemifusion. Cell *130*, 165-178.
84. Hanada, T., Suzuki, N., N., Satomi,Y., Ichimura, Y., Fujioka, Y., Takao, T., Inagaki, F., and Ohusmi, Y. (2007). The Atg12-Atg5 conjugate has a novel E3-like activity for protein lipidation in autophagy, J. Biol. Chem *282*, 37298-37302.

2) Invited reviews, book chapters

1. Ohsumi. Y. (1999). Molecular mechanism of autophgay in yeast, *Saccharomyces cerevisiae*. Phiols. Roy. Soc. Lond. *354*, 1577-1581.
2. Klionsky, D. J., and Ohsumi, Y. (1999). Vacuolar import of proteins and organelles from the cytoplasm. Annu. Rev. Cell Dev. Biol. *15*, 1-32.
3. Noda, T., Ohsumi, Y., and Klionsky, D. (2000). The yeast vacuole: A paradigm for Plant cell Biologist. Ann. Plant Reviews *5*, 1-191.
4. Ohsumi, Y. (2001). Molecular dissection of autophagy: two ubiquitin-like systems. Nature Reviews, Mol. Cell Biol. *2*, 211-216.
5. Noda, T., Suzuki, K., and Ohsumi, Y. (2002). Yeast autophagosomes: de novo formation of membrane structure. Trends Cell Biol. *12*, 231-235.
6. Mizushima, N., Yoshimori, T., and Ohsumi, Y. (2003). Role of the Apg12 conjugation system in mammalian autophagy. Int. J. Biochem. Cell Biol. *35*, 553-561.
7. Ohsumi, Y., and Mizushima, N. (2004). Two ubiquitin-like conjugation systems essential for autophagy. Semin. Cell Dev. Biol. *15*, 231-236.
8. Ohsumi, Y. (2004). Cellular recycling system- molecular mechanism of autophagy. In Cell Growth, (Hall, MN, Raff, M., Thomas G. eds) Cold Spring Harbor Press, 412-429.
9. Ohsumi, Y. (2004). Lytic function of vacuole, molecular dissection of autophagy in yeast. In Handbook of ATPase (Futai, M., Wada, Y., and Kaplan, JH eds) Wiley-VCH., pp443-45.
10. Kamada, Y., Sekito, T., and Ohsumi, Y. (2004). Autophagy in yeast: a TOR-mediated response to nutrient starvation. Curr. Top. Microbiol. Immunol. *279*,73-84.
11. Bassham, D.C., Laporte, M., Marty, F., Moriyasu, Y., Ohsumi, Y., Olsen, L.J., and Yoshimoto, K. (2006). Autophagy in development and stress responses of plants. Autophagy *2*, 2-11.
12. Ohsumi, Y. (2006). Protein turnover. IUBMB Life *58*, 363-369.
13. Suzuki, K., and Ohsumi, Y. (2007). Molecular machinery of autophagosome formation in yeast, *Saccharomyces cerevisiae*. FEBS Lett *581*, 2156-2161.

和田正三
光情報研究部門・教授（特任）

Professor Wada has been working on a very interesting question of plant cells, namely, photomovement of chloroplasts. Chloroplast photomovement refers to the gathering of chloroplasts along the cell surface when the light shed on the plant is weak, and their movement to the lateral side of cells when the light is strong. Using a variety of model plants, Wada's group has identified photoreceptors involved in these events, phototropins in the case of Arabidopsis and chimeric receptors that combine phytochrome and phototropin for ferns and green algae. Chloroplasts are destroyed under a strong light in mutants lacking the light avoidance response, which causes cell death, the discovery of which indicated the physiological importance of chloroplast movement.

The current focus of this group is to understand how chloroplasts move upon light stimulus. They have already demonstrated involvement of actin filaments in the movement and are now trying to unveil the underlying molecular mechanisms.

These studies are of very high originality and are well recognized in the field of plant physiology. Wada has received many awards for these achievements, including the BSJ Research Award of the Botanical Society of Japan in 2004, the JSPP Award of the Japanese Society of Plant Physiologists in 2006, and the Fellow of ASPB Award in 2007.

Again a big concern of the evaluation committee is how such high research activities can be succeeded when Wada retires this coming March. Complete breakup of this group would be a big loss for the field of plant physiology. Identification and/or recruitment of talented young researcher(s) is urgently needed to continue the project.

(和訳)

和田教授は、植物細胞での極めて興味深い疑問、すなわち葉緑体の光定位運動についての研究を進めてきた。葉緑体光定位運動とは、植物体への入射光が弱いときには葉緑体が細胞表面に沿って集まり、光が強いと、細胞の側壁に移動することを言う。様々なモデル植物を用いて、和田グループはこれらのイベントに関与している光受容体を同定してきた。シロイヌナズナの場合には、フォトトロピンであり、シダ植物や緑藻類の場合には、フィトクロームとフォロトロピンが複合したキメラ受容体である。光回避反応を欠失した突然変異植物では、強光下で葉緑体が破壊され、それにより細胞死を招く。この発見は、葉緑体の運動が生理的に重要であることを示すものである。

このグループの現在の関心は、光刺激により葉緑体がどのように移動するのかを解明することにある。この運動には、アクチンフィラメントが関与していることを彼らはすでに実証しており、現在では、背景にある分子機序を明らかにしようとしている。

これらの研究はオリジナリティーが極めて高く、植物生理学の分野では高く評価されている。和田は、2004 年に日本植物学会学術賞を受賞し、2006 年には日本植物生理学会賞、2007 年にはアメリカ植物生理学会の Fellow of ASPB Award を受賞した。

ここでも、外部評価委員会が大きく懸念していることは、そのような高水準の研究活動を、和田教授が（2008 年）3 月に退官した後にどのように継続するかという点である。この研究グループが完全に解散することは、植物生理学の分野にとって大きな損失であろう。プロジェクトを継続するためには、才能ある若手研究者を見つけたり採用することが急務である。

研究業績：

1) Research articles in peer reviewed journals

1. Furuya, M., Kanno, M., Okamoto, H., Fukuda, S., and Wada, M. (1997). Control of mitosis by phytochrome and a blue-light receptor in *Adiantum* spores. Plant Physiology *113*, 677-683.
2. Murata, T., Kadota, A., and Wada, M. (1997). Effects of blue light on cell elongation and microtubule orientation in dark-grown gametophytes of *Ceratopteris richardii*. Plant Cell Physiol. *38*, 201-209.
3. Murata, T., and Wada, M. (1997). Formation of phragmosome-like structure in centrifuged protonemal cells of *Adiantum capillus-veneris* L. Planta *201*, 273-280.
4. Iino, M., Shitanishi, K., and Wada, M. (1997). Phytochrome-mediated phototropism in *Adiantum* protonemata. II. Participation of phytochrome dark reversion. Photochem. Photobiol. *65*, 1032-1038.
5. Kagawa, T., Lamparter, T., Hartmann, E., and Wada, M. (1997). Phytochrome-mediated branch formation in protonemata of the moss *Ceratodon purpureus*. J. Plant Research *110*, 363-370.
6. Okamoto, H., Sakamoto, K., Tomizawa, K.-I., Nagatani, A., and Wada, M. (1997). Photoresponses of transgenic *Arabidopsis* over-expressing fern *Adiantum* PHY1. Plant Physiology *115*, 79-85.
7. Okamoto, H., Silverthorne, J., and Wada, M. (1997). Spatial patterns of phytochrome expression in young leaves of the fern *Adiantum capillus-veneris*. Plant Cell Physiol. *38*, 1397-1402.
8. Nozue, K., Kanegae, T., and Wada, N. (1997). A full length *Ty3/Gypsy*-type retrotransposon in the fern *Adiantum*. J. Plant Research *110*, 495- 499.
9. Wada, M., Nozue, K., and Kadota, A. (1998). Cytoskeletal pattern changes during branch formation in a centrifuged *Adiantum* protonema. J. Plant Research *111*, 53-58.
10. Christensen, S., Tokuoka, Y., Silverthorne, J., and Wada, M. (1998). Phytochrome regulation of expression of mRNA encording the major light-harvesting chlorophyll

a/b-binding proteins of photosystem II in the haploid phase of *Adiantum capilllus-veneris*. Plant Cell Physiol. *39*, 647-654.
11. Wunsch, C., and Wada, M. (1998). Nuclear recovery from centrifugation-caused elongation: Involvement of the microfilament system in the nuclear plasticity. J. Plant Research *111*, 389-398.
12. Wunsch, C., Kurachi, M., Kikumoto, M., Tashiro, H., and Wada, M. (1998). Detection of intranuclear forces by the use of laser optics during the recovery process of elongated interphase nuclei in centrifuged protonemal cells of *Adiantum capillus-veneris*. J. Plant Research *111*, 399-405.
13. Kanegae, T., and Wada, M. (1998). Isolation and characterization of homologues of plant blue-light photoreceptor (cryptochrome) genes from the fern *Adiantum capillus-veneris*. Mol. Gen. Genet. *259*, 345-353.
14. Wada, M. (1998). Branch formation induced by microbeam irradiation of *Adiantum* protonemata. J. Plant Research *111*, 587-590.
15. Nozue, K., Kanegae, T., Imaizumi, T., Fukuda, S., Okamoto, H., Yeh, K.-C., Lagarias, J.C., and Wada, M. (1998). A phytochorme from the fern *Adiantum* with features of the putative photoreceptor NPH1. Proc. Natl. Acad. Sci. USA *95*, 15826-15830.
16. Kadota, A., and Wada, M. (1999). Red light-aphototropic (rap) mutants lack red light-induced chloroplast relocation movement in the fern *Adiantum capillus-veneris*. Plant Cell Physiol. *40*, 238-247.
17. Kagawa, T., and Wada, M. (1999). Chloroplast-avoidance response induced by high-fluence blue light in prothallial cells of the fern *Adiantum capillus-veneris* as analyzed by microbeam irradiation. Plant Physiology *119*, 917-923.
18. Kadota, A., Yoshizaki, N., and Wada, M. (1999). Cytoskeletal changes during resumption of tip growth in nongrowing protonemal cells of the fern *Adiantum capillus-veneris* L. Protoplasma *207*, 195-202.
19. Christie, J.M., Salomon, M., Nozue, K., Wada, M., and Briggs, W.R. (1999). LOV (light, oxygen, or voltage) domains of the blue-light photoreceptor phototropin (nph1): Binding sites for the chromophore flavin mononucleotide. Proc. Natl. Acad. Sci. USA *96*, 8779-8783.
20. Esch, H., Hartmann, E., Cove, D.J., Wada, M., and Lamparter, T. (1999). Phytochrome-controlled phototropism of protonemata of the moss *Ceratodon purpureus*: physiology of wild-type and class 2 *ptr*-mutants. Planta *209*, 290-298.
21. Sato, Y., Kadota, A., and Wada, M. (1999). Mechanically-induced avoidance response of chloroplasts in fern protonemal cells. Plant Physiology *121*, 37-44.
22. Nakazato, T., Kadota, A., and Wada, M. (2000). Photoinduction of spore germination in *Marchantia polymorpha* L. is mediated by photosynthesis. Plant Cell Physiol. *40*, 1014 -1020.
23. Imaizumi, T., Kanegae, T., and Wada, M. (2000). Cryptochrome nucleocytoplasmic distribution and gene expression are regulate by light quality in the fern *Adiantum capillus-veneris*. Plant Cell *12*, 81-96.
24. Kagawa, T., and Wada, M. (2000). Blue light-induced chloroplast relocation in *Arabidopsis thaliana* as analyzed by microbeam irradiation. Plant Cell Physiol. *41*, 84-93.

25. Kadota, A., Sato, Y., and Wada, M. (2000). Intracellular chloroplast photorelocation in the moss *Physcomitrella patens* is mediated by phytochrome as well as by a blue-light receptor. Planta *210*, 932-937.
26. Kanegae, H., Tahir, M., Savazzini, F., Yamamoto, K., Yano, M., Sasaki, T., Kanegae, T., Wada, M., and Takano, M. (2000). Rice *NPH1* homologues, *OsNPH1a* and *OsNPH1b*, are differently photoregulated. Plant Cell Physiol. *41*, 415-423.
27. Kiyosue, T., and Wada, M. (2000). LKP1 (LOV kelch protein 1): a factor involved in the regulation of flowering time in Arabidopsis. Plant Journal *23*, 807-815.
28. Sato, Y., Wada, M., and Kadota, A. (2001). Choice of tracks, microtubules and/or actin filaments for chloroplast photo-movement is differentially controlled by phytochrome and a blue light receptor. J. Cell Science *114*, 269-279.
29. Kagawa, T., Sakai, T., Suetsugu, N., Oikawa, K., Ishiguro, S., Kato, T., Tabata, S., Okada, K., and Wada, M. (2001). *Arabidopsis* NPL1: A phototropin homologue controlling the chloroplast high-light avoidance response. Science *291*, 2138-2141.
30. Sakai, T., Kagawa, T., Kasahara, M., Swartz, T.E., Christie, J.M., Briggs, W.R., Wada, M., and Okada, K. (2001). Arabidopsis nph1 and npl1: Blue-light receptors that mediate both phototropism and chloroplast relocation. Proc. Natl. Acad. Sci. USA *98*, 6969-6974.
31. Sato, Y., Wada, M., and Kadota, A. (2001). External Ca^{2+} is essential for chloroplast movement induced by mechanical stimulation but not by light stimulation. Plant Physiology *127*, 497-504.
32. Kinoshita, T., Doi, M., Suetsugu, N., Kagawa, T., Wada, M., and Shimazaki, K. (2001). phot1 and phot2 mediate blue light regulation of stomatal opening. Nature *414*, 656-660.
33. Schultz, T.F., Kiyosue, T., Yanovsky, M., Wada, M., and Kay, S.A. (2001). A role for LKP2 in the circadian clock of Arabidopsis. Plant Cell *13*, 2659 - 2670.
34. Imaizumi, T., Kadota, A., Hasebe, M., and Wada, M. (2002). Cryptochrome light signals control development to suppress auxin sensitivity in the moss *Physcomitrella patens*. Plant Cell *14*, 373-386, 2002.
35. Kasahara, M., Kagawa, T., Oikawa, K., Suetsugu, N., Miyao, M., and Wada, M. (2002). Chloroplast avoidance movement reduces photodamage in plants. Nature *420*, 829-832.
36. Kikuchi, K., Terauchi, K., Wada, M., and Hirano, H. (2003). mPING is plant MITE mobilized in anther culture. Nature *421*, 167-170.
37. Kawai, H., Kanegae, T., Christensen, S., Kiyosue, T., Sato, Y., Imaizumi, T., Kadota, A., and Wada, M. (2003). Responses of ferns to red light are mediated by an unconventional photoreceptor. Nature *421*, 287-290.
38. Stoelzle, S., Kagawa, T., Wada, M., Hedrich, R., and Dietrichm, P. (2003). Blue light activates calcium-permeable channels in *Arabidopsis* mesophyll cells via the phototropin signaling pathway. Proc. Natl. Acad. Sci. USA *100*, 1456-1461.
39. Sato, Y., Wada, M., and Kadota, A. (2003). Accumulation response of chloroplasts induced by mechanical stimulation in bryophyte cells. Planta *216*, 772-777.
40. Iwata, T., Nozaki, D., Tokutomi, S., Kagawa, T., Wada, M., and Kandori, H. (2003). Light-induced structural changes in the LOV2 domain of *Adiantum* phytochrome3 studied by low-temperature FTIR and UV-visible spectroscopy. Biochemistry *42*, 8183-8191.
41. Oikawa, K., Kasahara, M., Kiyosue, T., Kagawa, T., Suetsugu, N., Takahashi, F., Kanegae,

T., Niwa, Y., Kadota, A., and Wada, M. (2003). CHOLOROPLAST UNUSUAL POSITIONING1 is essential for proper chloroplast positioning. Plant Cell *15*, 2805-2815.

42. Jiao, Y., Yang, H., Ma, L., Sun, N., Yu, H., Liu, T., Gao, Y., Gu, H., Chen, Z., Wada, M., Gerstein, M., Zhao, H., Qu, L.J., and Deng, X.W. (2003). A genome-wide analysis of blue-light regulation of Arabidopsis transcription factor gene expression during seedling development. Plant Physiology *133*: 1480-1493.
43. Srinivas, A., Behera, R.K., Kagawa, T., Wada, M., and Sharma, R. (2004). High pigment1 mutation negatively regulates phototropic signal transduction in tomato seedlings. Plant Physiology *134*, 790-800.
44. Lamparter, T., Kagawa, T., Brucker, G., and Wada, M. (2004). Positive and negative tropic curvature induced by microbeam irradiation of protonemal tip cells of the moss *Ceratodon purpureus*. Plant Biology *6*, 165-170.
45. Kagawa, T., Kasahara, M., Abe, T., Yoshida, S., and Wada, M. (2004). Function analysis of *Ac*phot2 using mutants deficient in blue light-induced chloroplast avoidance movement of the fern *Adiantum capillus-veneris* L. Plant Cell Physiol. *45*, 416-426.
46. Kagawa, T., and Wada, M. (2004). Chloroplast avoidance movement rate is fluence dependent. Photochem. Photobiol. Sciences *3*, 592-595.
47. Kasahara, M., Kagawa, T., Sato, Y., Kiyosue, T., and Wada, M. (2004). Phototropins mediate blue and red light-induced chloroplast movements in *Physcomitrella patens.* Plant Physiology *135*, 1388-1397.
48. Mochizuki, T., Onda, Y., Fujiwara, E., Wada, M., and Toyoshima, Y. (2004). Two independent light signals cooperate in the activation of the plastid *psbD* blue light-responsive promoter in *Arabidopsis*. FEBS Letters *571*, 26-30.
49. Kawai-Toyooka, H., Kuramoto, C., Orui, K., Motoyama, K., Kikuchi, K., Kanegae, T., and Wada, M. (2004). DNA interference: a simple and efficient gene-silencing system for high-throughput functional analysis in the fern *Adiantum*. Plant Cell Physiol. *45*, 1648-1657.
50. Ichikawa, K., Sugita, M., Imaizumi, T., Wada, M., and Aoki, S. (2004). Differential expression on a daily basis of plastid sigma factor (*PpSig*) genes from the moss *Physcomitrella patens*: Regulatory interactions among *PpSig5*, the circadian clock and blue light signaling mediated by cryptochromes. Plant Physiology *136*, 4285-4298.
51. Yamauchi, D., Sutoh, K., Kanegae, H., Horiguchi, T., Matsuoka, K., Fukuda, H., and Wada, M. (2005). Analysis of expressed sequence tags in prothallia of *Adiantum capillus-veneris.* J. Plant Research *118*, 223-227.
52. Suetsugu, N., Kagawa, T., and Wada, M. (2005). An auxilin-like J-domain protein, JAC1, regulates phototropin-mediated chloroplast movement in *Arabidopsis thaliana*. Plant Physiology *139*, 151-162.
53. Suetsugu, N., Mittmann, F., Wagner, G., Hughes, J., and Wada, M. (2005). A chimeric photoreceptor gene, NEOCHROME, has arisen twice during plant Evolution. Proc. Natl. Acad. Sci. USA *102*, 13705-13709.
54. Tucker, E.B., Lee, M., Alli, S., Sookhdeo, V., Wada, M., Imaizumi, T., Kasahara, M., and Hepler, P.K. (2005). UV-A induces two calcium waves in *Physcomitrella patens*. Plant Cell Physiol. *46*, 1226-1236.

55. Uenaka, H., Wada, M., and Kadota, A. (2006). Four distinct photoreceptors contribute to light-induced side branch formation in the moss *Physcomitrella patens*. Planta *222*, 623-631.
56. Doi, M., Wada, M., and Shimazaki, K. (2006). The fern *Adiantum capillus-veneris* lacks stomatal responses to blue light. Plant Cell Physiol. *47*, 748-755.
57. Tsuboi, H., Suetsugu, N., and Wada, M. (2006). Negative phototropic response of rhizoid cells in the fern *Adiantum capillus-veneris.* J. Plant Research *119*, 505-512.
58. Kanegae, T., Hayashida, E., Kuramoto, C., and Wada, M. (2006). A single chromoprotein with triple chromophores acts as both a phytochrome and a phototropin. Proc. Natl. Acad. Sci. USA *103*, 17997-18001.
59. Tsuboi, H., Suetsugu, N., Kawai-Toyooka, H., and Wada, M. (2007). Phototropins and neochrome1 mediate nuclear movement in the fern *Adiantum capillus-veneris*. Plant Cell Physiol. *48*, 892-896.
60. Takahashi, F., Yamagata, D., Ishikawa, M., Fukamatsu, Y., Ogura, Y., Kasahara, K., Kiyosue, T., Kikuyama, M., Wada, M., and Kataoka, H. (2007). AUREOCHROME: a newly found novel photoreceptor required for photomorphogenesis in Heterokonts. Proc. Natl. Acad. Sci. USA 104, 19625 -19630.

2) Invited reviews, book chapters

1. Wada, M., Kanegae, T., Nozue, K., and Fukuda, S. (1997). Cryptogam phytochrome. Plant Cell Environment *20*, 685-690.
2. Wada, M., and Kagawa, T. (2001). Light-controlled chloroplast movement. *In*: ESP Comprehensive Series in Photoscience, vol. 1. Photomovement. Edited by D-P. Haeder and M. Lebert, Elsevier Science Publishers, pp. 897-924.
3. Kagawa, T., and Wada, M. (2002). Blue light-induced chloroplast relocation. Plant Cell Physiol. *43*, 367-371.
4. Suetsugu, N., and Wada, M. (2003). Cryptogam blue-light photoreceptors. Current Opinion of Plant Biology *6*, 91-96.
5. Wada, M., Kagawa, T., and Sato, Y. (2003). Chloroplast movement. Annu. Rev. Plant Biol. *54*, 455-468.
6. Sato, Y., Kadota, A., and Wada, M. (2003). Chloroplast movement: Dissection of events downstream of photo- and mechano-perception. J. Plant Resarch *116*, 1-5.
7. Wada, M. (2003). Blue light receptors in fern and moss. *In*: ESP Comprehensive Series in Photoscience, vol 3. Photoreceptors and Light Signaling. Edited by A. Batchauer, Elsevier Science Publishers, pp. 329- 342.
8. Wada, M., and Suetsugu, N. (2004). Plant organelle positioning. Current Opinion of Plant Biology *7*, 626-631.
9. Kasahara, M., and Wada, M. (2004). Chloroplast avoidance movement. *In:* Plastids, Annual Plant Reviews, Volume 13 Edited by S. G. Moller, Blackwell, pp. 267-282.
10. Suetsugu, N., and Wada, M. (2005). Photoreceptor Gene Families in Lower Plants. *In*: Handbook of Photosensory Receptors. Edited by W.R. Briggs and J.L. Spudich Wiley-VCH

Verlag, Weinheim, pp. 349-369.
11. Wada, M. (2005). Chloroplast movement. *In*: Light Sensing in Plants, edited by Wada, M., K. Shimazaki, and M. Iino. Springer-Verlag, Tokyo. pp. 193-199.
12. Kanegae, T., and M. Wada (2006). Photomorphogenesis of Ferns. *In*: Photomorphogenesis in Plants 3rd Edition Edited by E. Schafer and F. Nagy, Kluwer Academic Publishers, Dordrecht, pp. 515-536.
13. Wada, M. (2007). Fern as a model system to study photomorphogenesis. J. Plant Research *120*, 3-16.
14. Suetsugu, N., and Wada, M. (2007). Phytochrome-dependent photomovement responses mediated by phototropin family proteins in Cryptogam plants. Photochem. Photobiol. *83*, 87-93.
15. Suetsugu, N., and M. Wada (2007). Chloroplast photorelocation movement mediated by phototropin family proteins in green plants. Biological Chemistry *388*, 927-935.

林　誠
高次細胞機構研究部門・准教授

Associate Professor Makoto Hayashi has been long collaborating with Professor Mikio Nishimura and is now leading the projects of this group on plant peroxisomes. He has been working on identification of diverse functions of plant peroxisomes, identification of mutants with a defect in fatty acid β-oxidation, and functional characterization of plant peroxins. For an earlier achievement along these studies, he received a Botanical Award for Young Scientists from the Botanical Society of Japan in 1998.

Peroxins are components involved in protein import to peroxisomes. Hayashi and coworkers have identified several peroxins in plants and are now studying their functions. There appear to be several interesting differences in the molecular mechanisms of peroxisomal import between plants and other systems such as yeast and animals. Discovery of peroxisomal structures, which look like invagination into the organelle, is particularly intriguing and may lead to the understanding of peroxisome-specific molecular mechanisms of import.

（和訳）

林　誠准教授は、西村 幹夫教授と長期間共同研究を進め、現在では、植物ペルオキシソームに関して、このグループのプロジェクトを率いている。彼は植物ペルオキシソームの様々な機能の同定、脂肪酸 β－酸化系欠損変異の同定、ならびに植物 peroxin の機能的特性解明に関する研究を行ってきた。これらの研究と共にこれまでの業績を評価して、日本植物学会から 1998 年に Botanical Award for Young Scientists（若手奨励賞）を受賞している。

peroxin 類はペルオキシソームへのタンパク質の取り込みに関与しているコンポーネントである。林らは、植物の中にいくつかの peroxin を同定し、現在その機能について調べている。植物と酵母や動物などの他の生物の間には、ペルオキシソームへのインポートの分子機序に関していくつか興味深い違いがあるようである。オルガネラに陥入しているように見えるペルオキシソームの構造が発見されたことはとりわけ興味深いものであり、ペルオキシソームに特有のインポートの分子機序を解明することにつながろう。

研究業績（2000 年より）：

1) Research articles in peer reviewed journals

1. Soichi, K., Hanzawa, S., Hayakawa, T., Hayashi, M., and Yamaya, T. (2000). Nucleotide sequence of a genomic DNA (Accession No. AB037664) and a cDNA (Accession No.AB037595) encoding cytosolic glutamine synthetase in sasanishiki, a leading cultivar of rice (*Oryza sativa* L) in Northern Japan. Plant Physiol *122*, 1459.
2. De Bellis, L., Gonzali, S., Alpi, A., Hayashi, H., Hayashi, M., and Nishimura M. (2000). Purification and characterization of a novel pumpkin short-chain acyl-CoA oxidase with structural similarity to acyl-CoA dehydrogenases. Plant Physiol. *123*, 327-334.
3. Takemoto, D., Hayashi, M., Doke, N., Nishimura, M., and Kawakita, K. (2000). Isolation of the gene for EILP, an elicitor-inducible LRR receptor-like protein, from tobacco by differential display. Plant Cell Physiol. *41*, 458-464.
4. Hayashi, M., Nito, K., Toriyama-Kato, K., Kondo, M., Yamaya, T., and Nishimura, M. (2000). *At*Pex14p maintains peroxisomal functions by determining protein targeting to three kinds of plant peroxisomes. EMBO J. *19*, 5701-5710.
5. Nito, K., Yamaguchi, K., Hayashi, M., and Nishimura, M. (2001). Pumpkin peroxisomal ascorbate peroxidase is localized on peroxisomal membranes and unknown membranous structures. Plant Cell Physiol. *42*, 20-27.
6. Obara, M., Kajiura, M., Fukuta, Y., Yano, M., Hayashi, M., Yamaya, T., and Sato, T. (2001). Mapping of QTLs associated with cytosolic glutamine synthetase and NADH-glutamate synthase in rice (*Oryza sativa* L.). J. Exp. Bot. *52*, 1209-1217.
7. Fukao, Y., Hayashi, Y., Mano, M., Hayashi, M., and Nishimura, M. (2001). Developmental analysis of a putative ATP/ADP carrier protein localized on glyoxysomal membranes during the peroxisome transition in pumpkin cotyledons. Plant Cell Physiol. *42*, 835-841.
8. Hayashi Y., Hayashi, M., Hayashi H., Hara-Nishimura, I., and Nishimura, M. (2001). Direct interaction between glyoxysomes and lipid bodies in cotyledons of *Arabidopsis thaliana ped1* mutant. Protoplasma *218*, 83-94.
9. Hayashi, M., Nito, K., Takei-Hoshi, R., Yagi, M., Kondo, M., Suenaga, A., Yamaya, T., and Nishimura, M. (2002). Ped3p is a peroxisomal ATP-binding cassette transporter that might supply substrates for fatty acid β-oxidation. Plant Cell Physiol. *43*, 1-11.
10. Mano, S., Nakamori, C., Hayashi, M., Kato, A., Kondo, M., and Nishimura, M. (2002). Distribution and characterization of peroxisomes in Arabidopsis by visualization with GFP: dynamic morphology and actin-dependent movement. Plant Cell Physiol. *43*, 331-341.
11. Nito, K., Hayashi, M., and Nishimura, M. (2002). Direct interaction and determination of binding domains among peroxisomal import factors in *Arabidopsis thaliana*. Plant Cell Physiol. *43*, 355-366
12. Fukao, Y., Hayashi, M., and Nishimura, M. (2002). Proteomic analysis of leaf peroxisomal proteins in green cotyledons of *Arabidopsis thaliana*. Plant Cell Physiol. *43*, 689-696.
13. Hayashi, H., De Bellis, L., Hayashi, Y., Nito, K., Kato, A., Hayashi, M., Hara-Nishimura, I., and Nishimura, M. (2002). Molecular characterization of an Arabidopsis acyl CoA synthetase localized on glyoxysomal membranes. *Plant Physiol. 130*, 2019-2026.

14. Kamigaki, A., Mano, S., Terauchi, K., Nishi, Y., Tachibe-Kinoshita, Y., Nito, K., Hayashi, M., Nishimura, M., and Esaka, M. (2003). Identification of peroxisomal targeting signal of pumpkin catalase and the binding analysis with PTS1 receptor. Plant J. *33*, 161-175.
15. Fukao, Y., Hayashi, M., and Nishimura, M. (2003). Novel glyoxysomal protein kinase, GPK1, identified by proteomic analysis of glyoxysomes in etiolated cotyledons of *Arabidopsis thaliana*. *Plant Cell Physiol. 44*, 1002-1012.
16. Kamada, T., Nito, K., Hayashi, H., Mano, S., Hayashi, M., and Nishimura, M. (2003). Functional differentiation of peroxisomes revealed by expression profiles of peroxisomal genes in *Arabidopsis thaliana*. Plant Cell Physiol. *44*, 1275-1289.
17. Mano, S., Nakamori, C., Kondo, M., Hayashi, M., and Nishimura, M. (2004). An Arabidopsis dynamin-related protein, DRP3A, controls both peroxisomal and mitochondrial division. Plant J. *38*, 487-498.
18. Hayashi, M., Yagi, M., Nito, K., Kamada, T., and Nishimura, M. (2005). Differential contribution of two peroxisomal protein receptors to the maintenance of peroxisomal functions in Arabidopsis. J. Biol. Chem. *280*, 14829-14835.
19. Nito, K., Kondo, M., Yagi, M., Hayashi, M., and Nishimura, M. (2007). Functional classification of *Arabidopsis* peroxisome biogenesis factors proposed from analyses of knockdown mutants. Plant Cell Phyisol. *48*, 763-774.
20. Yamada, K., Fukao, Y., Hayashi, M., Fukazawa, I., Suzuki, I., and Nishimura, M. (2007). Cytosolic HSP90 regulates the heat shock response that is responsible for heat acclimation in *Arabidopsis thaliana*. J. Biol. Chem. *282*, 37794-37804.

2) Invited reviewed, book chapters

1. Hayashi, M. (2000). Plant peroxisomes; molecular basis of the regulation of their functions. J. Plant Res. *113*, 103-109
2. Mano, S., Hayashi, M., and Nishimura, M. (2000). A leaf-peroxisomal protein, hydroxypyruvate reductase, is produced by light-regulated alternative splicing. Cell Biochem. Biophys. *32*, 147-154.
3. Kato, A., Hayashi, M., Kondo, M., and Nishimura, M. (2000). Transport of peroxisomal proteins that are synthesized as large precursors in plants. Cell Biochem. Biophys. *32*, 269-275.
4. Hayashi, M., Toriyama, K., Kondo, M., Kato, A., Mano, S., De Bellis, L., Ishimaru, Y., Yamaguchi, K., Hayashi, H., and Nishimura, M. (2000). Functional transformation of plant peroxisomes. Cell Biochem. Biophys. *32*, 295-304.
5. Hayashi, M., and Nishimura, M. (2002). Genetic approaches to understand plant peroxisomes. *In* Plant peroxisome. (Eds. Baker, A., Graham, I.) Kluwer Academic Publishers, Dordrecht. pp. 279-303.
6. Hayashi, M., and Nisimura, M. (2003). Entering a new era of research on plant peroxisomes. Cur. Opin. Plant Sci. *6*, 577-582.
7. Hayashi, M., and Nishimura, M. (2006). *Arabidopsis thaliana* - A model organism to study plant peroxisomes. Biochim. Biophys. Acta *1763*, 1382-1391.

２）発生生物学領域

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平成 19 年 11 月 28 日 ～ 29 日

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Dr. Ueno's major achievements over the previous 10 years include three areas.
1) Analysis of the role of BMP during animal development
2) Analysis of the mechanisms determining cell polarity during Xenopus gastrulation
3) Establishment of a cDNA array system and expression database of Xenopus embryos

1) Starting from earlier studies on TGFβ, Dr. Ueno has extended his research area to the analysis of the role of BMP during development. Using an excellent model animal, *Xenopus laevis*, for studying the mechanisms for germ layer development and morphogenesis, he reported the role of BMP in neural induction. He also actively reported on the mode of action of BMPs and the extracellular or intracellular molecules involved in the signal transduction of BMPs effectively using Xenopus and Zebrafish. After these important and original observations, he tried to elucidate the role of BMPs during the development of other animals such as nematode, Drosophila, and ascidians. Among the published results concerning these studies, very interestingly, BMP was found to be involved in the process for body size determination in the nematode. These studies are not only original and highly standard but also show the effectiveness of the evo-devo approach using and comparing the function of the same signaling molecule in different model animals.

2) Dr. Ueno has recently concentrated on the molecular and cellular mechanisms for gastrulation of Xenopus embryos. Dr. Ueno exploited his genome-wide approach described in next section and provided the evidence that genes controlling planar cell plarity (PCP) in Drosophila development are also involved in the morphogenesis process of Xenopus gastrulation. In these studies he identified novel genes and Xenopus homologues of the known genes that function in determining cell polarity have important roles during convergent extension (CE).

3) Dr. Ueno constructed a Xenopus embryonic cDNA library to produce a microarray system, including 12,000 independent clones. He not only put this system to use in his own research but he also opened this array system to other research groups. Using this array system he identified the target genes of FGF and nodal/activin. Dr. Ueno performed temporal and spatial expression analysis of 3000 genes during Xenopus embryonic development. The results of this project were effectively utilized in his research to select and identify the genes involved in CE. In addition this valuable expression database is openly available on the Web.

Future Plans
Dr. Ueno proposed the following three areas as future research projects based on his current studies.

1) Dr. Ueno demonstrated that the Wnt/PCP pathway has a crucial role in CE by controlling membrane trafficking and establishment of cell polarity. However many questions on the mechanisms for controlling the behavior of certain cell populations during CE have yet to be answered and he proposed to continue the research on this issue. Considering his current success in this issue and his published and unpublished scientific reservoir we can expect important advances in this future project.

2) Dr. Ueno currently is using the mouse system to analyze the function of the PCP system on morphogenesis. This study is proceeding successfully and this approach should enable him to figure out the role of PCP on morphogenesis during organogenesis that takes place at a relatively later stage in development.

3) Establishment of genome network for ascidians notochord development: This research is proposed for a genome-wide search of novel genes involved in PCP and mesodermal tissue development based on evo-devo aspects. He has established a searching system and database and already started this project. Coupled with Xenopus research and knowledge, this approach seems to be very effective.

Other Comments

Dr. Ueno has published 90 original papers in these past 10 years. Among them, he is the corresponding author of 34 papers including the papers that appeared in highest impact journals. He also collaborates very effective with the researchers in his laboratory and other laboratories resulting in excellent scientific advantage and this was proven by the productivity of published papers.

Dr. Ueno has successfully organized the research project “Dynamics of Developmental System”consisting of nearly one hundred researchers as a representative person. In addition, as a commissioner of the JSDB (Japanese Society of Developmental Biologists) and ISD (International Society of Differentiation) he contributed management of society activities. These indicate that he is one of the important key persons for leading developmental biology.

Overall Evaluation

Dr. Ueno has actively and constantly produced excellent original work including the results of effective collaboration. His future project based on his original findings is expected to be fruitful. He also largely contributed to the development of infrastructure, society activity and organizing international meetings. Considering these, Dr. Ueno carried out his accountability as a professor of NIBB completely. This and his current activity promise his continued achievement in the next term at the NIBB.

（和訳）

上野博士の過去 10 年間の主な業績は以下の 3 領域にまとめられる

1) 動物の発生における BMP の役割に関する分析
2) アフリカツメガエルの原腸形成中の細胞極性決定の機序に関する分析
3) アフリカツメガエルの胚における cDNA アレイシステムと発現データベースの確立

1) TGFβに関する先の研究から開始して、上野博士は発生過程の BMP の役割を研究する分野に研究を広げてきた。極めて優れた動物モデルであるアフリカツメガエル *Xenopus laevis* を胚葉形成と形態形成の機序の研究に用いて、神経誘導に BMP の調節が重要な役割を果たすことを報告した。博士はまた、アフリカツメガエルとゼブラフィッシュを用いて、BMP の作用様式や、BMP のシグナル伝達に関与する細胞内外の分子に関して活発に報告している。これらの重要でオリジナルな観察をもとに、博士は線虫、ショウジョウバエ、ホヤなどの他の動物の発生における BMP の役割を解明しようとした。これらの研究に関して発表された論文では、極めて興味深いことに、BMP は線虫の体長決定プロセスに関与していることがわかった。これらの研究はオリジナルで高い水準のものであるだけでなく、異なる動物モデルで evo-devo(進化発生生物学)アプローチを使い、シグナル伝達分子の機能を種間で比較することの有効性を示すものでもある。

2) 上野博士は最近、アフリカツメガエルの胚の原腸形成の分子機序ならびに細胞機序の研究に取り組んでいる。上野博士は以下に述べるゲノムワイドのアプローチを活用し、ショウジョウバエの発生中に平面内細胞極性(PCP)をコントロールしている遺伝子が、アフリカツメガエルの原腸形成の形態形成にも関与している証拠を示した。これらの研究の中で、博士は、細胞の極性を決定する機能を有している新たな遺伝子や既知の遺伝子のアフリカツメガエルの相同遺伝子が、収斂と伸長(convergent extension: CE)に重要な役割を果たしていることを発見した。

3) 上野博士はマイクロアレイシステムを構築するため、アフリカツメガエルの胚から 12,000 のクローンが含まれる cDNA ライブラリーを作成した。博士はこのシステムを自身の研究に用いるだけでなく、他の研究グループにもこのマイクロアレイシステムを供与している。このマイクロアレイシステムを用いて、博士は FGF および nodal/activin の標的遺伝子を同定した。上野博士はアフリカツメガエルの胚発生において、3,000 個の遺伝子の時間的空間的な発現解析を行った。このプロジェクトの結果は、CE に関与している遺伝子を選択し同定するのに彼の研究に効果的に活用されている。加えて、博士の貴重な発現データベースは、ウェブ上に公開されている。

将来計画

上野博士は現在の研究に基づき、今後の研究プロジェクトとして以下の 3 領域を提案した。

1) 上野博士は膜トラフィッキングのコントロールや細胞極性の確立を通じて CE に Wnt/PCP 経路が極めて重要な役割を果たすことを示した。しかし、CE 中のある種の細胞集団のふるまいをコントロールする機序については、解明すべき多くの疑問点があり、この点についての研究を継続したいと博士は提案した。博士のこの点に関する現在の成功と、既発表、準備中の論文を鑑みれば、この将来計画においても重要な進展が見られるものと期待される。

2)　上野博士は形態形成に対する PCP システムの機能を分析するのにマウスシステムを現在用いている。この研究は次第に成功しつつあり、このアプローチは、発生の比較的後期段階で行われる器官形成中の形態形成に関する PCP の役割について解明できるようになるはずである。

3)　ホヤの脊索形成のゲノムネットワークの確立。この研究は、evo-devo の観点から、PCP ならびに中胚葉組織発生に関与する新規遺伝子をゲノムワイドに検索するため計画されたものである。博士は、検索システムとデータベースをすでに確立しており、プロジェクトは開始されている。アフリカツメガエルに関する研究と知識を組み合わせることで、このアプローチは極めて有効なものとなると考えられる。

その他の意見

上野博士はこの 10 年間、90 件の原著論文を発表した。そのうち 34 件の論文の corresponding author であり、インパクトファクターが極めて高い論文誌の論文を含む論文が含まれている。博士はまた、研究室や他の研究室の研究者とも極めて有効な共同研究を行っており、極めて優れた科学的成果を得ており、論文の生産性も高いことで証明されている。

上野博士は、特定領域研究“Dynamics of Developmental System”(発生システムのダイナミクス)の研究プロジェクトの代表としてその運営にも成功しており、そこには100名ほどの研究者が結集している。加えて、JSDB および ISD のコミッショナーとして、学会運営活動にも貢献している。このことは、博士が発生生物学の重要人物の一人であることを示すものである。

総評

上野博士は、共同研究の成果を含み、極めて優れたオリジナル研究を積極的に常時生み出してきた。オリジナルの発見に基づく博士の将来計画は豊かな実りが得られるものと期待される。博士はまた、インフラ構築、学会活動、国際集会の運営にも大きく貢献している。これらのことを考えれば、上野博士は基礎生物学研究所の教授としての責任を十分に果たしてきた。このことや博士の現在の活動を考えれば、来期も基礎生物学研究所で著明な成果をあげ続けることが確実である。

研究業績：

1) Research articles in peer reviewed journals

1. Nikaido, M., Tada, M., Saji, T., and Ueno, N. (1997). Conservation of BMP signaling in zebrafish mesoderm patterning. Mech. Dev. *61*, 75-88.
2. Suzuki, A., Kaneko, E., Maeda, J., and Ueno, N. (1997). Mesoderm induction by BMP-4 and -7 heterodimers. Biochem. Biophys. Res. Commun. *232*, 153-156.

3. Natsume, T., Tomita, S., Iemura, S., Kintou. N., Yamaguchi, A., and Ueno, N. (1997). Interaction between soluble type I receptor for bone morphogenetic protein and bone morphogenetic protein-4. J. Biol. Chem. *272*, 11535-11540.
4. Tonegawa, A., Funayama, N., Ueno, N., and Takahashi, Y. (1997). Mesodermal subdivision along the mediolateral axis in chicken controlled by different concentrations of BMP-4. Development *124*, 1975-1984.
5. Suzuki, A., Ueno, N., and Hemmati-Brivanlou (1997). A. Xenopus msx1 mediates epidermal induction and neural inhibition by BMP4. *Development 124*, 3037-3044.
6. Suzuki, A., Kaneko, E., Ueno, N. and Hemmati-Brivanlou, A. (1997). Regulation of epidermal induction by BMP2 and BMP7 signaling. Dev. Biol. *189*, 112-122.
7. Namiki, M., Akiyama, S., Katagiri, T., Suzuki, A., Ueno, N., Yamaji, N., Rosen, V., Wozney, J.M. and Suda T. (1997). A kinase domain-truncated type I receptor blocks bone morphogenetic protein-2-induced signal transduction in C2C12 myoblasts. J. Biol. Chem. *272*, 22046-22052.
8. Akiyama, S., Katagiri, T., Namiki, M., Yamaji, N., Yamamoto, N., Miyama, K., Shibuya, H., Ueno, N., Wozney, J.M., and Suda, T. (1997). Constitutively active BMP Type I receptors transduce BMP-2 signals without the ligand in C2C12 myoblasts. Exp. Cell Res. *235*, 362-369.
9. Miya, T., Morita, K., Suzuki, A., Ueno, N., and Satoh, N. (1997). Functional analysis of an ascidian homologue of vertebrate Bmp-2/Bmp-4 suggests its role in the inhibition of neural fate specification. Development *124*, 5149-5159.
10. Higashijima, S., Okamoto, H., Ueno, N., Hotta, Y., and Eguchi, G. (1997). High frequency generation of transgenic zebrafish which reliably express GFP in whole muscles or the whole body by using promoters of zebrafish origin. Dev. Biol. *192*, 289-299.
11. Shibuya, H., Iwata, H., Masuyama, N., Gotoh, Y., Yamaguchi, K., Irie, K., Matsumoto, K., Nishida, E., and Ueno, N. (1998). Role of TAK1 and TAB1 in BMP signaling in early Xenopus development. EMBO J. *17*, 1019-1028.
12. Kurozumi, K., Nishita, M., Yamaguchi, K., Fujita, T., Ueno, N., and Shibuya, H. (1998). BRAM1, a BMP receptor-associated molecule involved in BMP signalling. Genes Cells *3*, 257-264.
13. Iemura, S., Yamamoto, T.S., Takagi, C., Uchiyama, H., Natsume, T., Shimasaki, S., Sugino, H., and Ueno, N. (1998). Direct binding of follistatin to a complex of bone morphogenetic protein and its receptor inhibits ventral and epidermal cell fates in early Xenopus embryo. Proc. Natl. Acad. Sci. USA *95*, 9337-9342.
14. Tomoyasu, Y., Nakamura, M., and Ueno, N. (1998). Role of Dpp signaling in prepattern formation of the dorsocentral mechanosensory organ in *Drosophila melanogaster*. Development *125*, 4215-4224.
15. Nikaido, M., Tada, M., Takeda, H., Kuroiwa, A., and Ueno, N. (1999). *In vivo* analysis using variants of zebrafish BMPR-IA: range of action and involvement of BMP in ectoderm patterning. Development *126*, 181-190.
16. Yamaguchi, K., Nagai, S-I., Ninomiya-Tsuji, J., Noshita, M., Tamai, K., Irie, K., Ueno, N., Nishida, E., Shibuya, H., and Matsumoto, K. (1999). XIAP, a cellular member of the

inhibitor of apoptosis protein family, links the receptors to TAB1-TAK1 in the BMP signaling pathway. EMBO J. *18*, 179-187.
17. Nagaso, H., Suzuki, A., Tada, M., and Ueno, N. (1999). Dual specificity of activin type II receptor ActRIIb in dorso-ventral patterning during zebrafish embryogeneisis. Dev. Growth Differ. *41*, 119-133.
18. Morita, K., Chow, K.L., and Ueno, N. (1999). Regulation of body length and male tail ray pattern formation of *Caenorhabditis elegans* by a member of TGF-β family. Development *126*, 1337-1347.
19. Adachi-Yamada, T., Nakamura, M., Irie, K., Tomoyasu, Y., Sano, Y., Mori, E., Goto, S., Ueno, N., Nishiada, Y., and Matsumoto, K. (1999). p38 mitogen-activated protein kinase can be involved in transforming growth factor β superfamily signal transduction in Drosophila wing morphogenesis. Mol. Cell Biol. *19*, 2322-2329.
20. Miyama, K., Yamada, G., Yamamoto, T.S., Takagi, C., Miyado, K., Sakai, M., Ueno, N., and Shibuya, H. (1999). A BMP-inducible gene, Dlx-5 regulates osteoblast differentiation and mesoderm induction. Dev. Biol. *208*, 123-133.
21. Hamada, F., Tomoyasu, Y., Takatsu, Y., Nakamura, M., Nagai, S., Suzuki, A., Fujita, F., Shibuya, H., Toyoshima, K., Ueno, N., and Akiyama, T. (1999). Negative regulation of wingless signaling by D-Axin, a Drosophila homologue of Axin. Science *283*, 1739-1742.
22. Nikaido, M., Masazumi, T., and Ueno, N. (1999). Restricted expression of the receptor serine/threonine kinase BMPR-IB in zebrafish. Mech. Dev. *82*, 219-222.
23. Suzawa, M., Takeuchi, Y., Fukumoto, S., Kato, S., Ueno, N., Miyazono, K., Matsumoto, T., and Fujita, T. (1999). Extracellular matrix-associated bone morphogenetic proteins are essential for differentiation of murine osteoblastic cells *in vitro*. Endocrinology *140*, 2125-2133.
24. Shimasaki, S., Zachow, R.J., Li, D., Kim, H., Iemura, S., Ueno, N., Sampath, K., Chang, R.J., and Erickson, G.F. (1999). A functional bone morphogenetic protein (BMP) system in the ovary. Proc. Natl. Acad. Sci. USA 96, 7282-7287.
25. Iemura, S., Yamamoto, T.S., Takagi, C., Kobayashi, H., and Ueno, N. (1999). Isolation and characterization of bone morphogenetic protein-binding proteins from the early Xenopus embryo. J. Biol. Chem. *274*, 26843-26849.
26. Hamada, F., Murata, Y., Nishida, A., Fujita, F., Tomoyasu, Y., Nakamura, M., Toyoshima, K., Tabata, T., Ueno, N., and Akiyama, T. (1999). Identification and characterization of E-APC, a novel Drosophila homologue of the tumour suppressor APC. Genes Cells *4*, 465-474.
27. Nishita, M., Ueno, N., and Shibuya, H. (1999). Smad8B, a Smad8 splice variant lacking the SSXS site that inhibits Smad8-mediated signalling. Genes Cells *4*, 583-591.
28. Mochii, M., Yoshida, S., Morita, K., Kohara, Y., and Ueno, N. (1999). Identification of transforming growth factor-β-regulated genes in *Caenorhabtidis elegans* by differential hybridization of arrayed cDNAs. Proc. Natl. Acad. Sci. USA *96*, 15020 -15025.
29. Yamamoto, T.S., Iemura, S., Takagi, C., Shimasaki, S., and Ueno, N. (2000). Characterization of follistatin isoforms in early Xenopus embryogenesis. Int. J. Dev. Biol. *44*, 341-348.

30. Yamamoto, T.S., Takagi, C., and Ueno, N. (2000). Requirement of Xmsx-1 in the BMP-triggered ventralization of Xenopus embryos. Mech. Dev. *91*, 131-141.
31. Nishita, M., Hashimoto, M.K., Ogata, S., Laurent, M.N., Ueno, N., Shibuya, H., and Cho, K.W.Y. (2000). Interaction between Wnt and TGF-β signalling pathways during formation of Spemann's organizer. Nature *403*, 781-785.
32. Takatsu, Y., Nakamura, M., Stapleton, M., Danos, M.C., Matsumoto, K., O'Connor, M.B., Shibuya, H., and Ueno, N. (2000). TAK1 participates in c-Jun N-terminal kinase signaling during Drosophila development. Mol. Cell. Biol. *20*, 3015-3026.
33. Haraguchi, R., Suzuki, K., Murakami, R., Sakai, M., Kamikawa, M., Kengaku, M., Sekine, K., Kawano, H., Kato, S., Ueno, N., and Yamada, G. (2000). Molecular analysis of external genitalia formation: the role of fibroblast growth factor (Fgf) genes during genital tubercle formation. Development *127*, 2471-2479.
34. Tomoyasu, Y., Ueno, N., and Nakamura, M. (2000). The decapentaplegic morphogen gradient regulates the notal wingless expression through induction of pannier and u-shaped in Drosophila. Mech. Dev. *96*, 37-49.
35. Wada, T., Kagawa, T., Ivanova, A., Zalc, B., Shirasaki, R., Murakami, F., Iemura, S., Ueno, N., and Ikenaka K. (2000). Dorsal spinal cord inhibits oligodendrocyte development. Dev. Biol. *227*, 42-55.
36. Masuda, Y., Sasaki, A., Shibuya, H., Ueno, N., Ikeda, K., and Watanabe, K. Dlxin-1, a novel protein that binds Dlx5 and regulates its transcriptional function. J. Biol. Chem. *276*, 5331-5338.
37. Hatta, T., Konishi, H., Katoh, E., Natsume, T., Ueno, N., Kobayashi, Y., and Yamazaki, T. (2000). Identification of the ligand-binding site of the BMP type IA receptor for BMP-4. Biopolymers *55*, 399-406.
38. Kurata, T., Nakabayashi, J., Yamamoto, T.S., Mochii, M., and Ueno, N. (2001). Visualization of endogenous BMP signaling during Xenopus development. Differentiation *67*, 33-40.
39. Ishizuya-Oka, A., Ueda, S., Amano, T., Shimizu, K., Suzuki, K., Ueno, N., and Yoshizato, K.(2001). Thyroid-hormone-dependent and fibroblast-specific expression of BMP-4 correlates with adult epithelial development during amphibian intestinal remodeling. Cell Tissue Res. *303*, 187-195.
40. Morita, K., Shimizu, M., Shibuya, H., and Ueno, N. (2001). A DAF-1-binding protein BRA-1 is a negative regulator of DAF-7 TGF-β signaling. Proc. Natl. Acad. Sci. USA *98*, 6284-6288.
41. Hanazawa, M., Mochii, M., Ueno, N., Kohara, Y., and Iino, Y. (2001). Use of cDNA subtraction and RNA interference screens in combination reveals genes required for germ-line development in *Caenorhabditis elegans*. Proc. Natl. Acad. Sci. USA *98*, 8686-8691.
42. Itoh, K., Udagawa, N., Katagiri, T., Iemura, S., Ueno, N., Yasuda, H., Higashio, K., Quinn, J.M., Gillespie, M.T., Martin, T.J., Suda, T., and Takahashi, N. (2001). Bone morphogenetic protein 2 stimulates osteoclast differentiation and survival supported by receptor activator of nuclear factor-kappab ligand. Endocrinology *142*, 3656-3662.

43. Sakuta, H., Suzuki, R., Takahashi, H., Kato, A., Shintani, T., Iemura, S., Yamamoto, T.S., Ueno, N., and Noda, M. (2001). Ventroptin: a BMP-4 antagonist expressed in a double-gradient pattern in the retina. Science *293*, 111-115.
44. Yamamoto, T.S., Takagi, C., Hyodo, A.C., and Ueno, N. (2001). Suppression of head formation by Xmsx-1 through the inhibition of intracellular nodal signaling. Development *128*, 2769-2779.
45. Sugawara, K., Morita, K., Ueno, N., and Shibuya, H. (2001). BIP, a BRAM-interacting protein involved in TGF-β signalling, regulates body length in *Caenorhabditis elegans*. Genes Cells *6*, 599-606.
46. Yoshida, S., Morita, K., Mochii, M., and Ueno, N. (2001). Hypodermal expression of *Caenorhabditis elegans* TGF-β type I receptor SMA-6 is essential for the growth and maintenance of body length. Dev. Biol. *240*, 32-45.
47. Otsuka, F., Moore, R.K., Iemura, S., Ueno, N., and Shimasaki, S. (2001). Follistatin inhibits the function of the oocyte-derived factor BMP-15. Biochem. Biophys. Res. Commun. *289*, 961-966.
48. Teraoka, H., Dong, W., Ogawa, S., Tsukiyama, S., Okuhara, S., Niiyama, M., Ueno, N., Peterson, R.E., and Hiraga, T. (2002). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin toxicity in the zebrafish embryo: altered regional blood flow and impaired lower jaw development. Toxicological Sciences *65*, 192-199.
49. Ohkawara, B., Iemura, S., ten Dijke, P., and Ueno, N. (2002). Action range of BMP is defined by its N-terminal basic amino acid core. Curr. Biol. *12*, 205-209.
50. Morita, K., Flemming, A.J., Sugihara, Y., Mochii, M., Suzuki, Y., Yoshida, S., Wood, B., Kohara, Y., Leroi, A.M., and Ueno, N. (2002). A *Canorhabaditis elegans* TGF-β , DBL-1, controls the expression of LON-1, a PR-related protein, that regulates polyploidization and body length. EMBO J. *21*, 1063-1073.
51. Koshida, S., Shinya, M., Nikaido, M., Ueno, N., Schulte-Merker, S., Kuroiwa, A., and Takeda, H. (2002). Inhibition of BMP activity by the FGF signal promotes posterior neural development in zebrafish. Dev. Biol. *244*, 19-20.
52. Hyodo-Miura, J., Urushiyama, S., Nagai, S., Nishita , M., Ueno, N., and Shibuya, H. (2002). Involvement of NLK and Sox11 in neural induction in Xenopus development. Genes Cells *7*, 487-496.
53. Yuasa, T., Kataoka, H., Kinto, N., Iwamoto, M., Enomoto-Iwamoto, M., Iemura, S., Ueno, N., Shibata, Y., Kurosawa, H., and Yamaguchi, A. (2002). Sonic hedgehog is involved in osteoblast differentiation by cooperating with BMP-2. J. Cell Physiol. *193*, 225-232.
54. Komatsu, Y., Shibuya, H., Takeda, N., Ninomiya-Tsuji, J., Yasui, T., Miyado, K., Sekimoto, T., Ueno, N., Matsumoto, K., and Yamada, G. (2002). Targeted disruption of the Tab1 gene causes embryonic lethality and defects in cardiovascular and lung morphogenesis. Mech. Dev. *119*, 239-249.
55. Ohkawara, B., Yamamoto, T.S., Tada, M., and Ueno, N. (2003). Role of glypican 4 in the regulation of convergent extension movements during gastrulation in *Xenopus laevis.* Development *130*, 2129-2138.
56. Takeuchi, M., Nakabayashi, J., Sakaguchi, T., Yamamoto, T.S., Takahashi, H., Takeda, H., and Ueno, N. (2003). The prickle-related gene in vertebrates is essential for gastrulation cell

movements. Curr. Biol. *13*, 674-679.
57. Ishitani, T., Kishida, S., Hyodo-Miura, J., Ueno, N., Yasuda, J., Waterman, M., Shibuya, H., Moon, R.T., Ninomiya-Tsuji, J., and Matsumoto, K. (2003). The TAK1-NLK mitogen-activated protein kinase cascade functions in the Wnt-5a/Ca(2+) pathway to antagonize Wnt/beta-catenin signaling. Mol. Cell. Biol. *23*, 131-139.
58. Kurata, T., and Ueno, N. (2003). Xenopus Nbx, a novel NK-1 related gene essential for neural crest formation. Dev. Biol. *257*, 30-40.
59. Suzuki, M., Ueno, N., and Kuroiwa, A. (2003). Hox proteins functionally cooperate with the GC box-binding protein system through distinct domains. J. Biol. Chem. *278*, 30148-30156.
60. Kinoshita, N., Iioka, H., Miyakoshi, A., and Ueno, N. (2003). PKC delta is essential for Dishevelled function in a non-canonical Wnt pathway that regulates Xenopus convergent extension movements. Genes Dev. *17*, 1663-1676.
61. Azumi, K., Takahashi, H., Miki, Y., Fujie, M., Usami, T., Ishikawa, H., Kitayama, A., Satou Y., Ueno, N., and Satoh, N. (2003). Construction of a cDNA microarray derived from the ascidian *Ciona intestinalis*. Zool. Sci. *20*, 1223-1229.
62. Hotta, K., Takahashi, H., Ueno, N., and Gojobori, T. (2003). A genome-wide survey of the genes for planar polarity signaling or convergent extension-related genes in *Ciona intestinalis* and phylogenetic comparisons of evolutionary conserved signaling components. Gene *317*, 165-185.
63. Carreira-Barbosa, F., Concha, M.L., Takeuchi, M., Ueno, N., Wilson, S.W., and Tada M. (2003). Prickle 1 regulates cell movements during gastrulation and neuronal migration in zebrafish. Development *130*, 4037-4046.
64. Iioka, H., Ueno, N., and Kinoshita, N. (2004). Essential role of MARCKS in cortical actin dynamics during gastrulation movements. J. Cell Biol. *164*, 169-174.
65. Ohkawara, B., Shirakabe, K., Hyodo-Miura, J., Matsuo, R., Ueno, N., Matsumoto, K., and Shibuya, H. (2004). Role of the TAK1-NLK-STAT3 pathway in TGF- β -mediated mesoderm induction. Genes Dev. *18*, 381-386.
66. Miyakoshi, A., Ueno, N., and Kinoshita, N. (2004). Rho guanine nucleotide exchange factor xNET1 implicated in gastrulation movements during Xenopus development. Differentiation *72*, 48-55.
67. Sugiura, T., Taniguchi, Y., Tazaki, A., Ueno, N., Watanabe, K., and Mochii M. (2004). Differential gene expression between the embryonic tail bud and regenerating larval tail in *Xenopus laevis*. Dev. Growth Differ. *46*, 97-105.
68. Hu, Q., Ueno, N., and Behringer, R.R. (2004). Restriction of BMP4 activity domains in the developing neural tube of mouse embryo. EMBO Rep. *5*, 734-739.
69. Sone, K., Hinago, M., Kitayama, A., Morokuma, J., Ueno, N., Watanabe, H., and Iguchi, T. (2004). Effects of 17beta-estradiol, nonylphenol, and bisphenol-A on developing *Xenopus laevis* embryos. Gen. Comp. Endocrinol. *138*, 228-236.
70. Chung, H.A., Hyodo-Miura, J., Kitayama, A., Terasaka, C., Nagamune, T., and Ueno, N. (2004). Screening of FGF target genes in Xenopus by microarray: temporal dissection of the signalling pathway using a chemical inhibitor. Genes Cells *9*, 749-761.
71. Sakamaki, K., Takagi, C., Kominami, K., Sakata, S., Yaoita, Y., Kubota, H.Y., Nozaki, M.,

Yonehara, S., and Ueno, N. (2004). The adaptor molecule FADD from *Xenopus laevis* demonstrates evolutionary conservation of its pro-apoptotic activity. Genes Cells *9*, 1249-1264.

72. Arima, K., Shiotsugu, J., Niu, R., Khandpur, R., Martinez, M., Shin, Y., Koide, T., Cho, K.W., Kitayama, A., Ueno, N., Chandraratna, R.A.S., and Blumberg, B. (2005). Global analysis of RAR-responsive genes in the Xenopus neurula using cDNA microarrays. Dev. Dyn. *232*, 414-431.
73. Baldessari, D., Shin, Y., Krebs, O., Konig, R., Koide, T., Vinayagam, A., Fenger, U., Mochii, M., Terasaka, C., Kitayama, A., Peiffer, D., Ueno, N., Eils, R., Cho, K.W., and Niehrs, C. (2005). Global gene expression profiling and cluster analysis in *Xenopus laevis*. Mech. Dev. *122*, 441-475.
74. Peiffer, D.A., Von Bubnoff, A., Shin, Y., Kitayama, A., Mochii, M., Ueno, N., and Cho, K.W. (2005). A Xenopus DNA microarray approach to identify novel direct BMP target genes involved in early embryonic development. Dev. Dyn. *232*, 445-456.
75. Sakamaki, K., Takagi, C., Yoshino, J., Yokota, H., Nakamura, S., Kominami, K., Hyodo, A., Takamune, K., Yuge, M., and Ueno, N. (2005). Transgenic frogs expressing the highly fluorescent protein venus under the control of a strong mammalian promoter suitable for monitoring living cells. Dev. Dyn. *233*, 562-569.
76. Shin, Y., Kitayama, A., Koide, T., Peiffer, D.A., Mochii, M., Liao, A., Ueno, N., and Cho, K.W. (2005). Identification of neural genes using Xenopus DNA microarrays. Dev. Dyn. *232*, 432-444. (Erratum; Dev. Dyn. *233*, 248).
77. Chung, H.A., Hyodo-Miura, J., Nagamune, T., and Ueno, N. (2005). FGF signal regulates gastrulation cell movements and morphology through its target NRH. Dev. Biol. *282*, 95-110.
78. Kataoka, K., Tazaki, A., Kitayama, A., Ueno, N., Watanabe, K., and Mochii, M. (2005). Identification of asymmetrically localized transcripts along the animal-vegetal axis of the Xenopus egg. Dev. Growth Differ. *47*, 511-521.
79. Takada, H., Hattori, D., Kitayama, A., Ueno, N., and Taira, M. (2005). Identification of target genes for the Xenopus Hes-related protein XHR1, a prepattern factor specifying the midbrain-hindbrain boundary. Dev. Biol. *283*, 253-267.
80. Tazaki, A., Kitayama, A., Terasaka, C., Watanabe, K., Ueno, N., and Mochii, M. (2005). Macroarray-based analysis of tail regeneration in *Xenopus laevis* larvae. Dev. Dyn. *233*, 1394-1404.
81. Terada, K., Kitayama, A., Kanamoto, T., Ueno, N., and Furukawa, T. (2006). Nucleosome regulator Xhmgb3 is required for cell proliferation of the eye and brain as a downstream target of Xenopus rax/Rx1. Dev. Biol. *291*, 398-412.
82. Hyodo-Miura, J., Yamamoto, T.S., Hyodo, A.C., Iemura, S., Kusakabe, M., Nishida, E., Natsume, T., and Ueno, N. (2006). XGAP, an ArfGAP, is required for polarized localization of PAR proteins and cell polarity in Xenopus gastrulation. Dev. Cell *11*, 69-79.
83. Takada, R., Satomi, Y., Kurata, T., Ueno, N., Norioka, S., Kondoh, H., Takao, T., and Takada, S. (2006). Monounsaturated fatty acid modification of Wnt protein: its role in Wnt secretion. Dev. Cell *11*, 791-801.
84. Waldner, C., Sakamaki, K., Ueno, N., Turan, G., and Ryffel, G.U. (2006). Transgenic

Xenopus laevis strain expressing cre recombinase in muscle cells. Dev. Dyn. *235*, 2220-2228.
85. Kominami, K., Takagi, C., Kurata, T., Kitayama, A., Nozaki, M., Sawasaki, T., Kuida, K., Endo, Y., Manabe, N., Ueno, N., and Sakamaki, K. (2006). The initiator caspase, caspase-10beta, and the BH-3-only molecule, Bid, demonstrate evolutionary conservation in Xenopus of their pro-apoptotic activities in the extrinsic and intrinsic pathways. Genes Cells *11*, 701-717.
86. Chung, H.A., Yamamoto, T.S. and Ueno, N. (2007). ANR5, an FGF target gene product, regulates gastrulation in Xenopus. Curr. Biol. *17*, 932-939.
87. Hotta, K., Yamada, S., Ueno, N., Satoh, N., and Takahashi, H. (2007). *Brachyury*-downstream notochord genes and convergent extension in *Ciona intestinalis* embryos. Dev. Growth Differ. *49*, 373-382.
88. Ogata, S., Morokuma, J., Hayata, T., Kolle, G., Niehrs, C., Ueno, N., and Cho, K.W. (2007). TGF-β signaling-mediated morphogenesis: modulation of cell adhesion via cadherin endocytosis. Genes Dev. *21*, 1817-1831.
89. Yoshikane, N., Nakamura, N., Ueda, R., Ueno, N., Yamanaka, S., and Nakamura, M. (2007). Drosophila NAT1, a homolog of the vertebrate translational regulator NAT1/DAP5/p97, is required for embryonic germband extension and metamorphosis. Dev. Growth Differ. *49*, 623-634.
90. Gerth, V. E., Katsuyama, K., Snyder, K.A., Bowes, J.B., Kitayama, A., Ueno, N., and Vize, P.D. (2007). Projecting 2D gene expression data into 3D and 4D space. Dev. Dyn. *236*, 1036-1043.
91. Hayes, J.M., Kim, S.K., Abitua, P.B., Park, T.J., Herrington, E.R., Kitayama, A., Grow, M.W., Ueno, N. and Wallingford, J.B. (2007). Identification of novel ciliogenesis factors using a new in vivo model for mucociliary epithelial development. Dev. Biol. *312*, 115-130.

2) Invited reviews, book chapters

1. Ueno, N. (1998). "BMP signaling in vertebrate embryogenesis." in Tissue Engineering for Terapeutics use 2, eds. Ikeda, Y. and Enomoto, S.
2. Iemura, S., Yamamoto, T.S., Takagi, C., and Ueno, N. (2000). The analysis of protein-protein interactions in early develoment: direct binding of follistatin, an organizer factor, to BMPs. in "Real time Analysis of Biomoelcular Interactions. Applications of BIACORE" eds. Nagata, K. and Handa, H. Springer, pp105-114.
3. Ueno, N. (2001). Obituary: Toshiya Yamada. 1960-2001. Differentiation *67*, S1-2.
4. Ohkawara, B., and Ueno, N. (2003). “Regulation of pattern formation by the intereaction brtween growth factors and proteoglycans.” In “Morphogenesis and Pattern Formation in Biological Systems” eds. Sekimura, T., Noji, S., Ueno, N. and Maini, P.K. Springer pp 69-82.
5. Ueno, N., and Greene, N.D. (2004). Planar cell polarity genes and neural tube closure. Birth Defects Res. Part C Embryo Today *69*, 318-324.

小林　悟
発生遺伝学研究部門（岡崎統合バイオサイエンスセンター）・教授

Research Achievement in the Past

Dr. Kobayashi joined the NIBB in 2001. Since that time he has made many important discoveries about germline development in *Drosophila*. These discoveries include: (1) proteins essential for pole cell formation, like *germ cell-less*, are translated from mitochondrial-type ribosomes on polar granules, highlighting a role for mitochondria in germline formation, (2) Nanos represses germ cell apoptosis for germline survival by suppressing the translation of pro-apoptotic genes, (3) the maternal factor Mamo, a regulator of chromatin structure and transcription, is essential for meiosis, indicating a novel epigenetic mechanism for regulating the meiotic cell cycle, (4) signal transduction from the germline to the somatic cells is required for the development of the stem cell niche in the gonad. In addition, Dr. Kobayashi's lab has identified over 100 genes predominantly expressed in pole cells, using isolated cells and microarray analysis. These studies have been facilitated by the Kobayashi lab's unique ability to perform the very difficult pole cell transplantation manipulation, allowing them to perform experiments that other labs cannot.

Future Plans

Dr. Kobayashi will continue his studies of germ cell development. A microarray analysis of Mamo mutant ovaries has revealed a set of genes that can be used to study how Mamo regulates meiosis. In addition, Dr. Kobayashi's large list of over 100 genes expressed in pole cells provides molecular tools to continue his successful studies of germline development.

Overall Evaluation

Dr. Kobayashi has generated outstanding results in defining the molecular mechanisms that regulate germline development in *Drosophila*. He has been highly productive, consistently publishing many papers in high impact journals. The committee was especially impressed with the clarity of his logic, quality of data, and oral and written presentation. He has also identified a wealth of new pole cell genes that will facilitate his future research. It is likely that Dr. Kobayashi will continue to be very productive with his future research plans. The committee also praises Dr. Kobayashi for his commitment to education, mentoring 6 graduate students and lecturing about science in high schools. The committee also noted Dr. Kobayashi's strong scientific leadership skills, serving on the board of the JSDB and chairing a recent NIBB Conference. The committee urges Dr. Kobayashi to continue to develop these leadership skills and extend them beyond Japan perhaps by serving on editorial boards of international scientific journals and helping to organize international scientific meetings.

（和訳）

小林博士は 2001 年に基礎生物学研究所に着任した。着任以来、ショウジョウバエの生殖細胞系の発生に関して多くの重要な発見を行った。そのような発見には以下のものがあげられる：(1)極細胞の形成に不可欠な *germ cell-les* などのタンパク質が、極細胞質のミトコンドリアタイプのリボソームから翻訳される。このことは、生殖系列の形成にミトコンドリアが一定の役割を果たしていることを示唆するものである。(2) Nanos は pro-apoptotic 遺伝子の翻訳を抑制することで生殖系列の生存のため、生殖細胞のアポトーシスを抑制している。(3)母性因子 Mamo（染色体の構造と転写の制御因子）が減数分裂に不可欠である。このことは減数分裂周期を制御する新しいエピジェネティックな機序を示している。(4)生殖系列から体細胞へのシグナル伝達が、生殖巣中での幹細胞のニッチの形成に必要である。加えて、小林研究室では、極細胞で多く発現される 100 個以上の遺伝子を、単離細胞とマイクロアレイ解析を用いて同定してきた。これらの研究は小林研究室が、極めて困難な極細胞移植操作が可能であるというユニークな能力を活用し、他の研究室ではできない実験を可能にすることで促進されてきた。

将来計画

小林博士は今後も生殖細胞発生に関する研究を継続する予定である。Mamo 突然変異卵巣のマイクロアレイ解析を行って、Mamo が減数分裂をどのように制御しているか研究するのに使えるいくつかの遺伝子を明らかにした。加えて、極細胞で発現される 100 個以上の遺伝子リストを小林博士が有していることは、生殖系列の発生に関して今後も成功を重ねて行く上での分子ツールとなっている。

総評

小林博士はショウジョウバエの生殖系列の発生を制御する分子機序を明らかにするのに傑出した成果をあげてきた。極めて生産性が高く、インパクトファクターの高い論文誌に多くの論文を発表し続けている。博士のロジックの明快さ、データの質の高さ、口頭発表および文書での表現力の高さに当委員会は強い印象を受けた。博士はまた極細胞の新しい遺伝子を多数同定しており、今後の研究を促進するであろう。小林博士は今後も将来研究で非常に高い成果をあげていくものと思われる。当委員会は、小林博士が教育に参加し、6 名の大学院学生の指導と、高校での科学講演を行っていることも評価する。また、小林博士は高いリーダーシップ能力があり、JSDB の運営会議委員や、最近行われた NIBB コンファレンスの大会長をつとめたことも、当委員会では認識している。小林博士にはこれらのリーダーシップを維持発展させ、日本国内を超えて、国際論文誌の編集委員を引き受けたり、国際会合をオーガナイズすることで、一層の役割拡大を当委員会は希望する。

研究業績（2001 年より）：

1) Research articles in peer reviewed journals

1. Sano, H., Mukai, M., and Kobayashi, S. (2001). Maternal Nanos and Pumilio regulate zygotic *vasa* expression autonomously in the germline progenitors of *Drosophila* embryos. Develop. Growth Differ. *43*, 545-552.
2. Nakamura, A., Amikura, R., Hanyu, K., and Kobayashi, S. (2001). Me31B silences translation of oocyte-localizing RNAs through the formation of cytoplasmic RNP complex during *Drosophila* oogenesis. Development *128*, 3233-3242.
3. Amikura, R., Kashikawa, M., Nakamura, A., and Kobayashi, S. (2001). Presence of mitochondrial-type ribosomes outside mitochondria in germ plasm of *Drosophila* embryos. Proc. Natl. Acad. Sci. USA. *98*, 9133-9138.
4. Amikura, R., Hanyu, K., Kashikawa, M., and Kobayashi, K. (2001). Tudor protein is essential for the localization of mitochondrial ribosomal RNAs in polar granules in germ plasm of *Drosophila* embryos. Mech. Dev. *107*, 97-104.
5. Kashikawa, M., Amikura, A., and Kobayashi, S. (2001). Mitochondrial small ribosomal RNA is a component of germinal granules in *Xenopus* embryos. Mech. Dev. *101*, 71-77.
6. Inoue, S.B., Shimoda, M., Nishinokubi, I., Siomi, M.C., Okamura, M., Nakamura, A., Kobayashi, S., Ishida, N., and Siomi, H. (2002). A role for the *Drosophila* fragile X-related gene in circadian output. Curr. Biol. *12*, 1331-1335.
7. Sano, H., Nakamura, A., and Kobayashi, S. (2002). Identification of a transcriptional regulatory region for germline-specific expression of *vasa* gene in *Drosophila melanogaster*. Mech. Dev. *112*, 129-139.
8. Tsuda, M., Sasaoka, Y., Kiso, M., Abe, K., Haraguchi, S., Kobayashi, S., and Saga, Y. (2003). Conserved role of nanos proteins in germ cell development. Science *301*, 1239-1241.
9. Unezaki, S., Nishizawa, M., Okuda-Ashitaka, E., Masu, Y., Mukai, M., Kobayashi, S., Sawamoto, K., Okano, H., and Ito, S. (2004). Characterization of the isoforms of MOVO zinc finger protein, a mouse homologue of *Drosophila ovom* as transcription factors. Gene *336*, 47-58.
10. Hanyu-Nakamura, K., Kobayashi, S., and Nakamura, A. (2004). Intrinsic and extrinsic lipid phosphate phosphatase defines cell viability that promotes directional migration of *Drosophila* germ cells. Development *131*, 4545-4553.
11. Hayashi, Y., Hayashi, M., and Kobayashi, S. (2004). Nanos suppresses somatic cell fate in *Drosophila* germline. Proc. Natl. Acad. Sci. USA. *101*, 10338-10342.
12. Hayashi, M., Aono, H., Ishihara, J., Oshima, S., Yamamoto, H., Makazato, Y., and Kobayashi, S. (2005). Left-right asymmetry in the alimentary canal of the *Drosophila* embryo. Develop. Growth Differ. *47*, 457-460.
13. Amikura, R., Sato, K., and Kobayashi, S. (2005). Role of mitochondrial ribosome-dependent translation in germline formation in *Drosophila* embryos. Mech. Dev. *122*, 1087-1093.

14. Sato, K., Shibata, N., Orii, H., Amikura, R., Sakurai, T., Agata, K., Kobayashi, S., and Watanabe, K. (2006). Identification and origin of the germline stem cells as revealed by the expression of *nanos*-related gene in planarians. Develop. Growth Differ. *48*, 615-628.
15. Shigenobu, S., Kitadate, Y., Noda, C., and Kobayashi, S. (2006). Molecular characterization of embryonic gonads by gene expression profiling in *Drosophila melanogaster*. Proc. Natl. Acad. Sci. USA. *103*, 13728-13733.
16. Sengoku, T., Nureki, O., Nakamura, A., Kobayashi, S., and Yokoyama, S. (2006). Structural basis for RNA unwinding by the DEAD-box protein *Drosophila* Vasa. Cell *125*, 287-300.
17. Shigenobu, S., Arita, K., Kitadate, Y., Noda, C., and Kobayashi, S. (2006). Isolation of germline cells from *Drosophila* embryos by flow cytometry. Develop. Growth Differ. *48*, 49-57.
18. Mukai, M., Kitadate, Y., Arita, K., Shigenobu, S., and Kobayashi, S. (2006). Expression of meiotic genes in the germline progenitors of *Drosophila* embryos. Gene Expr. Patterns *6*, 256-266.
19. Nakamura, Y., Kagesawa, T., Nishikawa, M., Hayashi, Y., Kobayashi, S., Niimi, T., and Matsuno, K. (2007). Soma-dependent modulations contribute to divergence of rhomboid expression during evolution of *Drosophila* eggshell morphology. Development *134*, 1529-1537.
20. Mukai, M., Hayashi, Y., Kitadate, Y., Shigenobu, S., Arita, K., and Kobayashi, S. (2007). MAMO, a maternal BTB/POZ-Zn-finger protein enriched in germline progenitors is required for the production of functional eggs in *Drosophila*. Mech. Dev. *124*, 570-583.
21. Sato, K., Hayashi, Y., Ninomiya, Y., Shigenobu, S., Arita, K., Mukai, M., and Kobayashi, S. (2007). Maternal Nanos represses *hid/skl*-dependent apoptosis to maintain the germ line in *Drosophila* embryos. Proc. Natl. Acad. Sci. USA. *104*, 7455-7460.
22. Kitadate, Y., Shigenobu, S., Arita, K., and Kobayashi, S. (2007). Boss/Sev signaling from germline to soma restricts germline-stem-cell-niche formation in the anterior region of *Drosophila* male gonad. Dev. Cell *13*, 151-159.

2) Invited reviews, book chapters

1. Kobayashi, S., Sato, K., and Hayashi, Y. (2005). The role of mitochondrial rRNAs and Nanos protein in germline formation in *Drosophila* embryos. Zool. Sci. *22*, 943-954.

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Dr. Takada joined the NIBB in 2002. Dr. Takada has made very important discoveries of vertebrate pattern formation mechanisms. These discoveries include: (1) Wnt-3a is post-translationally modified with palmitoleic acid at a conserved Ser that is dependent on the O-acyltransferase Porcupine for transit from the endoplasmic reticulum for secretion, suggesting a role for lipid modifications in higher order structure of Wnts and gradient formation (2) fibroblast growth factor signaling maintains oscillating gene expression in presomitic mesoderm by inducing Her13.2 expression for repression of Her1 for somite formation, (3) Ripply1 is essential for the transition of presomitic mesoderm to somites and termination of normal presomitic mesoderm patterns, (4) integrin $\alpha 5$ directs assembly of fibronectin for somite epithelialization and maintenance of somite boundaries. These discoveries were enabled by an in situ hybridization screen and ENU mutagenesis screen in zebrafish.

Future Plans

Dr. Takada plans to focus on two areas for future research, including (1) mechanisms of somite segmentation and (2) analysis of the molecular mechanisms of Wnt secretion and higher order structure of morphogen gradients. He is also extending his studies of segmentation to other regions of the embryo including the branchial arches. He has established the utility of his in situ hybridization and forward genetic screens and will continue these to identify other mechanisms of segmentation. These are reasonable plans, building on his success in these two areas of research.

Overall Evaluation

Dr. Takada has made very significant contributions to the Wnt and vertebrate segmentation fields. Since joining the NIBB in 2002, Dr. Takada has been very productive, publishing 34 papers in very high impact journals. Considering the excellence of Dr. Takada's research, the committee felt that he should write state of the art reviews for his field for publication in the top journals. The committee also praises Dr. Takada for his mentoring of 7 graduate students. The committee noted Dr. Takada's scientific leadership through the organization of practical courses and international symposia. Considering Dr. Takada's strong international scientific profile, the committee urges Dr. Takada to continue to develop these leadership skills and extend them beyond Japan by actively serving in scientific societies, serving on editorial boards of international scientific journals, and organizing international scientific meetings.

（和訳）

過去の研究業績

高田博士は 2002 年に基礎生物学研究所に着任した。高田博士は脊椎動物の体節形成機序に極めて重要な発見を行った。そのような発見としては、(1) Wnt-3a が翻訳後に、保存性の高い Ser の位置でパルミトレイン酸による修飾を受け、この修飾は小胞体から分泌のために移動するのに、O-アシルトランスフェラーゼ Porcupine に依存する。このことは、Wnt の高次構造と濃度勾配形成に脂質修飾が一定の役割を果たすことを示唆するものである。(2)FGF シグナル伝達が未分節中胚葉での遺伝子発現の振動を、Her13.2 の発現を誘発して、分節形成を Her1 が抑制することで維持している。(3) 未分節中胚葉から分節に移行し、正常な未分節中胚葉パターンが終了するには、Ripply1 が不可欠である。(4) integrin α5 が分節の上皮可および分節久代かいの維持のためにフィブロネクチンの集積を導いていることを発見した。これらの発見は、ゼブラフィッシュでの in situ hybridization スクリーニング法と ENU 変異スクリーニング法で可能になったものである。

将来計画

高田博士は将来の計画では(1) 体節形成の機序と、(2) Wnt 分泌ならびにモルフォゲン勾配の高次勾配の分子機序の分析の 2 領域に絞りたいとしている。博士は、鰓弓を含む胚の他の領域での分節形成の研究にも研究を広げている。in situ hybridization と順遺伝学的スクリーニング法の活用を確立しており、これらを引き続き活用して、体節形成の他の機序を解明する予定である。これらは妥当な計画であり、これら 2 領域の研究のこれまでの成功の上に構築されるものである。

総評

高田博士は Wnt および脊髄動物の体節形成の領域で極めて重要な貢献をしてきた。2002 年に基礎生物学研究所に着任以来、高田博士は極めて生産的で、極めてインパクトファクターの高い論文誌に 34 件の論文を発表している。高田博士の研究のすばらしさを考えれば、博士は、トップの論文誌に彼の分野の総説論文を執筆すべきであると当委員会では考える。高田博士が 7 名の大学院学生を指導していることも当委員会は評価する。高田博士が実習コースや国際シンポジウムをオーガナイズすることを通じてリーダーシップを発揮していることを当委員会は認識している。高田博士が国際的に高く認められていることを考えれば、高田博士には、リーダーとしての才能をさらに発揮し、日本を超えて、学会に積極的に貢献し、国際論文誌の編集委員となり、国際会合をオーガナイズすることで、一層の役割拡大を当委員会は希望する。

研究業績（2002 年より）：

1) Research articles in peer reviewed journals

1. Jimbo, T., Kawasaki, Y., Koyama, R., Sato, R., Takada, S., Haraguchi, K., and Akiyama, T.

(2002). Identification of a link between the tumour suppressor APC and the kinesin superfamily. Nat. Cell Biol. *4*, 323-327.

2. Ueda, Y., Hijikata, M., Takagi, S., Takada, R., Takada, S., Chiba, T., and Shimotohno, K. (2002). Wnt/beta-catenin signaling suppresses apoptosis in low serum medium and induces morphologic change in rodent fibroblasts. Int. J. Cancer. *99*, 681-688.
3. Ohbayashi, N., Shibayama, M., Kurotaki, Y., Imanishi, M., Fujimori, T., Itoh, N., and Takada, S. (2002). Fgf18 is required for cell proliferation and differentiation during osteogenesis and chondrogenesis. Genes Dev. *16*, 870-879.
4. Muroyama, Y., Fujihara, M., Ikeya, M., Kondoh, H., and Takada, S. (2002). Wnt signaling plays an essential role in neuronal specification of the dorsal spinal cord. Genes Dev. *16*, 548-553.
5. Yamanaka, H., Moriguchi, T., Masuyama, N., Kusakabe, M., Hanafusa, H., Takada, R., Takada, S., and Nishida, E. (2002). JNK functions in the non-canonical Wnt pathway to regulate convergent extension movements in vertebrates. EMBO Rep. *3*, 69-75.
6. Nakagawa, S., Takada, S., Takada, R., and Takeichi, M. (2003). Identification of the laminar-inducing factor: Wnt-signal from the anterior rim induces correct laminar formation of the neural retina in vitro. Dev. Biol. *260*, 414-425.
7. Oishi, I., Suzuki, H., Onishi, N., Takada, R., Kani, S., Ohkawara, B., Koshida, I., Suzuki, K., Yamada, G., Schwabe, G.C., Mundlos, S., Shibuya, H., Takada, S., and Minami, Y. (2003). The receptor tyrosine kinase Ror2 is involved in non-canonical Wnt5a/JNK signalling pathway. Genes Cells *8*, 645-654.
8. Fujino, T., Asaba, H., Kang, M.J., Ikeda, Y., Sone, H., Takada, S., Kim, D.H., Ioka, R.X., Ono, M., Tomoyori, H., Okubo, M., Murase, T., Kamataki, A., Yamamoto, J., Magoori, K., Takahashi, S., Miyamoto, Y., Oishi, H., Nose, M., Okazaki, M., Usui, S., Imaizumi, K., Yanagisawa, M., Sakai, J., and Yamamoto, T.T. (2003). Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion. Proc. Natl. Acad. Sci. USA *100*, 229-234.
9. Usui, H., Shibayama, M., Ohbayashi, N., Konishi, M., Takada, S., and Itoh, N. (2004). Fgf18 is required for embryonic lung alveolar development. Biochem. Biophys. Res. Commun. *322*, 887-892.
10. Hasegawa, H., Ashigaki, S., Takamatsu, M., Suzuki-Migishima, R., Ohbayashi, N., Itoh, N., Takada, S., and Tanabe, Y. (2004). Laminar patterning in the developing neocortex by temporally coordinated fibroblast growth factor signaling. J. Neurosci. *24*, 8711-8719.
11. Naito, M., Katayama, R., Ishioka, T., Suga, A., Takubo, K., Nanjo, M., Hashimoto, C., Taira, M., Takada, S., Takada, R., Kitagawa, M., Matsuzawa, S., Reed, J.C., and Tsuruo, T. (2004). Cellular FLIP inhibits beta-catenin ubiquitylation and enhances Wnt signaling. Mol. Cell Biol. *24*, 8418-8427.
12. Muroyama, Y., Kondoh, H., and Takada, S. (2004). Wnt proteins promote neuronal differentiation in neural stem cell culture. Biochem. Biophys. Res. Commun. *313*, 915-921.
13. Kamata, T., Katsube, K., Michikawa, M., Yamada, M., Takada, S., and Mizusawa, H. (2004). R-spondin, a novel gene with thrombospondin type 1 domain, was expressed in the dorsal neural tube and affected in Wnts mutants. Biochim. Biophys. Acta. *1676*, 51-62.
14. Satoh, K., Kasai, M., Ishidao, T., Tago, K., Ohwada, S., Hasegawa, Y., Senda, T., Takada,

S., Nada, S., Nakamura, T., and Akiyama, T. (2004). Anteriorization of neural fate by inhibitor of beta-catenin and T cell factor (ICAT), a negative regulator of Wnt signaling. Proc. Natl. Acad. Sci. USA *101,* 8017-8021.

15. Yamaguchi, Y., Ogura, S., Ishida, M., Karasawa, M., and Takada, S. (2005). Gene trap screening as an effective approach for identification of Wnt-responsive genes in the mouse embryo. Dev. Dyn. *233,* 484-495.
16. Takada, R., Hijikata, H., Kondoh, H, and Takada, S. (2005). Analysis of combinatorial effects of Wnts and Frizzleds on b-catenin/armadillo stabilization and Dishevelled phosphorylation. Genes Cells *10*, 919-928.
17. Shimizu, T., Wada, T., Muroyama, Y., Takada, S., and Ikenaka, K (2005). Wnt signaling controls the timing of oligodendrocyte development in the spinal cord. Dev. Biol. *282*, 397-410.
18. Riccomagno, M., Takada, S., and Epstein, D. (2005). Wnt dependent regulation of inner ear morphogenesis is balanced by the opposing and supposing roles of Shh. Genes Dev. *19,* 1612-1623.
19. Narita, T., Sasaoka, S., Udagawa, K., Ohyama, T., Wada, N., Nishimatsu, S.I., Takada, S,, and Nohno, T. (2005). Wnt10a is involved in AER formation during chick limb development. Dev. Dyn. *233*, 282-287.
20. Nakagiri, S., Murakami, A., Takada, S., Akiyama, T., and Yonehara, S. (2005). Viral FLIP enhances Wnt signaling downstream of stabilized beta-catenin, leading to control of cell growth. Mol. Cell Biol. *25*, 9249-9258.
21. Koshida, S., Kishimoto, Y., Ustumi, H., Shimizu, T., Furutani-Seiki, M., Kondoh, H., and Takada, S. (2005). Integrina5-dependent Fibronectin accumulation for maintenance of somite boundaries in zebrafish embryos. Dev. Cell *8*, 587-598.
22. Kawamura, A., Koshida, S., Hijikata, H., Ohbayashi, A., Kondoh, H., and Takada, S. (2005). Groucho-associated transcriptional repressor Ripply1 is required for proper transition from the presomitic mesoderm to somites. Dev. Cell *9*, 735-744.
23. Kawamura, A., Koshida, S., Hijikata, H., Sakaguchi, T., Kondoh, H., and Takada, S. (2005). These two authors contributed equally to this work.). Zebrafish Hairy/Enhancer of split protein links FGF signaling to cyclic gene expression in the periodic segmentation of somites. Genes Dev. *19*, 1156-1161
24. Kassai, Y., Munne, P., Hotta, Y., Penttila, E., Kavanagh, K., Ohbayashi, N., Takada, S., Thesleff, I., Jemvall, J., and Itoh, N. (2005). Regulation of mammalian tooth cusp patterning by ectodin. Science *309,* 2067-2070.
25. Yamaguchi, Y., Yonemura, S., and Takada, S. (2006). Grainyhead-related transcription factor is required for duct maturation in the salivary gland and the kidney of the mouse. Development *133,* 4737-4748.
26. Takada, R., Satomi, Y., Kurata, T., Ueno, N., Norioka, S., Kondoh, H., Takao, T., and Takada, S. (2006). Monounsaturated fatty acid modification of Wnt proteins: Its role in Wnt secretion. Dev. Cell *11*, 791-801.
27. Nishita, M., Yoo, S. K., Nomachi, A., Kani, S., Sougawa, N., Ohta, Y., Takada, S., Kikuchi, A., and Minami, Y. (2006). Filopodia formation mediated by receptor tyrosine kinase Ror2 is required for Wnt5a-induced cell migration. J. Cell Biol. *175*, 552-562.

28. Inoue, T., Kagawa, T., Fukushima, M., Shimizu, T., Yoshinaga, Y., Takada, S., Tanihara, H., and Taga, T. (2006). Activation of canonical Wnt pathway promotes proliferation of retinal stem cells derived from adult mouse ciliary margin. Stem Cells *24,* 95-104.
29. Horiuchi, K., Umetani, M., Minami, T., Okayama, H., Takada, S., Yamamoto, M., Aburatani, H., Reid, P. C., Housman, D. E., Hamakubo, T., and Kodama, T. (2006). Wilms' tumor 1-associating protein regulates G2/M transition through stabilization of cyclin A2 mRNA. Proc. Natl. Acad. Sci. USA *103,* 17278-17283.
30. Hayashi, T., Mizuno, N., Takada, R., Takada, S., and Kondoh, H. (2006). Determinative role of Wnt signals in dorsal iris-derived lens regeneration in newt eye. Mech. Dev. *123,* 793-800.
31. Ishioka, T., Katayama, R., Kikuchi, R., Nishimoto, M., Takada, S., Takada, R., Matsuzawa, S., Reed, J.C., Tsuruo, T., and Naito, M. (2007). Impairment of the ubiquitin-proteasome system by cellular FLIP. Genes Cells. *12*, 735-744.
32. Akanuma, T., Koshida, S., Kawamura, A., Kishimoto, Y., and Takada, S. (2007). Paf1 complex homologes are required for Notch-regulated transcription during somite segmentation. EMBO Rep. *8*, 858-863.
33. Takada, I., Mihara, M., Suzawa, M., Ohtake, F., Kobayashi, S., Igarashi, M., Youn, M-Y, Takeyama, K., Nakamura, T., Mezaki, Y., Takezawa, S., Yogiashi, Y., Kitagawa, H., Yamada, G., Takada, S., Minami, Y., Shibuya, H., Matsumoto, K. & Kato, S. (2007) A histone lysine methyltransferase activated by non-canonical Wnt signalling suppresses PPAR-gamma transactivation. Nat. Cell Biol. *9*, 1273-1285

木下典行
形態形成研究部門・准教授

Research Achievement in the Past

The research of Dr. Kinoshita for the reviewing period was focused on the mechanism for controlling cell movement with respect to cell polarity that is a basis of the conversion extension (CE) process during *Xenopus* gastrulation. He specifically investigated the intracellular signaling system of the Wnt/PCP pathway and the system that connects the Wnt/PCP pathway to polarized cell movement. First he demonstrated that PKCδ, MARCKS and xNET1 are crucial intra cellular components of the Wnt/PCP signaling pathway during CE. His next important finding is that the Wnt/PCP pathway regulates focal adhesion formation by controlling the dynamic equilibrium of the quantity of Paxillin by ubiquitination-mediated protein degradation. Finally he showed that the ubiquitination system controls Dsh localization by interacting with Dsh-associated kinase XMINK. These original results greatly contributed to understanding the molecular mechanisms of how the Wnt/PCP pathway controls the movement of a group of the cells during CE by regulating individual cell behavior.

Taking advantage of the merits of the *Xenopus* system, his research produced biochemical and cellular data that have been published in international journals. He is a first or corresponding author for six out of seven published papers and among them, two papers appeared in the journals with high impact factors such as Genes & Development and Nature Cell Biology. These prove that his research and his ability are internationally excellent.

Future Plans

Based on the published work, Dr. Kinoshita is currently extending his studies on the identification and isolation of the components involved in the Wnt-ubiquitination system and analysis of the Dsh trafficking system. Considering his proven ability in his past approach and the excellent investigation environment, these original studies are expected to produce important results in the near future.

Other Comments

He has supervised two graduate students and their work was published international journals. This successfully allowed them to get doctoral degrees within the designated term. This indicates that Dr. Kinoshita has good ability as a team leader. Dr. Kinoshita is an assistant professor in Dr. Ueno's laboratory. He nicely collaborates with Dr. Ueno, and this interaction seems to facilitate the progress of their research for each other and to create good scientific environment in their laboratory.

Overall Evaluation

In summary, Dr. Kinoshita has registered a success enough as an assistant professor in the NIBB and he has the ability for generating original and consistent research. His current and

future study is focused on more biochemical and cellular aspects. We hope that he will make efforts to connect these studies to understand whole embryonic phenomena.

（和訳）

過去の業績

外部評価対象期間内の木下博士の研究は、アフリカツメガエルの原腸形成中の収斂と伸長(CE)プロセスの基礎である細胞極性に関して細胞の移動をコントロールする機序に焦点を絞ってきた。博士は、Wnt/PCP 経路の細胞内シグナル伝達経路と、Wnt/PCP 経路を分極細胞の移動をつなぐシステムを特に研究した。まず、CE 中の Wnt/PCP シグナル伝達経路では、PKCδ、MARCKS、xNET1 が極めて重要な細胞内コンポーネントであることを博士は実証した。次の重要な発見は、Wnt/PCP 経路が、ubiquitination-mediated protein degradation により Paxillin 量の動的平衡をコントロールすることで、局所的接着形成を制御していることであった。最後に、ubiquitination system が Dsh-associated kinase である XMINK と相互作用することで Dsh の局在をコントロールすることを博士は示した。これらのオリジナルの研究結果は、CE 中に Wnt/PCP 経路が個別細胞のふるまいを制御することで、一連の細胞の移動を制御していることを示す分子機序の解明に大きく貢献した。

アフリカツメガエル系の利点を活用して、博士の研究は、生化学および細胞に関するデータを生み出し、国際論文誌に発表されている。博士は 7 件の論文のうち 6 件の第一著者もしくは corresponding author であり、中でも、2 件の論文は Genes & Development および Nature Cell Biology というインパクトファクターの高い論文誌に掲載されている。これらのことは、博士の研究と能力が国際的に優れていることを実証するものである。

将来計画

発表された研究に基づき、木下博士は Wnt-ubiquitination system に関与するコンポーネントの同定と単離、Dsh trafficking system の解析に研究を広げている。博士の過去の実証された能力と極めて優れた研究環境を考えれば、博士のオリジナル研究は、近い将来重要な成果をあげると期待される。

その他の意見

博士は 2 名の大学院生の指導を行っており、大学院生の研究は国際論文誌に掲載された。このことにより予定期間内に博士の学位を得ることができた。このことは、木下博士がチームリーダーとして高い能力があることを示すものである。木下博士は上野研究室の准教授である。上野博士と良好に協力しており、この交流が互いの研究を進展させ、研究室の良好な科学的環境を醸成しているように思われる。

総評

以上まとめると、木下博士は基礎生物学研究所の准教授として十分な成果をあげており、オリジナルの継続的な研究を創設する能力がある。博士の現在および将来の研究は、生化学や細胞の側面により重点を置いている。これらの研究を結びつける努力を行って、胚で生じている現象全体を解明することを当委員会は希望している。

研究業績（2001 年より）：

1) Research articles in peer reviewed journals

1. Kinoshita, N., Iioka, H., Miyakoshi, A., and Ueno, N. (2003). PKCδ is essential for Dishevelled function in a noncanonical Wnt pathway that regulates *Xenopus* convergent extension movements. Genes Dev. *17*, 1663-1676.
2. Miyakoshi, A., Ueno, N., and Kinoshita, N. (2004). Rho guanine nucleotide exchange factor xNET1 implicated in gastrulation movements during Xenopus development. Differentiation *72*, 48-55.
3. Iioka, H., Ueno, N., and Kinoshita, N. (2004). Essential role of MARCKS in cortical actin dynamics during gastrulation movements. J. Cell Biol. *164*, 169-174.
4. Lee, R.H., Iioka, H., Ohashi, M., Iemura, S., Natsume, T., Kinoshita N (2007). XRab40 and XCullin5 form a ubiquitin ligase complex essential for the noncanonical Wnt pathway. EMBO J. *26*, 3592-3606.
5. Iioka, H., Iemura, S., Natsume, T., and Kinoshita, N. (2007). Wnt signalling regulates paxillin ubiquitination essential for mesodermal cell motility. Nature Cell. Biol. *9*, 813-821.

2) Invited reviews, book chapters

1. Iioka, H., and Kinoshita, N. (2004). Wnt signaling regulates cell morphology and movements. Cell Technology *23*, 660-664.

望月敦史
理論生物学研究部門（情報生物学研究センター）・准教授

Research Achievement in the Past

Dr. Mochizuki is an excellent theoretical biologist, who has been playing a leading role at least in Japan. He has accomplished a large amount of work in his lab alone or by collaborating with experimental biologists in Japan. He has studied various biological phenomena: (1) cyanobacteria circadian rhythm, (2) pattern formation of neuronal dendrite, and (3) symmetry breaking during development. He has also published purely theoretical papers on pattern formation, reaction-diffusion system, and gene regulatory networks. In some cases, Dr. Mochizuki helped experimental biologists by providing ideas and predictions that can be tested. In more cases, however, he performed computational analysis of experimental data. He has been extremely productive in the last few years.

Future Plans

Dr. Mochizuki wishes to continue collaboration with experimental biologists and to reveal the principle behind several biological phenomena such as dendrite patterning of neurons, circadian rhythm of cyanobacteria, left-right symmetry breaking etc. We believe that such collaboration will provide exciting and entirely new ideas to experimental biologists. The proposed research should be feasible because it is a logical continuation of Dr. Michizuki's efforts over the last 5 years.

Dr. Mochizuki also wishes to reveal new principles governing biology. For instance, he has recently proposed a new idea called "steady state compatibility", which would explain the origin of cell diversity during development and help understanding the meaning of a complex gene regulatory network. This seems like a very interesting idea and should be studied further. He has applied the idea to sea urchin, but it may be a good idea to apply it to *C. elegans* as well because all types of information (cell fate, genetics, genome, gene regulation etc) are available for this organism.

Overall Evaluation

Dr. Mochizuki is a young and promising mathematical biologist. He is well known in Japan, but he may deserve more recognition from scientists aboard. He collaborates with many experimental biologists in Japan and has made/is making great contributions, which is evident in his impressive publication record. Also as a pure theoretical biologist, Dr. Mochizuki brings new ideas, which are fascinating and deserve more attention from experimental biologists. Colleagues in his lab are all theoretical biologists. It might be interesting to have an experimental biologist in his own lab because bench space is available in his lab.

In all, Dr. Mochizuki has performed very well, and will do so in the near future too.

(和訳)

過去の研究業績

望月博士は優れた理論生物学者であり、少なくとも日本では先導的な役割を果たしている。博士は、研究室単独で、および、日本の実験生物学者との共同研究で多数の研究を行ってきた。博士は以下のような生物現象について研究してきた：(1)シアノバクテリアの概日周期、(2)ニューロンの樹状突起のパターン形成、(3)発生中の対称性の破れ。博士はまた、パターン形成、反応拡散系、遺伝子制御ネットワークに関する純理論的論文も発表している。中には、望月博士がアイデアと検証可能な予測を示すことで、実験生物学者を支援したこともある。しかし、多くの場合は、実験データのコンピュータ解析を実施している。この数年間極めて高い生産性を示している。

将来計画

望月博士は、実験生物学者との共同研究を今後も続け、ニューロンの樹状突起パターン形成やシアノバクテリアの概日周期、左右対称性の破れなどの生物現象の背後にある原理を解明したいとしている。われわれは、そのような共同研究が、実験生物学者にとって興味深い全く新しいアイデアをもたらものと確信している。提案した研究は、望月博士の過去5年間と論理的継続性があるので妥当なものと判断すべきである。

望月博士はまた、生物学を規定する新たな原理を解明したいと考えている。例えば、博士は最近“steady state compatibility”と呼ぶ新たなアイデアを提唱した。このことで、発生中の細胞の多様性の起源が説明でき、複雑な遺伝子制御ネットワークの意味を解明するのに役立つであろう。これは極めて興味深い考えであり、さらに研究すべきである。この考えをウニに応用しているが、線虫 *C. elegans* にも応用することが良い方策であろう。この生物ではあらゆるタイプの情報（細胞の運命、遺伝学、ゲノム、遺伝子制御など）が揃っているからである。

総評

望月博士は若手の有望な数理生物学者である。博士は日本では良く知られているが、海外の科学者からの認識を高める必要があろう。日本の多くの実験生物学者と共同研究を行い、大きな貢献をこれまでに行い、現在でも行っている。このことは、博士の優れた論文発表の記録を見れば明らかである。また、純理論生物学者として、望月博士は新しいアイデアを発表し、実験生物学者から高い関心を集めている。博士の研究室の同僚は全て理論生物学者である。研究部門には空席があるので、研究室に実験生物学者を迎えることも検討に値する。

総合すると、望月博士は極めて良好な業績を示し、近い将来にも高い業績をあげるであろう。

研究業績（2002年より）：

1) Research articles in peer reviewed journals

1. Shoji, H., Mochizuki, A., Iwasa, Y., and Kondo, S. (2002). Directionality of stripes formed by anisotropic reaction-diffusion models. J. Theor. Biol. *214*, 549-561.
2. Honda, H., and Mochizuki, A. (2002). Formation and maintenance of distinctive cell patterns by co-expression of membrane-bound ligands and their receptors. Dev. Dyn. *223*, 180-192.
3. Mochizuki, A. (2002). Pattern formation of cone mosaic in zebrafish retina: A cell rearrangement model. J. Theor. Biol. *215*, 345-361.
4. Kurosawa, G., Mochizuki, A., and Iwasa, Y. (2002). Comparative study of circadian clock models, in search of processes promoting oscillation. J. Theor. Biol. *216*, 193-208.
5. Tohya, S., Mochizuki, A., and Iwasa, Y. (2003). Difference in the retinal cone mosaic pattern between zebrafish and medaka: cell-rearrangement model. J. Theor. Biol. *221*, 289-300.
6. Shoji, H., Mochizuki, A., Iwasa, Y., Hirata, M., Watanabe, T., Hioki, S., and Kondo, S. (2003). Origin of directionality in the fish stripe pattern. Dev. Dyn. *226*, 627-633.
7. Ryohji, T., Mochizuki, A., and Iwasa, Y. (2003). Possibility of tissue separation caused by cell adhesion. J. theor. Biol. *221*, 459-474.
8. Mochizuki, A. (2005). An analytical study of the number of steady states in gene regulatory networks. J. Ttheor. Biol. *236*, 291-310.
9. Feugier, F. G., Mochizuki, A., and Iwasa, Y. (2005). Self-organization of the vascular system in plant leaves: Inter-dependent dynamics of auxin flux and carrier proteins. J. Theor. Biol. *236*, 366-375.
10. Takigawa-Imamura, H., and Mochizuki, A. (2006). Transcriptional autoregulation by phosphorylated and non-phosphorylated KaiC in cyanobacterial circadian rhythms. J. Theor. Biol. *241*, 178-192.
11. Mochizuki, A., Yahara, K., Kobayashi, I., and Iwasa, Y. (2006). Genetic addiction: selfish gene's strategy for symbiosis in the genome. Genetics *172*, 1309-1323.
12. Fujita, H., and Mochizuki, A. (2006). Pattern formation by the positive feedback regulation between flow of diffusible signal molecule and localization of its carrier. J. Theor. Biol. *241*, 541-551.
13. Takigawa-Imamura, H., and Mochizuki, A. (2006). Predicting regulation of the phosphorylation cycle of KaiC clock protein using mathematical analysis. J. Biol. Rhythms *21*, 405-416.
14. Fujita, H., and Mochizuki, A. (2006). The origin of the diversity of leaf venation pattern. Dev. Dyn. *235*, 2710-2721.
15. Nakamura, T., Mine, N., Nakaguchi, E., Mochizuki, A., Yamamoto, M., Yashiro, K., Meno, C., and Hamada, H. (2006). Generation of robust left-right asymmetry in the mouse embryo requires a self-enhancement and lateral-inhibition system. Dev. Cell *11*, 495-504.
16. Ishihara, S., Otsuji, M., and Mochizuki, A. (2007). Transient and steady state of mass-conserved reaction-diffusion systems. Phys. Rev. *E* ***75***, 015203.

17. Otsuji, M., Ishihara, S., Co, C., Kaibuchi, K., Mochizuki, A., and Kuroda, K. (2007). A mass conserved reaction-diffusion system captures properties of cell polarity. PLoS Comput Biol. *3*, 1040-1054.
18. Sugimura, K., Shimono, K., Uemura, T., and Mochizuki, A. (2007). Self-organizing mechanism for development of space-filling neuronal dendrites. PLoS Comput Biol. *3*, 2143-2154.

2) Invited reviews, book chapters

1. Mochizuki, A. (2005). Patterns observed on surface of animals and mathematical modeling. Mathematics of Nonlinear-Nonequilibrium Phenomena 2 (Ed. Matsushita M.) p111-147. University of Tokyo Press.

野中茂紀
時空間制御研究室・准教授

Research Achievement in the Past

Dr. Nonaka has made invaluable contributions to developmental biology, and has published highly influential papers. His main research interest has been in left-right (L-R) symmetry breaking mechanism in vertebrate embryos. In his research, Dr. Nonaka found that the cilia in the node rotate uni-directionally and that this movement generates the leftward flow of the fluid in the node cavity (1998). These unexpected observations influenced not only people in the field of L-R patterning but also biologists in general. Dr. Nonaka went on to show that the flow (now called nodal flow) is indeed essential for L-R patterning, by developing a new culture system under which one can culture embryo with an artificial flow (2002). He further studied the origin of the L-R axis, and found that L-R asymmetry is generated *de novo* by utilizing pre-existing information (2005). His strength is that he addresses a question in a direct yet very unique way, by developing a new experimental system.

Dr. Nonaka moved to the NIBB only a year ago, so it is too early to evaluate his performance at the NIBB. He has had two responsibilities at the NIBB. One is to perform his own research projects while the other is to establish a new type of microscopy (SPIM) as a collaboration with EMBL. As for the first responsibility, he wished to understand how the nodal flow works and tested different hypotheses. Dr. Nonaka has obtained interesting results that lead him to propose a new model on nodal flow action. These are still preliminary data, but they should serve as a nice starting point for future development. As for the second responsibility, it took him a longer time than expected, but he patiently imported all necessary components of the SPIM microscope. All components have arrived by now, and his group has started assembling the microscope.

In terms of the number of papers published, Dr. Nonaka has not published many. However, each paper that he has published is of a high originality and is influential. Not surprisingly, his work is internationally well recognized. Overall, we find Dr. Nonaka's achievement during the last 5 years to be "very good."

Future Plans

Dr. Nonaka plans to study L-R symmetry breaking mechanism, in particular how the nodal flow works and the precise role of Ca2+ signaling. Recent preliminary data led him to propose a new model, which he wishes to test in the near future. Dr. Nonaka also wishes to study the cell fate of the node cells by developing a new imaging system. Given that his lab is well equipped and financed, these projects look feasible, and he will likely generate important results. His lab is relatively small (one post-doc, one student, one technician), but at this stage it may be a good idea to have this small size for the next 2-3 years so that the lab can focus on particular projects.

Overall Evaluation

From the past achievements, we consider that he has made seminal contributions to developmental biology. It appears that he is not a type of a person who competes with other scientists by performing things fast and efficiently. Instead, Dr. Nonaka has a unique capability to propose a unique idea and to develop new experimental systems. It may take some time, but there will be important achievements from his lab in the next 4-5 years.

（和訳）

過去の研究業績

野中博士は発生生物学に重要な貢献をしており、影響力の高い論文を発表している。博士の主な研究の関心は、脊椎動物の胚での左右(L-R)対称性が破れる機序の解明にあった。この研究の中で、ノードの中で鞭毛が一方向に回転しており、この運動がノード流に左向きの流れを作っていることを見いだした(1998)。この予想していなかった観察結果は、L-R パターン形成の分野の研究者だけでなく、生物学者全体にも影響を及ぼした。L-R はさらに、培養胚の中に人工的な流れを作る新たな培養系を開発して、（現在ではノード流と呼ばれている）この流れが、L-R パターン形成に実際に不可欠であることを示した(2002)。さらに L-R 軸の起源について調べ、L-R 非対称性は、既存の情報を使って *de novo* 生成されることを発見した(2005)。博士の長所は、新しい実験系を開発することで、疑問点を直接に極めてユニークな方法で解明していることである。

野中博士は 1 年前に基礎生物学研究所に着任したばかりであり、基礎生物学研究所での業績を評価するには早すぎる。博士は基礎生物学研究所で 2 つの任務を担っている。一つは、博士自身の研究プロジェクトを遂行することであり、もう一つは EMBL と共同で新しいタイプの顕微鏡(SPIM)を作ることである。第一の任務については、ノード流がどのように機能するかを理解し、様々な仮説を研究したいと博士は考えてきた。野中博士は興味深い結果を得、そのことで、ノード流の機能に関する新たなモデルを提唱するに至った。まだ予備的なデータであるが、今後の進展の良い出発点となるはずである。第二の任務に関しては、予想よりも時間を多く割く必要があったが、SPIM 顕微鏡に必要な全てのコンポーネントを辛抱強く輸入した。現在までに全てのコンポーネントが到着しており、彼のグループは顕微鏡の組み立てを開始した。

発表論文に関しては、野中博士は多くは発表していない。しかし、それぞれの論文は、オリジナリティーの高いものであり影響力の強いものである。驚くことではないが、博士の研究は国際的に良く知られている。総合して、野中博士の過去 5 年間の業績は“極めて良好”と当委員会は判断した。

将来計画

野中博士は L-R 対称性の破れ、とりわけ、ノード流がどのように作用するのか、Ca^{2+}イオンのシグナル伝達の詳細な役割について研究することを予定している。最近得られた予備的データから、新しいモデルを提唱し、博士は近い将来このことを検証したいとしている。野中博士はまた、新しいイメージングシステムを開発して、ノード細胞の運命

について調べたいとも考えている。研究室の設備が整っており、研究費が十分にあることを考えれば、これらのプロジェクトは妥当なものであると判断され、重要な成果をあげるであろう。博士の研究室は比較的小規模（ポストドク 1 名、研究補助員 1 名）であるが、現時点では、この小さな規模を今後 2–3 年維持して、特定のプロジェクトに注力することが良い考えであろう。

総評

過去の業績から、博士は発生生物学に先導的な寄与をしてきたとわれわれは判断した。博士や物事を迅速かつ効率的に行うことで他の研究者と競い合うようなタイプの人物ではないように思われる。そのかわり、野中博士にはユニークなアイデアを提唱し、新たな実験系を開発するユニークな能力があるように思われる。時間がかかるかも知れないが、今後 4–5 年間に研究室から重要な業績が出てくるものと考えられる。

研究業績（2006 年より）：

1) Research articles in peer reviewed journals

1. Marshall, W. F., and Nonaka, S. (2006). Cilia: tuning in to the cell's antenna. Curr. Biol. *16*, R604-614.

３）生殖・環境生物学領域

Peter Koopman
(Professor, Institute for Molecular Bioscience, University of Queensland, Australia)

星　元紀
（放送大学・教授）

佐藤英明
（東北大学大学院農学研究科・教授）

平成 19 年 11 月 27 日 ～ 28 日

長濱嘉孝
生殖生物学研究部門・教授

Prof Nagahama is the Deputy Director of NIBB. His research interests are in reproductive biology and the endocrine control of reproduction in vertebrates and invertebrates. He is an internationally known and respected leader in the field of sexual development. His research centres around three major models species: medaka, Tilapia, and a sex-changing species, *Trimma okinawae*.

Professor Nagahama's laboratory made a major international breakthrough in identifying DMY as the sex-determining gene in medaka. Loss of function of DMY causes male to female sex reversal, as he famously showed in a prominent paper in *Nature* in 2002. Recently, he has augmented these studies by showing that gain of function of DMY causes female to male sex reversal, as published in the prominent journal *PNAS* in 2007. This work was a breakthrough on many levels. Firstly, it was a triumph of positional cloning. Professor Nagahama began by identifying sex reversed mutant strains of fish, and genetically narrowed down the responsible region and genetic lesion, thereby identifying the sex-determining gene as DMY. Moreover, DMY is only the second sex-determining gene identified in the animal kingdom, after SRY. Needless to say, this work has provided a paradigm shift in the field of sex determination, and is being actively followed up, not only in Prof Nagahama's laboratory, but also in many other laboratories around the world.

More recently, Professor Nagahama has been examining the fascinating phenomenon of social sex reversal in fish. In colonies of the gobiid fish *Trimma okinawae*, the largest fish in any group will be male and the others female. If the male is removed, the largest remaining fish will reverse her sex to become male. This model provides unique and important opportunities to study mechanisms of sex determination and sex reversal. Because sex change appears to be triggered by visual cues processed by the brain in these fish, Professor Nagahama is able to examine hormonal changes stimulated by the brain in this phenomenon. Once again, we would expect the results of these studies to be highly significant at an international level, and to be publishable in major interdisciplinary journals.

Professor Nagahama is vice president of the Zoological Society of Japan. He has a long list of editorial responsibilities for national and international journals. He has a large number of committee responsibilities at a national level in Japan. He has presented a total of 36 invited talks and international conferences in the last 10 years, including presentations in Spain, Norway, the United States, Portugal, Singapore, Taiwan, Korea, China, India, the UK, Italy and Thailand. He has published 133 research articles, including papers in *Nature*, *PNAS*, *MCB*, and *Molecular Endocrinology*. In addition, he has published twelve reviews and book chapters.

Professor Nagahama is a very interactive scientist who collaborates broadly at both the national

and international levels. In Japan, he collaborates with scientists at Hokkaido University, and others in the Ryukyu Islands, in addition to collaborating with Prof Morohashi and Dr Tanaka at the NIBB. Internationally, he collaborates with scientists in Germany, the US, and Australia. He maintains collaborative links with many former postdocs who have gone to work in other countries.

Professor Nagahama is actively involved in teaching, training and mentorship. He is involved in teaching and the Graduate University for Advanced Studies (Sokendai), and hosts a number of international trainees in his laboratory. His lab currently has seven postdoctoral fellows and two associates; he has been able to attract postdocs from England, France, Spain, the US and Canada. He is a member of the selection committee for the Japan Students Science Award, the oldest national science award in Japan, which each year considers over 10,000 applications. Since 2007, he has acted as chairman of the selection committee for this award.

In summary, Professor Nagahama has made extremely strong contributions to research, collaboration and teaching in his distinguished career. He is exceptionally energetic, enthusiastic, productive and interactive, and is a prominent figure internationally. The committee notes that he was awarded the Howard A. Berne lecture award from the Society for Integrative and Comparative Biology, USA, in 2004, and the Richard E. Peter lecture award from the International Symposium on Fish Physiology, Canada, in 2007. It is extremely pleasing to see Professor Nagahama's achievements recognized in this way, and Professor Nagahama receives extremely strong support from the review committee.

（和訳）

長濱教授は基礎生物学研究所の副所長である。教授の関心は生殖生物学、ならびに脊椎動物や無脊椎動物の生殖の内分泌コントロールである。教授は性形成の分野で国際的に知られ尊敬されているリーダーである。教授の研究は、メダカ、ティラピア、および性転換を行うオキナワハゼ*Trimma okinawae*のモデル動物を中心に行っている。

長濱教授の部門では、メダカの性決定遺伝子としてDMY遺伝子を発見したことで、大きな国際的ブレークスルーとなった。DMYの機能が失われると、雄が雌に転換する。これを、彼は著明な論文誌*Nature*に2002年に発表した。最近、教授は、雌にDMYの機能を獲得させると、雄に転換することを示して、これらの研究結果を補強した。これについては有力論文誌*PNAS*に2007年に掲載された。この研究は多くのレベルで突破口を開いたものであった。第一に、この研究はポジショナルクローニングの勝利を示すものであった。長濱教授は、魚類の性転換変異株を見つけ始め、原因となる領域を遺伝学的に狭めて、その結果、性決定遺伝子がDMYであると特定した。さらに、DMYはSRYに続き、動物界で同定された2個目の決定遺伝子である。改めて言うまでもなく、この研究は、性決定の研究領域にパラダイムシフトをもたらし、長濱研究室だけでなく、世界中の多くの研究室が、活発にこの研究を続けている。

最近になって、長濱教授は魚類の社会的性転換という魅力的な現象について調べている。オキナワベニハゼ*Trimma okinawae*のコロニーでは、どのグループでも最大の大きさの魚が雄になり、他は雌になる。雄をコロニーから取り除くと、残ったコロニーの中で最大サイズの魚が性転換して雄になる。このモデルは、性決定と性転換の機序を研究するユニークで重要な機会をもたらすものである。性転換は、これらの魚の脳内で処理される視覚的キューが引き金になっているように思われるので、長濱教授はこの現象で脳により刺激を受けたホルモン変化を調べることが可能である。この研究でも、研究結果が国際的レベルで極めて有意義なもので、著明な総合論文誌に掲載されるものとわれわれは期待している。
長濱教授は日本動物学会の副会長である。教授は国内外の多数の論文誌の編集責任者をつとめている。日本国内の多数の団体の責任者である。教授は、この10年間に、スペイン、ノルウェイ、米国、ポルトガル、シンガポール、台湾、韓国、中国、インド、英国、イタリア、タイでの発表を含む合計36回の招待講演と国際学会への招待を受けている。133件の論文を発表し、これには、*Nature*、*PNAS*、*MCB*、*Molecular Endocrinolog*への掲載を含む。さらに、教授は12件の総説と単行本の章を執筆した。

長濱教授は極めて広い交流を持つ科学者で、国内外で広く共同研究を行っている。日本では、北海道大学や琉球列島を対象にする研究者と共同研究を行っており、さらに研究所内では諸橋教授や田中博士と共同研究している。国際的には、ドイツ、米国、オーストラリアの研究者と共同研究している。ポストドクとして教授のもとで研究し、その後外国で研究している研究者との共同研究のつながりも保っている。

長濱教授は後進の教育、トレーニング、指導も積極的に行っている。総合研究大学院大学（総研大）の大学院教育を行い、多くの海外からの研究生を研究室に迎えている。教授の研究室には、ポストドクフェローが7名、助教が2名いる。教授のもとに英国、フランス、スペイン、米国、カナダからのポストドクが研究を希望してきた。教授は日本学生科学賞の選考委員である。日本学生科学賞は日本でもっと古い国内科学賞であり、毎年1万件以上の応募がある。2007年から、教授は選考委員長をつとめている。

以上まとめると、長濱教授は、教授の傑出した経歴の中で、研究や共同研究、教育に極めて大きく貢献してきた。教授は極めて精力的で、熱意があり、生産性が高く、他の研究者との交流を深めており、国際的な名声が高い。Society for Integrative and Comparative Biology（米国）から2004年にHoward A. Berneレクチャー賞を受賞し、2007年にはInternational Symposium on Fish Physiology（カナダ）からRichard E. Peterレクチャー賞を受けていることを、当委員会は指摘したい。長濱教授の業績がこのように認められることは極めて喜ぶべきことであり、長濱教授については、この外部評価委員会から極めて高い評価を受けた。

研究業績：

1) Research articles in peer reviewed journals

1. Chang, X.T., Kobayashi, T., Kajiura, H., Nakamura, M., and Nagahama, Y. (1997). Isolation and characterization of the cDNA encoding the tilapia (*Oreochromis niloticus*) cytochrome P450 aromatase (P450arom): Changes in P450arom mRNA, protein and enzyme activity in ovarian follicles during oogenesis. J. Mol. Endocrinol. *18*, 57-66.
2. Mita, M., Yasumasu, I., Nagahama, Y., and Saneyoshi, M. (1997). Change in the levels of adenine-related compounds in starfish ovarian follicle cells following treatment with gonad-stimulating substance. Develop. Growth Differ. *38*, 413-418.
3. Tokumoto, T., Yamashita, M., Tokumoto, M., Katsu, Y. Kajiura, H., and Nagahama, Y. (1997). Initiation of cyclin B degradation by the 26S proteasome upon egg activation. J. Cell Biol. *22*, 1313-1322.
4. Iwao, Y., Yasumitsu, K., Narihira, M., Jiang, J.Q., and Nagahama, Y. (1997). Changes in microtubule structures during the first cell cycle of physiologically polyspermic newt eggs. Mol. Reprod. Develop. *47*, 210-221.
5. Ge, W., Miura, T., Kobayashi, H., Peter, R.E., and Nagahama, Y. (1997). Cloning of cDNA for goldfish activin βB subunit, and the expression of its mRNA in gonadal and non-gonadal tissues. J. Mol. Endocrinol. *19*, 37-45.
6. Ge, W., Tanaka, M., Yoshikuni, M., Eto, Y., and Nagahama, Y. (1997). Cloning and characterization of goldfish activin type IIB receptor. J. Mol. Endocrinol. *19*, 47-57.
7. Haraguchi, S., Naito, K., Azuma, S., Sato, E., Yamashita, M., and Nagahama, Y. (1997). Effects of phosphate on *in vitro* 2-cell block of AKR/N mouse embryos based on changes in cdc2 kinase activity and phosphorylation states. Biol. Reprod. *55*, 598-603.
8. Matsuyama, M., Morita, S., Hamaji, N., Kashiwagi, M., and Nagahama, Y. (1997). Diurnal spermatogenesis and spawning in the secondary male of protogynous wrasses, *Pseudolabrus japonicus* (Teleostie, labridae). Zool. Sci. *14*, 1001-1008.
9. Katsu, Y., Yamashita, M., and Nagahama, Y. (1997). Isolation and characterization of goldfish Y box protein, a germ-cell-specific RNA binding protein. Eur. J. Biochem. *249*, 854-861.
10. Oba, Y., Yoshikuni, M., Tanaka, M., Mita, M., and Nagahama, Y. (1997). Inhibitory guanine-nucleotide-binding-regulatory protein α subunits in medaka (*Oryzias latipes*) oocytes: cDNA cloning and decreased expression of proteins during oocyte maturation. Eur. J. Biochem. *249*, 846-853.
11. Miura, T., Kudo, N., Miura, C., Yamauchi, K., and Nagahama, Y. (1998). Two testicular cDNA clones suppressed by gonadotropin stimulation exhibit ZP2- and ZP3-like structures in Japanese eel. Mol. Reprod. Develop. *51*, 235-242.
12. Kobayashi, T., Nakamura, M., Kajiura-Kobayashi, H., Young, G., and Nagahama, Y. (1998). Immunolocalization of steroidogenic enzymes (P450scc, P450c17, P450arom, and 3β-HSD) in immature and mature testes of rainbow trout (*Oncorhynchus mykiss*). Cell Tissue Res. *292*, 573-577.
13. Morrey, C.E., Nakamura, M., Kobayashi, T., Grau, E.G., and Nagahama, Y. (1998). P450scc-like immunocytochemistry throughout gonadal restructuring in the protogynous

hermaphrodite *Thalassoma duperrey*. Int. J. Develop. Biol. *42*, 811-816.
14. Mita, M., Yasumasu, I., Saneyoshi, M., Yoshikuni, M., and Nagahama, Y. (1998). Production of the oocyte maturation-inducing substance of starfish by heat treatment of S-adenosylmethionine. Zool. Sci. *15*, 117-122.
15. Parhar, I.S., Nagahama, Y., Grau, E.G., and Ross, R.M. (1998). Immunocytochemical and ultrastructural identification of pituitary cell types in the protogynous *Thalassoma duperrey* during adult sexual ontogeny. Zool. Sci. *15*, 263-276.
16. Mita, M., Yoshikuni, M., and Nagahama, Y. (1998). Ecto-ATP diphosphohydrolase (apyrase) in ovarian follicle cells of starfish *Asterina pectinifera*. Comp. Biochem. Physiol. Part B, *119*, 577-583.
17. Parhar, I.S., Soga, T., Ishikawa, Y., Nagahama, Y., and Sakuma, Y. (1998). Neurons synthesizing gonadotropin-releasing hormone mRNA subtypes have multiple developmental origins in the medaka. J. Comp. Neurol. *401*, 217-226.
18. Horiguchi, R., Tokumoto, M., Yoshiura, Y., Aida, K., Nagahama, Y., and Tokumoto, T. (1998). Molecular cloning of cDNA encoding a 20S proteasome α2 subunit from goldfish (*Carassius auratus*) and its expression analysis. Zool. Sci. *15*, 773-777.
19. Kobayashi, T., Kajiura-Kobayashi, H., and Nagahama, Y. (1998). A novel stage-specific antigen is expressed only in early stages of spermatogenesis in Japanese eel, *Anguilla japonica* testis. Mol. Reprod. Develop. *51*, 355-361.
20. Jiang, J.Q., Young, G., Kobayashi, T., and Nagahama, Y. (1998). Eel (*Anguilla japonica*) testis 11β-hydroxylase gene is expressed in interrenal tissue and its product lacks aldosterone synthesizing activity. Mol. Cell. Endocrinol. *146*, 207-211.
21. Watanabe, M., Tanaka, M., Kobayashi, D., Yoshiura, Y., Oba, Y., and Nagahama, Y. (1999). Medaka (*Oryzias latipes*) FTZ-F1 potentially binds to promoter regions of P-450 aromatase: cDNA cloning and functional characterization. Mol. Cell. Endocrinol. *149*, 221-228.
22. Todo, T., Ikeuchi, T., Kobayashi, T., and Nagahama, Y. (1999). Fish androgen receptor: cDNA cloning, steroid activation of transcription in transfected mammalian cells, and tissue mRNA levels. Biochem. Biophys. Res. Comm. *254*, 378-383.
23. Guan, G., Tanaka, M., Todo, T., Young, G., Yoshikuni, M., and Nagahama, Y. (1999). Cloning and expression of two carbonyl reductase-like 20β-hydroxysteroid dehydrogenase cDNAs in ovarian follicles of rainbow trout (*Oncorhynchus mykiss*). Biochem. Biophys. Res. Comm. *255*, 123-128.
24. Tokumoto, T., Tokumoto, M., Seto, K., Horiguchi, R., Nagahama, Y., Yamada, S., Ishikawa, K., and Lohka, M.J. (1999). Disappearance of a novel protein component of the 26S proteasome during *Xenopus* oocyte maturation. Exp. Cell Res. *247*, 313-319.
25. Katsu, Y., Carnall, N., Nagahama, Y., and Standart, N. (1999). Phosphorylation of p82 clam CPEB by MAP kinase and cdc2 kinase. Develop. Biol. *209*, 186-199.
26. Kitano, T., Takamura, K., Kobayashi, T., Nagahama, Y., and Abe, S.-I. (1999). Suppression of P450 aromatase (P450arom) gene expression in sex-reversed males produced by rearing genetically female larvae at high temperature during a period of sex determination in Japanese flounder (*Paralichthys olivaceus*). J. Mol. Endocrinol. *23*, 167-176.
27. Mita, M., Yasumasu, I., Yoshikuni, M., and Nagahama, Y. (1999). 1-Methyladenine

production from ATP by starfish ovarian follicles. Biochem. Biophys. Acta *1428*, 13-20.
28. Mita, M., Saneyoshi, M., Yoshikuni, M., and Nagahama, Y. (1999). A methyl donor for 1-methyladenine biosynthesis in starfish ovarian follicle cells. Mol. Reprod. Develop. *54*, 63-68.
29. Katsu, Y., Yamashita, M., and Nagahama, Y. (1999). Translational regulation of cyclin B mRNA during 17α,20β-dihydroxy-4-pregnen-3-one (maturation-inducing hormone)-induced oocyte maturation in goldfish, *Carassius auratus*. Mol. Cell. Endocrinol. *158*, 79-85.
30. Ikeuchi, T., Todo, T., Kobayashi, T., and Nagahama, Y. (1999). cDNA cloning of a novel androgen receptor subtype. J. Biol. Chem. *274*, 25205-25209.
31. Chang, X.T., Kobayashi, T., Todo, T., Ikeuchi, T., Yoshiura, Y., Kajiura-Kobayashi, H., Morrey, C., and Nagahama, Y. (1999). Molecular cloning of estrogen receptors α and β in the ovary of a teleost fish, the tilapia (*Oreochromis niloticus*). Zool. Sci. *16*, 653-658.
32. Tokumoto, M., Nagahama, Y., and Tokumoto, T. (1999). Molecular cloning of cDNA encoding a cyclin-sensitive ubiquitin carrier protein (E2-C) from goldfish (*Carassius auratus*) and expression analysis of the cloned gene. FEBS Letters *458*, 375-377.
33. Oba, Y., Hirai, T., Yoshiura, Y., Yoshikuni, M., Kawauchi, H., and Nagahama, Y. (1999). Cloning, functional characterization and expression of a gonadotropin receptor cDNA in the ovary and testis of amago salmon (*Oncorhynchus rhodurus*). Biochem. Biophys. Res. Comm. *263*, 584-590.
34. Oba, Y., Hirai, T, Yoshiura, Y., Yoshikuni, M., Kawauchi, H., and Nagahama, Y. (1999). The duality of fish gonadotropin receptors: cloning and functional characterization of a second gonadotropin receptor cDNA expressed in the ovary and testis of amago salmon (*Oncorhynchus rhodurus*). Biochem. Biophys. Res. Comm. *265*, 366-371.
35. Tokumoto, M., Horiuchi, R., Nagahama, Y., and Tokumoto, T. (1999). Identification of the *Xenopus* 20S proteasome α4 subunit which is modified in the meiotic cell cycle. Gene. *239*, 301-308.
36. Hondo, E., Kobayashi, T., Ishiguro, N., Kurohmaru, M., Kitamura, N., Yamada, J., and Nagahama, Y. (1999). Prolactin induces protamine 2 mRNA expression in rat testis. J. Reprod. Dev. *45*, 205-212.
37. Tokumoto, M., Horiuchi, R., Nagahama, Y., Ishikawa, K., and Tokumoto, T. (2000). Two proteins, a goldfish 20S proteasome subunit and the protein interacting with 26S proteasome, change in the meiotic cell cycle. Eur. J. Biochem. *267*, 97-103.
38. Tokumoto, M., Yamaguchi, A., Nagahama, Y., and Tokumoto, T. (2000). Identification of the goldfish 20S proteasome β6 subunit bound to nuclear matrix. FEBS Letters *472*, 62-66.
39. Todo, T., Ikeuchi, T., Kobayashi, T., Kajiura-Kobayashi, H., Suzuki, K., Yoshikuni, M., and Nagahama, Y. (2000). Characterization of a nuclear 17α,20β-dihydroxy-4-pregnen-3-one (a spermiation-inducing steroid in fish) receptor cDNA from the testis of a teleost, Japanese eel (*Anguilla japonica*). FEBS Letters *465*, 12-17.
40. Guan, G., Todo, T., Tanaka, M., Young, G., and Nagahama, Y. (2000). Isoleucine-15 of rainbow trout carbonyl reductase-like 20β-hydroxysteroid dehydrogenase is critical for coenzyme (NADPH) binding. Proc. Natl. Acad. Sci. USA *97*, 3079-3083.
41. Kitano, T., Takamune, K., Nagahama, Y., and Abe, S. (2000). Aromatase inhibitor and

17α-methyltestosterone causes sex-reversal from genetical females to phenotypic males and suppression of P450 aromatase gene expression in Japanese flounder (*Paralichthys olivaceus*). Mol. Reprod. Develop. *56*, 1-5.

42. Shibata, Y., Iwamatsu, T., Oba, Y., Kobayashi, D., Tanaka, M., Nagahama, Y., Suzuki, N., and Yoshikuni, M. (2000). Identification and cDNA cloning of alveolin, an extracellular metalloproteinase responsible for chorion hardening of medaka (*Oryzias latipes*) eggs upon fertilization. J. Biol. Chem. *275*, 8349-8354.
43. Okida, N., Tokumoto, M., Tokumoto, T., Nagahama, Y., Ohe, Y., Miyamoto, K., and Ishikawa, K. (2000). Cloning of cDNA encoding thimet oligopeptidase from *Xenopus* oocytes and regulation of the mRNA during oogenesis. Zool. Sci. *17*, 431-436.
44. Guan, G., Kobayashi, T., and Nagahama, Y. (2000). Sexually dimorphic expression of DM (Doublesex/Mab-3)-domain genes during gonadal differentiation in tilapia. Biochem. Biophys. Res. Comm. *272*, 662-666.
45. Shinomiya, A., Tanaka, M., Kobayashi, T., Nagahama, Y., and Hamaguchi, S. (2000). The vasa-like gene, olvas, identifies migration path of primordial germ cells during embryonic formation stage in the medaka, *Oryzias latipes*. Develop. Growth Differ. *42*, 317-326.
46. Nakayama, Y., Yamamoto, T., Oba, Y., and Nagahama, Y. (2000). Molecular cloning, functional characterization, and gene expression of a follicle-stimulating hormone receptor in the testis of newt *Cynops pyrrhogaster*. Biochem. Biophys. Res. Comm. *275*, 121-128.
47. Tokumoto, M., Nagahama, Y., and Tokumoto, T. (2000). Molecular cloning of cDNA encoding a ubiquitin-activating enzyme (E1) from goldfish (*Carassius auratus*) and expression analysis of the cloned gene. Bioch. Biophys. Acta *1492*, 259-263.
48. Kajiura-Kobayashi, H., Yoshida, N., Sagata, N., Yamashita, M., and Nagahama, Y. (2000). The Mos/MAPK pathway is involved in metaphase II arrest as a cytostatic factor but is neither necessary nor sufficient for initiating oocyte maturation in goldfish. Dev. Genes Evol. *210*, 416-425.
49. Oba, Y., Hirai, T., Yoshiura, Y., Kobayashi, T., and Nagahama, Y. (2000). Cloning, functional characterization, and expression of thyrotropin receptors in the thyroid of amago salmon (*Oncorhynchus rhodurus*). Biochem. Biophys. Res. Comm. *276*, 258-263.
50. Kobayashi, T., Kajiura-Kobayashi, H., and Nagahama, Y. (2000). Differential expression of *vasa* homologue gene in the germ cells during oogenesis and spermatogenesis of a teleost fish, tilapia, *Oreochromis niloticus*. Mech. Develop. *99*, 139-142.
51. Tanaka, M., Kinoshita, M., and Nagahama, Y. (2001). Establishment of medaka (*Oryzias latipes*) transgenic lines with the expression of GFP fluorescence exclusively in germline cells: a useful model to monitor germline cells in a live vertebrate. Proc. Natl. Acad. Sci. USA *98*, 2544-2549.
52. Nakahata, S., Katsu, Y., Mita, K., Inoue, K., Nagahama, Y., and Yamashita, M. (2001). Biochemical identification of *Xenopus* Pumilio as a sequence-specific cyclin B1 mRNA-binding protein that physiologically interacts with a Nanos homolog, Xcat-2, and a cytoplasmic polyadenylation element-binding protein. J. Biol. Chem. *276*, 20945-20953.
53. Yamaguchi, A., Yamashita, M., Yoshikuni, M., and Nagahama, Y. (2001). Identification and molecular cloning of germinal vesicle B3 in goldfish (*Carassius auratus*) oocytes. Eur. J. Biochem. *268*, 932-939.

54. Matsuyama, M., Sasaki, A., Nakagawa, K., Kobayashi, T., Nagahama, Y., and Chuda, H. (2001). Maturation-inducing hormone of the tiger puffer, *Takifugu rubripes* (Tetraodontidae, Teleostei): biosynthesis of steroids by the ovaries and the relative effectiveness of steroid metabolites for germinal vesicle breakdown *in vitro*. Zool. Sci. *18*, 225-234.
55. Liu, S.J., Govoroun, M., D'Cotta, H., Ricordel, M.J., Lareyre, J.J., McMeel, O.M., Smith, T., Nagahama, Y., and Guiguen, Y. (2001). Expression of cytochrome $P450_{11\beta}$ (11β-hydroxylase) genes during gonadal sex differentiation and spermatogenesis of rainbow trout, *Oncorhynchus mykiss*. J. Steroid Biochem. Mol. Biol. *75*, 291-298.
56. Nakahata, S., Mita, K., Katsu, Y., Nagahama, Y., and Yamashita, M. (2001). Immunological detection and characterization of poly(A) polymerase, poly(A)-binding protein and cytoplasmic polyadenylation element-binding protein in goldfish and *Xenopus* oocytes. Zool. Sci. *18*, 337-343.
57. Matsuda, M., Kawato, N., Asakawa, S., Shimizu, N., Nagahama, Y., Hamaguchi, S., Sakaizumi, M., and Hori, H. (2001). Construction of a BAC library derived from the inbred Hd-rR strains of the teleost fish, *Oryzias latipes*. Gene Genetic Systems. *76*, 61-63.
58. Ikeuchi, T., Todo, T., Kobayashi, T., and Nagahama, Y. (2001). Two subtypes of androgen and progestogen receptors in fish testes. Comp. Physiol. Biochem. Part B. *129*, 449-455.
59. Imahara, J., Tokumoto, M., Nagahama, Y., Ishikawa, K., and Tokumoto, T. (2001). Reconstitution of sperm nuclei of zebrafish, *Danio rerio*, in *Xenopus* egg extracts. Marine Biotechnology *3*, 53-57.
60. Yamaguchi, A., and Nagahama, Y. (2001). Somatic lamins in germinal vesicles of goldfish vitellogenic oocytes. Cell Struc. Func. *26*, 693-703.
61. Kobayashi, T., Kajiura-Kobayashi, H., and Nagahama, Y. (2002). Two isoforms of *vasa* homologs in a teleost fish: their differential expression during germ cell differentiation. Mech. Develop. *111*, 167-171.
62. Tokumoto, M., Nagahama, Y., and Tokumoto, T. (2002). Molecular cloning of cDNA encoding a polypeptide chain elongation factor 1α from goldfish (*Carassius auratus*). DNA Sequence *12*, 419-424.
63. Tokumoto, M., Nagahama, Y., and Tokumoto, T. (2002). A major substrate for MPF: cDNA cloning and expression of polypeptide chain elongation factor 1α from goldfish (*Carassius auratus*). DNA Sequence *13*, 27-31.
64. Morrey, C.E., Nagahama, Y., and Grau, E. G. (2002). Terminal phase males stimulate ovarian function and inhibit sex change in the protogynous wrasse *Thalassoma duperrey*. Zool. Sci. *19*, 103-109.
65. Ikeuchi, T., Todo, T., Kobayashi, T., and Nagahama, Y. (2002). A novel progestogen receptor subtype in the Japanese eel, *Anguilla japonica*. FEBS Letters *510*, 77-82.
66. Tanaka, M., Nakajin, S., Kobayashi, D., Fukada, S., Guan, G., Todo, T., Senthilkumaran, B., and Nagahama, Y. (2002). Teleost ovarian carbonyl reductase-like 20β-hydroxysteroid dehydrogenase: Potential role in the production of maturation-inducing hormone in final maturation of oocytes. Biol. Reprod. *66*, 1498-1504.
67. Yokoi, H., Kobayashi, T., Tanaka, M., Nagahama, Y., Wakamatsu, Y., Takeda, H., Araki, K., Morohashi, K., and Ozato, K. (2002). *Sox9* in a teleost fish, medaka (*Oryzias latipes*): Evidence for diversified function of *Sox9* in gonad differentiation. Mol. Reprod. Develop.

63, 5-16.

68. Rahman, M.A., Ohta, K., Yoshikuni, M., Nagahama, Y., Chuda, H., and Matsuyama, M. (2002). Characterization of ovarian membrane receptor for 17α,20β-Dihydroxy-4-pregnen-3-one, a maturation-inducing hormone in yellowtail, *Serila qunqueradiata*. Gen. Comp. Endocrinol. *127*, 71-79.
69. Wang, D.S., Kobayashi, T., Senthilkumaran, B., Sakai, F., Sudhakumari, C.C., Suzuki, T., Yoshikuni, M., Matsuda, M., Morohashi, K., and Nagahama, Y. (2002). Molecular cloning of *DAX1* and *SHP* cDNAs and their expression patterns in the Nile tilapia, *Oreochromis niloticus*. Biochem. Biophys. Res. Comm. *297*, 632-640.
70. Tateno, H., Shibata, Y., Nagahama, Y., Hirai, T., Saneyoshi, M., Ogawa, T., Muramoto, K., and Kamiya, H. (2002). Tissue specific expression of rhamnose-binding lectins in the steelhead trout (*Oncorhynchus mykiss*). Biosci. Biotechnol. Biochim. *66*, 1427-1430.
71. Huang, Y.S., Yueh, W.S., Huang, J.D., Du, J.L., Sun, L.T., Nagahama, Y., and Chang, C.F. (2002). Cloning and expression of estrogen receptors in the protandrous black porgy (*Acanthopagrus schlegeli*): Implications of sex change mechanism. Mar. Biotechnol. *4*, 236-246.
72. Matsuda, M., Nagahama, Y., Shinomiya, A., Sato, T., Matsuda, C., Kobayashi, T., Morrey, C.E., Shibata, N., Asakawa, S., Shimizu, N., Hori, H., Hamaguchi, S., and Sakaizumi, M. (2002). *DMY* is a Y-specific DM-domain gene required for male development in the medaka fish. Nature *417*, 559-563.
73. Senthilkumaran, B., Sudhakumari, C.C., Chang, X.T., Kobayashi, T., Oba, Y., Guan, G., Yoshiura, Y., Yoshikuni, M., and Nagahama, Y. (2002). Ovarian carbonyl reductase-like 20β-hydroxysteroid dehydrogenase shows distinct surge in messenger RNA expression during natural and gonadotropin-induced meiotic maturation in Nile tilapia. Biol. Reprod. *67*, 1080-1086.
74. Hirai, T., Oba, Y., and Nagahama, Y. (2002). Fish gonadotropin receptors: molecular characterization and expression during gametogenesis. Fish. Sci. *68*, 675-678.
75. Kusakabe, M., Kobayashi, T., Todo, T., Lokman, P.M., Nagahama, Y., and Young, G. (2002). Molecular cloning and expression during spermatogenesis of a cDNA encoding testicular 11b-hydroxylase (P45011b) in rainbow trout (*Oncorhynchus mykiss*). Mol. Reprod. Dev. *62*, 456-469.
76. Yoshiura, Y., Senthilkumaran, B., Watanabe, M., Ova, Y., Kobayashi, T., and Nagahama, Y. (2003). Synergistic expression of Ad4BP/SF-1 and cytochrome P-450 aromatase (Ovarian type) in the ovary of Nile tilapia, *Oreochromis niloticus*, during vitellogenesis suggests transcriptional interaction. Biol. Reprod. *68*, 1545-1553.
77. Nakahata, S., Kotani, T., Mita, K., Kawasaki, T., Katsu, Y., Nagahama, Y., and Yamashita, M. (2003). Involvement of *Xenopus* Pumilio in the translational regulation that is specific to cyclin B1 mRNA during oocyte maturation. Mech. Develop. *120*, 865-880.
78. Matsuda, M., Sato, T., Toyazaki, Y., Nagahama, Y., Hamaguchi, S., and Sakaizumi, M. (2003). *Oryzias curvinotus* has D*MY*, a gene that is required for male development in the medaka, *O. latipes*. Zool. Sci. *20*, 159-161.
79. Jiang, J.Q., Wang, D.S., Senthilkumaran, B., Kobayashi, T., Kobayashi, H.K., Yamaguchi, A., Ge, W., Young, G., and Nagahama, Y. (2003). Isolation, characterization and

expression of 11β-hydroxysteroid dehydrogenase type 2 cDNAs from the testes of Japanese eel (*Anguilla japonica*) and Nile tilapia (*Oreochromis niloticus*). J. Mol. Endocrinol. *31*, 305-315.

80. Ohmuro-Matsuyama, Y., Matsuda, M., Kobayashi, T., Ikeuchi, T., and Nagahama, Y. (2003). Expression of *DMY* and *DMRT1* in various tissues of the medaka (*Oryzias latipes*). Zool. Sci. *20*, 1395-1398.
81. He, C.L., Du, J.L., Huang, Y.S., Lee, Y.H., Nagahama, Y., and Chang, C.F. (2003). Differential expression of androgen receptor and estrogen receptor in gonad in relation to the sex change in protandrous black porgy, *Acanthopagrus schlegeli*. Biol. Reprod. *69*, 455-461.
82. Kobayashi, T., Kajiura-Kobayashi, H., and Nagahama Y. (2003). Induction of XY sex reversal by estrogen involves altered gene expression in a teleost, tilapia. Cytogenet. Genome Res. *101*, 289-294.
83. Kobayashi, Y., Kobayashi, T., Nakamura, M., Sunobe T., Morrey, C.E., Suzuki, N., and Nagahama, Y. (2004). Characterization of two types of cytochrome P450 aromatase in serial-sex changing gobiid fish, *Trimma okinawae*. Zool. Sci. *21*, 417-425.
84. Suzuki, A., Tanaka, M., Nagahama, Y., and Shibata, N. (2004). Expression of aromatase mRNA and effects of aromatase inhibitor during ovarian development in the medaka, *Oryzias latipes*. J. Exp. Zool. *301A*, 266-273.
85. Wang, D.S., Zhou, L.Y., Kobayashi, T., and Nagahama, Y. (2004). Molecular cloning and gene expression of Foxl2 in the Nile tilapia, *Oreochromis niloticus*. Biochem. Biophys. Res. Comm. *320*, 83-89.
86. Mita, M., Oka, H., Thorndyke, M.C., Shibata, Y., Yoshikuni, M., and Nagahama, Y. (2004). Inhibitory effect of a SALMFamide neuropeptide on secretion of gonad-stimulating substance from radial nerves in the starfish *Asterina pectinifera*. Zool. Sci. *21*, 299-303.
87. Tokumoto, T., Tokumoto, M., Horiguchi, R., Ishikawa, K., and Nagahama, Y. (2004). Diethylstilbestrol induces fish oocyte maturation. Proc. Natl. Acad. Sci. USA *101*, 3686-3690.
88. Horiguchi, R., Yoshikuni, M., Tokumoto, M., Nagahama, Y., and Tokumoto, T. (2004). Identification of a protein kinase which phosphorylates a subunit of the 26S proteasome and changes in its activity during meiotic cell cycle in goldfish oocytes. Cell. Signal. *17*, 205-215.
89. Kobayashi-Kajiura, H., Kobayashi, T., and Nagahama, Y. (2004). The cloning of cyclin B3 and its gene expression during hormonally induced spermatogenesis in the teleost, *Anguilla japonica*. Biochem. Biophys. Res. Commun. *323*, 288-292.
90. Kobayashi, T., Kobayashi, H., and Nagahama, Y. (2004). Two DM domain genes, *DMY* and *DMRT1*, involved in testicular differentiation and development in the medaka, *Oryzias latipes*. Dev. Dyn. *231*, 518-526.
91. Sunobe, T., Nakamura, M., Kobayashi, Y., Kobayashi, T., and Nagahama, Y. (2004). Gonadal structure and P450scc and 3β-HSD immunoreactivity in the gobiid fish Trimma okinawae during bi-directionl sex change. Ichthyol. Res. *52*, 27-32.
92. Horiguchi, R., Tokumoto, M., Nagahama, Y., and Tokumoto, T. (2005). Molecular cloning and expression of cDNA coding four spliced isoforms of casein kinase Iα in goldfish

oocytes. Biochim. Biophys. Acta *1727*, 75-80.
93. Horiguchi, R., Yoshikuni, M., Tokumoto, M., Nagahama, Y., and Tokumoto, T. (2005). Identification of a protein kinase which phosphorylates α subunit of the 26S proteasome and changes in its activity during meiotic cell cycle in goldfish oocytes. Cell. Signal. *17*, 205-215.
94. Kobayashi-Kajiura, H., Kobayashi, T., and Nagahama, Y. (2005). Cloning of cDNAs and the differential expression of A-type cyclins and Dmc1 during spermatogenesis in the Japanese eel, a teleost fish. Dev. Dyn. *232*, 1115-1123.
95. Kobayashi, Y., Sunobe, T., Kobayashi, T., and Nagahama, Y. (2005). Gonadal structure of the serial-sex changing gobiid fish *Trimma okinawae*. Develop. Growth Differ. *47*, 7-13.
96. Kobayashi, Y., Sunobe, T., Kobayashi, T., Nakamura, M., Suzuki, N., and Nagahama, Y. (2005). Molecular cloning and expression of *Ad4BP/SF-1* in the serial sex changing gobiid fish, *Trimma okinawae*. Biochem. Biophys. Res. Comm. *332*, 1073-1080.
97. Zhou, L.Y., Wang, D.S., Senthilkumaran, S., Yoshikuni, M., Shibata, Y., Kobayashi, T., Sudhakumari, C.C., and Nagahama, Y. (2005). Cloning, expression and characterization of three types of 17α-hydroxysteroid dehydrogenases from the Nile tilapia, *Oreochromis niloticus*. J. Mol. Endocrinol. *35*, 103-116.
98. Sunobe, T., Nakamura, M., Kobayashi, Y., Kobayashi, T., and Nagahama, Y. (2005). Aromatase immunoreactivity and the role of enzymes in steroid pathways for inducing sex change in the hermaphrodite gobiid fish *Trimma okinawae*. Comp. Biochem. Physiol. Part A. *141*, 54-59.
99. Nakamura, I., Evans, J.C., Kusakabe, M., Nagahama, Y., and Young, G. (2005). Changes in steroidogenic enzyme and steroidogenic acute regulatory protein messenger RNAs in ovarian follicles during ovarian development of rainbow trout (*Oncorhynchus mykiss*). Gen. Comp. Endocrinol. *144*, 224-231.
100. Wayne, N.L., Kuwahara, K., Aida, K., Nagahama, Y., and Okubo, K. (2005). Whole-cell electrophysiology of gonadotropin releasing hormone (GnRH) neurons that express green fluorescent protein (GFP) in the terminal nerve of transgenic medaka (*Oryzias latipes*). Biol. Reprod. *73*, 1228-1234.
101. Chang, X.T., Kobayashi, T., Senthilkumaran, B., Kobayashi-Kajiura, H., Sudhakumari, C.C., and Nagahama, Y. (2005). Two types of aromatase with different encoding genes, tissue distribution and developmental expression in Nile tilapia. Gen. Comp. Endocrinol. *141*, 101-115.
102. Nakamoto, M., Suzuki, A., Matsuda, M., Nagahama, Y., and Shibata, N. (2005). Testicular type *Sox9* is not involved in sex determination, but might be in the development of testicular structures in the medaka, *Oryzias latipes*. Biochem. Biophys. Res. Comm. *333*, 729-736.
103. Kobayashi, Y., Sunobe, T., Kobayashi, T., Nagahama, Y., and Nakamura, M. (2006). Promoter analysis of two aromatase genes in the serial-sex changing gobiid fish, *Trimma okinawae*. Fish Physiol. Biochem. *31*, 123-127.
104. Sudhakumari, C.C., Senthilkumaran, B., Kobayashi, T., Kajiura-Kobayashi, H., Wang, D.S., Yoshikuni, M., and Nagahama, Y. (2005). Ontogenic expression patterns of several nuclear receptors and cytochrome P450 aromatases in brain and gonads of the Nile tilapia

Oreochromis niloticus suggests their involvement in sex differentiation. Fish Physiol. Biochem. *31*, 129-135.

105. Raghuveer, K., Garhwal, R., Wang, D.S., Bogerd, J., Kirubagaran, R., Rasheeda, M.K., Sreenivasulu, G., Bhattachrya, N., Tharangini, S., Nagahama, Y., and Senthilkumaran, B. (2005). Effect of methyl testosterone- and ethynyl estradiol-induced sex differentiation on catfish, *Clarias gariepinus*: expression profiles of DMRT1, cytochrome P450aromatases and 3β-hydroxysteroid dehydrogenase. Fish Physiol. Biochem. *31*, 143-147.
106. Sakai, F., Swapna, I., Sudhakumari, C.C., Ganesh, M.V.N.L., Kagawa, H., Kobayashi, T., Fan, H., Nagahama, Y., and Senthilkumaran, B. (2005). Immunocytochemical localization of gonadotropins during the development of XX and XY Nile tilapia. Fish Physiol. Biochem. *31*, 177-181.
107. Wang, D.S., Senthilkumaran, B., Sudhakumari, C.C., Sakai, F., Matsuda, M., Kobayashi, T., Yoshikuni, M., and Nagahama, Y. (2005). Molecular cloning, gene expression and characterization of the third estrogen receptor of the Nile tilapia, *Oreochromis niloticus*. Fish Physiol. Biochem. *31*, 255-266.
108. Supriya, A., Raghuveer, K., Swapna, I., Rasheeda, M.K., Kobayashi, T., Nagahama, Y., Gupta, A.D., Majumdar, K.C., and Senthilkumaran, B. (2005). Thyroid hormone modulation of ovarian recrudescence of air-breathing catfish *Clarias gariepinus*. Fish Physiol. Biochem. *31*, 267-270.
109. Wang, D.S., B. Senthilkumaran, Sudhakumari, C.C., Sakai, F., Matsuda, M., Kobayashi, T., Yoshikuni, M., and Nagahama, Y. (2005). Molecular cloning, gene expression and characterization of the third estrogen receptor of the Nile tilapia, *Oreochromis niloticus*. Fish Physiol. Biochem. *31*, 255-266.
110. Bhandari, R.K., Nakamura, M., Kobayashi, T., and Nagahama, Y. (2005). Suppression of steroidogenic enzyme expression during androgen-induced sex reversal in Nile tilapia (*Oreochromis niloticus*). Gen. Comp. Endocrinol. *145*, 20-24.
111. Okubo, K., Sakai, F., Lau, E.L., Yoshizaki, G., Takeuchi, Y., Naruse, K., Aida, K., and Nagahama, Y. (2006). Forebrain gonadotropin-releasing hormone neuronal development: insights from transgenic medaka and the relevance to X-linked Kallmann syndrome. Endocrinology *147*, 1076-1084.
112. Oshima, Y., Kato, T., Wang, D.S., Murakami, T., Matsuda, Y., Nagahama, Y., and Nakamura, M. (2006). Promoter activity and chromosomal location of the *Rana rugosa* P450 aromatase (CYP19) gene. Zool. Sci. *23*, 79-85.
113. Tokumoto, M., Nagahama, Y., Thomas, P., and Tokumoto, T. (2006). Cloning and identification of a membrane progestin receptor in goldfish ovaries and evidence it is an intermediary in oocyte meiotic maturation. Gen. Comp. Endocrinol. *145*, 101-108.
114. Yamaguchi, A., Katsu, Y., Matsuyama, M., Yoshikuni, M., and Nagahama, Y. (2006). Phosphorylation of the $p32^{cdc2}$ target site on goldfish germinal vesicle lamin B3 before oocyte maturation. Eur. J. Cell Biol. *85*, 501-517.
115. Paul-Prasanth, B., Matsuda, M., Lau, E.L., Suzuki, A., Sakai, F., Kobayashi, T., and Nagahama, Y. (2006). Knock-down of DMY initiates female pathway in the genetic male medaka, *Oryzias latipes*. Biochem. Biophys. Res. Comm. *351*, 815-819.
116. Nakamoto, M., Wang, D.S., Suzuki, A., Matsuda, M., Nagahama, Y., and Shibata, N.

(2007). *Dax1* suppresses *P450arom* expression in medaka ovarian follicles. Mol. Reprod. Develop. *74*, 1239-1246.
117. Wang, D.S., Kobayashi, T., Zhou, L.Y., Paul-Prasanth, B., Ijiri, S., Sakai, F., Okubo, K., Morohashi, K., and Nagahama, Y. (2007). Foxl2 up-regulates aromatase gene transcription female-specifically by binding to the promoter as well as interacting with Ad4BP/SF-1. Mol. Endocrinol. *21*, 712-725.
118. Ohmuro-Matsuyama, Y., Okubo, K., Matsuda, M., Ijiri, S., Wang, D.S., Guan, G.J., Suzuki, T., Matsuyama, M., Morohashi, K., and Nagahama, Y. (2007). Liver receptor homologue-1 activates brain aromatase promoter of medaka, *Oryzias latipes*. Mol. Reprod. Develop. *74*, 1065-1071.
119. Matsuda, M., Shinomiya, S., Kinoshita, M., Suzuki, A., Kobayashi, T., Paul-Prasanth, B., Lau, E.L., Hamaguchi, S., Sakaizumi, M., and Nagahama, Y. (2007). *DMY* gene induces male development in genetically female (XX) medaka fish. Proc. Natl. Acad. Sci. USA *104*, 3865-3870.
120. Mita, M., Yamamoto, K., Yoshikuni, M., Ohno, K., and Nagahama, Y. (2007). Preliminary study on the receptor of gonad-stimulating substance (GSS) as a gonadotropin of starfish. Gen. Comp. Endocrinol. *153*, 299-301.
121. Liu, Z.H., Wu, F.R., Jiao B.W., Zhang, X.Y., Hu, C.J., Huang, B.F., Zhou, L.Y., Huang X.G., Wang, Z.J., Zhang, Y.G., Nagahama, Y., Cheng, C.H.K., and Wang, D.S. (2007). Molecular cloning of Dmrt1, Foxl2 and Cyp19 in Southern catfish and their possible roles in sex differentiation. J. Endocrinol. *194*, 223-241.
122. Zhou, L.Y., Wang, D.S., Kobayashi, T., Yano, A., Paul-Prasanth, B., Suzuki, A., Sakai, F., and Nagahama, Y. (2007). A novel type of P450c17 lacking the lyase activity is responsible for C21-steroid biosynthesis in the fish ovary and head kidney. Endocrinology *148*, 4288-4291.
123. Zhou, L.Y., Wang, D.S., Shibata, Y., Paul-Prasanth, B., Suzuki, A., and Nagahama, Y. (2007). Characterization, expression and transcriptional regulation of *P450c17-I* and *-II* in the medaka, *Oryzias latipes*. Biochem. Biophys. Res. Comm. *362*, 619-624.
124. Mittelholzer, D., Andersson, E., Consten, D., Hirai, T., Nagahama, Y., and Norberg, B. (2007). 20ß-hydroxysteroid dehydrogenase and CYP19A1 are differentially expressed during maturation in Atlantic cod (*Gadus morhua*). J. Mol. Endocrinol. *39*, 319-328.
125. Ohmuro-Matsuyama, Y., Okubo, K., Matsuda, M., Ijiri, S., Wang, D.S., Guan, G.J., Suzuki, T., Matsuyama, M., Morohashi, K., and Nagahama, Y. (2007). Liver receptor homologue-1 activates brain aromatase promoter of medaka, *Oryzias latipes*. Mol. Reprod. Develop. *74*, 1065-1071.

2) Invited reviews, book chapters

1. Nagahama, Y., Miura, T., Kobayashi, T., and Ding, J. (1997). The role of activin in spermatogenesis in fish. *In* Inhibin, Activin and Follistatin (Aono, T., Sugino, H. and Vale, W.W., eds.), pp. 196-203, Springer-Verlag. New York.
2. Nagahama, Y. (1997). 17α,20β-Dihydroxy-4-pregnen-3-one, a maturation- inducing hormone in

fish oocytes: Mechanisms of synthesis and action. Steroids *62*, 190-196.
3. Nakamura, M, Kobayashi, T., Chang, X.T., and Nagahama, Y. (1998). Gonadal sex differentiation in teleost fish. J. Exp. Zool. *281*, 362-372.
4. Nagahama, Y. (2000). Gonadal steroid hormones: major regulators of gonadal sex differentiation and gemetogenesis in fish. *In* Reproductive Physiology of Fish (Norberg, B., Kjesbu, O.S., Taranger, G.L., Andersson, E. and Stefansson, S.O. eds.), pp. 211-222, Bergen.
5. Oba, Y., Hirai, T., Yoshiura, Y., Kobayashi, T., and Nagahama, Y. (2001). Fish gonadotropin and thyrotropin receptors: The evolution of glycoprotein hormone receptors in vertebrates. Comp. Physiol. Biochem. Part B. *129*, 441-448.
6. Devlin, R.H., and Nagahama, Y. (2002). Sex determination and sex differentiation in fish. Aquaculture *208*, 191-366.
7. Matsuda, M., and Nagahama, Y. (2002). Positional cloning of the sex-determining region of medaka using a Y congenic starain. Aquatic Genomes: Steps Toward a Great Future. N. Shimizu, T. Aoki, I. Hirono and F. Takashima (eds.), 236-243, Springer.
8. Nagahama, Y., Nakamura, M., Kitano, T., and Tokumoto, T. (2004). Sexual plasticity in fish: A possible target of endocrine disruptor actions. Environ. Sci. *11*, 73-82.
9. Senthilkumaran, B., Yoshikuni, M., and Nagahama, Y. (2004). A shift in steroidogenesis occurring in ovarian follicles prior to oocyte maturation. Mol. Cell. Endocrinol. *215*, 11-18.
10. Nagahama, Y. (2005). Molecular mechanisms of sex determination and gonadal sex differentiation in fish. Fish Physiol. Biochem. *31*, 105-109.

諸橋憲一郎
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Prof Morohashi joined the National Institute of Basic Biology (NIBB) in 1997. In the last ten years, his research has earned him the reputation of one of the leading researchers in the fields of gonad development, nuclear receptor function, transcriptional regulation, and adrenal development. These areas of work are all tied to the theme of sex differentiation of animal species.

Prof Morohashi has made several key discoveries in this period, including identifying the tissue specific enhancers of the Ad4BP/SF1 gene, discovery that the mammalian Y-linked testis determining gene Sry can be regulated by the transcription factor M33, discovery that mutations in the gene ARX are responsible for human X-linked mental retardation and sex development syndrome, discovery of a hypospadias gene, and discovery of the molecular basis of left-to-right asymmetry in gonad development in the chicken. These and other discoveries have led to the publication of 49 papers and four invited reviews or book chapters in the last ten years. Prof Morohashi has published many of these papers in highly respected journals such as Nature Genetics, Molecular Endocrinology, JBC, and PNAS.

Prof Morohashi's standing in the field internationally is evidenced by his large number of invited international symposium presentations and seminars in the last ten years. Prof Morohashi is also clearly in demand for seminars and conference presentations throughout Japan. In addition, Prof Morohashi has been very active in organising national and international symposia. Among these were the NIBB conference "Molecular Mechanisms of Sex Differentiation" in Okazaki in 2002, which drew together some 50 of the leading international researchers in the field of sexual development. He was also an organiser of the international symposium on the molecular mechanisms of sex determination and differentiation, held in Matsue in 2006, co-organised with the annual meeting of the Zoological Society of Japan. In a number of these cases, Prof Morohashi has been instrumental in instigating these meetings -- that is, holding them for the very first time -- indicating his ability to think beyond established structures and set up new ways of bringing scientists together.

One of Prof Morohashi's great triumphs has been to establish a national programme of research in Molecular Mechanisms of Sex Differentiation under the Priority Areas of Scientific Research Scheme of the Ministry of Education, Culture, Sports, Science and Technology of Japan. This five-year programme began in 2004, and currently funds 45 Japanese research groups working in this field. Not only was Prof Morohashi instrumental in bidding for this grant money, but he also plays a leading role in the continued administration of this grant, and organises an annual conference in which all 45 research groups are brought together to interact and discuss their research. This research consortium is a testament to Prof Morohashi's enormous standing in the field, and his ability to bring researchers together for collaborative benefit. This collaborative

grant has also played an important mentoring role for younger Japanese scientists in this field.

Prof Morohashi has undertaken a number of productive collaborations internationally, most notably those with Dr Blanche Capel (Duke University, USA), one of the most prominent figures internationally in the field of the early gonad development, and Dr Keith Parker (Southwestern University, Texas, USA), an internationally renowned figure in developmental endocrinology research. He also has a number of active collaborations in Japan, including projects with Dr Kanai (University of Tokyo), Dr Yoshioka (Hyogo), and Dr Ogata (Tokyo). Further, within NIBB, he maintains close links with the laboratories of Drs Nagahama and Tanaka.

Prof Morohashi has trained over 40 scientists in the last ten years, including approximately 12 PhD students. Several of these have moved on to prestigious positions in Japan and overseas. For example, Dr Yuko Fukui has recently moved to a partially independent position in the Ageing Institute in Nagoya. Another post doc has moved to an Assistant Professor position in Kyoto Prefectural University of Medicine, and a number of postdoc have found positions in overseas labs. Prof Morohashi lectures to PhD students within NIBB, and also lectures at the Nagoya medical school, the Fukui medical school and Kyushu University.

In summary, Prof Morohashi is very highly rated as a researcher and leader in Japanese developmental and reproductive biology, and is commended on the quality and depth of his accomplishments at NIBB.

（和訳）

諸橋教授は1997年に基礎生物学研究所に着任した。この10年間、教授の研究は生殖腺発生、核内受容体の機能、転写制御ならびに副腎発生領域をリードする研究者の一人としての名声を獲得した。これらの研究は、動物での性分化のテーマに全てつながるものである。

諸橋教授はこの期間に、いくつかの重要な発見をした。例えば、Ad4BP/SF1遺伝子の組織特異的エンハンサーの同定、ほ乳動物のY染色体上にある精巣決定遺伝子Sryが転写因子M33で制御できることを発見、ARX遺伝子の突然変異がX染色体連鎖性精神遅滞および性発達症候群の原因であることの発見、尿道下裂遺伝子の発見、ならびに、ニワトリの生殖腺発生における左右非対称性の分子的基礎の発見などである。これらの発見や他の発見で、過去10年間、49件の論文と、4件の依頼総説論文あるいは単行本の章の執筆を行っている。諸橋教授はこれらの論文を、Nature Genetics、Molecular Endocrinology、JBC、PNASなどの著名な論文誌に発表している。

諸橋教授が国際的に高い評価を得ていることは、この10年間に多数の国際シンポジウムやセミナーから招待を受けていることで明らかである。諸橋教授はまた、国内でもセミナーやコンファレンスに多数招待されている。加えて、諸橋教授は、国内シンポジウム

や国際シンポジウムのオーガナイズも精力的に行っている。そのようなものの中に2002年岡崎市で開催されたNIBBコンファレンス“Molecular Mechanisms of Sex Differentiation（性分化の分子機序）”がある。このコンファレンスは、性発達の分野を国際的にリードする研究者約50名が参加した。教授はまた、日本動物学会年次総会との共催で、2006年に松江市で開催された性決定と性分化の分子メカニズムに関する国際シンポジウムのオーガナイザーでもあった。このような場合の多くで、諸橋教授は、これらのイベントを創設する － すなわち、初めて開催する － のに高い才覚を示し、既存の構造を超えて考え、科学者を一同に集める新たな方法を構築する能力があることを示すものである。

諸橋教授の大きな業績の一つは、文部科学省特定領域研究に「性分化機構の解明」プログラムを確立したことである。この5年間のプログラムは2004年に開始され、現在、45の日本の研究グループに研究費を支出している。諸橋教授は研究費の獲得に貢献しただけでなく、この研究費の運営に主導的役割を果たしており、45の研究グループが毎年開催するコンファレンスをオーガナイズし、研究の意見交換を行っている。この研究コンソーシアムは、諸橋教授がこの分野で極めて高い地位を占めていることや、研究者を集結して共同の利益を得る能力が高いことを実証するものである。この特定領域研究は、この分野の若い日本人研究者の指導にも重要な役割を果たしている。

諸橋教授はいくつかの国際共同研究を行い、成果をあげている。その中でも注目されるのは、Dr Blanche Capel（Duke University, USA）（生殖腺の早期発達分野で国際的に最も優れた研究者の一人）とDr Keith Parker（Southwestern University, Texas, USA（発生内分泌学研究の国際的に名声の高い研究者）との共同研究である。日本国内でもいくつか共同研究を行っており、金井 克晃准教授（東京大学）、吉岡　秀文教授（兵庫教育大学）、緒方　勤博士（国立成育医療センター）とのプロジェクトがあげられる。さらに基礎生物学研究所内では、長濱教授や田中准教授と密接な協力体制を敷いている。

諸橋教授は過去10年間に40名以上の研究者を教育し、これには約12名のPhD学生がいる。この中には、日本や海外の有力なポストに就任した人々がいる。例えば、福井由宇子博士は愛知県の国立長寿医療センターに最近転任した。もう一人のポストドクは、京都府立医科大学の助教に就任し、数名のポストドクが海外の研究室にポストを得ている。諸橋教授は、基礎生物学研究所および名古屋大学医学部、福井大学、九州大学でPhDの大学院生に講義を行っている。

以上まとめると、諸橋教授は、日本の発生生物学および生殖生物学の研究者および指導者として極めて高い評価を受けており、基礎生物学研究所での業績の質の高さと深さは高く評価される。

研究業績：

1) Research articles in peer reviewed journals

1. Wehrenberg, U., Wulff, C., Husen, B., Morohashi, K., and Rune, G.M. (1997). The expression of SF-1/Ad4BP is related to process of luteinization in the marmoset (*Callithrix jacchus*) ovary. Histochem. Cell Biol. *107*, 345-350.
2. Imada, S., Hattori, M.A., Fujihara, N., and Morohashi, K. (1997). In vivo gene transfer into blastoderm of early developmental stage of chicken. Reprod. Nutr. Dev. *37*, 13-20.
3. Kakiki, M., Morohashi, K., Nomura, M., Omura, T., and Horie, T. (1997). Regulation of aldosterone synthase cytochrome P450 (CYP11B2) and 11β-hydroxylase cytochrome P450 (CYP11B1) expression in rat adrenal zona glomerulosa cells by low sodium diet and angiotensin II receptor antagonists. Biol. Pharm. Bull. *20*, 962-968.
4. Leers-Sucheta, S., Morohashi, K., Mason, J.I., and Melner, M.H. (1997). Synergistic activation of the human type II 3β-hydroxysteroid dehydrogenase/$\Delta^5\Delta^4$ isomerase promoter by the transcription factor steroidogenic factor-1/adrenal 4-binding protein and phorbol ester. J. Biol. Chem. *272*, 7960-7967.
5. Kawano, K., Miura, I., Morohashi, K., Takase, M., and Nakamura, M. (1998). Molecular cloning and expression of the SF-1/Ad4BP gene in the frog, *Rana rugosa*. Gene. *222*, 169-176.
6. Nomura, M., Kawabe, K., Matsushita, S., Oka, S., Hatano, O., Harada, N., Nawata, H., and Morohashi, K. (1998). Adrenocortical and gonadal expression of the mammalian Ftz-F1 gene encoding Ad4BP/SF-1 is independent of pituitary control. J. Biochem. *124*, 217-224.
7. Morohashi, K., Tsuboi-Asai, H., Matsushita, S., Suda, M., Nakashima, M., Sasano, H., Hataba, Y., Li, C., Fukuta, J., Irie, J., Watanabe, T., Nagura, H., and Li, E. (1999). Structural and functional abnormalities in the spleen of mFtz-F1 gene disrupted mouse. Blood. *93*, 1586-1594.
8. Ohmori, S., Nawata, Y., Kiyono, K., Murata, H., Tsuboi, S., Ikeda, M., Akagi, R., Morohashi, K., and Ono, B. (1999). Saccharomyces cerevisiae cultured under aerobic and anaerobic conditions: air-level oxygen stress and protein against stress. Biochem. Biophys. Acta *1472*, 587-594.
9. Nagamine, C.M., Morohashi, K., Carlisle, C., and Chang, D.K. (1999). Sex reversal caused by Mus musculus domesticus Y chromosomes linked to variant expression of the testis-determining gene Sry. Dev. Biol. *216*, 182-194.
10. Kabe, Y., Goto, M., Shima, D., Imai, T., Wada, T., Morohashi, K., Shirakawa, M., Hirose, S., and Handa, H. (1999). The role of human MBF1 as a taranscriptional coactivator. J. Biol. Chem. *274*, 34196-34202.
11. Kawabe, K., Shikayama, T., Tsuboi, H., Oka, S., Oba, K., Yanase, T., Nawata, H., and Morohashi, K. (1999). Dax-1 as one of the target genes of Ad4BP/SF-1. Mol. Endocrinol. *13*, 1267-1284, .
12. Kimura, R., Yoshii, H., Nomura, M., Kotomura, N., Mukai, T., Ishihara, S., Ohba, K., Yanase, T., Gotoh, O., Nawata, H., and Morohashi, K. (2000). Identification of novel first exons in Ad4BP/SF-1 (NR5A1) gene, and their tissue- and species-specific usage. Biochem.

Biophys. Res. Commun. *278*, 63-71.
13. Shibata, H., Ikeda, Y., Mukai, T. Morohashi, K., Kurihara, I., Ando, T., Suzuki, T., Kobayashi, K., Murai, M., Saito, I., and Saruta, T. (2000). Expression profiles of COUP-TF, DAX-1 and SF-1 in the human adrenal gland and adrenocortical tumors: Possible implications in steroidogenesis. Mol. Genet. Metab. *74*, 206-216.
14. Ikeda, Y., Takeda, Y., Shikayama, T., Mukai, T., Hisano, S., and Morohashi, K. (2001). Comparative localization of Dax-1 and Ad4BP/SF-1 during development of the hypothalamic-pituitary-gonadal axis implies their closely related and distinct functions. Develop. Dynam. *220*, 363-376.
15. Kitamura, K., Yanazawa, M., Sugiyama, N., Miura, H., Iizuka-Kogo, A., Kusaka, M., Suzuki, R., Kato-Fukui, Y., Kamiirisa, K., Omichi, K., Kasahara, M., Yoshioka, H., Ogata, T., Fukuda, T., Kondo, I., Kato, M., Dobyns, W.B., Yokoyama, M., and Morohashi, K. (2002). Mutations of Arx/ARX cause abnormal migration and differentiation of GABAergic interneurons and abnormal development of testes in mice, and X-linked lissencephaly with abnormal genitalia in humans. Nature Genetics *32*, 359-369.
16. Wang, D.S., Kobayashi, T., Senthilkumaran, B., Sakai, N., Sudhakumari, C.C,, Suzuki, T., Yoshikuni, M., Matsuda, M., Morohashi, K., and Nagahama, Y. (2002). Molecular cloning of DAX-1 and SHP cDNAs and their expression patterns in the Nile tilapia, *Oreochromis niloticus*. Biochem. Biophys. Res. Commun. *297*, 632-640.
17. Mukai, T., Kusaka, M., Kawabe, K., Goto, K., Nawata, H., Fujieda, K., and Morohashi, K. (2002). Sexually dimorphic expression of Dax-1 in the adrenal cortex. Genes Cells. *7*, 717-729.
18. Yokoi, H., Kobayashi, T., Tanaka, M., Nagahama, Y., Wakamatsu, Y., Takeda, H., Araki, K., Morohashi, K., and Ozato, K. (2002). sox9 in a teleost fish, medaka (*Oryzias latipes*): evidence for diversified function of Sox9 in gonad differentiation. Mol. Reprod. Dev. *63*, 5-16.
19. Asoy, R., Mellgren, G., Morohashi, K., and Lund, J. (2002). Activation of cAMP-dependent protein kinase increases the protein level of Steroidogenic Factor-1.Endocrinology *143*, 295-303.
20. Kawajiri, K., Ikuta, T., Suzuki, T., Kusaka, M., Watanabe, J., Muramatsu, M., Fujieda, K., Tachibana, M., and Morohashi, K. (2003). NR boxes of Dax-1 participate both in Ad4BP/SF-1 dependent nuclear import and in cytoplasmic retention of Dax-1. Mol. Endocrinol. *17*, 994-1004.
21. Mizusaki, H., Kawabe, K., Mukai, T., Ariyoshi, E., Kasahara, M., Yoshioka, H., Swain, A., and Morohashi, K. (2003). Dax-1 gene transcription is regulated by Wnt4 in the female developing gonad. Mol. Endocrinol. *17*, 507-519.
22. Meeks, J.J., Crawford, S.E., Russell, T.A., Morohashi, K., Capel, B., Weiss, J., and Jameson, J.L. (2003). Dax1 regulates testis cord organization during gonadal differentiation. Development *130*, 1029-1036.
23. Suzuki, T., Kasahara, M., Yoshioka, H., Morohashi, K., and Umesono, K. (2003). LXXLL motifs in Dax-1 have target specificity for the orphan receptors Ad4BP/SF-1 and LRH-1. Mol. Cell. Biol. 23, 238-249.
24. Hasegawa, T., Fukami, M., Sato, N., Sasaki, G., Fukutani, K ., Morohashi, K., and Ogata, T.

(2004). Testicular dysgenesis without adrenal insufficiency in a 46,XY patient with a heterozygous inactive mutation of Steroidogenic Factor-1. J. Clin. Endocrinol. Metab. *89*, 5930-5935.

25. Komatsu, T., Mizusaki, H., Mukai, T., Ogawa, H., Baba, D., Shirakawa, M., Hatakeyama, S., Nakayama, K., Yamamoto, H., Kikuchi, A., and Morohashi, K. (2004). SUMO-1 modification of the synergy control motif of Ad4BP/SF-1 regulates synergistic transcription between Ad4BP/SF-1 and Sox9. Mol. Endocrinol. *18*, 2451-2462.
26. Ogawa, H., Yu, R.T., Haraguchi, T., Hiraoka, Y., Nakatani, Y., Morohashi, K., and Umesono, K. (2004). Nuclear structure-associated TIF2 interacts with glucocorticoid receptor and its target DNA. Biochem. Biophys. Res. Commun. *320*, 218-225.
27. Mitsunaga, K., Araki, K., Mizusaki, H., Morohashi, K., Haruna, H., Nakagata, N., Giguere, V., Yamamura, K., and Abe, K. (2004). Loss of PGC-specific expression of the orphan nuclear receptor ERR-b results in regulation of germ cell number in mouse embryos. Mech. Dev. *121*, 237-246.
28. Toda, K., Okada, Y., Zubair, M., Morohashi, K., Saibara, T., and Okada, T. (2004). Aromatase- knockout mouse carrying an estrogen-inducible enhanced green fluorescent protein gene facilitates detection of estrogen actions in vivo. Endocrinology *145*, 1880-1888.
29. Kato, M., Das, S., Petras, K., Kitamura, K., Morohashi, K., Abuelo, D.N., Barr, M., Bonneau, D., Brady, A., Carpenter, N.J., Frisone, F., Fukuda, T., Guerrini, R., Iida, E., Itoh, M., Lewanda, A.F., Nanba, Y., Oka, A., Proud, V.K., Russel, K.L., Saugier-Veber, P., Schelley, S.L., Selicorni, A., Shaner, Silengo, M., Stewart, F., Sugiyama, N., Toyama, J., Toutain, A., Vargas, A.L., Yanazawa, M., Zackai, E.H., and Dobyns, W.B. (2004). Mutations of ARX are associated with striking pleiotropy and consistent genotype-phenotype correlation. Human Mutation *23*, 147-159.
30. Baba, T., Mimura, J., Nakamura, N., Harada, N., Yamamoto, M., Morohashi, K., and Fujii-Kuriyama, Y. (2005). Ah (dioxin) receptor as a key factor in the regulation of female reproduction. Mol. Cell. Biol. *25*, 10040-10051.
31. Shima, Y., Zubair, M., Ishihara, S., Shinohara, Y., Oka, A., Kimura, A., Suita, S., and Morohashi, K. (2005). VMH specific enhancer of Ad4BP/SF-1 gene. Mol. Endocrinol. *19*, 2812-2823.
32. Katoh-Fukui, Y., Owaki, A., Sotoyama, Y., Kusaka, M., Shinohara, Y., Maekawa, M., Toshimori, K., and Morohashi, K. (2005). Mouse Polycomb M33 is required for splenic vascular and adrenal gland formation through regulating Ad4BP/SF-1 expression. Blood *106*, 1612-1620.
33. Kamei, Y., Aoyama, Y., Fujimoto, T., Kenmotsu, N., Kishi, C., Koushi, M., Sugano, S., Morohashi, K., Kamiyama, R., and Asakai, R. (2005). A steroidogenic cell line with differentiation potential from mouse granulosa cells, transfected with Ad4BP and SV40 large T antigen genes. J. Endocrinol. 185, 187-195.
34. Matsuyama, M., Mizusaki, H., Shimono, A., Mukai, T., Okumura, K., Abe, K., Shimada, K., and Morohashi, K. (2005). Novel isoform of vinexin, vinexin g, regulates Sox9 gene expression through activation of MAPK cascade in mouse fetal gonad. Genes Cells *10*, 421-434.

35. Yoshioka, H., Ishimaru, Y., Sugiyama, N., Tsunekawa, N., Noce, T., Kasahara, M., and Morohashi, K. (2005). Mesonephric FGF signaling is associated with the development of sexually indifferent gonadal primordium in chick embryos. Dev. Biol. *280*, 150-161.
36. Ishihara, S., and Morohashi, K. (2005). Identification of the boundary for histone acetylation between nuclear receptor genes, Ad4BP/SF-1 and GCNF, aligned in tandem. Biochem. Biophys. Res. Commun. *329*, 554-562.
37. Toda, K., Hayashi, Y., Okada, T., Morohashi, K., and Saibara, T. (2005). Expression of the estrogen-inducible EGFP gene in aromatase-deficient mice reveals differential tissue-response to estrogenic compounds. Mol. Cell. Endocrinol. *229*, 119-126.
38. Fukami, M., Wada, Y., Miyabayashi, K., Nishino, I., Hasegawa, T., Camerino, G., Kretz, C., Buj-Bello, A., Laporte, J., Yamada, G., Morohashi, K., and Ogata, T. (2006). CXorf6 is a causative gene for hypospadias. Nature Genetics *38*, 1369-1371.
39. Kojima, Y., Sakaki, S., Hayashi, Y, Umemoto, Y., Morohashi, K., and Kohri, K. (2006). Role of transcription factors Ad4BP/SF-1 and DAX-1 in steroidogenesis and spermatogenesis in human testicular development and idiopathic azospermia. Int. J. Urol. *13*, 785-793.
40. Zubair, M., Ishihara, S., Oka, S., Okumura, K., and Morohashi, K. (2006). Two-step regulation of Ad4BP/SF-1 gene transcription during fetal adrenal development; initiation by a Hox-Pbx1-Prep1 complex and maintenance via autoregulation by Ad4BP/SF-1. Mol. Cell. Biol. *26*, 4111-4121.
41. Fatchiyah., Zubair, M., Shima, Y., Oka, S., Ishihara, S., Fukui-Katoh, Y., and Morohashi, K. (2006). Differential gene dosage effects of Ad4BP/SF-1 on target tissue development. Biochem. Biophys. Res. Commun. *341*, 1036-1045.
42. Fan, W., Yanase, Y., Morinaga, H., Gondo, S., Okabe, T., Nomura, M., Komatsu, T., Morohashi, K., Hayes, T.B., Takayanagi, R., and Nawata, H. (2007). Atrazine-induced aromatase expression is SF-1-dependent: Implications for endocrine disruption in wildlife and reproductive cancers in humans. Environmental Health Perspectives *115*, 720-727.
43. Wang, D.S., Kobayashi, T., Shou, L., Ohmuro-Matsuyama, Y., Guan, G., Ijiri, S., Sakai, F., Matsuda, M., Shibata, Y., Okubo, K., Morohashi, K., and Nagahama, Y. (2007). Foxl2 up-regulates aromatase gene transcription in a female-specific manner by binding to the promoter as well as interacting with Ad4BP/SF-1. Mol. Endocrinol. *21*, 712-725.
44. Sato, N., Kamachi, Y., Kondoh, H., Shima, Y., Morohashi, K., Horikawa, R., and Ogata, T. (2007). Hypogonadotropic hypogonadism in an adult female with a heterozygous hypomorphic mutation of SOX2. Eur. J. Endocrinol. *156*, 169-173.
45. Kurokawa, H., Saito, D., Katoh-Fukui, Y., Ohta, K., Baba, T., Morohashi, K., and Tanaka, M. (2007). Germ cells are essential for sexual dimorphism in the medaka gonad. Proc. Natl. Acad. Sci. UAS. *104*, 16958-16963.

2) Invited reviews, book chapters

1. Morohashi, K. (1997). The ontogenesis of the steroidogenic tissues. Genes Cells. *2*, 95-106.
2. Morohashi, K. (1999). Gonadal and extragonadal functions of Ad4BP/SF-1-developmental

aspects - Trends in Endocrinol. Metab. *10*, 169-173.
3. Morohashi, K. (2002). Sex differentiation of the gonads–factors implicated in testicular and ovarian developments. Environmental Sciences *9*, 13-22.
4. Suzuki, T., Mizusaki, H., Kawabe, K., Yoshioka, H., and K. Morohashi (2002). Concerted regulation of gonad differentiation by transcription factors and growth factors. P68-75 in "The genetics and biology of sex determination" in Novartis Found Symposium 244, John Wiley & Sons Ltd, UK.

井口泰泉
分子環境生物学研究部門（岡崎統合バイオサイエンスセンター）・教授

Prof Iguchi heads an enormously successful team at NIBB, conducting research in the field of endocrine disrupters. The issue of environmental chemicals that disrupt development and physiology of humans and animal species has become a hot international area of research and a high-profile area of public concern, and Prof Iguchi's research is at the leading edge of this field internationally.

Prof Iguchi joined the NIBB in 2000, and now heads a team of 12, including two postdoctoral researchers, two PhD students, three faculty scientists and several technicians. This team is addressing issues that fall under seven different project areas: Molecular mechanisms of environmental estrogens, Microarray analysis of estrogen-responsive genes, Unexpected effects of organotin compounds, Temperature-dependent sex-determination mechanisms, Sexual development in Daphnids, Phylogeny of estrogen receptors, and Cataloguing receptor genes from diverse species. Although this is a very broad research palette, Prof Iguchi makes a strong case for continuing in all these areas, since he has been able to maintain a high level of productivity in each of these areas.

Prof Iguchi's work has provided important insights into the mechanism by which perinatal exposure to diethylstilbestrol (DES), a drug given to pregnant women to prevent premature birth, causes cancer of the reproductive tract. He has found a link between DES exposure and vaginal epithelial hyperproliferation, and is now exploring the molecular mechanisms involved in this response, using a range of technologies such as microarray, DNA methylation and protein phosphorylation assays.

Prof Iguchi has also made great strides in the use of Daphnia, a small crustacean species, as a monitor for environmental endocrine disruptors. Daphnia is commonly used as an indicator of water quality, because it is extremely sensitive to disruptive agents and changes sex as a result of exposure. Prof Iguchi is taking this system to a higher level by implementing in-depth analysis of the pathways involved in sex development in this species, so that the power of Daphnids to detect endocrine disruptors can be harnessed more effectively.

Prof Iguchi is also making inroads into a molecular understanding if the mechanism of temperature-dependant sex determination (TSD). Many reptile species use this mechanism of sex determination, yet the mechanism is not understood, despite major research efforts internationally. Using sophisticated molecular techniques and in an international collaborative team, Prof Iguchi's group has focused on ion channels as a possible mechanism for this phenomenon. Solving this issue will not only answer one of the great unknowns in the basic biology of sex determination, but will also contribute to a clearer understanding of the future of TSD species in the face of global warming.

Prof Iguchi is extremely productive, having published 102 papers and 29 reviews/book chapters in the last seven years. This is especially admirable given that his group is relatively small. His papers have appeared in major journals such as Molecular Endocrinology, Endocrinology, Molecular and Cellular Endocrinology, and Journal of Molecular Endocrinology. In addition, Prof Iguchi has been invited to present 43 talks at conferences since joining NIBB. A large proportion of these are overseas, and it is noted that he is invited to the Gordon Research Conference in his field every year, a powerful indicator of his status in the field.

Prof Iguchi collaborates with international groups in Exeter (UK), Florida (USA), Irvine (USA), Canada and Pretoria (South Africa). At a local level, he also collaborates with other investigators at NIBB, as well as groups in Yokohama and Okayama. He is an adjunct professor at the University of Florida.

Prof Iguchi has two PhD students, and teaches undergraduate courses at Tokyo Science and Technology, Yokohama City University, Shimane University, Okayama University, University of Tokyo, and University of Florida. He is also involved in outreach programs at Yokohama Futaba Gakuen School.

Prof Iguchi has a wide range of peer review, conference organization, advisory, regulatory, and other administrative roles at international, national and local levels. He is Editor-in Chief of the journal Environmental Sciences, and a member of a number of professional societies.

The committee felt that Prof Iguchi's research was proceeding at an extremely high level, and encouraged Prof Iguchi to take advantage of his national and international profile to attract more students and post docs into his group, including post docs from other countries. In view of the high degree of public (as well as scientific) interest in this area of work, the committee also encouraged him to submit more manuscripts to very high ranking interdisciplinary journals such as Nature, which has a keen eye for high-profile public-interest stories.

In summary, Prof Iguchi is an accomplished, enthusiastic, energetic, productive and authoritative scientist. He ranks in the top five in his field internationally, and is a great ambassador for NIBB and also for Japanese science. His research is a fine example of basic research meeting the needs of our society, and is strongly supported by the review committee.

（和訳）

井口教授は基礎生物学研究所の極めて高い成功を収めたチームを率いて、内分泌かく乱物質の分野での研究を行っている。ヒトや動物の発生や生理を阻害する環境化学物質の問題は国際的にもホットな研究分野になってきており、一般の関心も高い領域である。井口教授の研究はこの分野で世界的な先端を進んでいる。

井口教授は2000年に基礎生物学研究所に着任し、現在では2名のポストドク研究員、2名のPhD大学院学生、3名の助手、数名の技術支援員を含む12名のチームを率いている。このチームは、以下に示す7つのプロジェクト領域の問題について研究している：環境エストロゲンの分子機序、エストロゲン応答遺伝子のマイクロアレイ解析、有機スズ化合物の予想しない効果、温度依存的な性決定の機序、オオミジンコの性形成、エストロゲン受容体の系統発生学、および様々な種の受容体遺伝子のカタログ作成。これらは極めて広範な研究領域であるが、井口教授には、これらそれぞれの領域に高い生産性を維持できる才能があるので、これらの分野を力強く進めている。

井口教授の研究は、ジエチルスチルベストロール(DES)（未熟児出産を予防するために妊娠女性に投与する薬剤）が生殖器にがんを引き起こす機序についての重要な洞察を与えた。教授は、DES暴露と、膣上皮の過増殖との間に関連性があることを発見し、この応答に関与する分子機序を、マイクロアレイ法やDNAメチル化、タンパク質リン酸化アッセイ法などの様々な方法を用いて探っている。

井口教授はまた、オオミジンコ（小さな甲殻類）を環境内分泌かく乱物質のモニターとして使用することにも大きな進展をもたらした。水質モニターにオオミジンコが広く用いられている。オオミジンコはかく乱物質に対して極めて感受性が高く、暴露したことで、性転換するからである。井口教授は、この動物種の性発生に関与する経路を深く分析することで、このモニターシステムを高いレベルに向上させ、オオミジンコの環境内分泌かく乱物質検出能力をより高めることができるようになった。

井口教授はまた、温度依存性の性決定(TSD)の分子機序の理解に成功しつつある。は虫類の多くの種が、性決定にこの機序を用いているが、世界的に多くの研究がなされたにも関わらず、その機序については解明されていない。高度の分子解析法と国際共同研究チームを使って、井口教授のグループはこの現象の機序としてイオンチャネルに着目してきた。この問題の答えを見つけることは性決定の基礎生物学の未解明の問題を解決するだけでなく、地球温暖化に直面しているTSDの動物種の今後をより明確に理解することにも貢献しよう。

井口教授は極めて生産性が高く、102報の論文と29件の総説／単行本の章の執筆をこの7年間に行っている。教授のグループが比較的小規模のものであることを考えれば、これは特に賞賛すべきことである。教授の論文はMolecular Endocrinology、Endocrinology、Molecular and Cellular Endocrinology、Journal of Molecular Endocrinology誌などの主要論文誌に掲載されている。加えて、井口教授は基礎生物学研究所に着任以来、43件の招待講演をおこなっている。この多くは海外での講演であり、この分野でGordon Research Conferenceに毎年招待されていることは注目すべき点である。これは、この分野での教授の地位の高さを如実に示すものである。

井口教授はエクスター（英国)、フロリダ（米国)、アーバイン（米国)、カナダ、プレトリア（南アフリカ）の国際グループとも共同研究している。国内レベルでは、基礎生物学研究所内の他の部門や、横浜、岡山のグループと共同研究している。教授は、フロリダ大学の特任教授である。

井口教授は2名のPhD大学院生を指導しており、東京工業大学や横浜市立大学、島根大学、岡山大学、東京大学、フロリダ大学の学部教育を行っている。また横浜雙葉学園のアウトリーチプログラムにも関係している。

井口教授は査読者、コンファレンスのオーガナイズ、諮問委員、規制委員その他国内外での行政的役割を幅広くこなしている。教授はEnvironmental Sciences誌の編集責任者であり、多数の学会の会員である。

当委員会では、井口教授の研究は極めて高レベルで進んでいると判断し、井口教授には国内外での評価の高さをもとに、より多くの大学院生やポストドク（海外出身のポストドクを含む）を惹き付けることを期待する。研究分野の一般の（および科学的）関心が高いことを考えれば、教授には、Nature 誌などの極めて高レベルの総合論文誌により多くの論文を投稿することを当委員会としては勧める。Nature 誌は一般の関心の高い話題については鋭い見方をしている。

以上まとめると、井口教授は立派な業績をあげ、熱心で、エネリギッシュ、生産的で権威ある研究者である。教授は当該研究領域では国際的にもトップファイブに属しており、基礎生物学研究所にとっても、また日本の科学にとっても優れた大使的役割を担う研究者である。教授の研究は、基礎研究が社会のニーズに合致することを示す優れた実例であり、外部評価委員会としては強く支持するものである。

研究業績（2000年より）:

1) Research articles in peer reviewed journals

1. Hashimoto, S., Bessho, H., Hara, A., Nakamura, M., Iguchi, T., and Fujita, K. (2000). Elevated serum vitellogenin levels and gonadal abnormalities in wild flounder (*Pleuronectes yokohamae*) from Tokyo Bay, Japan. Marine Environ. Res. *49*, 37-53.
2. Yamamura, Y., Sayama, K., Takeda, Y., Matsuzawa, A., Iguchi. T., and Ohta, Y. (2000). Further study of methallothionein expression in transplantble mouse mammary tumors. Anticancer Res. *20*, 379-384.
3. Seiwa, C., Sugiyama, I., Yagi, Y., Iguchi, T., and H. Asou (2001). Fyn tyrosine kinase participates in the compact myelin sheath formatrion in the central nervous system. Neurosci. Res. *37*, 21-31.
4. Yamamura, Y., Ohta, Y., Iguchi, T., and Matsuzawa, A. (2001). Metallothionein expression and apoptosis in pregnancy-dependent and -independent mouse mammary tumors. Anticancer Res. *21*, 1145-1150.
5. Yamamura, Y., Tamano, M., Iguchi, T., and Ohta, Y. (2001). Methallothionein expression and tumor growth in the transplantable pregnancy-independent mouse mammary tumor. J. Vet. Med. Sci. *63*, 687-689.

6. Okada, A., Sato, T., Ohta, Y., Buchanan, D.L., and Iguchi, T. (2001). Effect of diethylstilbestrol on cell proliferation and expression of epidermal growth factor in the developing female rat reproductive tract. J. Endocrinol. *170*, 539-554.
7. Shibayama, T., Fukata, H., Sakurai, K., Adachi, T., Komiyama, M., Iguchi, T., and Mori, C. (2001). Neonatal exposure to genistein reduces expression of estrogen receptor a and androgen receptor in testes of adult mice. Endocr. J. *48*, 655-663.
8. Miyagawa, S., Buchanan, D.L., Sato, T., Ohta, Y., Nishina, Y., and Iguchi, T. (2002). Characterization of diethylstilbestrol-induced hypospadias in female mice. Anat. Rec. *266*, 43-50.
9. Suzuki, A., Sugihara, A., Uchida, K., Sato, T., Ohta, Y., Katsu, Y., Watanabe, H., and Iguchi, T. (2002). Developmental effects of perinatal exposure to bisphenol-A and diethylstilbestrol on reproductive organs in female mice. Reprod. Toxicol. *16*, 107-116.
10. Buchanan, D.L., Ohsako, S., Tohyama, C., Cooke, P.S., and Iguchi, T. (2002). Dioxin inhibition of estrogen-induced mouse uterine epithelial mitogenesis involves changes in cyclin and transforming growth factor-b expression . Toxicol. Sci. *66*, 62-68.
11. Okada, A., Ohta, Y., Buchanan, D.L., Sato, T., Inoue, S., Hori, H., Muramatsu, M., and Iguchi, T. (2002). Changes in ontogenetic expression of estrogen receptor a and not of estrogen receptor b in the female rat reproductive tract. J. Mol. Endocrinol. *28*, 87-97.
12. Uchida, D., Yamashita, M., Kitano, K., and Iguchi, T. (2002). Oocyte apoptosis during the transition from ovary-like tissue to testes during sex differentiation of juvenile zebrafish. J. Exp. Biol. *205*, 711-718.
13. Honma, S., Suzuki, A., Buchanan, D.L., Katsu, Y., Watanabe, H., and Iguchi, T. (2002). Low dose effect of *in utero* exposure to bisphenol A and diethylstilbestrol on female mouse reproduction. Reprod. Toxicol. *16*, 117-122.
14. Shimamura, M., Kodaira, K., Hino, K., Ishimoto, Y., Tamura, H. and Iguchi, T. (2002). Comparison of antiandrogenic activities of vinclozolin and d,l-camphorquinone in androgen receptor gene transcription assay *in vitro* and mouse *in utero* exposure assay *in vivo*. Toxicology *174*, 97-107.
15. Watanabe, H., Suzuki, A., Mizutani, T., Kohno, S., Lubahn, D.B., Handa, H., and Iguchi, T. (2002). Genome-wide analysis of changes in early gene expression induced by estrogen. Genes Cells *7*, 497-507.
16. Tatarazako, N., Takao, Y., Kishi, K., Onikura, N., Arizono, K., and Iguchi, T. (2002). Styrene dimers and trimers affect reproduction of daphnia (*Ceriodaphnia dubia*). Chemosphere, *48*, 597-601.
17. Ishibashi, H., Kobayashi, M., Koshiishi, T., Moriwaki, T., Tachibana, K., Tsuchimoto, Soyano, K., Iguchi, T., Mori, C., and Arizono, K. (2002). Induction of plasma vitellogenin synthesis by the commercial fish diets in male goldfish (*Carassius auratus*) and dietary phytoestrogens. J. Health Sci. *48*, 427-434.
18. Adachi, T., Komiyama, M., Ono, Y., Koh, K.-B., Sakurai, K., Shibayama, T., Kato, M., Yoshikawa, T., Seki, N., Iguchi, T., and Mori, C. (2002). Toxicogenomic effects of neonatal exposure to diethylstilbestrol on mouse testicular gene expression in the long term: a study using cDNA microarray analysis. Mol. Reprod. Develop. *63*, 17-23.
19. Katsu, Y., Takasu, E., and Iguchi, T. (2002). Estrogen-independent expression of neuropsin,

a serin protease in the vagina of mice exposed neonatally to diethylstilbestrol. Mol. Cell. Endocrinol. *195*, 99-107.

20. Urushitani, H., Shimizu, A., Katsu, Y., and Iguchi, T. (2002). Early estrogen exposure induces abnormal development of *Fundulus heteroclitus*. J. Exp. Zool. *293*, 693-702.
21. Okada, A., Ohta, Y., Buchanan, D.L., Sato, T., and Iguchi, T. (2002). Effect of estrogens on ontogenic expression of progesterone receptor in the fetal female rat reproductive tract. Mol. Cell. Endocrinol. *195*, 55-64.
22. Uchida, K., Suzuki, A., Kobayashi, Y., Buchanan, D.L., Sato, T., Watanabe, H., Katsu, Y., Suzuki, J., Asaoka, K., Mori, C., Arizono, K., and Iguchi, T. (2002). Bisphenol-A administration during pregnancy results in fetal exposure in mice and monkeys. J. Health Sci. *48*, 579-582.
23. Ura, K., Kai, T., Sakata, S., Iguchi, T., and Arizono, K. (2002). Aquatic acute toxicity testing using the nematode *Caenorhabditis elegans*. J. Health Sci. *48*, 583-586.
24. Matsuno, T., Ura, K., Sonoda, R., Kohara, Y., Uesugi, H., Arizono, K., Iguchi, T., and Tominaga, N. (2002). Sensing of chemical substances using gene expression patterns in *C. elegans*. Sensors Materials *14*, 395-406.
25. Ohko, Y., Iuchi, K.-I., Niwa, C., Tatsuma, T., Nakashima, T., Iguchi, T., Kubota, Y., and Fujishima, A. (2002). 17β-Estradiol degradation by TiO_2 photocatalysis as a means of reducing estrogenic activity. Environ. Sci. Technol. *36*, 4175-4181.
26. Tominaga, N., Ura, K., Kawakami, M., Kawaguchi, T., Kohra, S., Mitui, Y., Iguchi, T., and Arizono, K. (2003). *Caenorhabditis elegans* responses to specific steroid hormones. J. Health Sci. *49*, 28-33.
27. Adachi, T., Matsuno, Y., Sugimura, A., Takano, K., Koh, K.-B., Sakurai, K., Shibayama, T., Iguchi, T., Mori, C., and Komiyama, M. (2003). ADAM7 (a disintegrin and metalloprotease 7) mRNA is suppressed in mouse epididymis by neonatal exposure to diethylstilbestrol. Mol. Reprod. Develop. *64*, 414-421.
28. Kato, H., Ota, T., Furuhashi, T., Ohta, Y., and Iguchi, T. (2003). Changes in reproductive organs of female rats treated with bisphenol A during the neonatal period. Reprod. Toxicol. *17*, 283-288.
29. Sato, T., Fukazawa, Y., Ohta, Y., and Iguchi, T. (2003). Multiple mechanisms are involved in apoptotic cell death in the mouse uterus and vagina induced by ovariectomy. Reprod. Toxicol. *17*, 289-297.
30. Katsu, Y., Lubahn, D., and Iguchi, T. (2003). Expression of novel C-type lectin in the mouse vagina. Endocrinology *144*, 2597-2605.
31. Urushitani, H., Nakai, M., Inanaga, H., Shimohigashi, Y., Shimizu, A., Katsu, K., and Iguchi, T. (2003). Cloning and characterization of estrogen receptor α in mummichog, *Fundulus heteroclitus*. Mol. Cell. Endocrinol. *203*, 41-50.
32. Okada, A., Ohta, Y., Inoue, S., Hiroi, H., Muramatsu, M., and Iguchi, T. (2003). Expression of estrogen, progesterone and androgen receptors in the oviduct of developing, cycling and pre-implantation rats. J. Mol. Endocrinol. *30*, 301-315.
33. Watanabe, H., Suzuki, A., Kobayashi, K., Lubahn, D., Handa, H., and Iguchi, T. (2003). Analysis of temporal changes in the expression of estrogen regulated genes in the uterus. J. Mol. Endocrinol. *30*, 347-358.

34. Kohno, S., Kamishima, Y., and Iguchi, T. (2003). Molecular cloning of an anuran V_2 type [Arg^8] vasotocin receptor and mesotocin receptor: functional characterization and tissue expression in the Japanese tree frog (*Hyla japonica*). Gen. Comp. Endocrinol. *132*, 485-498.
35. Guillette, L.J.Jr., and Iguchi, T., (2003). Interspecies variation in the estrogenicity of *p,p'*-DDE. Organohalogen Compounds *65*, 71-73.
36. Tatarazako, N., Oda, S., Watanabe, H., Morita, M., and Iguchi, T. (2003). Juvenile hormone agonists affect the occurrence of male *Daphnia*. Chemosphere *53*, 827-833.
37. Inui, M., Adachi, T., Takenaka, S., Inui, H., Nakazawa, M., Ueda, M., Watanabe, H., Mori, C., Iguchi, T., and Miyatake, K. (2003). Effect of UV screens and preservaties on vitellogenin and choriogenin production in male medaka (*Oryzias latipes*). Toxicology *194*, 43-50.
38. Watanabe, H., Suzuki, A., Kobayashi, M., Lubahn, D.B., Handa, H., and Iguchi, H. (2003). Similarities and differences in uterine gene expression patterns caused by treatment with physiological and non-physiological estrogen. J. Mol. Endocrinol. *31*, 487-497.
39. Miyahara, M., Ishibashi, H., Inudo, M., Nishijima, H., Iguchi, T., Guillette, L.J.Jr., and Arizono, K. (2003). Estrogenic activity of a diet to estrogen receptors-α and -β in an experimental animal. J. Health Sci. *49*, 481-491.
40. Tominaga, N., Kohra, S., Iguchi, T., and Arizono, K. (2003). A multi-generation sublethal assay of phenols using the nematode *Caenorhabditis elegan*s. J. Health Sci. *49*, 459-463.
41. Sato, N., Doi, R., Fujieda, H., Iguchi, T., Matsubara, J., and Saruta, K. (2003). Determination of bisphenol A migrating from polycarbonate school-lunch plastics to food-simulating liquids. Bull. Yokohama City Univ. Natural Sci. *55*, 1-12.
42. Adachi, T., Koh, K.-B., Tainaka, H., Matsuno, Y., Ono, Y., Sakurai, K., Fukata, H., Iguchi, T., Komiyama, M., and Mori, C. (2004). Toxicogenomic difference between diethylstilbestrol and 17β-estradiol in mouse testicular gene expression by neonatal exposure. Mol. Reprod. Develop. *67*, 19-25.
43. Miyagawa, S., Katsu, Y., Watanabe, H., and Iguchi, T. (2004). Estrogen-independent activation of ErbBs signaling and estrogen receptor α in the mouse vagina exposed neonatally to diethylstilbestrol. Oncogene *23*, 340-349.
44. Uchida, D., Yamashita, M., Kitano, T., and Iguchi, T. (2004). An aromatase inhibitor or high water temperature induce oocyte apoptosis and depletion of P450 aromatase activity in the gonads of genetic female zebrafish during sex-reversal. Comp. Biochem. Physiol. Part A, *137*, 1-20.
45. Katsu, Y., Bermudez, D.S., Braun, E.L., Helbing, C., Miyagawa, S., Gunderson, M.P., Kohno, S., Bryan, T.E., Guillette, J.L.Jr., and Iguchi, T. (2004). Molecular cloning of the estrogen and progesterone receptors of the American alligator. Gen. Comp. Endocrinol. *136*, 122-133.
46. Matsuno, Y., Adachi, T., Koh, K.B., Fukata, H., Sugimura, A., Sakurai, K., Shibayama, T., Iguchi, T., Komiyama, M., and Mori, C. (2004). Effect of neonatal exposure to diethylstilbestrol on testicular gene expression in adult mouse: comprehensive analysis with cDNA subtraction method. Int. J. Androl. *27*, 115-122.
47. Adachi, T., Ono, Y., Koh, K.B., Takashima, K., Tainaka, H., Matsuno, Y., Nakagawa, S.,

Todaka, E., Sakurai, K., Fukata, H., Iguchi, T., Komiyama, M., and Mori, C. (2004). Long-term alteration of gene expression without morphological change in testis after neonatal exposure to genistein in mice: Toxicogenomic analysis using cDNA microarray. Food Chem. Toxicol. *42*, 445-452.

48. Kato, H., Iwata, T., Katsu, Y., Watanabe, H., Ohta, Y., and Iguchi, T. (2004). Evaluation of estrogenic activity in diets for experimental animals using *in vitro* assay. J. Agric. Food Chem. *52*, 1410-1414.
49. Adachi T, Koh, K.B., Tanikawa, H., Matsuno, Y., Ono, Y., Sakurai, K., Fukata, H., Iguchi, T., Komiyama, M., and Mori, C. (2004). Toxicogenomic difference between diethylstilbestrol and 17β-estradiol in mouse testicular gene expression by neonatal exposure. Mol. Reprod. Develop. *67*, 19-25.
50. Tatarazako, N., Koshio, M., Hori, H., Morita, M., and Iguchi, T. (2004). Validation of an enzyme-linked immunosorbent assay method for vitellogenin in the medaka. J. Health Sci. *50*, 301-308.
51. Miyagawa, S., Suzuki, A., Katsu, Y., Kobayashi, M., Goto, M., Handa, H., Watanabe, H., and Iguchi, T. (2004). Persistent gene expression in mouse vagina exposed neonatally to diethylstilbestrol. J. Mol. Endocrinol. *32*, 663-677.
52. Okada, A., Ohta, Y., Brody, A.L., Krust, A., Chambon, P., and Iguchi, T. (2004). Essential role of foxj1, but not of estrogen receptor alpha in ciliated epithelial cell differentiation of the neonatal oviduct. J. Mol. Endocrinol. *32*, 615-625.
53. Watanabe, H., Suzuki, A., Goto, M., Lubahn, D.B., Handa, H., and Iguchi, H. (2004). Tissue-specific estrogenic and non-estrogenic effects of a xenoestrogen, nonylphenol. J. Mol. Endocrinol. *33*, 243-252.
54. Okada, A., Ohta, Y., Brody, S.L., and Iguchi, T. (2004). Epithelial c-jun and c-fos are temporally and spatially regulated by estradiol during neonatal rat oviduct differentiation. J. Endocrinol. *182*, 219-227.
55. Sato, T., Fukazawa, Y., Ohta, Y., and Iguchi, T. (2004). Involvement of growth factors in induction of persistent proliferation of vaginal epithelium of mice exposed neonatally to diethylstilbestrol. Reprod. Toxicol. *19*, 43-51.
56. Kohno, S., Fujime, M., Kamishima, Y., and Iguchi, T. (2004). Sexually dimorphic basal water absorption at the isolated pelvic patch of Japanese tree frog, *Hyla japonica*. J. Exp. Zool. *301A*, 428-438.
57. Seiwa, C., Tanaka, K., Nakahara, J., Komiyama, T., Katsu, Y., Iguchi, T., and Asou, H. (2004). Bisphenol A exerts thyroid-hormone-like effects on mouse oligodendrocyte precursor cell. Neuroendocrinology *80*, 21-30.
58. Sone, K., Hinago, M., Kitayama, A., Morokuma, J., Ueno, N., Watanabe, H., and Iguchi, T. (2004). Effect of 17β-estradiol, nonylphenol and bisphenol-A on developing *Xenopus laevis* embryos. Gen. Comp. Endocrinol. *138*, 228-236.
59. Yoshinaga, N., Shiraishi, E., Yamamoto, T., Iguchi, T., Abe, S.-I., and Kitano, T. (2004). Sexually dimorphic expression of a teleost homologue of Müllerian inhibitory substance (MIS) during gonadal sex differentiation in Japanese flounder, *Paralichthys olivaceus*. Biochem. Biophys. Res. Comm. *322*, 508-513.
60. Inudo, M., Ishibashi, H., Matsumura, N., Matsuoka, M., Mori, T., Taniyama, S., Kadokami,

K., Koga, M., Shinohara, R., Hutchinson, T., Iguchi, T., and Arizono, K. (2004). Levels of estrogenicity, dietary phytoestrogen and organochlorine pesticide in an experimental fish diet and reproduction and hepatic vitellogenin expression in medaka *(Oryzias latipes)*. Comp. Med. *54*, 673-680.

61. Tominaga, N., Kohra, S., Iguchi, T., and Arizono, K. (2005). Effects of perfluoro organic compound toxicity on nematode *Caenorhabditis elegans* fecundity. J. Health Sci. *50*, 545-550.
62. Watanabe, H., Suzuki, A., Goto, M., Ohsako, S., Tohyama, C., Handa, H., and Iguchi, T. (2005). Comparative uterine gene expression analysis after dioxin and estradiol administration. J. Mol. Endocrinol. *33*, 763-771.
63. Nakada, N., Nyunoya, H., Nakamura, M., Hara, A., Iguchi, T., and Takada, H. (2005). Identification of estrogenic compounds in wastewater effluent. Environ. Toxicol. Chem. *23*, 2807-2815.
64. Watanabe, H., Tatarazako, N., Oda, S., Nishide, H., Uchiyama, I., Morita, N., and Iguchi, T. (2005). Analysis of expressed sequence tags of the water flea *Daphnia magna*. Genome *48*, 606-609.
65. Todaka, E., Sakurai, K., Fukuta, H., Miyagawa, H., Uzuki, M., Omori, M., Osada, H., Ikezuki, Y., Tsutsumi, O., Iguchi, T., and Mori, C. (2005). Fetal exposure to phytoestrogens - the difference in phytoestrogen status between mother and fetus. Environ. Res. *99*, 195-203.
66. Oda, S., Tatarazako, N., Watanabe, H., Morita, M., and Iguchi, T. (2006). Production of male neonates in 4 cladoceran species exposed to a juvenile hormone analog, fenoxycarb. Chemosphere *60*, 74-78.
67. Sone, K., Hinago, M., Itamoto, M., Katsu, Y., Watanabe, H., Urushitani, H., Tooi, O., Guillette, L.J.Jr., and Iguchi, T. (2006). Effects of an androgenic growth promoter 17β-trenbolone on masculinization of mosquitofish (*Gambusia affinis affinis*). Gen. Comp. Endocrinol. *143*, 151-160.
68. Oda, S., Tatarazako, N., Watanabe, H., Morita, M., and Iguchi, T. (2006). Production of male neonates in *Daphnia magna* (Cladocera, Crustacea) exposed to juvenile hormones and their analogs. Chemosphere *61*, 1168-1174.
69. Watanabe, H., Takahashi, E., Kobayashi, M., Goto, M., Krust, A., Chambon, P., and Iguchi, T. (2006). The estrogen-responsive adrenomedullin and receptor-modifying protein 3 gene identified by DNA microarray analysis are directly regulated by estrogen receptor. J. Mol. Endocrinol. *36*, 81-89.
70. Katsu, Y., Myburgh, J., Kohno, S., Swan, G.E., Guillette, J.J.Jr., and Iguchi, T. (2006). Molecular cloning of estrogen receptor α of the Nile crocodile. Comp. Biochem. Physiol., Part A *143*, 340-346.
71. Katsu, Y., and Iguchi, T. (2006). Tissue specific expression of Clec2g in mice. Europ. J. Cell Biol. *85*, 345-354.
72. Inada, K., Hayashi, S., Iguchi, T., and Sato, T. (2006). Establishment of a primary culture model of mouse uterine and vaginal stroma for studying *in vitro* estrogen effects. Exp. Biol. Med. *231*, 303-310.
73. Matsuno, T., Tominaga, N., Arizono, K., Iguchi, T., and Kohara, Y. (2006). Graphical

Gaussian modeling for gene association structures based on expression deviation patterns induced by various chemical stimuli. Ieice Trans. Inf. Syst. *E89-D*, 1563-1574.

74. Oka, T., Mitui, N., Hinago, M., Miyahara, M., Fujii, T., Tooi, O., Santo, N., Urushitani, H., Iguchi, T., Hanaoka, Y., and Mikami, H. (2006). All ZZ male *Xenopus laevis* provides a clear sex reversal test for feminizing endocrine disruptors. Ecotoxicol. Environ. Safety *63*, 236-243.
75. Suzuki, A., Watanabe, H., Mizutani, T., Sato, T., Ohta, Y., and Iguchi, T. (2006). Global gene expression in mouse vaginae exposed to diethylstilbestrol at different ages. Exp. Biol. Med. *231*, 632-640.
76. Oda, S., Tatarazako, N., Watanabe, H., Morita, M., and Iguchi, T. (2006). Genetic differences in the production of male neonates in *Daphnia magna* exposed to juvenile hormone analogs. Chemosphere *63*, 1477-1484.
77. Gunderson, M.P., Kohno, S., Blumberg, B., Iguchi, T., and Guillette, L.J.Jr. (2006). Up-regulation of an alligator Cyp3A gene by toxaphene and dexamethasone and its effect on plasma testosterone concentrations. Aquat. Toxicol. *78*, 272-283.
78. Mitsui, N, Fujii, T., Miyahara, M., Oka, T., Kashiwagi, A., Kashiwagi, K., Handa, H., Urushitani, H., Santo, N., Tooi, O., and Iguchi, T. (2006). Development of metamorphosis assay using *Silurana tropicalis* for the detection of thyroid hormone disrupting chemicals. Ecotoxicol. Environ. Safety *64*, 281-287.
79. Kato, H., Furuhashi, T., Tanaka, M., Katsu, Y., Watanabe, H., Ohta, Y., and Iguchi, T. (2006). Effects of bisphenol A given neonatally on reproductive functions of male rats. Reprod. Toxicol. *22*, 20-29.
80. Grün, F., Watanabe, H., Zamanian, Z., Maeda, L., Arima, K., Chubacha, R., Gardiner, D.M., Kanno, J., Iguchi, T. and Blumberg, B. (2006). Endocrine disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. Mol. Endocrinol. *20*, 2141-2155.
81. Katsu, Y., Kohno, S., Oka, T., Mitsui, N., Tooi, O., Santo, N., Urushitani, H., Fukumoto, Y., Kuwabara, K., Ashikaga, K., Minami, S., Kato, S., Ohta, Y., Guillette, L.J.Jr., and Iguchi, T. (2006). Molecular cloning of estrogen receptor alpha (ERα; ESR1) of the Japanese giant salamander, *Andrias japonicus*. Mol. Cell. Endocrinol. *257-258*, 84-94.
82. Kajiwara, M., Kuraku, S., Kurokawa, T., Kato, K., Toda, S., Hirose, H., Takahashi, S., Shibuya, Y., Iguchi, T., Matsumoto, T., Miyata, T., Miura, T., and Takahashi, Y. (2006). Tissue preferential expression of estrogen receptor gene in the marine snail, *Thais clavigera*. Gen. Comp. Endocrinol. *148*, 315-326.
83. Kobayashi, M., Takahashi, E., Miyagawa, S., Watanabe, H., and Iguchi, T. (2006). Chromatin immunoprecipitation-mediated identification of aquaporin 5 as a regulatory target of estrogen in the uterus. Genes Cells *11*, 1133-1143.
84. Orlando, E.F., Katsu, Y., Miyagawa, S., and Iguchi, T. (2006). Cloning and differential expression of estrogen receptor and aromatase genes in the self-fertilizing hermaphrodite and male mangrove Rivulus, *Kryptolebias marmoratus.* J. Mol. Endocrinol. *37*, 353-365.
85. Kato, H., Naito, K., Katsu, Y., Watanabe, H., Ohta, Y., and Iguchi, T. (2006). Ontogenic expression of estrogen receptor a in female rat corneas. Ophthalmic Res. *38*, 358-362.

86. Takashima-Sasaki, K., Komiyama, M., Adachi, T., Sakurai, K., Kato, H., Iguchi, T., and Mori, C. (2006). Effect of exposure to high isoflavone containing diets on prenatal and postnatal offspring mice. Biosci. Biotech. Biochem. *70*, 2874-2882.
87. Kirigaya, A., Hayashi, S., Iguchi, T., and Sato, T. (2006). Developmental effects of ethinylestradiol on reproductive organs of female mice. In Vivo *20*, 867-873.
88. Kato, Y., Kobayashi, K., Oda, S., Tatarazako, N., Watanabe, H., and Iguchi, T. (2007). Cloning and characterization of the ecdysone receptor and ultraspiracle protein from the water flea *Daphnia magna*. J. Endocrinol. *193*, 183-194.
89. Suzuki, A., Urushitani, H., Sato, T., Watanabe, H., Ohta, Y., and Iguchi, T. (2007). Gene expression change in the Müllerian duct of the mouse fetus exposed to diethylstilbestrol *in utero*. Exp. Biol. Med. *232*, 503-514.
90. Watanabe, H., Takahashi, E., Nakamura, Y., Oda, S., Tatarazako, N., and Iguchi, T. (2007). Development of *Daphnia magna* DNA microarray for the evaluation of toxicity of environmental chemicals. Environ. Toxicol. Chem. *26*, 669-676.
91. Takase, M., and Iguchi, T. (2007). Molecular cloning of two isoforms of *Xenopus (Silurana) tropicalis* estrogen receptor mRNA and their expression during development. Biophys. Biochem. Acta *1769*, 172-181.
92. Iguchi, T., Katsu, Y., Horiguchi, T., Watanabe, H., Blumberg, B., and Ohta, Y. (2007). Endocrine disrupting organotin compounds are potent inducers of imposex in gastropods and adipogenesis in vertebrates. Mol. Cell. Toxicol. *3*, 1-10.
93. Sumi, M., Kawashima, Y., Fukumaki, T., Ishibashi, H., Arizono, K., Iguchi, T., and Shimizu, M. (2007). Comparison of serum vitellogenin, steroid hormone, gonad histopathology and bioaccumulation in common carp (*Cyprinus carpio*) between two rivers and a lake in Japan: Potential for endocrine disruption. Environ. Sci. *14*, 41-54.
94. Katsu, Y., Lange, A., Ichikawa, R., Urushitani, H., Paull, G.C., Cahill, L.L., Jobling, S., Tyler, C.R., and Iguchi, T. (2007). Functional associations between two estrogen receptors, environmental estrogen and sexual disruption in the roach (*Rutilus rutilus*). Environ. Sci. Technol. *41*, 3360-3374.
95. Oda, S., Tatarazako, N., Dorgerloh, M., Johnson, R., Kusk, O., Leverett, D., Marchini, S., Nakari, T., Williams, T., and Iguchi, T. (2007). Strain difference in sensitivity to 3,4-dichloroaniline and insect growth regulator, fenoxycarb, in *Daphnia magna*. Ecotoxicol. Environ. Safety *67*, 399-405.
96. Hara, A., Hirano, K., Shimizu, M., Fukada, H., Fujita, T., Itoh, F., Takada, H., Nakamura, M., and Iguchi, T. (2007). Carp (*Cyprinus carpio*) vitellogenin: characterization of yolk proteins, development of immunoassays and use as a biomarker of exposure to environmental estrogens. Environ. Sci. *14*, 95-108.
97. Kobayashi, T., Iguchi, T., and Ohta, Y. (2007). A beta-lipoproteinemia induced by ORP150 over-expression in mice. Comp. Med. *57*, 247-254.
98. Suzuki, A., Urushitani, H., Watanabe, H., Sato, T., Iguchi, T., Kobayashi, T., and Ohta, Y. (2007). Comparison of estrogen responsive genes in the mouse uterus, vagina and mammary gland. J. Vet. Med. Sci. *69*, 725-731.
99. Katsu, Y., Hinago, M., Sone, K., Guillette, L.J. Jr., and Iguchi, T. (2007). Analysis of the ligand-specificity of the estrogen and androgen receptors of mosquitofish, *Gambusia affinis*

affinis. Mol. Cell. Endocrinol. *276*, 10-17.
100. Chojnowski, J.L., Franklin, J., Katsu, Y., Iguchi, T., Guillette, L.J.Jr, Kimball, R.T., and Braun, E.L. (2007). Patterns of vertebrate isochore evolution revealed by comparison of expressed mammalian, avian and crocodilian genes. J. Mol. Evolution *65*, 259-266.

2) Invited reviews, book chapters

1. Iguchi, T (2000). Hormonal chaos. Nature Med. *6*, 246-247.
2. Iguchi, T. (2000). Developmental effects of estrogenic agents on mice, fish and frogs. Trabajos del Instituto Cajal. Tomo *LXXVII*, 52-53.
3. Iguchi, T. (2000). Embryonic and neonatal exposure to endocrine-altering contaminants: effects on mammalian female reproduction. In: Environmental Endocrine Disrupters. Eds. L. Guillette,Jr. and D.A. Crain, Taylor & Francis, New York, pp. 234-268.
4. Iguchi, T., and Sato, T. (2000). Endocrine disruption and developmental abnormalities of female reproduction. Am. Zoologist *40*, 402-411.
5. Watanabe, H., Buchanan, D.L., Handa, H., and Iguchi, T. (2001). Global analysis of gene expression induced by environmental endocrine disruptors. Perspective in Comparative Endocrinology: Unity and Diversity, Goos, H.J.Th., Rastogi, R.K., Vaudry, H. and Pierantoni, R. (eds.), Monduzzi Editore, pp.147-151.
6. Iguchi, T., Watanabe, H., and Katsu, Y. (2001). Developmental effects of estrogenic agents on mice, fish and frogs: a mini review. Horm. Behav. *40*, 248-251.
7. Iguchi, T., Watanabe, H., Katsu, Y., Mizutani, T., Miyagawa, S., Suzuki, A., Sone, K., and Kato, H. (2002). Developmental toxicity of estrogenic chemicals on rodents and other species. Congen. Anorm. *42*, 94-105.
8. Iguchi, T., Sumi, M., and Tanabe, S. (2002). Endocrine disruptor issues in Japan. Congen. Anorm. *42*, 106-119.
9. Iguchi, T. (2002). Endocrine disrupters and sexual differentiation. Clin. Pediatr. Endocrinol. *11* (Suppl. 18), 51-58.
10. Arizono, K., Ura, K., Tominaga, N., Kai, T., Kohara, Y., and Iguchi, T. (2002). *C. elegans* as a tool for environmental toxicology. *In* Toxicogenimics, Inoue, T. and Pennie, W.D. (eds.), Springer, p. 129-134.
11. Watanabe, H., Suzuki, A., Mizutani, T., Handa, H., and Iguchi, T. (2003). Large-scale gene expression analysis for evaluation of endocrine disruptors. *In* Toxicogenimics, Inoue, T. and Pennie, W.D. (eds.), Springer, p. 149-155.
12. Iguchi, T., and Watanabe, H., (2003). Developmental effects of hormonally active agents on animals: from daphnia to humans. Environ. Sci. *10 Suppl.*, 43-60.
13. Watanabe, H., and Iguchi, T. (2003). Evaluation of endocrine disruptors based on gene expression using a micorarray. Environ. Sci. *10 Suppl.*, 61-67.
14. Guillette, L.J.Jr., and Iguchi, T. (2003). Contaminant-induced endocrine and reproductive alterations in reptiles. Pure Appl. Chem. *75*, 2275-2286.
15. Okada, A., Sato, T., Ohta, Y., and Iguchi, T. (2005). Sex steroid hormone receptors in the developing female reproductive tract of laboratory rodents. J. Toxicol. Sci. *30*, 75-89.

16. Ankley, G.T., Black, M.C., Garric, J., Hutchinson, T.H., and Iguchi, T. (2005). Capter 6: A framework for assessing the hazard of pharmaceutical materials to aquatic species. In Human Pharmaceuticals: Assessing the Impacts on Aquatic Ecosystems. R.T. Williams ed. SETAC Press, pp.183-237.
17. Watanabe, H., and Iguchi, T. (2006). Using ecotoxicogenomics to evaluate the impact of chemicals on aquatic organisms. Marine Biol. *149*, 107-115.
18. Iguchi, T., Watanabe, H., and Katsu, Y. (2006). Application of ecotoxicogenomics for studying endocrine disruption in vertebrates and invertebrates. Environ. Health Perspect. *114 Suppl.1*, 101-105.
19. Iguchi, T., Irie, F., Urushitani, H., Tooi, O., Kawashima, Y., Roberts, M., Norrgren, L., and Hutchinson, T.H. (2006). Availability of *in vitro* vitellogenin assay for screening of estrogenic and anti-estrogenic activities of environmental chemicals. Environ. Sci. *13*, 161-183.
20. Cook, J., Iguchi, T., Linney, E., Miracle, A., Shaw, J., Viant, M., and Zacharewski, T. (2007). "Omic" Approaches in the context of environmental toxicology. *In* Benson, W.H. and Di Giulio, R.T. (eds.) Genomic Approaches for Cross-Species Extrapolation in Toxicology. Taylor and Francis, CRC Press, pp. 1-31.
21. Iguchi, T. (2007). What are the data on environmental contaminants disrupting reproductive function? Examples of mosquitofish, roach and medaka. In: Kruger, T.F., van der Spuy, Z. and Kempers, R.D. eds. Advances in Fertility Studies and Reproductive Medicine, pp.361-373.
22. Iguchi, T., Watanabe, H., and Katsu, Y. (2007). Toxicogenomics and ecotoxicogenomics for studying endocrine disruption and basic biology in vertebrates and invertebrates. Gen. Comp. Endocrinol. *153*, 25-29.
23. Iguchi, T., Katsu, Y., Urushitani, H., Lange, A., and Tyler, C.R. (2007). Developmental reproductive effects of exposure to pharmaceutical steroids in the aquatic environment: Studies on mosquitofish (*Gambusia affinis affinis*), roach (*Rutilus rutilus*) and medaka (*Oryzias latipes*). J. Marine Sci. Technol. *15*, 29-36.
24. vom Saal, F.S., Akingbemi, B.T., Belcher, S.M., Birnbaum, L.S., Crain, D.A., Eriksen, M., Guillette, L.J., Hauser, R., Heindel, J.J., Ho, S.-K., Iguchi, T., Jobling, S., Kanno, J., Keri, R.A., Knudsen, K.E., LeBlanc, G.A., Marcus, M., McLachlan, J.A., Myers, P., Nadal, A., Newbold, R.R., Olea, N., Prins, G.S., Richter, C.A., Rubin, B.S., Sonnenschein, C., Soto, A,M., Talsness, C.E., Vandernbergh, J.G., Vandenberg, L.N., Walser-Kuntz, D.R., Watson, C.S., Welshons, W.V., Wetherill, Y., and Zoeller, R.T. (2007). Capel Hill bisphenol A expert panel consensus statement: Integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure. Reprod. Toxocol. *24*, 131-138.
25. Crain, D.A., Eriksen, M., Iguchi, T., Jobling, S., Laufer, H., LeBlanc, G.A., and Guillette, L.J.Jr. (2007). An ecological assessment of bisphenol-A: Evidence from comparative biology. Reprod. Toxicol. *24*, 225-239.
26. Urushitani, H., Katsu, Y., Kato, Y., Tooi, O., Santo, N., Kawashima, Y., Kisaka, Y., Ohta, Y., Lange, A., Tyler, C.R., Johnson, R.D., and Iguchi, T. (2007). Medaka (*Oryzias latipes*) for use in evaluating developmental effects of endocrine active chemicals with special

reference to gonadal intersex (testis-ova). Environ. Sci. *14*, 211-233.
27. Tyler, C.R., Lange, A., Paull, G.C., Katsu, Y., and Iguchi, T. (2007). The roach (*Rutilus rutilus*) as a sentinel for assessing endocrine disruption. Environ. Sci. *14*, 235-253.
28. Takase, M., Mitsui, N., Oka, T., Tooi, O., Santoh, N., Pickford, D., and Iguchi, T. (2007). Development of biomarkers for endocrine disrupting activity in the emerging amphibian model, *Silurana (Xenopus) tropicalis*. Environ. Sci. *14*, 285-296.

渡邉　肇
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Dr Watanabe is an associate professor at the NIBB whose research interests revolve around the issue of endocrine chemical disrupters, in particular addressing the question of how the organism responds to environmental toxicants.

One important outcome of his research has been an understanding of the mode of action of the common herbicide atrazine as a human toxicant. In an effort to identify the molecular target of atrazine, he developed a high affinity bead system that allowed him to identify F1F0 as a target. This work was published in Nature Biotechnology, which is recognised as an extremely prestigious journal in international biology. Further research revealed that atrazine effects sperm ability by inhibiting ATP synthesis in the sperm cell.

Dr Watanabe is making seminal contributions to the use of the small crustacean Daphnia (the water flea), which is extremely sensitive to environmental toxicants and has assured life cycle. Under normal circumstances, Daphnia reproduce asexually, producing only females, but some chemicals can induce male development in these organisms. This system is rapidly being adopted as an environmental toxicants assay for drinking water worldwide, and Dr Watanabe has played a leading role in this area by creating a Daphnia genome database, available to all researchers. In addition he also plays a prominent role in the international society of Daphnia research.

Dr Watanabe is also making important advances in toxicogenomics -- that is, understanding molecular mechanisms of toxicants by looking at gene responses, not phenotypic or morphological responses. This avenue of research presents the exciting prospect of using alternatives to whole animals in toxicology studies, and Dr Watanabe has published nine papers on this subject in recent years.

Dr Watanabe has published 41 papers in the last eight years, including papers in the prominent journals Nature Biotechnology, JBC, Oncogene, and PNAS. In addition, he has published nine reviews and book chapters. This is a very pleasing rate of productivity for such a small group. He has presented 15 invited conference talks, including presentations in Korea, Italy, the United States and France. He was the organiser of the 2002 meeting of the molecular biology society of Japan. He has been successful in attracting a number of independent grants. These factors indicate that Dr Watanabe is becoming increasingly successful and well-recognised as a prominent researcher in environmental toxicology.

Dr Watanabe is highly active in collaborations at both the international and national levels. He is a member of the OECD/IPCS advisory group on toxicogenomics, and of the validation management group for the ecotoxicity testing OECD invertebrate expert group. He collaborates

with researchers at the national Institute of environmental studies, Tsukuba, the National Institutes of Health science, the Tokyo Institute of technology, the Tokyo University of pharmaceuticals, RIKEN, and the universities of Hokkaido, Tokyo, Kyoto, Kobe, Indiana and California. He is a visiting scientist of the national Institute of environmental studies in Tsukuba.

Dr Watanabe supervises two PhD students through Tohoku University and Hirosaki University. In addition, he undertakes undergraduate teaching and Nagoya City University, Osaka University, and Nihon University. These activities represent solid contributions to the education of young scientists in Japan.

In summary, Dr Watanabe has played an important role in introducing the concept of ecotoxicogenomics, and in establishing a worldwide database for researchers using the organism Daphnia. He is a dynamic, respected and productive scientist whose efforts receive strong support from the committee.

（和訳）

渡邉博士は基礎生物学研究所の准教授であり、内分泌かく乱物質の問題、とりわけ、生物が環境毒物に対してどのように応答するかの疑問を解明することに興味をもっている。

博士の研究の重要な成果の一つは、よく使われる農薬アトラジンのヒトへの毒物としての作用機序を解明したことであった。アトラジンの分子ターゲットを同定するため、博士は、高親和性ビーズシステムを開発し、この研究は、Nature Biotechnologyに掲載された。Nature Biotechnologyは生物学の極めてレベルの高い論文誌として認められている。この親和性ビーズシステムを用いてアトランジの分子ターゲットがF1F0であることを発見した。さらに研究を行って、アトラジンが精子のATP合成を阻害することで、精子の能力に影響を及ぼすことを明らかにした。

渡邉博士は小さな甲殻類のオオミジンコを活用することに先導的役割を果たした。オオミジンコは環境毒物に対する感受性が極めて高く、安定したライフサイクルを有している。正常な環境では、オオミジンコは無性生殖し、雌しか生じないが、ある種の化学物質は雄の発生を誘導できる。このシステムは、飲料水中の環境毒物アッセイ法として世界中で短期間に採用されることとなり、渡邉博士は、オオミジンコのゲノムデータベースを作成し、全ての研究者が利用可能にすることに主な役割を果たした。加えて、オオミジンコ研究の国際的分野に主要な役割も担っている。

渡邉博士はまたトキシコゲノミクス（表現型や形態的応答ではなく遺伝子応答を調べることで、毒物の分子機序を解明すること）にも大きな進展をもたらしている。この研究分野は、毒物学研究において動物全体に代わって代替動物を用いるという興味深い展望を示すものであり、渡邉博士はこの点に関して最近9件の論文を発表した。

渡邉博士は過去8年間に、有力な論文誌Nature Biotechnology、JBC、Oncogene、PNASを含め、41報の論文を発表している。加えて、9件の総説論文と本の章の執筆を行っている。少人数のグループでこのように高い生産性を示しているのは極めて歓迎すべきものである。博士は15件の招待講演を、韓国、イタリア、米国、フランスを含め、行っている。博士は日本分子生物学会の2002年次大会のオーガナイザーであった。博士は多数の助成金獲得に成功している。これらのことは、渡邉博士が環境毒性学の分野の傑出した研究者として成功し認められつつあることを示すものである。

渡邉博士は国際共同研究や国内共同研究を積極的に行っている。博士はトキシコゲノミクスに関するOECD/IPCS諮問委員会や、OECD無脊髄動物専門家グループの環境毒性検査妥当性管理グループの委員である。博士は国立環境研究所（つくば市）、国立医薬品衛生研究所、東京工業大学、東京大学薬学部、理化学研究所、北海道大学、東京大学、京都大学、神戸大学、インディアナ大学、カリフォルニア大学の研究者と共同研究を行っている。国立環境研究所（つくば市）の非常勤研究員である。

渡邉博士は東京大学と弘前大学の2名のPhD大学院生の指導を行っている。加えて、名古屋市立大学、大阪大学、日本大学の学部教育を行っている。これらの活動は、日本の若手研究者の教育に確実に貢献している。

まとめると、渡邉博士はエコトキシコゲノミクスの概念を導入すること、およびオオミジンコを研究者が利用するための世界的データベースを確立することに重要な役割を果たした。博士はダイナミックで尊敬され生産的な研究者で、博士の努力を当委員会は強く支持する。

研究業績（2000 年より）:

1) Research articles in peer reviewed journals

1. Shimizu, N., Sugimoto, K., Tang, J., Nishi, T., Sato, I., Hiramoto, M., Aizawa, S., Hatakeyama, M., Ohba, R., Hatori, H., Yoshikawa, T., Suzuki, F., Oomori, A., Tanaka, H., Kawaguchi, H., Watanabe, H., and Handa H. (2000). High-performance affinity beads for identifying drug receptors. Nat. Biotechnol. *18*, 877-881.
2. Ishizu, K.-i., Watanabe, H., Han, S.-i., Kanesashi, S.-n., Hoque, M., Yajima, H., Kataoka, K., and Handa, H. (2001). Roles of disulfide linkage and calcium ion-mediated interactions in assembly and disassembly of virus-like particles composed of simian virus 40 VP1 capsid protein. J. Virol. *75*, 61-72.
3. Uchida, K., Suzuki, A., Kobayashi, Y., Buchanan, D.L., Sato, T., Watanabe, H., Katsu, Y., Suzuki J., Asaoka, K., Mori, C., Arizono, K., and Iguchi, T. (2002). Bisphenol-A administration during pregnancy results in fetal exposure in mice and monkeys. J. Health Sci. *48*, 579-582.

4. Watanabe, H., Suzuki, A., Mizutani, T., Kohno, S., Lubahn, D.B., Handa, H., and Iguchi T. (2002). Genome-wide analysis of changes in early gene expression induced by estrogen. Genes Cells *7*, 497-508.
5. Honma, S., Suzuki, A., Buchanan, D.L., Katsu, Y., Watanabe, H., and Iguchi, T. (2002). Low dose effect of in utero exposure to bisphenol A and diethylstilbestrol on female mouse reproduction. Reprod. Toxicol. *16*, 117-122.
6. Suzuki, A., Sugihara, A., Uchida, K., Sato, T., Ohta, Y., Katsu, Y., Watanabe, H., and Iguchi, T. (2002). Developmental effects of perinatal exposure to bisphenol-A and diethylstilbestrol on reproductive organs in female mice. Reprod. Toxicol. *16*, 107-116.
7. Sawa, C., Yoshikawa, T., Matsuda-Suzuki, F., Delehouzee, S., Goto, M., Watanabe, H., Sawada, J., Kataoka, K., and Handa, H. (2002). YEAF1/RYBP and YAF-2 are functionally distinct members of a cofactor family for the YY1 and E4TF1/hGABP transcription factors. J. Biol. Chem. *277*, 22484-22490.
8. Nishi, T., Shimizu, N., Hiramoto, M., Sato, I., Yamaguchi, Y., Hasegawa, M., Aizawa, S., Tanaka, H., Kataoka, K., Watanabe, H., and Handa, H. (2002). Spatial redox regulation of a critical cysteine residue of NF-kappa B in vivo. J. Biol. Chem. *277*, 44548-44556.
9. Kanesashi, S.-n., Ishizu, K.-i., Kawano, M.-a., Han, S.-i., Tomita, S., Watanabe, H., Kataoka, K., and Handa, H. (2003). Simian virus 40 VP1 capsid protein forms polymorphic assemblies in vitro. J. Gen. Virol. *84*, 1899-1905.
10. Watanabe, H., Suzuki, A., Kobayashi, M., Lubahn, D., Handa, H., and Iguchi, T. (2003). Analysis of temporal changes in the expression of estrogen regulated genes in the uterus. J. Mol. Endocrinol. *30*, 347-358.
11. Tatarazako, N., Oda, S., Watanabe, H., Morita, M., and Iguchi, T. (2003). Juvenile hormone agonists affect the occurrence of male *Daphnia*. Chemosphere *53*, 827-833.
12. Watanabe, H., Suzuki, A., Kobayashi, M., Lubahn, D., Handa, H., and Iguchi, T. (2003). Similarity and differences in uterine gene expression patterns caused by treatment with physiological and non-physiological estrogens. J. Mol. Endocrinol. *31*, 487-497.
13. Miyagawa, S., Katsu, Y., Watanabe, H., and Iguchi, T. (2003). Estrogen-independent activation of ErbBs signaling and estrogen receptor in the mouse vagina exposed neonatally to diethylstilbestrol. Oncogene *23*, 340-349.
14. Han, S.-i., Kawano, M., Ishizu, K.-i., Watanabe, H., Hasegawa, M., Kanesashi, S.-n., Kim, Y.-s., Nakanishi, A., Kataoka, K., and Handa, H. (2004). Rep68 protein of adeno-associated virus type 2 interacts with 14-3-3 proteins depending on phophorylation at serine 535. Virology *320*, 144-155.
15. Inui, M., Adachi, T., Takenaka, S., Inui, H., Nakazawa, M., Ueda, M., Watanabe, H., Mori, C., Iguchi, T., and Miyatake, K. (2003). Effect of UV screens and preservaties on vitellogenin and choriogenin production in male medaka (*Oryzias latipes*). Toxicology *194*, 43-50.
16. Endoh, M., Zhu, W., Hasegawa, J., Watanabe, H., Kim, D.-k., Aida, M., Inukai, N., Narita, T., Yamada, T., Furuya, A., Sato, H., Yamaguchi, Y., Mandal, S.S., Reinberg, D., Wada, T., and Handa, H. (2003). Human Spt6 stimulates transcription elongation by RNA polymerase II in vitro. Mol. Cell. Biol. *24*, 3324-3336.
17. Kato, H., Iwata, T., Katsu, Y., Watanabe, H., Ohta, Y., and Iguchi, T. (2004). Evaluation of

estrogenic activity in diets for experimental animals using in vitro assay. J. Agric. Food Chem. *52*, 1410-1414.
18. Watanabe, H., Suzuki, A., Kobayashi, M., Lubahn, D., Handa, H., and Iguchi, T. (2004). Tissue-specific estrogenic and non-estrogenic effects of a xenoestrogen, nonylphenol. J. Mol. Endocrinol. *33*, 243-252.
19. Miyagawa, S., Suzuki, A., Katsu, Y., Kobayashi, M., Goto, M., Handa, H., Watanabe, H., and Iguchi, T. (2004). Persistent gene expression in mouse vagina exposed neonatally to diethylstilbestrol. J. Mol. Endocrinol. *32*, 663-677.
20. Okada, A., Ohta, Y., Brody, S.L., Watanabe, H., Krust, A., Chambon, P., and Iguchi, T. (2004). Role of foxj1 and estrogen receptor alpha in ciliated epithelial cell differentiation of the neonatal oviduct. J. Mol. Endocrinol. *32*, 615-25.
21. Sone, K., Hinago, M., Kitayama, A., Morokuma, J., Ueno, N., Watanabe, H., and Iguchi, T. (2004). Effects of 17beta-estradiol, nonylphenol, and bisphenol-A on developing *Xenopus laevis* embryos. Gen. Comp. Endocrinol. *138*, 228-236.
22. Watanabe, H., Suzuki, A., Goto, M., Ohsako, S., Tohyama, C., Handa, H., and Iguchi, T. (2004). Comparative uterine gene expression analysis after dioxin and estradiol administration. J. Mol. Endocrinol. *33*, 763-771.
23. Ohtsu, Y., Ohba, R., Imamura, Y., Kobayashi, M., Hatori, H., Zenkoh, T., Hatakeyama, M., Manabe, T., Hino, M., Yamaguchi, Y., Kataoka, K., Kawaguchi, H., Watanabe, H., and Handa, H. (2005). Selective ligand purification using high-performance affinity beads. Anal. Biochem. *338*, 245-252.
24. Sone, K., Hinago, M., Itamoto, M., Katsu, Y., Watanabe, H., Urushitani, H., Tooi, O., Guillette, L.J. Jr., and Iguchi, T. (2005). Effects of an androgenic growth promoter 17beta-trenbolone on masculinization of Mosquitofish (*Gambusia affinis affinis*). Gen. Comp. Endocrinol. *143*, 151-160.
25. Shimizu, N., Ouchida, R., Yoshikawa, N., Hisada, T., Watanabe, H., Okamoto, K., Kusuhara, M., Handa, H., Morimoto, C., and Tanaka, H. (2005). HEXIM1 forms a transcriptionally abortive complex with glucocorticoid receptor without involving 7SK RNA and positive transcription elongation factor b. Proc. Natl. Acad. Sci. USA *102*, 8555-8560.
26. Oda, S., Tatarazako, N., Watanabe, H., Morita, M., and Iguchi, T. (2005). Production of male neonates in four cladoceran species exposed to a juvenile hormone analog, fenoxycarb. Chemosphere *60*, 74-78.
27. Watanabe, H., Tatarazako, N., Oda, S., Nishide, H., Uchiyama, I., Morita, M., and Iguchi, T. (2005). Analysis of expressed sequence tags of the water flea *Daphnia magna*. Genome *48*, 606-609.
28. Oda, S., Tatarazako, N., Watanabe, H., Morita, M., and Iguchi, T. (2005). Production of male neonates in *Daphnia magna* (Cladocera, Crustacea) exposed to juvenile hormones and their analogs. Chemosphere *61*, 1168-1174.
29. Watanabe, H., Takahashi, E., Kobayashi, M., Goto, M., and Iguchi, T. (2006). The estrogen-responsive adrenomedullin gene identified by DNA microarray analysis is directly regulated by estrogen receptor. J. Mol. Endocrinol. *36*, 81-89.
30. Oda, S., Tatarazako, N., Watanabe, H., Morita, M., and Iguchi, T. (2006). Genetic differences in the production of male neonates in *Daphnia magna* exposed to juvenile

hormone analogs. Chemosphere *63*, 1477-1484.
31. Suzuki, A., Watanabe, H., Mizutani, T., Sato, T., Ohta, Y., and Iguchi, T. (2006). Global gene expression in mouse vaginae exposed to diethylstilbestrol at different ages. Exp. Biol. Med. *231*, 632-640.
32. Ogura, Y., Azuma, M., Tsuboi, Y., Kabe, Y., Yamaguchi, Y., Wada, T., Watanabe, H., and Handa, H. (2006). TFII-I down-regulates a subset of estrogen-responsive genes through its interaction with an initiator element and estrogen receptor alpha. Genes Cells. *11*, 373-381.
33. Kato, H., Furuhashi, T., Tanaka, M., Katsu, Y., Watanabe, H., Ohta, Y., and Iguchi, T. (2006). Effects of bisphenol A given neonatally on reproductive functions of male rats. Reprod. Toxicol. *22*, 20-29.
34. Kato, H., Naito, K., Katsu, Y., Watanabe, H., Ohta, Y., and Iguchi, T. (2006). Ontogenic expression of estrogen receptor-alpha in female rat corneas. Ophthalmic Res. *38*, 361-365.
35. Kobayashi, M., Takahashi, E., Miyagawa, S., Watanabe, H., and Iguchi, T. (2006). Chromatin immunoprecipitation-mediated target identification proved aquaporin 5 is regulated directly by estrogen in the uterus. Genes Cells *11*, 1133-1143.
36. Grun, F., Watanabe, H., Zamanian, Z., Maeda, L., Arima, K., Cubacha, R., Gardiner, D.M., Kanno, J., Iguchi, T., and Blumberg, B. (2006). Endocrine disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. Mol. Endocrinol. *20*, 2141-2155.
37. Kabe, Y., Ohmori, M., Shinouchi, K., Tsuboi, Y., Hirao, S., Azuma, M., Watanabe, H., Okura, I., and Handa, H. (2006). Porphyrins Accumulate in Mitochondria via 2-oxoglutarate Carrier. J. Biol. Chem. *281*, 31729-31735.
38. Suzuki, A., Urushitani, H., Sato, T., Watanabe, H., Ohta, Y., and Iguchi, T. (2007). Gene expression change in the Müllerian duct of the mouse fetus exposed to diethylstilbestrol in utero. Exp. Biol. Med. *232*, 503-514.
39. Watanabe, H., Takahashi, E., Nakamura, Y., Oda, S., Tatarazako, N., and Iguchi, T. (2007). Development of a *Daphnia magna* DNA microarray for evaluating the toxicity of environmental chemicals. Environ. Toxicol. Chem. *26*, 669-676.
40. Kato, Y., Kobayashi, K., Oda, S., Tatarazako, N., Watanabe, H., and Iguchi, T. (2007). Cloning and characterization of the ecdysone receptor and ultraspiracle protein from the water flea *Daphnia magna*. J. Endocrinol. *193*, 183-194.

2) Invited reviews, book chapters

1. Watanabe, H., Buchanan, D.L., Handa, H., and Iguchi, T. (2001). Global analysis of gene expression induced by environmental endocrine disruptors. Perspective in Comparative Endocrinology: Unity and Diversity, Goos, H.J.Th., Rastogi, R.K., Vaudry, H. and Pierantoni, R. (eds.) p.147-151, Monduzzi Editore Printing.
2. Tatarazako, N., Oda, S., Morita, M., Sonobe, H., Watanabe, H., and Iguchi, T. (2002). Insecticides for juvenile hormone agonists exert the influence on the occurrence of the male daphnid. Proc. Jap. Comp. Endocrinol. *17*, 87
3. Watanabe, H., Suzuki, A., Mizutani, T., Handa, H., and Iguchi, T. (2002). Large-scale gene

expression analysis for evaluation of endocrine disruptors. Toxicogenimics, Inoue, T. and Pennie, W.D. (eds.), p149-155, Springer Printing.
4. Iguchi, T., Watanabe, H., Katsu, Y., Mizutani, T., Miyagawa, S., Suzuki, A., Sone, K., and Kato, H. (2002). Developmental toxicity of estrogenic chemicals on rodents and other species. Congenital Anomalies *42*, 94-105.
5. Iguchi, T., and Watanabe, H. (2003). Developmental effects of hormonally active agents on animals: from daphnia to humans. Environ. Sci. *10 Suppl*., 43-60.
6. Watanabe, H., and Iguchi, T. (2003). Evaluation of endocrine disruptors based on gene expression using a micorarray. Environ. Sci. *10 Suppl.*, 61-67.
7. Horiguchi, T., Katsu, Y., Ohta, Y., Watanabe, H., Iguchi, T., Morishita, F., Matsushima, O., Shiraishi, H., and Morita, M. (2004). Is inhibition of aromatase activity due to TBT exposure the primary factor for gastropod imposex? Mar Environ Res 58, 459-460
8. Watanabe. H,, and Iguchi, T. (2006). Using ecotoxicogenomics to evaluate the impact of chemicals on aquatic organisms. Marine Biol. *149*, 107-116.
9. Iguchi, T., Watanabe, H., and Katsu, Y. (2006). Application of ecotoxicogenomics for studying endocrine disruptionin vertebrates and invertebrates. Environ. Health Perspectives *114 Suppl 1*, 101-105.
10. Iguchi, T., Watanabe, H., and Katsu, Y. (2007). Toxicogenomics and ecotoxicogenomics for studying endocrine disruption and basic biology. Gen Comp Endocrinol. *153*, 25-29.

田中　実
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Dr Tanaka joined the NIBB in 2004. His research aims to reveal the molecular mechanisms of gonad development and sex differentiation, using the Medaka fish as his primary model. Medaka has become a very important model system in developmental biology, primarily through the efforts of Japanese researchers. Dr Tanaka has played a key role in providing national resources for Medaka research.

Dr Tanaka has made special programs in his mutagenesis programs aimed at discovering genes which when mutated give rise to increased number of germ cells, a decrease number of germ cells, or irregular clustering or patterning of the germ cells. In order to do this efficiently and effectively, Dr Tanaka has developed several new strains of transgenic Medaka fish in which germ cells and other populations of the developing gonad are marked with fluorescent markers so that they can be easily visualised. In all, Dr Tanaka has developed ten new transgenic lines for this purpose. Using this system, he has been able to address fundamental issues such as the importance of germ cells in the sex differentiation process. He has found that germ cell deficient Medaka exhibit female to male sex reversal, underlining the critical role of germ cells, in contrast to other species. This important finding was published this year in the prestigious journal PNAS.

Dr Tanaka has a relatively small group comprising only five scientists. Despite this, he has been very successful in publishing high-profile papers in impressive international journals. These include PNAS, Developmental Biology and Cell. Perhaps more importantly, Dr Tanaka has played a lead role in establishing NIBB as one of the three core centres of Medaka research in Japan, and has made major contributions to the adoption of Medaka has a standard research tool in that country and worldwide. In this role, he has acted as a national bioresource project committee member, which plays an important role in strategic planning for Medaka research in Japan. He has been active in organising training workshops and technology meetings to foster this area of research. The committee notes that next February, he will be organising the international conference entitled "New frontiers for the Medaka model -- genome, bioresources and biology". In his role as a leading Medaka researcher, Dr Tanaka has been invited to present several talks in Germany and the USA.

Dr Tanaka fulfils a number of important other administrative roles, such as membership of the promotions committee of ERATO, and as an examiner for the JSPS fellowship scheme. He is a member of the committee that promotes collaboration and exchange between NIBB and the EMBL.

Dr Tanaka also collaborates strongly, but internationally, with laboratories in Australia and Germany, and nationally, with laboratories at Kyoto University, and Niigata University.

Dr Tanaka participates in undergraduate lecturing and the Graduate University for Advanced Studies (Sokendai), and acts as a part-time lecturer for Hokkaido University. He is on the NIBB student selection committee, and currently supervises to graduate students and one post doc.

In summary, the committee was very pleased to see Dr Tanaka's research program coming to an exciting head, with important and high profile papers now regularly being published. Dr Tanaka is clearly a very hard-working and committed advocate of Medaka research, and receives our strong support. The next five years will be critical period for Dr Tanaka, and we believe that a more ambitious approach to grant application will prove to be a rewarding strategy.

（和訳）

田中博士は2004年に基礎生物学研究所に着任した。博士の研究は、生殖腺発生と性分化の分子機序を、メダカを主なモデルに用いて解明することを目的としている。メダカは、主に日本人研究者の努力によって、発生生物学での極めて重要なモデル系となってきている。田中博士はメダカ研究の国内リソースを提供するのに重要な役割を果たしてきている。

田中博士は、変異体作製研究の中でも特に、生殖細胞が増加したり減少したり，また生殖細胞の集まり方や分布が異常をもたらすような遺伝子を見いだそうとする研究を行った。これを効率的かつ有効に行うため、田中博士はトランスジェニックメダカの系統をいくつか作成し、発生期の生殖腺の生殖細胞やその他の細胞に蛍光マーカーをつけ、容易に視覚化できるようにした。この目的のため、田中博士は合計10種のトランスジェニック系統を新たに作成した。この系を用いて、性分化プロセスでの生殖細胞の重要性などの基本的問題を解明することが可能になった。博士は，生殖細胞欠損メダカが雌から雄への性転換を示すことを発見し、他の動物種とは対照的に、生殖細胞が極めて重要な役割を果たすことを示した。この重要な発見は、高名な論文誌PNASに本年（2007年）掲載された。

田中博士の研究グループは、研究者がわずか5名と比較的小さなグループである。それにも関わらず、博士はよく知られた論文誌に良質の論文を掲載するのに極めて高い成果をあげている。掲載された論文誌としては、PNAS、Developmental Biology、Cellがある。おそらくそれよりも重要なこととして、田中博士は基礎生物学研究所を日本のメダカ研究センターの3大中核センターの一つとして確立することに率先的な役割を果たし、国内外でメダカを標準的な研究ツールとして用いることに大きな貢献を果たした。この役割において、博士は、ナショナルバイオリソースプロジェクトの委員となっている。この委員会は、日本のメダカ研究の戦略立案に重要な役割を果たしている。この分野の研究を促進させるための実習ワークショップや技術会合を主催するのに積極的であった。2008年2月に、“New frontiers for the Medaka model -- genome, bioresources and biology”と題する国際コンファレンスをオーガナイズする予定であることを当委員会では認識している。メダカ研究を主導する研究者として、田中博士はドイツと米国で数

回招待講演を行っている。

田中博士は、ERATO推進委員会の委員や、JSPSフェローシップ審査委員などのその他の重要な運営的役割を果たしている。基礎生物学研究所とEMBLの研究協力と人材交流を促進する委員会の委員である。

田中博士は、国際的にはオーストラリアやドイツと、国内的には、京都大学や新潟大学との共同研究も積極的に進めている。

田中博士は学部教育や総合研究大学院大学（総研大）の教育に参加しており、北海道大学の非常勤講師である。博士は、基礎生物学研究所の大学院選考委員会の委員であり、2名の大学院学生と1名のポストドクを指導している。

以上まとめると、田中博士の研究プログラムが極めて高い成功を収めつつあり、良質の論文を発表し続けていることを、当委員会は極めて高く評価している。田中博士は激務をこなし、メダカ研究を提唱するのに積極的であり、当委員会も強く支持する。今後5年間は、田中博士にとって重要な時期となるであろう。研究費申請に対してより積極的なアプローチをとることが、実りの多い戦略となるであろうと、われわれは考えている。

研究業績（2004年より）：

1) Research articles in peer reviewed journals

1. Suzuki, A., Tanaka, M., Shibata, N., and Nagahama, Y. (2004). Expression of aromatase mRNA and effects of aromatase inhibitor during ovarian development in the medaka, *Oryzias latipes*. J. Exp. Zool. *301*, 266-273.
2. Naruse, K., Tanaka. M., Mita, K., Shima, A., Postlethwait, J., and Mitani, H. (2004). A Medaka Gene Map: The Trace of Ancestral Vertebrate Proto-chromosomes Revealed by Comparative Gene Mapping. Genome Res. *14*, 820-824.
3. Morinaga, C., Tomonaga, T., Sasado, T., Suwa, H., Niwa, K., Yasuoka, A., Henrich, T., Watanabe, T., Deguchi, T., Yoda, H., Hirose, Y., Iwanami, N., Kunimatsu, S., Okamoto, Y., Yamanaka, T., Tanaka, M. (Corresponding Auhor) Kondoh, H., and Furutani-Seiki, M. (2004). Mutations affecting gonadal development in Medaka, *Oryzias latipes*. Mech. Dev. *121*, 829-839.
4. Sasado, T., Morinaga, C., Niwa, K., Shinomiya, A., Yasuoka, A., Suwa, H., Hirose, Y., Yoda, H., Henrich, T., Deguchi, T., Iwanami, N., Watanabe, T., Kunimatsu, S., Osakada, M., Okamoto, M., Kota, Y., Yamanaka, T., Tanaka, M., Kondoh, H., and Furutani-Seiki, M. (2004). Mutations affecting early distribution of primordial germ cells in Medaka (*Oryzias latipes)* embryo. Mech. Dev. *121*, 817-828.
5. Hano, T., Oshima, Y., Oe, T., Kinoshita, M., Tanaka, M., Wakamatsu, Y., Ozato, K., and

Honjo, T. (2005). Quantitiative Bio-imaging analysis for evaluation of sexual differentiation in germ cells of *olvas*-GFP/STII YI medaka (*Oryzias latipes*) nanoinjected in ovo with ethinylestradiol. Environ. Toxicol. Chem. *24*, 70-77.

6. Kurokawa, H., Aoki, Y., Nakamura, S., Ebe, Y., Kobayashi, D., and Tanaka, M. (2006). Time-lapse analysis reveals different modes of primordial germ cell migration in the medaka *Oryzias latipes*. Develop. Growth Differ. *48*, 209-221.
7. Nakamura, S,. Kobayashi, D., Aoki, Y., Yokoi, H., Ebe, Y., Wittbrodt, J., and Tanaka, M. (2006). Identification and lineage tracing of two populations of somatic gonadal precursors in medaka embryos. Dev. Biol. *295*, 678-688.
8. Saito, T., Fujimoto, T., Maekawa, S., Inoue, K., Tanaka, M., Arai, K., and Yamaha, E. (2006). Visualization of primordial germ cells in vivo using GFP-*nos*1 3'UTR mRNA. Int. J. Dev. Biol. *50*, 691-700.
9. Hano, T., Oshima, Y., Kinoshita, M., Tanaka, M., Mishima, N., Ohyama, Y., Yanagawa, T., Wakamatsu, Y., Ozato, K., and Honjo, T. (2007). Quantitative bioimaging analysis of gonads in olvas-GFP/ST-II YI medaka (transgenic *Oryzias latipes*) exposed to ethinylestradiol, Environ. Sci. Tech. *41***,** 1473-1479.
10. Takamatsu, N., Kurosawa, G., Takahashi, M., Inokuma, R., Tanaka, M., Kanamori, A., and Hori, H. (2007). Duplicated Abd-B class genes in medaka hoxAa and hoxAb clusters exhibit different expression patterns in pectoral fin buds. Dev. Genes Evol. *217*, 263-273.
11. Morinaga, C., Saito, D., Nakamura, S., Sasaki, T., Asakawa, S., Shimizu, N., Mitani, H., Furutani-Seiki, M., Tanaka, M (Corresponding author)., and Kondoh, H. (2007). The *hotei* mutation of medaka in the anti-Müllerian hormone receptor causes the dysregulation of germ cell and sexual development. Proc. Acad. Natl. Sci. USA *104*, 9691-9696.
12. Saito, D., Morinaga, C., Aoki, Y., Nakamura, S., Mitani, H., Furutani-Seiki, M., Kondoh, H., and Tanaka, M. (2007). Proliferation of germ cells during gonadal sex differentiation in medaka: insights from germ cell depleted mutant *zenzai*. Dev. Biol. *310*, 280-290.
13. Kurokawa, H., Saito, D., Nakamura, S., Katoh-Fukui, Y., Ohta, K., Aoki, Y., Baba, T., Morohashi, K., and Tanaka, M. (2007). Germ cells are essential for sexual dimorphism in the medaka gonad. Proc. Acad. Natl. Sci. USA *104*, 16958-16963.

2) Invited reviews, book chapters

1. Mitani, H., Shima, A., Naruse, K., and Tanaka, M. (2004). Medaka genome mapping for functional genomics. In Fish Development and Genetics. pp.612-636. (eds: Gong, Z. and Korzh, V.) World Scientific.

４）神経生物学領域

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Professor Noda is an established scientist of international reputation. He has continually chosen important biological problems to study and publishes these studies in the top peer reviewed journals. Additionally, his lab has pioneered creative and important technical advances such as substrate trapping using the yeast system. He has been invited to present his work at prestigious scientific meetings and has written several timely reviews. He has also contributed to the scientific community at large by organization of symposia in his research area.

Dr. Noda's recent work concerns two general topics very important for the future of biomedical science and human disease : 1) molecular mechanisms responsible for wiring of neuronal circuits, and 2) mechanisms of communication between glia and neurons. To address the former topic, Dr. Noda's lab has exploited the formation of topographic maps during developing retina. He has utilized the chick retina because of its accessibility to experimental manipulations. He used the very clever strategy of screening for molecules that are expressed asymmetrically in the retina, with the idea that these molecules should account for the corresponding asymmetric functional topology. He found such molecules and has been characterizing their functions over the past several years. The result of this work is a unifying principle of gene cascades that both establish retinal patterning and fine-tune the retinotectal projections. Despite the fact that this area of Neuroscience is very competitive, Dr. Noda's creative approaches have advanced the field, as evidenced by publications in *Nature Genetics*, *Proceedings of the National Academy of Science, USA*, and *Science* magazine, all journals of wide general readership and stature. He has also utilized clever strategies to identify and study the phosphatases that modulate tyrosine kinase receptors important in fine tuning axonal projections.

With respect to the second topic, neuronal glial interactions, Dr. Noda's lab has again, in our opinion, led the field. While glia have been thought previously to be simply structural components of the brain, more recent work by others has suggested that glia play important functional roles as well, via mysterious interactions with their intimate neuronal neighbors. It was becoming apparent that some perturbations of glial activity may cause changes in neuronal activity, but how this occurred has been enigmatic. Dr. Noda and his colleagues have shown unequivocally that a particular type of glia, astrocytes, regulate salt balance in mice via their interactions with a particular class of neurons. Specifically, in an elegant series of experiments (in which Dr. Watanabe took part), Dr. Noda's lab showed that it was a metabolic product of astrocytes, lactate, which had the dramatic effects on neuronal activity. They pursued this finding using innovative genetic manipulations to show that there was an interaction between the sodium channel (Na_x/Na_v2/NaG), originally discovered in their lab, and another membrane protein. The two proteins together regulate glial metabolism. To my knowledge, this is the

first direct demonstration of a glial effect on animal behavior. I suspect that this will turn out to be a more common occurrence such that the work of Noda et al., will have opened up an entire field. These studies have been published in the *Journal of Neuroscience*, *Neuron* and *Nature Neuroscience*, the premier journals in the area of Neuroscience. Finally, the work on body fluid homeostasis has direct relevance to human disease. Dr. Noda is collaborating with a medical doctor to understand why a patient with an unusual salt balance disorder has antibodies to this same sodium channel.

Future projects: Dr Noda's lab will analyze how to go from gene to behavior using the glial-GABA circuit underlying body fluid homeostasis. He will also continue to analyze how receptor tyrosine kinases are regulated by phosphatases for fine-tuning of the neuronal projection patterns. We are very enthusiastic about the proposed studies. He has written and secured grants for these studies.

（和訳）

野田教授は国際的に名声の高い科学者である。教授は常に生物学的に重要な問題を研究テーマに選び、これらの研究結果を、最高の査読付き論文誌に発表している。さらに、教授の研究室は酵母系を用いた基質トラッピング法(substrate trapping)などのクリエーティブで重要な技術的進展を先導してきた。教授は一流の学会に招待されており、タイムリーな総説論文をいくつも書いている。教授はまた、研究領域のシンポジウムをオーガナイズすることで、学界への貢献も大である。

野田博士の最近の研究は、今後の医科学やヒトの疾患にとって極めて重要な 2 つのテーマに関するものである。すなわち、1)神経回路網の配線の分子機序、2)グリア細胞とニューロンの間のコミュニケーションの機序である。前者のテーマを研究するため、野田博士の研究室では、発生期の網膜にトポグラフィックマップが形成されることを利用した。実験操作がしやすいため、ニワトリ胚の網膜を用いた。網膜内で非対称的に発現される分子があれば、それに対応する非対称性の機能的トポロジーを説明できるはずだという考えのもとに、そのような分子をスクリーニングするという極めて巧妙な戦略を採用した。教授はそのような分子群を発見し、この数年間それらの機能の特性解明を行ってきた。この研究結果は、網膜のパターン化と、網膜視蓋投射のファインチューニングの両方を確立する遺伝子カスケードの統合原理である。神経科学のこの領域は極めて競争が激しいにも関わらず、野田博士のクリエーティブなアプローチは、この分野をリードしている。このことは、*Nature Genetics* 誌、*Proceedings of the National Academy of Science, USA* 誌、ならびに *Science* 誌に掲載されたことからも示される。これらは全て、広い読者層と高い評価を得ている論文誌である。教授はまた、賢明な戦略を用いて、軸索投射のファインチューニングに重要なチロシンキナーゼ受容体を制御するホスファターゼを同定し、研究してきた。

第二のテーマのニューロンとグリア細胞間の相互作用に関しても、われわれの印象では、この分野をリードしている。グリア細胞は、従来は、単純に脳の構造的要素であると考

えられてきたが、他の研究者による最近の研究で、グリア細胞は近隣のニューロンとの精妙な相互作用を介して、重要な機能上の役割もあることが示唆されている。グリア細胞の活動を人為的に撹乱すると、ニューロンの活動が変化することが次第に明らかになってきたが、どのようにしてこのようなことが生じるかについては謎であった。野田博士らは、グリア細胞の一種であるアストロサイト（星状細胞）が、マウスでは、特定のクラスのニューロンとの相互作用を介して、体液の塩分バランスを制御していることを明確に示した。特に、一連のエレガントな実験（渡辺博士も参加した）で、野田博士の研究室では、神経活動に劇的な影響を及ぼしていたのは、アストロサイトの代謝産物である乳酸であることを示した。彼らはさらに、革新的な遺伝子操作法を使ってこの知見を追究し、研究室で発見したナトリウムチャネル(Na_x/Na_v2/NaG)と他の膜タンパク質の間に相互作用があることを示した。2つのタンパク質は共にグリア細胞の代謝を制御している。評価者の知る限り、これは、動物行動にグリア細胞が影響を及ぼすことを初めて直接的に実証したものである。このようなことは将来、より普遍的に起こっていることが明らかになるであろうと予想され、野田博士らの研究が、全く新しい分野を開くのではないかと評価者は考える。これらの研究は、神経科学の一流論文誌である *Journal of Neuroscience* 誌、*Neuron* 誌、*Nature Neuroscience* 誌に掲載されている。最後に、体液ホメオスタシスに関する研究はヒトの疾患に直接関係のあるものである。野田博士は、医学領域の研究者と共同研究を行い、塩分バランス異常の患者が、何故ナトリウムチャネルに対する抗体を持っているのかを解明しようとしている。

将来のプロジェクト：野田研究室では、体液ホメオスタシスの基礎にあるグリア-GABA回路を使って、遺伝子から行動に至る過程を分析する予定にしている。博士はまた、受容体チロシンキナーゼ群が、ニューロン投射パターンのファインチューニングのため、ホスファターゼ群による制御をどのように受けているかについての分析も引き続き行っていくことを予定している。われわれは、提案されている研究について極めて楽しみにしている。彼は、これらの研究についての研究費申請を行い、助成金を確保している。

研究業績:

1) **Research articles in peer reviewed journals**

1. Shintani, T., Maeda, N., Nishiwaki, T., and Noda, M. (1997). Characterization of rat receptor-like protein tyrosine phosphatase γ isoforms. Biochem. Biophys. Res. Commun. *230*, 419-425.
2. Hamanaka, H., Maeda, N., and Noda, M. (1997). Spatially and temporally regulated modification of the receptor-like protein tyrosine phosphatase ζ/β isoforms with keratan sulfate in the developing chick brain. Eur. J. Neurosci. *9*, 2297-2308.
3. Nishiwaki, T., Maeda, N., and Noda, M. (1998). Characterization and developmental regulation of proteoglycan-type protein tyrosine phosphatase ζ/RPTPβ isoforms. J. Biochem. *123*, 458-467.
4. Shintani, T., Watanabe, E., Maeda, N., and Noda, M. (1998). Neurons as well as astrocytes

express proteoglycan-type protein tyrosine phosphatase ζ/RPTPβ: Analysis of mice in which the *PTPζ/RPTPβ* gene was replaced with the *LacZ* gene. Neurosci. Lett. *247*, 135-138.

5. Yamagata, M., and Noda, M. (1998). The winged-helix transcription factor CWH-3 is expressed in developing neural crest cells. Neurosci. Lett. *249*, 33-36.
6. Maeda, N., and Noda, M. (1998). Involvement of receptor-like protein tyrosine phosphatase ζ/RPTPβ and its ligand pleiotrophin/heparin-binding growth-associated molecule (HB-GAM) in neuronal migration. J. Cell Biol. *142*, 203-216.
7. Takahashi, M., Yamagata, M., and Noda, M. (1999). Specific expression of ezrin, a cytoskeletal-membrane linker protein, in a subset of chick retinotectal and sensory projections. Eur. J. Neurosci. *11*, 545-558.
8. Maeda, N., Ichihara-Tanaka, K., Kimura, T., Kadomatsu, K., Muramatsu, T., and Noda, M. (1999). A receptor-like protein-tyrosine phosphatase PTPζ/RPTPβ binds a heparin-binding growth factor midkine: Involvement of arginine 78 of midkine in the high affinity binding to PTPζ. J. Biol. Chem. *274*, 12474-12479.
9. Revest, J.-M., Faivre-Sarrailh, C., Maeda, N., Noda, M., Schachner, M., and Rougon, G. (1999). The interaction between F3 immunoglobulin domains and protein tyrosine phosphatase ζ/β triggers bidirectional signalling between neurons and glial cells. Eur. J. Neurosci. *11*, 1134-1147.
10. Kawachi, H., Tamura, H., Watakabe, I., Shintani, T., Maeda, N., and Noda, M. (1999). Protein tyrosine phosphatase ζ/RPTPβ interacts with PSD-95/SAP90 family. Mol. Brain Res. *72*, 47-54.
11. Yamagata, M., Mai, A., Pollerberg, G.E., and Noda, M. (1999). Regulatory interrelations among topographic molecules CBF1, CBF2 and EphA3 in the developing chick retina. Dev. Growth Differ. *41*, 575-587.
12. Yamakawa, T., Kurosawa, N., Kadomatsu, K., Matsui, T., Itoh, K., Maeda, N., Noda, M., and Muramatsu, T. (1999). Levels of expression of pleiotrophin and protein tyrosine phosphatase ζ are decreased in human colorectal cancers. Cancer Lett. *135*, 91-96.
13. Meng, K., Rodriguez-Peña, A., Dimitrov, T., Chen, W., Yamin, M., Noda, M., and Deuel, T.F. (2000). Pleiotrophin signals increased tyrosine phosphorylation of β-catenin through inactivation of the intrinsic catalytic activity of the receptor-type protein tyrosine phosphatase β/ζ. Proc. Natl. Acad. Sci. USA *97*, 2603-2608.
14. Watanabe, E., Fujikawa, A., Matsunaga, H., Yasoshima, Y., Sako, N., Yamamoto, T., Saegusa, C., and Noda, M. (2000). Na_v2/NaG channel is involved in control of salt intake behavior in the central nervous system. J. Neurosci. *20*, 7743-7751.
15. Fukada, M., Watakabe, I., Yuasa-Kawada, J., Kawachi, H., Kuroiwa, A., Matsuda, Y., and Noda, M. (2000). Molecular characterization of CRMP5, a novel member of the collapsin response mediator protein family. J. Biol. Chem. *275*, 37957-37965.
16. Suzuki, R., Shintani, T., Sakuta, H., Kato, A., Ohkawara, T., Osumi, N., and Noda, M. (2000). Identification of RALDH-3, a novel retinaldehyde dehydrogenase, expressed in ventral region of the retina. Mech. Develop. *98*, 37-50.
17. Goldin, A.L., Barchi, R.L., Caldwell, J.H., Hofmann, F., Howe, J.R., Hunter, J.C., Kallen, R.G., Mandel, G., Meisler, M.H., Netter, Y.B., Noda, M., Tamkun, M.M., Waxman, S.G.,

Wood, J.N., and Catterall, W.A. (2000). Nomenclature of voltage-gated sodium channels. Neuron *28*, 365-368.

18. Shintani, T., Maeda, N., and Noda, M. (2001). Receptor-like protein tyrosine phosphatase γ (RPTPγ), but not PTPζ/RPTPβ, inhibits NGF-induced neurite outgrowth in PC12D cells. Dev. Neurosci. *23*, 55-69.
19. Qi, M., Ikematsu, S., Maeda, N., Ichihara-Tanaka, K., Sakuma, S., Noda, M., Muramatsu, T., and Kadomatsu, K. (2001). Haptotactic migration induced by midkine: Involvement of protein-tyrosine phosphatase ζ, mitogen-activated protein kinase, and phosphatidylinositol 3-kinase. J. Biol. Chem. *276*, 15868-15875.
20. Kawachi, H., Fujikawa, A., Maeda, N., and Noda, M. (2001). Identification of GIT1/Cat-1 as a substrate molecule of protein tyrosine phosphatase ζ/β by the yeast substrate-trapping system. Proc. Natl. Acad. Sci. USA *98*, 6593-6598.
21. Sugawara, T., Tsurubuchi, Y., Agarwala, K.L., Ito, M., Fukuma, G., Mazaki-Miyazaki, E., Nagafuji, H., Noda, M., Imoto, K., Wada, K., Mitsudome, A., Kaneko, S., Montal, M., Nagata, K., Hirose, S., and Yamakawa, K. (2001). A missense mutation of the Na^+ channel α_{II} subunit gene *$Na_v1.2$* in a patient with febrile and afebril seizures causes channel dysfunction. Proc. Natl. Acad. Sci. USA *98*, 6384-6389.
22. Sakuta, H., Suzuki, R., Takahashi, H., Kato, A., Shintani, T., Iemura, S., Yamamoto, T.S., Ueno, N., and Noda, M. (2001). Ventroptin: A novel BMP-4 antagonist expressed in a double-gradient pattern in the retina. Science *293*, 111-115.
23. Thomaidou, D., Coquillat, D., Meintanis, S., Noda, M., Rougon G., and Matsas, R. (2001). Soluble forms of NCAM and F3 neuronal cell adhesion molecules promote Schwann cell migration: identification of protein tyrosine phosphatases ζ/β as the putative F3 receptors on Schwann cells. J. Neurochem. *78*, 767-778.
24. Zubair, M., Watanabe, E., Fukada, M., and Noda, M. (2002). Genetic labelling of specific axonal pathways in the mouse central nervous system. Eur. J. Neurosci. *15*, 807-814.
25. Hiyama, T.Y., Watanabe, E., Ono, K., Inenaga, K., Tamkun, M.M., Yoshida, S., and Noda, M. (2002). Na_x channel involved in CNS sodium-level sensing. Nature Neurosci. *5*, 511-512.
26. Watanabe, E., Hiyama, T.Y., Kodama, R., and Noda, M. (2002). Na_x sodium channel is expressed in non-myelinating Schwann cells and alveolar type II cells in mice. Neurosci. Lett. *330*, 109-113.
27. Sakaguchi, N., Muramatsu, H., Ichihara-Tanaka, K., Maeda, N., Noda, M., Yamamoto, T., Michikawa, M., Ikematsu, S., Sakuma, S., and Muramatsu, T. (2003). Receptor-type protein tyrosine phosphatase ζ as a component of the signaling receptor complex for midkine-dependent survival of embryonic neurons. Neurosci. Res. *45*, 219-224.
28. Fujikawa, A., Shirasaka, D., Yamamoto, S., Ota, H., Yahiro, K., Fukada, M., Shintani, T., Wada, A., Aoyama, N., Hirayama, T., Fukamachi, H., and Noda, M. (2003). Mice deficient in protein tyrosine phosphatase receptor type Z are resistant to gastric ulcer induction by VacA of *Helicobacter pylori*. Nature Genet. *33*, 375-381.
29. Asahi, M., Tanaka, Y., Izumi, T., Ito, Y., Naiki, H., Kersulyte, D., Tsujikawa, K., Saito, M., Sada, K., Yanagi, S., Fujikawa, A., Noda, M., and Itokawa, Y. (2003). *Helicobacter pylori* CagA containing ITAM-like sequences localized to lipid rafts negatively regulates

VacA-induced signaling *in vivo*. Helicobacter *8*, 1-14.
30. Tanaka, M., Maeda, N., Noda, M., and Marunouchi, T. (2003). A chondroitin sulfate proteoglycan PTPζ/RPTPβ regulates the morphogenesis of Purkinje cell dendrites in the developing cerebellum. J. Neurosci. *23*, 2804-2814.
31. Watanabe, U., Shimura, T., Sako, N., Kitagawa, J., Shingai, T., Watanabe, E., Noda, M., and Yamamoto, T. (2003). A comparison of voluntary salt-intake behavior in Na_x-gene deficient and wild-type mice with reference to peripheral taste inputs. Brain Res. *967*, 247-256.
32. Yuasa-Kawada, J., Suzuki, R., Kano, F., Ohkawara, T., Murata, M., and Noda, M. (2003). Axonal morphogenesis controlled by antagonistic roles of two CRMP subtypes in microtubule organization. Eur. J. Neurosci. *17*, 2329-2343.
33. Takahashi, H., Shintani, T., Sakuta, H., and Noda, M. (2003). CBF1 controls the retinotectal topographical map along the anteroposterior axis through multiple mechanisms. Development *130*, 5203-5215.
34. Nakayama, M., Kimura, M., Wada, A., Yahiro, K., Ogushi, K., Niidome, T., Fujikawa, A., Shirasaka, D., Aoyama, N., Kurazono, H., Noda, M., Moss, J., and Hirayama, T. (2004). *Helicobacter pylori* VacA activates the p38/activating transcription factor 2-mediated signal pathway in AZ-521 cells. J. Biol. Chem. *279*, 7024-7028.
35. Ohyama, K., Ikeda, E., Kawamura, K., Maeda, N., and Noda, M. (2004). Receptor-like protein tyrosine phosphatase ζ/RPTPβ is expressed on tangentially aligned neurons in early mouse neocortex. Develop. Brain Res. *148*, 121-127.
36. Shintani, T., Kato, A., Yuasa-Kawada, J., Sakuta, H., Takahashi, M., Suzuki, R., Ohkawara, T., Takahashi, H., and Noda, M. (2004). Large-scale identification and characterization of genes with asymmetric expression patterns in the developing chick retina. J. Neurobiol. *59*, 34-47.
37. Ohkawara, T., Shintani, T., Saegusa, C., Yuasa-Kawada, J., Takahashi, M., and Noda, M. (2004). A novel basic helix-loop-helix (bHLH) transcriptional repressor, NeuroAB, expressed in bipolar and amacrine cells in the chick retina. Mol. Brain Res. *128*, 58-74.
38. Hiyama, T.Y., Watanabe, E., Okado, H., and Noda, M. (2004). The subfornical organ is the primary locus of sodium-level sensing by Na_x sodium channels for the control of salt-intake behavior. J. Neurosci. *24*, 9276-9281.
39. Muramatsu, H., Zou, P., Suzuki, H., Oda, Y., Chen, G-Y., Sakaguchi, N., Sakuma, S., Maeda, N., Noda, M., and Muramatsu, T. (2004). $\alpha_4\beta_1$- and $\alpha_6\beta_1$-integrins are functional receptors for midkine, a heparin-binding growth factor. J. Cell Sci. *117*, 5405-5415.
40. Fukada, M., Kawachi, H., Fujikawa, A., and Noda, M. (2005). Yeast substrate-trapping system for isolating substrates of protein tyrosine phosphatases: Isolation of substrates for protein tyrosine phosphatase receptor type z. Methods *35*, 54-63.
41. Niisato, K., Fujikawa, A., Komai, S., Shintani, T., Watanabe, E., Sakaguchi, G., Katsuura, G., Manabe, T., and Noda, M. (2005). Aged-dependent enhancement of hippocampal long-term potentiation and impairment of spatial learning through the Rho-associated kinase pathway in protein tyrosine phosphatase receptor type Z-deficient mice. J. Neurosci. *25*, 1081-1088.
42. Watanabe, E., Hiyama, T.Y., Shimizu, H., Kodama, R., Hayashi, N., Miyata, S., Yanagawa, Y., Obata, K., and Noda, M. (2006). Sodium-level-sensitive sodium channel Na_x is expressed in glial laminate processes in the sensory circumventricular organs. Am. J.

Physiol. - Regul. Integr. Comp. Physiol. *290*, 568-576.
43. Tamura, H., Fukada, M., Fujikawa, A., and Noda, M. (2006). Protein tyrosine phosphatase receptor type Z is involved in hippocampus-dependent memory formation through dephosphorylation at Y1105 on p190 RhoGAP. Neurosci. Lett. *399*, 33-38.
44. Shintani, T., Ihara, M., Sakuta, H., Takahashi, H., Watakabe, I., and Noda, M. (2006). Eph receptors are negatively controlled by protein tyrosine phosphatase receptor type O. Nature Neurosci. *9*, 761-769.
45. Fukada, M., Fujikawa, A., Chow, J.P.H., Ikematsu, S., Sakuma, S., and Noda, M. (2006). Protein tyrosine phosphatase receptor type Z is inactivated by ligand-induced oligomerization. FEBS Lett. *580*, 4051-4056.
46. Sugitani, K., Matsukawa, T., Koriyama, Y., Shintani, T., Nakamura, T., Noda, M., and Kato, S. (2006). Upregulation of retinal transglutaminase during the axonal elongation stage of goldfish optic nerve regeneration. Neuroscience *142*, 1081-1092.
47. Sakuta, H., Takahashi, H., Shintani, T., Etani, K., Aoshima, A., and Noda, M. (2006). Role of bone morphogenic protein 2 in retinal patterning and retinotectal projection. J. Neurosci. *26*, 10868-10878.
48. Shimizu, H., Watanabe, E., Hiyama, T.Y., Nagakura, A., Fujikawa, A., Okado, H., Yanagawa, Y., Obata, K., and Noda, M. (2007). Glial Na_x channels control lactate signaling to neurons for brain $[Na^+]$ sensing. Neuron *54*, 59-72.
49. Fujikawa, A., Chow, J.P.H., Shimizu, H., Fukada, M., Suzuki, R., and Noda, M. (2007). Tyrosine phosphorylation of ErbB4 is enhanced by PSD95 and repressed by protein tyrosine phosphatase receptor type Z. J. Biochem. *142*, 343-350.

2) Invited reviews, book chapters

1. Noda, M., Yamagata, M., Yuasa, J., and Takahashi, M. (1997). Topographic and laminar connection in the chick retinotectal system. *In* Molecular basis of axon growth and nerve pattern formation (H. Fujisawa, *ed.*) pp. 197-214. Japan Scientific Societies Press, Tokyo.
2. Nishiwaki, T., Maeda, N., and Noda, M. (1999). Characterization and developmental regulation of proteoglycan-type protein tyrosine phosphatase ζ/RPTPβ isoforms. *In* Neural Development, Keio University Symposia for Life Science and Medicine, vol. 2 (K. Uyemura, K. Kawamura & T. Yazaki, *eds.*) pp. 291-297. Springer-Verlag Tokyo.
3. Noda, M., and Hiyama, T.Y. (2005). Sodium-level-sensitive sodium channel and salt-intake behavior. Chem. Senses *30 (Supple. 1)*, i44-i45.
4. Noda, M. (2006). The subfornical organ, a specialized sodium channel, and the sensing of sodium levels in the brain. The Neuroscientist *12*, 80-91.
5. Fukada, M., and Noda, M. (2006). Yeast substrate-trapping system for isolating substrates of protein tyrosine phosphatases. Methods in Mol. Biol. *365*, 371-382.
6. Noda, M. (2007). Hydromineral neuroendocrinology: Mechanism of sensing sodium levels in the brain. Exp. Physiol. *92*, 513-522.

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Professor Yamamori's lab is interested in the important question of how brain functions coordinate animal behaviors. To address this question, he and his co-workers have been developing two systems: understanding the functional anatomy of the primate neocortex and understanding neuronal circuitry underlying behavioral tasks in rodents. These are two areas that are going to be extremely important in the future of systems neuroscience, and Dr. Yamamori is an active scientist in this emerging area. He has already isolated genes that are expressed differentially in primate cortex. Interestingly, and surprisingly, he has found that most genes are regulated only minimally between different cortical regions. This has led to a new hypothesis about the genetic basis of neurological disorders. For example, it may be very difficult to isolate a single gene that is responsible for aberrant neuronal circuitry. Instead, investigators may have to develop approaches that can examine the effects of simultaneous changes in expression of several genes. None-the-less, Dr. Yamamori has identified five genes that are more dramatically regulated between different brain regions in primate cortex and these mRNAs are identified in very specific anatomical boundaries in the cortex. Furthermore, although these genes are also expressed in rodents, their pattern of expression in the brain is distinct in primates, suggesting that higher order cortical functions have evolved differently in primate and rodent. Thus, Dr. Yamamori's work has led to at least two new hypotheses regarding higher brain function in primates.

In another set of experiments, Dr. Yamamori has been developing methods of analysis for motor function in rodents. This is a new area of research that he is developing in his laboratory and one that is rapidly developing within the whole field of Neuroscience. While Dr. Yamamori has developed some new technology in his own lab, he has also initiated collaborations with other investigators. For example, he is collaborating with Dr. Graybiel at MIT to monitor electrical activity in behaving mice performing certain behavioral tasks. In collaboration with Dr. Sakurai (Kyoto University), Dr. Yamamori is examining which neurons are activated in response to auditory stimuli using a unique modality. He is doing this by combining immunohistochemistry and task performance. Dr. Yamamori is very good at anticipating the methodology that will be required to reveal neural circuitry underlying behavior and is systematically working through the technical aspects to bring this work to fruition. His work is likely to be very important in analyzing mouse behavior in the existing mouse models for neurological diseases that have been characterized poorly to date.

Future studies: Dr. Yamamori has several manuscripts in preparation for submission to journals. For the future, he will develop lentiviral approaches in order to test whether the genes he has already isolated play important roles in higher order cortical function in primates and marmosets. Marmosets are an ideal preparation for these studies because they are smaller and they can be colonized. He will also continue to develop and optimize approaches for

studying neural circuitry underlying behavior of rodents.

Dr. Yamamori has been an excellent mentor. He has trained 16 students since moving to NIBB and 11 of these were students of the Graduate University for Advanced Studies. Four have obtained their PhDs, one is a researcher in RIKEN, another is a research fellow in the USA at Case Western Reserve university. Two have remained as postdocs with Dr. Yamamori and several have gone abroad for postdoctoral training. He has organized symposia in Japan and written invited reviews on his subjects of research.

（和訳）

山森教授の研究室は、脳の機能が動物の行動をどのようにコーディネートしているかにについて関心がある。この疑問を解明するため、教授らは、2 つの実験系、すなわち、霊長類新皮質の機能解剖学の解明と、げっ歯類での行動課題実施の背景にある神経回路網の解明の実験系を開発してきた。これらは、システム神経科学の将来に極めて重要なものとなりつつある 2 領域であり、山森博士はこの新しい分野で活発に研究している科学者である。博士はすでに霊長類の大脳皮質で異なる発現を示す遺伝子を分離している。興味深く、かつ驚くべきことに、ほとんどの遺伝子は、異なる皮質領野間でわずかな制御しか受けていないことを博士は見いだした。このことから神経疾患の遺伝的基礎についての新たな仮説が導かれた。例えば、神経回路の異常の原因となる一つの遺伝子を分離することは極めて困難と予想される。そうではなく、いくつかの遺伝子の発現レベルが同時に変化する効果を調べられるアプローチを開発する必要があるものと考えられる。しかし、山森博士は、霊長類の大脳皮質の領野でより劇的に制御されている 5 個の遺伝子を同定し、これらの遺伝子の mRNA の発現が、大脳皮質の極めて特異的な解剖領野内に限定していることが明らかになった。さらに、これらの遺伝子はげっ歯類でも同様に発現されているが、脳内の発現パターンは霊長類のものとは違っている。このことは、高次皮質機能は、霊長類とげっ歯類では異なる進化をしてきたことを示唆するものである。このように、山森博士の研究から、霊長類の高次脳機能に関して少なくとも 2 つの新たな仮説が導かれた。

別の実験シリーズで、山森博士は、げっ歯類の運動機能を分析する方法を開発してきている。これは、研究室で開発中の新たな研究領域であり、神経科学の全領域内で急速に発展しつつある領域である。山森博士は研究室で新たな技術を開発してきたが、他の研究者との共同研究も始めている。例えば、MIT の Dr. Graybiel との共同研究で、ある行動課題を実施中の行動中のマウスの電気活動をモニターしようとしている。櫻井芳雄教授（京都大学）との共同研究で、山森博士は、ユニークな実験法を用いて、聴覚刺激に応答してどのニューロンが活性化されるか調べている。博士は、免疫組織化学法と課題実施を組み合わせてこの研究を行っている。山森博士は行動の背景にある神経回路網を明らかにするのに必要な研究法を予想するのに優れており、研究を結実させるため、システマチックな研究開発を行っている。彼の研究が、これまで解明がほとんど進んでいない神経疾患の既存のマウスモデルでのマウスの行動を解析するのに決めて重要なものである可能性が高い。

今後の研究：山森博士は、論文誌に投稿する原稿を数件準備中である。今後は、レンチウイルスを用いた実験法を開発して、博士がすでに分離した遺伝子が、霊長類やマーモセットの高次皮質機能に重要な役割を果たすかどうかを検証しようとしている。マーモセットは、サイズが小さく、コロニーを作るので、これらの研究には理想的な実験動物である。博士はまた、げっ歯類の行動の背景にある神経回路を調べるアプローチの開発と至適化をさらに継続していく予定である。

山森博士は極めて優れたメンター(指導者)であった。基礎生物学研究所に移って以来、16 人の大学院学生の指導を行ってきた。そのうち 11 名は総合研究大学院大学の大学院生であった。4 名が PhD を取得し、一人が理化学研究所の研究員になり、もう一人は、Case Western Reserve 大学（米国）の research fellow になっている。2 名は山森博士のもとでポストドクフェローを続けており、数名がポストドクトレーニングのため海外留学している。山森博士は日本でシンポジウムをオーガナイズし、彼の研究テーマに関する総説の執筆を依頼されて書いている。

研究業績:

1) Research articles in peer reviewed journals

1. Matsuzawa, M., Muramatsu, T., Yamamori, T., Knoll, W., and Yano, R. (1999). Novel neuronal effects of midkine on embryonic cerebellar neurons examined using a defined culture system. Cell Mol Neurobiol. *19*, 209-221.
2. Komine, Y., Tanaka, N., Yano, R., Takai, S., Yuasa, S., Shiroishi, T., Tsuchiya, K., and Yamamori, T. (1999). A novel type of non-coding RNA expressed in the rat brain. Mol Brain Res. *66*, 1-13.
3. Onishi, A., Koike, S., Ida, M., Imai, H., Shichida, Y., Takenaka, O., Hanazawa, A., Komatsu, H., Mikamai, A., Goto, S., Suryobroto, B., Kitahara, K., and Yamamori, T. (1999). Dichromatism in macaque monkeys. Nature *402*, 139-140.
4. Liang, F., Hatanaka, Y., Saito, H., Yamamori, T., and Hashikawa, T. (2000). Differential expression of gamma-aminobutyric acid type B receptor-1a and 1b mRNA variants in GABA and non-GABAergic neurons of the rat brain. J Comp Neurol. *416*, 475-495.
5. Serizawa, S., Ishii, T., Nakatani, H., Tsuboi, A., Nagawa, F., Asano, M., Sudo, K., Sakagami, J., Sakano, H., Ijiri, T., Matsuda, Y., Suzuki, M., Yamamori, T., Iwakura, Y., and Sakano, H. (2000). Mutually exclusive expression of odorant receptor transgenes. Nat Neurosci. *3*, 687-693.
6. Karachot, L., Shirai, Y., Vigot, R., Yamamori, T., and Ito, M. (2000). Rapidly turned over protein maintains metabotropic synaptic transmission. Neuroreport *11*, 2903-2906.
7. Tochiani, S., Liang, F., Watakabe, A., Hashikawa, T., and Yamamori T. (2001). The occ1 gene is preferentially expressed in the primary visual cortex in an activity-dependent manner: a pattern of gene expression related to the cytoarchitectonic area in adult macaque

neocortex. Eur. J. Neurosci. *13*, 297-307.
8. Watakabe, A., Fujita, H., Hayashi, M., and Yamamori, T. (2001). Growth/differentiation factor 7 is preferentially expressed in the primary motor area of the monkey neocortex. J. Neurochem.76, 1455-1464.
9. Watakabe, A., Sugai, T., Nakaya, N., Wakabayashi, K., Takahashi, H., Yamamori, T., and Nawa, H. (2001). Similarity and variation in gene expression among human cerebral cortical subregions revealed by DNA macroarrays: Technical consideration of RNA expression profiling from postmortem samples. Mol. Brain Res. *88*, 74-82.
10. Fujiwara, T., Yamamori, T., and Akagawa, K. (2001). Suppression of transmitter release by Tat HPC-1/syntaxin 1A fusion protein. Biochimica et Biophysica Acta *1539*, 225-232.
11. Karachot, L., Shirai, Y., Vigot, R., Yamamori, T, and Ito, M. (2001). Induction of long-term depression in cerebellar Purkinje cells requires a rapidly turned over protein. J. Neurophysiol. *86*, 280-289.
12. Hanazawa, A., Mikamai, A., Angelika, P.S., Takenaka, O., Goto, S., Onishi, A., Koike, S., Yamamori, T., Kato, K., Kondo, A., Suryobroto, B., Farajallah, A., and Komatsu, H. (2001). Electroretinogram analysis of relative spectral sensitivity in genetically identified dichromatic macaques. Proc. Natl Acad. Sci. USA *98*, 8124-8127.
13. Vigot, R., Batini, C., Kado, R.T., and Yamamori, T. (2002). Synaptic LTD in vivo recorded on the rat cerebellar cortex. Arch. Ital. Biol. *140*, 1-12.
14. Onishi, A., Koike, S., Ida-Hosonuma, M., Imai, H., Shichida, Y., Takenaka, O., Hanazawa, A., Komatsu, H., Mikami, A., Goto, S., Suryobroto, B., Farajallah, A., Varavudhi, P., Ekavhibata, C., Kitahara, K., and Yamamori, T. (2002). Variations in long- and middle-wavelength-sensitive opsin gene loci in crab-eating monkeys. Vision Res. *42*, 281-292.
15. Sakata, S., Kitsukawa, T., Kaneko, T., Yamamori, T., and Sakurai, Y. (2002). Task-dependent and cell-type-specific Fos enhancement in rat sensory cortices during audio-visual discrimination. *Eur.* J. Neuroscience. *15*, 735-743.
16. Hata, K., Araki, M., and Yamamori, T. (2002). CNTF is specifically expressed in the developing rat pineal gland and eyes. NeuroReport. *13*, 735-739.
17. Tochitani, S., Hashikawa, T., Yamamori, T. (2003). Expression of occ1 mRNA in the visual cortex during postnatal development in macaques. *Neurosc. Lett*. *337*, 114-116.
18. Nakayama, T., Mikoshiba, K., Yamamori, T., and Akagawa, K. (2003). Expression of syntaxin 1C, an alternative splice variant of HPC-1/syntaxin 1A, is enhanced by phorbol-ester stimulation in astroglioma: participation of the PKC signaling pathway. FEBS Lett. *536*, 209-214.
19. Suga, K., Yamamori, T., and Akagawa, K. (2003). Identification of the carboxyl-terminal membrane- anchoring region of HPC-1/syntaxin 1A with the substituted-cysteine-accessibility method and monoclonal antibodies. J. Biochem. *133*, 325-334.
20. Hata, K., Araki, M., and Yamamori, T. (2003). Ciliary neurotrophic factor inhibits differentiation of photoreceptor-like cells in rat pineal glands in vitro. *Dev. Brain Res*. 143, 179-187.
21. Tochitani, S., Hashikawa, T., and Yamamori, T. (2003). occ1 mRNA reveals a characteristic

feature in the hippocampal CA2 field of adult macaques. *Neuroscience Lett*. 346, 105-108.
22. Nakayama, T., Mikoshiba, K., Yamamori, T., and Akagawa, K. (2004). Activation of syntaxin 1C, an alternative splice variant of HPC-1/syntaxin 1A, by phorbol 12-myristate 13-acetate (PMA) suppresses glucose transport into astroglioma cells via the glucose transporter-1 (GLUT-1). *J Biol Chem*. 279, 23728-23739.
23. Sakata, S., Yamamori, T., and Sakurai, Y. (2004). Behavioral studies of auditory-visual spatial recognition and integration in rats. *Exp Brain Res*. 159, 409-417.
24. Ichinohe, N., Watakabe, A., Miyashita, T., Yamamori, T., Hashikawa, T., and Rockland, K.S. (2004). A voltage-gated potassium channel, Kv3.1b, is expressed by a subpopulation of large pyramidal neurons in layer 5 of the macaque monkey cortex. Neuroscience *129*, 179-185.
25. Komatsu, Y., Watakabe, A., Hashikawa, T., Tochitani, S., and Yamamori, T. (2005). Retinol-binding protein gene is highly expressed in higher-order association areas of the primate neocortex. Cereb Cortex. *15*, 96-108.
26. Sakata, S., Komatsu, Y., and Yamamori, T. (2005). Local design principles of mammalian cortical networks. Neurosci Res. *51*, 309-315.
27. Sakata, S., Yamamori, T., and Sakurai, Y. (2005). 7-12 Hz cortical oscillations: Behavioral context and dynamics of prefrontal neuronal ensembles. Neuroscience *134*, 1099-111.
28. Komine, Y., Nakamura, K., Katsuki, M., and Yamamori, T. (2006). Novel transcription factor zfh-5 is negatively regulated by its own antisense RNA in mouse brain. Mol Cell Neurosci. *31*, 273-283.
29. Takahata, T., Komatsu, Y., Watakabe, A., Hashikawa, T., Tochitani, S., and Yamamori, T. (2006). Activity- dependent expression of occ1 in excitatory neurons Is a characteristic Feature of the primate visual cortex. Cereb Cortex. *16*, 929-940.
30. Watakabe, A., Ohsawa, S., Hashikawa, T., and Yamamori, T. (2006). Binding and complementary expression patterns of semaphorin 3E and plexin D1 in the mature neocortices of mice and monkeys. J Comp Neurol. *499*, 258-273.
31. Sakata, S., and Yamamori, T. (2007). Topological relationships between brain and social networks. Neural Networks. *20*, 12-21.
32. Watakabe, A., Ichinohe, N., Ohsawa, S., Hashikawa, T., Komatsu, Y., Rockland, K.S., and Yamamori, T. (2007). Comparative analysis of layer-specific genes in mammalian neocortex. Cereb Cortex. *17*, 1918-1933.

2) Invited reviews, book chapters

1. Yamamori, T., and Rockland, K.S. (2006). Neocortical areas, layers, connections, and gene expression. Neurosci Res. *55*, 11-27.
2. Watakabe, A., Komatsu, Y., Nawa, H., and Yamamori T. (2006). Gene expression profiling of primate neocortex: molecular neuroanatomy of cortical areas. Genes Brain Behav. *5 Suppl 1*, 38-43.

渡辺英治
神経生理学研究室（形質転換生物研究施設）・准教授

Dr. Watanabe has been an Associate Professor since 1998. He works on research projects exclusively with Professor Noda and also helps supervise the transgenic facility at NIBB. His primary contribution to research occurred in 2000 as first author on important paper on the identity of the sodium channel (Nav2/NaG) required for control of salt intake behavior in the CNS. Since that time, Dr. Watanabe has been co author on several publications involved in this biological pathway as well as other publications related to the other main project in Dr. Noda's lab, activity of a protein tyrosine phosphatase receptor important in neuronal wiring in the mammalian brain. Dr. Watanabe is a talented experimentalist. He was originally trained as a biochemist and anatomist. He then acquired expertise in cell imaging. He is a productive scientist in the joint projects with Dr. Noda. He has Grant In Aid funding through 2008.

Future studies: Together with Dr. Noda, Dr. Watanabe plans to extend his studies of the important sodium channel. In addition to performing his research projects, he is a major supervisor of the transgenic facility at NIBB, which takes at least 40% of his time because of the scope of the animal studies at CTAP. The activities of CTAP are to provide materials and techniques for gene targeting and transgenic animals, to teach technology for analyzing the transgenic mice, and to preserve and store all transgenic strains. The numbers of investigators and lines of mice generated require a large staff of trained personnel. His role in this facility is to teach gene transfer techniques to investigators and oversee the daily responsibilities of maintaining the mouse colonies.

（和訳）

渡辺博士は 1998 年から准教授（助教授）である。博士の研究プロジェクトでの研究は野田教授とのものだけであり、基礎生物学研究所の形質転換生物研究施設の管理運営も補助している。博士の研究への主な貢献は、2000 年に、塩分摂取行動の制御に必要とされるナトリウムチャネル(Nav2/NaG)を神経系内で同定した、重要な論文の第一著者となったことである。それ以来、渡辺博士は、この生物学的研究分野に関するいくつかの論文の共著者であり、また野田研究室の別の主なプロジェクトである、ほ乳動物の脳内での神経回路網のワイヤリングに重要なタンパク質であるチロシンホスファターゼ受容体の活動に関する論文の共著者でもある。渡辺博士は才能ある実験科学者である。もともと生化学者および解剖学者としてのトレーニング受け、その後、細胞イメージングに熟達した。野田博士との共同研究では生産性の高い科学者である。2008 年の科研費助成を受けている。

今後の研究：野田博士と共同で、渡辺博士は重要なナトリウムチャネルの研究をさらに

拡張することを計画している。研究を進めることに加え、博士は基礎生物学研究所のトランスジェニック施設（形質転換生物研究施設：CTAP）の主な管理者である。CTAP での動物実験の範囲が広いため、この業務に 40%以上の時間を割いている。CTAP の活動は、遺伝子ターゲティングとトランスジェニック動物の材料とテクニックを提供すること、トランスジェニックマウスを分析する技術の教育を行うこと、全てのトランスジェニック系統の維持と保存を行うことである。トランスジェニック動物を使う研究者が多いことや、作成するマウス系統が多数になることから、熟練スタッフが多数必要となる。形質転換生物研究施設での博士の役割は、研究者に遺伝子トランスファー技術を教え、マウスコロニーの日常管理を監督することである。

研究業績（1998 年より）：

1) Research articles in peer reviewed journals

1. Yasuda, Y., Tokita, Y., Aono, S., Matsui, F., Ono, T., Sonta, S., Watanabe, E., Nakanishi, Y., and Oohira, A. (1998). Cloning and chromosomal mapping of the human gene of neuroglycan C (NGC), a neuronal transmembrane chondroitin sulfate proteoglycan with an EGF module. Neurosci. Res. *32*, 313-322.
2. Matsui, F., Nishizuka, M., Yasuda, Y., Aono, S., Watanabe, E., and Oohira, A. (1998). Occurrence of an N-terminal proteolytic fragment of neurocan, not a C-terminal half, in a perineuronal net in the adult rat cerebrum. Brain Res. *790*, 45-51.
3. Katoh-Semba, R., Matsuda, M., Watanabe, E., Maeda, N., and Oohira, A. (1998). Two types of brain chondroitin sulfate proteoglycan: their distribution and possible functions in the rat embryo. Neurosci. Res. *31*, 273-282.
4. Shintani, T., Watanabe, E., Maeda, N., and Noda, M. (1998). Neurons as well as astrocytes express proteoglycan-type protein tyrosine phosphatasez/ RRTP β: Analysis of mice in which the PTPζ/ RRTP β gene was replaced with the *lacZ* gene. Neurosci. Lett. *247*, 135-138.
5. Watanabe, E., Fujikawa, A., Matsunaga, H., Yasoshima, Y., Sako, N., Yamamoto, T., Saegusa, C., and Noda, M. (2000). Na_v2/NaG channel is involved in control of salt intake behavior in the CNS. J. Neurosci. *20*, 7743-7751.
6. Zubair, M., Watanabe, E., Fukada, M., and Noda, M. (2002). Genetic labeling of specific axonal pathways in the mouse central nervous system. Eur. J. Neurosci. *15*, 807-814.
7. Hiyama, T.Y., Watanabe, E., Ono, K., Inenaga, K., Tamkun, M.M., Yoshida, S., and Noda, M. (2002). Na_x channel involved in CNS sodium-level sensing. Nat. Neurosci. *5*, 511-512.
8. Watanabe, E., Hiyama, T.Y., Kodama, R., and Noda, M. (2002). Na_x sodium channel is expressed in non-myelinating Schwann cells and alveolar type II cells in mice. Neurosci.Lett. *330*, 109-113.
9. Watanabe, U., Shimura, T., Sako, N., Kitagawa, J., Shingai, T., Watanabe, E., Noda, M., and Yamamoto, T. (2003). A comparison of voluntary salt-intake behavior in Na_x-gene deficient and wild-type mice with reference to peripheral taste inputs. Brain Res. *967*, 247-256.

10. Hiyama, T.Y., Watanabe, E., Okado, H., and Noda, M. (2004). The subfornical organ is the primary locus of sodium-level sensing by Na_x sodium channels for the control of salt-intake behavior. J. Neurosci. *24*, 9276-9281.
11. Niisato, K., Fujikawa, A., Komai, S., Shintani, T., Watanabe, E., Sakaguchi, G., Katsuura, G., Manabe, T., and Noda, M. Age-dependent enhancement of hippocampal LTP and impairment of spatial learning through the ROCK pathway in protein tyrosine phosphatazse receptor type Z-deficient mice. J. Neurosci. *25*, 1081-1088.
12. Watanabe, E., Hiyama, T.Y., Shimizu, H., Kodama, R., Hayashi, N., Miyata, S., Yanagawa, Y., Obata, K., and Noda, M. (2006). Sodium-level-sensitive sodium channel Na_x is expressed in glial laminate processes in the sensory circumventricular organs. Am. J. Physiol. (Regul Integr Comp Physiol) *290*, R568-R576.
13. Shimizu, H., Watanabe, E., Hiyama, T.Y., Nagakura, A., Fujikawa, A., Okado, H., Yanagawa, Y., Obata, K., and Noda, M. (2007). Glial Na_x channels control lactate signaling to neurons for brain [Na^+] sensing. Neuron *54*, 59-72.

笹岡俊邦
神経生化学研究室（形質転換生物研究施設）・准教授

Dr. Sasaoka is an Associate Professor. He moved to NIBB in 2003, so this review only covers his work since that time. He is an expert in gene targeting approaches. In work that is not yet submitted, Dr. Sasaoka has collaborated with Professor Yo-ichi Nabeshima to develop a technology that permits introduction of mutant exons by a clever conditional splicing strategy. Using this new technology, they have identified a new mutant mouse phenotype due to aberrant activation of NMDA receptors. These receptors are critical components of excitatory transmission and, as such, are of wide general interest to the Neuroscience community. This work will be submitted to the prestigious journal, *Cell.* It should be noted that the technology will have wide applications to genes other than the NMDA receptors outside the field of Neuroscience.

Future studies: Dr Sasaoka will not longer work on NMDA receptors but instead will continue his interest in dopamine receptors, an interest he generated as a graduate student. These are important molecules for study as they are the basis for Parkinson's disease. He has generated mice that are new models for the disease using a complex conditional genetic strategy and is continuing to analyze them for locomotion and eating behavior. He spends at least 40% of his time doing his own research projects and, like Dr. Watanabe, spends the remaining amount of time managing the transgenic facility. He is responsible for the daily activities, training of investigators in aspects of the technology, and maintaining the cryopreserved specimens. He has also been responsible for cooperating with the RIKEN BRC in generating genetically modified mouse strains for individual investigators.

（和訳）

笹岡博士は准教授である。博士は 2003 年に基礎生物学研究所に転任してきた。従って、彼の外部評価は、その時点以降のものに限定される。博士は遺伝子ターゲッテング法の専門家である。まだ論文投稿していない研究で、笹岡博士は鍋島陽一教授との共同研究で、巧妙なコンディショナルスプライシング戦略を用いて変異エキソンを導入できる技術を構築した。この新技術を用いて、彼らは、NMDA 受容体が異常に活性化されることによる新たな変異マウス表現型を同定した。これらの受容体は、興奮性伝達に重要なコンポーネントであり、そのため、神経科学の分野では広く関心を持たれている。この研究は、一流の論文誌 *Cell* に投稿される予定である。このコンディショナル変異導入法は、神経科学領域を超えて、NMDA 受容体以外の遺伝子にも応用できることを付記しておく。

今後の研究：笹岡博士は NMDA 受容体の研究を現在では行っておらず、大学院学生の時に関心を持っていたドーパミン受容体の研究を継続する予定である。ドーパミン受容体

はパーキンソン病の基礎であるので、研究するのに重要性のある分子である。彼は、複雑なコンディショナル遺伝子操作法を使って、パーキンソン病の新たなモデルとなるマウスをすでに作成しており、それらの歩行や摂食行動の解析を継続している。彼は、40%以上の時間を彼の研究プロジェクトに使っており、渡辺博士と同様、残りの時間を、形質転換生物研究施設の運営に費やしている。博士は、日常業務や、研究者の技術教育、低温保存検体の管理の責任者である。博士はまた、理研バイオリソースセンターとの業務提携で、遺伝的改変したマウス系統を作成し、それぞれの研究者に提供する業務も担ってきている。

研究業績（2003 年より）:

1) Research articles in peer reviewed journals

1. Sasaoka, T., Imamura, M., Araishi, K., Noguchi, S., Mizuno, Y., Takagoshi, N., Hama, H., Wakabayashi-Takai, E., Yoshimoto-Matsuda, Y., Nonaka, I., Kaneko, K., Yoshida, M., and Ozawa, E. (2003). Pathological analysis of muscle hypertrophy and degeneration in muscular dystrophy in gamma-sarcoglycan-deficient mice. Neuromuscul. Disord. *13*, 193-206.
2. Mizuno, Y., Guyon,J. R., Watkins, S. C., Mizushima, K., Sasaoka, T., Imamura, M., Kunkel, L. M., and Okamoto, K. (2004). Beta-Synemin localizes to regions of high stress in human skeletal myofibers. Muscle Nerve *30*, 337-346.
3. Tanaka, T., Watanabe, N., and Sasaoka, T. (2005). Unidirectional subcloning to generate more than 109 transformants from 1 microgram of vector DNA. Nihon Univ. J. Med. *47*, 43-56.
4. Imai, F., Hirai, S., Akimoto, K., Koyama, H., Miyata, T., Ogawa, M., Noguchi, S., Sasaoka, T., Noda, T., and Ohno, S. (2006). Inactivation of aPKC lambda results in the loss of adherens junctions in neuroepithelial cells without affecting neurogenesis in mouse neocortex. Development *133*, 1735-1744.
5. Ishii, Y., Oya, T., Lianshun, Z., Gao, Z., Kawaguchi, M., Sabit, H., Takako Matsushima, T., Tokunaga, A., Ishizawa, S., Hori, E., Nabeshima, Y., Sasaoka T., Fujimori, T., Mori, H., and Sasahara, M. (2006). Mouse brains deficient in neuronal PDGF receptor-beta develop normally but are vulnerable to injury. J. Neurochem. *98*, 588-600.
6. Hagiwara, Y., Fujita, M., Imamura, M., Noguchi, S., and Sasaoka, T. (2006). Caveolin-3 deficiency decreases the gene expression level of osteopontin in *mdx* mouse skeletal muscle. Acta Myol. *25*, 53-61.
7. Watanabe, N., Sasaoka, T., Noguchi, S, Nishino, I., and Tanaka, T. (2007). Cys669-Cys713 disulfide bridge formation is a key to dystroglycan cleavage and subunit association. Genes Cells *12*, 75-88.
8. Ohi, Y., Ishii, Y., Haji, A., Noguchi, S., Sasaoka, T., Fujimori, T., Nabeshima, Y,, Sasahara, M., and Hattori, Y. (2007). Platelet-derived growth factor (PDGF)-BB inhibits AMPA receptor-mediated synaptic transmission via PDGF receptor-beta in murine nucleus tractus solitarius. Brain Res. *1159*, 77-85.

2) Invited reviews, book chapters

1. Ozawa, E., Mizuno, Y., Hagiwara, Y., Sasaoka, T., and Yoshida, M. (2005). Molecular and cell biology of the sarcoglycan complex. Muscle Nerve *32*, 563-576.

5）進化多様性領域

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Scientific programme

In this Division the science programme is divided between work on *Ipomoea* (Morning Glories) and rice. Both areas involve the exploitation of transposons, which is a major interest of the Professor.

Genetics and epigenetics of flower pigmentation in Morning Glories

This part of the programme is focused on explaining the diversity of coloration patterns of the flowers of Morning Glories both by studying how different colors are generated and how different patterns of variation are created. Important contributions have included cloning and characterizing major transposon families from Morning Glories, isolating genes encoding key enzymes in the formation of pigments, transcription factors with regulatory functions and transporters that control the pH of the vacuole. The work established the interesting observation that differences in pH of the vacuole between Petunia and Morning glory are created by transporters and can partially explain differences in flower coloration between species, and between flowers at different developmental stages. Epigenetic variation associated with transposons can explain the flower variegation in some cases.

Homologous recombination and transposon tagging in rice

To enable reverse genetics in rice two methods were developed in the Division. Transposon tagging was performed using *Dart* elements. The autonomous *Dart* element was characterized and approaches to reactivate the element explored. In some cases new mutable alleles of genes of interest were recovered.

The laboratory established a method for homologous recombination in rice using *Agrobacterium*-mediated transformation as well as positive and negative selection stratagies. Considerable effort was expended in characterizing the recovered events and distinguishing true homologous recombination events from one-sided recombination and ectopic versions. The established approach was used to create mutations in genes such as *Waxy* and *Adh*. More recently, the approach was used to identify alleles of genes of unknown function implicated in epigenetics such as *DDM*, *MET*, *CMT*, *DRM* and *ROS*. The average targeting efficiency was about 1%.

Profile, productivity and funding

The group has an international profile in both of its major scientific areas. The rice work has created more international interest, because of the general importance of establishing efficient homologous recombination methods in plants and the widespread use of rice as a model crop species.

The group has shown good and continuous productivity throughout the 10 year reporting period. Highlights in the publication record are the paper in *Nature* (published in 2000) describing the cloning of a transporter required to maintain pH of the vacuole, and the paper in *Nature Biotechnology* describing the method for gene targeting in rice. The latter is the group's most highly cited publication during this period and generated extensive national and international interest. In addition to these high profile publications several papers were published in more specialized plant journals, notably *Plant Journal*. The Division appears to have a good publication culture, and to publish their work efficiently and in a timely manner in international journals.

The Division appears to be well funded, and particularly the rice work has received large national grants.

Collaborations

The Division is interactive and interested in establishing collaborations. Inside the NIBB active collaborations with the Hasebe and Horiuchi groups were described. At the national level collaborations are being established to target genes of interest to University groups, and specific collaborations on methylation enzyme mutants are being formed. The rice homologous recombination method is an example of a generally applicable method developed in the NIBB that could be offered widely to University groups. The Division exhibited a general awareness of the importance of collaborations and a willingness to establish these.

General comments

The Division has done well during the last 10 years, publishing extensively in international journals and developing new methods of wide interest. Some of the work on the effects of transposons on gene expression is somewhat derivative of what was shown previously in maize and *Antirrhinum*. However, the focus on Morning Glories has established new principles in floral pigmentation, notably the reverse effect of vacuole pH between Petunia and Morning Glory, how this is established at the molecular level and how it varies with flower development. The work on homologous recombination in rice has the most potential for collaboration and represents a major technical achievement. The relatively high citation rate for the paper describing the method illustrates the international interest in this work.

Professor Iida is due to retire in April 2009, and during the next 18 months the continued work of the Division is likely to be complicated by researchers starting to leave and seek new positions. A presence in the national and international rice communities may well be important for NIBB, and some strategic thinking is required to assess whether a successor in rice biology should be specifically sought.

（和訳）

研究プログラム

この部門の研究プログラムは、アサガオ *Ipomoea* 研究とイネの研究に分かれている。両方の研究とも、教授の主な関心領域であるトランスポゾンの活用が関与している。

アサガオの花色形成の遺伝学とエピジェネティックス

この領域では、アサガオの様々な花色がどのように発現され、変異パターンがどのように作られるかを調べることで、アサガオの花色の多様性を説明することに重点を置いている。重要な業績としては、アサガオから主要なトランスポゾンファミリーをクローニングし特性を解明したこと、色素形成において重要な役割を果たす酵素や制御機能を有する転写因子、液胞の pH をコントロールするトランスポーターをコードしている遺伝子を分離したことなどが挙げられる。この研究で、ペチュニアとアサガオの液胞の pH の違いは、トランスポーターにより作られるものであり、このことが種の間、様々な発達段階の花の間での花色の違いを一部説明できるという興味深い観察結果が得られた。トランスポゾンと関係するエピジェネティックな変異で、一部の花色の違いを説明できる。

イネの相同組換えとトランスポゾンタギング

イネの逆遺伝学を可能にするため、当部門では 2 つの手法を開発した。*Dart* エレメントを用いて、トランスポゾンタギングを実施した。自律性因子 *Dart* の特性について調べ、自律性因子を再活性化させる方法を探った。一部では、興味深い遺伝子の新たな易変性変異を同定できた。

研究室では、アグロバクテリウムを使ったトランスフォーメーション法と、ポジティブ・ネガティブ選択法を用いたイネでの相同組換え法を確立した。得られたイベントの特性を解明すること、ならびに期待通りの真の相同組換えイベントと、片側だけの組換えや異所的な組換えとを識別することに相当の努力を行った。確立したアプローチは、*Waxy* や *Adh* などの遺伝子の突然変異の創出に使われた。最近、このアプローチは、*DDM*、*MET*、 *CMT*、*DRM*、*ROS* などのエピジェネティックスに関係あると思われる機能未知の遺伝子に変異を導入するのに使われた。ターゲッティング効率は約 1%であった。

プロフィール、生産性、研究予算

この研究グループは、2 つの研究領域の両方に国際的な名声を得ている。イネの研究は、より高く国際的な関心を集めた。植物での効率の高い相同組換え法を確立することが全般に重要であり、また、モデル作物としてイネが広く使われているからである。

10 年間の報告対象期間全体を通じて、この研究グループは良好で継続的に高い生産性を維持してきた。発表論文でもっとも目覚ましいのは、*Nature* 誌(2000 年)に掲載された液胞の pH を維持するのに必要なトランスポーターのクローニングについての論文と、*Nature Biotechnology* 誌に掲載されたイネでの遺伝子ターゲッティング法を記述した論文である。後者の論文は、今回の評価期間中に引用された回数が最も多く、国内外の

強い関心を引き起こした。このような高く評価される論文誌への掲載に加え、いくつかの論文は、植物学の専門論文誌、とりわけ *Plant Journal* 誌に掲載されている。当部門は、良好な論文掲載文化を有しており、業績を効率的かつタイムリーに国際論文誌に掲載しているように思われる。

当部門の研究予算は潤沢であり、とりわけイネの研究は、大規模な国の助成金を受けてきた。

共同研究

当部門は共同研究に熱心である。基礎生物学研究所内では、長谷部グループや堀内グループとの活発な共同研究があることが示されている。国内レベルでは、大学グループが関心のある遺伝子レベルのターゲッティングに関する共同研究が進んでおり、メチル化酵素に関する特別共同研究が行われている。イネの相同組換え法は基礎生物学研究所が開発し、広く応用できる方法の例であり、大学グループに広く提供できる方法である。当部門は共同研究の重要性を総じて認識しており、共同研究を確立することに積極的である。

総評

当部門はこの 10 年間良好な業績をあげ、国際論文誌に活発に投稿し、広く関心の持たれる新しい研究方法を開発した。遺伝子発現に対するトランスポゾンの効果についての研究の一部は、先行するトウモロコシやキンギョソウ *Antirrhinum* の研究に幾分かは導かれた研究である。しかし、アサガオに着目したことで、花色形成の新たな原理、とりわけ、ペチュニアとアサガオで、液胞の pH が花色に逆の効果をもたらすこと、このような効果が分子レベルでどのように確立しているかを示したこと、および花の形成によりどのように変化するかについて明らかにすることができた。イネでの相同組換えの研究は、高い共同研究の可能性を有するものであり、大きな技術的進展を示すものである。この方法を記述した論文の引用率が比較的高いことは、この研究が国際的関心を集めていることを示している。

飯田教授は 2009 年 4 月に退任予定であり、これからの 18 ヶ月間は、研究者たちが退任し、新たなポストを探し始めることで当部門での研究は困難になるものと予想される。イネに関する国内的、国際的コミュニティーが存在することは、基礎生物学研究所にとって重要なことであろう。イネの生物学の後継者を探すかどうかについて、戦略的検討が必要である。

研究業績：

1) Research articles in peer reviewed journals

1. Abe, Y., Hoshino, A., and Iida, S. (1997). Appearance of flower variegation in the mutable *speckled* line of the Japanese morning glory is controlled by two genetic elements. Genes

Genet. Syst. *72*, 57-62.
2. Habu, Y., Fukada-Tanaka, S., Hisatomi, Y., and Iida, S. (1997). Amplified restriction fragment length polymorphism-based mRNA fingerprinting using a single restriction enzyme that recognizes a 4-bp sequence. Biochem. Biophys. Res. Commun. *234*, 516-521.
3. Fukada-Tanaka, S., Hoshino, A., Hisatomi, Y., Habu, Y., and Iida, S. (1997). Identification of new chalcone synthase genes for flower pigmentation in the Japanese and common morning glories. Plant Cell Physiol. *36*, 754-758.
4. Hoshino, A., Abe, Y., Saito, N., Inagaki, Y., and Iida, S. (1997). The gene encoding flavanone 3-hyroxylase is expressed normally in the pale yellow flowers of the Japanese morning glory carrying the *speckled* mutation which produce neither flavonol nor anthocyanin but accumulate chalcone, aurone and flavanone. Plant Cell Physiol. *38*, 1049-1056.
5. Hisatomi, Y., Yoneda, Y., Kasahara, K., Inagaki, Y., and Iida, S. (1997). DNA rearrangements at the region of the dihydroflavonol 4-reductase gene for flower pigmentation and incomplete dominance in morning glory carrying the mutable *flaked* mutation. Theor. Appl. Genet. *95*, 509-515.
6. Hisatomi, Y., Harada K., and Iida, S. (1997). The retrotransposon *RTip1* is integrated into a novel type of minisatellite *MiniSip1* in the genome of the common morning glory, and carries another new type of minisatellite *MiniSip2*. Theor. Appl. Genet. *95*, 1049-1056.
7. Saito, N., Tatsuzawa, F., Kasahara, K., Iida, S., and Honda, T. (1998). Acylated cyanidin 3-sophorosides in the brownish-red flowers of *Ipomoea purpurea*. Phytochemistry 49, 875-880.
8. Habu, Y., Hisatomi, Y., and Iida, S. (1998). Molecular characterization of the mutable *flaked* allele for flower variegation in the common morning glory. Plant J. *16*, 371-376.
9. Hasebe, A., Tsushima, S., and Iida, S. (1998). Isolation and characterization of IS*1416* from *Pseudomonas glumae*, an new member of the IS*3* family. Plasmid *39*, 196-204.
10. Nakai, K., Inagaki, Y., Nagata, H., Miyazaki, C., and Iida, S. (1998). Molecular characterization of the gene for dihydroflavonol 4-reductase of *Japonica* rice varieties. Plant Biotechnology 15, 221-225.
11. Iida, S., Hiestand-Nauer, R., Sandmeier, H., Lehnherr, H., and Arber, W. (1998). Accessory genes in the *darA* operon of bacteriophage P1 affect anti-restriction function, generalized transduction, head morphogenesis and host cell lysis. Virology *251*, 49-58.
12. Inagaki, Y., Johzuka-Hisatomi, Y., Mori, T., Takahashi, S., Hayakawa, Y., Peyachoknagul, S., Ozeki, Y., and Iida, S. (1999). Genomic organization of the genes encoding dihydroflavonol 4-reductase for flower pigmentation in the Japanese and common morning glories. Gene *226*, 181-188.
13. Takahashi, S., Inagaki, Y., Satoh, H., Hoshino, A., and Iida, S. (1999). Capturing of a genomic *HMG* domain sequence by an *En/Spm* related transposable element *Tpn1* in the Japanese morning glory. Mol. Gen. Genet. *261*, 447-451.
14. Johzuka-Hisatomi, Y., Hoshino, A., Mori, T., Habu, Y., and Iida, S. (1999). Characterization of the chalcone synthase genes expressed in flowers of the common and Japanese morning glories. Genes Genet. Syst. *74*, 141-147.
15. Shiokawa, K., Inagaki, Y., Morita, H., Hsu, T.-J., Iida, S., and Noguchi, H. (2000). The functional expression of the *CHS-D* and *CHS-E* genes of the common morning glory

(*Ipomoea purpurea*) in *Escherichia coli* and characterization of their gene products. Plant Biotechnology. *17*, 203-210.
16. Fukada-Tanaka, S., Inagaki, Y., Yamaguchi, T., Saito, N., and Iida, S. (2000). Colour-enhancing protein in blue petals. Nature *407*, 581.
17. Hasebe, A., and Iida, S. (2000). The novel insertion sequences IS*1417*, IS*1418* and IS*1419* from *Burkholderia glumae* and their strain distribution. Plasmid *44*, 44-53.
18. Kojima, T., Habu, Y., Iida, S., and Ogihara, Y. (2000). Direct isolation of differentially expressed genes from a specific chromosome region of common wheat: Application of the amplified fragment length polymorphism-based mRNA fingerprinting (AMF) method in combination with a deletion line of wheat. Mol. Gen. Genet. *263*, 635-641.
19. Hoshino, A., Johzuka-Hisatomi, Y., and Iida, S. (2001). Gene duplication and mobile genetic elements in the morning glories. Gene *265*, 1-10.
20. Fukada-Tanaka, S., Inagaki, Y., Yamaguchi T., and Iida, S. (2001). Simplified transposon display (STD): a new procedure for isolation of a gene tagged by a transposable element belonging to the *Tpn1* family in the Japanese morning glory. Plant Biotechnology. *18*, 143-149.
21. Yamaguchi, T., Fukada-Tanaka, S., Inagaki, Y., Saito, N., Yonekura-Sakakibara, K., Tanaka, Y., Kusumi, T., and Iida, S. (2001). Genes encoding the vacuolar Na^+/H^+ exchanger and flower coloration. Plant Cell Physiol. *42*, 451-461.
22. Toki, K., Saito, N., Iida, S., Hoshino, A., Shigihara, A., and Honda, T. (2001). Acylated pelargonidin 3-sophoroside-5-glucosides from the flowers of the Japanese morning glory cultivar 'Violet'. Heterocycles *55*, 1241–1248.
23. Toki, K., Saito, N., Iida, S., Hoshino, A., Shigihara, A., and Honda, T. (2001). A novel acylated pelargonidin 3-sophoroside-5-glucosides from greyish-purple flowers of the Japanese morning glory. Heterocycles *55*, 2261–2267.
24. Ishikawa, N., Johzuka-Hisatomi, Y., Sugita, K., Ebinuma, H., and Iida, S. (2002). The transposon *Tip100* from the common morning glory is an autonomous element that can transpose in tobacco plants. Mol. Gen. Genomics *266*, 732-739.
25. Terada, R., Urawa, H., Inagaki, Y., Tsugane, K., and Iida, S. (2002). Efficient gene targeting by homologous recombination in rice. Nature Biotechnology 20, 1030-1034.
26. Kamiunten, H., Inoue, S., Yakabe, Y., and Iida, S. (2002). Characterization of ISPsy2 and ISPsy3, newly identified insertion sequences in *Pseudomonas syringae* pv. *Eriobotryae*. J. Gen. Plant Pathol. *68*, 75-80.
27. Hoshino, A., Morita, Y., Choi, J.D., Saito, N., Toki, K., Tanaka, Y., and Iida, S. (2003). Spontaneous mutations of the flavonoid 3'-hydroxylase gene conferring reddish flowers in the three morning glory species. Plant Cell Physiol. 44, 990-1001.
28. Terada, R., Asao, H., and Iida, S. (2003). A large-scale *Agrobacterium*-mediated transformation procedure with a strong positive-negative selection for gene targeting in rice (*Oryza sativa* L.). Plant Cell Reports *22*, 653-659.
29. Park, K.I., Choi, J.D., Hoshino, A., Morita, Y., and Iida, S. (2004). An intragenic tandem duplication in a transcriptional regulatory gene for anthocyanin biosynthesis confers pale-colored flowers and seeds with fine spots in *Ipomoea tricolor*. Plant J. *38*, 840-849.
30. Li, H.-Q., Terada, R., Li, M.-R., and Iida, S. (2004). The *E. coli* RecQ helicase enhances

homologous recombination in rice cells. FEBS Lett. 574, 151-155, Erratum in: FEBS Lett. *576*, 284.

31. Toki, K., Saito, N., Morita, Y., Hoshino, A., Iida, S., Shigihara, A., and Honda, T. (2004). An acylated pelargonidin 3-sophoroside from the pale-brownish red flowers of *Ipomoea nil*. Heterocycles *63*, 1449-1454.
32. Yoshida, H., Akimoto, H., Yamaguchi, M., Shibata, M., Habu, Y. Iida, S., and Ozeki, Y. (2004). Alteration of methylation profiles in distinct cell lineages of the layers during vegetative propagation in carnation (*Dianthus caryophyllus*). Euphytica *135*, 247-253.
33. Kitazawa, D., Hatakeda, Y., Kamada, M., Fujii, N., Miyazawa, Y., Hoshino, A., Iida, S., Fukaki, H., Morita, M.T.,, Tasaka, M., Suge, H., and Takahashi, H. (2005) Shoot circumnutation and winding movements require gravisensing cells. Proc. Natl. Acad. Sci. USA *102*, 18742-18747.
34. Saito, N., Toki, K., Morita, Y., Hoshino, A., Iida, S., Shigihara, A., and Honda, T. (2005). Acylated peonidin glycosides from *duskish* mutant flowers of *Ipomoea nil*. Phytochemistry *66*, 1852-1860.
35. Ohnishi, M., Fukada-Tanaka, S., Hoshino, A., Takada, J., Inagaki, Y., and Iida, S. (2005). Characterization of a novel Na^+/H^+ antiporter gene *InNHX2* and comparison of *InNHX2* with *InNHX1*, which is responsible for blue flower coloration by increasing the vacuolar pH in the Japanese morning glory. Plant Cell Physiol. *46*, 259-267.
36. Morita, Y., Hoshino, A., Kikuchi, Y., Okuhara, H., Ono, E., Tanaka, Y., Fukui, Y., Saito, Nitasaka, E., Noguchi, H., and Iida, S. (2005). Japanese morning glory *dusky* mutants displaying reddish-brown or purplish-grey flowers are deficient in a novel glycosylation enzyme for anthocyanin biosynthesis, UDP-glucose:anthocyanidin 3-O-glucoside-2"-O-glucosyltransferase, due to 4-bp insertions in the gene. Plant J. *42*, 353-363.
37. Hagihara, E., Itchoda, N., Habu, Y., Iida, S., Mikami, T., and Kubo, T. (2005). Molecular mapping of a fertility restorer gene for Owen cytoplasmic male sterility in sugar beet. Theor. Appl. Genet. *111*, 250-255.
38. Morita, Y., Saitoh, M., Hoshino, A., Nitasaka, E., and Iida, S. (2006). Isolation of cDNAs for R2R3-MYB, bHLH, and WDR transcriptional regulators and identification of *c* and *ca* mutations conferring white flowers in the Japanese morning glory. Plant Cell Physiol. *47*, 457-470.
39. Tsugane, K., Maekawa, M., Takagi, K., Takahara, H., Qian, Q., Eun, C.H., and Iida, S. (2006). An active DNA transposon *nDart* causing leaf variegation and mutable dwarfism and its related elements in rice. Plant J. *45*, 46-57.
40. Furukawa, T., Maekawa, M., Oki, T., Suda, I., Iida, S., Shimada, H., Takamure, I., and Kadowaki, K. (2007). The *Rc* and *Rd* genes are involved in proanthocyanidin synthesis in the rice pericarp. Plant J. *49*, 91-102.
41. Park, K.I., Ishikawa, N., Morita, Y., Choi, J.D., Hoshino, A., and Iida, S. (2007). A *bHLH* regulatory gene in the common morning glory, *Ipomoea purpurea*, controls anthocyanin biosynthesis in flowers, proanthocyanidin and phytomelanin pigmentation in seeds, and seed trichome formation. Plant J. *49*, 641-659.
42. Choi, J.D., Hoshino, A., Park, K.I., Park, I.S., and Iida, S. (2007). Spontaneous mutations

caused by an active *Helitron* transposon, *Hel-It1*, in morning glory, *Ipomoea tricolor.* Plant J. *49*, 924-934.
43. Takagi, K., Ishikawa, N., Maekawa, M., Tsugane, K., and Iida, S. (2007). Transposon display for active DNA transposons in rice. Genes Genet. Syst. *82*, 109-122.
44. Terada, R., Johzuka-Hisatomi, Y., Saitoh, M., Asao, H., and Iida, S. (2007). Gene targeting by homologous recombination as a biotechnological tool for rice functional genomics. Plant Physiol. *144*, 846-856.

2) Invited reviews, book chapters

1. Izawa, T., Ohnishi, T., Nakao, T., Ishida, N., Enoki, H., Hashimoto, H., Itoh, K., Terada, R., Wu, C., Miyazaki, C., Endo, T., Iida, S., and Shimamoto, K. (1997). Transposon tagging in rice. Plant Mol. Biol. *35*, 219-229.
2. Habu, Y., and Iida, S. (1998). AFLP (amplified restriction fragment length polymorphism)-based mRNA fingerprinting. Plant Biotechnology *15*, 249-251.
3. Iida, S., Hoshino, A., Johzuka-Hisatomi, Y., Habu, Y., and Inagaki, Y. (1999). Floricultural traits and transposable elements in the Japanese and common morning glories. Annal. New York Acad. Sci. *870*, 265-274.
4. Iida, S., and Hoshino, A. (1999). Spontaneous mutagenesis and transposable elements in the Japanese morning glory. Gamma Field Symposia *38*, 1-10.
5. Iida, S., Hoshino, A., and Cjoi, J.-D. (2000). Floricultural traits and transposable elements in morning glories. Kor. J. Hort. Sci. & Technol. *18*, 845-846.
6. Iida, S., and Terada, R. (2002). Gene modification of an endogenous gene in rice plants. ISB News Report December, 7-8.
7. Iida, S., Morita, Y., Choi, J.D., Park, K.I., and Hoshino, A. (2004). Genetics and epigenetics in flower pigmentation associated with transposable elements in morning glories. Adv. Biophys. *38*, 141-159.
8. Iida, S., and Terada, R. (2004). A tale of two integrations, transgene and T-DNA: gene targeting by homologous recombination in rice. Curr. Opin. Biotechnol. *15*, 132-138.
9. Iida, S., and Terada, R. (2005). Modification of endogenous natural genes by gene targeting in rice and other higher plants. Plant Mol. Biol. *59*, 205-219.
10. Chopra, S., Hoshino, A., Boddu, J., and Iida, S. (2006). Flavonoid pigments as tools in molecular genetics. E. Glotewold ed., The Science of Flavonoids, pp.147-173, Springer, Berlin, Heidelberg, New York.
11. Iida, S., Johzuka-Hisatomi, Y., and Terada, R. (2007). Gene targeting by homologous recombination for rice functional genomics. N.M. Upadhyaya ed., Rice Functional Genomics-Challenges, Progress and Prospects, pp.273-289, Springer, Berlin, Heidelberg, New York.

堀内　嵩
ゲノム動態研究部門・教授

Scientific programme

The work of this division is focused on genome structure and variation and was presented in 4 sections: amplification mechanism of rDNA; mechanism of maintenance of rDNA copies; amplification of drug resistance and the effects of making the *E.coli* genome linear rather than circular.

Amplification of rDNA

The work on amplification of rDNA was initiated based on earlier work on *E.coli*. The *ter* cis element and TAS trans-acting protein, which binds to *ter*, blocks movement of the replication fork. This block stimulates recombination behind the replication fork. However, if blocking is prevented in mutants no phenotype is observed.

In yeast a similar system was discovered in the Division and shown to be important in the amplification of the number of genes encoding rRNA. There are around 150-200 copies of rDNA in yeast. A replication fork barrier (RFB) is present in the rRNA cluster. Mutations in the *FOB1* gene prevent blocking of replication. A link between the RFB and *FOB1* and increasing the copy number of rRNA genes could be shown by using the *pol1* mutant. In RNA *pol1* mutants rDNA copy number falls by half, so there is less rDNA and chromosome 12 is smaller. In *fob1* mutants the copy number stays low and is not restored.

Maintenance mechanism of rDNA

The number of rDNA repeats is dynamic, continuously falling and rising. FOB1 is required for this dynamism, but once the number of repeats is reduced then this smaller number of repeats is stable. To identify how repeat number is stabilized a genetic screen was carried out to identify genetic enhancers of *fob1*. Six mutants were analyzed and all carried mutations in subunits of condensin, which plays a role in mitosis and chromosome compaction. Condensin binds to the RFB site in a FOB1 dependent manner. A model was proposed in which mutant condensins still show some activity in the absence of FOB1, but in the double mutant all activity is abolished. An ectopic RFB site can recruit condensin to chromosome 6. Also, the group proposed that other factors in addition to FOB1 are required to recruit condensin, and therefore screened for new mutations that show a *fob1* like phenotype in condensin mutant background. Interesting new mutants have been recovered.

Amplification of drug resistance

A novel model system to study gene amplification was established in yeast. The system was based on double rolling circle replication and was shown to allow amplification of up to 100 copies of an introduced sequence on chromosome 6. The system was shown to be dependent on double-stranded breaks. A second system reliant on Cre-lox was constructed but has not yet been published. The system is now being tested in mammalian cells.

Linear *E.coli* chromosome.

The Division also tested whether the circular chromosome of *E.coli* was essential or whether it could survive just as well with a linear chromosome. The *tos* site of phage N15 was used. This site is cleaved and repaired to generate stable ends during the phage life cycle. The *tos* site was inserted in the *E.coli* genome opposite to *oriC*, and the strain infected with N15 tail protein. This combination allowed cleavage of the *E.coli* genome, and the linear genome was elegantly shown to be present and to be stable using fluorescently labeled proteins. However, the linear chromosome had no effect on the bacteria which appeared to be equally as viable as those with circular genomes.

Profile, productivity and funding

The division has published papers in general, international journals such as *EMBO Journal* and *EMBO Reports*. Such recognition is deserved, as the experiments carried out in this group appear to be thoughtful, well planned and well executed. Some of the experimental designs appear to be elegant and satisfying, such as the linear chromosome of *E.coli* and some of the forward enhancer based screens used in yeast. Nevertheless, the work does not appear to make a general impact, none of the papers in the last 7 years are well cited. Possibly the ongoing work to transfer the gene amplification system to mammals will be of more general interest and provide a method of general importance for control of gene expression in mammalian cells.

Productivity has been good, with papers published in general journals and more specific journals when required. The work is of good quality. However, the output may well be limited by resources, and the division needs to be more proactive in obtaining external resources. The Professor made the point during his presentation that this is the smallest division, and that may well be due to limited external funds. Obtaining increased funding might require broadening the research programme to include topics of more general interest.

Collaborations

The work of the Division has obvious connections with that of Iida on transposon biology and some collaboration was mentioned. Also, some of the model building had benefited from the EMBL conference and contacts with EMBL scientists. Further collaborations might be possible, for example the expertise of this group may be useful in the genome analysis of *Physcomitrella* or *Selaginella* being carried out in the Hasebe Dvision.

General comments

The Division has published in good journals and carried through thoughtfully designed experiments. The overall activity of the Division could be increased by raising more external funds and broadening its activities. The future plans of the Division were not clearly presented.

（和訳）

研究プログラム

当部門の研究は、ゲノムの構造と変異に焦点を絞ったもので、rDNA の増幅機序、rDNA コピーの維持の機序、薬剤耐性の増幅、ならびに環状ではなく線状の大腸菌ゲノムの作成の効果の 4 セクションでの研究を行っている。

rDNA の増幅

rDNA の増幅に関する研究は、大腸菌に関する先の研究を基礎に開始されたものであった。*ter* cis エレメントと、*ter* に結合する TAS trans-acting protein は複製フォークの移動をブロックする、このブロックが複製フォークの背後の部分での組換えを刺激する。しかし突然変異でブロックが生じないようにすると表現型は全く観察されない。
酵母では、同様のシステムが当部門により発見され、rRNA をコードしている遺伝子の増幅に重要であることが示されている。酵母では rDNA は約 150-200 コピーである。複製フォーク阻害部位(RFB)が rRNA クラスター中に存在している。*FOB1* 遺伝子に突然変異が生じると、複製がブロックされなくなる。RFB と *FOB1* 遺伝子、さらに rRNA 遺伝子のコピー数の増大の間の関連性については、*pol1* 突然変異を使って示すことができた。RNA に *pol1* 突然変異があると、rDNA のコピー数が半分に減った。そのため rDNA の数は少なく、染色体 12 が小さくなっている。*fob1* 突然変異では、コピー数が低いままであり、回復しない。

rDNA の維持機序

rDNA リピートの数は動的であり、常に低下したり増加したりしている。このダイナミズムには FOB1 が必要である。しかし、一端リピート数が低下すると、この低いリピート数のままで安定である。リピート数がどのように安定化されているか明らかにするため、遺伝子スクリーニングを実施して *fob1* 遺伝子の遺伝的エンハンサーを同定した。6 種の突然変異株を分析し、condensin のサブユニットに全ての変異株が突然変異を有していることがわかった。condensin は有糸分裂と染色体コンパクションに一定の役割を果たしている。condensin は FOB1 依存性に RFB に結合する。condensin に突然変異があるだけでは、FOB1 が存在しなくてもある程度の活性を示すが、condensin に加えて FOB1 にも突然変異があると、全ての活性が消失するというモデルが提唱された。異所性 RFB 部位は、染色体 6 に condensin を動員できる。また、研究グループは、condensin を動員するには、FOB1 に加えて他の因子が必要であると提唱し、そのため、condensin 変異株で、*fob1* 様の表現型を示す新たな突然変異株のスクリーニングを実施した。興味深い新たな突然変異がいくつか見つかっている。

薬剤耐性の増幅

遺伝子増幅を研究する新たなモデル系を酵母で確立した。このシステムは double rolling circle 複製に基づくもので、染色体 6 に導入したシーケンスを最大 100 コピー増幅できることが示されている。このシステムは二重鎖切断に依存することが示されている。Cre-lox に依存する第二のシステムを構築したが、まだ論文としては発表していない。このシステムについては、現在ほ乳動物の細胞でテスト中である。

線状 *E. coli* 染色体

当部門では大腸菌の環状染色体が生存に不可欠なの、線状染色体でも生存できるのかについても調べた。ファージ N15 の *tos* サイトを用いた。このサイトを開裂させ、ファージのライフサイクル中に修復して安定端を生成させた。この *tos* サイトを酵母ゲノムの *oriC* の反対側に挿入し、N15 tail タンパク質と一緒に感染させた。この組み合わせで、大腸菌ゲノムを開裂させることができ、線状ゲノムが存在し、安定であることが、蛍光標識させたタンパク質を用いてエレガントに示された。しかし、線状染色体は、細菌に対して何ら影響がなく、環状ゲノムのものと同程度に生育可能であるように見えた。

プロフィール、生産性、研究予算

当部門では *EMBO Journal* や *EMBO Reports* などの総合国際論文誌に論文を発表している。このことは評価する価値がある。このグループが行った実験は、良く考えられ、良好に計画実行されたものであるように思われるからである。実験デザインの中には、大腸菌の線状染色体や、酵母で用いた forward enhancer ベースのスクリーニングなどのように、エレガントで満足できるレベルのものがあるように思われる。しかし、彼らの研究は、一般のインパクトが低いように思われる。過去 7 年間に発表された論文のうち他の論文から多く引用されている論文は少ない。現在続けられている遺伝子増幅系をほ乳動物に移す研究が進めば、おそらく一般の関心も高くなり、ほ乳動物の細胞で遺伝子発現をコントロールする方法として重要なものを提供することになろう。

生産性は良好であり、総合論文誌に論文を発表し、必要があれば、より専門的な論文誌に発表している。研究は高品質のものである。しかし、リソースが限られているため、出力が少ないものと考えられ、外部からのリソースを獲得するよう、一層の努力が当部門には必要である。教授は発表にあたって、(研究所内で) 最も規模の小さな部門であると言っているが、それはおそらく外部からの助成金が少ないことが一因と思われる。助成金の獲得量を高めるには、研究プログラムを拡大させて、一般の関心がより高いテーマを含めるようにする必要があろう。

共同研究

当部門の研究は、トランスポゾンの生物学の点で飯田教授の研究と明らかな関連性があり、いくつか共同研究を行ったことが言及されていた。また、モデル構築のいくつかについては、EMBL コンファレンスや EMBL の研究者たちとの接触が役立っている。さらに共同研究を拡大することが可能であろう。例えば、このグループの専門技術、長谷部教授の部門で現在実施されているヒメツリガネゴケ *Physcomitrella* やクラマゴケ *Selaginella* のゲノム解析に有用であろう。

総評

当部門は良質の論文誌に論文を発表し、慎重にデザインされた実験を行っている。外部からの助成金獲得を増やし、研究活動の範囲を広げることで、当部門の全体の活動が高まるであろう。当部門の将来計画については明確に示されなかった。

研究業績：

1) Research articles in peer reviewed journals

1. Kobayashi, T., Heck, J. D., Nomura, M., and Horiuchi, T. (1998). Expansion and contraction of ribosomal DNA repeats in *Saccharomyces cerevisiae*: requirement of replication fork blocking (Fob1) protein and the role of RNA polymerase I. Genes Dev. *12*, 3821-3830.
2. Taki, K., and Horiuchi, T. (1999). The SOS response is induced by replication fork blockage at a Ter site located on a UC-derived plasmid: dependence on the distance between ori and Ter sites. Mol. Gen. Genet. *262*, 302-309.
3. Mori, H., Isono, K., Horiuchi, T., and Miki, T. (2000). Functional genomics of *Escherichia coli* in Japan. Res. Microbiol. *151*, 121-128.
4. Kobayashi, T., Nomura, M., and Horiuchi, T. (2001). Identification of DNA cis-elements essential for expansion of ribosomal DNA repeats in *Saccharomyces cerevisiae*. Mol. Cell. Biol. *21*, 136-147.
5. Urawa, H., Hidaka, M., Ishiguro, S., Okada, Y., and Horiuchi, T. (2001). Enhanced homologous recombination caused by a non-transcriptional spacer of the ribosomal RNA genes in *Arabidopsis*. Mol. Genet. Genomics *266*, 546-555
6. Wai, H., Johzuka, K., vu, L., Eliason, K., Kobayashi, T., Horiuchi, T., and Nomura, M. (2001). Yeast RNA polymerase enhancer is dispensable for growth and its apparent transcription enhancement form ectopic promoter requires Fob1 protein implicated in replication and recombination or rDNA. Mol. Cell. Biol. *21*, 5541-5553.
7. Kodama, K., Kobayashi, T., Niki, H., Hiraga, S., Oshima, T., Mori, H., and Horiuchi, T. (2002). Amplification of Hot DNA segments in *Escherichia coli*. Mol. Microbiol. *45*, 1575-1588.
8. Johzuka, K., and Horiuchi, T. (2002). Replication fork block protein, Fob1, acts as an rDNA region specific recombinator in *S. cerevisiae*. Genes Cells *7*, 99-113
9. Takeuchi, Y., Horiuchi, T., & Kobayashi, T. (2003). Transcription-dependent recombination and the role of fork collision in yeast rDNA. Genes Dev. *17*, 1497-1506.
10. Serizawa, N., Horiuchi, T., and Kobayashi, T. (2004). Transcription-mediated hyper-recombination in HOT1. Genes Cells *9*, 305-315.
11. Kobayashi, T., Horiuchi, T., Tongaonlar, T., Vu, L., and Nomura, M. (2004). SIR2 regulates recombination between different rDNA repeats, but not recombination within individual rDNA genes in Yeast. Cell *77*, 441-453.
12. Kasarjian, J.A., Hidaka, M., Horiuchi, T., and Ryu, J. (2004). The recognition and modification sites for the bacterial type I restriction systems KpnAI, StySEAI, StySENI and StySGI. Nucleic Acids Res. *32*, (publish on line)
13. Komori, K., Hidaka, M., Horiuchi, T., Fujikane, R., Shinagawa, H., and Ishino, Y. (2004). Cooperation of the N-terminal helicase and C-terminal endonuclease activities of archaeal Hef protein in processing stalled replication fork. J. Biol. Chem. *279*, 53175-53185.
14. Watanabe, T., and Horiuchi, T. (2005). A novel gene amplification system in yeast based on double rolling-circle replication. EMBO J. *24*, 190-198.
15. Ganley, A.R., Hayashi, K., Horiuchi, T., and Kobayashi T. (2005). Identifying

gene-independent noncoding functional elements in the yeast ribosomal DNA by phylogenetic footprinting. Proc. Natl. Acad. Sci. U S A *102*, 11787-11792.

16. Riley, M., Abe, T., Arnaud, M.B., Berlyn, M.K., Blattner, F.R., Chaudhuri, R.R., Glasner, J.D., Horiuchi, T., Keseler, I.M., Kosuge1, T., Mori, H., Perna, N.T., Plunkett III, G., Rudd, K.E., Serres, M.H., Thomas, G.H., Thomson, N.R., Wishart, D., and Wanner, B.L. (2006). *Escherichia coli* K-12: a cooperatively developed annotation snapshot – 2005. Nucleic Acids Res. *34*, 1-9.
17. Hayashi, K., Morooka, N., Yamamoto, Y., Fujita, K., Isono, K., Choi, S., Ohtsubo, E., Baba, T. Wanner, B. L., Mori H., and Horiuchi, T. (2006). Highly accurate genome sequences of *Escherichia coli* K-12 strains MG1655 and W3110. Mol. Systems Biol. doi:10.1038 msb100049:E1-E5.
18. Johzuka, K., Terasawa, M., Ogawa, H., Ogawa,T., and Horiuchi, H. (2006). Condensin loaded onto the replication fork barrier site in ribosomal DNA (rDNA) repeats during S-phase in a *FOB1*-dependent fashion to prevent contraction of a long repeats in *S.cerevisiae*. Mol. Cell. Biol. *26*, 2226-2236.
19. Inagaki, S., Suzuki, T., Ohto, M., Urawa, H., Horiuchi, T., Nakamura, K., and Morikamid, A. (2006). *Arabidopsis* TEBICHI, with helicase and DNA polymerase domains, is required for regulated cell division and differentiation in meristems. Plant Cell *18*, 879-892.
20. Cui, T., Moro-oka, N., Ohsumi, K., Kodama, K., Ohshima, T., Ogasawara, N., Mori, H., Wanner, B., Niki, H., and Horiuchi, T. (2007). *E. coli* with a linear genome. EMBO Rep. *8*, 181-187.
21. Johzuka, K., and Horiuchi, H. (2007). RNA polymerase I transcription obstructs condensin association with 35S rRNA coding regions and can cause contraction of long repeat in *Saccharomyces cerevisiae*. Genes Cells *12*, 759-771.

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Scientific programme

The major interests of the Professor have been in the phylogeny of land plants and in developing new model plant species to study aspects of plant evolution. More recently a large ERATO laboratory was established to study the basis of totipotency and the transdifferentiation of differentiated cells into stem cells. During the last 10 years, strong emphasis has been given to using *Physcomitrella* as a model to study Bryophyte biology and to provide insight into the evolution of higher plants.

***Physcomitrella patens* – evolution, biology and genome**

To isolate genes from *Physcomitrella patens* that are involved in early differentiation, a forward genetic screen was developed based on overexpression of random cDNAs. During regeneration from protoplasts the first division is asymmetric and can be considered as a stem cell giving rise to a stem cell and a non-stem cell. Four thousand cDNAs were transformed and transgenic lines identified that behaved differently to the wild-type. Two cDNAs were identified that caused both cells to behave as stem cells, and nine cDNAs that caused both cells to be differentiated. The genes identified included transcription factors, kinases and receptor-like proteins, and these will be studied in the future. Similarly, genes involved in stem cell regulation were identified using a gene trap system. One encodes kinesin the other a ubiquitin-like protein. These approaches were encouraging as they allowed using *P. patens* for gene discovery, rather than to analyze the function of genes initially studied in higher plants.

The Division has played a major role in the sequencing of the *P. patens* genome, which will be very valuable for future projects. A paper describing the sequence was recently released for publication in *Science*. However, this genome sequence still includes 2,106 scaffolds. Sequencing BACs derived from a library made in the division will help assembly. Further sequencing projects going on involve the use of Solexa sequencing to identify SNPs for genetic mapping and SAGE to characterize cDNAs (so far 1,1,22,000 SAGE sequences are available). The Division has also been heavily involved in annotating the *P. patens* genome sequence. Seven hundred genes from Arabidopsis involved in developmental processes were selected using key words. Approximately 85% of these have orthologues in *P. patens*. Interesting principles are emerging from the sequence. Many of the gene families have either expanded or shrunk during evolution of higher plants. None of the genes involved in ethylene biosynthesis in *Arabidopsis* are present in *P. patens*, suggesting a different biosynthetic mechanism. Also, although *P. patens* diverged from higher plants about 480 mya, the number of types of genes present has not changed radically, perhaps suggesting a different type of evolution than observed in animals.

Several projects are carried out relating to the evolution of molecular mechanisms in plant

development. One of these relates to the evolution and maintenance of stem cells. In *P. patens*, and other lower plants, the branching form is haploid, so higher plants were thought to have co-opted their stem cell control from the haploid form of lower plants. In higher plants, KNOX genes have a major role in maintaining stem cells. In *P. patens* there are three KNOX genes, but the triple mutant showed no phenotype in the haploid form and is not expressed in the haploid meristem. However, in the diploid form there is an effect, suggesting that the KNOX genes are involved in cell division and growth in the diploid. These observations suggest that the ancestral function of these genes was in controlling cell division in diploids.
The roles of genes involved in epigenetic gene regulation were also studied in *P. patens*.

Finally MIKC* MADS box genes were studied and suggested that they might be involved in cell wall loosening in higher plants and expressed in the gametophyte of *P. patens*, suggesting an ancestral function in gametophyte development.

Establishment of additional model species
To extend the success of using *Physcomitrella patens* as a model Bryophyte, other model systems are being established for other parts of the plant Kingdom. These include a model Gymnosperm (*Gnetum parvifolium*), Fern (*Ceratopteris richardii*), Lycopod (*Selaginella moellendorffii*) and Charophytes. Of these *S. moellendorffii* is particularly well developed and the Division is part of an international effort to sequence the genome of this organism.

Evolution of novel characters
Projects have been initiated to study processes specific to particular groups of plants. For example, proteins found in the pitchers of carnivorous plants were identified using protein mass spectrometry. Several of these were found to be encoded by orthologues of genes present in Arabidopsis, where the genes are implicated in pathogenesis and responses to pathogens.

ERATO laboratory
This laboratory is very large and employs more people than the rest of the Division. The aim is to study transdifferentiation from differentiated cells on the gametophore to stem cells. Light is necessary for this process, and it involves the expression of a variety of genes.

Profile, productivity and funding
The Division has an outstanding research programme with an international reputation. The energy and ambition of the Professor is impressive, and many interesting research projects showing great promise are going on in the Division. Analyzing developmental programmes in a wider range of plant species is likely to be a major area of activity in the plant research community in the future to broaden the range of processes studied and to determine how universal discoveries made in higher plant models such as Arabidopsis are. The Division is at the forefront of this process and its work is likely to be recognized even more widely in the coming years. The Division showed an impressive willingness to adapt different technologies and approaches, including genome sequencing and adoption of the latest genomics approaches as well as forward genetics.

The Division has published very well during the period including publications in high impact general journals. The willingness of the Professor to enter productive collaborations contributed to this process so that collaborative papers were published in *Science* on the evolution of *LEAFY* and on the genome sequence of *Physcomitrella patens*. In addition, his group working independently also published detailed and thorough analyses, such as the analysis of the function of *LEAFY* in *P. patens*, published in *Development*.
The Division is well funded and through the ERATO grant can build resources such as the imaging facility that has contributed to many ongoing projects.

Collaborations
The Division has excellent international collaborations and establishes tools available to the national and international communities. They are clearly an important part of the international effort to analyze the *Physcomitrella patens* genome, and are part of the consortium developed to analyze the *Selaginella* genome. In addition, international collaborations on *P. patens* biology have been influential, for example in studying the *P. patens LEAFY* gene, which led to papers in *Science* as well as *Development*. The Division also provides tools and courses that are of general importance to the community, including PHYSCObase, which provides information on *P. patens* from the NIBB web site (http://moss.nibb.ac.jp), *P. patens* cDNA clones, which are distributed through RIKEN and lab courses on *P. patens* that attract national and international participants.

General comments
This is an outstanding and ambitious group with an international reputation in an important area of plant biology. Ongoing projects promise very good productivity in the coming years, and a clear vision based on using SOLiD sequencing and ChIP seq to study the evolution of gene networks was expressed. Such technologies being developed within the ERATO laboratory can benefit the whole NIBB.
One reservation might be that the programme may be too broad and constant assessment of the most promising avenues to follow would be worthwhile. For example, the work on pollen tube guidance in Arabidopsis seemed isolated from the rest of the programme and might not be as internationally competitive as other aspects of the work.

（和訳）

研究プログラム
教授の主な関心領域は、陸上植物の系統発生論であり、植物の進化を探るための、植物種に関する新たなモデルを構築することであった。最近、大規模な ERATO（戦略的創造研究推進事業）分化全能性進化プロジェクト研究室が創設され、分化細胞が幹細胞に戻る分化全能性と分化転換の基礎について研究することとなった。過去 10 年間に、ヒメツリガネゴケ *Physcomitrella patens* をモデルとしてコケ植物の生物学を重点的に研究し、高等植物の進化に関する洞察を得る研究が行われてきた。

ヒメツリガネゴケ *Physcomitrella* - 進化、生物学、ゲノム

初期の分化に関係している遺伝子をヒメツリガネゴケ *Physcomitrella* から分離するため、ランダム cDNA の過剰発現に基づく正遺伝学的方法を開発した。プロトプラストからの再生中に、最初の細胞分裂は不等分裂であり、幹細胞が、幹細胞と非幹細胞を生成するものと考えることができる。4000 の cDNA を遺伝子導入し、形質転換させた細胞系統は、野生型とは異なる振る舞いをすることがわかった。2 つの cDNA が同定され、両方の細胞とも幹細胞として振る舞うようになることがわかり、9 種の cDNA では、両方の細胞が分化細胞となった。同定された遺伝子には、転写因子、キナーゼ、受容体様のタンパク質が含まれており、これらについては今後研究していく予定である。同様に、幹細胞の制御に関与している遺伝子が遺伝子トラップシステムを用いて同定された。一つはキネシンをコードしている遺伝子であり、もう一つはユビキチン様のタンパク質をコードしている。これらのアプローチは有望なものであった。彼らは、高等植物で当初行われていたような遺伝子の機能を解析するのではなく、遺伝子の発見にヒメツリガネゴケを使ったからである。

当部門はヒメツリガネゴケ *Physcomitrella* の配列決定に主要な役割を果たした、このことは今後のプロジェクトに極めて有用なものとなろう。配列について記載した論文が、*Science* 誌に最近掲載された。しかし、このゲノムにはまだ 2,106 個の scaffold が含まれている。当部門で作成したライブラリー由来の BAC を配列決定することがアセンブリに役立つであろう。現在進行中の配列決定プロジェクトでは、Solexa sequencing を用いて遺伝子マッピングでの SNP を同定し、SAGE を用いて cDNA の特性を調べている(現時点で 1,1,22,000 個の SAGE シーケンスがある)。当部門はまたヒメツリガネゴケ *Physcomitrella* のゲノムシーケンスの annotation にも深く関わってきている。発生プロセスに関与しているシロイヌナズナの 700 個の遺伝子をキーワードを使って選択した。これらの 85%がヒメツリガネゴケ *Physcomitrella* のゲノムと類似性を有している。これらの配列から興味深い原理が浮き彫りにされてきている。これら遺伝子ファミリーの多くは、高等植物の進化の過程で、拡大あるいは収縮されてきている。シロイヌナズナでエチレンの生合成に関係している遺伝子はヒメツリガネゴケにはいずれも存在していなかった。このことは生合成機序が異なることを示唆している。また、ヒメツリガネゴケは約 4 億 8 千万年前に高等動物から分岐したが、存在している遺伝子タイプの数は、それほど大きく変化しておらず、おそらく動物で観察されているものとは異なるタイプの進化であることを示唆するものであろう。

植物の発生の分子機序の進化に関連づけたプロジェクトがいくつか実施されている。このうちの一つは、進化と幹細胞の維持に関するものである。ヒメツリガネゴケやその他の下等植物では、枝系は１倍体に形成される。従って高等植物は、下等植物の１倍体から幹細胞のコントロールを取り込んだものと考えられた。高等植物では、KNOX 遺伝子が、幹細胞の維持に大きな役割を果たしている。ヒメツリガネゴケには 3 つの KNOX 遺伝子があるが、3 遺伝子とも突然変異させても、１倍体の表現型を示さず、１倍体分裂組織では発現されない。しかし、２倍体では影響があり、KNOX 遺伝子は、細胞分裂と２倍体の増殖に関係していることを示唆するものである。これらの観察結果からは、これらの遺伝子の先祖の機能は、２倍体の細胞分裂の制御にあったことが示唆される。

エビジェネティックな遺伝子制御に関与している遺伝子の役割についてもヒメツリガネゴケで研究が行われた。*CURLY LEAF* (*CLF*)ホモローグの突然変異を作成した。

最後に、MIKC* MADS ボックス遺伝子について調べられ、高等植物の細胞壁の loosening に関与していることが示唆され、ヒメツリガネゴケの配偶体に発現されており、配偶体の形成に先祖的な役割を有していることを示唆するものである。

その他のモデル種の確立

モデルのコケ植物としてヒメツリガネゴケ *Physcomitrella patens* を用いて成功したことを拡張するため、植物界の他の部門から別のモデルを現在確立中である。それらのモデルとしては裸子植物モデル(*Gnetum parvifolium*)、シダ植物モデル（リチャードミズワラビ *Ceratopteris richardii*)、イヌカタヒバ（*Selaginella moellendorffii*)ならびにシャジクモ類が含まれる。この中でヒカゲノカズラのモデルは良好に進んでおり、当部門は、イヌカタヒバのゲノム配列決定の国際研究に参加している。

新規特性の進化

特別な植物群に特異的なプロセスを研究するプロジェクトが開始されている。例えば、食虫植物の壺状葉 （嚢状葉）に見つかるタンパク質を、タンパク質質量分析器を用いて同定した。これらのタンパク質のいくつかは、シロイヌナズナのオルソログ遺伝子がコードしていることがわかった。これらの遺伝子は、発病や病原体に対する応答に関係していると考えられている。

ERATO 研究室

この研究室は極めて大規模で、当部門より多くのスタッフを雇用する。プロジェクトの目的は、茎葉体上の分化した細胞から幹細胞への分化転換について研究することである。このプロセスには光が必要で、様々な遺伝子の発現が関与している。

プロフィール、生産性、研究予算

当部門には、国際的評価の高い傑出した研究プログラムがある。教授のエネルギーと大望は印象的であり、将来展望の大きな興味深い研究プロジェクトが当部門で進行中である。より広い植物種で発生プログラムを分析することが、研究しているプロセスの範囲を広げるため、およびシロイヌナズナなどの高等植物モデルでの普遍的な発見になるかどうかを調べるため、植物研究領域での今後の主な活動内容となるものと思われる。当部門は、このプロセスの最先端を進んでおり、当部門の研究結果は、今後数年間にさらに広く認知される可能性が高い。当部門は、ゲノム配列解析などの様々なテクノロジーとアプローチを積極的に採用し、最新のゲノミクスアプローチや正遺伝学的手法を採用する姿勢を示している。

当部門では、高インパクトの総合論文誌への掲載を含む論文を評価対象期間中に多数発表している。教授が生産的な共同研究に積極的に参加する姿勢を示していることが、この発表論文の多さに貢献しており、共同研究の論文が、*LEAFY* 遺伝子の進化に介して *Science* 誌に掲載され、ヒメツリガネゴケの遺伝子配列に関する論文が同じ *Science* 誌に掲載される結果となっている。加えて、独立に研究している彼のグループも、ヒメツ

リガネゴケの *LEAFY* 遺伝子の機能分析などの、詳細で網羅的な解析結果を、*Development* 誌に発表している。
当部門の研究資金は潤沢であり、ERATO 助成金を使って、イメージング施設などのリソース構築を行うことができ、多くの進行中のプロジェクトに貢献している。

共同研究
当部門には極めて優れた国際共同研究があり、国内外の研究者コミュニティーに使えるツールを確立している。これらのものは、ヒメツリガネゴケの国際ゲノム解析の重要な部分を占めており、イヌカタヒバのゲノム解析のために開発されたコンソーシアムの一部となっている。加えて、ヒメツリガネゴケの生物学に関する国際共同研究は、例えば *LEAFY* 遺伝子の研究などで影響が大きく、*Science* 誌や *Development* 誌に論文が掲載される結果となっている。当部門は PHYSCO（基生研ウェブサイト(http://moss.nibb.ac.jp)からアクセスできるヒメツリガネゴケの情報)、ヒメツリガネゴケ cDNA クローン（理化学研究所を通じて配布)、および国内外から参加するヒメツリガネゴケに関する研究コースを含む学界全体に重要なツールやコースも提供している。

総評
植物生物学の重要な領域で国際的な名声を得ている傑出した大望のある研究グループである。現在実施中のプロジェクトは、今後極めて良好な生産性が得られることが予想され、SOLiD シーケンシングは ChIP seq を用いて遺伝子ネットワークについて研究するという明確なビジョンが示された。ERATO 研究室内で開発されているそのような新技術は、基礎生物学研究所全体に恩恵をもたらすことができる。
一つ懸念されることは、プログラムが手を広げすぎているのではないかという点で、最も有望と思われる方向性を常に評価し続けることが有用であろう。例えば、シロイヌナズナでの花粉管のガイダンスに関する研究は、他のプログラムとは孤立しているように思われ、他の研究と比べると、国際的競争力がないと思われる。

研究業績：

1) Research articles in peer reviewed journals

1. Fukada-Tanaka, S., Hoshino, A., Hisatomi, Y., Habu, Y., Hasebe, M., and Iida, S. (1997). Identification of new chalcone synthase genes for flower pigmentation in the Japanese and common morning glories. Plant Cell Physiol. *38*, 754-758.
2. Hasebe, M., and Banks, J.A. (1997). Evolution of MADS gene family in plants. In K. Iwatsuki and P.H. Raven eds., Evolution and Diversification in Land Plants, Springer-Verlag, Tokyo, pp179-197.
3. Hasebe, M., Ando, T., and Iwatsuki, K. (1998). Intrageneric relationships of maple trees based on the chloroplast DNA restriction fragment length polymorphisms. J. Plant Res. *111*, 441-451.

4. Hasebe, M., Wen, C.-K., Kato, M., and Banks, J.A. (1998). Characterization of MADS homeotic genes in the fern *Ceratopteris richardii*. Proc. Natl. Acad. Sci. USA *95*, 6222-6227.
5. Aso, K., Kato, M., Banks, J.A., and Hasebe, M. (1999). Characterization of homeodomain-leucine zipper genes in the fern, *Ceratopteris richardii* and the evolution of the homeodomain-leucine zipper gene family in vascular plants. Molec. Biol. Evol. *16*, 544-552.
6. Shindo, S., Ito, M., Ueda, K., Kato, M., and Hasebe, M. (1999). Characterization of MADS genes in the gymnosperm *Gnetum parvifolium* and its implication on the evolution of reproductive organs in seed plants. Evol. Dev. *1*, 180-190.
7. Yokoyama, J., Suzuki, M., Iwatsuki, K., and Hasebe, M. (2000). Molecular phylogeny of *Coriaria*, with special emphasis on the disjunct distribution. Molec. Phyl. Evol. *14*, 11-19.
8. Sano, R., Takamiya, M., Ito, M., Kurita, S., and Hasebe, M. (2000). Phylogeny of lady fern group, tribe Physematieae (Dryopteridaceae) based on chloroplast *rbcL* gene sequences. Molec. Phyl. Evol. *15*, 403-413.
9. Nishiyama, T., Hiwatashi, Y., Sakakibara, K., Kato, M., and Hasebe, M. (2000). Tagged mutagenesis and gene-trap in the moss, *Physcomitrella patens* by shuttle mutagenesis. DNA Res. *7*, 1-9.
10. Sano, R., Takamiya, M., Kurita, S., Ito, M., and Hasebe, M. (2000). *Diplazium subsinuatum* and *Di. tomitaroanum* should be moved to *Deparia* according to molecular, morphological, and cytological characters. J. Plant Res. *113*, 157-163.
11. Sano, R., Ito, M., Kurita, S., and Hasebe, M. (2000). *Deparia formosana* (Rosenst.) as the new name for *Diplazium formosanum.* Acta Phototaxa Geobot. *51*, 17-20.
12. Yoshimoto, Y., Higeta, D., Ito, Y., Yoshida, H., Hasebe, M., and Ozeki, Y. (2000). Isolation and characterization of a cDNA for Phenylalanine ammonia-lyase (PAL) from *Dianthus caryophyllus* (carnation). Plant Biotechnol. *17*, 325-329.
13. Sakakibara, K., Nishiyama, T., Kato, M., and Hasebe, M. (2001). Isolation of homeodomain- leucine zipper genes from the moss *Physcomitrella patens* and the evolution of Homeodomain-leucine zipper genes in land plants. Mol. Biol. Evol. *18*, 491-502.
14. Hiwatashi, Y., Nishiyama, T., Fujita, T., and Hasebe, M. (2001). Establishment of gene-trap and enhancer-trap systems in the moss *Physcomitrella patens*. Plant J. *28*, 105-116.
15. Himi, S., Sano, R., Nishiyama, T., Tanahashi, T., Kato, M., Ueda, K., and Hasebe, M. (2001). Evolution of MADS-box gene induced by *FLO/LFY* genes. J. Mol. Evol. *53*, 387-393.
16. Shindo, S., Sakakibara, K., Sano, R., Ueda, K., and Hasebe, M. (2001). Characterization of a *FLORICAULA/LEAFY* homologue of *Gnetum parvifolium*, and its implications for the evolution of reproductive organs in seed plants. Int. J. Plant Sci. *162*, 1199-1209.
17. Henschel, K., Kofuji, R., Hasebe, M., Saedler, H., Munster, T., and Theissen, G.. (2002). Two ancient classes of MIKC-type MADS-box genes are present in the moss *Physcomitrella patens*. Mol. Biol. Evol. *19*, 801-814.
18. Imaizumi, T., Kadota, A., Hasebe, M., and Wada, M. (2002). Cryptochrome light signals control development to suppress auxin sensitivity in the moss *Physcomitrella patens*. Plant Cell *14*, 373-386.
19. Iwakawa, H., Ueno, Y., Semiarti, E., Onouchi, H., Kojima, S., Tsukaya, H., Hasebe, M.,

Soma, T., Ikezaki, M., Machida, C., and Machida, Y. (2002). The *ASYMMETRIC LEAVES2* gene of *Arabidopsis thaliana*, required for formation of a symmetric flat leaf lamina, encodes a member of a novel family of proteins characterized by cysteine repeats and a leucine zipper. Plant Cell Physiol. *43*, 467-478.

20. Rivadavia, F., Kondo, K., Kato, M., and Hasebe, M. (2003). Phylogeny of the sundews, *Drosera* (Droseraceae) based on chloroplast *rbcL* and nuclear 18S ribosomal DNA sequences. Amer. J. Bot. *90*, 123-130.
21. Itoh, Y., Hasebe, M., Davies, E., Takeda, J., and Ozeki, Y. (2003). Survival of *Tdc* transposable elements of the *En/Spm* superfamily in the carrot genome. Mol. Genet. Genomics *269*, 49-59.
22. Tanabe, Y., Uchida, M. Hasebe, M., and Ito, M. (2003). Characterization of the *Selaginella remotifolia* MADS-box gene. J. Plant Res. *116*, 71-75.
23. Wolf, P.G., Rowe, C.A., Sinclair, R.B., and Hasebe, M. (2003). Complete nucleotide sequence of the chloroplast genome from a leptosporangiate fern, *Adiantum capillus-veneris* L. DNA Res. *10*, 59-65.
24. Nishiyama, T., Fujita, T., Shin-I, T., Seki, M., Nishide, H., Uchiyama, I., Kamiya, A., Carninci, P., Hayashizaki, Y., Shinozaki, K., Kohara, Y., and Hasebe, M. (2003). Comparative genomics of *Physcomitrella patens* gemetophytic transcriptome and *Arabidopsis thaliana*: Implication for land plant evolution. Proc. Natl. Acad. Sci. USA *100*, 8007-8012.
25. Sakakibara, K., Nishiyama, T., Sumikawa, N., Kofuji, R., Murata, T., and Hasebe, M. (2003). Involvement of auxin and a homeodomain-leucine zipper I gene in rhizoid development of the moss *Physcomitrella patens*. Development *130*, 4835-4846.
26. Kofuji, R., Sumikawa, N., Yamasaki, M., Kondo, K., Ueda, K., Ito, M., and Hasebe, M. (2003). Evolution and divergence of MADS-box gene family based on genome wide expression analyses. Mol. Biol. Evol. *20*, 1963-1977.
27. Aoki, S., Uehara, K., Imafuku, M., Hasebe, M., and Ito, M. (2004). Phylogeny and divergence of basal angiosperms inferred from *APETALA3*- and *PISTILLATA*-like MADS-box genes. J. Plant Res. *117*, 229-244.
28. Nishiyama, T., Wolf, P.G., Kugita, M., Sinclair, R.B., Sugita, M., Sugiura, C., Wakasugi, T., Yamada, K., Yoshinaga, K. Yamaguchi, K., Ueda, K., and Hasebe, M. (2004). Chloroplast phylogeny indicates that bryophytes are monophyletic. Mol. Biol. Evol. *21*, 1813-1819.
29. Wolf, P.G., Rowe, C.A., and Hasebe, M. (2004). High levels of RNA editing in a vascular plant chloroplast genome: analysis of transcripts from the fern *Adiantum capillus-veneris*. Gene *339*, 89-97.
30. Rutherford, G., Tanurdzic, M., Hasebe, M., and Banks, J.A. (2004). A systemic gene silencing method suitable for high throughput, reverse genetic analyses of gene function in fern gametophytes. BMC Plant Biology *4*, 6.
31. Tamura, M.N., Fuse, S., Azuma, H., and Hasebe, M. (2004). Biosystematic studies on the family Tofieldiaceae I. Phylogeny and circumscription of the family inferred from DNA sequences of *mat*K and *rbc*L. Plant Biol. *6*, 562-567.
32. Hattori, M., Hasebe, M., and Sugita, M. (2004). Identification and characterization of cDNAs encoding pentatricopeptide repeat (PPR) proteins in the earliest land plant, the moss

Physcomitrella patens. Gene *343*, 305-311.
33. Kishi, M., Murata, T., Hasebe, M., and Watanabe, Y. (2005). An extraction method for tobacco mosaic virus movement protein localizing in plasmodesmata. Protoplasma *225*, 85-92.
34. Sano, R., Juárez, C. M., Hass, B., Sakakibara, K., Ito, M., Banks, J.A, and Hasebe, M. (2005). KNOX class of homeobox genes potentially have similar function in both diploid unicellular and multicellular meristems, but not in haploid meristems. Evol. Dev. *7*, 69-78.
35. Tanahashi, T., Sumikawa, N., Kato, M., and Hasebe, M. (2005). Diversification of gene function: homologs of the floral regulator *FLO*/*LFY* control the first zygotic cell division in the moss *Physcomitrella patens*. Development *132*, 1727-1736.
36. Tanabe, Y., Hasebe, M., Sekimoto, H., Nishiyama, T., Kitani, M., Henschel, K., Münster, T., Theißen, G., Nozaki, H., and Ito, M. (2005). Characterization of MADS-box genes in charophycean green alga and its implication for the evolution of MADS-box genes. Proc. Natl. Acad. Sci. USA *102*, 2436-2441.
37. Hayashida, A., Takechi, K., Sugiyama, M., Kubo, M., Itoh, R.D., Takio, S., Fujita, T., Hiwatashi, Y., Hasebe, M., and Takano, H. (2005). Isolation of mutant lines with decreased number of chloroplasts per cell from tagged mutant library of moss *Physcomitrella patens*. Plant Biol. *54*, 300-306.
38. Maizel, A., Bush, M. A., Tanahashi, T., Perkovic, J., Kato, M., Hasebe, M., and Weigel, D. (2005). The floral regulator LEAFY evolves by substitutions in the DNA binding domain. Science *308*, 260-263.
39. Nakamura, T., Fukuda, T., Nakano, M., Hasebe, M., Kameya, T., and Kanno, A. (2005). The modified ABC model explains the development of the petaloid perianth of *Agapanthus praecox* ssp. *orientalis* (Agapanthaceae) flowers. Plant Mol. Biol. *58*, 435-445.
40. Murata, T., Sonobe, S., Baskin, T. I., Hyodo, S., Hasezawa, S., Nagata, T., Horio, T., and Hasebe, M. (2005). Microtubules are nucleated on extant microtubules via gamma-tubulin in plant cortical arrays. Nature Cell Biology *7*, 961-968.
41. Shigyo, M., Shindo, S., Hasebe, M., and Ito, M. (2006). Phylogenetic analysis of AP2 domain-containing genes. Gene *366*, 256-265.
42. Machida, M., Takechi, K., Sato, H., Chung, S.J., Kuroiwa, H., Takio, S., Seki, M., Shinozaki, K., Fujita, T., Hasebe, M., and Takano, H. (2006). Genes for the peptidoglycan synthesis pathway are essential for chloroplast division in moss. Proc. Natl. Acad. Sci. USA *103*, 6753-6758.
43. Tsuji,S., Ueda, K., Nishiyama, T., Hasebe, M., Yoshikawa, S., Konagaya, A., Nishiuchi, T., and Yamaguchi, K. (2007). The chloroplast genome from a lycophyte (microphyllophyte), *Selaginella uncinata*, has a unique inversion, transpositions and many gene losses. J. Plant Res. *120*, 281-290.
44. Odahara, M., Inouye, T., Fujita, T., Hasebe, M., and Sekine, Y. (2007). Involvement of mitochondrial-targeted RecA in the repair of mitochondrial DNA in the moss, *Physcomitrella patens*. Genes Genet. Syst. *82*, 43-51.
45. Hirano, K., Nakajima, M., Asano, K., Nishiyama, T., Sakakibara, H., Kojima, M., Katoh, E., Xiang, H., Tanahashi, T., Hasebe, M., Banks, J.-A., Ashikari, M., Kitano, H., Ueguchi-Tanaka, M., and Matsuoka, M. The GID1-mediated GA perception mechanism is

conserved in the lycophyte *Selaginella moellendorffii* but not in the bryophyte *Physcomitrella patens.* Plant Cell *19*, 3058-3079.

2) Invited reviews, book chapters

1. Hasebe, M. (1997). Molecular phylogeny of *Ginkgo biloba*. In T. Hori, ed., *Ginkgo biloba*, Springer-Verlag, Tokyo, pp. 173-181.
2. Wolf, P.G., Pryer, K.M., Smith, A.R., and Hasebe, M. (1998). Phylogenetic studies of extant Pteridophytes. In D. Soltis et al. eds, Molecular Systematics of Plants (2nd), Chapmann and Hall, New York. pp. 541-556.
3. Hasebe, M. (1999). Evolution of reproductive organs in land plants. J. Plant Res. *112*, 463-474.
4. Hasebe, M., and Ito, M. (1999). Evolution of reproductive organs in vascular plants. In M. Kato ed, The Biology of Biodiversity, Springer-Verlag, Tokyo. pp. 243-255.
5. Fujita, T**.**, Nishiyama, T., Hiwatashi, Y., and Hasebe, M. (2003). Gene tagging, gene- and enhancer-trap systems, and full-length cDNA overexpression in *Physcomitrella patens.* p. 111-132. In *New Frontiers in Bryology: Physiology, Molecular Biology & Applied Genomics* (eds. by Wood, AJ., Oliver, MJ. and Cove, DJ.), Kluwer Academic Publishers, Netherlands.
6. Murata, T., and Hasebe, M. (2006). Formation of cortical microtubules in a cell-free system prepared from plasma membrane ghosts and a cytosolic extract of BY-2 cells. In Biotechnology in Agriculture and Forestry, Vol. 58, "Tobacco BY-2 Cells: From Cellular Dynamics to Omics". eds., T. Nagata, K. Matsuoka, and D. Inze. pp. 41-49. Springer-Verlag Berlin Heidelberg.
7. Murata, T., Tanahashi, T., Nishiyama, T., Yamaguchi, K., and Hasebe, M. (2007). How do plants organize microtubules without a centrosome? J. Integr. Pl. Biol. *49*, 1455-1463.
8. Murata, T. and Hasebe, M. (2007). Microtubule-dependent microtubule nucleation in plant cells. J. Plant Res. *120*, 73-78.

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Scientific Programme

Dr Murata made an important contribution to the field of plant cell biology. He showed how cortical microtubules increase their numbers and how the phragmoplast expands centrifugally.

Cortical microtubules affect plant cell shape by regulating the orientation of cellulose wall microfibril deposition. As the morphology of an individual plant depends to a great extent on the shape of its individual cells, the studies on cortical microtubules, which control cell shape, are indispensable for studies of the morphology of plants. Cortical microtubule array, which is found during G1- and S phase but not during M-phase, is reinstated soon after the completion of cytokinesis. After cytokinesis, microtubules appear around the daughter nuclei and then translocate to the cell periphery to form cortical arrays. The translocation of microtubules from the nuclei to the cell periphery ceases in due course, and at the time when the daughter cells expand and the cell surface areas increase, no microtubules are supplied from the nuclei. If there is no other source than the nuclei, the distance between adjacent microtubules increases as the cells expand. Cortical microtubules regulate the orientation of cellulose microfibrils by guiding movement of cellulose synthesizing complexes in the plane of the plasma membrane. So, if the distance between adjacent microtubules becomes too long, as the result of cell expansion, cortical microtubules cannot guide cellulose synthesizing complexes properly. Notwithstanding the situation, under which microtubules are not supplied from the nuclei and the cell surface areas are increasing, the distance between two adjacent microtubules does not increase. This indicates that microtubules increase in number without supply from the nuclei. How cortical microtubules increase in number has long been a question of importance for plant cell biologists. Dr. Murata answered this question. He showed that cortical microtubules increase in number by branching of preexisting microtubules. According to him, preexisting microtubules bind gamma-tubulin complexes and at the sites where the complexes are bound new microtubules are organized and elongate as branches of preexisting microtubules. He hypothesized that branch microtubules elongate along the adjacent microtubules and are incorporated into cortical microtubule arrays.

Dr. Murata's finding is important and was highly evaluated by us. Nevertheless, to verify his hypothesis, he should clarify the molecular mechanism of binding of gamma-tubulin complexes to preexisting microtubules, that of the association of branch microtubules with adjacent preexisting microtubules, and that of the abscission of branch microtubules from stem microtubules. To achieve these results we strongly recommend Dr. Murata establishes collaborations with collaborators who are highly educated in biochemistry and appreciate his work. Plant hormones change the orientation of cell expansion by changing the orientation of microtubules. An interesting issue is whether the branching of microtubules is involved in the change in the orientation of microtubules. I would like Dr. Murata to establish the method to

inhibit microtubule branching in living cells. Such a method would greatly help to examine whether microtubule branching is involved in the formation of other microtubule arrays, such as the preprophase band of microtubules.

Dr. Murata showed that the branching of microtubules is involved also in the centrifugal outgrowth of the phragmoplast. The result of the experiment, in which the equatorial plane of the phragmoplast was irradiated by an ultraviolet light microbeam, suggested that the organizing center of phragmoplast microtubules was present at the equatorial plane. Centrifugal outgrowth of the phragmoplast has been considered to occur by the polymerization of new microtubules at the outer margin of the phragmoplast. If the phragmoplast expands centrifugally by the polymerization of new microtubules at the outer margin, the phragmoplast must be shaped like a puck. However, the phragmoplast is not shaped like a puck, but rather like a curling stone. Dr. Murata showed that centrifugal outgrowth of the phragmoplast is accomplished by the addition of microtubules generated from preexisting microtubules by branching. This finding urges the revision of the description about the phragmoplast development in textbooks. The finding also gives the answer to the question of why the phragmoplast is shaped like a curling stone. Dr. Murata's finding clearly explains how the phragmoplast expands centrifugally. But, it is still not clear how phragmoplast microtubules are organized in the early stages of development. We expect him to reexamine the results of the ultraviolet light irradiation experiment by employing modern techniques and clarify the mechanism of the development of the phragmoplast. We also want him to provide an answer to the question of how branch microtubules elongated toward the equatorial plane are captured at the plane.

General comments

Dr Murata is a committed young scientist who has made interesting discoveries and published papers of international interest in general journals. In particular his paper in Nature Cell Biology appears to be a major breakthrough in understanding the biogenesis of microtubules. However, his work is severely limited by resources, and although he had managed to purchase a microscope with external funds he did not have sufficient funds to employ even a part-time technician. We suggest that the management of the NIBB looks at this situation and if possible finds a way of supplementing his funds or in supporting his work with personnel.

（和訳）

研究プログラム

村田博士は植物細胞生物学の分野に重要な貢献をした。博士は、表層微小管がどのように数を増やすか、および、隔膜形成体（フラグモプラスト）が遠心性に伸長していくのかについて示した。表層微小管は、セルロース壁ミクロフィブリルの沈着方向を制御することで、植物細胞の形状に影響を及ぼす。植物体の形態はそれぞれの細胞の形状の影響を強く受けるので、細胞の形状をコントロールする表層微小管に関する研究は、植物の形態に関する研究に欠かせないものである。G1 期と S 期に見つかるが、M 期には見つ

からない表層微小管は、細胞質分裂が終了した直後に再出現する。細胞質分裂後に、娘核の周辺に微小管が出現し、細胞周辺にトランスロケートして皮質アレイを形成する。核から細胞周辺への微小管のトランスロケーションはその後止まり、娘細胞が拡大し、細胞表面積が増加する時点では、微小管の細胞核からの供給はなくなる。細胞核以外からの微小管の供給源がないのであれば、細胞が拡大するにつれて隣接する微小管の間の距離は増えていくことになる。表層微小管は、原形質膜面でのセルロース合成複合体の運動をガイドすることで、セルロースミクロフィブリルの配向を制御している。従って、細胞が拡大する結果、隣接する微小管の間の距離が長くなりすぎると、表層微小管はセルロース合成複合体を適切にガイドできなくなる。微小管が核から供給を受けず、細胞の表面積が増加するという状況であるにも関わらず、隣接する微小管の間の距離は（実際には）増加していない。つまり、微小管は、核からの供給がなくても数を増している。表層微小管がどのように数を増すかは、長い間、植物細胞生物学の重要な疑問であった。村田博士がこの疑問を解いた。表層微小管は、既存の微小管が分岐することで数を増やすことを博士は示した。博士によると、既存の微小管がγ-チューブリン複合体と結合し、γ-チューブリン複合体が結合している部位から新たな微小管が作られ、既存の微小管の枝として伸長していく。分岐した微小管は、隣接微小管に沿って伸長し、表層微小管アレイに取り込まれると博士は仮定した。

村田博士の発見は重要で、高い評価を受けた。しかし、博士の仮説を検証するには、γ-チューブリン複合体が既存の微小管と結合する分子機序、分岐微小管が隣接する既存の微小管とassociationする分子機序、ならびにステム微小管から分岐微小管が離脱する分子機序について、博士は明らかにしなければならない。これらの結果を達成するため、村田博士には、生化学の高度な教育を受け、彼の研究を理解できる共同研究者との共同研究の実施をわれわれは強く勧める。植物ホルモンは、微小管の配向を変えることで、細胞伸長の方向を変化させる。興味深い点は、微小管の分岐が微小管の配向の変化に関与しているかどうかという点である。評価者は、村田博士に対して、生きた細胞で微小管の分岐を阻害する方法を確立することを希望する。そのような方法が確立すれば、微小管の分岐が、微小管の前期前微小管束などの他の微小管アレイの形成に関与しているかを調べるのに多いに役立つであろう。

村田博士は、隔膜形成体の遠心的成長にも微小管の分岐が関係していることを示した。紫外線マイクロビームで隔膜形成体の赤道面を照射した実験結果からは、隔膜形成体微小管（フラグモプラスト微小管）の合成部位は赤道面にあることを示唆していた。隔膜形成体の遠心性成長は、隔膜形成体の外縁で新たな微小管が重合することで生じるとこれまで考えられてきた。新たな微小管が重合形成されることで隔膜形成体が隔膜形成体の外縁で遠心性に拡張するのであれば、隔膜形成体は（アイスホッケーの）パックのような（薄い）形状になるはずである。しかし、隔膜形成体はパックではなく、カーリングのストーンのような（中央が膨らんだ）形状をしている。村田博士は、隔膜形成体の遠心性の成長は、既存の微小管から生成した微小管が付加されることで行われることを示した。この発見で、教科書の隔膜形成体発達についての記述が変わることとなっている。この知見はまた、隔膜形成体がカーリングストーンの形状をしていることの疑問にも答えるものである。村田博士の得た知見は、隔膜形成体が遠心性にどのように拡張していくかについて明確に説明できるものである。しかし、発達の初期段階で隔膜形成体

微小管がどのように組織化されるのかについては、依然として明確になっていない。博士に対しては、最新技術を使って、紫外線照射実験で得られた結果を再検証し、隔膜形成体形成の機序を明確にすることを、われわれは期待する。また、赤道面方向に伸長している分岐微小管が、赤道面でどのようにキャプチャーされるかについての疑問に博士は答えを出して欲しいとわれわれは希望する。

総評

村田博士は興味深い発見をし、総合論文誌に国際的な関心を集めた論文を発表した有望な若手研究者である。とりわけ、*Nature Cell Biology* 誌に発表した博士の論文は、微小管のバイオジェネシスの理解を画期的に深めたもののように思われる。しかし、彼の研究は、リソース不足という問題を大きく抱えており、外部助成金で顕微鏡をなんとか購入することはできたが、アルバイトのテクニシャンを雇用する資金には不足している。基礎生物学研究所の運営にあたっては、博士の状況を検討し、可能なら研究費を補助するか、研究を支援するスタッフを手当することを、われわれは提案する。

研究業績（2001 年より）:

1) Research articles in peer reviewed journals

1. Yoshihara, S., Geng, X. X., Okamoto, S., Yura, K., Murata, T., Go, M., Ohmori, M., and Ikeuchi, M. (2001). Mutational analysis of genes involved in pirus structure, motility and transformation competency in the unicellular motile cyanobacterium *Synechocystis* sp. PCC 6803. Plant Cell Physiol. *42*, 63-73.
2. Kurumatani, M., Yagi, K., Murata, T., Tezuka, M., Mander, L. N., Nishiyama, M., and Yamane, H. (2001). Isolation and identification of antheridiogens in the ferns, *Lygodium microphyllum* and *Lygodium reticulatum*. Biosci. Biotechnol. Biochem. *65*, 2311-2314.
3. Murata, T., Karahara, I., Kozuka, T., Giddings, T.H. Jr., Staehelin, L.A., and Mineyuki, Y. (2002). Improved method for visualizing coated pits, microfilaments, and microtubules in cryofixed and freeze-substituted plant cells. J. Electron Microscopy *51*, 133-136.
4. Kumagai, F., Nagata, T., Yahara, N., Moriyama, Y., Horio, T., Naoi, K., Hashimoto, T., Murata, T., and Hasezawa, S. (2003). γ-tubulin distribution during cortical microtubule reorganization at the M/G1 interface in tobacco BY-2 cells. Eur. J. Cell Biol. *82*, 43-51.
5. Sakakibara K., Nishiyama T., Sumikawa N., Kofuji R., Murata T., and Hasebe M. (2003). Involvement of auxin and a homeodomain-leucine zipper I gene in rhizoid development of the moss *Physcomitrella patens*. Development *130*, 4835-4846.
6. Kishi-Kaboshi, M., Murata, T., Hasebe, M., and Watanabe, Y. (2005). An extraction method for tobacco mosaic virus movement protein localizing in plasmodesmata. Protoplasma *225*, 85-92
7. Murata, T., Sonobe, S., Baskin, T. I., Hyodo, S., Hasezawa, S., Nagata, T., Horio, T., and Hasebe, M. (2005). Microtubule-dependent microtubule nucleation based on recruitment of γ-tubulin in higher plants. Nature Cell Biol. *7*, 961-968.

2) Invited reviews, book chapters

1. Murata, T., and Hasebe, M. (2006). Formation of cortical microtubules in a cell-free system prepared from plasma membrane ghosts and a cytosolic extract of BY-2 cells. In: Nagata T, Matuoka K, Inze D (ed) Tobacco BY-2 Cells: From Cellular Dynamics to Omics. Springer-Verlag, Berlin.
2. Murata, T., Tanahashi, T., Nishiyama, T., Yamaguchi, K., and Hasebe, M. (2007). How do plants organize microtubules without a centrosome? J. Integrative Plant Biol. *49*, 1154–1163.
3. Murata, T., and Hasebe, M. (2007). Microtubule-dependent microtubule nucleation in plant cells. J. Plant Res. *120*, 73-78.

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Scientific Programme

Dr. Ogawa is one of the pioneers in the research field of dynein, a microtubule-based motor protein first found in cilia and flagella. As early as in 1975, Dr. Ogawa obtained a specific antibody against a dynein heavy chain and showed that dynein is present in the cytoplasm of animal cells also. This finding was a big surprise at that time. Later, the presence of cytoplasmic dynein was established, and many studies have since been performed. In 1991, simultaneously with a group at Hawaii University, he determined the entire sequence of a dynein heavy chain (the beta heavy chain of sea urchin sperm flagellar outer-arm dynein) by himself, for the first time in the world. It was a monumental achievement; many researchers had previously tried to determine the sequence but never succeeded, because the heavy chain is extremely large (~500 kD). Since then, Dr. Ogawa's research was focused on the determination of other protein subunits of outer arm dynein. The outer arm dynein of sea urchin sperm flagella is composed of two heavy chains, three intermediate chains, and at least six light chains. Dr. Ogawa cloned the cDNAs of the three intermediate chains (1995, 1996), five light chains (2003) and a novel protein that interacts with dynein (2006). Dr. Ogawa has thus determined the sequences of the major subunits of sea urchin outer arm dynein. This is important and highly evaluated, because the flagellum of this organism has been one of the best studied, particularly in physiology and biophysics, among all kinds of cilia and flagella, and also because no other organisms except *Chlamydomonas* offer such detailed information about outer arm dynein.

Recently, Dr. Ogawa's interest has turned to the primary cilium, a non-motile cilium borne by many kinds of animal cells. It has recently become the target of extensive studies because it has been shown to play an essential role in the transduction of mechanical and chemical signals in multi-cellular organisms. It is now regarded as the antenna of cell. Dysfunction of the primary cilia results in serious congenital diseases such as polycystic kidney disease and hydrocephalus. Therefore, the function of primary cilia in mammals is important in medicine as well as in biology. A biologically interesting problem is why some cells like those in the renal tube bear non-motile cilia while other cells like those in the trachea and the oviduct bear motile cilia.

Productivity and general comments

Overall, Dr. Ogawa's recent research activity does not appear to be very high. This is partly understandable given that he is, as an associate professor at the Center of Radioisotope Facilities, in charge of controlling the use of radioisotopes in all of the three institutes in the Okazaki area. The lack of any grant, collaborators, and memberships of academic societies suggests that Dr. Ogawa is working in isolation. We believe he can improve this situation by making more of an effort to interact with other researchers inside or outside of the NIBB, and carrying out collaborative studies.

（和訳）

研究プログラム

小川博士はダイニンの研究分野のパイオニアの一人である。ダイニンは微小管ベースのモータータンパク質で繊毛や鞭毛で最初に発見された。1975 年に小川博士はすでにダイニン重鎖に対する特異抗体を見つけており、動物細胞の細胞質にもダイニンが存在することを示した。この発見は、その当時大きな驚きで迎えられた。後に、細胞質内にダイニンが存在することが確立され、それ以降多くの研究が行われた。1991 年にハワイ大学の研究グループと同時に、彼はダイニン重鎖の全配列を単独で世界で初めて決定した（ウニ精子の鞭毛外腕アーム ダイニンのβ重鎖)。これは記念碑的業績であった。多くの研究者が配列を決定しようとそれまで努力してきたが、重鎖は極めて大きき分子(~500 kD)であったため、誰も成功していなかったからである。それ以降、小川博士の研究は、外腕アーム ダイニンンの他のタンパク質サブユニットの決定に主眼が向けられてきた。ウニの精子の外腕アーム ダイニンは 2 個の重鎖、3 個の中間鎖、そして 6 個以上の軽鎖から構成されている。小川博士は 3 種の中間鎖(1995, 1996)、5 個の軽鎖(2003)そして、ダイニンと作用する新規タンパク質のクローニング(2006)に成功した。このように小川博士はウニの外腕アームのダイニンの主要サブユニットの配列を決定した。このことは重要で高く評価されるべきものである。ウニの鞭毛は、鞭毛や繊毛の中で、とりわけ生理学や生物物理学で詳しく研究されてきたものの一つであり、クラミドモナス *Chlamydomonas* を除けば、外腕アームのダイニンについて詳しい情報をもたらしているものは他にないからである。

最近、小川博士の関心は、一次繊毛に移ってきている。一次繊毛は多くの動物の細胞が持っている非運動性の繊毛である。一次繊毛は、最近幅広く研究されるようになってきた。多細胞生物で機械的シグナルや化学的シグナルを伝達するのに本質的な役割を一次繊毛が果たすことが明らかになったからである。現在では、一次繊毛は細胞のアンテナと考えられている。一次繊毛に機能障害があると、嚢胞性腎疾患や水頭症などの重篤な先天性疾患を招く。従って、ほ乳動物での一次繊毛の機能は、生物学だけでなく医学にも重要である。生物学的にみて興味深い問題は、尿細管のような細胞は非運動性繊毛を持ち、一方、気管や卵管のような細胞には運動性の繊毛があるのかという点である。

生産性と総評

総体的に、小川博士の最近の研究活動はそれほど高いものとは言えないようである。彼が、アイソトープ実験センターの准教授であり、岡崎地区の 3 研究所の放射性アイソトープの使用に関する責任者であることを考えれば、ある程度理解できることである。助成金や共同研究者、研究職がいないことは、小川博士は単独で研究にあたっていることを示唆するものである。基礎生物学研究所内外の研究者との交流により一層努力し、共同研究を実施すれば、博士の状況は改善できるとわれわれは考えている。

研究業績：

1) Research articles in peer reviewed journals

1. Ogawa, K., and Inaba, K. (2003). Sperm motility-activating complex formed by *t*-complex distorters. Biochem. Biophys. Res. Commun. *310*, 1155-1159.
2. Ogawa, K., and Inaba, K. (2006). Ap58: A novel in situ outer dynein arm-binding protein. Biochem. Biophys. Res. Commun. *343*, 385-390.

２．研究所事業評価

１）細胞生物学領域外部評価委員からのコメント

REPORT OF NIBB ACTIVITIES FOR THE PAST DECADE

NIBB has conducted the five major items as its important mission, and we reviewers formed the judgment by hearing the explanation of activities of NIBB for the past decade that the institute has produced good results as a whole. The special-mentioned activities are as follows.

1. Promotion of collaborate research projects as the center of excellence for biological research. In the projects, NIBB has played an important role as an inter-university institute. Furthermore, various collaboration research projects such as the priority collaboration research project, the individual collaboration project, the NIBB workshop and so on, has been conducted so many times. These activities are highly evaluated for having **EVALUATION** given a strong impact to the promotion of basic biology in Japan.
The Large Spectrograph Laboratory as a world-leading research facility has greatly contributed to development of the field of photobiology through a large number of collaboration researches.

2. On the international cooperation as the core of worldwide community of research.
The collaborative research programs between the NIBB and the EMBL, which were launched in 2005, have well been succeeded through the past five symposia. These programs should be further continued in future in order to promote the exchange between researchers and graduate students, and the interaction of experimental equipments.
Concerning the NIBB conference, which has been carried out once or twice a year since 1977, it has been available for providing the opportunities for international exchange of the biological information. As this conference is very important, it should be more effectively continued in future as well.
Regarding the first international practical course for the cooperation of researchers from Japan and foreign countries, this course was launched in 2007, entitled by “Developmental genetics of Zebrafish and Medaka”. It is also very meaningful that this practical course becomes in many ways an expansion type of the former NIBB practical training course which had been conducted.
As to the National BioResearch Project (NBRP) as a research center for Medaka (*Oryzias latipes*), it is evaluated to be useful as a vertebrate model developed in Japan. Furthermore, it is worthy of special mention that NIBB works as a sub-center for zebrafish and Japanese morning glory. It is also important that NIBB has a crucial role as a provider of databases on some plants and animal genomes, and plant cell organelle.

3. Activities as a center for developing new fields of biology
NIBB has been trying to apply various bio-imaging techniques to visualize biological phenomena and to develop new imaging techniques.
As to Okazaki Biological Conference (OBC), although being held as closed meeting, it seems to be highly meaningful to construct international communities for new research issues in future

biology. We reviewers think NIBB should much more actively promote the above two projects as its activities. However, it is a little regrettable that OBC has not been widely known in Japan in spite of the past 5-times of the conference since 2004. From now on, therefore, NIBB should endeavor much more the publicity activity of OBC. For example, the conference should be internationally opened to all the scientists who want to participate, because science can no longer be done in a closed environment.

4. Activities of cultivation of future researchers in biology by admission of graduate students; Sokendai and other universities
NIBB has accepted a number of graduate students from not only Sokendai but also other universities in Japan and foreign countries , and given excellent education to them to become a high quality of researchers. The role of NIBB in this respect is also important, and this activity is seemingly well achieved now although some problems appear to remain to be solved.

Additional Comments for Future Development of NIBB

1. The scientific researches of NIBB should be at least maintained at the same level as at the present, or more enhanced in biology, (in particular, in the field of basic biology).

2. NIBB should progressively promote the researches using model organisms.

3. NIBB should support adjunctive laboratories as much as possible and tactfully manage them.

4. In NIBB, an introduction of pliable managing systems should be accelerated; for example, 1) an incentive system to researching staff, 2) a giving system of the researching space to competent researchers even after their retirement, and so on.

5. Adoption of foreign researchers as regular staff will be needed to further raise the overall activities of NIBB, and in addition NIBB should make every attempt to recruit foreign post-docs, because this will be good not only for the international reputation of the Institute but also good for the scientific environment as well.

（和訳）

過去 10 年間の基礎生物学研究所活動報告

基礎生物学研究所は、重要な使命として 5 項目を実施してきた。われわれ外部評価委員は、過去 10 年間の基礎生物学研究所の活動についての説明を聴聞して、同研究所は、全体として良好な業績をあげてきたと判断した。特記すべき活動は以下の通りである。

1. 生物学研究の COE として共同研究プロジェクトを推進すること。
プロジェクトでは、全国大学共同利用研究機関として、基礎生物学研究所は重要な役割

を果たしてきた。さらに、重点共同利用研究や個別共同利用研究、基生研ワークショップなどの様々な共同研究プロジェクトを多数実施してきている。日本の基礎生物学に強い影響を及ぼしていることを考えれば、これらの活動は、高く評価されるべきものである。
大型スペクトログラフ室は、世界的に先端を行く研究施設として、多数の共同研究を通じて光生物学分野の発展に貢献してきた。

2.　世界的研究コミュニティーの中核としての国際協力に関して
基礎生物学研究所と EMBL（欧州分子生物学研究所）の間に 2005 年に創設された共同研究プログラムは、過去 5 回のシンポジウムを通じて、成功を得ている。研究者や大学院学生の交流を促進し、実験機器の相互技術協力を図るため、これらのプログラムを今後も継続すべきである。
1977 年から年 1、2 回実施されてきた NIBB コンファレンスに関しては、生物学に関する情報の国際交換の機会となってきた。このコンファレンスは極めて重要であるので、今後もより有効に継続すべきである。
日本と外国の国際協力のための第 1 回国際実習コースが、2007 年に“ゼブラフィッシュとメダカの発生生物学”と題して、開始された。この実習コースが、これまでに実施されてきた NIBB 実習トレーニングコースを拡大するものとしても極めて有意義なものである。
ナショナルバイオリソースプロジェクト(NBRP)のメダカ(*Oryzias latipes*)の研究センターとなっていることに関しては、日本で開発された脊椎動物モデルの維持として有用であると評価される。さらに、基礎生物学研究所は、ゼブラフィッシュと日本アサガオのサブセンターとして活動していることも特記する価値がある。また、いくつかの動植物のゲノムデータベースや植物細胞オルガネラに関するデータベースの提供者としての重要な役割を基礎生物学研究所が担っていることも重要な点である。

3.　生物学の新分野開発センターとしての活動
基礎生物学研究所は様々なバイオイメージング技術を用いて生物現象を視覚化することや、新しいイメージング技術を開発する努力を行ってきた。
OBC（Okazaki Biology Conference：生物学国際高等コンファレンス）については、非公開で開催されているものであるが、将来の生物学の研究テーマに関して国際コミュニティーを構築するのに極めて有意義なものであるように思われる。われわれ外部評価委員は、前述の 2 つのプロジェクトを研究所の活動として基礎生物学研究所は、より積極的に促進するべきであると考える。しかし、少し残念なことに、2004 年からこれまでに 5 回開催されたにも関わらず、OBC が日本ではあまり知られていない。従って、今後基礎生物学研究所は OBC の広報か活動により精力を注ぐ必要がある。例えば、このコンファレンスは参加希望する研究者全てに国際的に開かれたものでなければならない。科学はもはや閉鎖環境で実施できるものではないからである。

4.　大学院学生を受け入れることによる生物学の未来の研究者を育成;総合研究大学院大学（総研大）ならびに他大学からの受け入れ
基礎生物学研究所は、総合研究大学院大学（総研大）だけでなく、日本の他大学や外国の大学からの大学院学生を多数受け入れ、高水準の研究者になるよう、極めて優れた教

育を実施してきた。この点に関する基礎生物学研究所の役割も重要であり、この活動は良好に達成されているように思われるが、いくつか未解決の問題点もあるようである。

基礎生物学研究所の将来発展に関する補足意見

1.　基礎生物学研究所の研究者は、少なくとも現在と同じ研究水準のレベルを保ち、さらには、生物学（とりわけ基礎生物学の分野）での水準を高める必要がある。

2.　基礎生物学研究所は、モデル動物を用いた研究を一層促進すべきである。

3.　基礎生物学研究所は、附属研究施設をできるだけサポートし、適切な運営を行わなければならない。

4.　基礎生物学研究所では、柔軟な運営システムの導入を加速化させるべきである。例えば、1)研究スタッフに対するインセンティブシステム、2)有能な研究者に対しては、退官後も研究場所を提供するシステム、等である。

5.　基礎生物学研究所全体の活動レベルをさらに高めるには、外国人研究者を常勤スタッフに採用することが必要となろう。加えて、基礎生物学研究所は外国人ポストドクを採用するためあらゆる努力を払う必要がある。これは、基礎生物学研究所の国際的名声を高めるのに良いだけでなく、科学的環境としても良いことになるからである。

２）発生生物学領域外部評価委員からのコメント

Review Comments on the NIBB

1. Collaborative Research Projects

As an inter-university research institute, the NIBB carried out a large number of "individual collaborative research projects" (about 30~40 projects/year). In addition, "Priority collaborative research projects" (6 projects in the last 3 years) and "Collaborative research projects for model organisms/technology development" (currently 2 projects) promoted development of new technology and model organisms. These activities of the NIBB have played a major role in promoting collaboration in Japan.

2. International Cooperation

In 2005, the NIBB set up collaborative research programs with the EMBL. As a part of these programs, the NIBB-EMBL symposia have been held five times either in Okazaki or at the EMBL. It appears that these symposia have greatly promoted exchange of information and personnel. For instance, a new type of microscopy called SPIM was introduced from EMBL to the NIBB as a collaboration between the EMBL and the NIBB.

The NIBB Conferences (international conferences organized by professors in the NIBB) have been held one or twice a year since 1977, and have provided a platform for international exchange of information. Timely topics have been carefully chosen by the NIBB.

International Practical Course given by the NIBB is a new training course for graduate students mainly in East Asia. The first course was held in 2007 on the Developmental Genetics of Zebrafish and Medaka. Because the course was successful, it should be continued. Because Medaka is a unique model organism developed in Japan, the same topic may be chosen for next year.

As a part of the National Bioresource Project, the NIBB collects and maintains bioresources, and distributes them to requesting scientists throughout the world. In particular, a large number of Medaka (*Oryzias latipes*) strains that have been developed in Japan are now maintained at the NIBB. These bioresources are very useful not only to developmental biology but also to other aspects of biology. Currently, funds for the bioresources are available for the next 5 years, but we hope that such invaluable bioresources will be maintained by continuous funding.

3. Development of New Fields

Bioimaging is a new field that the NIBB wishes to emphasize in the near future. To promote bioimaging at the NIBB, a new lab (headed by Dr. Shigenori Nonaka) has been created. As a collaboration with the EMBL, a new type of microscope called SPIM has been established in the imaging lab. We believe that SPIM is a very important addition and will be very useful to observe fine structures of a whole embryo. Also, the addition of bioimaging labs would promote close interaction and collaboration between the NIBB and two other institutes located in Okazaki.

The OBC (Okazaki Biology Conference) is another international meeting sponsored by the

NIBB. This conference has been held once~twice a year since 2004, to investigate new research fields/issues. The conference successfully formed international research communities in potential new fields.

4. Admission of Graduate Students

Each year, about 10 graduate students enroll in the NIBB. Perhaps, researchers in the NIBB would like to accept more students. The NIBB has been making every effort to attract undergraduate students in Japan. Such efforts should be continued, but given that the number of undergraduate students in Japan is decreasing, it may be difficult to see improvement in the short term.

5. Academic Research

The NIBB has maintained a high level of research activity in the past decade, notably in cell biology and developmental biology. Our only concern is how this high level of research activity will be maintained in the next decades. Given that several PI positions are currently vacant and that a number of professors will be retired in the next few years, this is a very important period for the future direction of the NIBB.

（和訳）

1. 共同研究プロジェクト

大学共同利用研究機関として、基礎生物学研究所は多数の“個別共同利用研究”を実施している（年間約 30～40 件）。加えて、“重点共同利用研究”（過去 3 年間に 6 件）と“モデル生物・技術開発共同利用研究”（現在 2 件）で新技術開発とモデル生物の開発を進めている。基礎生物学研究所のこのような活動は、日本での共同研究を推進するのに主要な役割を果たしてきた。

2. 国際協力

2005 年に基礎生物学研究所は EMBL（欧州分子生物学研究所）との共同研究プログラムを創設した。このプログラムの一環として、岡崎市あるいは EMBL で NIBB-EMBL シンポジウムが 5 回開催されている。これらのシンポジウムで情報交換や研究者の交流が多いに促進されたように思われる。例えば、EMBL と NIBB の共同事業として、新タイプの顕微鏡システム SPIM が EMBL から NIBB に導入された。

NIBB コンファレンス（基礎生物学研究所の教授がオーガナイズする国際コンファレンス）が 1977 年から年に 1、2 回開催されており、情報の国際交換の場となってきた。基礎生物学研究所によりタイムリーなトピックが慎重に選ばれてきている。

基礎生物学研究所が行っている International Practical Course（国際実習コース）は、主に東アジアの大学院学生のための新たなトレーニングコースである。第 1 回は 2007 年にゼブラフィッシュとメダカの発生遺伝学について開催された。このコースが成功を収めたため、継続すべきである。メダカは、日本で研究が進められたユニークな

生物モデルであるので、同じトピックを翌年も用いても良いであろう。

ナショナルバイオリソースプロジェクトの一環として、基礎生物学研究所ではバイオリソースの収集と維持を行っており、世界の研究者から求めがあれば配布している。とりわけ、日本で作られた多数のメダカ(*Oryzias latipes*)系統が基礎生物学研究所で飼育されている。これらのバイオリソースは、発生生物学だけでなく、他の生物学分野でも極めて有用である。現在、バイオリソースに関する予算は今後5年間確保されているが、このような欠かせないバイオリソースについては、継続的な予算で維持されることを希望する。

3. 新分野の開発

バイオイメージングは、基礎生物学研究所が近い将来重点を置きたいと考えている新分野である。基礎生物学研究所でのバイオイメージングを促進するため、新しい研究部門（野中茂紀博士が責任者）が創設されている。EMBL との共同事業として、SPIM と呼ばれる新しいタイプの顕微鏡をイメージングラボに設置している。SPIM は極めて重要な新設備であり、胚全体の微細構造を観察するのに極めて有用であろうとわれわれは確信している。またバイオイメージングラボが新たに加わることで、基礎生物学研究所と、岡崎地区の他の2研究所間の密接な関係が深まるであろう。

OBC（Okazaki Biology Conference：生物学国際高等コンファレンス）は基礎生物学研究所が主催するもう一つの国際学術研究集会である。このコンファレンスは 2004 年から年に 1〜2 回開催されており、新たな研究分野や問題点について探っている。このコンファレンスを開催することで、有望な新分野の国際的研究コミュニティーが良好に形成されてきた。

4. 大学院学生の受け入れ

毎年 10 名程度の大学院学生が基礎生物学研究所に入ってくる。おそらく、基礎生物学研究所の研究者は大学院生をもっと採用したいのであろう。基礎生物学研究所では、日本の大学院学生を勧誘する努力を多いに積み重ねてきている。そのような努力を継続すべきであるが、日本では大学院学生が年々減少していることを考えれば、短期に状況が改善することは困難であろう。

5. 学術研究

基礎生物学研究所では、この 10 年間高水準の研究を行ってきており、とりわけ細胞生物学と発生生物学での業績が目覚ましい。われわれが唯一懸念していることは、このような高水準の研究が今後数十年間どのようにすれば維持されるかという点である。現在 PI ポストのいくつかが空席で、この数年間に多数の教授が定年退官することを考えれば、基礎生物学研究所の将来方向にとって、現在が極めて重要な時期である。

３）生殖・環境生物学領域外部評価委員からのコメント

Institute Activity

The National Institute for Basic Biology has continued to enjoy a prestigious position as a top research institute in biology in the thirty years since its inauguration. We are delighted to have found that NIBB is achieving high standards of scientific excellence. However, it is a concern that professors are increasingly required to engage in administrative and managerial duties not directly related to their activities in research and education. This situation seems to be caused partly at least, if not all, by recent major changes in the management system of national universities and institutes in Japan. It will be essential for the senior staff of NIBB, and other institutions as well, to be able to devote their time and energy to creative work in the future, if standards of research excellence are to continue. The review committee recommends that NIBB devise a new management system to deal with these issues.

The accomplishments of the group of reproductive biology in NIBB are very highly commended also by the review committee. It is strongly hoped that NIBB keeps this tradition for another thirty years to come, despite of difficulties and problems which might be caused by Prof Morohashi's recent transfer to Kyushu University, and by Prof Nagahama's retirement in the very near future. The committee is very keen for strategic plans to be made so that the proud tradition at NIBB as a major centre of reproductive biology in Japan will live on in the future.

（和訳）

研究所の活動

基礎生物学研究所は設立以来 30 年間、生物学のトップを行く研究所としての地位を確保し続けている。基礎生物学研究所が高水準の科学的成果を達成していることがわかり、われわれはうれしく思う。しかし、懸念されることは、教授が研究や教育活動とは直接関係のない管理運営の業務を行う必要性が次第に増加している点である。このような状況は、全てではないにしても、一部には日本の国立大学や国立研究機関の運営システムが最近大きく変貌したことによるものであると考えられる。基礎生物学研究所ならびに他の研究所の上級スタッフは、高い研究水準を今後も維持したければ、今後はクリエーティブな仕事に時間とエネルギーを割くことができるようにならなければならないであろう。外部評価委員会は、基礎生物学研究所がこれらの問題に対処できる新たな管理運営システムを構築するよう勧告する。

基礎生物学研究所の生殖生物学グループの業績は、極めて高く、外部評価委員会も高く評価する。諸橋教授が九州大学に転任になり、長濱教授が近い将来退官されることによって生じるであろう様々な困難や問題があっても、基礎生物学研究所は、これからの

30 年間も生殖生物学グループの伝統を維持することが強く望まれる。日本の生殖生物学の主なセンターとしての基礎生物学研究所の栄誉ある伝統を今後も長らえるための戦略プランを基礎生物学研究所が策定するよう評価委員会は強く希望する。

４）神経生物学領域外部評価委員からのコメント

Institute Activity

Director-General: NIBB performs many functions for contribution to the community of biologists. It has a new director-General, Dr. Kiyotaka Okada. Dr. Okada is a well-known and respected scientist dedicated to preserving the excellent reputation of NIBB and improving it further by implementing new community, national and international activities and cutting edge technologies.

NIBB organizes several collaborative research projects at the individual level as well as larger scale collaborations. NIBB also sponsors workshops and practical courses for students. For example, it sponsored its first course entitled: "Developmental Genetics of Zebrafish and Medaka" for graduate students from East Asian nations. This course is nicely integrated with the National Bioresource Project for the systematic accumulation of experimental animals and plants such as Medaka fish. NIBB also sponsors international conferences once or twice a year in basic biology. Most recently, it has sponsored a new type of conference entitled the Okazaki Biology Conferences to foster formation of international communities in the biology of the future. This conference has been written about in the prestigious journal, Nature.

Suggestions for improving the stature and organization of NIBB:

The stature of NIBB is regarded highly. However, there is always room for improvement. One problem identified by this external review committee is that it is difficult for the investigators here to recruit graduate students. Some attention should be devoted to this matter in terms of creative ways to attract top students to NIBB. Possibilities include dormitories to provide living arrangements for out of town students, research competitions for prestigious graduate student award that would pay tuition and expenses, tuition exemptions for students based on merit and/or financial need, advertising in the major cities, such as Tokyo, and finally, visits of NIBB faculty to smaller undergraduate institutions throughout Japan to advertise the cutting edge research and facilities at NIBB. Students in Neuroscience are particularly enamored now in imaging and behavior. It is also important that NIBB invest in creativity on its website as this is the resource used most frequently by students in deciding which programs to apply to for graduate studies. For example, NIBB is wisely investing in bioimaging and could highlight this facility on their website. Also, the graduate department information section on the website could use some different images to entice students to apply.

With respect to organization, the review committee questions the efficiency of having two separate transgenic facilities at NIBB and NIPS. A committee should be formed to examine whether it would be more efficient to combine the facilities into one.

（和訳）

研究所の活動

研究所長：基礎生物学研究所は、生物学者に寄与するため多くの任務を遂行している。新たに岡田 清孝博士を所長に迎えた。岡田博士は良く知られ尊敬されている科学者で、基礎生物学研究所の優れた名声を保ち、加えて、新たなコミュニティーを形成し、国内、国際的な活動を高め、最新の技術を導入することにより、その名声を更に高めようとしている。

基礎生物学研究所は、個別レベルでの共同研究プロジェクトをいくつかオーガナイズしており、さらに大規模な共同研究事業も行っている。基礎生物学研究所はまた、学生のためのワークショップや実習コースも主催している。例えば、“Developmental Genetics of Zebrafish and Medaka（ゼブラフィッシュとメダカの発生遺伝学)”と題した第一回実習コースを東アジアの大学院生のために主催している。このコースは、ナショナルバイオリソースプロジェクトとうまく一体化されており、メダカなどの実験動物や植物をシステマチックに収集している。基礎生物学研究所はまた、年に 1、2 回、基礎生物学に関する国際コンファレンスを主催している。最近では、OBC（Okazaki Biology Conferences、生物学国際高等コンファレンス）という新たなタイプのコンファレンスを主催し、今後の生物学における国際コミュニティーの形成を支援している。このコンファレンスについては、*Nature* 誌に紹介された。

NIBB の地位向上および組織改善のための意見：

基礎生物学研究所の地位は高いと見なされている。しかし、どのようなものでも改善の余地がある。外部評価委員会が見つけた問題点の一つは、研究所の研究者が大学院学生を採用するのが困難である点である。優秀な大学院生を基礎生物学研究所に惹き付けるための創造的な方法を構築することに関して関心を持つ必要がある。そのような方法として、自宅から通えない大学院生のために宿舎を用意すること、研究を競わせて優秀な学生に賞を与え授業料や生活費を支援すること、学業成績や経済状況に応じて、学生の授業料免除措置をとること、東京などの大都市で宣伝すること、日本全国の小規模の大学院を基礎生物学研究所の教官が訪問して、基礎生物学研究所の最新の研究内容や研究施設を宣伝することなどが考えられる。神経科学の大学院生はとりわけ、イメージング法や行動に関心を示している。基礎生物学研究所では、クリエイティビティーに対する投資をウェブサイトに紹介することも重要である。大学院学生が、大学院研究でどのプログラムに応募しようか決めるのに、ウェブサイトを閲覧して決めることが極めて多いからである。例えば、バイオイメージングへの投資を基礎生物学研究所はうまく行っており、この施設のことをウェブサイトでは強調して示すことができるはずである。また、ウェブサイトの大学院に関する情報のセクションには、学生を惹き付けるような様々なイメージを使えるはずである。

組織に関しては、外部評価委員会では、基礎生物学研究所と生理学研究所にそれぞれ別のトランスジェニック施設を有することが効率的であるかどうか疑問を抱いた。この 2

つの施設を一つに統合したほうが効率性がさらに高まるものかどうか検討する委員会を設立する必要がある。

５）進化多様性領域外部評価委員からのコメント

General Impressions

Opportunities

Several Professors are due to retire in the next few years and four Professorships have already been advertised. These vacancies provide a unique opportunity to restructure the NIBB and to implement a strategic vision for the science of the institute. We felt that the management of the institute should formulate a scientific vision for how they would like to position the institute in the future and on which scientific areas they would like to focus, and then actively recruit scientists in these areas. For example, areas such as rice biology and fish research have obvious strategic value given the possible national collaborations and traditions of the institute. Similarly, groups with strong emphasis on technology development or resource building as well as excellent biology will assist in the mission of the institute to build university collaborations. The present approach of recruiting the best applicants who respond to advertisements has benefits, but may be too passive an approach to create a dynamic institute in the future.

Students

We met five graduate students who appeared motivated and generally positive about their experience of the NIBB. However, the management could more actively include students and oversee their training. In particular, annual meetings of student committees (in which the student, their supervisor and one or two other Professors discuss the progress of the student) did not always occur and the system was in danger of lapsing. Also, a system in which the views of students are channeled to the management would be helpful and should be reinvigorated.

The scarcity of graduate students, particularly that of doctor course students, is a general problem in Japan. Many universities are devising means to increase the number of applicants; for example, some universities have decided to pay the tuition of its doctor course students, and some other graduate schools now admit students by interview only. For the SOKENDAI graduate school, one of the possible means to attract students could be to pay some salary to promising students, just as many graduate schools do in the USA and Europe. In further support of this point graduate students mentioned that they can experience financial difficulties and several Professors mentioned the difficulty of recruiting good graduate students. We felt that it would be in the interests of NIBB to start a graduate fellowship programme that is advertised internationally and offers to pay the support of several graduate students a year. These students could be placed in laboratories of their choice within NIBB. Such a system would increase the profile of NIBB, provide Professors with a wider choice of Graduate students and help with the support of students. We felt that there is likely to be sufficient flexibility in the NIBB budget to fund such a system.

The future of basic biological research will naturally depend on the advancement in other related fields, such as medical sciences and physical chemistry. An outstanding advantage of

Okazaki is the presence of three prominent institutes of molecular science, physiology, and basic biology, on the same campus. We felt that the NIBB could lead the future of biology by promoting interdisciplinary research through cooperation between laboratories and institutes in research and education. NIBB would become a true center of excellence if this is realized, particularly because such collaboration is very difficult in most universities.

The system that affords graduate students already enrolled in the graduate school of other university opportunities to study and do research at NIBB is splendid. The students came to special research school are sure to learn how high the standard of their own research fields. What the students studied at NIBB will be brought back to the laboratory from which the students came to NIBB and will activate the laboratories. NIBB seminars held once a month by guest lecturers were also admired, and seen as a great asset for the students of the special research school in NIBB.

Institute activities

The first objective of the NIBB must be to produce excellent research, because from this all other activities such as national and international collaborations will follow.

We saw convincing examples of NIBB providing excellent collaborations and infrastructure to Universities. We recognized that NIBB has devoted itself to its task as an Inter-University Research Institute. Collaborative research projects have supported many researchers who belong to other universities and institutes than NIBB by offering them utilization of facilities in NIBB. Such examples include the Medaka Resource Centre, the Physcomitrella courses and web site as well as the rice homologous recombination methodology. Careful thought needs to be given to how to continue and expand these through the future Professor appointments. The collaborative project scheme is an excellent method of strengthening these collaborations, and we welcomed the idea to reduce the number of such projects but to increase their value. However, during a considerable period, it was not easy for external researchers who had no connections with staff of NIBB to join these projects. We hope that this difficulty no longer exists and that consideration is given to the balance between reducing the number of projects and satisfying the demand from University researchers.

The NIBB conferences covered well chosen areas and increased the profile of the institute. The conferences provide Japanese young researchers with opportunities to learn the science of outstanding foreign researchers.

The NIBB must function as a hub institute for international cooperation, particularly between Asian countries. We thus highly evaluate that the NIBB started the International Practical Course. Such a course should not only provide students with a chance to learn new techniques, but also help Japanese students, as well as students from other countries, learn to communicate in English. This would attract more graduate students and researchers from abroad, and result in internationalization of the whole institute in the future. Similarly, NIBB started recently new research projects with the EMBL and the new conferences, OBCs. The EMBL symposia and

exchange of students had had a positive effect on the institute and we saw some examples of this directly benefiting the research. A clear difficulty mentioned by students was that EMBL did not include plant groups, and that these were therefore less involved in this exchange.

We were anxious that the obligations of the staff towards the general activities should not detract from their primary role in carrying out excellent research. The most important task is for the NIBB to function as “the center of excellence for biological research” and maintaining the high standard of science being carried out at NIBB is likely to be the most effective means of attracting many researchers to collaborative research. For this purpose, it is desirable that the NIBB researchers are free from trivial activities other than research. At the same time, the institute should provide many visitors with various facilities, workshops and conferences, all of which may take up time for research. Therefore, one of the important things for the management to consider is the balance between the research of its own and the service for others. We wondered whether the number of conferences and symposia directly or indirectly organized by the NIBB researchers is appropriate. If these meetings seem to require too much time and energy of the staff, then the NIBB may well consider reducing the number of conferences, or changing the system of the conferences so that most of them are organized by researchers outside the NIBB, as is the case with the OBC, and the NIBB just provides the budget and space.

（和訳）

総合印象

機会

数名の教授が今後数年間に定年退官を予定しており、4 つの教授のポストの公募がすでに発表されている。このようにポストに空きが生じることが、基礎生物学研究所の構造改革、ならびに研究所の科学研究に戦略的展望をもたらすことに、またとない機会を与えている。研究所の運営にあたっては、研究所の将来をどのように展望しているのかについて科学的ビジョンを明確化し、今後の重点領域についてのビジョンを確定した上で、その分野の研究者を積極的に採用すべきであるとわれわれは考える。例えば、イネの生物学や魚類の研究は、全国共同研究や研究所の伝統を考えれば、明らかに戦略的価値がある。同様に、技術開発やリソース構築、ならびに卓越した生物学研究に強く重点を置いた研究グループが、研究所と大学の連携を構築するという基礎生物学研究所の使命遂行を助けることになろう。公募に応募した中から最良の応募者を採用するという現在のアプローチには確かに利点があるが、今後ダイナミックな研究所を構築するというアプローチに対しては、受身的すぎるものとも考えられる。

大学院生

この視察中に、5 名の大学院生と面接した。これらの大学院生は、研究に対するモチベーションが十分にあり、基礎生物学研究所での経験をおおむね肯定的に捉えているようであった。しかし、研究所運営の中に大学院生教育をもっと積極的に取り入れ、トレー

ニングを監督するようにすることができるはずである。とりわけ、大学院生との年次面接（大学院生、指導教官および他の教授 1、2 名で、院生の研究の進展状況について討論する）は必ずしも実施されておらず、このシステムが有名無実化する危険に曝されている。また、大学院生の意見を研究所の運営に反映されるようなチャンネルがあれば有用であろうし、再活性化させるべきである。

大学院生、とりわけ博士課程の大学院生が少ないことは、日本の大学全体に共通する問題である。多くの大学では、入学希望者を増やすための様々な対策を講じている。例えば、一部の大学では、博士課程の学生の授業料を（大学が）負担することを決定し、また別の大学では、面接のみで学生を受け入れている。総合研究大学院大学（総研大）の大学院生については、学生を惹き付ける一つの方法は、米国やヨーロッパの多くの大学院で実施されているように、有望な学生に給料を支払うことであろう。このような状況をさらに裏付ける点として、大学院生は経済的困窮を経験する場合があると回答し、教授の中には、優秀な大学院生を採用するのが困難であると述べていた。研究所が大学院フェローシッププログラムを創設し、国際的に周知させて、一部の大学院学生に対しては金銭的支援を行えば有用であろうとわれわれは考える。このような学生が基礎生物学研究所内の研究室を選べるようにする。そのようなシステムにすることで、基礎生物学研究所の印象が高まり、教授にとっては、大学院生選択の幅が広がり、大学院生の支援にもつながるであろう。基礎生物学研究所にはそのようなシステムを構築するための予算の十分な柔軟性があるとわれわれは考えている。

基礎生物学研究の未来は、当然のことながら、医科学や物理化学などの関連分野の進展に依存することになろう。基礎生物学研究所が岡崎市にある極めて有利な点は、分子科学研究所、生理学研究所、基礎生物学研究所の 3 つの有数の研究所が同じ敷地内に存在していることである。研究や教育に関して異なる研究室間や研究所間を横断する学際的研究を促進することで、基礎生物学研究所は今後の生物学研究をリードできるとわれわれは考える。このような点が実現されれば、基礎生物学研究所は真の意味での COE となるであろう。このような共同研究は多くの大学では極めて困難であるからである。

他大学の大学院にすでに入学している大学院生を基礎生物学研究所で受け入れ、研究できるようにしているシステムは極めて優れたものである。基礎生物学研究所にやってきた大学院生は、それぞれの分野の研究水準の高さを目の当たりにするであろう。基礎生物学研究所で研鑽を積んだ大学院生は、出身大学の研究室に戻り、それぞれの研究室の研究を活性化させることになろう。来訪研究者によって行われる月一度の基生研セミナーも賞賛に値するものであり、基礎生物学研究所の大学院生にとっては、極めて役立つものと受け止められていた。

研究所の活動

基礎生物学研究所の第一の目的は、極めて優れた研究業績をあげることでなければならない。国内共同研究や国際共同研究などの他の全ての活動はこの目的から生じるものであるからである。

基礎生物学研究所が極めてすぐれた共同研究を行い、大学のインフラストラクチャーと

なっていることを如実に示す例をいくつか確認した。基礎生物学研究所は大学共同利用研究機構としての役割を担ってきた。基礎生物学研究所の施設利用を提供することで、共同研究プロジェクトは、基礎生物学研究所以外の大学や研究機関に所属する多くの研究者を支援してきた。そのような例として、メダカバイオリソースプロジェクト(Medaka Resource Centre)やヒメツリガネゴケ *Physcomitrella* 研究部門とウェブサイト、イネ相同組換え法の研究などがあげられる。これらの共同利用研究を今後どのように継続し、今後の教授採用を通じてどのように展開していくかについては、慎重な検討が必要である。共同プロジェクトのスキームは、これらの共同研究を強化するのに優れた方法であり、そのようなプロジェクトの件数を減らしてその有用性を高めるという考えについては、われわれも歓迎する。しかし、相当期間、基礎生物学研究所スタッフとつながりのない外部の研究者が、これらの共同利用プロジェクトに参加するのは容易ではなかった。そのような困難は、もはや存在しないと期待しており、プロジェクトの件数を減らすことと、大学の研究者の需要を満たすことの間に均衡をとることに相当の配慮がなされているものと期待する。

基生研コンファレンスは選び抜かれた分野をカバーし、研究所の名声を高めてきた。このコンファレンスは、若い日本人研究者が、優れた海外研究者の研究を学ぶ機会となっている。

基礎生物学研究所は国際協力、とりわけ、アジア諸国との国際共同研究における中核研究所としての機能を果たす必要がある。この点では、International Practical Course（国際実習コース）を基礎生物学研究所が始めたことを、われわれは高く評価する。そのような実習コースは、学生に新技術を習得させる機会をもたらすだけでなく、日本人学生や、他国からの学生に、英語でのコミュニケーション法を習得させるものともなるはずである。このようにすることで、海外の大学院生や研究者がさらに基礎生物学研究所に惹き付けられ、将来の基礎生物学研究所の国際化につながることになろう。また、基礎生物学研究所は最近 EMBL（欧州分子生物学研究所）との新たな研究プロジェクトと新たなコンファレンス OBC（Okazaki Biology Conferences、生物学国際高等コンファレンス）を開始した。EMBL シンポジウムの開催と学生交換の実施は、基礎生物学研究所にポジティブな効果をもたらしてきており、研究に直接役立った事例をいくつか確認した。大学院生が指摘した明確な問題点は、EMBL に植物研究部門がないこと、そのため、この交換留学があまり関係ないことであった。

研究所スタッフに一般業務への負担があり、優秀な研究を実施するというスタッフの第一の役割が阻害されることがないか、われわれは懸念している。基礎生物学研究所にとって最も重要な任務は、“生物学研究の COE”として機能することであり、基礎生物学研究所が高水準の科学研究を維持し続けることが、多くの研究者や共同研究を惹き付ける最も有効な手段であると考えられる。この目的には、基礎生物学研究所の研究者は、研究以外の雑務からは解放されることが望ましい。同時に、研究所は、多くの来訪者や施設提供、ワークショップ、コンファレンスを開催しなければならない。これらの活動は全て、研究時間を削ってしまう。そのため、研究所の運営で考慮すべき重要な点の一つは、研究者自身の研究と他者に対するサービスの均衡をはかることである。基礎生物学研究所の研究者が直接あるいは間接的にオーガナイズするコンファレンスやシンポ

ジウムの件数が適切なものであるかどうか懸念している。これらの会議開催に、スタッフの時間とエネルギーが過大に使われるのであれば、研究所は、コンファレンスの数を減らすか、あるいは、コンファレンスのシステムを変えて、ほとんどのコンファレンスを、OBC のように基生研以外の研究者がオーガナイズするものにし、基礎生物学研究所は予算と場所を提供するだけとするようにすることを検討する価値があろう。

３．資　　料

研究所事業についての評価のために評価委員に示した資料

１．欧州分子生物学研究所 (EMBL) との研究連携活動として開催した NIBB-EMBL シンポジウムの概要 (Page 205-211)
２．海外からの招待講演者を交えて開催する国際会議（基生研コンファレンス）の開催記録 (Page 213-218)
３．平成 19 年に開催した国際実習コース (International Practical Course) において実習生に配布した資料の抜粋 (Page 219-227)
４．メダカバイオリソース事業の説明 (Page 229-233)
５．生物学国際高等コンファレンス (Okazaki Biology Conference) の創設についての Nature 誌の記事 (Page 237) と開催記録 (Page 235-243)

1) Collaborative research projects with the EMBL

The European Molecular Biology Laboratory (EMBL) is a research institute funded by 18 European states and established in 1974. It conducts comprehensive, high-level basic research programs, leading the world in the field of molecular biology. The NIBB takes the leading role in collaborative research programs between the EMBL and the National Institutes of Natural Sciences (NINS), which were launched in 2005, and promotes personal and technological exchange through symposia, exchanges between researchers and graduate students, and the introduction of experimental equipments.

Past EMBL symposia:

1st	**Developmental Biology**	**July, 2005**	**Heidelberg (Germany)**
2nd	**Frontiers in Bioimaging**	**March, 2006**	**Okazaki (Japan)**
3rd	**Mouse Biology**	**April, 2006**	**Monterotondo (Italy)**
4th	**Biology of Protein Conjugation**	**December, 2006**	**Okazaki (Japan)**
5th	**Cell and Developmental Biology**	**May, 2007**	**Okazaki (Japan)**

NIBB-EMBL 1st Symposium on Developmental Biology

"Current Work in the Areas of Developmental and Cellular Biology" & Imaging Meeting

July 1 (Fri) - 2 (Sat) & 4 (Mon), 2005 at EMBL, Germany

Organizers: Stephen Cohen, EMBL & Naoto Ueno, NIBB

Speakers:

Darren Gilmour, EMBL
Jochen Wittbrodt, EMBL
Detlev Arendt, EMBL
Pernille Rorth, EMBL
Mathias Treier, EMBL
Anne Ephrussi, EMBL
Eileen Furlong, EMBL
Carl Neumann, EMBL
Chrsitof Niehrs, DKFZ
Shigenori Nonaka, UCSF Dept. Biochem & Biophys
Hirokazu Tsukaya, NIBB
Shinji Takada, NIBB
Minoru Tanaka, NIBB
Satoru Kobayashi, NIBB

Shinichi Aizawa, RIKEN, CDB
Masahiko Hibi, RIKEN, CDB
Yoshiko Takahashi, RIKEN, CDB
Hiroshi Sasaki, RIKEN, CDB
Yumiko Saga, NIG
Atsushi Kuroiwa, Nagoya Univ.
Kimiko Fukuda, Tokyo Metrop. Univ.
Hiroyuki Takeda, Univ. Tokyo
Tetsuya Tabata, Univ. Tokyo
Kouji Tamura, Tohoku Univ.

The Second NIBB-EMBL Symposium
Frontiers in Bioimaging

Organizing Chair: Naoto Ueno
Jan Ellenberg (EMBL Grenoble, Germany)
March 22 (Wed) – 23 (Thu), 2006

Bioimaging is one of the chief subjects of the collaboration between NIBB and EMBL. This meeting was held with the aim of exchanging information and discussing emerging and innovative technologies including chemical probes, microscopes with new concepts, and image data processing.

Dr. Stelzer (EMBL) reported on the Selective Plane Illumination Microscopy (SPIM), which is a recently developed microscope that allows scientists to observe large-sized (up to a few millimeters) and even living specimens. Dr. Sedat (UCSF) talked about the advanced microscopic system "OMX", the first practical implementation of structured illumination (SI) in which the grid is superimposed onto the sample to gain sharper images. Dr. Ellenberg talked about the genome-wide screening of mitosis-regulating genes called "MitoCheck" based on the mass image analysis of cultured cells combined with the disruption of genes with RNA interference.

Because of the high quality of the presentations and the lively discussions among the participants, this meeting was of significant importance for the field of bioimaging.

Scientific topics:

Imaging Diffusion & Activity

Emerging Technologies

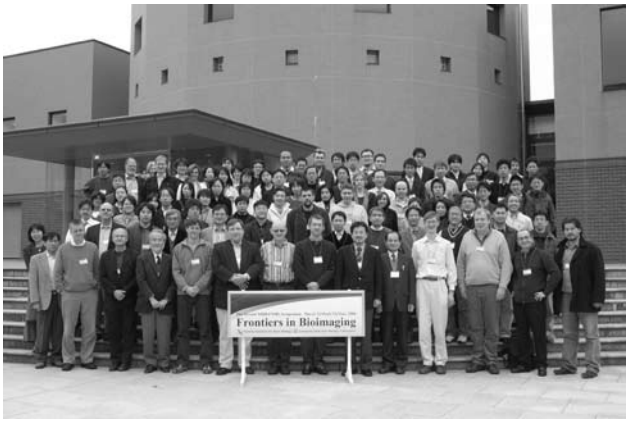
Bioluminescence

Networks & Screening

3D Imaging

Mitosis/Trafficking

Organism Model



Speakers

BASTIAENS, Philippe I. (European Molecular Biology Laboratory (EMBL), Germany), BRUNNER, Damian (European Molecular Biology Laboratory (EMBL), Germany), DENK, Winfried (Max-Planck Institute for Medical Research, Germany), ELLENBERG, Jan (European Molecular Biology Laboratory (EMBL), Germany), ISSAD, Tarik (CNRS, France), JOHNSSON, Kai (Ecole Polytechnique Federale de Lausanne, Switzerland), KERPPOLA, Tom K. (University of Michigan and Howard Hughes Medical Institute, USA), LIPPINCOTT-SCHWARTZ, Jennifer A. (National Institutes of Health, USA), MEYER, Tobias (Stanford University School of Medicine, USA), SEDAT, John W. (University of California, San Francisco, USA), SINGER, Robert H. (Albert Einstein College of Medicine, USA), SO, Peter T. C. (Massachusetts Institute of Technology, USA), STELZER, Ernst H. K. (EMBL Heidelberg, Germany), SWEDLOW, Jason (University of Dundee, UK), WEIJER, Cornelis J. (University of Dundee, UK), WITTBRODT, Joachim (European Molecular Biology Laboratory (EMBL), Germany)

HAMADA, Hiroshi (Osaka University, Japan), HIRAOKA, Yasushi (Kansai Advanced Research Center, NICT, Japan), ITO, Kei (The University of Tokyo, Japan), KASAI, Haruo (The University of Tokyo, Japan), KINJO, Masataka (Hokkaido University, Japan), KODAMA, Ryuji (National Institute for Basic Biology, Japan) KUSUMI, Akihiro (Kyoto University, Japan), MIYAWAKI, Atsushi (Brain Science Institute, RIKEN, Japan), NAGAYAMA, Kuniaki (National Institute for Physiological Sciences, Japan), OHSUMI, Yoshinori (National Institute for Basic Biology, Japan), OZAWA, Takeaki (Institute for Molecular Science, Japan), TABATA, Tetsuya (University of Tokyo, Japan), TANAKA, Minoru (National Institute for Basic Biology, Japan), TERAKAWA, Susumu (Hamamatsu University School of Medicine, Japan), UENO, Naoto (National Institute for Basic Biology, Japan), WADA, Masamitsu (National Institute for Basic Biology, Japan

Monterotondo Mouse Biology Meeting

via Ramarini 32
00016 Monterotondo-Scalo (RM)

19 – 20 April 2006

Wednesday 19 April

09.00 - Shuttle departure from Best Western

09.30 - Welcome – Nadia Rosenthal: *Introduction to the EMBL Mouse Biology Unit*
10.00-10.20 – Cornelius Gross
10.20-10.50 – Walter Witke: *Actin dynamics in the synapse regulates neurotransmitter release and complex behaviour*
10.50-11.10 – Liliana Minichiello
11.10-11.30 – Claus Nerlov: *Genetic analysis of C/EBP function*

11.30-11.40 - COFFEE

11.40-12.30 – Naoto Ueno: *Introduction. The role of Prickle in the mouse development*

12.30-14.00 - LUNCH

14.00-14.20 – Hitoshi Sakano: *Transgenic analysis of the mouse olfactory system*
14.20-14.40 - Yumiko Saga: *Mechanism of somite segmentation*
14.40-15.00 – Toshihiko Shiroishi: *Exploration of genome function based upon mouse inter-subspecific difference*

15.00-15.30 – Tour of Monoclonal Antibody Facility

15.30-16.00 - Tour of Animal House

16.00-16.45 - Tour of Phenotyping Facility

17.00 - Shuttle back to Best Western

19.00 - Shuttle from Best Western to Rome

20.00 - DINNER

23.00 - Shuttle back to Best Western

Thursday 20 April

09.00 - Shuttle departure from Best Western

09.30–09.50 – Shinichi Aizawa: *Otx2 gene cascade in A-P axis formation*
09.50-10.10 – Shinji Takada: *A gene trap screening for identification of Wnt-responsive genes*
10.10-10.30 – Toshikumi Sasaoka: *Role of the sarcoglycan complex in the muscle degeneration and hypertrophy in the sarcoglycan-deficient mice*
10.30 -10.50 - Yoichi Gondo: *Forward and reverse genetics with ENU mouse mutagenesis at RIKEN*

10.50-11.10 – COFFEE

11.10-12.30 - Glauco Tocchini-Valentini: *Introduction. EMMA-ICBEG-IBC*

12.30-14.00 - LUNCH

14.00-15.00 – Tour of EMMA

15.00 - Final remarks - END

The Fourth NIBB-EMBL Symposium
Biology of Protein Conjugation: Structure and Function

Organizing Chair: Yoshinori Ohsumi
Winfried Weissenhorn (EMBL Grenoble, Germany)
December 3 (Sun) – 5 (Tue), 2006

The fourth NIBB-EMBL Symposium was held gathering distinguished researchers in the field of the biology of protein conjugation from Europe, USA and Japan. There were 27 oral presentations, of which 12 were by foreign invitees, and 18 poster presentations. The symposium was a successful one as shown in the comment given by a participant presented below.

The NIBB-EMBL conference in Okazaki, Japan this past December was an outstanding international conference that included scientist from Japan, Europe and the US. It was an exciting meeting with considerable discussion both during the meeting sessions and the social activities. The program included innovative technologies in structural biology, live cell imaging and molecular biology. Each speaker presented new unpublished data and discussed the key questions that need to be addressed in their field. New insights into the roles for ubiquitin and ubiquitin-related molecules in cell signaling, membrane trafficking and protein turn-over were presented. It was the best meeting in 2006 that I attended covering these key topics in cell and molecular biology. (Scott D. Emr, UCSD, USA)

Scientific topics:

SUMO

Membrane Biology

Ubiquitin

Mechanism of UBL Conjugation

Modification by Lipid and Sugar

Speakers

DIKIC, Ivan (Johann Wolfgang Goethe University Hospital, Germany), EMR, Scott D. (UCSD School of Medicine, USA), GOODY, Roger S. (Max-Planck-Institute of Molecular Physiology, Germany), KLEVIT, Rachel E. (University of Washington, USA), LIMA, Christopher D. (Sloan-Kettering Institute, USA), POLO, Simona (IFOM, The FIRC Institute for Molecular Oncology, Italy), RORTH, Pernille (European Molecular Biology Laboratory, Germany), SCHULMAN, Brenda A. (St. Jude Children's Research Hospital, USA), SOMMER, Thomas (Max-Delbruck-Center for Molecular Medicine, Germany), ULRICH, Helle D. (Cancer Research UK, UK), WALTERS, Kylie J. (University of Minnesota, USA), WEISSENHORN, Winfried (European Molecular Biology Laboratory, France)

INAGAKI, Fuyuhiko (Hokkaido University, Japan), IWAI, Kazuhiro (Osaka City University, Japan), KAMURA, Takumi (Nagoya University, Japan), KATO, Shigeaki (The University of Tokyo, Japan), KATO, Koichi (Nagoya City University, Japan), KAWAHARA, Hiroyuki (Hokkaido University, Japan), KIHARA, Akio (Hokkaido University, Japan), KONDO, Takao (Nagoya University, Japan), MOROHASHI, Ken-ichirou (National Institute for Basic Biology, Japan), OHNO, Ayako (RIKEN, Japan), OHSUMI, Yoshinori (National Institute for Basic Biology, Japan), SAITOH, Hisato (Kumamoto University, Japan), SHIRAKAWA, Masahiro (Kyoto University, Japan), SUZUKI, Tadashi (Osaka Univeristy, Japan), TANAKA, Keiji (The Tokyo Metropolitan Institute of Medical Science, Japan), TENNNO, Takeshi (Kyoto University, Japan), WAKATSUKI, Soichi (KEK (High Energy Accelerator Research Organization), Japan), YOSHIDA, Minoru (RIKEN, Japan)

The Fifth NIBB-EMBL Meeting
Cell and Developmental Biology

Organizing Chair: Naoto Ueno
Stephen Cohen (EMBL Heidelberg, Germany)
May 24 (Thu) – 26 (Sat), 2007

The 5th NIBB-EMBL joint meeting, entitled "Cell and Developmental Biology", was held in Okazaki on May 24-26, 2007. The scientific sessions were organized in consideration of the recent trend of understanding macro developmental phenomena at the micro/single cell level. During the two years since the 1st NIBB-EMBL joint meeting, "Developmental Biology", we have gradually realized the importance of understanding complex developmental processes as an integration of individual cell behaviors. During this most recent joint meeting, the cytoskeltal rearrangement underlying cellular morphogenesis and movement, the cellular mechanism of cell polarity, cell-to-cell interaction in organogenesis, and other related topics were discussed in a variety of developmental contexts. NIBB and EMBL share a common interest in these topics and it is hoped that further international collaboration between our institutions will result from 2007's fruitful and stimulating meeting.

Hoping to catch the big wave of genomics of many experimental organisms now sweeping the worldwide scientific community, we also aimed in this meeting to explore the possibilities of genome-wide biology unveiling a "Gene Regulatory Network" (GNR) of development. GRN is a key to understanding not only the structure of gene regulatory pathways but also the evolutional capacity that generates biodiversity. Several speakers covered this topic and presented insightful talks, generating a great deal of interest in the future of "Systems Biology" among those attending.

Speakers

BRUNNER, Damian (EMBL Heidelberg, GERMANY), EPHRUSSI, Anne (EMBL Heidelberg, GERMANY), FURLONG, Eileen (EMBL Heidelberg, GERMANY), KNOP, Michael (EMBL Heidelberg, GERMANY), SPITZ, Francois (EMBL Heidelberg, GERMANY), WITTBRODT, Jochen (EMBL Heidelberg, GERMANY), ROSENTHAL, Nadia (EMBL Monterotondo, ITALY)

AIZAWA, Shin (Riken CDB, JAPAN), HASEBE, Mitsuyasu (NIBB, JAPAN), HAYASHI, Shigeo (Riken CDB, JAPAN), KAGEYAMA, Yuji (NIBB, JAPAN), KAIBUCHI, Kozo (Nagoya Univ., JAPAN), KINOSHITA, Noriyuki (NIBB, JAPAN), KOBAYASHI, Satoru (NIBB, JAPAN), MURATA, Takashi (NIBB, JAPAN), NARUSE, Kiyoshi (NIBB, JAPAN), NOJI, Sumihare (Univ. Tokushima, JAPAN), OKADA, Kiyotaka (NIBB, JAPAN), SAGA, Yumiko (NIG, JAPAN), SATOH, Nori (Kyoto Univ., JAPAN), TABATA, Tetsuya (Univ. Tokyo, JAPAN), TAKADA, Shinji (NIBB, JAPAN), TAKAHASHI, Yoshiko (NAIST, JAPAN), TAKEDA, Hiroyuki (Univ. Tokyo, JAPAN), TAMURA, Koji (Tohoku Univ., JAPAN), TANAKA, Minoru (NIBB, JAPAN), UEMURA, Tadashi (Kyoto Univ., JAPAN), UENO, Naoto (NIBB, JAPAN), YAMAMORI, Tetsuo (NIBB, JAPAN)

2) NIBB conference

The NIBB Conference is an international conference organized by the NIBB's professors once or twice a year with the participation of a guest lecturer from abroad. Since the first conference in 1977 (the year of the NIBB's foundation), the NIBB Conference has provided researchers in basic biology with valuable opportunities for international exchange.

Recent NIBB conference:

50th	**Structure and Dynamics of Complex Biological Networks**	**February, 2005**
51st	**New Aspects of Gene Amplification**	**November, 2005**
52nd	**Reproductive Strategies**	**January, 2006**
53rd	**Dynamic Organelles in Plants**	**June, 2006**

50th NIBB conference
Structure and Dynamics of Complex Biological Networks

Organizing Chair : Atsushi Mochizuki
February 8 (Tue) -10 (Thu), 2005

For these several years, we have seen rapid increase of biological information by the progress of molecular genetics technologies. It is the next theme for us to find out the essential principles of higher-order phenomena in biology from enormous amount of information. Non-experimental methods are now attracting attentions and expected as new methods for integrating information or for understanding the whole systems of biology. Many researchers from physics, mathematics or computer science are starting to enter problems in biology.

We need to enhance interaction between researchers working in different disciplines for the progress of theoretical methods in biology. For this purpose we held an international conference on February 2005 in Okazaki, Japan. In this conference, we called researchers studying various biological phenomena, network systems, spatio-temporal patterns, ecology and evolution, by using different theoretical methodology. Especially, we focused on the network structures in different fields of biology; including gene regulation, metabolic pathway or ecology. One of the notable themes was relation between structure and dynamical behavior of systems including such complex interactions.

In this conference, we had 91 participants including 12 researchers from foreign countries. We had 39 research presentations including 8 short talks and 12 poster presentations. Participants enjoyed discussions and interactions between different fields of theoretical biology. We have received many mails from participants that say thanks for holding this conference. We hope that this conference leads to a start of creation of new theoretical bioscience in the future.

Scientific topics:

Network systems in biology
Mathematical property of network
Application and understanding for biological network

Regulations in cells, tissues and organisms
Dynamical regulation in metabolism or cellular systems
Morphogenesis in development

Ecology and evolution
Dynamics in ecological network system

Speakers

AKUTSU, Tatsuya	(Kyoto University, Japan)
ALBERT, Réka	(Pennsylvania State University, USA)
ALMAAS, Eivind	(University of Notre Dame, USA)
ALVAREZ-BUYLLA, Elena Roces	(Universidad Nacional Autonoma de Mexico, Mexico)
ARITA, Masanori	(University of Tokyo, Japan)
CHING, Wai Ki	(University of Hong Kong, China)
CRACIUN, Gheorghe	(Ohio State University, USA)
IWASA, Yoh	(Kyushu University, Japan)
KANEKO, Kunihiko	(University of Tokyo, Japan)
KING, Ross	(University of Wales, UK)
KONDO, Shigeru	(Riken, Kobe / Nagoya University, Japan)
MARTINEZ, Neo	(Pacific Ecoinformatics and Computational Ecology Laboratory, USA)
MOCHIZUKI, Atsushi	(National Institute for Basic Biology, Japan)
MURATOV, Cyrill	(New Jersey Institute of Technology, USA)
NAKAI, Kenta	(University of Tokyo, Japan)
PAULSSON, Johan	(University of Cambridge, UK)
REINITZ, John	(Stony Brook University, USA)
TOKITA, Kei	(Osaka University, Japan)
VERT, Jean-Philippe	(Ecole des Mines de Paris, France)

51st NIBB conference
New Aspects of Gene Amplification-Mechanisms and Biological Function

Organizing Chair : Takehiko Kobayashi
November 5 (Sat) - 8 (Tue), 2005

Gene amplification not only results in genome alteration, it also plays wide-ranging roles in many biological function. In multicellular organisms, it is observed in many stages of the life-cycle, such as development, differentiation, senescence, and tumorgensis. In unicellular organisms, it is one of the main strategies for adaptation to the surroundings. Moreover, it is well-known that gene amplification has played critical roles in evolution.

Despite its involvement in these important biological functions, gene amplification has not been a central focus for discussion. One of the reasons is the mechanisms responsible have remained elusive. In this conference, we called researchers studying DNA recombination, DNA replication, chromatin structure and evolution, and discussed the molecular mechanisms and biological functions of gene amplification (including maintenance mechanism of amplified genes).

In this conference, we had ~50 participants including 11 researchers from foreign countries. There were 22 oral and 11 poster presentations. We had exciting discussion and a lot of exchange of information.

Now, with the enormous increases in genomic information and the rapid progression of molecular biology, we are in a good position to look at new aspects of gene amplification. At this point, this conference was timely and good opportunity to develop amplification study.

Scientific topics:

Molecular Mechanism of Gene Amplification

Adaptation and Gene Amplification

Evolution and Gene Amplification

Speakers

ARCANGIOLI, Benoit	(Pasteur Institute, France)
BENSIMON, Aaron	(Pasteur Institute, France)
DEBATISSE, Michelle	(Curie Institute, France)
GANLEY, Austen	(National Institute for Basic Biology, Japan)
HERNANDEZ, Pablo	(CSIC, Spain)
HISHIDA, Takashi	(Osaka University, Japan)
HORIUCHI, Takashi	(National Institute for Basic Biology, Japan)
IWASAKI, Hiroshi	(Yokohama City University, Japan)
JOHZUKA, Katsuki	(National Institute for Basic Biology, Japan)
KIKUCHI, Akihiko	(Nagoya University, Japan)
KOBAYASHI, Takehiko	(National Institute for Basic Biology, Japan)
LOBACHEV, Kirill	(Georgia Institute of Technology, USA)
MAKI, Hisaji	(Nara Institute of Science and Technology, Japan)
ROTH, John	(University of California-Davis, USA)
SASAKI, Hiroki	(National Cancer Center Research Institute, Japan)
SCHVARTZMAN, Jorge	(CSIC, Spain)
SHIBATA, Takehiko	(RIKEN Institute, Japan)
SHIMIZU, Noriaki	(Hiroshima University, Japan)
SHORE, David	(University of Geneva, Switzerland)
SOGO, José	(ETH, Switzerland)
STRUNNIKOV, Alexander	(NIH, USA)
TOWER, John	(University of Southern California, USA)

52nd NIBB Conference
Reproductive Strategies

Organizing Chair: Motonori Hoshi (Keio University)
January 20 (Fri) - 23 (Mon), 2006

Reproduction is one of the most characteristic features of living organisms. Essential for preserving species, this ability to reproduce has maintained life since its beginnings 3.8 billion years ago. For mammals, including human beings, reproduction and sex (a mechanism for shuffling genes) are inseparable and each individual has a fixed sex. There exists, however, a great variety of reproductive strategies. Some living organisms reproduce asexually, while others use either sexual or asexual reproduction strategies depending upon the circumstances. Some organisms change their sex during their lifetime.

This conference brought together participants ranging in experience from veteran scientists whose names appear in the history of molecular biology to graduate students. The participants engaged in intense and spirited discussions on many aspects of sex and reproduction. Why does sex exist? How much diversity is there among reproductive strategies? How did such strategies evolve? What is the biological significance of such strategies? Discussions on these and other topics provided research training opportunities as well as opportunities to establish and develop friendships transcending age, experience, and nationality.

Scientific topics:

Origin and Evolution of Sexual Reproduction

Determination and Differentiation of Sex

Germ Differentiation and Meiosis

Gamete Interactions

Allo-Recognition in Sexual Reproduction

Epigenetics

Evolution and Adaptation of Embryos and Larvae

Conflict and Competition in Sexual Reproduction

Speakers

BIRKHEAD, Tim R. (University of Sheffield, UK), DARSZON, Alberto (Universidad Nacional Autonoma de Mexico, Mexico), DORRESTEIJN, Adriaan (University of Giessen, Germany), EPEL, David (Stanford University, USA), EXTAVOUR, Cassandra (University of Cambridge, UK), HEINZE, Jurgen (University of Regensburg Germany), HEYLAND, Andreas (The Whitney Laboratory for Marine Bioscience, USA), JOLY, Dominique (Centre National de la Recherche Scientifique, France), MESELSON, Matthew (Harvard University, USA), MICHIELS, Nico (University of Tuebingen, Germany), NIELSEN, Claus (University of Copenhagen, Denmark), NORMARK, Benjamin (University of Massachusetts, USA), OLSSON, Mats (University of Wollongong, Australia), PRUITT, Robert E. (Purdue University, USA), SCHARER, Lukas (University of Innsbruck, Austria), STEWART, James R. (East Tennessee State University, USA), VACQUIER, Victor D. (University of California, San Diego, USA), WAKE, Marvalee H. (University of California Berkeley, USA)

AIGAKI, Toshiro (Tokyo Metropolitan University, Japan), ABE, Shin-ichi (Kumamoto University, Japan), HASEBE, Mitsuyasu (National Institute for Basic Biology, Japan), HOSHI, Motonori (Keio University, Japan), INABA, Kazuo (Tsukuba University, Japan), ISHIKAWA, Fuyuki (Kyoto University, Japan), ISHINO, Fumitoshi (Tokyo Medical and Dental University, Japan), IWASA, Yoh (Kyushu University, Japan), KAKUTANI, Tetsuji (National Institute of Genetics, Japan), KISHIMOTO, Takeo (Tokyo Institute of Technology, Japan), KOBAYASHI, Ichizo (University of Tokyo, Japan), KOBAYASHI, Kazuya (Keio University, Japan), KOBAYASHI, Satoru (National Institute for Basic Biology, Japan), KUROIWA, Asato (Hokkaido University, Japan), MATSUI, Yasuhisa (Tohoku University, Japan), MOHRI, Hideo (Professor Emeritus, National Institute for Basic Biology, Japan), MOROHASHI, Ken-ichirou (National Institute for Basic Biology, Japan), NAGAHAMA, Yoshitaka (National Institute for Basic Biology, Japan), NOCE, Toshiaki (Mitsubishi Kagaku Institute of Life Sciences, Japan), OKABE, Masaru (Osaka University, Japan), SAWADA, Hitoshi (Nagoya University, Japan), SUNANAGA, Takeshi (Kochi University, Japan), TACHIBANA, Kazunori (Tokyo Institute of Technology, Japan), TAKAHASHI, Yoshiko (Center for Developmental Biology, RIKEN, Japan), YAMAMOTO, Masayuki (University of Tokyo, Japan)

53rd NIBB Conference
Dynamic Organelles in Plants

Organizing Chair: Mikio Nishimura
June 14 (Wed) -17 (Sat), 2006

Because they spread their roots in the ground, plants must survive in a given environment. In order to adapt, they utilize environmental changes in the life cycle as important signals that are necessary for their survival. Recent studies have shown that plant cells can induce, degenerate and differentiate their organelles to adapt to environmental changes.

This conference provided an excellent opportunity to review recent advances in the field of plant organelle studies with special emphasis on their dynamics. Thirty-three lectures were presented in five sessions, namely 1) Differentiation and degradation, 2) Biogenesis and protein transport, 3) Post-genome approach, 4) Metabolic regulation and signal transduction, and 5) Integrated functions. Over 200 researchers, including 20 researchers from overseas, participated in the conference, which also included one plenary lecture and 89 poster presentations.

The participants were inspired to develop their own research on dynamic organelles. The conference was well-timed to provide an excellent opportunity to clarify the molecular mechanisms underling organelle dynamics in plants.

The conference was supported by JSPS (Japanese Society of Promotion of Science), Grant-in Aid for Scientific Research of Priority Areas on “Organelle Differentiation”, National Institute for Basic Biology, Japan Plant Science Foundation and the Daiko Foundation.

Scientific topics:

Differentiation and Degradation

Biogenesis and protein Transport

Post-Genome Approach

Metabolic Regulation and Signal Transduction

Integrated Functions

Speakers

BAKER, Alison (University of Leeds, UK), BRODSKY, Jeffrey (University of Pittsburgh, USA), CHRISTELLER, John (Horticulture and Food Research Institute of NZ, New Zealand), DENECKE, Jurgen (University of Leeds, UK), DUPREE, Paul (University of Cambridge, UK), EHRHARDT, David (Carnegie Institution, USA), GREENBERG, Jean (The University of Chicago, USA), HUANG, Anthony (University of California, USA), INOUE, Kentaro (University of California at Davis, USA), KOROLEVA, Olga (John Innes Centre, UK), LEE, Youngsook (POSTECH, South Korea), MITTLER, Ron (University of Nevada, USA), THIEL, Gerhard (Darmstadt University of Technology, Germany)

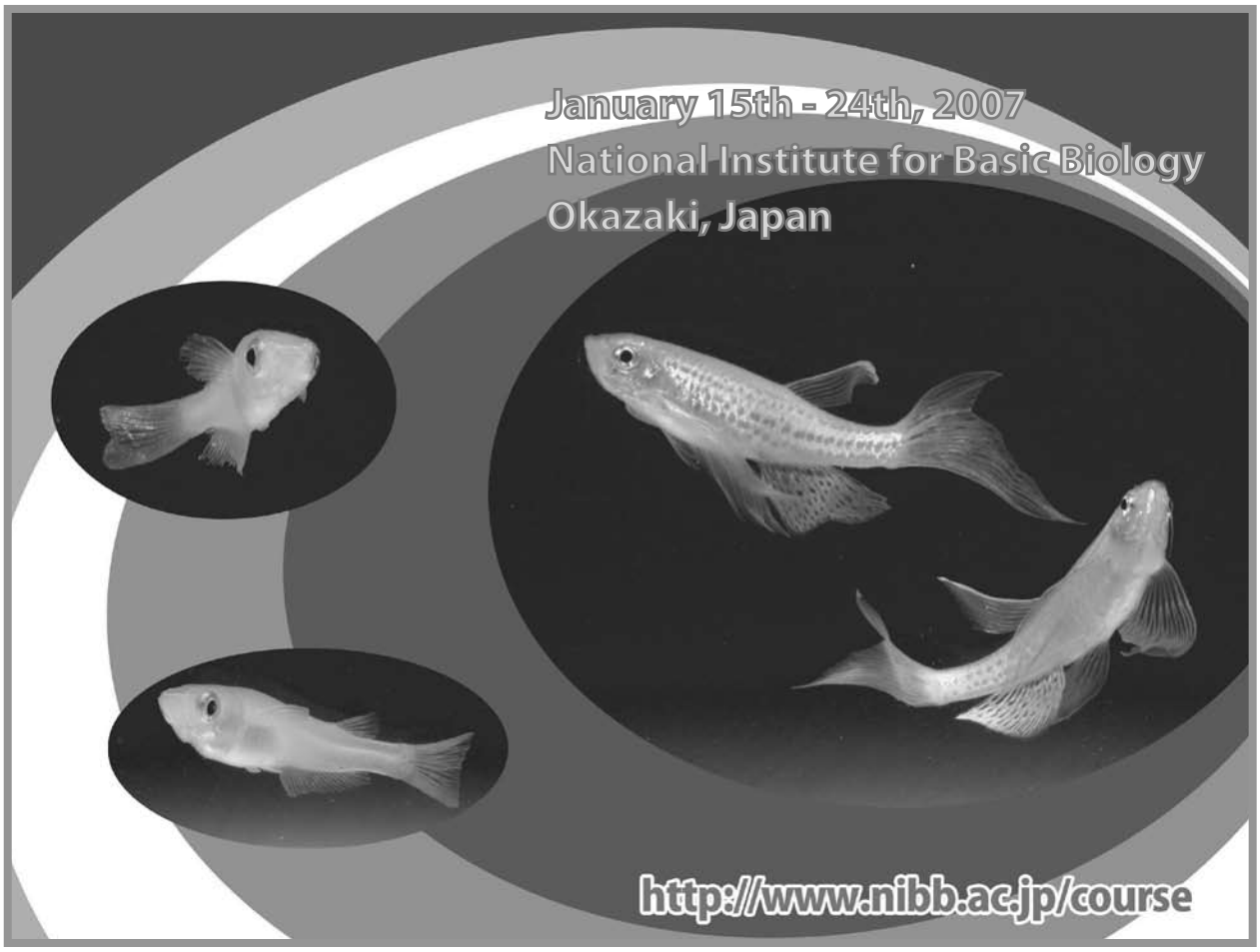
ASADA, Kozi (Fukuyama University, Japan) HARA-NISHIMURA, Ikuko (Kyoto University, Japan), ISHIGURO, Sumie (Nagoya University, Japan), MIMURA, Tetsuro (Kobe University, Japan), MORITA, Miyo (Nara Institute of Science and Technology, Japan), NAKANO, Akihiko (The University of Tokyo, Japan), NISHIKAWA, Shuh-ichi (Nagoya University, Japan), NISHIMURA, Mikio (National Institute for Basic Biology, Japan), NISHITANI, Kazuhiko (Tohoku University, Japan), NISHIZAWA, Naoko K. (The University of Tokyo, Japan), OHSUMI, Yoshinori (National Institute for Basic Biology, Japan), SAITO, Kazuki (Chiba University/ RIKEN, Japan), SAKAMOTO, Wataru (Okayama University, Japan), SHIBATA, Daisuke (Kazusa DNA Research Institute, Japan), SHIKANAI, Toshiharu (Kyushu University, Japan), SHIMAZAKI, Ken-ichiro (Kyushu University, Japan), SHIRASU, Ken (RIKEN, Japan), TAKANO, Hiroyoshi (Kumamoto University, Japan), TANAKA, Kan (The University of Tokyo, Japan), UCHIMIYA, Hirofumi (The University of Tokyo, Japan), YAMAYA, Tomoyuki (Tohoku University, Japan)

3) International Practical Course

With the cooperation of researchers from Japan and abroad, the NIBB international practical training course is given in a laboratory specifically prepared for the course in the NIBB. The first course, titled "Developmental Genetics of Zebrafish and Medaka," was held in 2007. Graduate students from various East Asian nations and areas, including China, Hong Kong, Taiwan, and India, were provided with training in state-of-the-art techniques for small fish research.

The 1st NIBB International Practical Course

Developmental Genetics of Zebrafish and Medaka



Supervised by:
Taisen Iguchi (NIBB)

Organized by:
Shinji Takada (NIBB), Shin-ichi Higashijima (NIPS), Koichi Kawakami (NIG),
Hitoshi Okamoto (RIKEN), Hiroyuki Takeda (Univ. Tokyo), Minoru Tanaka (NIBB)

COURSE MANUAL

Preface

Zebrafish (*Danio rerio*) and medaka (*Oryzias latipes*) are the leading vertebrate models for the study of genetics as well as gene function in development. The combination of lineage analysis, gene-knockout strategies, experimental manipulation of the embryo, and genomic/bioinformatic techniques, makes it ideal for studies on the molecular control of embryo patterning, morphogenesis and organogenesis. As you can see in this text, the course covers basic technologies, including gene knockdown by injecting anitisense morpholino-oligo, as well as a number of advanced techniques such as BAC homologous recombination mediated transgenesis, genomic/bioinformatic techniques, and lineage analysis with Kaede. The course also combines intensive laboratory training with daily lectures from recognized experts in the field.

I hope students will learn both emerging technologies and classical techniques to study gene function in the developing zebrafish and medaka using this text. Important elements in this course are the informal interaction between students and course faculties and establishment of friendship among students and faculties.

Taisen Iguchi,
National Institute for Basic Biology

Table of Contents

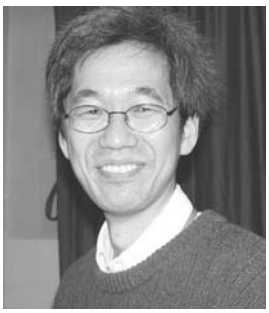
Appendix

Teachers

Higashijima, Shin-ichi

Department of Development, Differentiation and Regeneration
National Institute for Physiological Sciences
JAPAN
shigashi@nips.ac.jp

"BAC Homologous Recombination Techniques for Zebrafish Transgenesis"



Naruse, Kiyoshi

Department of Biological Sciences
The University of Tokyo
JAPAN
naruse@biol.s.u-tokyo.ac.jp

"How to Clone Your Favorite Medaka Mutants: Theory and Practice Using the High-Quality Medaka

Wada, Hironori

Laboratory for Developmental Gene Regulation
RIKEN Brain Science Institute
JAPAN
wada@brain.riken.jp

"Tracing Cell Lineages with Caged Fluorescein-Conjugated Dextran"

Lecturer

Sampath, Karuna

Temasek Life Sciences Laboratory
National University of Singapore
SINGAPORE
karuna@tll.org.sg

"RNA Localization in Zebrafish"

Program

Monday, January 15th, 2007

09:00-09:50	*Breakfast*
10:00-10:30	Registration (Meeting Room at NIBB B1 Floor)
10:30-11:00	Opening Remarks
11:00-12:00	Lecture on exp. 1 "BAC homologous recombination techniques for zebrafish transgenesis"
12:00-13:00	*Lunch*
13:00-18:00	Exp. 1 (PCR for targeting DNA, Purification and precipitation of targeting DNA)
19:00-20:30	*Welcome Party*

Tuesday, January 16th, 2007

08:00-08:50	*Breakfast*
09:00-11:00	Exp. 1 (Demonstration of injection)
11:00-12:00	Exp. 1 (Agarose gel electrophoresis of the purified DNA)
12:00-13:00	*Lunch*
13:00-15:00	Exp. 1 (Homologus recombination and transformation)
15:00-18:00	Lecture on exp. 2 "How to clone your favorite medaka mutants"
19:00-20:30	*Dinner*

Wednesday, January 17th, 2007

08:00-08:50	*Breakfast*
09:00-12:00	Exp. 2 (PCR with the balked samples by M markers, electrosoresis and determination of candidate LG)
12:00-13:00	*Lunch*
13:00-16:00	Exp. 2 continued
16:00-17:00	Exp. 1 (Colony Picking up)
17:00-18:00	Evening Lecture I (S. Takada)
19:00-20:30	*Dinner*

Thursday, January 18th, 2007

08:00-08:50	*Breakfast*
09:00-12:00	Exp. 1 (PCR for Checking) and Exp. 2 (Determination of the map position of the mutant locus and the most adjacent DNA markers of the mutant locus)
12:00-13:00	*Lunch*
13:00-17:00	Exp. 2 (Identification of responsible region of mutant phenotype on the medaka draft genome)
17:00-18:00	Evening Lecture II (T. Iguchi)
19:00-20:30	*Dinner*

Friday, January 19th, 2007

08:00-08:50	*Breakfast*
09:00-12:00	Exp. 1 (BAC Injection into cytoplasm of zebrafish embryos)
12:00-13:00	*Lunch*
13:00-17:30	Exp. 2 (Narrowing down the responsible region with DNA markers and identification mutation site by DNA sequencing)
17:30-18:30	Evening Lecture III (H. Takeda)
19:00-20:30	*Dinner*

Saturday, January 20th, 2007

Lab is open for participants.

09:00-17:00	Exp. 1 (Injection and observation)

Sunday, January 21st, 2007

Lab is closed.

Monday, January 22nd, 2007

08:00-08:50	*Breakfast*
09:00-10:00	Lecture on exp. 3 "Tracing cell lineages with a fluorescent protein Kaede"
10:00-12:00	Exp. 3 (Kaede injection into zebrafish embryos)
12:00-13:00	*Lunch*
13:00-17:00	Exp. 3 (UV Irradiation)
17:00-18:00	Evening Lecture III (Y. Nagahama)
19:00-20:30	*Dinner*

Tuesday, January 23rd, 2007

08:00-08:50	*Breakfast*
09:00-12:00	Exp. 3 (Observation of injected embryos under Microscopes)
12:00-13:00	*Lunch*
13:00-16:00	Exp. 3 continued (Observation under Microscopes)
16:00-17:30	NIBB Seminar (K. Sampath)
18:00-20:00	*Farewell Party*

Wednesday, January 24th, 2007

08:00-08:50	*Breakfast*
09:00-11:50	Lecture (K. Sampath)
11:50-12:00	Closing Remarks
12:00-13:00	*Lunch*

◆Lecture

Wednesday, January 24th, 2007

Sampath, Karuna (National University of Singapore)

"RNA Localization in Zebrafish "

◆Evening Lectures

Wednesday, January 17th, 2007

Takada, Shinji (NIBB)

"Forward and Reverse Genetic Approaches for Understanding Somite Segmentation "

Thursday, January 18th, 2007

Iguchi, Taisen (NIBB)

"Endocrine Disruption of Aquatic Vertebrates "

Friday, January 19th, 2007

Takeda, Hiroyuki (The University of Tokyo)

"The Analysis of Vertebrate Organogenesis Using Medaka Developmental Mutants "

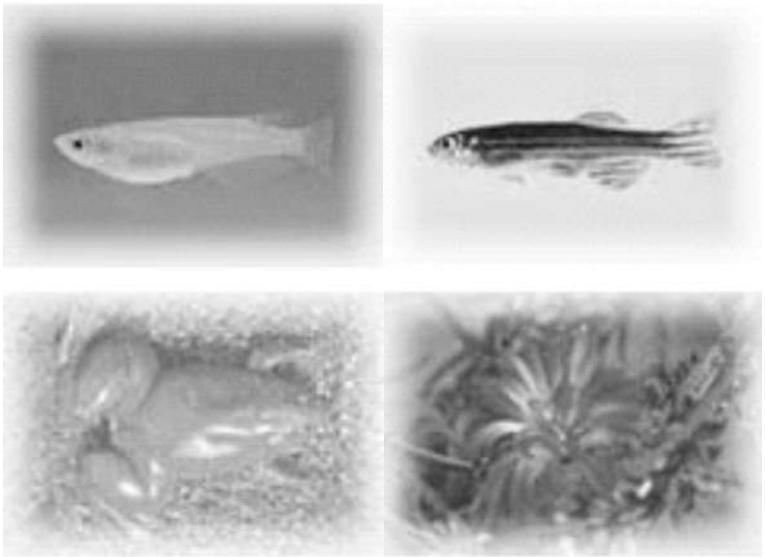
Monday, January 22nd, 2007

Nagahama, Yoshitaka (NIBB)

"Molecular Mechanisms of Sex Determination/Differentiation and Gametogenesis in Fish "

4) Bio Resources

The National BioResource Project (NBRP) is a national project for the systematic accumulation, storage, and supply system of nationally recognized bio resources (experimental animals and plants, cells, DNA, and other genetic resources), which are widely used as materials in life science research. To promote this national project, the NIBB has been appointed as a research center for research on "Medaka (*Oryzias latipes*)" whose usefulness as a vertebrate model was first demonstrated in Japan. The usability of Medaka as a research material in biology has drawn increasing attention since its full genome sequence recently became available. The NIBB also works as a sub-center for this national project for research on Japanese morning glory and Zebrafish. In addition, the NIBB provides databases containing research data on *Physcomitrella patens* (moss), *Daphnia*, *Xenopus laevis*, plant cell organelles, bacterial genomes, and gene expressions in the brain.



National BioResource Project
MEDAKA

Center - National Institute for Basic Biology -

1. Background:

Medaka, *Oryzias latipes* (Order Beloniformes), is a small, egg-laying freshwater teleost fish found in the brooks and rice paddies of China, Korea and Japan. This fish has been developed as a research material (Aida, T., 1921; Yamamoto, T., 1953; For reviews see Shima, A. and Mitani, H., 2004; Naruse K., et al 2004; Furutani-Seiki, M. and Wittbrodt J., 2004) in Japan and is now widely used in various research fields including biology, medical science and environmental science. Furthermore, a large scale ENU mutagenesis screening has been performed and identified more than 300 mutants with defects in organogenesis. A draft level genome sequence and more than 30,000 unique gene/EST sequences (DFCI Medaka Gene Index) and BAC/Fosmid clones are available. Medaka has the largest genetic variation (an average of 4%) in vertebrate species so far and these variations are clearly correlated with geographical distribution. This is a distinctive characteristic compared with other model vertebrates like zebrafish. Furthermore, several inbred strains which represent each regional population have also been established. Alternative vertebrate models with these features are not available.

Comparative genomic study among medaka and other vertebrates clearly showed that the synteny among teleosts was strongly conserved on the chromosomal level and even between the teleosts and mammals, and that they shared many common genomic features including the mechanism of development and organogenesis and gene expression machineries. From the evolutionary point of view, the molecular phylogenetic analysis of the natural population of medaka and medaka-related species allows for new perspectives of the natural environment of East and South-East Asia and the establishment of fish fauna in Asia.

Along with the development and collection of strains, several methods related to embryo manipulation and gene manipulation including the generation of transgenics and visualization technology with single cell level have also been developed.

Thus, all of these unique features have allowed medaka to be established as the representative "model vertebrate" system for analyzing a variety of biological phenomena.

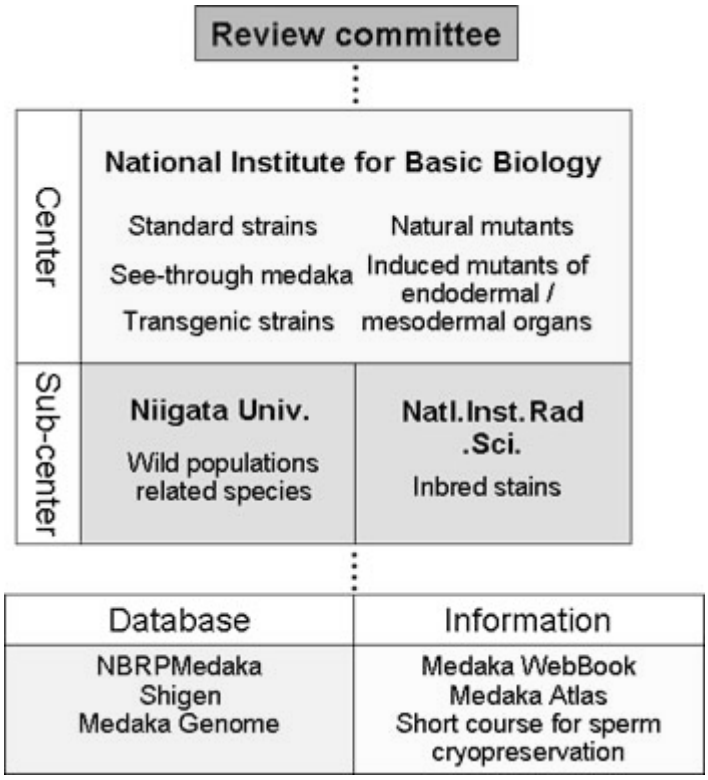
PURPOSES

In the second term of National BioResource Project (NBRP) Medaka, three organizations - the National Institute for Basic Biology (Core Institute), Niigata University, and the National Institute of Radiological Sciences - were appointed at the 2006 meeting (NBRP genetic resources committee for medaka) to efficiently provide, maintain and collect living and frozen medaka resources and the integrated information on medaka with the goal of facilitating and enhancing the use of medaka as a model organism.

The living resources include standard strains, wild stocks, inbred strains, medaka-related species and spontaneous and induced mutants. In addition to these live resources, the BAC/Fosmid clones will be provided, which cover 90 % of medaka genome and over 15,000 non-redundant EST clones. NBRP Medaka serves to develop, support and update the latest genetic and biological information, including genomic data (genome sequences, transcription initiation site (TSS) and predicated genes).

Thus, NBRP Medaka is aiming to establish a first rate biological resource with the highest possible levels of accessibility and ease of use .

2. Organization:



Available Resources

Wild populations: 66

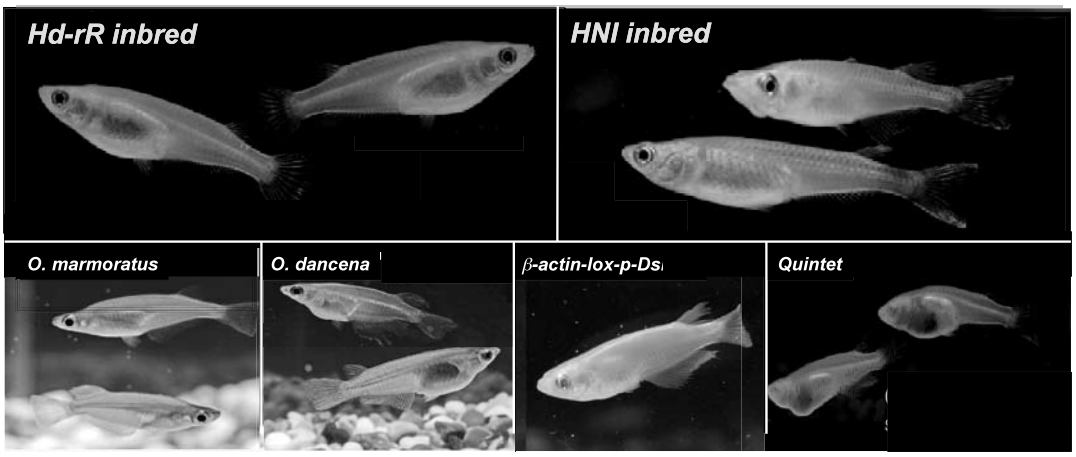
Related species: 17

Inbred strains: 10

Mutants: 357

Transgenic: 14

http://www.nbrp.jp/index.jsp

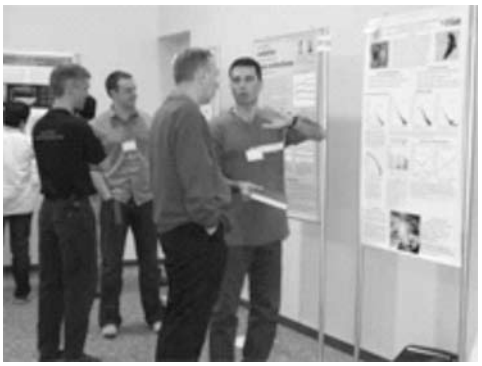


5) Okazaki Biology Conferences

The NIBB holds Okazaki Biology Conferences (OBC) that, under the endorsement of the Union of Japanese Societies for Biological Science, support the formation of international communities in future biological research fields with the goal of identifying new research issues in biology. Dozens of top-level researchers from Japan and abroad spend about one week together in exhaustive discussions seeking strategies for addressing future critical issues in biology. The past Conferences have promoted the formation of international researcher communities.

Past OBCs:

OBC1	**The Biology of Extinction**	**January, 2004**
OBC2	**Terra Microbiology**	**September, 2004**
OBC3	**The Biology of Extinction 2**	**March, 2006**
OBC4	**Terra Microbiology 2**	**September, 2006**
OBC5	**Speciation and Adaptation**	**March, 2007**
OBC6	**Marine Biology**	**December, 20071) Collaborative**



A. BERNARD/CORBIS SYGMA

Humboldt University of Berlin: Germany is concerned over the global standing of such institutions.

Universities battle for extra funds in bid to boost quality

Quirin Schiermeier, Munich

Germany's top universities are being asked to compete for top-up grants from the federal government to help them pack more of a punch internationally.

Five winning institutions will each get extra funding of €50 million (US$60 million) every year for five years from 2006, in a bold scheme designed to help them compete on a global stage with the likes of Harvard University and the University of Tokyo.

A competition for the money will start in the summer, Germany's science minister Edelgard Bulmahn announced at a meeting in Berlin on 26 January. She called on all of Germany's 100 or so research universities to apply by setting out a plan of how they would use the money to improve teaching and research. The winners will be chosen next year by a committee of German and foreign researchers and administrators.

"We urgently need more money for research, but we also need more quality for our money," Bulmahn says.

Other participants at the meeting included Horst Störmer of Columbia University in New York, who won the 1998 Nobel physics prize, and Chancellor Gerhard Schröder, who said last month that Germany must do more to promote its élite universities (see *Nature* **427,** 271; 2004).

The federal government has promised €1.25 billion to the competition. One option for finding the money is to sell part of the German central bank's gold reserves (see *Nature* **427,** 386; 2004).

In 1996, the government launched a similar competition, called BioRegio, in which different regions of the country competed for biotechnology funding for grants and equipment. Policy-makers think that this initiative had some success in strengthening German biotechnology.

Critics argue that it will take more than a cash competition to reform the country's university system. "It is not sufficient that universities send around applications boasting how well they can perform," says Dagmar Schipanski, science minister of the east German state of Thuringia. She thinks it would be better just to give the money to the DFG, the country's main research funding agency, so that all researchers could compete for it.

But Peter Gaehtgens, president of the German Conference of University Rectors, says he is optimistic that the competition will help to increase the international standing of Germany's top universities. In a Chinese survey of research universities released last month, no German university came in the top 40.

"Fresh money is always welcome," says DFG president Ernst-Ludwig Winnacker. "But it takes more than that. German university laws still promote equality, rather than competition for the best students and young scientists."

Winnacker, Gaehtgens and the heads of several other research organizations meet with Bulmahn later this month to hammer out the details of the competition, and to discuss further steps that could be taken to modernize Germany's universities. ■

Extinction meeting kicks off Japan's plans for networking

David Cyranoski, Okazaki

East Asian researchers can sometimes feel cut off from the merry-go-round of small but prestigious meetings that help to further the careers of their colleagues in Europe and North America. Now a series of conferences in Japan aims to give these scientists similar benefits.

On 25–30 January, at the First Okazaki Biology Conference, 70 researchers from 10 countries met in the coastal city of Okazaki on Japan's main island to discuss the biology of species extinction.

The conference's organizers hope that it is the first of what will become a significant series, modelled loosely on the Gordon Research Conferences held in the United States. "There's nothing like the Gordon Conferences in this region," says Yoshitaka Nagahama, a developmental biologist at Okazaki's National Institute for Basic Biology, and chair of the series.

Motoya Katsuki, the institute's director, who thought up the idea of the conferences, says the plan is to bring together "many researchers who are climbing different sides of the same mountain and can't see one another".

The extinction meeting brought together specialists in long-term climate modelling, the geographical distribution of animals, and the origin and evolution of species.

But getting Japanese researchers to join the international networks that serve to build new fields of research won't be easy: much of the meaningful exchange at small meetings goes on informally in conversations between sessions. The organizers say that Japanese researchers sometimes fade into the background at such times, mixing mainly with one another.

Yoh Iwasa, a theoretical biologist at Kyushu University who helped to organize the meeting, concedes that "Japanese researchers are not used to getting involved". But he says that at the meeting they became more vocal as the week progressed, and he is optimistic about the future. "This was only the first one," he says.

A second meeting on species extinction is set for 2006, and Okazaki meetings are also planned for September to discuss organisms living in extreme conditions, and for March next year on reproduction. Many more could follow, the organizers say, if the model proves successful. ■

The First Okazaki Biology Conference
The Biology of Extinction

Organizing Chair: Yoh Iwasa (Kyushu University, Japan)
Stuart Pimm (Duke University, USA)
January 25 (Sun) – 30 (Fri), 2004

The purpose of the conference "The Biology of Extinction" was to discuss a wide range of aspects in biological sciences related to the extinction of species, and to explore the possibility of forming a new research field of basic biology centered around this theme.

On each day of the conference except for Wednesday, there were two oral sessions, one in the morning and another in the afternoon. These sessions constituted seven sets of papers with specific themes, each of which included three to five speakers. The contents of these oral sessions were as follows:

[1] Historic and prehistoric extinction.

[2] Phylogenetic approaches to extinction and the consequences of non-random species loss.

[3] Mechanisms of maintenance of production of species diversity.

[4] Populations and extinction risk. Extinction of a species started with the extinction of local populations.

[5] Mechanisms of population extinction- genetical approaches.

[6] Toward developmental biology of extinction: molecular biology of extinction enhanced by morphological specialization.

[7]Consequence of extinction.

The Wednesday morning was a time for poster presentations. In the Friday morning eight short talks were presented who were selected among 40 poster presenters, avoiding overlapping of the themes of these short talks with long talks. The quality of all of the posters and short talks were very high.

In summary, we believe that the meeting was successful one. This First OBC conference gave an opportunity for experts in different branches of biology and non-biology to meet.

The conference was about connections. There are connections between extinctions in the past and those in the future, connections between our knowledge of local populations in space and time and the general patterns of which species are most vulnerable to extinction. The hope of the conference was to bring together those who study extinctions and different spatial and temporal scales. We can provide many examples where, in doing that, the speakers had raised the possibility for new and exciting work.

Speakers

Akcakaya, Resit H. (Applied Biomathematics), Brook, Barry W. (Charles Darwin Univ.), Brooks, Thomas (Conservation InterNatl.), Cardillo, Marcel (Imperial College London), Colegrave, Nick (Univ. of Edinburgh), Colwell, Robert K. (Univ. of Connecticut), Cooper, Steven (South Australian Museum), Courchamp, Franck (CNRS), Dunn, Robert R. (Curtin Univ.), Etienne, Rampal S. (Univ. of Groningen), Flannery, Tim F. (South Australian Museum), Frankham, Richard (Macquarie Univ. [also James Cook Univ. and Australian Museum]), Halley, John M. (Aristotle Univ. of Thessaloniki), Hanski, Ilkka A. (Univ. of Helsinki), Helgen, Kristofer M. (Univ. of Adelaide), Inchausti, Pablo (Universite de Rennes 1), Jackson, Jeremy B. C. (Univ. of California, San Diego), Jetz, Walter (Princeton Univ.), Koh, Lian Pin (Natl. Univ. of Singapore), Kunin, William E. (Univ. of Leeds), Lande, Russell S. (Univ. California, San Diego), MacMynowski, Dena P. (Stanford Univ.), McCarthy, Michael A. (Royal Botanic Gardens Melbourne), Naeem, Shahid (ColumbiA Univ.), Nee, Sean P. (Univ. of Edinburgh), Pimm, Stuart L. (Duke Univ.), Purvis, Andy (Imperial College London), Roberts, Callum M. (Univ. of York), Roopnarine, Peter D. (California Academy of Sciences), Root, Terry L.. (Stanford Univ.), Roy, Kaustuv (Univ. of California San Diego), Russell, Gareth J. (Columbia Univ.), Saether, Bernt-Erik (Norwegian Univ. of Science and Technology), Schneider, Stephen H. (Stanford Univ.), Shaffer, Bradley H. (Univ. of California, Davis), Sodhi, Navjot S. (Natl. Univ. of Singapore), Strecker, Ulrike (Univ. of Hamburg, Zool. Institute and Zool. Museum), Thomas, Chris (Univ. of Leeds), Voss, Stephen R. (Univ. of Kentucky), Vrijenhoek, Robert C. (Monterey Bay Aquarium Research Institute), Weisrock, David W. (Univ. of Kentucky), Wilcox, Chris (The Ecology Centre), Wilkens, Horst (Univ. of Hamburg)

Chiba, Satoshi (Tohoku Univ.), Eda, Masaki (The Univ. of Tokyo), Hakoyama, Hiroshi (Natl. Research Institute of Fisheries Science), Hasebe, Mitsuyasu (Natl. Institute for Basic Biology), Ikeda, Hiroaki (Natl. Institute for Agro-Environmental Sciences), Ishihama, Fumiko (Univ. of Tokyo), Iwasa, Yoh (Kyushu Univ.), Kawata, Masakado (Graduate School of Life Scienes, Tohoku Univ.), Masuda, Michiko (Nagoya Institute of Technology), Matsuda, Hiroyuki (Yokohama Natl. Univ.), Mochizuki, Atsushi. (Natl. Institute for Basic Biology), Natuhara, Yoshihiro (Osaka Prefecture Univ.), Ota, Hidetoshi (Univ. of the Ryukyus), Shimada, Masakazu (Univ. of Tokyo), Tainaka, Kei-ichi (Shizuoka Univ.), Takahashi, Kazuhiko (Natl. Institute for Basic Biology), Tanaka, Yoshinari (Chuo Univ.), Tomimatsu, Hiroshi (Hokkaido Univ.), Tsuji, Nobuyuki (Natl. Institute for Environmental Studies), Washitani, Izumi (Institute of Agricultural and Life Sciences, The Univ. of Tokyo), Yahara, Tetsukazu (Kyushu Univ.), Yokomizo, Hiroyuki (Kyushu Univ.)

The Second Okazaki Biology Conference
Terra Microbiology

Organizing Chair: Masayuki Ohmori (Saitama University, Japan)
James M. Tiedje (Michigan State University, USA)
September 26 (Sun) – 30 (Thu), 2004

The purpose of the conference "Terra microbiology" was to discuss a wide rage of aspects in biological sciences related to structure, function and ecology of microorganisms in terrestrial habitat. Not only scientists who have strong backgrounds in microbiology and molecular biology but also those who work more on environmental sciences and geology presented various aspects and foresights to cover vast area in Terra Microbiology.

There were 32 oral talks, 2 keynote lectures and posters. Posters were presented all through the meeting and special time was provided for poster presentation.

From 10 different countries, 53 scientists participated to this conference (U.S.A., 10; Germany, 3; Switzerland, 3; China, 1; New Zealand,1; Norway, 1; Singapore, 1; Swden,1; U.K.,1; Japan, 31). The half of the members consists of established scientists and the rest consists of very young scientists selected for this meeting. All participants discussed on the subjects reported in the sessions earnestly day and night, even in an open-yard hot spring. At last, we agreed to continue this activity in future. The purpose of the next meeting will be to reveal the structure and function of bacterial community from new molecular biological aspects.

Scientific sessions:

Session 1: Environmental Constraints and Evolutionary Diversity
Prof. Kenji Kato, Shizuoka Univ., Japan
Prof. Joseph L. Kirschvink, CalTech., USA
Session 2: Biogeochemical Cycling and Terra Formation
Prof. Hiroyuki Ohta, Ibaraki Univ., Japan
Prof. Vigdis Torsvik (University of Bergen, Norway)
Session 3: Symbiosis and Interactions
Dr. Masanori Saito, Nat·l Inst. Agro-Environ. Sci, Japan
Prof. Bengt Söderström, Lund Univ., Sweden
Session 4: Novel Approaches for Microbial Systems
Prof. Kiwamu Minamisawa, Tohoku Univ., Japan
Prof. Eugene L. Madsen (Cornell University, USA)

Speakers

Allen, Eric E. (University of California, Berkeley), Arp, Daniel J. (Oregon State University), Broughton, William (Universite de Geneve), Engel, Annette Summers (Louisiana State University), Gorbushina, Anna A. (Carl v. Ossietzky University), Hennecke, Hauke (Institute of Microbiology, ETH), King, Gary M. (University of Maine), Kirshchvink, Joseph L. (California Institute of Technology), Koch, Alexander M. (University of Lausanne), Lake, James A. (University of California, Los Angeles), Liu, Shuang-Jiang (Institute of Microbiology Chinese Academy of Sciences), Liu, Wen-Tso (National University of Singapore), Madsen, Eugene L. (Cornell University), Murray, Alison (Desert Research Institute), Neu, Thomas R. (UFZ Centre for Environmental Research), Olsen, Gary J. (University of Illinois at Urbana-Champaign), Rainey, Paul (The University of Auckland), Soderstrom, Bengt (Lund University), Tiedje, James M (Michigan State University), Torsvik, Vigdis (University of Bergen), Treusch, Alexander H. (Darmstadt University of Technology), Whiteley, Andrew S. (Centre for Ecology and Hydrology)

Fukatsu, Takema (National Institute of Advanced Industrial Science and Technology), Fukui, Manabu (Tokyo Metropolitan University), Hayatsu, Masahito (Shizuoka University), Hiraishi, Akira (Toyohashi University of Technology), Inagaki, Fumio (Japan Agency for Marine-Earth Science and Technology), Kakegawa, Takeshi (Tohoku University), Katayama, Yoko (Tokyo University of Agriculture and Technology), Kato, Kenji (Shizuoka University), Kimura, Hiroyuki (Shizuoka University), Kuga, Yukari (Shinshu University), Kurokawa, Ken (Nara Institute of Science and Technology), Minamisawa, Kiwamu (Tohoku University), Mochizuki, Atushi (National Institute for Basic Biology), Nanba, Kenji (The University of Tokyo), Nomura, Nobuhiko (University of Tsukuba), Ohkuma, Moriya (RIKEN), Ohmori, Masayuki (Saitama University), Ohta, Hiroyuki (Ibaraki University), Okabe, Satoshi (Hokkaido University), Saeki, Kazuhiko (Osaka University), Saito, Masanori (National Institute for Agro-Environmental Sciences), Sasaki, Mayumi (National Institute of Advanced Industrial Science and Technology), Sekiguchi, Yuji (National Institute of Advanced Industrial Science and Technology), Senoo, Keishi (The University of Tokyo), Suwa, Yuichi (National Institute of Advanced Industrial Science and Technology), Tsuda, Masataka (Tohoku University), Wada, Minoru (The University of Tokyo), Yasuta, Tsuyoshi (National Institute of Technology and Evaluation), Yoshimura, Jin (Shizuoka University)

The Third Okazaki Biology Conference
The Biology of Extinction 2

Organizing Chair: Tetsukazu Yahara (Kyushu University, Japan)
Callum Roberts (University of York, USA)
March 12 (Sun) – 17 (Fri), 2006

Extinction and speciation are two key processes that contributed to the formation of global patterns of biodiversity. Extinction is, therefore, a natural process. On the other hand, increasing human influence upon global ecosystems is accelerating species extinction. How does extinction occur? How do natural and anthropogenic factors interact upon extinction? What consequences are to be expected following mass extinction? These are critical questions from both basic and applied standpoints.

The purpose of the conference "The Biology of Extinction 2" was to discuss these questions by following up progress in biological sciences related to the extinction of species since the first OBC “The Biology of Extinction” in 2004. The goal of this series of conferences was to explore the possibility of forming a new research field of basic biology centered on the theme of extinction.

We invited nine non-Japanese and five Japanese researchers to attend the first OBC conference and they made significant contributions to its success. In addition, we invited ten new members in order to broaden our perspectives and stimulate discussion.

There were two oral sessions, one in the morning and one in the afternoon, on each day of the conference, excepting Wednesday. These sessions constituted seven sets of papers with specific themes, each of which included three or four speakers. Wednesday afternoon was a time for poster presentations. On Friday morning, eight short talks were given by presenters selected from among the poster presenters. The quality of all of the posters and short talks was very high.

In the seven sessions listed below, we identified some critical progress in our understanding of extinction proneness, the dynamics of extinction, speciation and migration, climatic change effects upon extinction, the role of human psychology upon anthropogenic extinction, and other issues. After the sessions, we had a general discussion about how extinction biology can be developed and synthesized. All of the participants were enthusiastic about participating in the birth of a new research field.

In conclusion, we believe that the meeting was a successful one. This third OBC conference provided an opportunity for experts in different branches of biology to meet and interact productively.

Scientific topics:

Historic and Prehistoric Extinctions
Patterns and Genetics of Extinction
Population Perspectives for Extinctions
Community Perspectives for Extinction
Invasion and Extinction
Climate Change, Extinction and Management
Toward an Integrated Understanding of Extinction

Speakers

ARAUJO, Miguel B. (MNCN, Spain), BIELBY, Jon N. (Imperial College London, UK), BRADSHAW, Corey J. A. (Charles Darwin Univ., Australia), BROOK, Barry W. (Charles Darwin Univ., Australia), CALEY, Julian (AIMS, Australia), COURCHAMP, Franck (CNRS, France), DUFFY, David C. (Univ. Hawaii Manoa, USA), FRANKHAM, Richard (Macquarie Univ., Australia), GOLDBERG, Emma E. (Univ. California, San Diego, USA), HALLEY, John M. (Aristotle Univ. Thessaloniki, Greece), HAMER, Keith C. (Univ. Leeds, UK), HANSKI, Ilkka (Univ. Helsinki, Finland), HARRISON, Ian J. (AMNH, USA), HASTINGS, Alan (Univ. California, Davis, USA), HUME, Julian P. (Natural History Museum, England), JACKSON, Jeremy B. C. (Univ. California, San Diego, USA), JETZ, Walter (Univ. California, San Diego, USA), KOH, Lian Pin (Princeton Univ., USA), LANDE, Russell (Univ. California, San Diego, USA), MARTINEZ-MEYER, Enrique (UNAM, Mexico), OLSON, Storrs L. (Smithsonian Inst., NMNH, USA), ORME, David (Imperial College London, UK), PURVIS, Andy (Imperial College London, UK), RIPA, Jorgen (Lund Univ., Sweden), ROBERTS, Callum (Univ. York, USA), SALA, Enric (CMBC, USA), SEKERCIOGLU, Cagan H. (Stanford Univ., USA), SHAFFER, H. Bradley (Univ. California, Davis, USA), SODHI, Navjot S. (National Univ. Singapore, Singapore), STIASSNY, Melanie L. (AMNH, USA), VIE, Jean-Christophe (IUCN, Switzerland), WILMERS, Christopher C, (Univ. California, Davis, USA)
HAKOYAMA, Hiroshi (NRIFS, Japan), ISHIHAMA, Fumiko (NIES, Japan), IWASA, Yoh (Kyushu Univ., Japan), KUDO, Gaku (Hokkaido Univ., Japan), MASUDA, Michiko (NIT, Japan), MATSUDA, Hiroyuki (Yokohama National Univ., Japan), NATUHARA, Yosihiro (Osaka Pref. Univ., Japan), OTA, Hidetoshi, (Univ. Ryukyus, Japan), TAKAGAWA, Shinichi (Univ. Tokyo, Japan), TAKENAKA, Akio (NIES, Japan), TANAKA, Yoshinari (Chuo Univ., Japan), TOKITA, Kei (Osaka Univ., Japan), TOMIMATSU, Hiroshi (TMU, Japan), WASHITANI, Izumi (Univ. Tokyo, Japan), YAHARA, Tetsukazu (Kyushu Univ., Japan), YOKOMIZO, Hiroyuki (Kyushu Univ., Japan)

The Fourth Okazaki Biology Conference
Terra Microbiology 2

Organizing Chair: Kenji Kato (Shizuoka University, Japan)
Daniel J. Arp (Oregon State University, USA)
September 10 (Sun) – 15 (Fri), 2006

The conference was held at the Okazaki Conference Center and was attended by 54 invited participants from the USA (11), the UK (3), Switzerland (2), the Netherlands (2), Australia (2), Singapore (2), Germany (1), China (1), New Zealand (1) and Japan (29). Inspired by the achievements of the previous conference, the "Terra Microbiology 2" conference was organized with the intention of embodying the results of the conference more directly by initiating several cooperative research programs. A fast developing field of the research on nitrogen metabolism from both metabolic sequence and genome analysis was focused on during Session 1. Session 2 and Session 3 focused on other important aspects of microbial ecology.

Session 1: Bio-geochemical cycling and microbial function.

Session 2: Gene hopping among microbes, from clinical and environmental evidence to the evolution of life.

Session 3: Bacterial cross talk.

In addition to the intensive discussions, the conference included two keynote lectures, 30 oral presentations, and 27 poster presentations. The development of meta-genomics was one of the principle topics of discussion during the conference.

Scientific topics:

Bio-Geochemical Cycling and Microbial Functions

Gene Hopping Among Microbes
-From Clinical and Environmental Evidences to Evolution of Life -

Bacterial Cross Talk

Speakers

AMINOV, Rustam (The Rowett Research Institute, UK), ARP, Daniel J. (Oregon State University, USA), BARKAY, Tamar (Rutgers University, USA), BAUER, Wolfgang D. (University of California, USA), EBERL, Leo (University of Zurich, Switzerland), GU, Ji-Dong (The University of Hong Kong, PR China), HENNECKE, Hauke H. (ETH, Switzerland), HETTICH, Robert L. (Oak Ridge National Laboratory, USA), KJELLEBERG, Staffan L. (The University of New South Wales, Australia), KLOTZ, Martin G. (University of Louisville, USA), LAANBROEK, Hendrikus J. (Netherlands Institute of Ecology, The Netherlands), LIU, Wen-Tso (National University of Singapore, Singapore), MURRELL, Colin (University of Warwick, UK), RAINEY, Paul B. (University of Auckland, New Zealand), RIVERA, Maria C. (University of California Los Angeles, USA), ROHWER, Forest (San Diego State University, USA), SALMOND, George P. C. (University of Cambridge, UK), SCHUSTER, Stephan C. (Penn State University, USA), SMALLA, Kornelia (Federal Biological Research Centre for Agriculture and Forestry, Germany), SOBECKY, Patricia A. (Georgia Institute of Technology, USA), SPIRO, Stephen (University of Texas at Dallas, USA), STROUS, Marc (Radboud University Nijmegen, The Netherlands), TIEDJE, James M. (Michigan State University, USA), ZHANG, Lian-Hui (Institute of Molecular and Cell Biology, Singapore), ZHOU, Jizhong (Institute for Environmental Genomics, USA)

ARITA, Masanori (The University of Tokyo, Japan), EDA, Shima (Tohoku University, Japan), FUJIWARA-NAGATA, Erina (Kinki University, Japan), IKEDA, Tsukasa (Utsunomiya University, Japan), KAMAGATA, Yoichi (National Institute of Advanced Industrial Science and Technology (AIST), Japan), KATAYAMA, Yoko (Tokyo University of Agriculture and Technology, Japan), KATO, Kenji (Shizuoka University, Japan), KATO, Junichi (Hiroshima University, Japan), KAWARABAYASI, Yutaka (National Institute of Advanced Industrial Science and Technology (AIST), Japan), KOBA, Keisuke (Tokyo Institute of Technology, Japan), KUGA, Yukari (Shinshu University, Japan), MINAMISAWA, Kiwamu (Tohoku University, Japan), MIYASHITA, Hideaki (Kyoto University, Japan), MORISAKI, Hisao (Ritsumeikan University, Japan), NANBA, Kenji (Fukushima University, Japan), NASU, Masao (Osaka University, Japan), OHTA, Hiroyuki (Ibaraki University, College of Agriculture, Japan), OHTOMO, Ryo (National Institute of Livestock and Grassland Science, Japan), OKABE, Satoshi (Hokkaido University, Japan), SAITO, Masanori (National Institute for Agro-Environmental Sciences, Japan), SENOO, Keishi (The University of Tokyo, Japan), SHOUN, Hirofumi (The University of Tokyo, Japan), SUNAMURA, Michinari (The University of Tokyo, Japan), SUWA, Yuichi (National Institute of Advanced Industrial Science and Technology (AIST), Japan), SUZUKI, Satoru (Ehime University, Japan), TAKAI, Ken (Japan Agency for Marine-Earth Science & Technology, Japan), UCHIYAMA, Ikuo (National Institute for Basic Biology, Japan), WADA, Minoru (The University of Tokyo, Japan), YOSHINAGA, Ikuo (Graduate School of Agriculture, Kyoto University, Japan), OHMORI, Masayuki (Saitama University, Japan)

The Fifth Okazaki Biology Conference
Speciation and Adaptation
-Ecological Genomics of Model Organisms and Beyond-

Organizing Chair: Kentaro Shimizu (University of Zurich, Switzerland)
Ian Dworkin (North Carolina State University, USA)

March 11 (Sun) – 16 (Fri), 2007

With the advent and widespread use of genomic tools, it is clear that the study of evolutionary genetics is undergoing a transformation. To promote the advancement and synthesis of the various fields of evolutionary and ecological genomics, the 5th Okazaki Biological Conference was held in March of 2007. The conference began with a social function to welcome 70 scientists from 10 countries and was followed by Plenary Lectures at the National Institute for Basic Biology (NIBB). Following the plenary lectures, the participants moved to Yamaha Resort Tsumagoi, where the scientists had opportunities to share their work during the oral platform sessions, in addition to poster sessions by many additional young scientists. The talks represented a broad overview of current areas of active research in ecological and evolutionary genomics, including studies of adaptation, speciation, domestication, genome duplication, co-evolution, canalization and theoretical population genetics.

The real goal of such an intimate meeting was to encourage interaction between leading researchers and to facilitate interactions between scientists using different approaches but asking related questions and using similar model systems.. We believe that it is only when apparently disparate aspects of biology are integrated that we can hope to make real progress in our understanding of evolutionary mechanisms. During the conference, therefore, there was plenty of time for discussions on each of these subjects, both formally after each session with a panel discussion as well as more informally during social events and meals. The feedback from the participants on all aspects of the conference, including the scientific discussions, opportunities for developing new contacts, and the help of the supporting staff, was very positive.

Scientific sessions:
1. Adaptive evolution
2. Genetics of speciation
3. Genome duplication and epigenetics
4. Artificial selection in domestication
5. Canalization, robustness and hidden genetic variation
6. Theory
7. Coevolution

Invited Speakers

AGUADE, Montserrat (Univ. Barcelona, Spain), ARAKI, Hitoshi (Oregon State Univ., USA), BARBASH, Daniel (Cornell Univ., USA), BRYSTING, Anne (Univ. Oslo, Norway), CAICEDO, Ana (Univ. Massachusetts, USA), COMAI, Luca (UC Davis, USA), COOP, Graham (Univ. Chicago, USA), DWORKIN, Ian (North Carolina State Univ., USA), FELIX, Marie-Anne (Institut Jacques Monod, France), GROSSNIKLAUS, Ueli (Univ. Zurich, Switzerland), HERMISSON, Joachim (Univ. Munich, Germany), HIRATE, Yoshikazu (Fred Hutchinson Cancer Research Center, USA), HOEKSTRA, Hopi (Harvard Univ., USA), IGIC, Boris (Univ. Illinois, Chicago, USA), KANAOKA, Masahiro (Univ. Washington, USA), KOBAYASHI, Yasushi (MPI for Developmental Biology, Germany), KUITTINEN, Helmi (Univ. Oulu, Finland), LAWTON-RAUH, Amy (Clemson Univ., USA), MABLE, Barbara (Univ. of Glasgow, UK), MACHADO, Carlos (Univ. Arizona, USA), OLSEN, Kenneth (Washington Univ., St. Louis, USA), PURUGGANAN, Michael (New York Univ., USA), RESCH, Alissa (NCBI, USA), RUTHERFORD, Suzannah (Fred Hutchinson Cancer Research Center, USA), SHIMIZU, Kentaro (Univ. Zurich, Switzerland), SHIMIZU-INATSUGI, Rie (Univ. Zurich, Switzerland), SHUSTER, Stephen (Northern Arizona Univ., USA), SIEGAL, Mark (New York Univ., USA), STEPHAN, Wolfgang (Univ. Munich, Germany), TANAKA, Kenta (Univ. Sheffield, UK), TIAN, Dacheng (Nanjing Univ., China), TSIANTIS, Miltos (Univ. Oxford, UK), VERGEER, Philippine (Univ. Leeds, UK), WIDMER, Alex (ETH Zurich, Switzerland), YANG, Hsiao-Pei (Cornell Univ., USA)

FUKATSU, Takema (AIST, Japan), HARUSHIMA, Yoshiaki (NIG, Japan), HASEBE, Mitsuyasu (NIBB, Japan), INNAN, Hideki (SOKENDAI, Japan), ISHIKAWA, Ryuji (Hirosaki Univ., Japan), IZAWA, Takeshi (NIAS, Japan), KUDOH, Hiroshi (Kobe Univ., Japan), MOCHIZUKI, Atsushi (NIBB, Japan), OKADA, Kiyotaka (Kyoto Univ., Japan), TAJIMA, Fumio (Univ. Tokyo, Japan), TAKAHASHI, Aya (NIG, Japan), TSUKAYA, Hirokazu (Univ. Tokyo, Japan), TSUMURA, Yoshihiko (FFRPI, Japan), YAHARA, Tetsukazu (Kyushu Univ., Japan)

The Sixth Okazaki Biology Conference
Marine Biology

Organizing Chair: Noriyuki Satoh (Kyoto University, Japan)
Billie J. Swalla (University of Washington, USA)
Don R. Levitan (Florida State University, USA)

December 2 (Sun) – 8 (Sat), 2007

We conceived this conference in order to bring together Marine Scientists from across the globe to discuss approaches to research in Marine Sciences. Most Marine Science is carried out at Marine Biological Laboratories, so we invited a number of Marine Laboratory Directors from Canada, France, Italy, Norway, Sweden and Japan to get an idea of what sort of studies are being conducted globally. Marine Biology covers an enormous number of research topics and we endeavored to bring together researchers in all of the main fields: reproductive biology, evolution and development, neurobiology, marine fungi/algae, marine genomics, behavior, ecology and conservation biology. This diverse group of speakers is united by their research on marine systems and the fact that they are internationally known for the quality of their research. We expected this group of brilliant leading Marine Scientists to find much in common to share about research techniques, approaches and future prospects and were delighted to see the many positive interactions that took place among the participants.

The diverse research presented at the OBC-6 Marine Biology Conference showed the vast potential of the marine environment in biological studies and highlighted current ecological problems that threaten the unprecedented biodiversity and untapped knowledge in the world's oceans. We heard many talks about the advances in genomics and marine exploration applied in novel and creative ways to understanding the marine environment and the biological organisms that live within it. The talks described research on a wide range of life forms from marine algae to invertebrates to vertebrates.

Towards the end of conference, it was suggested that an academic society for Marine Biologists in Japan be organized in the very near future. This may prove to be one of the most important achievements of this highly successful conference.

Scientific topics:

Reproduction
Evolution and Development
Neurobiology and Physiology
Marine Algae and Fungi
Marine Genomics
Behavior
Ecology

Speakers

BERNARDI, Giorgio (Stazione Zoologica Anton Dohrn, Italy), BOYEN, Catherine (CNRS & Univ. Paris 6, France), CHOURROUT, Daniel (Univ. Bergen, Norway), KLOAREG, Bernard (CNRS, Universit&eacute, France), KNOWLTON, Nancy (Smithsonian Inst., USA), LEVITAN, Don R. (Florida State Univ., USA), MATZ, Mikhail V. (Univ. Texas, Austin, USA), SARDET, Christian (CNRS UPMC, France), SPENCER, Andrew N. (Malaspina Univ.-College, Canada), SWALLA, Billie J. (Univ. Washington, USA), THORNDYKE, Michael C. (The Royal Swedish Academy of Sci., Sweden), VIZE, Peter D. (Univ. Calgary, Canada), WIDDER, Edith A. (Ocean Research & Conservation Assoc., USA)

AKASAKA, Koji (Univ. Tokyo, Japan), HARADA, Yoshito (Sugashima Marine Biological Laboratory, Japan), HIDAKA, Michio (Univ. Ryukyus, Japan), HOSHI, Motonori (Open Univ., Japan), INABA, Kazuo (Univ. Tsukuba, Japan), KIYOMOTO, Masato (Ochanomizu Univ., Japan), KUSAKABE, Takehiro G. (Univ. Hyogo, Japan), NAKAMURA, Masaru (Univ. Ryukyus, Japan), NARUSE, Kiyoshi (NIBB, Japan), NOZAKI, Masumi (Niigata Univ., Japan), OKAMURA, Yasushi (Okazaki Inst. Integrative Biosci., Japan), OTA, Kinya G. (RIKEN CDB, Japan), SAGA, Naotsune (Hokkaido Univ., Japan), SAKAMOTO, Tatsuya (Okayama Univ., Japan), SATO, Katsufumi (Univ. Tokyo, Japan), SATOH, Nori (Kyoto Univ., Japan), SAWADA, Hitoshi (Nagoya Univ., Japan), TAKEI, Yoshio (Univ. Tokyo, Japan), TSUKAMOTO, Katsumi (Univ. Tokyo, Japan), UEDA, Hiroshi (Hokkaido Univ., Japan), UENO, Naoto (NIBB, Japan), YASUI, Kinya (Hiroshima Univ., Japan)

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外部点検評価報告書

第一部

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