行政院及所屬各機關出國報告

（出國類別：考　察）

參訪日本理化研究所

服務機關：台北榮民總醫院

出國人職　稱：主治醫師

姓　名：謝仁俊

出國地區：日本

出國期間：90. 4. 22. — 90. 4. 25.

報告日期：90. 年 7. 月 12. 日

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報告名稱:

參訪日本理化研究所

主辦機關:

行政院輔導會臺北榮民總醫院

聯絡人／電話:

／

出國人員:

謝仁俊　行政院輔導會臺北榮民總醫院　教研部　主治醫師

出國類別: 考察

出國地區: 日本

出國期間: 民國 90 年 04 月 22 日 -民國 90 年 04 月 25 日

報告日期: 民國 90 年 07 月 12 日

分類號/目: J3／醫療　J3／醫療

關鍵詞:　理化研究所

內容摘要: 緣三校兩院之合作概念，職謝仁俊奉 院長指示於民國九十年四月二十二日隨同陽明大學吳妍華校長、徐明達教授、洪蘭教授、錢嘉韻教授、林寄宏教授，偕同交大張俊彥校長、林松山院長、楊裕雄教授、毛仁淡教授等一行搭機赴日本東京參訪理化研究所PIKEN (The inst. Physical and Chemical Research) 。Riken爲日本最大之國家級研究機構，除了物理及化學領域之外，生物科技及腦科學研究是目前最重要之目標。有關經費由陽明大學追求卓越計劃勻支。

本文電子檔已上傳至出國報告資訊網

參訪日本理化研究所報告

一、 目的

緣三校兩院之合作概念，職謝仁俊奉 院長指示於民國九十年四月二十二日隨同陽明大學吳妍華校長、徐明達教授、洪蘭教授、錢嘉韻教授、林寄宏教授，偕同交大張俊彥校長、林松山院長、楊裕雄教授、毛仁淡教授等一行搭機赴日本東京參訪理化研究所 PIKEN (The inst. Physical and Chemical Research) 。Riken 為日本最大之國家級研究機構，除了物理及化學領域之外，生物科技及腦科學研究是目前最重要之目標。有關經費由陽明大學追求卓越計劃勻支。

二、 過程

四月二十三日上午十時首先抵 RIKEN 總部，參加由小林理事長（Dr. S. Kobayashi）所主持之簡報，介紹 RIKEN 創立以來的沿革及現況。RIKEN 在 1917 年創辦，原為一私立之研究機構，第二次大戰後於 1958 年起改隸國家研究單位，自此蓬勃發展。現共有四個研究園區：Wako Main Campus, Yokohama, Tsukuba and Harima 等 Campus。本次參觀之重點研究所 Brain Science Inst., BSI，位於 Wako Main Campus；而 Genomic Sciences Center(GSC)，則位在 Yokohama Campus 另外尚有重要的生醫研究中心如 Spring 8 為世界級同步輻射研究園區在 Harima Campus; Developmental Biology Center 位在 Tsukuba Campus. RIKEN 年度研究經費在 750 億日元（合台幣 187 億），研究人力共計 2680 人，每年發表千篇國際期刊論文，其諮詢委員會共有十四位世界級學者（含諾貝爾獎得主）， 協助規劃其發展策略。同日上午十一時，轉往 Brain

Science Institute(BSI)參觀，由伊藤所長(Professor M.ITO)簡報BSI之創立與現況。Brain Science Research Group 自 1997 年由 Frontier Research System 獨立創所迄今短短三年餘已卓然有成，研究目標有三大方向：(1).Understanding the brain, (2).Protecting the brain, (3).Creating the brain。共計有 38 個研究群，除 38 位負責之研究者外，共有 400 餘研究人員；含 Research Scientists 及 Technical Staffs。每年經費在台幣 30 億左右，佔 RIKEN 總經費 16%，為重點研究領域。三項大研究主軸下各自有數個研究群（research group），每個 group 下再設有數個研究室，領域從基礎神經科學、神經網路、人腦功能、臨床研究、藥物發展、發育、分子神經病理、老化及精神疾病機制、神經再升及修復、人機介面以致擬人腦之人工智慧及應用，真正涵蓋了由基因至認知以迄生物電子工程科技（附件二）。有關其內部之人事組成、經費情形、運作機制請詳見附件一之資料。硬體建築共三棟 Central Building 為十層樓，總面積 27,000 ㎡，East Building 為六層樓，面積：8,909 ㎡，West Building 為三層樓，面積 2,541 ㎡。中午由小林理事長，吉良副理事（Dr. A. Kira）及伊藤所長陪同午餐。下午由 BSI 三位研究群負責人各就 BSI 三個大目標作簡報：Dr. S. Amari 簡報 Mathematical Neuroscience Research, Dr. K. S. Rockland 簡報 Cortical Organization and Systematics Research, Dr. A. Takashima 簡報 Alzheimer's Disease Research.此外，並參觀 BSI 向社會大眾，高中學生推廣神經科學研究重要性之展示區 "Brain Box".

四月二十四日下午一時半抵達 RIKEN Yokohama Institute,聽取 Genomic Sciences Center(GSC)主任 Dr. A. Wada

之簡報。GSC 於 1998 年成立次今二年餘，研究目標共分六大方向：1.Genome Exploration Research, 2.protein Research, 3.Human Genome Research, 4.Mouse Functional Genomic Research, 5.Plant Functional Genomic Research, 6.Bioinformatics。現有設施規模為完成後之三分之一。研究人員已有 350 人，年度經費五億台幣，Yokohama 將有 100 台 NMR，合併在 Harima Campus 之 Spring 8，將成為世界少有之蛋白質結構分析重鎮。規模之大固然令人稱羨，更重要的是研究架構充分表徵了日本人做事的系統化態度，從上到下巨細靡遺之追根究底之精緻精神。除了人類基因體計劃外，也展開黑猩猩基因體計劃，佔國際主導地位。其後分別由 Dr. Hattori 簡報人類基因體研究現況，Dr. Hirota 簡報蛋白質研究現況，Dr. Hyashizaki 簡報探索基因功能研究現況，並參觀相關研究設施及運作模式（見附件三）。

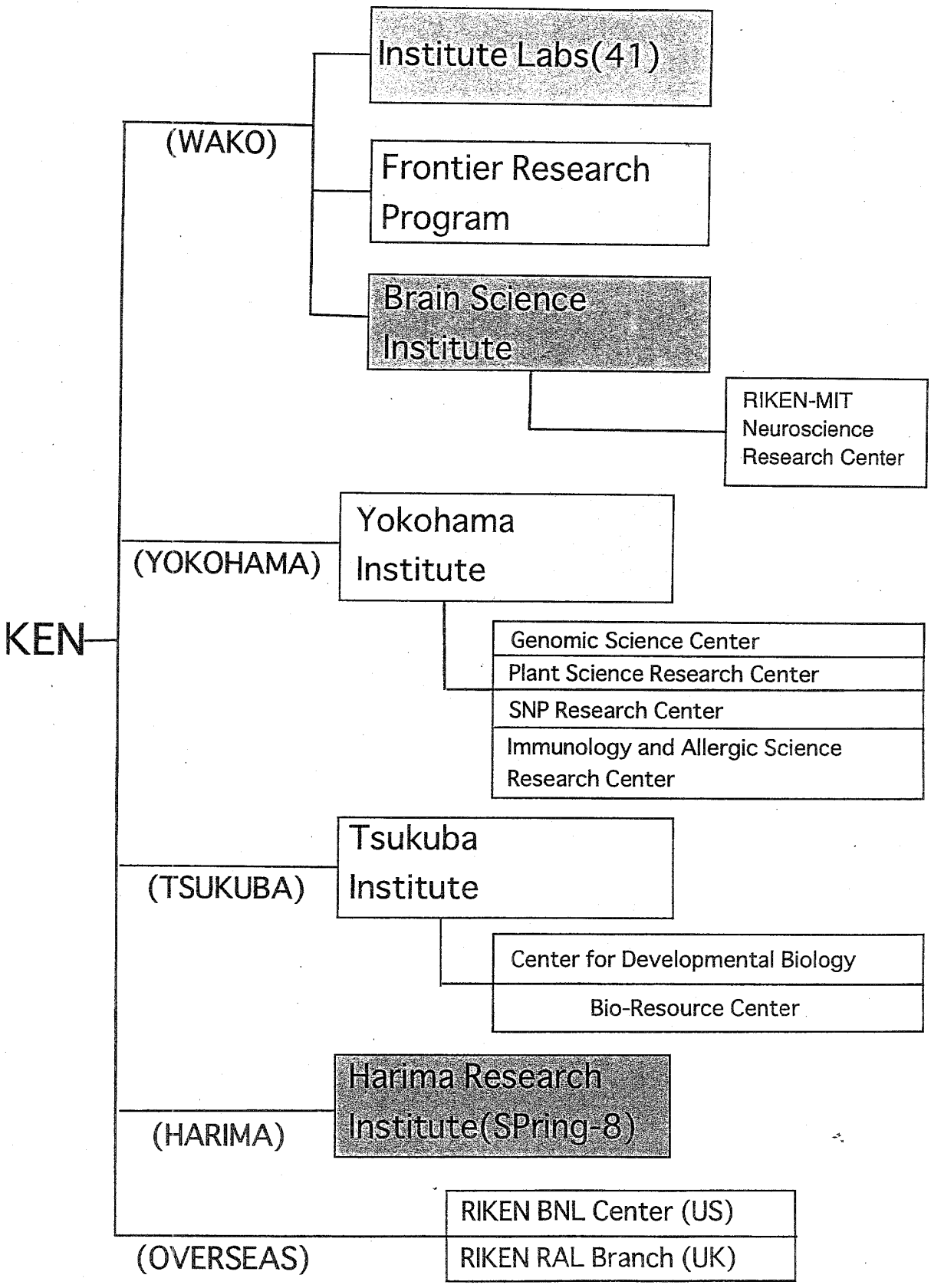
三、 心得及建議

日本為了推動科技生根，由國會訂定國家科學法以立法保障每年之科研及科教經費之年度國家經費比例，這點值得我國積極效法。因此雖然長期歷經經濟低迷，但是每年的科研經費卻未見刪減反倒有增加之趨勢。而 RIKEN 之歷史規劃及沿革，也正代表了日本政府對科學發展前瞻性的具遠見之政策。總結 RIKEN 參觀之印象深感日本對長期科技發展之用心與重視。目前正值三校兩院積極討論及規劃跨領域及跨學門和跨校際之合作，如何結合彼此之科技及人文長處而達到互補的加成效益，及規劃重點研究及發展方向將是切要之務。RIKEN 其規模及前瞻性規劃均予人深刻印象，應可作

我國科技政策擬定之重要參考。本院素與陽明及清華大學兩校有榮陽及榮清合作研究計劃之機制，應可推動榮交（榮總及交通大學）或者榮陽交之三邊計劃以結合資訊科學及生物醫學。

附件一

RIKEN Research Structure



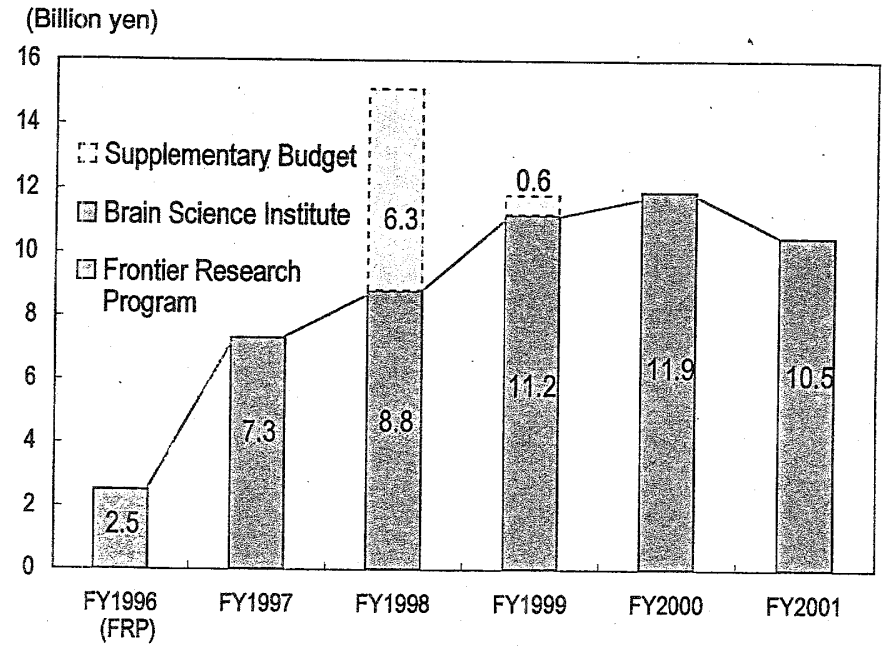
Organization of RIKEN Brain Science Institute (As of April 1, 2001)

- President
  - Director
    - Executive Advisor
    - Advisory Council
    - Research Review Committee
    - Institutional Review Board
    - Search Committee
  - **Understanding the Brain**
    - Neuronal Function Research Group (Dr. Takao K. Hensch, *Ph.D.*)
      - Neuronal Circuit Development (Dr. Takao K. Hensch, *Ph.D.*)
      - Neurobiology of Synapse (Dr. Yoshihiro Yoshihara, *Ph.D.*)
    - Neuronal Circuit Mechanisms Research Group (Dr. M. Ito, *M.D., Ph.D.*)
      - Memory and Learning (Dr. Masao Ito, *M.D., Ph.D.*)
      - Neurobiology of Emotion (Dr. Hiroaki Niki, *Ph.D.*)
      - Neuronal Circuit Dynamics (Dr. Thomas Knöpfel, *M.D., Ph.D.*)
      - Cellular Information Processing (Dr. Ryoji Yano, *Ph.D.*)
    - Cognitive Brain Science Group (Dr. K. Tanaka, *Ph.D.*)
      - Cognitive Brain Mapping (Dr. Keiji Tanaka, *Ph.D.*)
      - Integrative Neural Systems (Dr. Manabu Tanifuji, *D.Eng.*)
      - Human Brain Dynamics (Dr. Andreas A. Ioannides, *Ph.D.*)
      - Cortical Organization and Systematics (Dr. Kathleen L. Rockland, *Ph.D.*)
    - Communicative Function Research Group*
    - RIKEN-MIT Neuroscience Research Center (Dr. S. Tonegawa, *Ph.D.*)
  - **Protecting the Brain**
    - Developmental Brain Science Group (Dr. K. Mikoshiba, *M.D., Ph.D.*)
      - Developmental Neurobiology (Dr. Katsuhiko Mikoshiba, *M.D., Ph.D.*)
      - Neural Regeneration (Dr. Katsuhiko Mikoshiba, *M.D., Ph.D.*)
      - Developmental Gene Regulation (Dr. Hitoshi Okamoto, *M.D., Ph.D.*)
      - Molecular Neurogenesis (Dr. Tei-ichi Furuichi, *Ph.D.*)
    - Molecular Neuropathology Group (Dr. N. Nukina, *M.D., Ph.D.*)
      - CAG Repeat Diseases (Dr. Nobuyuki Nukina, *M.D., Ph.D.*)
      - Neurogenetics (Dr. Kazuhiro Yamakawa, *Ph.D.*)
      - Motor System Neurodegeneration (Dr. Ryosuke Takahashi, *M.D., Ph.D.*)
      - Neurodegeneration Signal (Dr. Takashi Okamoto, *M.D.*)
    - Aging and Psychiatric Research Group (Dr. M. Ito, *M.D., Ph.D.*)
      - Proteolytic Neuroscience (Dr. Takaomi Saido, *Ph.D.*)
      - Alzheimer's Disease (Dr. Akihiko Takashima, *Ph.D.*)
      - Molecular Psychiatry (Dr. Takeo Yoshikawa, *M.D., Ph.D.*)
      - Molecular Dynamics of Mental Disorders (Dr. Tadafumi Kato, *M.D., Ph.D.*)
    - Recovery Mechanisms Research Group (Dr. K. Mikoshiba, *M.D., Ph.D.*)
      - Cell Recovery Mechanisms (Dr. Masayuki Miura, *Ph.D.*)
  - **Creating the Brain**
    - Brainway Group (Dr. G. Matsumoto, *Ph.D.*)
      - Brain-operative Expression (Dr. Gen Matsumoto, *Ph.D.*)
      - Brain-operative Device (Dr. Michinori Ichikawa, *Ph.D.*)
    - Brain-Style Intelligence Research Group (Dr. S. Amari, *D.Eng.*)
      - Language-Based Intelligent Systems (Dr. Michio Sugeno, *D.Eng.*)
      - Dynamics of Emergent Intelligence (Dr. Yoko Yamaguchi, *Ph.D.*)
      - Behavior and Dynamic Cognition (Dr. Jun Tani, *D.Eng.*)
    - Brain Style Information Systems Research Group (Dr. S. Amari, *D.Eng.*)
      - Mathematical Neuroscience (Dr. Shun-ichi Amari, *D.Eng.*)
      - Visual Neurocomputing (Dr. Shigeru Tanaka, *Ph.D.*)
      - Advanced Brain Signal Processing (Dr. Andrzej Cichocki, *Ph.D.*)
      - Perceptual Dynamics (Dr. Cees V. Leeuwen, *Ph.D.*)
    - Application of Brain Style Systems Research Group*
  - Advanced Technology Development Center (ATDC) (Dr. C. Itakura, *D.V.M., Ph.D.*)
    - Cell Function Dynamics (Dr. Atsushi Miyawaki, *M.D.,Ph.D.*)
    - Neural Architecture (Dr. Tsutomu Hashikawa, *Ph.D.*)
    - Behavioral Genetics (Dr. Shigeyoshi Itohara, *D.V.M., Ph.D.*)
    - Cell Culture Development (Dr. Masaharu Ogawa, *Ph.D.*)
  - Research Resources
  - Information Center
  - Research Planning Section

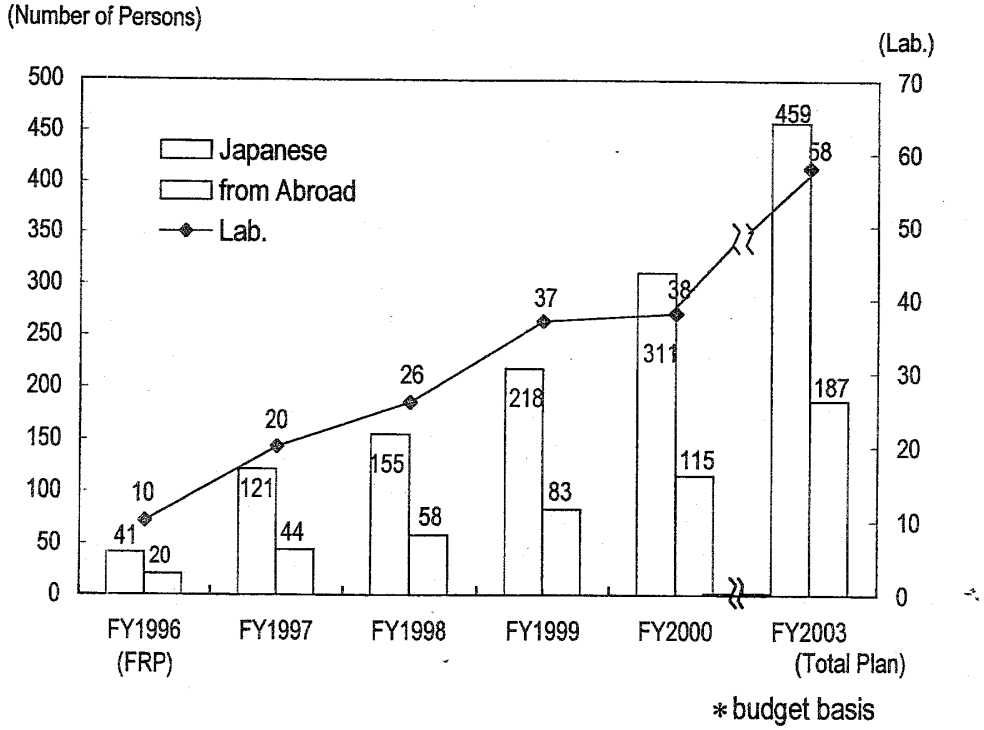
Trend of Brain Science Budget and Researchers

Budget

As of Jan. 2001



Researchers



* budget basis

BSI Researchers by Group

( ) = Foreign Researchers

Group	As of April 1, 2001					
	Scientists	Technical Staff	Total	Fellow	Other	Part-time
Neuronal Function Research	10 (3)	13 (1)	23 (4)	3 (0)	0 (0)	4 (0)
Neuronal Circuit Mechanisms Research	30 (8)	20 (2)	50 (10)	2 (0)	0 (0)	13 (0)
Cognitive Brain Science	23 (10)	12 (8)	35 (18)	1 (0)	4 (3)	4 (2)
RIKEN-MIT Neuroscience Research Center	12 (12)	2 (2)	14 (14)	0 (0)	0 (0)	4 (4)
Developmental Brain Science	38 (1)	21 (0)	59 (1)	12 (1)	6 (0)	10 (0)
Molecular Neuropathology	22 (5)	30 (1)	52 (6)	4 (0)	0 (0)	9 (0)
Aging and Psychiatric Research	18 (2)	26 (1)	44 (3)	5 (0)	0 (0)	16 (1)
Recovery Mechanisms Research	3 (0)	5 (0)	8 (0)	3 (0)	0 (0)	0 (0)
Brainway	16 (4)	8 (1)	24 (5)	1 (0)	0 (0)	13 (2)
Brain-Style Intelligence Research	16 (1)	4 (0)	20 (1)	4 (0)	3 (0)	10 (4)
Brain-Style Infomation Systems Research	23 (9)	9 (5)	32 (14)	12 (0)	0 (0)	21 (5)
Advanced Technology Development Center (ATDC)	34 (3)	10 (0)	44 (3)	4 (0)	0 (0)	51 (3)
Total	245 (58)	160 (21)	405 (79)	51 (4)	13 (3)	155 (21)

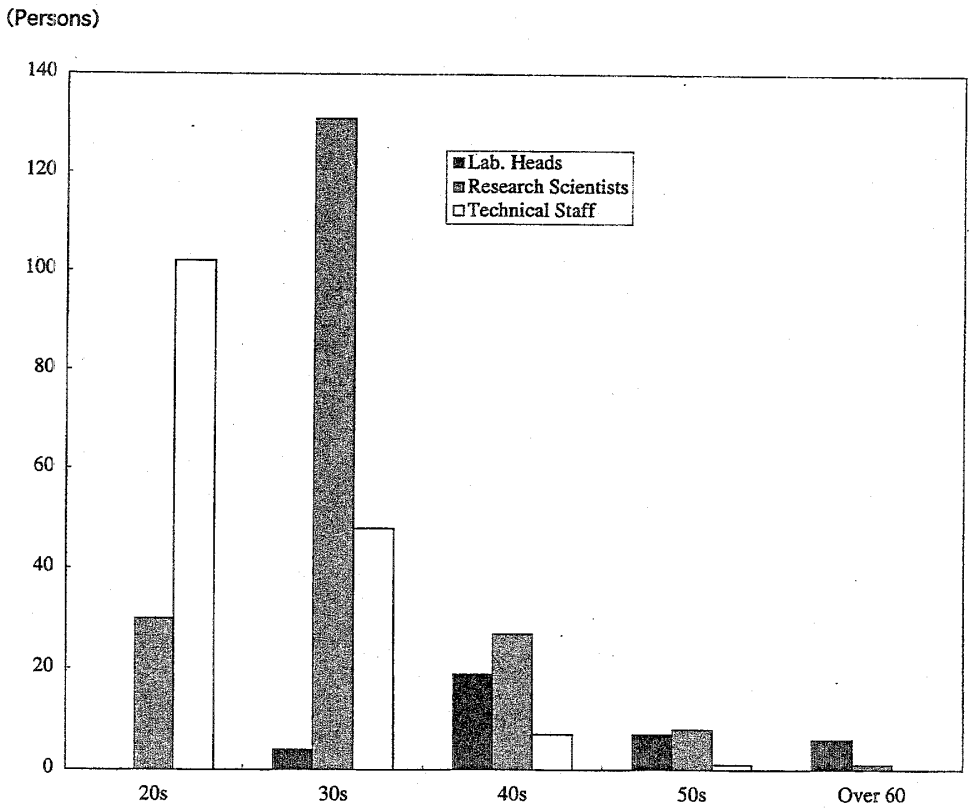
- ( ) number including the corresponding column
- RIKEN Fellow : Special Postdoctoral Researcher, Junior Research Associate
- Other : Sakigake Researcher(JST), CREST(JST)
- Part-time : belongs to organizations outside BSI

Number of Researchers by Age (Wako)

( )=Foreign Researchers

Age \ Position	Lab. Heads	Research Scientists	Technical Staff
20s	0 (0)	28 (2)	93 (9)
30s	3 (1)	104 (27)	42 (6)
40s	17 (2)	21 (6)	3 (4)
50s	4 (3)	4 (4)	1 (0)
Over 60	6 (0)	0 (1)	0 (0)
Total	30 (6)	157 (40)	139 (19)
Average Age	Total 45.1 Japanese 45.0 Foreign 45.7	Total 35.1 Japanese 34.4 Foreign 37.8	Total 29.3 Japanese 29.2 Foreign 30.2

(As of April 1, 2001)



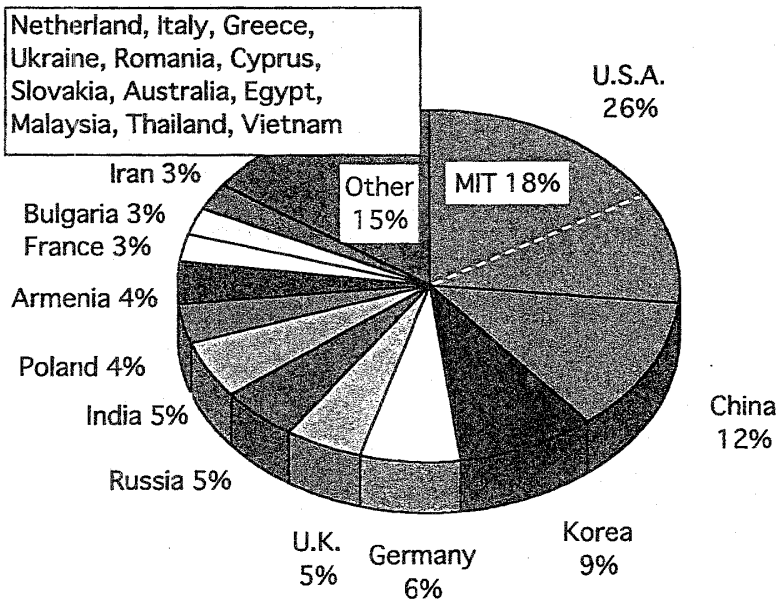
Nationality of BSI Researchers

Country	Number of Persons	Percent
U.S.A. *	21	26%
MIT	14	18%
China	10	12%
Korea	7	9%
Germany	5	6%
U.K.	4	5%
Russia	4	5%
India	4	5%
Poland	3	4%
Armenia	3	4%
France	2	3%
Bulgaria	2	3%
Iran	2	3%
Other	12	15%
Total	79	100%

Joint Laboratories

(As of April 1, 2001)

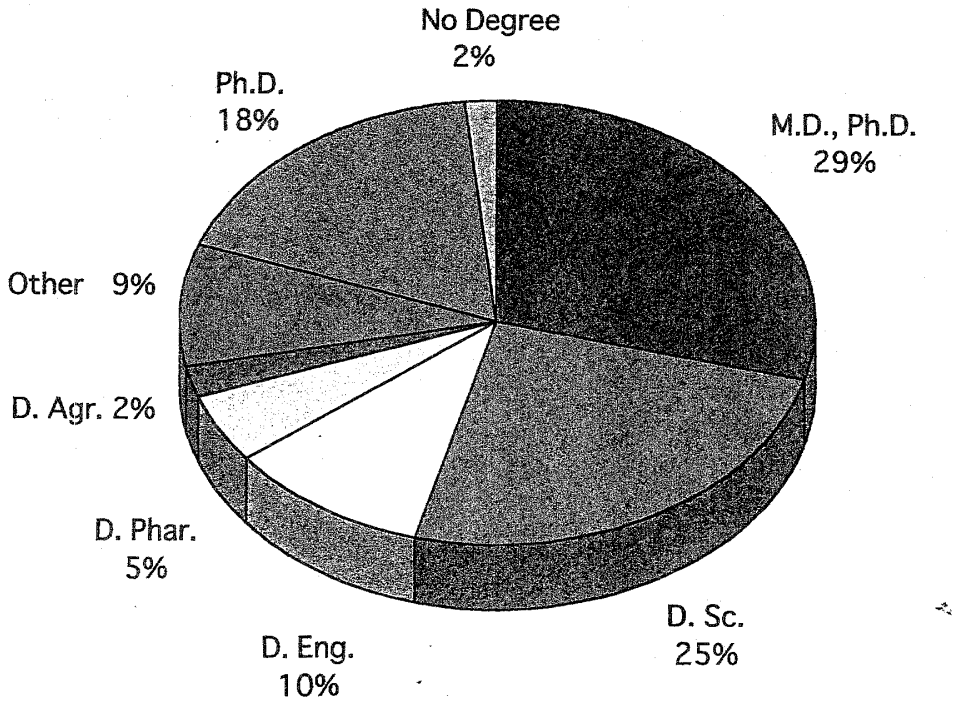
※Includes staff from RIKEN-MIT Neuroscience Research Center



Number of Researchers by Degree (Wako)

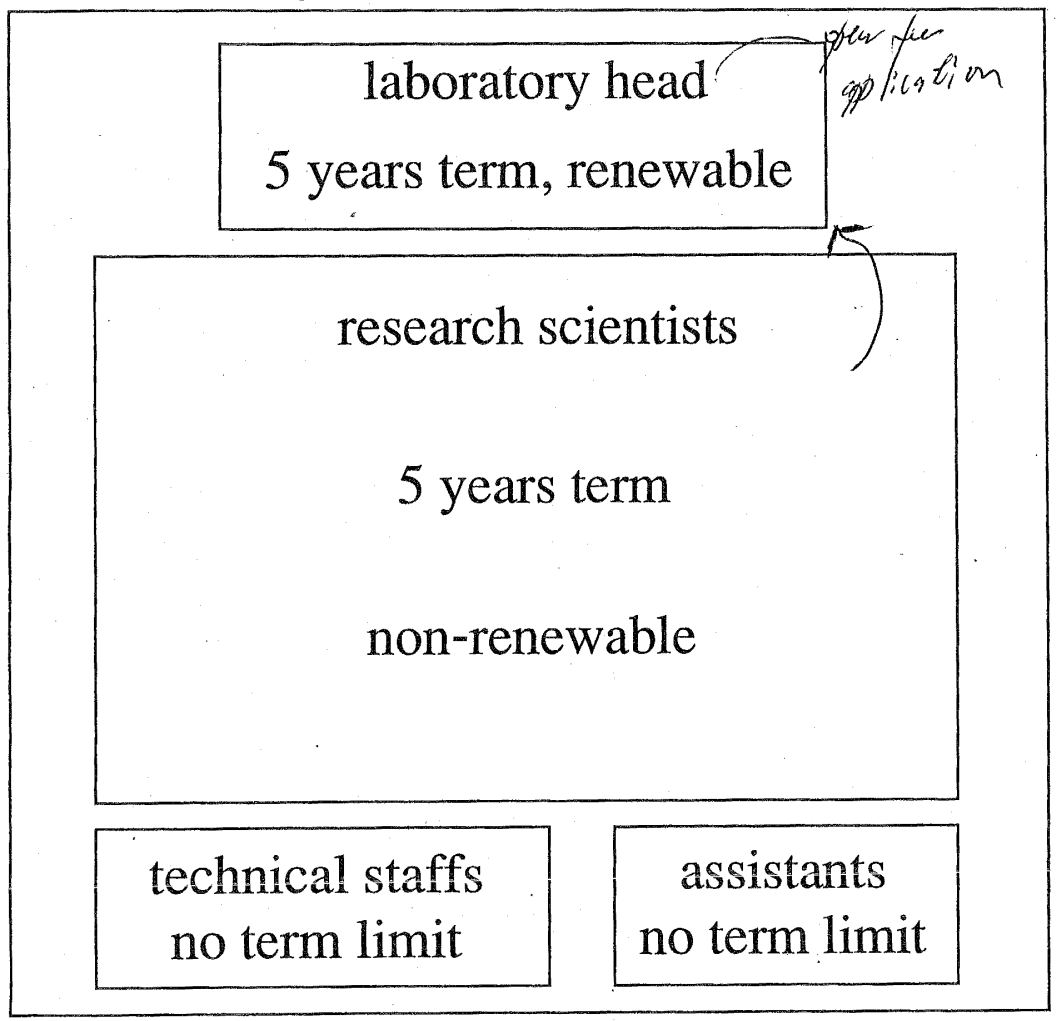
Degree	Researchers	Percent
M.D., Ph.D.	68	29%
D. Sc.	58	25%
D. Eng.	24	10%
D. Phar.	12	5%
D. Agr.	5	2%
Other	21	9%
Ph.D.	41	18%
No Degree	4	2%
Total	233	100%

(As of April 1, 2001)

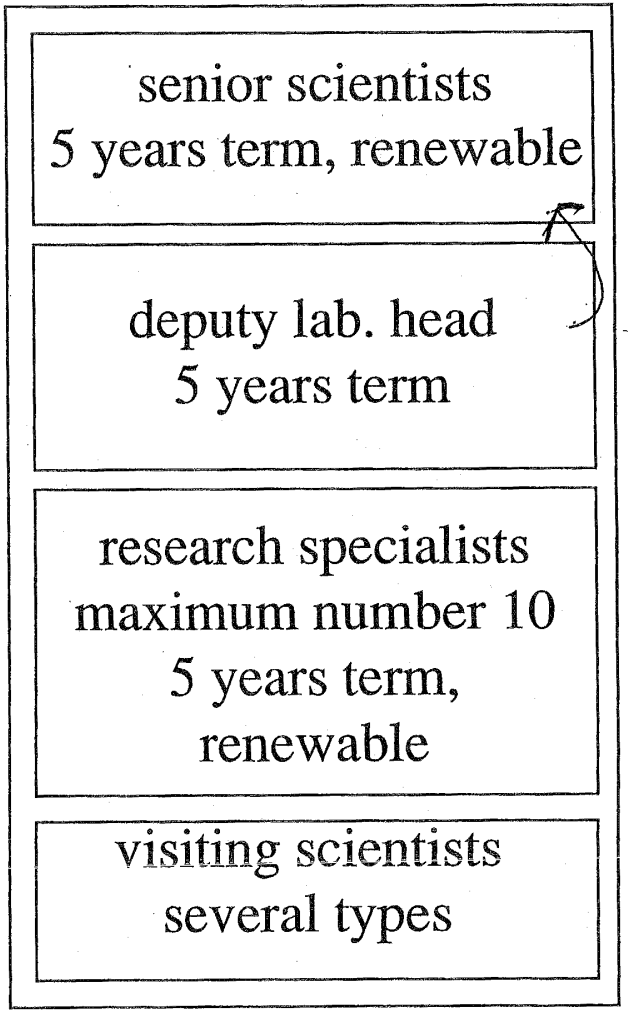


<Status and Term Structure>

standard organization of one laboratory



special research positions



All contract must be renewed every year.

SCIENCE 6 AUGUST 1999

RIKEN Brain Science Institute, JAPAN
Senior Staff Scientists

The Brain Science Institute (BSI), RIKEN, Japan, established October 1997, is seeking four young, highly-motivated researchers with postdoctoral experience for newly created senior staff positions. Research in the Institute is organized under the three headings: "Understanding, Protecting, and Creating the Brain" and applicants are invited to apply if they believe they can contribute an innovative research project leading a small independent research team, to the BSI program. Successful candidates will take up their posts as soon as possible after the fall, 1999.

Contracts are yearly renewable for an initial five year period and may be continued after the first five years if the project is independently judged in Year 4 as worthwhile.

Candidates should reside in Japan for the duration of the research.

Applications in the first instance should be sent to the address below and include:

1. Full curriculum vitae + copies of three papers
2. Names and contact details of three referees
3. A research proposal of about 2000 words

Application deadline: September 20, 1999

Brain Science Institute (RIKEN)
2-1 Hirosawa, Wako-shi
Saitama 351-0198, Japan
Fax: +81-48-462-4914
E-mail: search9@brain.riken.go.jp
http://www.brain.riken.go.jp

SCIENCE 24 FEBRUARY 2000

RIKEN Brain Science Institute
JAPAN

LABORATORY HEAD: RECOVERY CONTROL RESEARCH GROUP

RIKEN Brain Science Institute (RBSI) promotes three strategic research areas: "understanding the brain", "protecting the brain" and "creating the brain". RBSI is currently accepting applications for a laboratory head post in the recovery control research group of the "protecting the brain" area.

The new laboratory will start in 2000 and concentrate on regeneration and repair of the diseased brain by gene and cell therapy, manipulation of ES cells, or transplantation of tissues, and study on the morphological and functional analysis of repairing process.

The laboratory head is required to recruit a team of 5–10 researchers including technicians and will receive generous research support for 5 years. Progress will be assessed every 5 years by international committee. The research arrangement may be renewed if appropriate.

Applicants should send a full curriculum vitae listing all publications and a statement of their research interests and plans (max 2,000 words) plus names, addresses and telephone numbers of three references to:

Search Committee 13, Brain Science Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

Deadline for applications: March 31st 2000

For further information please write to the search committee (Fax: +81-48-467-9744 or e-mail<search13@brain.riken.go.jp>)
http://www.riken.go.jp

(W1991)R

NATURE 2 NOVEMBER 2000

RIKEN BRAIN SCIENCE INSTITUTE, JAPAN

Two Laboratory Heads

Applications invited for two laboratory heads in the Neuronal Function Research Group at BSI (RIKEN)

The Institute of Physical and Chemical Research (RIKEN) established the Brain Science Institute (BSI) in October 1997 to promote three strategic research areas: 'Understanding', 'Protecting' and 'Creating' the brain. The Neuronal Function Research Group is a cornerstone of 'Understanding the Brain'. During the first phase, it has established a unique tradition of research at the interface between cell biology and neuroscience – applying cellular/molecular techniques to elucidate complex neural systems (Olfaction: Drs. Mori, Yoshihara; Cerebellum: Drs. Kano, Yano; Vision: Dr. Hensch).

To promote research in the next five-year term, the Neuronal Function Research Group will establish two new teams with a similar multi-disciplinary perspective in closely related but distinct fields. Candidates interested in pursuing the following areas will be preferred:

(1) Local circuit interactions (e.g. electrophysiology or imaging of neural network activity in slices/cell culture)

(2) Circuits underlying specific behavior (e.g. learning, audition, sleep, critical period plasticity)

A major focus of our work involves gene-targeted animal models, which will serve as a basis for collaboration. More information about the Institute and RIKEN in general can be seen on the web site: http://www.riken.go.jp.

New laboratory heads will be required to organize a team of 5–10 researchers and technical staff and will be provided with full support for 5 years. Progress review by an international review committee occurs every 5 years with the possibility of contract renewal. Applications are encouraged from outside Japan, but researchers must be willing to work at BSI full time. A strong desire for interaction with the 37 teams at BSI is essential. Applicants should send a full CV listing all publications with a statement of research interests and project proposal at BSI (max 2000 words), plus names and addresses of three referees to:

Search Committee (14), Brain Science Institute, RIKEN
2-1 Hirosawa, Wako-shi, Saitama 351-0198, JAPAN

Fax: +81-48-462-4796. e-mail: search14@brain.riken.go.jp

Deadline: March 15, 2001

For further information, please contact the search committee (14)

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Research Collaborations between BSI and Other Institutes

General Cooperative Agreement

	Institute	Date of Signing
	KNIH、KAIST (Korea)	Oct.,1999
	NBRC (India)	Oct.,1999
	UCSF (USA)	May,2000
	L.A. Orbeli Institute of Physiology, National Academy of Sciences of Armenia (Armenia)	Oct.,2000

Research Collaboration

Understanding the Brain Research

BSI Group/Laboratory	Institute	Term(Plan)
Neurobilogy of Synapse	Graduate School of Faculty of Medicine, University of Tokyo	Apr.,2001 ~ Mar.,2003 (2 years)
Neuronal Circuit Mechanisms Research	Toyohashi University of Technology	Dec.,2000 ~ Nov.,2002 (2 years)
Neurobiology of Emotion	Basic Research Laboratories, TORAY Inc.	Apr.,2000 ~ Mar.,2002 (2 years)
Neurobiology of Emotion	Tokyo Institute of Psychiatry	Nov.,2000 ~ Oct.,2002 (2 years)
Cognitive Brain Mapping	University of Shaheed Beheshti Medical Science, Iran	Sep.,2000 ~ Aug.,2002 (2 years)

Protecting the Brain Research

BSI Group/Laboratory	Institute	Term(Plan)
Developmental Brain Science Group	Case Western Reserve University, USA	Oct.,2000 ~ Sep.,2003 (3 years)
Developmental Neurobiology	Tokyo Metropolitan Institute of Gerontology	Apr.,1999 ~ Mar.,2002 (3 years)
Developmental Neurobiology	Eisai Co., Ltd.	Nov.,2000 ~ Mar.,2002 (1 year and 5 months)
CAG Repeat Diseases	Graduate School of Faculty of Medicine, University of Tokyo	July,1999 ~ Mar.,2002 (2 years and 9 months)
CAG Repeat Diseases	Nippon Laser & Electronics Lab.	Oct.,1999 ~ Sep.,2001 (2 years)
Neurogenetics	UCLA, USA	Dec.,1999 ~ Dec.,2002 (3 years)
Neurogenetics	Medical Research Institute, Tokyo Medical and Dental University	Sep.,1999 ~ May,2001 (1 year and 9 months)
Neurogenetics	Institute for Genetic Medicine, Hokkaido University	Feb.,2000 ~ Nov.,2002 (2 years and 10 months)
Proteolytic Neuroscience	Graduate School of Pharmaceutical Sciences, Tokyo University	June,1999 ~ Mar.,2002 (2 years and 10 months)
Proteolytic Neuroscience	Mitsubishi-Tokyo Pharmaceuticals, Inc.	Apr.,2001 ~ Dec.,2002 (1 year and 9 months)

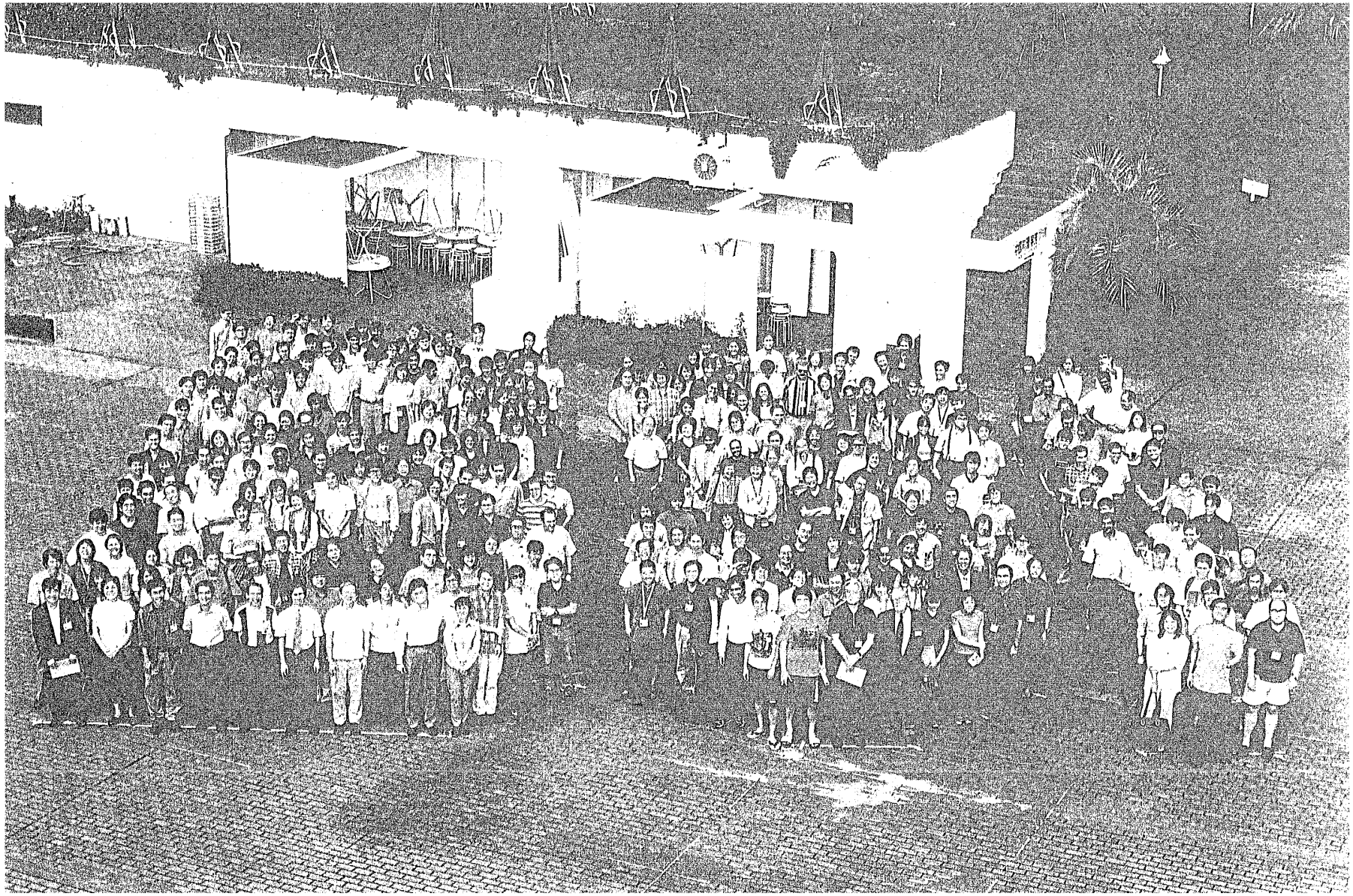
Creating the Brain Research

BSI Group/Laboratory	Institute	Term(Plan)
Brainway Group	Toyama Medical and Pharmaceutical University	Apr.,1999 ~ Mar.,2002 (3 years)
Brainway Group	Electrotechnical Laboratory, AIST, METI	Apr.,1998 ~ Mar.,2002 (4 years)
Brain-operative Expression	Honda R & D Co., Ltd.	Dec.,1997 ~ Mar.,2002 (4 years and 4 months)
Brain-operative Expression	Ehime University	Oct.,1999 ~ Mar.,2002 (2 years and 6 months)
Brain-operative Expression	Honda R & D Co., Ltd.	Feb.,2000 ~ Mar.,2002 (2 years and 2 months)
Brain-operative Device	Honda R & D Co., Ltd.	Aug.,1998 ~ Mar.,2002 (3 years and 8 months)
Brain-operative Device	Stanley Electric Co., Ltd.	July,1999 ~ Mar.,2002 (2 years and 9 months)
Brain-operative Device	Brain Vision Inc.	Apr.,1999 ~ Mar.,2002 (2 years)
Language-Based System	Doushisha University	Apr.,2001 ~ Mar.,2003 (2 years)

Advanced Technology Development Center

BSI Group/Laboratory	Institute	Term(Plan)
Cell Function Dynamics	Olympus Optical Co., Ltd.	Oct.,1999 ~ Mar.,2002 (2 years and 6 months)
Cell Function Dynamics	Medical & Biological Laboratories Co., Ltd.	Apr.,2001 ~ Mar.,2003 (2 years)
Neural Architecture	Medical Research Institute, Tokyo Medical and Dental University	Nov.,1999 ~ Mar.,2002 (2 years and 5 months)
Behavioral Genetics	Graduate School Agricultural and Life Sciences, University of Tokyo	Nov.,2000 ~ Mar.,2002 (1 year and 5 months)

As of April 1, 2001



INTERNSHIP (PLAN A)
June 28 - August 24, 2001

Summer interns will work in BSI laboratories for two months and participate in research activities of the host laboratories. Interns will make an oral presentation at the end of the course.

Laboratories at RIKEN BSI

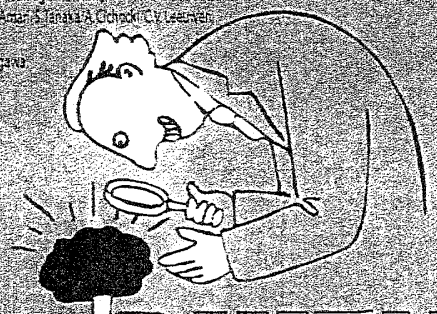
Neuronal Function Research Group [T.K. Hensch, K. Yoshii, I. Ichinohara, R. Yanai]
Neuronal Circuit Mechanisms Research Group [M. Mishina, T. Knöpfel]
Cognitive Brain Science Group [K. Tanaka, M. Tanifuji, A. Iriki, S. Kobatake, K.S. Rockland]
Developmental Brain Science Group [K. Mikoshiba, K. Kaibuchi, H. Okamoto, T. Furuichi]
Molecular Neuropathology Group [N. Nukina, K. Yamakawa, H. Takahashi, T. Okamoto]
Aging and Psychiatric Research Group [T. Ookido, A. Takashima, T. Yoshikawa, T. Kato]
Recovery Mechanisms Research Group [M. Mori]
Brainway Group [G. Matsumoto, M. Michikawa]
Brain-Style Intelligence Research Group [M. Sugeno, Y. Yamaguchi, J. Tani]
Brain-Style Information Systems Research Group [S. Amari, S. Tanaka, A. Cichocki, C.v. Leeuwen]
Advanced Technology Development Center
[C. Takahara, A. Miyawaki, T. Hashikawa, S. Itohara, M. Ogawa]

LECTURE COURSE (PLAN B)
"Brain Dysfunctions: Molecular and Cellular Bases"
June 28 - July 6, 2001

The purpose of the course is to present basic concepts as well as cutting edge research that will promote the understanding of neurological and psychiatric disorders at multiple levels including molecular, cellular and systems. The lectures will be given in special reference to the basic mechanisms regulating the normal function and development of the nervous systems. Individual lecturers will provide the basis of their field and advanced topics.

Lecturers

William C. Mobley (Stanford University)
Jürg Nüsslein-Volhard (Harvard Medical School)
Don W. Cleveland (University of California San Diego)
Masashi Yanagisawa (University of Texas Southwestern)
Kenneth S. Kosik (Harvard Medical School)
Peter H. St George-Hyslop (University of Toronto)
Nobuyuki Nukina (RIKEN)
Shoji Tsuji (Niigata University)
Pasko Rakic (Yale University School of Medicine)
Nobutaka Hirokawa (University of Tokyo)
Takeshi Yagi (Osaka University)
Katsuhiko Mikoshiba (RIKEN/University of Tokyo)
Hideyuki Okano (Osaka University)
Derek van der Kooy (University of Toronto)
Toru Nishikawa (Tokyo Medical and Dental University)
Ulrike Heberlein (University of California San Francisco)
Martin C. Raff (University College London)



RIKEN Brain Science Institute Summer Program 2001

The Brain Science Institute (BSI) at RIKEN is offering a summer program to train advanced students interested in brain function.
Applicants may choose either a laboratory internship for two months with one of the 37 laboratories at BSI, or participate in an intensive 9 day lecture course featuring a distinguished international faculty.
Summer Interns (Plan A) also can enroll in the Lecture Course (Plan B).
Generous support towards travel and lodging expenses will be provided.
Deadline : February 26, 2001

Application forms : visit our web site http://summer.brain.riken.go.jp/
or send inquiries to Summer Program Organizing Committee, BSI, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, JAPAN
E-mail : info@summer.brain.riken.go.jp Fax : +81-48-462-4914

Brain Science Institute RIKEN

RIKEN BSI Summer Program 2000

1. Theme: How the Brain Works: Theoretical and Experimental Approaches

2. Application: via BSI web site
   - Access to Web site: 6000 hits
   - Plan A applications: 90
   - Plan B applications: 250

3. Participants:

Internship (Plan A):	17	July 4 - Sep. 1 (2 months)
Lecture Course (Plan B):	30	July 4 - 15 (2 weeks)

(Sweden)
Karolinska Institute

(Finland)
Abo Academi Univ., Helsinki Univ. of Tech.

(Canada)
Memorial University of Newfoundland(Canada)

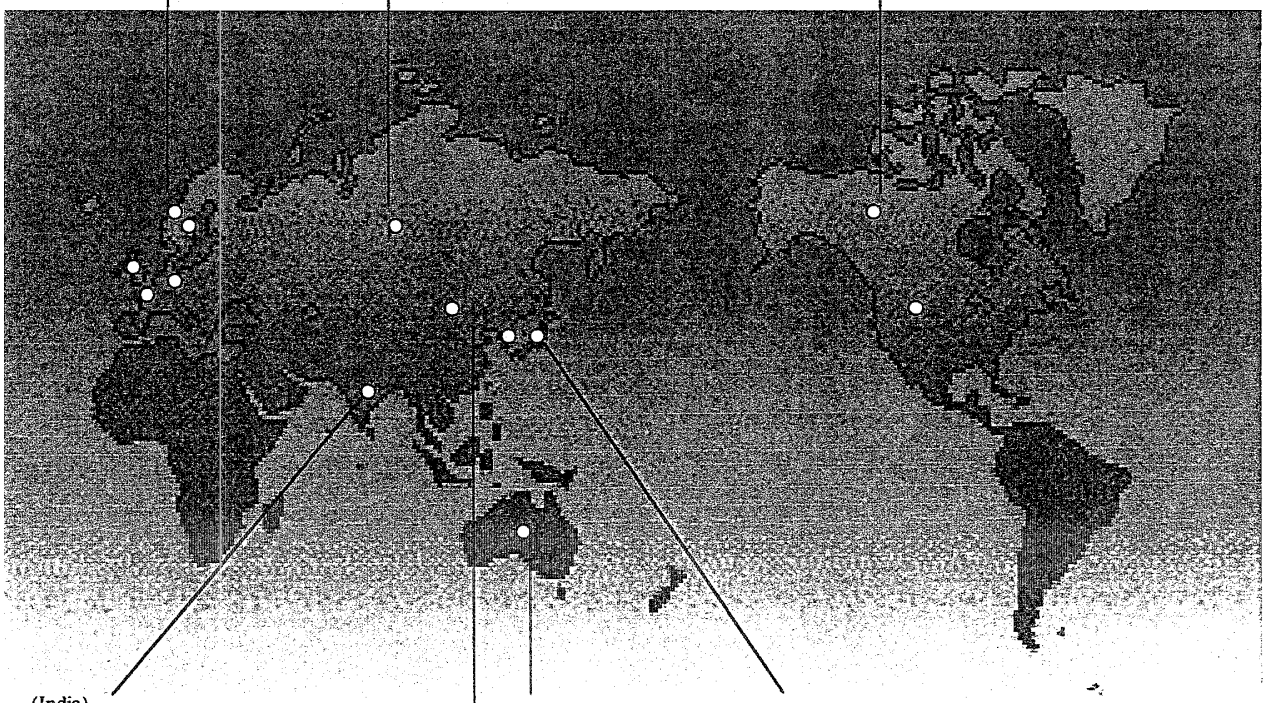
(UK)
Aston Univ., Institute of Neurology, Univ. of Bradford, Univ. of Cambridge, Univ. College London, Univ. of Paisley, Univ. of Sussex

(USA)
Albany Medical College Northwestern Univ., Beth Israel Deaconess Medical Center, Dartmouth Medical School, MIT, Mass. General Hospital/Harvard Medical School, Rockefeller Univ., Stanford Univ., UC Berkeley, Univ. of Michigan, Univ. of Minnesota, Univ. of Notre Dame, Wake Forest Univ., Yale Univ.

(France)
CNRS

Germany)
Ruhr-Univ.t Bochum

(Russia)
Russian Academy of Sciences



(India)
Centre for biochemical technology, NIMHANS

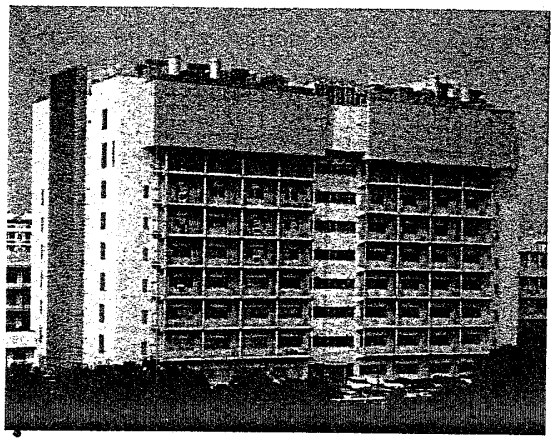
(Australia)
Brain Sciences Institute

(China)
Chineses Academy of Sciences, Fudan Univ.

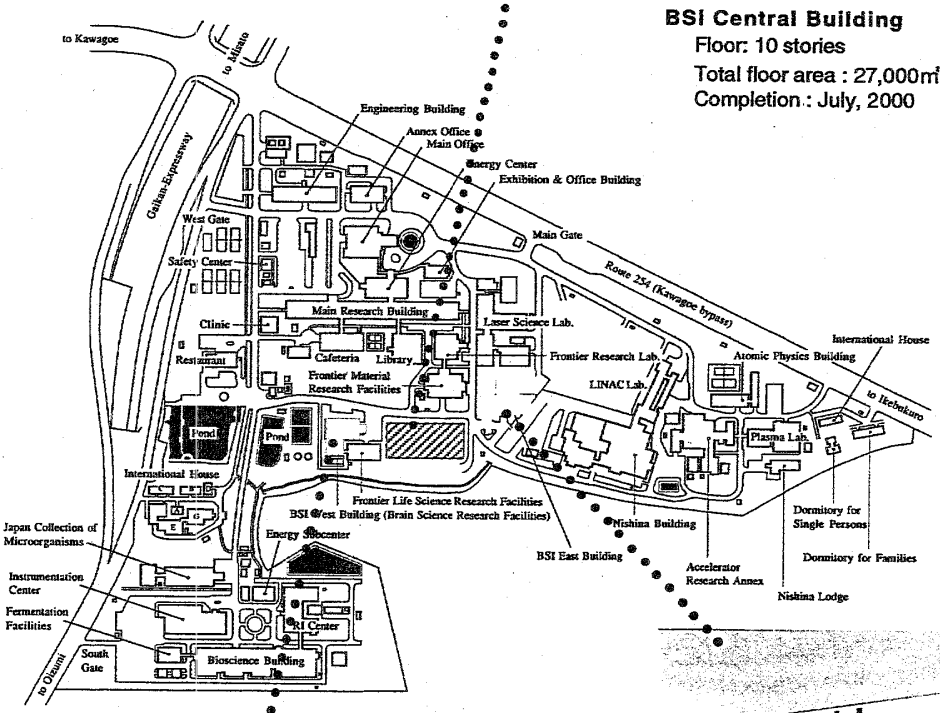
(South Korea)

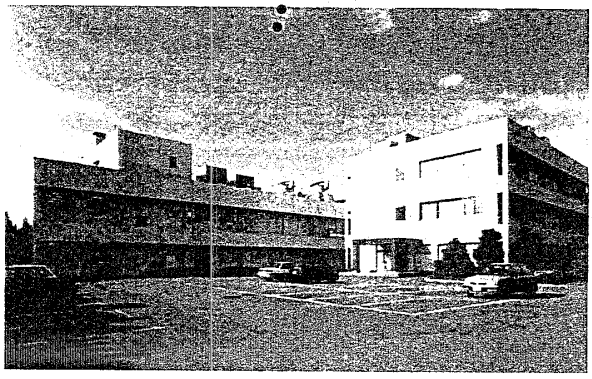
(Japan)
Chiba Univ., Electrotechnical Lab., Kyoto Univ., Japan Science and Technology Corporation, Nagasaki Univ., National Institute of Bioscience and Human-Technology, Univ. of Tokyo

The Brain Science Institute Facilities

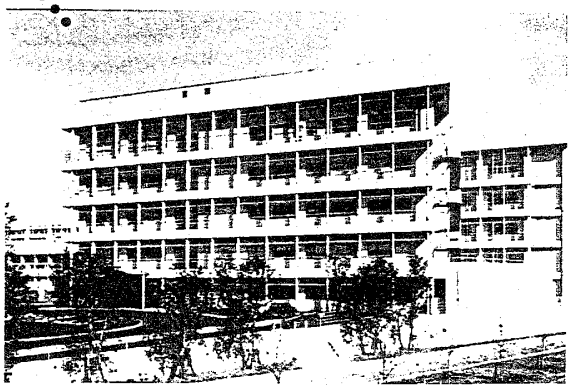


BSI Central Building
Floor: 10 stories
Total floor area : 27,000㎡
Completion : July, 2000





BSI West Building
Floor : 3 stories
Total floor area : 2,541㎡
Completion : June, 1991



BSI East Building
Floor : 6 stories
Total floor area : 8,909㎡
Completion : August, 1997

BSI Laboratories

Discovering the depths of
the world within

Brain Science Institute

RIKEN

Understanding the Brain

President of RIKEN

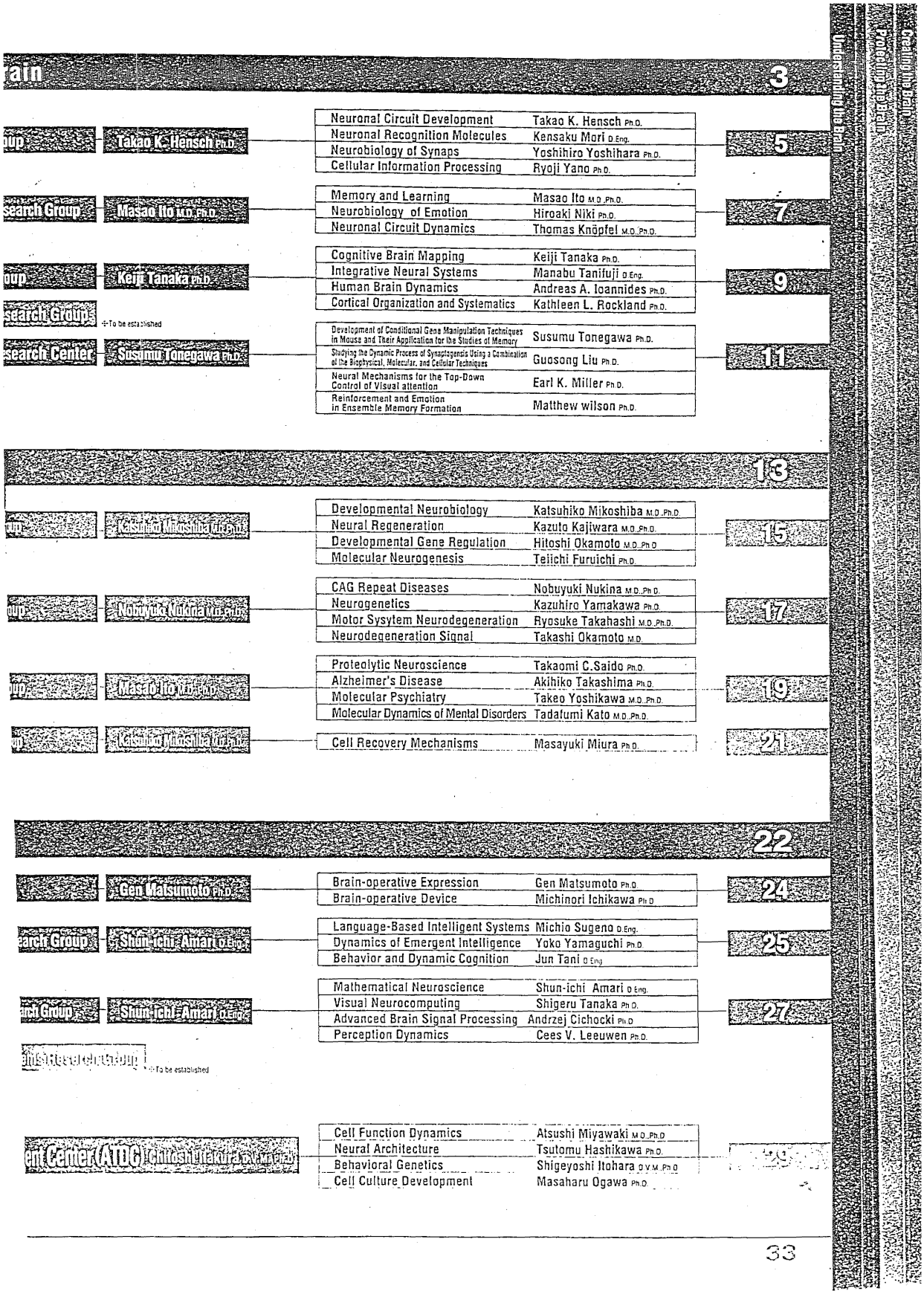
Dr.Shun-ichi Kobayashi Ph.D.

Director of RIKEN Brain Science Institute

Dr.Masao Ito M.D.,Ph.D.

The Brain Science Institute (BSI), which is part of RIKEN (the Institute of Physical and Chemical Research), was established in October 1997 with the aim of encouraging creative progress in brain science in the 21st century. Building on more than ten years of valuable experience gained from the Frontier Research Program Study (FRS), BSI has been able to continue in RIKEN's 80 years traditional of brilliance. The goals of BSI are to stretch human understanding and respond to society's needs by conducting the latest and most technologically advanced research related to the three key areas of "Understanding, Protecting and Creating the brain". The new Central Building for research at BSI has been completed and various laboratories and equipment are already in full service with young and motivated scientists from all over the globe conducting some of the world's most advanced research.

This brain science research deals with issues related to the roots of our human experience, making it one of the most critical and fundamental fields of study. And even though new research continually sheds lights on the inner workings of the brain, we still find ourselves at the starting line. It is a point from which we hope to make giant steps forward. To that end, we will actively promote the most ambitious, adventurous and flexible research programs possible.


Takao K. Hensch Ph.D.
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Takao K. Hensch Ph.D.
Neuronal Recognition Molecules
Kensaku Mori D.Eng.
Neurobiology of Synaps
Yoshihiro Yoshihara Ph.D.
Cellular Information Processing
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Cognitive Brain Mapping
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Integrative Neural Systems
Manabu Tanifuji D.Eng.
Human Brain Dynamics
Andreas A. Ioannides Ph.D.
Cortical Organization and Systematics
Kathleen L. Rockland Ph.D.
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Susumu Tonegawa Ph.D.
Studying the Dynamic Process of Synaptogensis Using a Combination of the Biophysical, Molecular, and Cellular Techniques
Guosong Liu Ph.D.
Neural Mechanisms for the Top-Down Control of Visual attention
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Tsutomu Hashikawa Ph.D.
Behavioral Genetics
Shigeyoshi Itohara D.V.M.,Ph.D.
Cell Culture Development
Masaharu Ogawa Ph.D.

What does it mean to be human?

Understanding the Brain

Understanding begins by elucidating basic brain mechanisms

Here, new discoveries about brain functions and information processing principles unique to the brain are in progress. In addition, new technologies for brain science research are being established. What defines humans will gradually become clear in the future as we further probe brain structure and activity. We are aiming for an understanding of higher level cognitive functions, including memory, recognition, thought, language, and decision-making.

Neuronal Function Research Group

The brain is an organ of considerable size, consisting of more than 100 billion neurons. In this research group, these basic building blocks, neurons and their synaptic connections, are being characterized. Research is conducted at the interface between cell biology and neuroscience-applying cellular/molecular techniques to elucidate complex neural systems. The successful control of synaptic plasticity and tracing of connections from specific cell types has already been achieved.

Group Director: **Takao K.Hensch** Ph.D.

Neuronal Circuit Mechanism Research Group

A neural network in which numerous neurons are connected expresses memory and learning functions. In this research group, the expression mechanisms of the functions of neural networks as well as the relationship between the structure of a neural network and its functions are being studied. Thus far, a complex chemical signal transmission process in the neural circuit in the cerebellum during the learning of motion has been identified.

Group Director: **Masao Ito** M.D., Ph.D.

Cognitive Brain Science Research

High-level functions such as recognition and thinking emerge in the cortical area, which is created by the integration of neuronal networks, and the large-scale system, which is composed of multiple cortical areas and subcortical sites. In this research group, the relationship between the structure and functions in cortical areas and large-scale systems are being studied using combinations of functional magnetic resonance imaging (fMRI), magnetic encephalography (MEG) , optical imaging, single-cell recordings and morphological tracer method. Thus far, the principle underlying visual pattern sorting recognition has been successfully determined.

Group Director: **Keiji Tanaka** Ph.D.

RIKEN-MIT Neuroscience Research Center

The research collaboration between the RIKEN Brain Science Institute and the MIT Center for Learning and Memory enables further study of the mechanisms of learning and memory. Our research group focuses on the role of the cerebellum, the cerebral cortex, and the hippocampus in learning and memory, and on the function of each of these structure as part of brain's entire memory mechanisms.

Group Director: **Susumu Tonegawa** Ph.D.

Neuronal Function Research Group

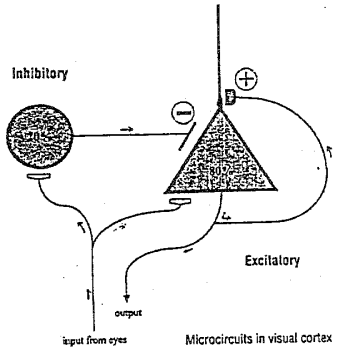
Lab.head
Takao K.Hensch
Ph.D.

Neuronal Circuit Development

Connections in the brain are shaped by experience. Our laboratory is focused on the functional and structural refinements of the developing visual system. The primary function of thalamic afferents to visual cortex is the transmission of incoming sensory signals. In early life, visual experience drives a competition between inputs serving the two eyes to sculpt the basic organization found in the adult. However, the cellular and molecular bases of this activity-dependent plasticity remain unknown. Furthermore, thalamocortical interactions underlie the generation of behavioral states. Since appropriate maturation of the neocortex is governed by activity, internally-generated rhythms which accompany Rapid-Eye Movement (REM) or non-REM sleep may be an important form of input independent of vision. To understand the cellular and molecular mechanisms in cortical circuit development, our approach is to assay pharmacological blockade or the gene-targeted deletion of candidate plasticity proteins using a mouse model. Moreover, selective disruptions of behavioral states are elucidating the interplay of visual experience-dependent plasticity with endogenous sleep rhythms emerging along the same circuits.

Research interests:

(1) Molecular Mechanisms of Visual Cortical Plasticity
(2) Thalamocortical Interactions in Visual Cortical Development
(3) Visual Cortical Plasticity and Developing Sleep States



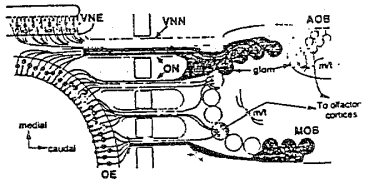
Microcircuits in visual cortex

Lab.head
Kensaku Mori
D.eng.

Neuronal Recognition Molecules

The functional properties of the nervous system depend on sophisticated neuronal networks that are constructed during development and show plastic modifications during higher brain functions, such as learning and memory. Development includes axonal and dendritic elongation, axonal guidance, and very importantly, adhesive interactions between axonal growth cones and soma-dendritic membranes of target neurons, interactions that give rise to the formation of synaptic connections. The plastic modifications include morphological changes of presynaptic axon terminals and postsynaptic dendritic structures that accompany the long-term change in synaptic transmission.

The main task of the Laboratory for Neuronal Recognition Molecules is to identify neuronal recognition (adhesion) molecules that are involved in the formation and plastic modification of synaptic connections. This research is currently focusing on the telencephalon-specific membrane glycoprotein, telencephalin, and a novel cell adhesion molecule OCAM that is involved in guiding olfactory axons to their target zones in the olfactory bulb. We are also studying functions of central olfactory nervous system which includes the olfactory bulb and the olfactory cortex.

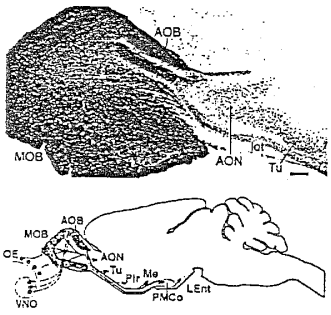


Zonal organization of olfactly system

Lab.head
Yoshihiro Yoshihara
Ph.D.

Neurobiology of Synapse

Information transfer between neurons takes place at the synapse. The wiring patterns among various types of neurons via specific synaptic connections are the basis of functional logic employed by the brain for information processing. Thus, detailed knowledge of neuronal networks is essential for understanding a wide range of brain functions. We developed an effective method for analyzing the neuronal connectivity patterns by delivering a tracer selectively to specific types of neurons while simultaneously trans-synaptically labeling their axonal target neurons using a novel genetic approach. This method combines a neuroanatomical tracing method with genetic engineering technology. A plant lectin (wheat germ agglutinin: WGA) cDNA was introduced as a transgene and expressed by restricted types of neurons under the control of specific promoter elements. We have succeeded in visualizing the mouse olfactory, visual, and cerebellar efferent pathways using the WGA transgene. This technique will be applied to various neural systems to visualize and characterize selective and functional neuronal pathways in various animal species, and to elucidate brain structures and their functions. We are also studying the structures, expressions, and functions of cell recognition/adhesion molecules at synapses in both the developing and the mature brain.

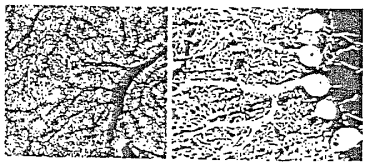


Mouse olfactory pathways visualized with WGA transgene.

Lab.head
Ryoji Yano
Ph.D.

Cellular Information Processing

In the brain, neurons are connected together and construct neural networks to express higher functions, such as learning, memory, cognition and so forth. Information processing of the network is determined by the properties of the signal transmission between neurons and the signal-transduction process inside them. In neurons, many kinds of molecules are highly organized to form molecular machinery that determines the cellular structure and properties of the inter- and intracellular signal-transduction process. Our research focuses on determining the molecular mechanisms underlying the organization and interaction of the molecular components inside neurons that realize neuronal functions in the brain. To meet this research goal, we are focusing in particular on the molecular mechanisms of synaptic formation and the signal transduction involved in it. At synapses, neurons are connected to each other to transmit information, thus, synapses are important functional domain structures for information processing in neural circuits. We are attempting to answer several questions: How are molecular components, receptors, channels, kinases and so on localized at the precise site? How does the organization of these components change according to neuronal activities? By answering these questions, we are attempting to reveal the molecular mechanisms underlying the higher functions of the brain.



Cerebellar Purkinje cells and their synapses

Neuronal Circuit Mechanisms Research Group

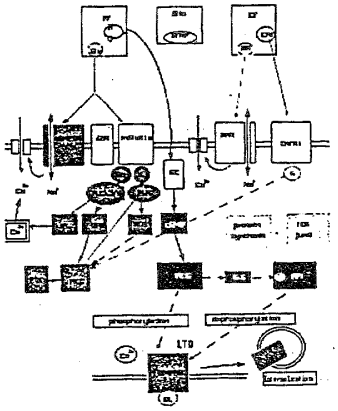
Lab.head

Ito Masao

M.D.,Ph.D.

Memory and Learning

The brain's superb memory and learning capabilities are generated based on the process of synaptic plasticity. Synaptic plasticity is the experience-dependent persistent modification of synaptic transmission efficacy, in the front of either an increase (long-term potentiation, LTP) or a decrease (long-term depression, LTD). The cerebellum exhibits characteristic LTD. It is the learning principle of the cerebellum that if some action, such as a movement, deviates from that initially intended, the neuronal circuitry of the cerebellum is rewired during exercise until the errors are minimized by LTD induction. In this laboratory, we aim at elucidating mechanisms of LTD at the cellular and molecular levels, mainly using electrophysiological, biochemical, molecular-biological and genetic approaches. Thus far, complex chemical signal transduction processes have been revealed to underlie the LTD induction and to involve glutamate receptors, nitric oxide, cyclic GMP, protein kinases and phosphatases, corticotropin-releasing hormone (CRF), immediate early genes and a rapidly turned over protein. Our goal is to reveal the process that converts LTD to permanent memory traces in the cerebellum.



Signal Trancediction in Ltd.

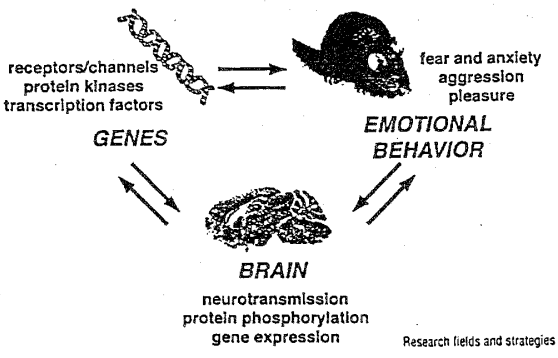
Lab.head

Hiroaki Niki

Ph.D.

Neurobiology of Emotion

Understanding the brain mechanisms involved in emotions is an important topic in brain research. In order to understand these mechanisms we must employ a variety of methods, such as molecular, biochemical, neurophysiological and behavioral techniques. We investigate the behavioral phenotypes of knockout and transgenic mice along with their neurochemical and neurophysiological correlates. We also examine molecular mechanisms of fear conditioning and positive emotion (pleasure) using mice as subjects.



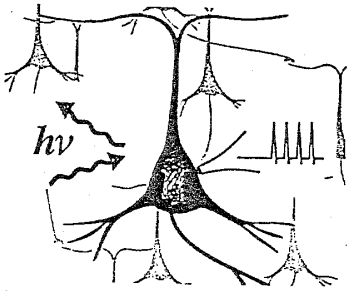
Research fields and strategies

Lab.head
Thomas Knöpfel
M.D.,Ph.D.

Neuronal Circuit Dynamics

Information processing in the brain involves electrical and chemical signals which are spatially confined at the subcellular level and which occur at the time scale of milliseconds. While changes of membrane voltage and concentrations of various intracellular signaling chemicals are well characterized at the level of single cells, much less experimental data are available on the electrical and chemical signaling of multiple interacting neurons. To bridge the gap between our understanding of signals in single neurons and of network theories, we need to monitor the dynamics of membrane voltage and chemical signals in neuronal circuits at many sites simultaneously and with high temporal resolution. With this viewpoint, we are developing and applying innovative optical imaging techniques based on environmental-sensitive fluorescent probes. Membrane voltage, ion concentrations or second messenger levels modulate the optical properties of such probes. Furthermore, some of these probes can be genetically encoded and targeted to specific neuronal compartments. We apply these techniques in the cerebellar and cerebral cortex in order to understand the principles of the spatio-temporal information flow and its use-dependent modifications in these brain structures.

Please check our laboratory homepage at http://neurodynamics.brain.riken.go.jp for more details.



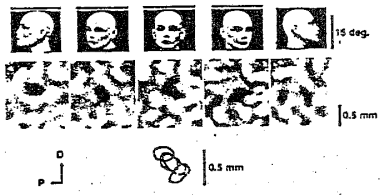
Artistic illustration of our idea to use optical recordings in neuronal networks

Cognitive Brain Science Group

Lab.head
Keiji Tanaka
Ph.D.

Cognitive Brain Mapping

The cerebral cortex is well developed in the mammal, and in particular its association regions have developed in the primate to support the variety and flexibility of the primate behavior. The association areas in the parietal and temporal lobes store the internal models which interpret and conceptualize the external world. The frontal association areas draw the concepts from the parietal and temporal association areas to working memory, and perform operations using these concepts to infer causal relationships between the past events and the present situation, assess possible action plans, and conduct more pure thinking. With an aim to elucidate the mechanisms of these higher functions, we investigate the functional division among various association cortical areas, interactions between the different areas, and functional architectures in individual areas. Half of researchers in our laboratory are now involved in single-cell recordings from non-human primates trained to perform various behavioral tasks. We have revealed, for example, that the stimulus selectivity of cells in the inferotemporal cortex can be changed even in the adult by a long-term shape discrimination training. The other half of researchers are involved in measuring the neural activity of normal human subjects using fMRI at 4T. We have succeeded in imaging the ocular dominance column in the human primary visual cortex.



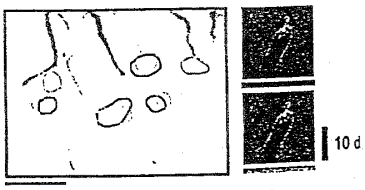
Continuous map of the face view in the inferotemporal cortex: the activation spot systematically moved as the face rotates.

Lab.head
Manabu Tanifuji
D.Eng.

Integrative Neural Systems

When we perceive a visual image of an object in the external world, the brain constructs a representation which mediates recognition. The ultimate goal of our research is to understand the framework of such representations, the neural mechanisms by which they are constructed, and the processes which accomplish recognition based on such representations. In order to achieve this goal, we are investigating the structure and function of the primate visual association cortices. In particular, we are focusing on the inferotemporal area TE. This area is the final, purely visual stage of the occipitotemporal pathway, which is thought to be essential for the recognition of objects based on their visual images. In addition, this area has strong connections with the medial temporal structures essential for the formation of recognition memory.

Single neurons in area TE respond optimally to moderately complex visual features. Because none of the visual features are specific enough, it requires the combined activation of multiple neurons to generate the representation of a particular object in area TE. Because it is essential to investigate the spatial as well as the temporal patterns of neural activity, we are using intrinsic signal imaging and multicellular recording techniques. We are also developing imaging techniques with improved spatial and temporal resolutions.

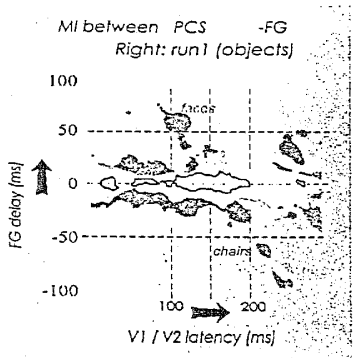


Changes in activation pattern in area TE by manipulating visual stimuli.

Lab.head
Andreas A. Ioannides
Ph.D.

Human Brain Dynamics

Accumulating evidence suggests that a unified percept is formed by bringing together the output from specialised brain areas. How precisely segregation and integration of brain function is organised is uncertain, but it must involve the recruitment of regions separated a few millimeters to centimeters interacting for a few milliseconds to seconds. Magnetoencephalography (MEG) is a completely non-invasive technique which is ideally suited for these spatial and temporal scales. Our laboratory uses MEG together with other imaging methods to explore human brain function. We have developed MEG analysis tools to study interactions between areas from unaveraged data and their relationship to stimulus properties, the subject's state and behaviour. These tools are applied to the non-invasive exploration of human brain processes that support perception, higher cognitive functions, learning and the experience and recognition of emotions. We have already demonstrated that the segregation and integration of brain function is expressed in time as well as space.



The mutual information landscape between visual areas (V1/V2) and the fusiform gyrus (FG) in an object recognition task. Faces are processed first, fast and automatically.

ab.head
'athleen S. Rockland
h.D.

Cortical Organization and Systematics

Cerebral cortex is composed of multiple areas and their interconnections. These areas are closely implicated in complex functions, and their inactivation often results in debilitating deficits. As a simplification, cortical connections may be described as point-to-point relays between pairs of structures. In actuality, however, the organization is considerably more complicated, with multiple levels of convergence and divergence, and separable but interlocking networks of neurons. This laboratory is investigating connectional patterns and interactions in several visual and auditory association areas. We adopt a systems-anatomical approach, using multiple techniques. One major emphasis is to make small injections of tracer substances in physiologically identified regions in experimental animals. Immediate goals are to determine how connections interact and what are the quantitative parameters and relationships, such as the numbers of neurons contributing to a given connectional system, the divergence pattern of single axons, and the convergence of different connections at the level of single neurons and columns. Feedback, feedforward, intrinsic, and thalamocortical connections are investigated. Results address structural-functional correlations; provide a baseline for interpreting changes during development or aging; and interface with neuroinformatics and imaging studies in humans.

Ocular dominance columns (black and white) are optically imaged, and then aligned 1) with segments of axons (shown as colored lines), labeled by tracer injection and 2) with the pattern of surface cortical blood vessels. Anatomically labeled axon terminations are shown in the inset box (Lt.Tanifuji and Rockland).

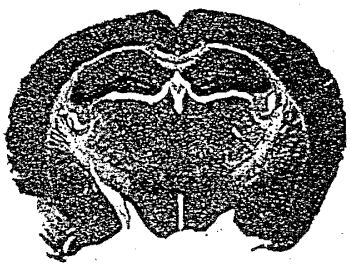
RIKEN-MIT Neuroscience Research Center

Lab.head
Susumu Tonegawa
Ph.D.

Development of Conditional Gene Manipulation Techniques in Mouse and Their Application for the Studies of Memory

Our research focuses on the molecular, cellular, and neuronal ensemble mechanisms underlying learning and memory and associated cognitive functions of rodents

Since an animal's cognitive functions such as learning and memory is manifested only as its behaviors, it is essential to utilize an experimental methodology with which the behavior of a whole live animal can be monitored and yet the underlying mechanisms can be deduced. For this purpose we have been developing the "second generation" gene knockout and transgenic technologies, in which deletion or overexpression of a specific gene is restricted to a certain area or cell type in the brain and/or to a certain period of the animal's life. For instance, we have generated a new strain of mouse in which the NMDA-type glutamate receptor is specifically knocked out in the CA1 pyramidal cells of the hippocampus. Analyses of these mutant mice have shown that the function of a single protein (i.e., NMDA receptor) in a single type of neuron plays a crucial role in the acquisition of memory

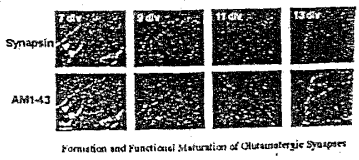


Gene targeting for hippocampus CA3 and dentate gyrus

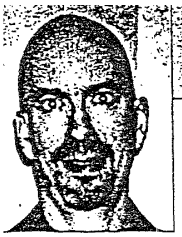
Lab.head
Guosong Liu
Ph.D.

Studying the Dynamic Process of Synaptogensis Using Combination of the Biophysical, Molecular, and Cellular Techniques

In the cerebral cortex and the hippocampus, excitatory synaptic neurotransmission is mediated mainly by glutamatergic synapses. These synapses undergo changes in strength depending upon paired presynaptic and postsynaptic activity, which has long been predicted to underlie associative learning. Activity-dependent formation and elimination of these synapses have been linked to long-term synaptic plasticity, which may underlie long-term memory. Clearly, better understanding of the factors determining the strength of glutamatergic synapses, their plasticity, and their formation and elimination, will bring us closer to understanding the cellular basis of learning and memory. The specific questions that we are exploring include: 1) How does synaptic activity regulate the strength of connections at single synapses in the central nervous system? 2) How are newly-formed silent synapses transformed into mature functional synapses? 3) What signals and molecules are involved in synapse formation and maturation? We address these questions using a combination of the biophysical, molecular, and cell biology techniques.



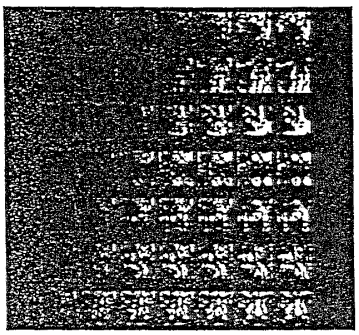
Formation and Functional Maturation of Glutamatergic Synapses



Neural Mechanisms for the Top-Down Control of Visual attention

Lab.head
Earl. Miller
Ph.D.

Research interests of the Miller Lab center around the neural mechanisms needed for voluntary, goal-directed, behavior. Much effort is directed at the prefrontal cortex, a brain region associated with the highest levels of cognition. We explore prefrontal function largely by combining a sophisticated behavioral methodology with techniques for examining the activity of ensembles of neurons in behaving monkeys. Our results have shown that prefrontal neurons have complex properties expected for the brain's "executive". They are involved in directing attention, in recalling stored memories, and they piece together the diverse information needed for a common behavioral goal. Perhaps most importantly, they transmit acquired knowledge. Their activity reflects the learned associations between cues, actions, and consequences that describe the contingencies of a given task. In short, they seem to underlie our internal representations of the "rules of the game." This may provide a foundation for the complex behavior of primates, in whom this structure is most elaborate.



Receptive field plots of prefrontal neurons to preferred and non-preferred objects. Blue indicates the neuron's baseline level of activity, red indicates the neuron's maximum activity.

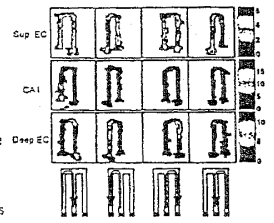
Reinforcement and Emotion in Ensemble Memory Formation

Lab.head
Matthew Wilson
Ph.D.

Research in the Wilson laboratory focuses on the study of the formation and maintenance of memories within the hippocampus and neocortex using a combination of molecular genetic, electrophysiological, pharmacological, behavioral, and computational approaches with particular emphasis on techniques that allow the simultaneous activity of ensembles of hundreds of single neurons to be examined in freely behaving animals.

These studies have led to the exploration of the nature of sleep and its role in memory. Recent findings have identified explicit correlates of dreaming during periods of REM sleep allowing examination of dream content as it relates to memory. Experiments involving simultaneous monitoring of areas in the hippocampus and neocortex demonstrated coordinated activity between the hippocampus and the prefrontal cortex during both awake and sleep states. Recordings in the entorhinal cortex, which provides input and receives output from the hippocampus, revealed responses dependent upon future behavioral trajectory as well as reflecting generalization across tasks and environments. Combining the measurement of neuronal activity with manipulation of molecular genetic targets has allowed the study of how specific cellular mechanisms regulate neural function to produce learning and memory at the behavioral level.

Taken together, these approaches contribute to the overall research objective: to understand the link from cellular/subcellular mechanisms of plasticity, to neural ensemble representations and interactions, to learning, memory, behavior, and cognition.



Firing rate maps for representative neurons in the superficial/ deep entorhinal cortex and hippocampus

Can humans escape from diseases and aging?

Protecting the Brain

The academic study of brain protection
Searching for ways to overcome brain agi
and nervous or mental diseases

In this study, the functions of brain cells and biochemical mechanisms of information transmission are being investigated. If the causes of nervous or mental diseases and brain aging are clarified, aggressive treatments or preventive measures can be developed based on new knowledge. In the academic study of brain protection, in order to characterize and eliminate nervous or mental diseases which are attracting public concern, such as Alzheimer's disease, the acquisition of basic knowledge that contributes to the development of treatments or preventive measures based on new knowledge is pursued.

Group Director: **Katsuhiko Mikoshiba** M.D., Ph.D.

Developmental Brain Science group

It is extremely important to understand developmental brain formation processes because they will provide fundamental information for the treatment of brain disease and disorders. In this research group, research related to the clarification of brain development/differentiation mechanisms is being conducted. Thus far, genes important for brain formation processes have been identified.

Group Director: **Nobuyuki Nukina** M.D., Ph.D.

Molecular Neuropathology Group

Determining the cause of brain and neurological diseases and curing them are very difficult. To clarify the pathomechanism of those diseases and to develop the treatment of them are important. In this research group, research related to the identification of genes responsible to brain and neurological diseases and analysis of their functions is conducted. Thus far, the gene products responsible for certain type of neurological diseases have been identified and the abnormality of their functions has been clarified.

Group Director: **Masao Ito** M.D., Ph.D.

Aging and Psychiatric Research Group

Senile dementia and neurological diseases such as Alzheimer's disease are important issues to be resolved in our aging society. In this research group, factors related to the onset mechanism of Alzheimer's disease and factors related to the onset of schizophrenia are being studied. Thus far, the decomposition process of substances considered to be causes of Alzheimer's disease has been clarified.

Group Director: **Katsuhiko Mikoshiba** M.D., Ph.D.

Recovery Mechanisms Research Group

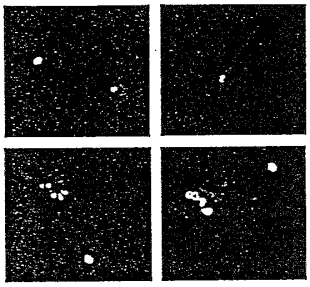
The reason why brain damage results in serious conditions is related to the fact that damage to neural cells is not easily repaired, neural cells are not easily restored or regenerated. This research group conducts research on the differentiation of neuronal system cells, which is the basic requirement for neural cell repair processes, and the mechanism of the death of neural cells or neuronal stem cells.

Molecular Neuropathology Group

Lab.head
Nobuyuki Nukina
M.D.,Ph.D.

CAG repeat diseases

The genes responsible for hereditary neurological diseases have been identified for the past 10 years. However, we still do not know the pathomechanism of these diseases yet and as a rsult we have been unable to develop appropriate therapy for them. Thus, we have been studying CAG repeat diseases as a model for investigating disease pathomechanism and developing a suitable therapy. CAG repeat diseases are linked to the abnormal expansion of the CAG repeat within the coding regions of disease genes and include SBMA, Huntington disease, SCA1, DRPLA, Machado-Joseph disease and so on. Although the symptoms of CAG repeat diseases vary, they share common features such as that expansion of the CAG repeat is related to the onset of the disease, and that the expanded CAG repeat is translated into a polyglutamine stretch, which forms nuclear inclusions. It is also believed that they might share a common pathomechanism with conformational diseases such as Alzheimer disease, Parkinson disease and prion disease in which abnormal proteins accumulate. Thus, a common pathomechanism and appropriate therapy can be discovered for all CAG repeat diseases and hopefully for all conformational diseases. We have now established molecular, cellular and animal models for CAG repeat diseases and are currently investigating them and searching for ways to prevent neuronal cell death.

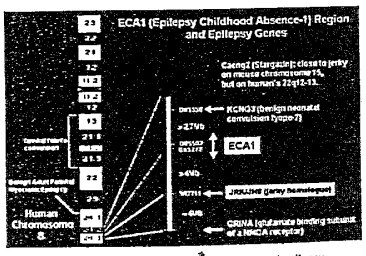


Nuclear and cytoplasmic inclusions
Neuroblastoma cells were transfected with huntingtin exon 1-GFP construct. They show nuclear and cytoplasmic inclusions.

Lab.head
Kazuhiro Yamakawa
Ph.D

Neurogenetics

The Human Genome project is now almost finished, and results of this project will accelerate the identification and characterization of disease genes. We in the laboratory for neurogenetics, focus our effort on identifying and characterizing genes responsible for neurological diseases including epilepsy and mental retardation. The objectives of the epilepsy project include identification of genes such as those responsible for jeuvenile myoclonus epilepsy on 6p11, and childhood absence epilepsy on 8q24. We are also characterizing functions of identified genes including Lafora's-type progressive myoclonus epilepsy gene, EPM2A, by methods including the mouse model analysis. The project on mental retardation includes studies of the Down syndrome (DS) and Rett syndrome. DS is the most common genetic mental retardation caused by trisomy 21. We are analyzing a gene on chromosome21 encoding a neural cell adhesion molecule, DSCAM as a candidate gene responsible for the mental retardation phenotype of DS. These studies will lead not only to the accurate diagnosis, treatment and cure of neurological diseases, but will also contribute to the understanding of molecular mechanisms of fundamental brain functions such as memory, cognition and personality formation.



Candidate region for childhood absence epilepsy and epilepsy-related genes on the long arm of human chromosome 8.

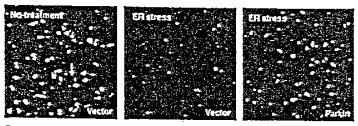
Lab.head
Ryosuke Takahashi
M.D.,Ph.D.

Motor Sysytem Neurodegeneration

Amyotrophic lateral sclerosis (ALS) and Parkinson's disease are among the most common moter-system-associated neurodegenerative diseases that affect elderly people and our main research goal is to elucidate the pathogenic mechanisms of these two devastating disorders.

We are currently focusing our attention on *superoxide dismutase 1 (SOD1)* and *Parkin*, which are genes responsible for familial ALS of autosomal dominant trait and autosomal recessive juvenile parkinsonism (AR-JP), respectively. Although a mutated SOD1 protein or deletion of the *Parkin* gene causes motor-system-selective neuronal death, the underlying mechanisms are yet to be elucidated. We have recently discovered that Parkin is an E3 ubiquitin ligase and suppresses endoplasmic reticulum (ER) stress-induced cell death via its E3 activity. We are also interested in the possibility of using anti-cell death genes to treat neurodegenerative diseases.

Given that the apoptotic machinery is essential to neurodegenerative processes, apoptosis inhibitors are promising candidates for use in the gene therapy of neurodegenerative diseases such as ALS. We are examining if the X-chromosome-linked inhibitor of apoptosis protein (XIAP) could block neurodegenerative processes involving SOD1 mutation by generating XIAP-overexpressing transgenic mice.



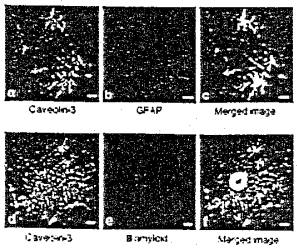
Deletion of the *Parkin* gene causes autosomal recessive juvenile parkinsonism (AR-JP). Parkin is an E3 ubiquitin ligase and, when overexpressed, suppresses endoplasmic reticulum (ER) stress-induced death of human SH-SY5Y neuroblastoma cells.

Lab.head
Takashi Okamoto
M.D.

Neurodegeneration Signal

Alzheimer's disease (AD) is a leading disease that causes dementia in the elderly. The elucidation of its pathogenesis and the development of a disease-specific therapeutic approach are urgent issues of public health worldwide. Familial AD provides an excellent clue to elucidating its precise pathogenesis, since mutations of single genes always give rise to disease manifestations. The gene encoding the amyloid precursor protein (APP) is one of the causative genes. APP is the source of beta amyloid peptide, which is a major component of senile plaques, one of the hallmark pathological changes in the AD brain. The mechanism whereby beta amyloid peptide is produced from APP has been the central topic of the AD research in the last decade. Our recent effort has contributed to the progress of AD research by providing multiple lines of evidence that caveolin serves as a positive regulator of the enzymatic processing of APP. Caveolin is the chief structural protein of the caveola or the raft, which is a membrane microdomain and is mainly composed of cholesterol and glycosphingolipid. Caveolin is involved in intracellular cholesterol metabolism. In brain, apolipoprotein E (ApoE) plays a major regulatory role in cholesterol homeostasis. One of its isoforms, ApoE4, is a genetic risk factor of Alzheimer's disease. Our studies will focus on elucidating the molecular pathogenesis of AD from the standpoint of cholesterol metabolism that involves caveolin, caveolaeor raft and Apo E.

Immunohistochemistry of brain sections from Alzheimer 's disease patient

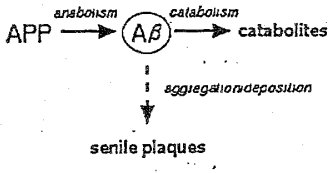


Aging and Phyciatric Research Group

Lab.head
Takaomi C. Saido
Ph.D.

Proteolytic Neuroscience

Proteolytic reactions often play critical roles in both physiological and pathological circumstances because of their irreversible nature. However, their actual in vivo functions particularly in neuronal systems are not yet well understood. Among various aspects of protease involvement in neuropathophysiology, we aim to elucidate the mechanisms by which the life span of proteins in brain is determined. Our primary target is amyloid β peptide (Aβ), the cortical deposition of which is closely associated with development of Alzheimer's disease. Under physiological conditions, Aβ is constantly produced from its precursor and is immediately catabolized; however dysmetabolism of Aβ seems to lead to its pathological deposition upon aging. Therefore, it is important to understand both the physiological and pathological catabolic pathways of Aβ for the purpose of conquering the disease that represents brain aging in more general terms. We have successfully established a novel experimental paradigm of such pathways and the knowledge obtained thereby is being utilized not only for understanding but also for controlling brain aging.

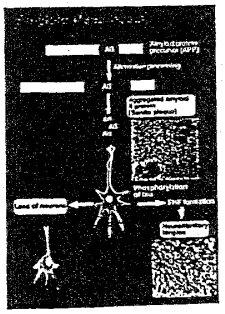


Metabolism and deposition of amyloid β peptide (Aβ). Amyloid β peptide (Aβ) is constantly produced from the amyloid precursor protein (APP) and immediately catabolized under physiological situations. Dysmetabolism of Aβ causes its pathological deposition, triggering the cascade that lead to disease development.

Lab.head
Akihiko Takashima
Ph.D.

Alzheimer's Disease

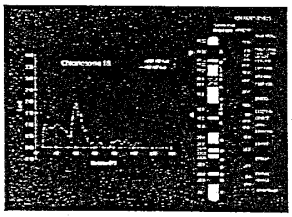
Alzheimer's disease (AD) is one of the most devastating brain diseases of middle-aged and elderly people in the world. The disease is pathologically characterized by a loss of neurons, accumulation of ß-amyloid (Aß) in senile plaques and abnormally phosphorylated tau in neurofibrillary tangles (NFTs), neuropil threads and plaque-associated neurites. The loss of neurons is proportional to the degree of dementia of AD patients. Therefore, the mechanism of neuron loss in the AD brain can provide a useful theory for defining diagnostic criteria and monitoring the progression of therapies in this disease. Currently, genetic studies of familial AD have revealed the causative genes. From those results, the ß-amyloid hypothesis, which claims that the accumulation of ß-amyloid is the cause of AD, has been proposed, and strategic prevention and therapies have been worked out following this hypothesis. Since NFTs are generally observed in neurodegenerative disorders with dementia, the formation of NFTs is considered a common mechanism of neuronal loss in neurological disorders, while their presence is thought to be a marker for aging brains. In our laboratory, we are focusing on the mechanisms of NFT formation and attempting to clarify the mechanisms of neuronal death in aging brains with AD. Our achievement should contribute to the development of effective therapies not only for AD but also for other neurological disorders related to brain aging.



Molecular Psychiatry

ab.head
Takeo Yoshikawa
t.D.,Ph.D.

Schizophrenia and mood disorders are severe mental illnesses with complex genetic characteristics and unknown etiologies. Multiple genes that exert weak to moderate effects and undefined environmental factors are believed to contribute to overall susceptibility to these diseases. To date, large-scale linkage analyses have been conducted, and results revealed several chromosomal loci with replication. However, these loci are yet to be narrowed down to regions of positionally clonable sizes. On the other hand, recent progress in the Human Genome Project has rendered the analyses of large genomic area feasible. Our strategies to identify susceptibility genes responsible for functional psychoses include the linkage disequilibrium mapping approach for narrowing in the linkage regions and approaches to determine subsequent positional efforts, in parallel with intensive characterization of candidate genes. In addition, we also aim to identify of genes controlling animal behaviors by quantitative trait loci mapping and microarray-based expression profile analysis to obtain clues to better understand human behavioral pathologies relevant to psychiatric illenesses.



Linkage analysis of bipolar disorder on chromosome 18, and the physical map of 18p11.2, a candidate susceptibility region

Molecular Dynamics of Mental Disorders

b.head
adafumi Kato
D.,Ph.D.

The goal of this team is to clarify the molecular basis of two major mental disorders, which are bipolar disorder and schizophrenia, using cultured cells, autopsied brains, and other specimens. Bipolar disorder is thought to be caused by altered sensitivity of intracellular signal transduction systems to neurotransmitters such as serotonin. In this study, molecular mechanisms of alteration of this pathway are examined by measuring of intracellular calcium response, analyzing mitochondrial functions, examining of gene expressions using DNA microarrays, and by cloning genes disrupted by chromosomal balanced translocations associated with this disorder. Using these strategies, mood-regulating molecules will be identified and new methods for diagnosis and treatment of bipolar disorder will be developed. Schizophrenia is caused by disrupted development of the neural network constituting ego, that is localized to the hippocampus - nucleus accumbens - prefrontal lobes, due to interaction between environmental insults such as perinatal complications and virus infections, and genetic vulnerability to these insults. In this project, this interaction between gene and environment will be clarified.

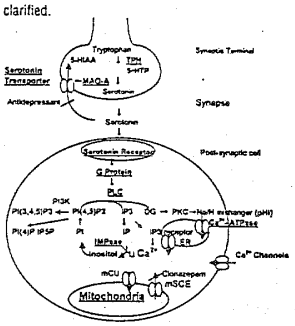


Figure. Intracellular phosphatidylinositol - calcium signaling system linked to serotonin receptors.

Recovery Mechanism Research Group

Lab.head

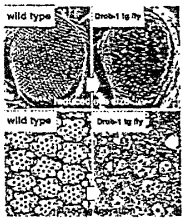
Masayuki Miura

Ph.D.

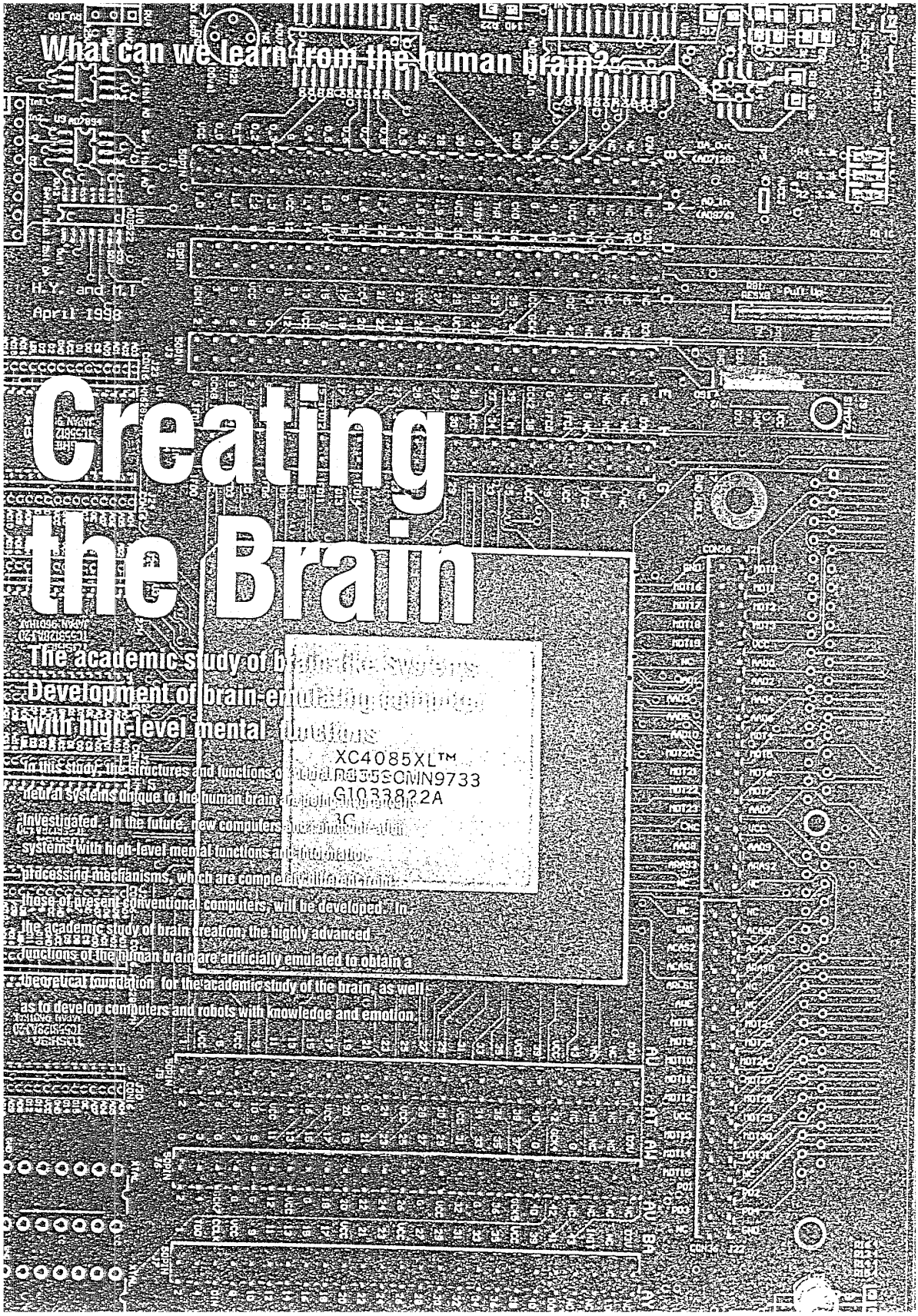
Cell Recovery Mechanisms

Programmed cell death is an important mechanism underlying the development of the nervous system. During the early stage of development, cell death is essential for normal neural closure. Cell death in the ventricular zone plays a role in regulating the size of the progenitor pool. In the later stage of development, cell death regulates the number of postmitotic neurons to match the size of their targets. In addition to these developmental cell death, massive cell death in specific regions of the brain are observed in various neurodegenerative diseases. We are interested in the evolutionarily conserved mechanisms of programmed cell death in the nervous system, and we believe that common mechanisms are involved in cell death during the development of the nervous system and of neurodegenerative diseases. By using the power of genetics, we are studying basic mechanisms of neural cell death in Drosophila as well as in mammals. Based on the studies of basic cell death mechanisms, we are attempting to manipulate cell death during neural development and neurodegeneration. Through these approaches, we hope to determine the biological roles of neural cell death during neural development, and develop strategies to treat neurodegenerative diseases.

In Drosophila, the size of the larval brain of a homozygous mutant with caspase activator Dapaf-1 is larger than that of the wild type, and the number of dead cells in the brain is reduced in this mutant. Dead cells can be visualized as green spots by staining with acridine orange.



Ectopic expression of the proapoptotic member of the Bcl-2 family, Drob-1, in the compound eyes of Drosophila causes neurodegeneration.


What can we learn from the human brain?
H.Y. and M.I
April 1998
Creating
the Brain
The academic study of b
Development of brain-em
with high-level mental
In this study, the structures and functions o
neural systems unique to the human brain
investigated. In the future, new computers
systems with high-level mental functions a
processing mechanisms, which are comple
those of present conventional computers, will be developed. In
the academic study of brain creation, the highly advanced
functions of the human brain are artificially emulated to obtain a
theoretical foundation for the academic study of the brain as well
as to develop computers and robots with knowledge and emotion.
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G1033822A

Group Director: **Gen Matsumoto** Ph.D.

Brainway Group

The brain differs from a conventional computer in that the brain can develop information-processing algorithms in a self-organized fashion. In this research group, elucidation of the brain concept such as its objective, its operation and structurization principles, leading to development of devices which will enable an engineering realization of the conceptual brain are being attempted. Thus far, a neuron chip in which 1000 neuron-simulated elements are all mutually connected has been developed.

Group Director: **Shun-ichi Amari** D.Eng.

Brain-Style Intelligence Research Group

In the brain, various functions such as recognition, memory and thinking are distributed in different locations, and the functions are integrated such that a total information function is realized. In this research group, the underlying principle of these functions and their realization are being attempted in terms of engineering and theoretical perspectives.

Group Director: **Shun-ichi Amari** D.Eng.

Brain Style Information Systems Research Group

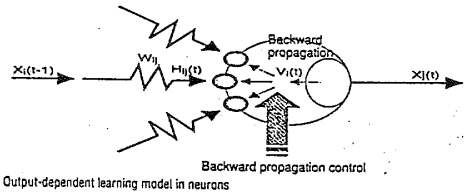
The theoretical analysis of the information-processing principle of the brain is expected to be beneficial to the application of new information-processing systems such as brain-type computers and IT-based technologies. In this research group, the information-processing principle of the brain in terms of mathematical theory and information theory is being analyzed, and theoretical models of brain functions are being developed. Furthermore, a study which combines theory and experiments is being conducted and the development of a new processing method for brain signals is being attempted.

Brainway Group

Lab.head
Gen Matsumoto
Ph.D.

Brain-operative Expression

Our stage to elucidate how the brain (neurons) can develop by itself involves understanding the brain processes by multiple approaches of molecular biology, biochemistry, electrophysiology and photophysiology, ethology, and biophysics. For this research purpose, we study brains including those of rats, mice, squid and chicks. The brain is an open information system; it interprets the meanings of and conceptualizes multi-models and large numbers of input signals by outputting as for information. The brain develops a mechanism (algorithm) of its specific task and establishes this mechanism. In other words, learning is developed in an output-dependent manner at every level of the brain structure of a single neuron, neuronal networks and the brain as a whole. Based on this premise, we perform research, experimentally and theoretically in order to clarify the neuronal networks with respect to the intuition. We also conduct research to study the role of emotion how it governs to control the process of learning and memory for algorithm acquisition. Our research efforts will focus on elucidating the wonder how the brain can self-organize its algorithm and resulting in developing an engineering expression for a model of the brain.

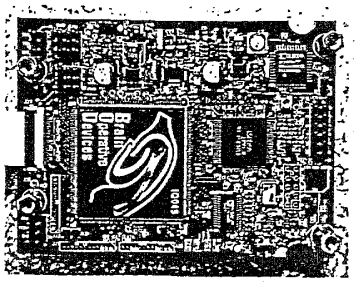


Output-dependent learning model in neurons

Lab.head
Michinori Ichikawa
Ph.D.

Brain-operative Device

Our ultimate goal is to create a brain computer which mimic human intelligence. We are investigating both brain-learning mechanism and related technologies using electronic devices. To accomplish the first aim, we are developing novel measurement methods such as a fast CCD camera system and a super-multiple electrode system. These real-time multi-site recording methods eneble us to study the functional modification of local neural circuitry in rat hippocampal slices. The results could provide ideas of computational bases of brain learning mechanisms. Secondly, we are attempting to create actual leaning computer systems to implement intelligence on a autonomous model helicopter, a lane tracking model car and a small robot with a mental map. Through the building of small systems, we can develop a large scale brain computer constructively. The collaboration of biology and technology inspires each other to design unique biological experiments and electronic circuitry. A brain computer is as yet a dream right now, however we are confident that our efforts put it into practice in the near future. We are returning a part of our research results through a venture bossiness company, BrainVision Inc. , as leading apparatus.



A brain computer board being developed with an image processing.

Brain-Style Intelligence Research Group

Lab.head
Michio Sugeno
D.Eng.

Language-Based Intelligent Systems

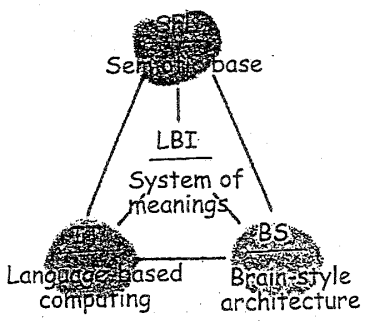
The human brain has evolved in connection with language. One of the outstanding functions of the brain is to manage the highly complex system of language. Language can be described as a social semiotic system, to the extent that humans have built up a system of meanings through social interaction. In this way, language supports explicit human intelligence.Taking this into account, our research aims to realize brain-style intelligent systems incorporating the system of language. We attempt to shed light on the higher-order brain functions related to language: memorization, cognition, and cogitation.

Current research topics are:

- Developing an architecture to implement the model of the semiotic base developed in systemic functional linguistics into computers. Studying practical applications of the semiotic base to interpretation and generation of linguistic texts.
- Attempting to realize computing based on language as it is represented within the human brain, instead of the conventional computing based on numbers.

Future research topics will be:

- Managing multimodal information.
- Proposing brain-style architectures which are appropriate for the language system.



Research Area Map

Lab.head
Yoko Yamaguchi
Ph.D.

Dynamics of Emergent Intelligence

The important feature of brain-style intelligence is the ability to create and exercise the self-constraint under indefinite environmental changes. We aim to clarify the dynamical theory of emergent intelligence where the self-constraint is created, controlling the processes of cognition and behavior instantaneously. A theoretical study of brain dynamics in these processes is focused on the evolutionary and collective properties of nonlinear neural dynamics. Collaboration with interdisciplinary fields as well as neurophysiology is encouraged to understand the brain and mental processes.

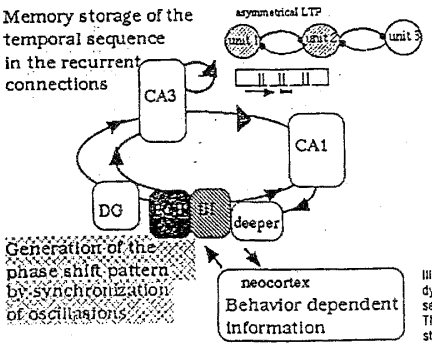


Illustration of the hypothesis of the hippocampal theta dynamics on the memory storage of the temporal sequence. (Yamaguchi and McNaughton 1998) The temporal sequence of the behavioral experience is stored in the hippocampal network by theta phase coding.

Lab.head
Jun Tani
D.Eng.

Behavior and Dynamic Cognition

We conduct research on the adaptation and the development of cognitive behavior based on the engineering synthesis approach. More specifically, we attempt to answer the following specific questions:

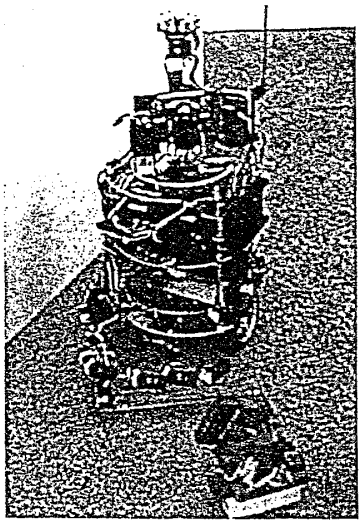
(1) How can the modular and hierarchical structures can be dynamically organized in the brain such that the diverse cognitive functions from the sensory-motor to the higher-order cognitive levels could be naturally realized?

(2) How can people acquire symbols and language through behavioral interactions.

(3) What are the cognitive roles of imitation, play and exploration in developmental processes?

(4) How do people start to become "conscious" about themselves and others?

We are exploring these issues by conducting multidisciplinary researches, including neural network modeling, robotic experiments, complex systems analysis, experimental psychology, brain imaging and phenomenology.



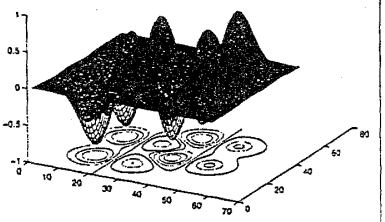
A robot exploring the environment

Brain-Style Information Systems Research Group

Mathematical Neuroscience

Lab.head
Shun-ichi Amari
D.Eng.

Information is represented in the brain by spatiotemporal patterns of excitation distributed over a large number of neurons. The brain processes information by parallel dynamic interactions among neurons, and modifies its behavior by learning and self-organization. The brain forms a model of the world such that it can recognize, memorize, plan and control the outer world including itself.The objective of this laboratory is to establish a new branch of brain information science which elucidates fundamental principles of information processing in the brain. We also aim at constructing mathematical foundations of neurocomputing. We have thus far studied representations of information in the brain, various types of dynamics of recurrent neural networks, its learning and self-organization including capacities and generalization abilities. We have established a unique position in our field using these profound mathematical theories with significant results. We have used information geometry, a new differential-geometrical theory, to construct mathematical foundations.

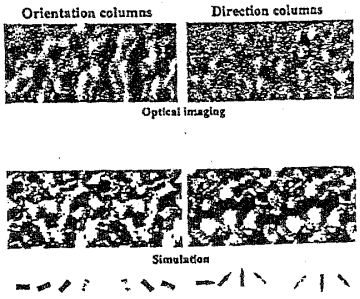


Emergence of information patterns under spatio-temporal dynamics of neural fields

Visual Neurocomputing

Lab.head
Shigeru Tanaka
Ph.D.

This laboratory is engaged in visual neuroscience research using both theoretical and experimental approaches to understand the mechanisms underlying the formation of neural networks and their information processing capability. In particular, we focus mainly on the functional architecture in the primary visual cortex of mammals, which is called columnar organization (e.g., orientation column, ocular dominance column and direction column). We examine mutual relationships and information representation of various types of columns by observing the 2D patterns of the columns using the optical imaging technique. We also carry out computer simulation based on our activity-dependent self-organization model to reproduce experimentally observed columnar structures, and investigate possible roles of visual experience in the formation of the columns. Furthermore, we attempt to clarify information processing mechanisms of the primary visual cortex by conducting computer simulations of neural dynamics of a large-scale network reproduced based on the self-organization model. We expect to obtain basic principles of brain information processing through theoretical and experimental approaches.

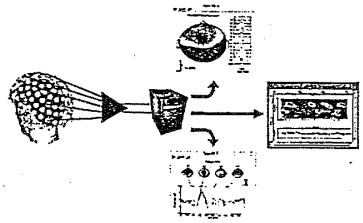


2D patterns of orientation and direction columns obtained by optical imaging from cat area 18 (top).
2D patterns of orientation and direction columns obtained by computer simulation based on theself-organization model (bottom).

Lab.head
Andrzej Cichocki
Ph.D.

Advanced Brain Signal Processing

Laboratory for Advanced Brain Signal Processing investigates and develops tools and software for analysis (extraction, enhancement, denoising, detection, localization, recognition and classification tasks) of brain signals and patterns, especially measured by high-density array EEG/MEG and ERP/EMG machines. In this laboratory, the general interest is in intelligent biomedical signal processing and a nonlinear system theory approaches in computational neuroscience, with an emphasis on neural network models with underlying components (processing units) and unsupervising learning algorithms.
We analyze models of biologically plausible neural networks and adaptive learning methods, to elucidate brain functions, especially visual, auditory, olfactory and somatosensory systems and to realize engineering designs of brain-style pattern recognition, classification and cognitive systems. We are actually developing dynamic nonlinear independent component (DICA) analysis and other techniques, like Higher Order Statistics (HOS) and Joint Time Frequency Analysis (JTFA) for real brain data in cooperation with other laboratories. Our main goal is elucidation of signal processing in the brain and its engineering applications to realize higher order brain functions by information technology.

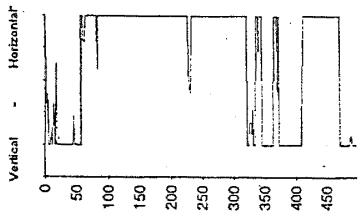


Extraction and classification of brain source signals and patterns

Lab.head
Cees V. Leeuwen
Ph.D.

Perception Dynamics

Research in this group is focused on the micro-dynamics of visual perception and its associated memory functions such as iconic and visual working memory, and perceptual and classification learning. We aim at computational modelling of these processes and testing resulting hypotheses by psychological experiment. Globally and locally coupled maps build a convenient architecture for our modelling endeavours. Following the thread of pioneering studies, predominantly by Japanese authors, we are developing coupled map-based models for application in the domain of visual perception. Their dynamics involve chaotic and near-chaotic behaviors, such as itinerancy and spatio-temporal intermittency. Phenomena of perceptual processing, which could be understood by this dynamics, include spontaneous reorganization of the visual field and the active maintenance of memory representations through spontaneous rehearsal. These phenomena are being studied in the human visual system by time-resolved and noninvasive experimental methods, such as synchronization and temporal coherence in EEG, and eye-movement measurement.



The time course of spontaneous reorganization of a pattern of phase-synchronized activity in a Coupled-Map model of visual perception (van Leeuwen, Steyvers, & Nooter (1998). Journal of Mathematical Psychology, 41, 319-344). A visual pattern consisting of an array of dots is presented to the model. This pattern is ambiguous to human visual perception, resulting in rivalling 'horizontal' and ' vertical' grouping phenomena. In accordance with this behavior, the model switches spontaneously between these two alternative forms of synchronized activity.

New technologies enable new discoveries

Advanced Technology Development Center (ATDC)

Scientific discoveries owe much to technological innovations, while technological advances are stimulated by scientific breakthroughs.

The Advanced Technology Development Center (ATDC) has two objectives. One is to create innovative technologies including noninvasive measurements and biological methods and materials for brain science research. These are research laboratories of this type. The other is to provide researchers with services of scientific technologies and resources. These are research resources of this type.

Research Laboratories

Research Resources

- Advanced Technology Development Center (ATDC)
  - Research Laboratories
  - Research Resources

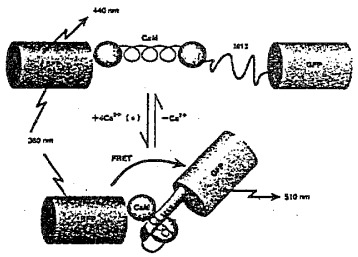
Lab.head

Atsushi Miyawaki

M.D.,Ph.D.

Cell Function Dynamics

Our primary goal is to gain a better understanding of how the molecules responsible for life behave in space and time. For example, signal transduction cascades involve multiple enzymes and are orchestrated by specific protein-protein interactions. Such dynamics can be revealed by optical means such as by a fluorescence readout. The green fluorescent protein (GFP) of the jellyfish, *Aequorea victoria*, is a spontaneously fluorescent protein that can be incorporated into other proteins through genetic fusion. Our preferred approach is to use two GFPs of different colors to permit fluorescence resonance energy transfer (FRET). FRET is highly sensitive to the relative orientation and distance between two fluorophores and alters the ratio of their emission intensities, creating an ideal readout for fast imaging and confocal microscopy. Cameleons are genetically encoded fluorescent indicators for Ca^{2+} based on FRET with GFPs. Because cameleons can be targeted genetically and imaged by one- or two-photon excitation microscopy, they offer great promise for monitoring Ca^{2+} in entire organisms, tissues, organelles, and submicroscopic environments where measurements were previously impossible. We plan to extend optical methods in order to observe many intracellular signaling events, which currently must be assayed by grinding millions of cells.



Schematic showing how FRET from BFP to GFP measures Ca^{2+} ions.

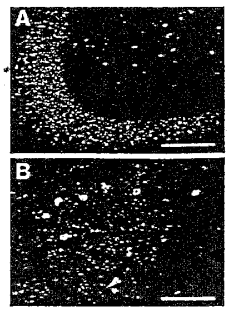
Lab.head

Tsutomu Hashikawa

Ph.D.

Neural Architecture

The complexity of the structure of the brain makes it difficult to understand principle mechanisms of how it functions. Because various brain functions must be derived from the structure of networks and systems highly organized in the brain, the understanding of structural bases of these functions is important. In order to include the structural background in the analysis of brain functions at molecular, cellular and system levels, our laboratory focuses on the morphological analysis of structural elements that are crucial for expression of brain functions. An insight into the structural aspects of neural functions will lead to the substantial understanding of working mechanisms of the brain. Our main research subjects are: 1) microscopic analyses, such as laser-scanning microscopy, transmission and scanning electron microscopy, and atomic force microscopy, of the cellular and subcellular distribution of molecules essential to the control of neural transmission, particularly that of cell adhesion molecules, neurotransmitter receptors and ion channels at synapses, 2) search and immunohistochemical detection of novel marker molecules to differentiate specific types of cell in neural tissues, 3) development and application of experimental probes for the analysis of local cortical circuits, and 4) analysis of the connectional organization of high functional areas in the cerebral cortex.



Layer specific distribution of inhibitory neurotransmitter GABA (green) and pyramidal cell expression of mRNA of GABABR1b (red), one of its metabotropic receptors, in the hippocampal CA2-3 region can be detected simultaneously by immunohistochemistry and in situ hybridization histochemistry. Lower: High magnification of a part of upper picture.

Lab.head
Shigeyoshi Itohara
D.V.M.Ph.D.

Behavioral Genetics

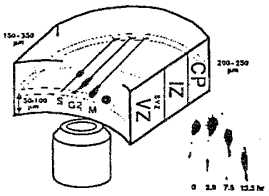
The brain integrates multiple external stimuli and internal information to express animal behavior. This complex information processing is supported by the precise and fine neuronal network formation. Genetic and epigenetic factors including environmental stimuli are known to affect the formation of neuronal networks. We are particularly interested in the molecular basis underlying the plasticity of the neuronal networks associated with external stimuli. In order to analyze the molecular mechanisms underlying highly sophisticated biological phenomena, it is essential to manipulate given molecule(s) in unambiguous manners. Genetically engineered animals are very useful for this purpose. Thus, we aim to develop novel genetical methods in mice and to generate animal resources that are useful for various aspects of brain sciences. We are currently focusing on: 1) molecular mechanisms underlying the formation and plasticity in cerebellar circuitry associated with motor learning. 2) molecular mechanisms underlying the experience-dependent development in cerebral cortex, and 3) the functional significance and mechanisms of astrocyte-neuron interaction.

Cerebral-cortex-restricted mutation system: Emx-1-Cre transgenic mice allow us to selectively manipulate a given gene in the excitatory neurons of the cerebral cortex, hippocampus, and olfactory bulb. Mutations can be induced in the dark blue regions.

Lab.head
Masaharu Ogawa
Ph.D.

Cell Culture Development

Our interest is to understand the way by which the cerebral cortex organizes itself during development. At the onset of neuronogenesis, the cerebral cortex consists of a morphologically uniform population of neuroepithelial cells. During embryonic development, neuroepithelial cells generate young neurons that migrate and differentiate into distinct neuronal types, and are eventually organized into a precise laminar pattern. Each cell type is characterized by its unique morphology, position, and function. We study the molecular and cellular mechanisms involved in neural migration, cell-fate decision, and laminar patterning in the developing cortex. A recent interest in our laboratory is on the development of slice cultures using embryonic cortices and the labeling of progenitor cells with fluorescent dyes, which enable us to view, with microscopic resolution, newly generated viable and migrating neurons. We apply these techniques to define the sequence and the pattern of mitosis of progenitor cells to become postmitotic neurons and the pattern of neural migration in the early cortex.



A single neuronal precursor cell was labeled with DiI and its elevator movement was microscopically visualized.

Senior Scientist

Neuronal Circuit Mechanisms
Research Group
Yoshio Hirabayashi Ph.D.

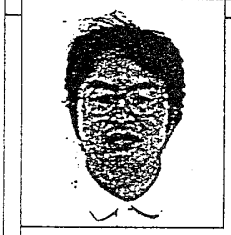
A reciprocal relationship existing between glia and neurons is vital for brain development and the maintenance of functional neurons. We have found that the neuronal survival and morphological development of hippocampal neurons and Purkinje cells in vitro are completely dependent on the nonessential amino acid, L-serine, released actively from the astroglia. We will continue to study this novel metabolic communication via L-serine between glia and neurons at the molecular genetic level. In vivo roles of L-serine will be addressed using transgenic mouse models. The exogenous L-serine is taken up and utilised for the synthesis of neuronal sphingolipids that are a component of membrane microdomain "rafts". Research on the involvement of sphingolipids in signal transduction pathways such as apoptosis and survival has been rapidly expanding. We have cloned the genes encoding the key enzymes for the synthesis of sphingolipids including ceramide glucosyltransferase (GlcT-1). We are now generating conventional and conditional knockout mice for these genes to get new insights into in vivo roles of neuronal "rafts"sphingolipids.

Neuronal Circuit Mechanisms
Research Group
Shogo Endo Ph.D.

Humans have survived in a wide variety of given environments as a result of the remarkable flexibility of the nervous system called neuronal plasticities. The elucidation of the mechanisms involved in neuronal plasticities is one of the most attractive and important questions in the field of modern neuroscience. Currently, we are studying the basic molecular mechanisms underlying neuronal plasticities.
The cerebellum is considered to be the center for non-declarative memories. Non-declarative memories are those memories that we can not put into words. One example of non-declarative memory is the memory of body motions such as those involved in throwing a ball. Long-term depression involves the use-dependent decrease of signal transmission efficiency and lasts for a significant period of time. Cerebellar long-term depression is important for memories mediated by cerebellum. Our research group have selected cerebellar long-term depression as a model of neuronal plasticity and we have focused on the molecular mechanisms underlying cerebellar long-term depression.

Neuronal Circuit Mechanisms
Research Group
Raymond Kado Ph.D.

The aim of this project is to study the suitability of using short pulse laser light to reveal ongoing processes in the brain tissues of freely moving animals. In the last half century, many properties of the nervous system have been discovered using methods which required isolation of the tissues being studied. The method we are developing is expected to allow studying these properties and their interactions in the intact, freely performing animal. It is different from most brain imaging approaches, in that measurements will be within the limits of the focal point of the probe. At present, it is about 10 x30 μm, about the size of the neuron. The 790 nm light from the present laser should not destroy tissues even at it focal point, thus assuring that the same volume of tissues can be studied repeatedly over very long periods of time. Since the probe and the laser are of original design, our present work is concerned with the characterization of the laser light and its ability to produce fluorescence. Thus far, the results of these studies indicate that the projected application of the probe will be successful.



RIKEN-MIT
Neuroscience Research Center
Yasunori Hayashi M.D.Ph.D.

The "mechanism involved in memory" have remained unclarified. We focus on hippocampus, which plays a critical role in memory. In the hippocampus, a phenomenon, called 'synaptic plasticity' is observed. Neurons communicate through synapses. When a presynapse is intensely stimulated (mimicking the learning process), the synaptic transmission is enhanced for hours or days. Since this phenomenon long-term potentiation (LTP), was first described, it has been attracting neuroscientists as a potential cellular correlate of memory. We investigate the LTP phenomenon by combining different technologies: we construct various recombinant neuronal proteins and express them in neurons. Then, we analyze these cells using electrophysiological and imaging techniques. In addition to LTP, another interesting phenomenon is observed in the hippocampus: neurons are continually regenerated even in adulthood and are involved in existing neuronal circuits. We study the roles of this phenominon on learning and memory. Through these analyses we would like to elucidate the molecular mechanisms of memory.

Developmental
Brain Science Group
Hiroyuki Kamiguchi M.D.,Ph.D.

Complex neural networks are formed by axons that have elongated and reached their proper targets. The tip of an elongating axon, called the growth cone, explores guidance cues in its environment and navigates the axon through the correct pathway. The growth cone expresses a variety of cell adhesion molecules (CAMs) that interact with guidance cues. In addition, the signaling molecules and cytoskeletal elements essential for axonal elongation are expressed inside the growth cone. We have demonstrated that dynamic growth cone adhesion regulated by CAM trafficking and signaling plays a critical role in axonal elongation. Using state-of-the-art microscopic techniques, our group is currently studying the dynamic interactions between CAMs, signaling molecules and cytoskeletal elements in live growth cones. Other techniques such as gene/protein loading into neurons, laser activation/inactivation of functional molecules and laser manipulation of CAMs are employed to elucidate the molecular mechanisms that control growth cone migration. These revelations will help elucidate the fundamental mechanisms by which axons elongate to form proper networks during neural development and regeneration.

Developmental
Brain Science Group
Takashi Kondo Ph.D.

Although most of the cells within a body share the same variety of genes, cells in different organs often need functions of different group of genes. In many cases, switching of genes are controlled in transcriptional level. Transcriptions of many genes are regulated temporally and spatially restricted manners. Some genes are expressed and have functions specifically in certain variety of organs but not in others. Sometimes ectopic expression of a certain gene in some cells can be even detrimental. It is not yet understood how these regulations are achieved without confusion on genome which contains many genes and regulatory regions. Some of genes must be expressed to construct brain, some of genes must be expressed to maintain brain, whereas, some others must never be transcribed within brain. We are investigating which kinds of events are taking place on chromosomes and within nuclei when genes are switched on or off.

Developmental
Brain Science Group
Etsuko Muto Ph.D.

It has been suggested that microtubule could function as a substrate forinformation processing and/or energy transduction. Our research goal is to study microtubule dynamics and explore their possible active role in signal transmission and motility of motor proteins (e.g., kinesin and dynein). We have previously demonstrated that the transition state of microtubule has very unique properties such as long-range cooperativity, anisotropy and a memory effect. To examine how these properties are related to the possible active role of microtubule, We shall directly observe the conformational states of microtubules in cells, using high-resolution single-molecule imaging combined with fluorescence spectroscopy. In addition, to understand the molecular mechanism that underlies the microtubule dynamics, the vibrational states of tubulin and/or water molecules are also analyzed, using dielectric spectroscopy and infrared spectroscopy. We believe that these approaches will enable us to identify a novel system of information processing in living organisms, i.e., "cytoskeletal information processing."

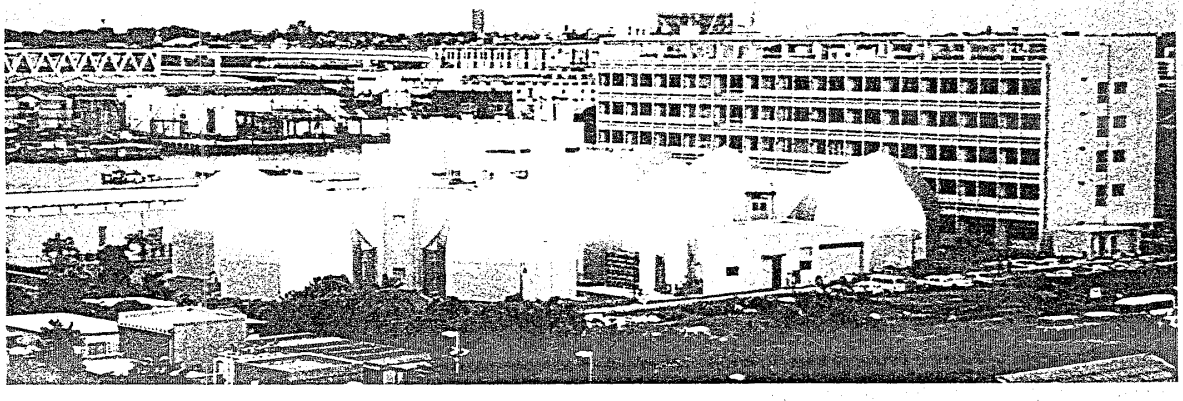
Molecular Neuropathology Group
Jun Motoyama Ph.D.

The sonic hedgehog (shh) signaling cascade is essential for cell-to-cell interaction during vertebrate neural tube development. In human, the misregulation of this signaling cascade is closely related to neural tube defects, mental retardation and brain tumors. Our laboratory has been using the mouse as a model to study the role of shh signaling cascade in neural tube development and in the adult brain. The shh signaling cascade has been shown to be required for the development of midline structure of the neural tube. However, little is known about how misregulations of the shh signaling cascade cause human diseases such as holoprosencephaly, exencephaly and medulloblastom as. We are making targeted mutant mice using embryonic stem cell technology, which have the same type of mutations as those found in these human diseases. By studying their etiology of the abnormalities at the molecular, cellular and tissue levels, we attempt to understand how the development and maintenance of the brain is regulated.

RIKEN Yokohama Institute
General Description

he Institute of Physical and Chemical Research
RIKEN) conducts a diversity of research, ranging
om foundation studies through to applications, in
ıch fields as physics, engineering, chemistry,
ioscience, and medical science.
IKEN is also active in diffusing the fruits of this
esearch throughout society.
esearch at the RIKEN Yokohama Institute (Director:
ice president Dr. Akira Kira) opened in April 2000,
ocuses on the basis of all biological activity, the
enome (the entire genetic code possessed by every
rganism) and aims to compile a comprehensive
esearch base in the field of genomics.
he well-established Genomic Sciences Center
GSC, Director: Dr. Akiyoshi Wada) and the more
ecently-established SNP Research Center (SRC,
irector: Dr. Kumao Toyoshima) and Plant Science
enter (PSC, Director: Dr. Tatsuo Sugiyama) have
ined forces at the RIKEN Yokohama Institute with
ıe aim of advancing genomic research in a
stematic and centralized manner.

The GSC is expected to commence research at the newly-completed RIKEN Yokohama Institute facilities, located in Yokohama's Tsurumi-ku, in the autumn of 2000; the SRC and PSC respectively are expected to gradually integrate their research on the new campus as soon as expansion of facilities allow.
The GSC research involves a comprehensive examination of the structures and functions of genes, genomes, and proteins, from the study of organisms at a molecular level to the study of individual plants and animals.
The SRC research, striving towards the development of "personalized" medical treatments and preventative medicines tailored to the needs of individual people, examines the connection between diseases and differences in the genetic codes (DNA sequences) of individuals.
The PSC studies the connection between higher-order functions and genes/biomolecules for the purpose of enhancing and developing plant functions.

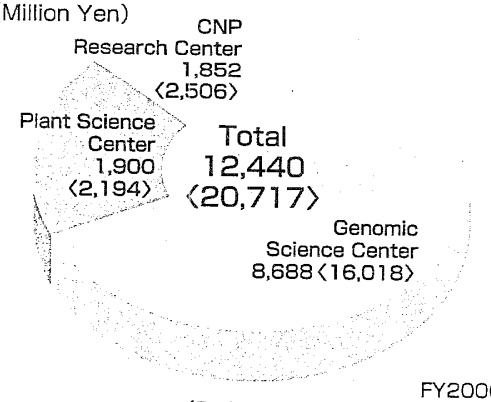


Site area: 4.6ha(RIKEN Yokohama Institute)
0.8ha(Yokohama City University of Integrated Science)

RIKEN Yokohama Institute

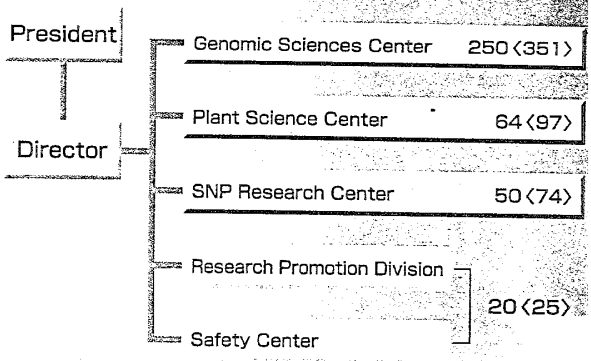
Budget

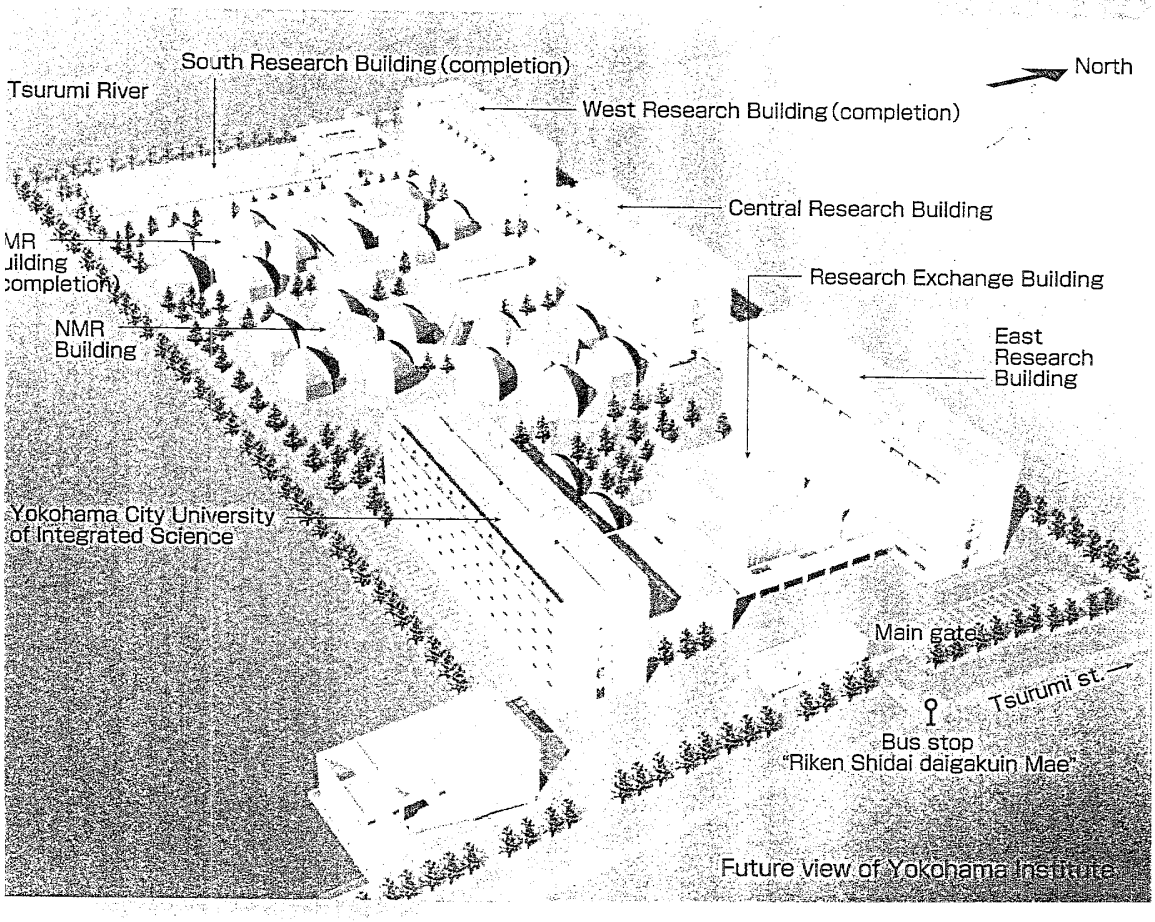
(Million Yen)



FY2000
〈Budgetary requestes FY2001〉

Organization & Personnel





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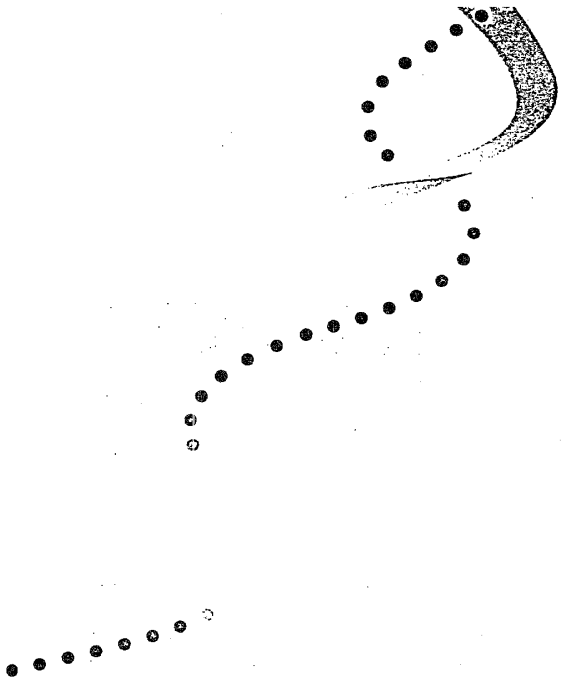

GSC

RIKEN Genomic Sciences Center

RIKEN Yokohama Institute

Genome sciences create life sciences of the 21st century.

Greetings

The genome is the comprehensive blueprint of life, and every organism is created based on the information stored within its own genome. While an organism receives information from its surrounding environments, the structures and functions essential to life are being expressed throughout its entire body through effective utilization of chemical reactions and physical characteristics of molecules and atoms. That is to say, life exists as a collective body formed by the basic principles and laws of chemistry, physics, engineering, and also as a result of the various states of the earth's environment. Therefore collective bodies must be studied as a whole, as this will lead to advancements in fundamental areas of human thought such as pure science, medicine, agriculture and pharmacology, while establishing a sound basis within the fields of biology, chemistry and physics to create new earth-friendly industries. This is what the comprehensive study of genomes is truly about.

In light of this novel approach to science, The Institute of Physical and Chemical Research (RIKEN) established The Genomic Sciences Center (GSC) to act as the central genomic research institute in Japan. At the GSC, integrated and systematic research will be carried out on the structure and function of genes, genomes and proteins, which taken as a whole, represent the fundamental building blocks of life. In the twenty-first century, this shift in the focus of life science research will become a global one. It is our intention to become pioneers in the integrated research and development of life-sciences in an attempt to respond the expectations of people throughout Japan and the world.

Director of RIKEN Genomic Sciences Center
Akiyoshi Wada (D.Sci.)

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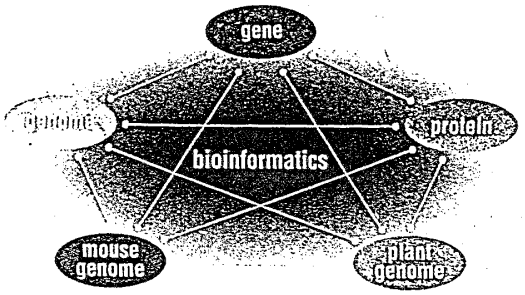
From the basic science to the applied science



What is a gene?

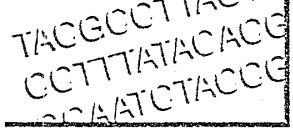
Genes determine the amino acid sequence of proteins. Each gene is composed of the four distinct molecular bases; adenine, thymine, cytosine and guanine. Any given sequence of three of these molecular bases codes for a particular amino acid. Surprisingly, while there are approximately 10^3-10^5 different proteins found within living organisms, the sequence of amino acids that constitute all of these different proteins is determined by the sequence of only four molecular bases.

We can determine the amino acid sequence for all of the proteins found within living organisms by clarifying our understanding of the complete nature of genes. This will be an important step in the clarification of the functioning and interaction of proteins. Once databases for the base sequence of genes (and thus the amino acid sequence of proteins) have been compiled, and systematic research into genomes, proteins and genes have been undertaken, biological and medical problems that had proven too difficult to solve using conventional approaches should be within our grasp.

What is a protein?

A protein consists of a chain of amino acids in the order of 10^1-10^3, drawn from a population of twenty different amino acids. The amino acid sequence of a protein constitutes its primary structure. The primary structure in turn organizes into local structural components known as the secondary structure. The two known types of secondary structures are tubular (helices) and planar (sheets). Further, the interaction of secondary structural elements forms what is known as the tertiary structure and it is this final stage of organization that is largely responsible for determining the specific functions of a protein. Thus, information related to the tertiary structures of proteins should greatly enhance the functional analyses of all proteins with a variety of applications such as the creation of artificial proteins.

Recent research suggests that proteins could be constructed from limited number of patterns or structural entities (folds). Once all folds have been determined and their functional relationships established, it will enable scientists to predict functions of unknown proteins, to improve to the function of existing proteins and to design new proteins for use in medicine and other fields.



What is a genome?

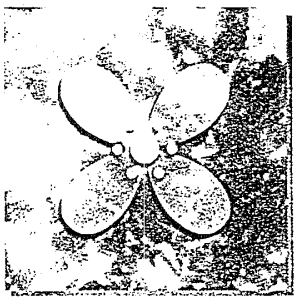
A genome is an integral body of genetic information located within nucleus. It contains not only all of the genes that define a particular organism but also the information that regulates a variety of biological functions including the expression of each gene.

The information is coded and written in DNA molecules as sequence of four nucleotides, A, G, T, and C. Thus, through the determination of the entire nucleotide sequence of the genome, we will understand how and what kind of information is used to build and maintain living organisms, which will eventually deepen our understanding of life.

Many research projects are now being undertaken to determine the entire structure of genomes of variety of different organisms, including human. Further research on genomes will lead to a more complete understanding of life.

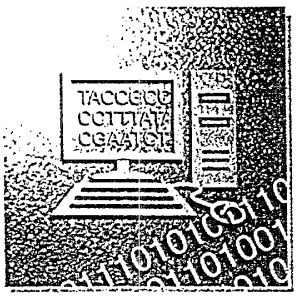
Mouse genome research

Recent progress in genome sequencing and cDNA exploration will soon reveal the structure of all genes of the human and the mouse. The next goal of genome research is to elucidate the functions of this vast number of genes. One of the most efficient ways to do this is to compare the phenotype of a mutant that has a defect in a specific gene with that of the wild-type animal at the whole body level. In mice, the mammalian species in which genetic studies are the most advanced, administration of a chemical mutagen ENU induces point mutations by base-substitutions at high frequency. If the mice mutagenized with ENU are systematically screened for abnormal phenotypes, such as tumorigenic, metabolic, neurological, sensory, and behavioral anomalies, we will be able to develop animal models for human heredity diseases. These mice will be used as indispensable bioresources for biomedical research in the 21st century.



Plant genome research

Both plants and animals are composed of cells and these cells contain a genome of genetic information. The genome consists of large numbers of genes that serve as a blueprint for both plants and animals. Since plants can not move freely like animals, they grow by adapting to their environments. Therefore, plants show a high level of environmental response. In plant functional genomics research, the mechanisms by which the plants grow in response to external stimulation are studied by examining all of the genes in the blueprint. Since plants provide an environment, including food, required for the survival of humans and animals, research on the functions of plants is important from the viewpoint of clarifying the diversity of genes and preservation of the environment that includes humans. Based on the plant functional genomics information obtained in this research, it should be possible to modify plants as environmental resources for humans so that they can withstand adverse environmental conditions such as dryness and high and low temperatures, to create plants which will play a role in preserving the environment, to create low allergen plants, and to create high yield plants to meet population increases in the future.



What is bioinformatics?

Behavior of life is expressed as a series of chemical reactions among biomolecules such as DNA and RNA. The aim of bioinformatics research is to clarify such behavior from the standpoint of "information." This information includes not only data but also wider meanings such as computational models, simulation, and databases. This is called informatics.

Bioinformatics consists of the following researches.

1) Deciphering sequence information from DNA, determining the structure of proteins using X-ray and NMR equipments, and developing information processing technology to assure that such research runs smoothly.
2) Constructing databases on DNA sequence information and obtaining blueprints for life and the history of life from DNA sequence information from these databases.
3) Elucidating the structures and functions of proteins obtained on the basis of these blueprints for life.
4) Determining how individual proteins combine to express complex, large-scale biological phenomena.

In recent bioinformatics research, it is necessary to handle vast amounts of data and perform large-scale, precise analyses, and an infrastructure is essential for such work.

Data obtained from experiments and other sources is compiled using bioinformatics, computational models are developed and these results are fed back to more experiments, which should assure further advances in genomics research.

GSC : The research institute extending the genomic concept

Research objectives

One research objective of the GSC is to clarify the foundations of life science by conducting research on the structure of genes, genomes, and proteins - the building blocks of life - from the molecular level to the individual organism. Another research objective is to develop new research for the 21st Century in the area of pure science, such as intellectual property, as well as providing a strong platform for developments in a broad spectrum of areas, such as overcoming diseases, protecting the environment, and generating new industries, to create a prosperous future.

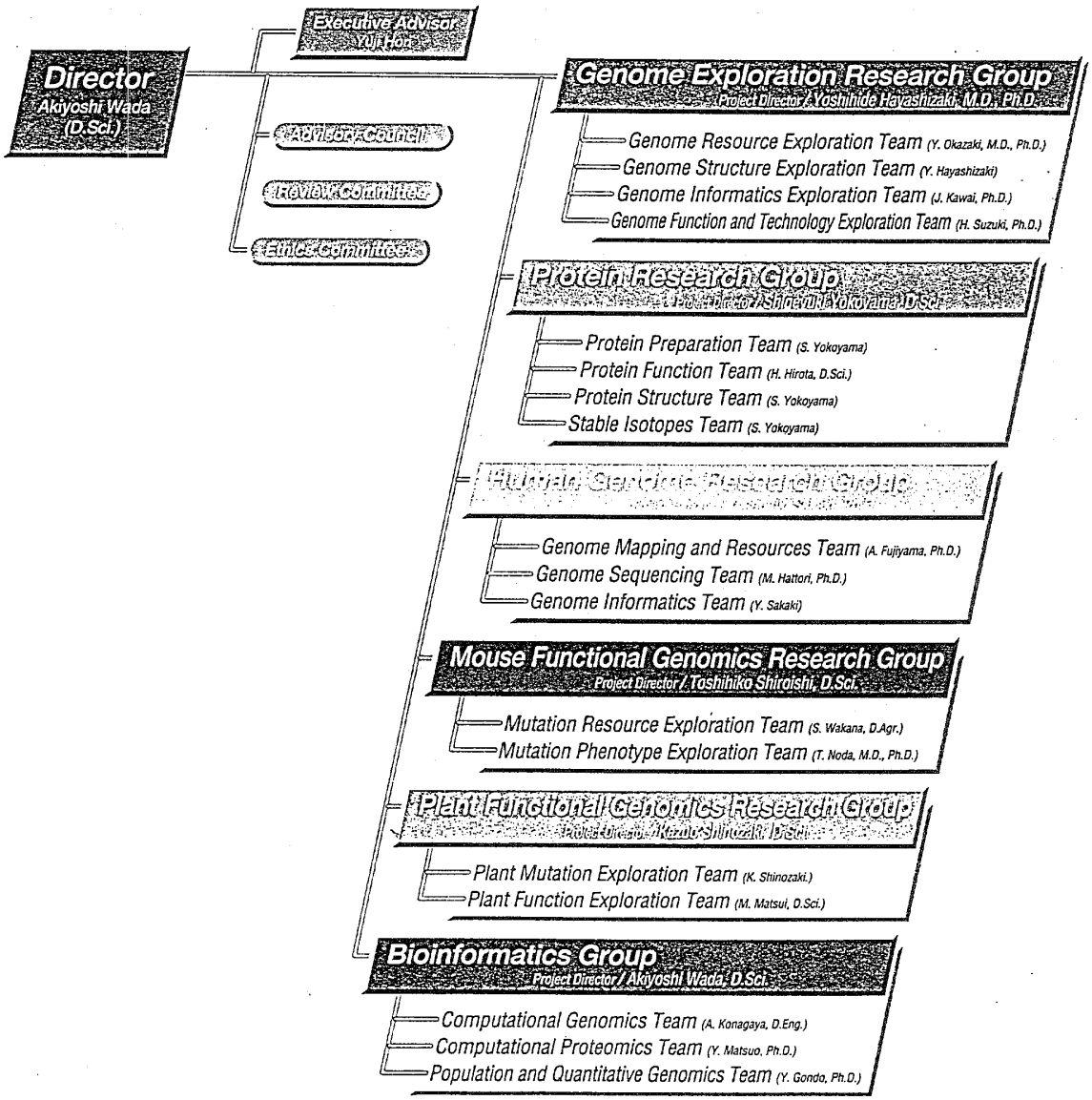
Research activities

- The GSC, a research institute for extending the genomic concept, includes several research groups studying the range of genomic science areas, from the molecular level to the individual level. Such an institute is unique in the world.
- The GSC is developing new aspects of genomic science, placing emphasis on progressiveness and originality.
- GSC research is conducted in interdisciplinary fields, not only in biology, but also in chemistry, physics, and information science.
- Research focuses on higher animals and plants, such as humans (human disease models) and model plants.
- Research results are actively published and practically applied.

Research system

- Cooperation within GSC research groups is well-organized and research methods are efficient and effective.
- Administration of the research center and research results are evaluated by national and international experts.
- GSC has established strong research cooperation networks, both within Japan and internationally, and performs as a center for international genomic science research.

RIKEN Genomic Sciences Center (GSC)



The introduction of the research groups

Genome Exploration Research Group

The advances made in genome research in recent years have contributed greatly to the fields of medicine and biology, and have changed the way in which research is conducted. The goal of the Genome Exploration Research Group (GERG) is to extract genetic information from genomic DNA and to understand the functional units by exhaustive collection of genetic molecules and in this way to comprehensively study the phenomena of life. Initially, a gene encyclopedia (total genetic dictionary) will be completed by constructing full-length gene clones and compiling the genetic information. Once such a gene encyclopedia has been compiled, it will then be used as an investigative tool for the following research topics. Comparing the encyclopedia with our expression data and public databases such as human genome, the genetic background of diseases will be clarified. In protein-protein interaction research using the two hybrid system, the function of proteins will be analyzed. Using microarray technology, cascade regulation of gene expression will be studied. By investigating interactions between proteins and their target DNA segments, the mechanism of transcription control will be elucidated.

- **Genome Resource Exploration Team**
  Gene clone resources such as full-length cDNA will be prepared in an effort to analyze the function of genes.
- **Genome Structure Exploration Team**
  Riken's original high-speed DNA analyzing technology will be improved for the preparation of a gene encyclopedia.
- **Genome Informatics Exploration Team**
  A computer analysis of the function of genes will be carried out based on genetic information obtained by the research team.
- **Genome Function and Technology Exploration Team**
  DNA chips and other materials will be used to analyze regulatory cascades for the expression of genes.

Protein Research Group

Proteins are composed of one or more functional domains. The three-dimensional structures of these functional domains are classified into about one thousand types of basic structural units or folds, which are in turn broken down into approximately 10,000 subtypes. The functions of proteins are expressed by combinations of molecular functions corresponding to the basic folds. The Protein Research Group is applying "structural genomics" in a comprehensive study of the structure and function of many types of proteins using NMR and X-ray crystallography. An "Encyclopedia of Basic Protein Folds" covering the basic folds and molecular functions is being prepared through an analysis of several thousand subtypes based on international collaboration. With this "Encyclopedia of Basic Protein Folds," it will be possible to predict three-dimensional structures and functions of proteins from genetic information (i.e., amino acid sequences). These results will be applied not only in biology but also more widely in medicine, drug discovery, and other industrial fields.

- **Protein Preparation Team**
  The functional domain of proteins will be predicted at the DNA level and expressed.
- **Protein Function Team**
  The molecular function of folds will be investigated.
- **Protein Structure Team**
  The protein 3D structure determined by a combination of folds, plus the folds that constitute them will be identified.
- **Stable Isotopes Team**
  The advanced preparative methods will be established for isotopically labeled proteins.

Human Genome Research Group

We participate in the international human genome project to completely decipher the human genome as a genetic blueprint for humans as the Japanese representative. The human genome is divided into units consisting of 24 chromosomes from 1 to 22, plus X and Y, but the Human Genome Research Group is concentrating on chromosomes 21, 18, and 11. In May 2000, we succeeded in determination of the complete base sequence and identification of all genes on chromosome 21, our initial target. We are currently studying the complete base sequences of chromosomes 11 and 18. The group also clarifies the functions and analyzes the control regions of newly discovered genes. Important genome information concerning the functions of living organisms is known to be preserved unchanged during the course of evolution. We are comparing important sequences in the human genome with those in the mouse genome. We also hope to discover genotypes inherent to humans by comparisons with chimpanzees, which are closely related to humans.

- **Genome Mapping and Resources Team**
  Libraries from various genomes will be prepared for high-speed sequencing and genome analysis. The resources will be used to conduct studies focused on genome functions.
- **Genome Sequencing Team**
  A high-speed genome sequencing system will be established, which will enable researchers to determine the base sequence of the human and mouse genome with a high degree of accuracy.
- **Genome Informatics Team**
  Information analysis/management systems for structural genomics, functional genomics, comparative genomics, and computational genomics will be developed.

Mouse Functional Genomics Research Group

The genome, consisting of more than ten thousand genes, designs the whole body of the human and the mouse. After fertilization, certain genes play essential roles in formation of the body and maintenance of its homeostasis through gene-environment and gene-gene interactions. During this process, expression of the genes is appropriately regulated in tissue- and stage-specific manners. One of the most efficient ways to gain a better understanding of the function of each gene is to use mutant animals. Comparison of the mutant phenotype with that of the wild-type animal enables us to investigate the function of the gene relevant to the mutation. The Mouse Functional Genomics Research Group intends to induce point mutations in the mouse genome with a chemical mutagen, ENU, and to produce as many mutant mouse strains as possible. We plan to analyze the mutant mice and construct a database to integrate all information on the mutant mice. All mutants will be cryopreserved as embryos or sperm, and will be available to the international research community. Thus, we have established a large-scale mouse mutagegnesis project to develop an infrastructure, including development of mouse models for human diseases and mutant mice useful in basic biological research, for biomedical research in the 21st century.

- **Mutation Resource Exploration Team**
  This team is developing techniques to induce mutations in mice efficiently and to establish genetic methods to analyze these mutant mouse strains.
- **Mutation Phenotype Exploration Team**
  This team systematically screens for mice with induced mutations and looks for changes, mutant phenotypes, at the individual level. The team is also developing a methodology for phenotype screening.

Plant Functional Genomics Research Group

Plants differ in various ways from animals and plants have inherent capabilities that animals do not have. To understand these inherent capabilities of plants, the Plant Functional Genomics Research Group is studying genome information and functions using *Arabidopsis thaliana* as a model plant. The function of the genes is being clarified by comprehensive insertion of T-DNA or transposons into about 25,000 genes to produce gene inactivation mutations. The structure and modes of expression of the functional genes in the genome are being clarified by the construction and analysis of full-length cDNA libraries. Using these two approaches, the aim is to decipher in as much detail as possible the information encoded in the genome of *Arabidopsis thaliana*. Information on the functions of various plant genes obtained in this way should be useful in improvement of other useful plants.

- **Plant Mutation Exploration Team**
  This team produces and analyzes transposon insertion mutants, and also produces and analyzes full-length cDNA libraries and microarrays.
- **Plant Function Exploration Team**
  This team produces and analyzes T-DNA insertion mutants.

Bioinformatics Group

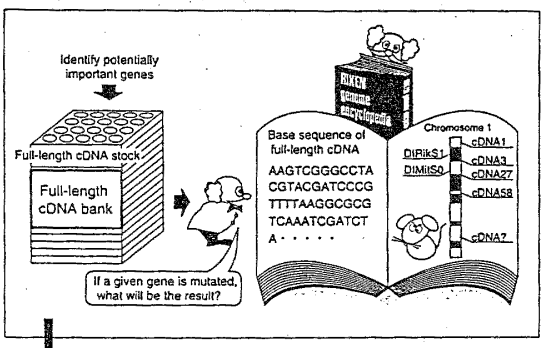
It is our task to clarify life phenomena expressed on the genome by means of integration of genomic information on DNA, information on proteins and animals and plants, information from other groups, and information from public databases. In genomic research, various results have been obtained by both the biochemical approach and informatics approach. These methods were based on sequences, but in the current post-sequence age, analysis of information on structures and functions of proteins, as well as expression and interactions of genes is important. We use computer simulation to reproduce activities with information flow from genes to individuals via proteins and cells. The Bioinformatics Group also analyzes data from individual mutations to causative genes against the natural information flow. By clarification of life phenomena using genome information, advances can be made in elucidation of lifestyle diseases and order-made medicine, which will enrich human life.

- **Computational Genomics Team**
  This team simulates behavior of gene network using computer and develops integrated database by utilizing advanced information sciences and technologies.
- **Computational Proteomics Team**
  This team clarifies mechanisms of cell functions through information analysis and computer simulation.
- **Population and Quantitative Genomics Team**
  Individual's symptoms and physiological conditions will be understood in terms of each DNA information.

Genome Exploration Research Group

What is the mandate of the Genome Exploration Research Group?

A number of genome analysis centers capable of sequencing in excess of 100 million molecular bases per year are now being constructed in various cities throughout the world. A genome bank containing all of the genes in the completed form from mice (full-length cDNA:cDNA is an artificial copy of genes made from mRNA) will be made using the data collected at RIKEN Tsukuba Institute and an innovative super high-speed base sequence determination system on those genes will be developed. A gene encyclopedia will be compiled from a determination of the DNA structure (base sequence) of the genes and their location on the genome using the innovative sequencing technology.

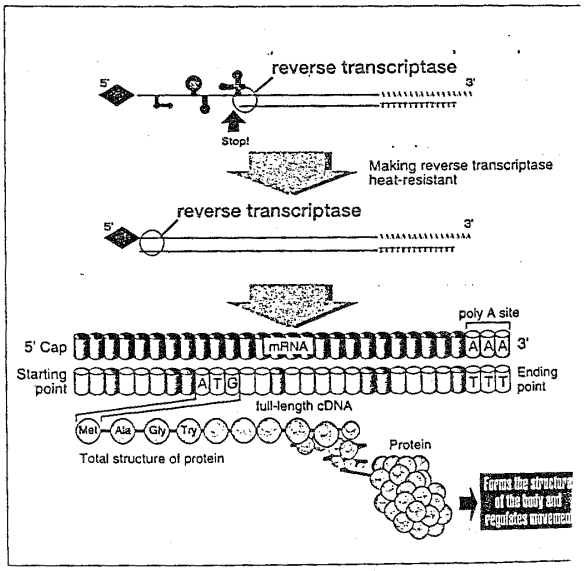


Goals for the Genome Exploration Research Group

- Establishment of a new high-speed sequencing system
- Preparation of a mouse genome encyclopedia

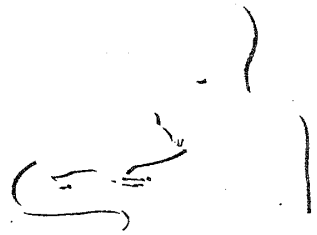
Development of a full-length cDNA

The Institute of Physical and Chemical Research developed a new and completely original method for copying the entire length of mRNA and synthesizing full-length cDNA. This method enables researchers to efficiently isolate genes as cDNA. Furthermore, as proteins are determined by genes, their primary structures can be determined from full-length cDNA. In addition, it is now possible to directly obtain a desired protein by expressing target genes in cells. This technology adopting a novel thermoactivation mechanism of enzymes will have applications not only for genomic research, as in studies conducted on the heat-resistance of certain enzymes, but also for industrial fields.



Why use the mouse?

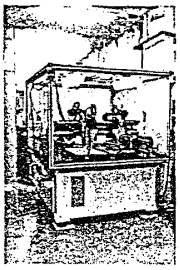
For diseases which are caused by a single defective gene; eg. myodystrophy, etc., the disease genes have been cloned directly from human genes. In adult diseases such as diabetes, hypertension, arteriosclerosis and some cancers, there apparently are genetic causes, but the genes have not been identified. Further complicating identification of the genes in such cases is the factor that numerous genes may be involved in causing such diseases. To study these genetic diseases in human, we need a genetic approach for breeding and cross breeding, which is clearly difficult to achieve. Therefore, by using the mouse these breeding approaches become feasible. Since there is a high homology between human and mouse genomes, human genes can be targeted once a mouse gene has been isolated. The use of the mouse is effective for the study of multiple genes caused diseases both scientifically and economically.



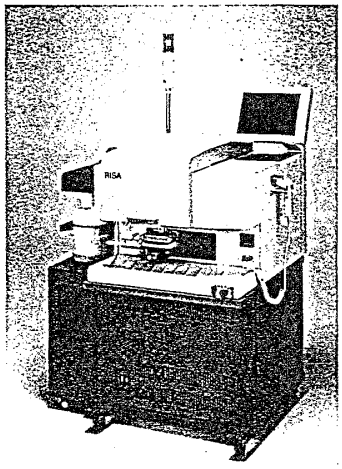
Project Director
Yoshihide Hayashizaki, M.D., Ph.D.

Development of a new large-volume DNA analysis system

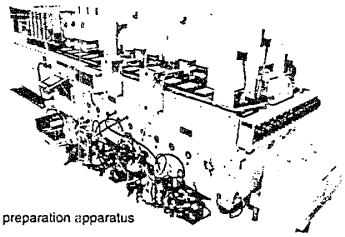
Development of a new large-volume DNA analysis system capable of rapidly determining DNA structures (base sequence) is an essential part of future research that will enable scientists to search for genes from all areas of the genome. We are in the process of building a new-generation DNA analysis system, based on innovative RIKEN technology.



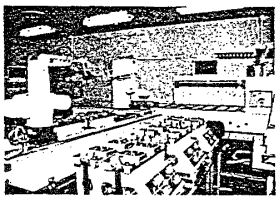
DNA microarrayer



Sequencer



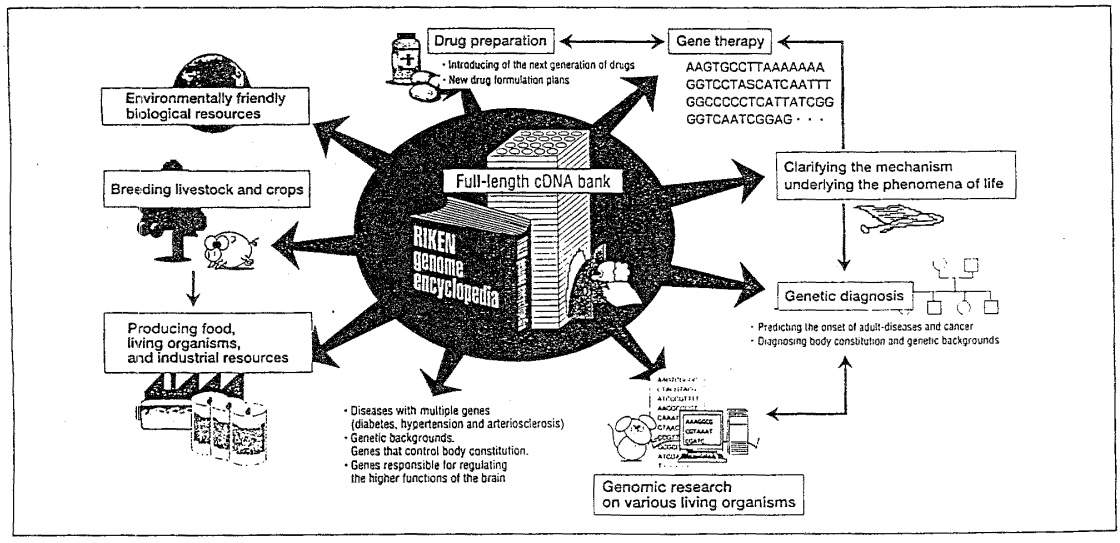
Plasmid preparation apparatus

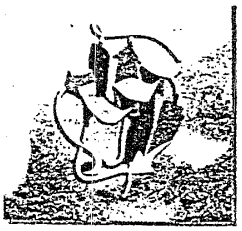


PCR apparatus

Flexibility of RIKEN's system

The genetic function search system designed according to the above mentioned guidelines will be applicable to all living organisms. It will have a significant impact on a variety of different fields of research, including the establishment of a high-speed genetic diagnostic protocol, the establishment of gene therapy and new drug making procedures, crop breeding, and the development of new earth-friendly biological resources. Furthermore, clinical and biological research on diseases with unknown etiological genes can be approached from a novel angle. In effect, RIKEN's system will change the way in which research is carried out.





Protein Research Group

Structural Genomics: role of the Protein Research Group

Structural genomics is an emerging field of research, which examines the enormous amounts of information stored in the genomes of living organisms. For example, the estimated 50,000 to 100,000 genes encoded in the human genome are studied in two ways. One way is to determine the three-dimensional structure of the proteins encoded in the genes; the other is to systematically and comprehensively analyze the structure-function relationship of all proteins. As plans are made to begin structural genomics project in countries around the world, Japan has taken the initiative to begin this new field of research. Our project is currently gathering attention from around the globe.

Basic principles underlying protein structure

About 50,000-100,000 proteins exist in the human body. These proteins are produced by stringing together building blocks called amino acids in a chain from the N terminus to the C terminus (Figure 1). Altogether, there are twenty different types of amino acids. These chains of amino acids fold into a three-dimensional shape (Figure 2), giving rise to biologically active proteins. In this process, regions distant from each other in the extended form of the chain come in close contact in the three-dimensional form. Cooperative interaction allows the protein to express its function. Therefore, an overall view of the mechanisms by which proteins express their functions is made clear only when the three-dimensional structure of proteins has been determined (Figure 3 shows structures that have been determined by our group).

Figure 1. Amino acids are strung together in a protein.

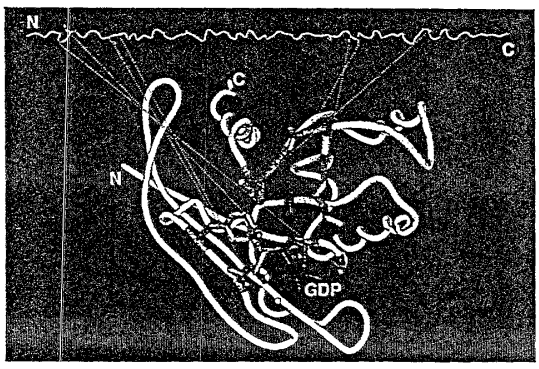


Figure 2. Proto-oncogenic Ras protein folded in the three-dimensional space (structure determined at RIKEN). Regions shaded in blue indicate those involved in the GDP-binding activity (MidasPlus (UCSF) software was used for the graphics).

Basic structural units of proteins (folds)

Scientists have recently begun to realize that seemingly random protein structures are actually constructed from a combination of basic protein folds. Moreover, it is the combination of these basic protein folds that is believed to diversify protein function. Our group, together with our international partners, is working to determine all the basic folds, including the subtype structures that account for about 10,000 structures, to create the "Encyclopedia of Basic Protein Folds." Using the knowledge contained in this encyclopedia, we aim to clarify the relationship between the structure and function of proteins. To accomplish this task, we are implementing automation and mechanization in the process used in protein structural determination. This process includes the following four steps: (1) Bioinformatics is applied to the genome sequence to predict domains in proteins targeted for structural determination. Bioinformatics is also used to assess the suitability of proteins for structural determination; (2) High throughput experimental screening is designed to assess the solubility and structural stability of proteins. Large-scale expression and preparation processes are also designed; (3) Processes involved in NMR and X-ray crystallographic analyses are automated; and (4) finally, high throughput and accurate screening for functional analysis are established.

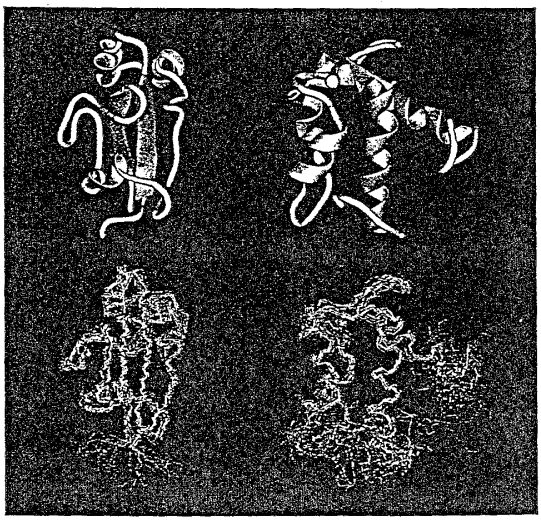


Figure 3. Ribon models (upper) and superimposed NMR-derived structures (lower) of hPar14 Protein (left) and EH Domain (right)

Project Director
Shigeyuki Yokoyama, D.Sci.

Development of the cell-free protein synthesis system: A new method for protein sample preparation

We have developed the "cell-free protein synthesis system" to assess the solubility and structural stability of proteins, as well as to express and prepare proteins on a large scale, as indicated in step (2) and Figure 4. With this cutting-edge technology, it has become possible to express and prepare large numbers of protein samples efficiently. In addition, we have been successful in preparing labeled protein samples, in the order of milligrams, that are suitable for structural analysis using NMR or X-ray crystallography. Currently, we are working to automate and mechanize this system.

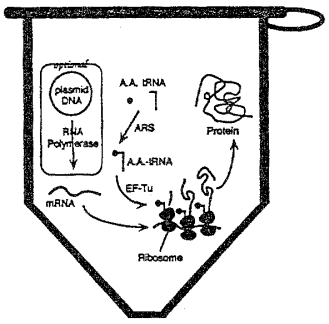


Figure 4. Schematic diagram of the cell-free protein synthesis system.

Using NMR to determine three dimensional structures of proteins

We have chosen nuclear magnetic resonance (NMR) and X-ray crystallography as our main tools for determining the basic protein folds. The NMR Park facility at the GSC and the SPring-8 facility at Harima will both be used for NMR and X-ray crystallographic analysis. Using NMR, a wide range of information, including the structure and dynamics of proteins with a molecular weight of under 30,000, can be efficiently obtained (Figure 5). In addition, NMR has the advantage of analyzing protein structures in solutions that are close to the environment in which the proteins actually function. Currently, we are attempting to raise the efficiency of the processes involved in NMR structural determination through automation.

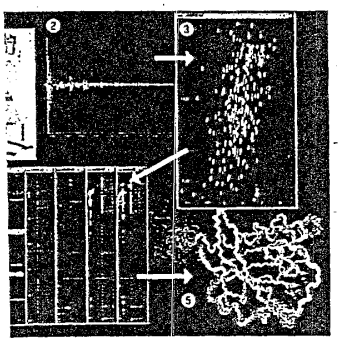


Figure 5. Outline of the structural analysis of proteins using NMR. Protein sample is placed inside a super-conducting magnet ①, and raw data ② is obtained. The raw data is processed by a mathematical operation called Fourier transformation, which gives a spectrum ③. Structural information ④ is extracted from further analysis of the spectrum. The final protein structure is deduced from the structural information.

Research on protein function

The key to a clear understanding of the role of genes inside cells and living organisms is to understand the functions of proteins at the molecular level. However, considering that the huge genome sequence contains enormous amounts of information on protein functions, all which must be examined through high throughput analysis, such methods require much thought and careful planning. We are currently combining biochemical analysis with modified spectrochemical methods, including mass spectrometry, to study proteins with unknown functions at the molecular level.

What can we expect in the future from research on protein structure and function?

With the "Encyclopedia of Basic Protein Folds" containing all basic folds and the basic functions of proteins identified (Figure 6), it should be possible to accurately predict the structure and function of a protein by simply observing the protein's amino acid sequence. For example, the active site and the mechanism of functional expression of a protein involved in a particular disease can be accurately predicted. Using such knowledge, we could adopt a more logical and precise approach to the cure and prevention of diseases. Our knowledge of protein structure and function is directly linked to the design and development of high quality drugs that target proteins selectively and specifically.

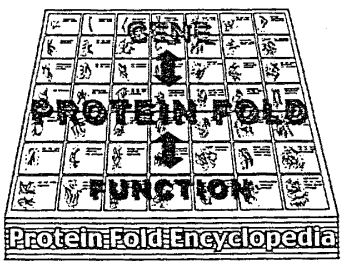


Figure 6. Encyclopedia of Basic Protein Folds

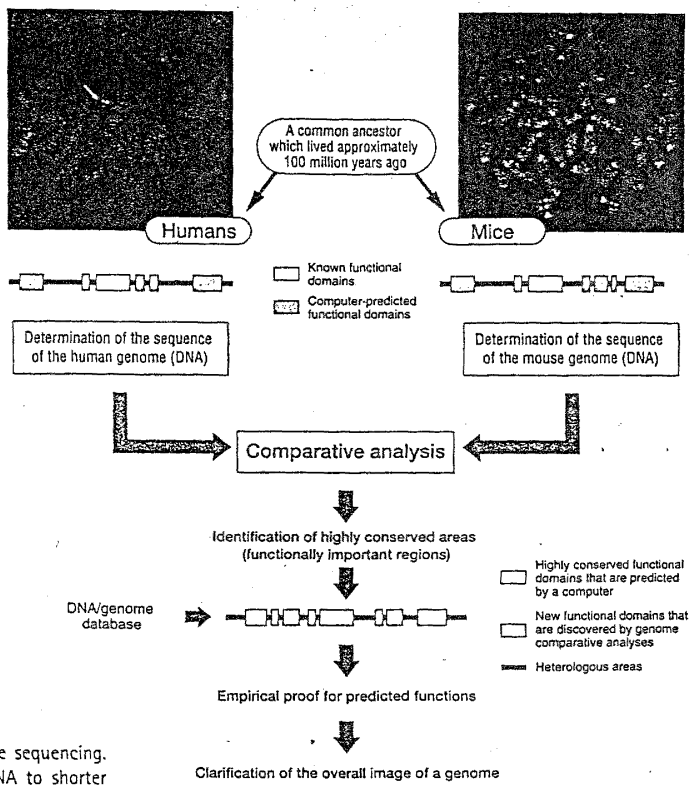
Human Genome Research Group

Goal and overall plan

Genome is the blueprint of life. Our goal is to determine the entire sequence of the human genome (DNA) through international collaboration and thus to decode the blueprint of human life. Our effort will be focused on chromosome 21, 11, and 18. Chromosome 21 is an etiologic gene responsible for Down's syndrome, whereas chromosome 11 contains genes responsible for a number of different diseases including diabetes and neurodegenerative diseases. Analyses will be conducted according to the following three steps:

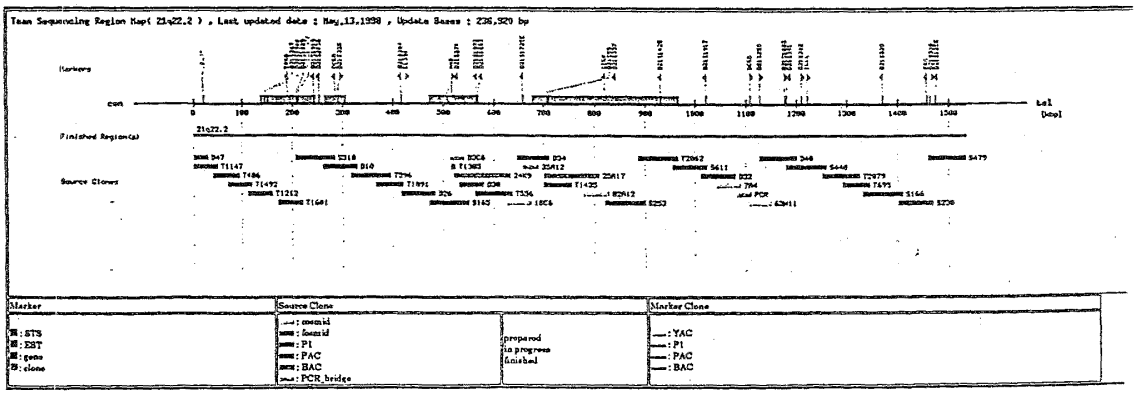
i) Construction of a genome map (According to the mapping data a minimum overlapping set of contigs are selected for sequencing)
ii) Determination of the genomic base sequence
iii) Analysis of sequence data

As functionally important base sequences have been preserved throughout evolution, data analyses will be performed by comparing human and mouse sequences (see the figure on the right).
As well chimp genome will be analyzed to discover human-specific genotypes.



Construction of a genome map

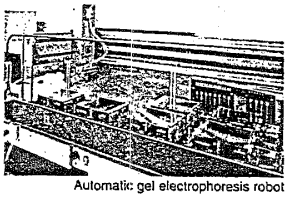
Mapping of genome is the first step of the genome sequencing. The mapping includes digestion of the genomic DNA to shorter fragments, multiplied in bacteria, and then each fragment is aligned along with original genomic DNA.



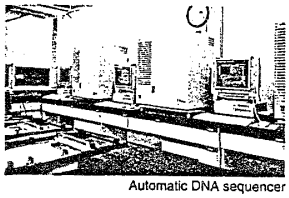
Project Director
Yoshiyuki Sakaki, Ph.D.

Determination of sequences

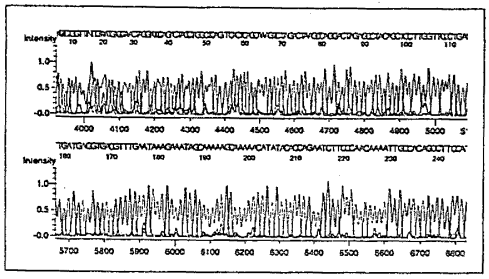
Through the use of an aligned DNA map, the base sequence of sequential DNA fragment is determined. The sample DNAs are further fragmented into smaller pieces so that their base sequences can be determined by an automatic DNA sequencer. The resulting data will be assembled to determine the base sequence of the entire DNA fragment. New technology for high throughput sequencing will be also developed.



Automatic gel electrophoresis robot



Automatic DNA sequencer

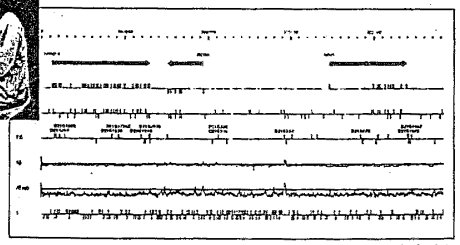


Sequence data profile

Analysis of sequence data

Computational analysis of the genomic sequences enables us to find biologically important information including genes, regulatory signals and other functional regions in the genomic sequences. Furthermore, comparison of human and mouse sequences also provides the evolutionary conserved regions which may retain common biological importance between them. These signals and regions are then experimentally analyzed to understand the biological roles.

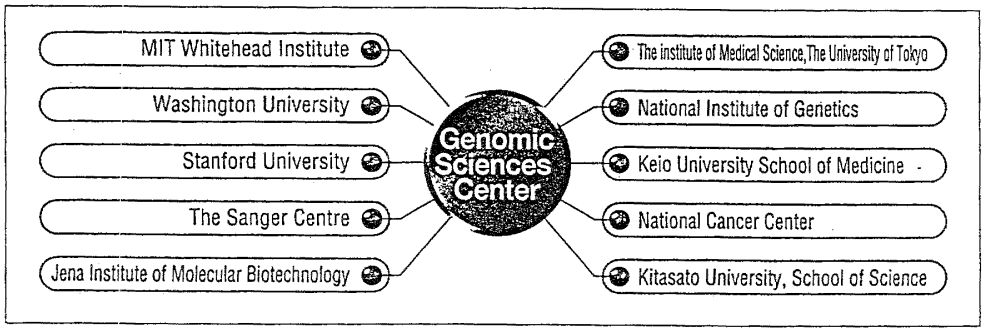
Comparative analysis

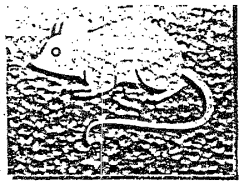


Some analysis data

International collaboration

Sequencing of the human genome is an international effort supported by a number of different countries including Japan, the United States of America, United Kingdom and Germany among others.





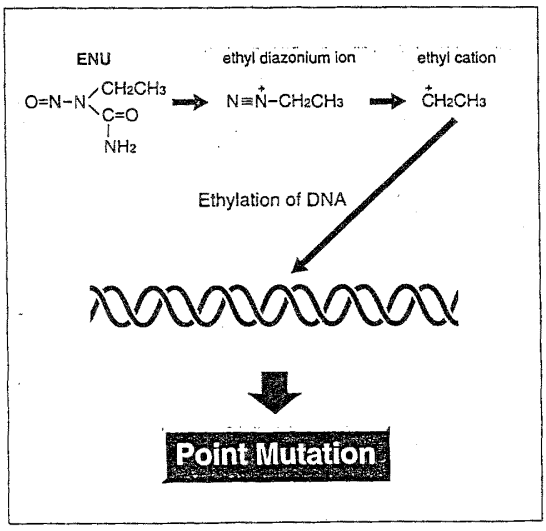
Mouse Functional Genomics Research Group

Objectives

Animal models are an indispensable tool for studying the biological functions of genes that are involved in the pathogenesis of human diseases. They are also essential to develop the therapy for and diagnosis of human diseases. In particular, mouse mutants have become the ideal model because of the close similarity in the genomes between the two species and the extensive knowledge of mouse genetics that has been compiled over the last 70 years. In addition, many elaborate techniques such as transgenesis and gene targeting have recently facilitated a "gene driven" analysis of the functions of pre-existing genes. Our objective is firstly to develop and establish a large number of mouse mutants which will be useful mainly for the "phenotype driven" approach. The ultimate goal is to provide a mutant mouse resource encompassing the whole genome, namely, 100,000 mutant mice for each gene in the mammalian genome.

Mouse mutagenesis

Genetic information, or DNA sequences in the genome, is inherited from parents to offspring with extremely high fidelity to maintain each species; mutation only arises at an extremely low frequency. To make our project feasible, it is necessary to utilize some effective mutagens. *N*-Ethyl-*N*-nitrosourea (ENU) is an ideal mutagen for our purpose, since it induces mutations 1000-fold more often than those occur by natural inheritance. ENU is well known and used as one of the most effective alkylating mutagens to randomly induce point mutations in male mouse germ cells.



Generation of mutant mice

We utilize well-established inbred mouse strains as the basis for mutagenesis. Inbred strains are genetically uniform, so any inherited anomalies that arise in inbred strains are basically due to mutations. ENU is intraperitoneally injected into male mice. The treated males (G0) are then mated, and the first generation of the offspring (G1) are generated. Dominant mutations may be detected in these G1 mice by systematic and complete phenotype screening, as will be described later. Recessive traits are detected as follows: Firstly, G1 males are mated again to obtain the second generation (G2) of females. Then, by backcrossing the G2 females with each paternal G1 mouse, homozygous mice for induced mutations may be propagated in the third generation (G3) of the offspring. We again carefully and thoroughly investigate any genetic variations in the G3 mice to detect recessive mutations. At the same time, it is crucial to create a preservation system for the mutant mice as a genetic resource for both the pure and applied science communities. Any mutant mice found in our project are preserved for such future use by freezing the sperm of all the G1 males.

Screening the phenotypes

Any detectable inherited difference from the original inbred strains is systematically screened. Visible mutations like eye-and coat-color changes, and structural and behavioral anomalies are screened. Physiological, biochemical, neurological, and anatomical analyses are also systematically conducted in order to discover any genetic variations that have been caused by mutations. They are categorized as early-onset phenotype screenings. Tumorigenesis susceptibility and senescence anomaly are additional screening categories for the late-onset phenotypes. We also develop novel techniques to detect mouse mutant phenotypes, which should be subsequenctly applicable to examining the human physiological conditions. New methods and approaches to the genetic diagnosis for human diseases will be facilitated through these developments in our mouse mutagenesis project.

Project Director
Toshihiko Shiroishi, D.Sci.

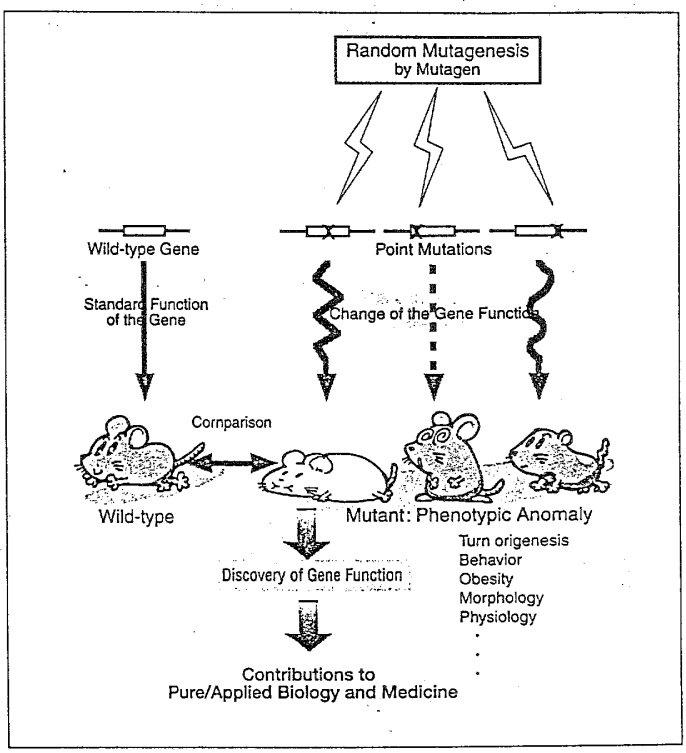
Unique features

We have set several unique features in our mutagenesis project:

i) We conduct late-onset phenotype screening for tumorigenesis and senescence. Current large-scale mouse mutagenesis projects are basically conducted only for early-onset phenotypes up to 3 months old. We have extended the observation period to more than one full year.

ii) Original Japanese inbred strains like MSM are used, in addition to conventional laboratory inbred strains that have been developed in Europe and the United States. MSM still represents most of the wild-type phenotypes that have been lost in many laboratory inbred mouse strains. Thus, unique mutant phenotypes related to novel gene functions could be expected from MSM mutagenesis.

iii) Synthetic mutant phenotypes or polygenic characteristics with epistatic interaction are analyzed. Many human diseases are known to be influenced not only by environmental factors but also by each individual's genetic background. The understanding of both gene-gene interaction and gene-environment interaction is the key to develop future medical science based upon functional genomics.

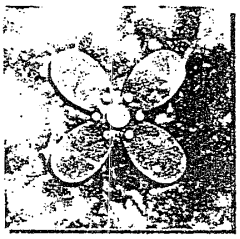


Consortium

Any large-scale mouse mutagenesis project in the world would currently be able to produce only a couple of hundred mutant mice a year at the most. To achieve the ultimate goal of at least one mutant for all the 100,000 genes in the mouse genome, it is therefore necessary to establish an international consortium like the case of the Human Genome Project. In order to develop such a consortium, we explore the feasibility of effective interaction at various levels of the project. An integrated database system is also being developed to maintain the mutant resources and conduct the project. The obtained information, database and resources will be open to public through the Internet.

House mouse (*Mus musculus*)

The house mouse, the most common laboratory animal in biomedical research, was created from the European wild mouse *Mus musculus domesticus*. Genes of mutant mice that had been bred by Japanese mouse fanciers in the Edo period were also introduced into the inbred mouse strains, and now contribute to the success of modern mouse genetics in this century. The mouse has almost the same genome size and gene numbers as the human being, and is widely used as an animal model for human diseases. The method of gene targeting was established in the beginning of the 1990s. Thus, the mouse is the only mammal with which we can employ two genetic approaches, "from phenotype to gene" and "from gene to phenotype."



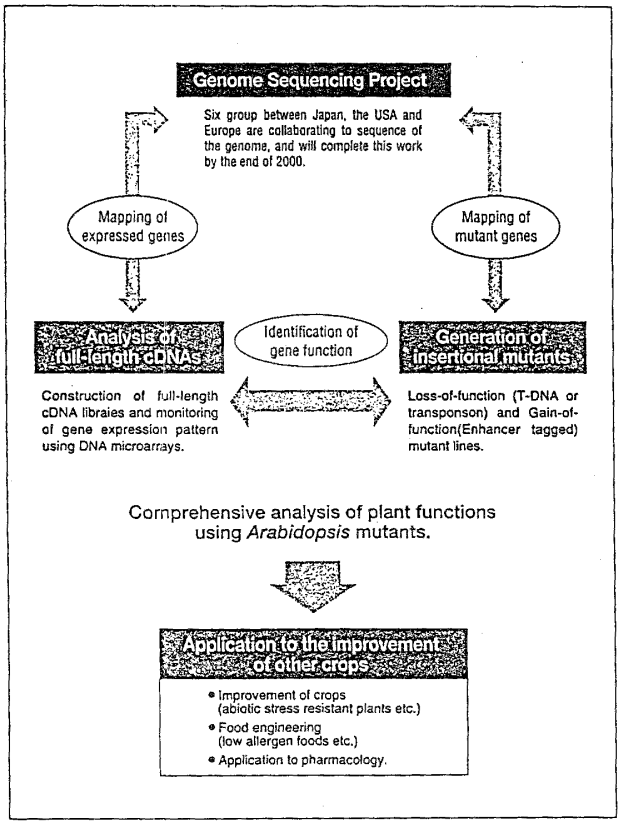
Plant Functional Genomics Research Group

Objectives and research plans

Plants are indispensable in our lives to provide vegetables, fruits and cereals. We also feed plants to cattle. While forests are necessary to maintain the earth's environment. It is important to understand the various physiological functions of plants to produce useful plants for our lives. By using *Arabidopsis* as a model plant, Plant Functional Genomics Research Group will comprehensively elucidate the functions of around 25,000 genes of the *Arabidopsis* genome and characterize their functions on plant physiology. We will take two genomic approaches for this purpose.

1. We will make an inventory of the expressed genes by using full-length cDNA libraries.
2. We will elucidate the functions of individual genes by characterizing a complete set of T-DNA and transposon insertional mutant lines.

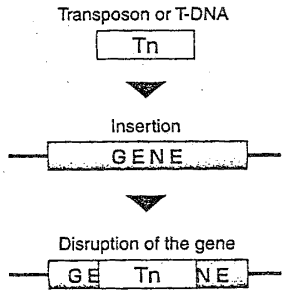
These approaches will help understanding of the genetic information written in the *Arabidopsis* genome.

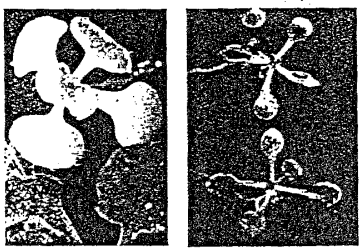


Functional analyses of genes by T-DNA and transposon insertion lines

1. We will characterize the gene functions by disrupting them with the transposon that translocates among chromosomes and T-DNA harboured on Agrobacterium.

Analysis of the gene function by using T-DNA or transposon insertional mutants



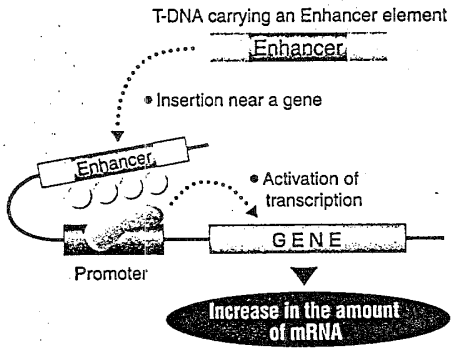


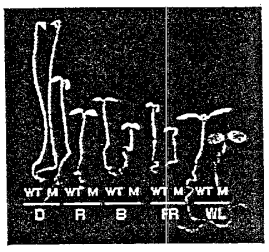
Examples of insertional mutants
Insertion of a transposon caused the albino phenotype (left panel) and the abnomal shape of leaves (right).

Project Director
Kazuo Shinozaki, D.Sci.

2. By using T-DNA (or the transposon) that has transcriptional enhancer, we will activate gene expression located proximal to the insertion sites. We can expect the phenotype which cannot be obtained by gene disruption. This method is called enhancer tagging or activation tagging.

Analysis of the gene function by using Enhancer tagged mutants

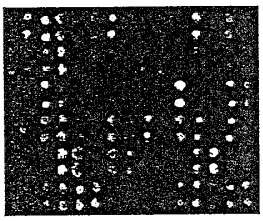




Example of an enhancer tagged mutant.
Insertion of an enhancer caused an abnormal light response phenotype.WT; wild type, M; mutant, D, R, B, FR, WL; lights with different wave lengths.

Gene expression monitoring by using an *Arabidopsis* full-length cDNA microarray

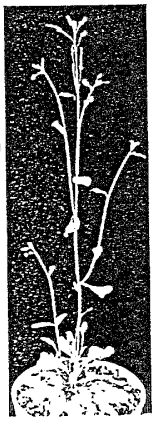
We are constructing a full-length cDNA bank which will represent all *Arabidopsis* genes as a complete set (cDNA is a synthetic copy of mRNA). We are also making a full-length cDNA microarray in which full-length cDNAs are sorted on side glasses. This microarray can be used to isolate and identify those genes controlled by environmental stress (drought, cold and salt), plant hormones (ABA and ethylene) and light response.



A gene expression pattern was prepared using a full-length cDNA of *Arabidopsis thaliana*

New era of plant biology from analyses of the *Arabidopsis* genome functions

Although *Arabidopsis* is not a useful crop, analyses of its genomic functions aid an understanding of the various functions of the plant. The information obtained through this research will be applied to the production of crops with high productivity, and resistance to plant diseases, resistance to pests, and resistance to environmental conditions such as drought, cold, strong light intensity and salt. It can also be applied for food production such as low allergenic crops, production of new medicines, and production of plants useful for our living environment.



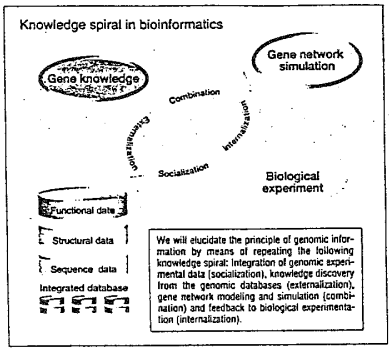
Arabidopsis thaliana

Arabidopsis thaliana is a brassica plant. It is widely studied throughout the world due to its short life, compactness and small genome size.
The genomic sequence is going to be determined by international cooperation among Japan, the United Sates and Europe.

Bioinformatics Group

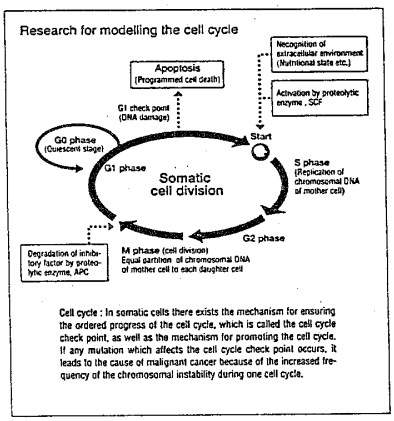
Knowledge spiral in bioinformatics

The main topic in bioinformatics is the approaching shift from gene sequence information analysis and protein structural information analysis to functional information analysis. Application of biological knowledge is indispensable in the clarification of functional information. With the conventional knowledge processing technology, there was a bias toward knowledge that can easily be input into a computer, i.e., explicit knowledge and little consideration was given to tacit knowledge obtained in human beings. In the gene knowledge spiral, bioinformatics technology is being developed from the standpoint of this tacit knowledge. The aim is to extract common, integrated knowledge from experimental data, construct a gene network, and create gene information by feedback from simulation to biological experiments.



Clarification of genome information principles

There are various types of genes including genes in structural constituents of cells, those that control chemical reactions within cells, and those that regulate the expression of other genes. It is clear that these genes interact and form a network for the cell as a whole in which the expression of certain genes controls the expression of other genes. To analyze this gene network, the following information is necessary: (1) details of metabolic reactions within cells, (2) molecular interactions involved in protein complex formation, (3) sequential changes in the expression levels of RNAs and proteins, and (4) the effects of deletion or duplication of specific genes and changes in the expression level such as over-expression. With the development of models incorporating this information in differential equations, it will be possible to simulate the biological behavior of genes within the cells. This approach should allow us to predict the effects of gene mutations, as well as the efficacy and/or adverse reactions of pharmaceuticals on a computer.

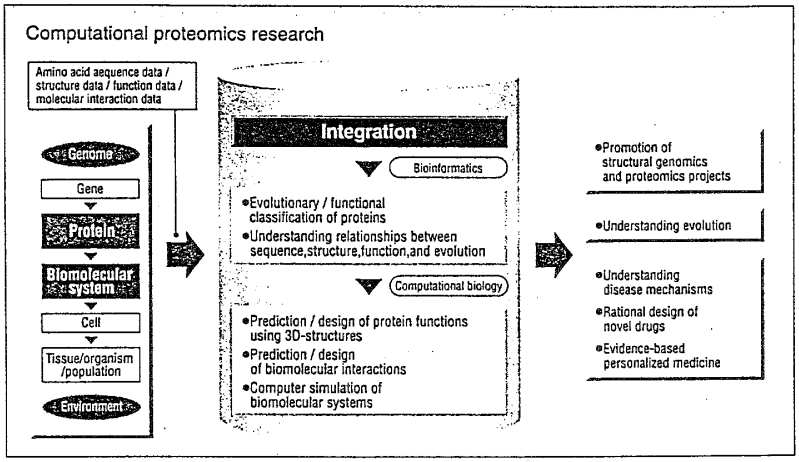


Elucidating mechanisms of cell functions through information analysis and computer simulation

Complex behavior of living cells is achieved by networks of interactions between proteins and other biomolecules. We conduct information analysis and computer simulation to elucidate the cellular mechanisms on the basis of information on protein structure and function. Using vast amounts of amino acid sequence and structure data, proteins are systematically classified. Through such classification, useful knowledge is acquired concerning relationships among sequence, structure, function, and evolution. A large number of examples of interactions of proteins with other proteins and molecules are being collected and organized into a database. In this

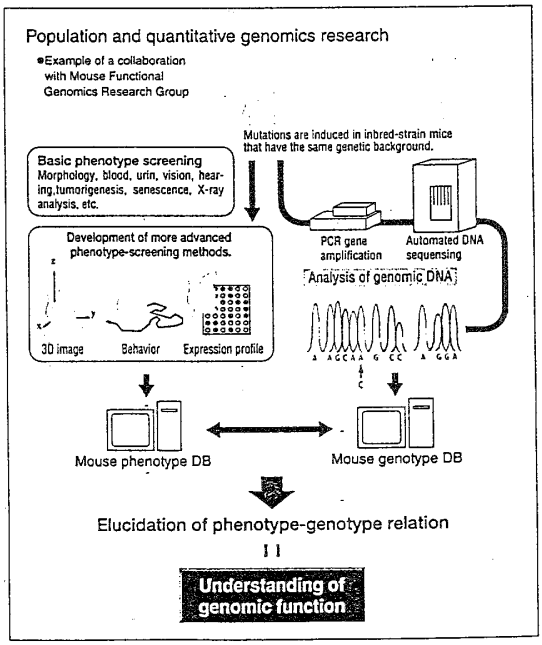
Project Director
Akiyoshi Wada, D.Sci.

way, on the basis of information on structures and functions of individual molecules, the functions and behavior of a system are theoretically modeled. Using computer simulations, behavior of cells is predicted in response to such external and internal factors as environmental conditions, drugs, and genetic mutations and polymorphisms. The research described here is expected to make a major contribution to medical science. For example, it will help to elucidate molecular mechanisms of various diseases and to rationally design novel drugs. It will also be useful for predicting effects of differences in genotypes such as SNPs on phenotypes, e.g., disease susceptibility and drug response, and achieving evidence-based personalized medicine (the right drug for the right patient at the right time in the right dose) that provides proper treatment and medication according to the individuals' characteristics.



Understanding the genomic functions at the organism level

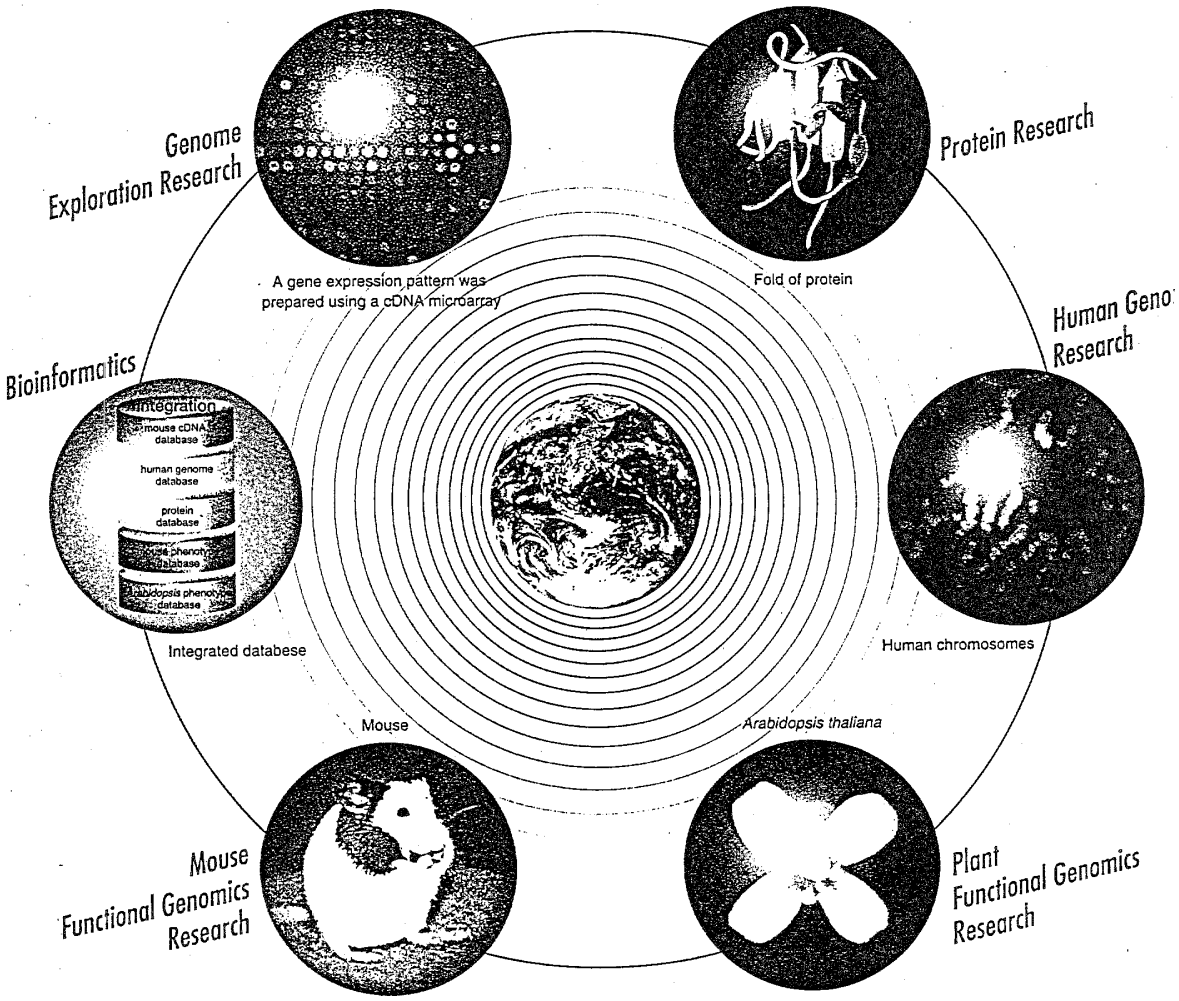
DNA changes (mutations) are reflected in not only heredity diseases but also in individual constitutional differences, such as fatigability and response to foods, medicine, and the environment. The objective of the project is to identify what genetic difference (genotype) is responsible for what constitutional variance (phenotype) at the organism level. At present, genotypes can be determined precisely at the DNA sequence level. However, measurement of phenotypes is still a problem because of environmental effects. It is necessary to effectively collect many highly reliable information to detect genetic factors. Thus, it is necessary for future "informatics biology and medicine" with animal model systems such as the mouse 1) to establish a reliable phenotype assessment system, 2) to detect the affected phenotype(s) based on each identified genotype, 3) to depict DNA change(s) due to each recognized phenotype, 4) to consolidate information on phenotypes and genotypes, and 5) to construct an integrated functional genomics database on a large scale. This work will make "order-made therapy" feasible and lead to the improvement of "Quality of Life". Mutant mice with clear genotypes and phenotypes will contribute to medicine and drug discovery as animal models for human disease and development of new treatment methods. By using plant model systems such as Arabidopsis, a similar approach will also contribute to the development of novel inbreeding systems.



A rich and bright future

Establishing global partnerships

The RIKEN Genomic Sciences Center (GSC) has a three-fold aim: to systematically comprehend the constituent organic elements of DNA and proteins, the building-blocks of life; to popularize this research at the individual level; and to gather organic data on the various substances involved in the life process. These activities are expected to shed light, not only on the important genes encoded in the genome and their related proteins, but also on data that will contribute to innovations in such fields as medicine and agriculture. Through the efficient processing of this accumulated data, GSC intends also to participate in the generation of new industries creating a prosperous future.

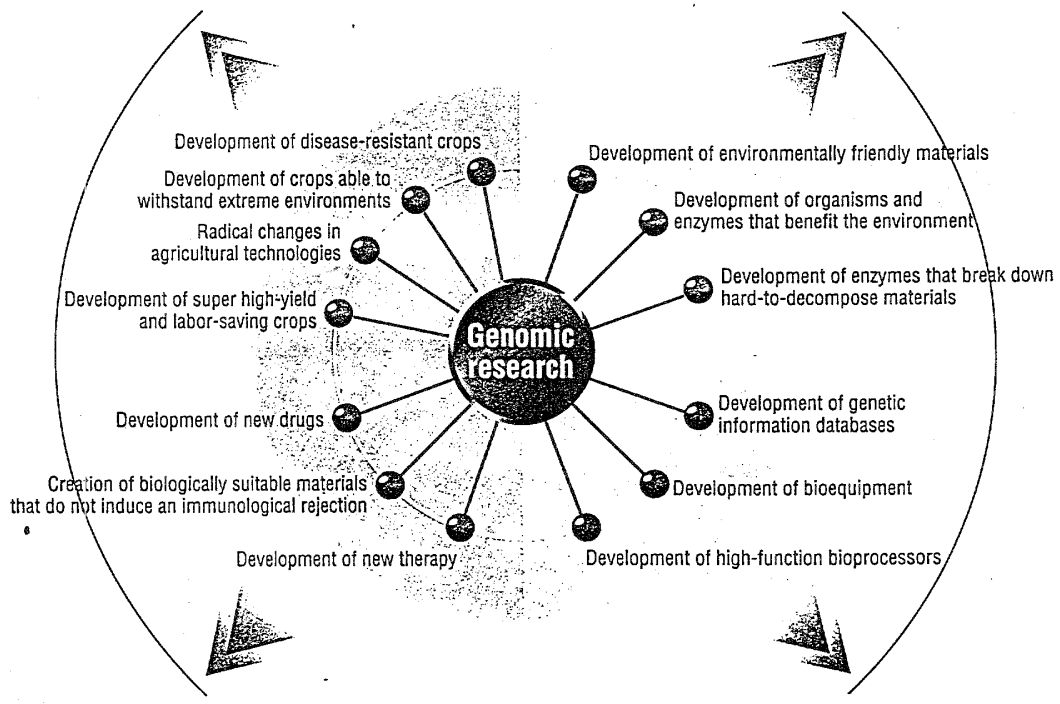


Continuous production and procurement of food

- Improvement of grain production
- Establishment of environmentally sound practices methods that do not require the use of pesticides
- Creating lands suitable for farming out of extreme environments
- Establishment of diagnostic methods for genetic diseases for livestock
- Development of radically new breeds and preservation of the environment

Preservation of the environment

- Decomposition and elimination of raw oil and gasoline
- Improvement of contaminated underground water and recovery of high-nutrition ponds and lakes
- Greening of desert regions
- Reducing loads on the earht's environment through the use of completely biodegradable materials.



Application to medicine

- Conquering cancer, diabetes,hypertension and allergy
- Preventing diseases by high-speed and accurate diagnoses
- Developing bone marrow transplantation techniques using blood stem cells
- Improving technology associated with the manufacture of artificial skin and blood
- Developing and making gene therapy widely available

Laying a foundations for new industries

- Developing databases for human gene information
- Developing equipment systems utilizing biological functions: such as biosensor,biochip,micromachines,etc
- Application to the chemical infustry and energy production: such as bioreactor,biomass,etc

The Genomic Sciences Center's Mission in the 21st Century

Akiyoshi Wada

Some 4 billion years ago, a system of self-reproduction that was later termed "life" appeared in our solar system on the planet Earth. Organisms subsequently evolved through a process of selection that acted on the genes of this life. Specifically, these genes, which formed an unbroken intergenerational chain, were subjected, through individual organisms, to pressure from the environment. With a range of living species executing leading roles, stunning nature not found on any other planet was created. Wisdom for survival in a volatile environment is concentrated in each organism's genome, where it is stored as genetic information written in DNA molecules. Even today, this genetic code continues to be rewritten as it handed down in the society of living organisms, including human beings.

A few millennia ago-a mere millionth of the history that has elapsed'the human race established techniques for recording and teaching. It has also displayed some uniquely human talents: the ability to reason and to measure as well as powers of originality and foresight. In human society, wisdom for living came to be passed on to posterity through such systematic, non-genetic means, thus ushering in the age of science. If we think of the history of science as being written on a scroll measuring one meter, the history of life itself would unfold over a length of 1,000 kilometers, which is the distance from Tokyo to Kagoshima at the southern tip of Japan.

I believe that the ultimate objective of the Genomic Sciences Center is to contribute to the development of human society by elucidating and comprehending the essence of the wisdom found in these two disparate historical contexts and then synthesizing it into a single body of knowledge. There is a reason for pursuing this synthesis. To wit, human beings are the only creatures for whom the transmission of information across generations flows through two parallel channels. This duality actually forms the epicenter of problems that rock contemporary human society. Why does this occur?

Unlike the evolution of life through a process involving heredity and natural selection, human society's cross-generation transmission of information transpires swiftly and in enormous quantities. Our ability to learn from experience and then educate others further accelerates the momentum. Such positive feedback linked to a sense of purpose is not found in heredity. In this manner, human beings have actively harnessed science and technology to enlarge and develop civilization at a rate far faster than the evolution of nature. As a result, the social and cultural environment distinct to the human race has begun to interfere with genome activity. Such activity has been assiduously undertaken throughout the history of the universe, which is a million times the duration of human civilization. The pressure exerted by this interference is escalating exponentially. If the swift computer race and industrial development that are visible today simply continue on their present course, it is feared, only one of the two aforementioned parallel transmission channels will become swollen with information traveling at a high velocity. This could engender incalculably dire consequences for the future of the human race.

I am confident, though, that humankind, with the convergence of global disruption in the first half of the 20th century, is coming to its senses. At the very least, conscientious individuals with the gift of foresight recognize that the preservation of biological diversity and a rich global environment is an absolute requirement for the advancement of a prolific society among the intelligent creatures known as the human race. People have recognized that bitter experiences related to the destruction of the natural environment must be fed into the above information pipeline as negative feedback. Humanity has also become cognizant of the existence within itself of what is known as the "soul." From within it originates the idea of optimization of the whole, that is, symbiosis. Humanity has begun to ponder the enormous implications that this concept has with respect to the future of the human race and civilization.

What is life? What does it mean to be human? At this juncture, human society needs to discover answers to these eternal questions. We can only find answers through understanding based on the integration of three threads-genome-embedded information; physical and chemical structures; and physical, chemical, and biological functions-into a single strand.

The 21st century will unfold as an age in which we synthesize the scientific and technological gains of the 20th century and then pursue ways to funnel their collective strengths into a new level of prosperity for humankind. Given this quest, genomic science research holds unmistakable significance for 21st century humankind. That the onus is on researchers is self-evident. Committed to fulfilling the expectations of Japan and the rest of the international community, the Genomic Sciences Center, which subscribes to the basic philosophy I have outlined here, will strive to play an instrumental role in the realm of science and technology in the new century.

<starting date> : **October 1, 2000**

<Number of Personnel in 2000> : **250**

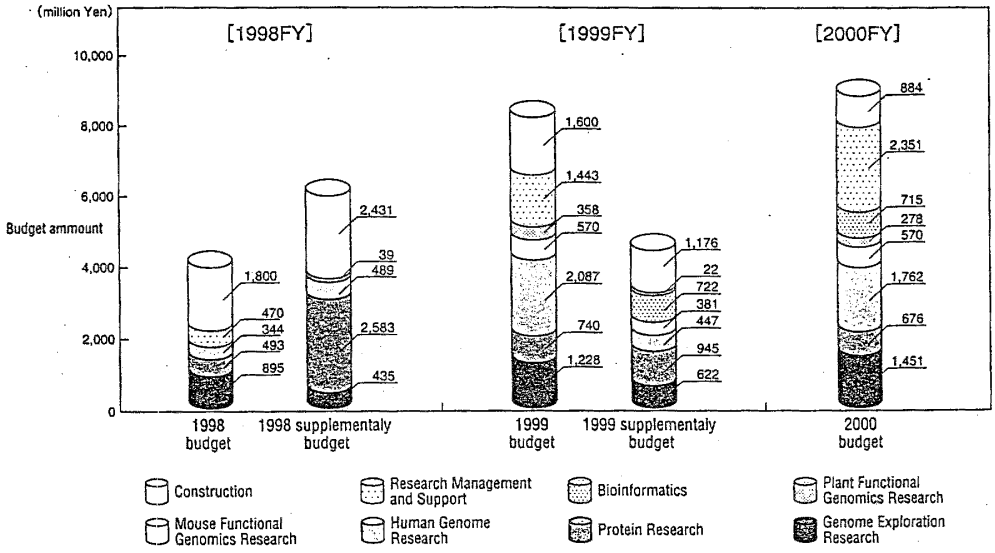
<Publication of Research Findings> : ●Between October 01, 1998 and March 31, 1999:
11 / International Conferences **06** / Publications in Western Journals
10 / Domestic Conferences **01** / Publication in Japanese Journals

●Between April 01, 1999 and March 31, 2000:
48 / International Conferences **15** / Publications in Western Journals
81 / Domestic Conferences **35** / Publication in Japanese Journals

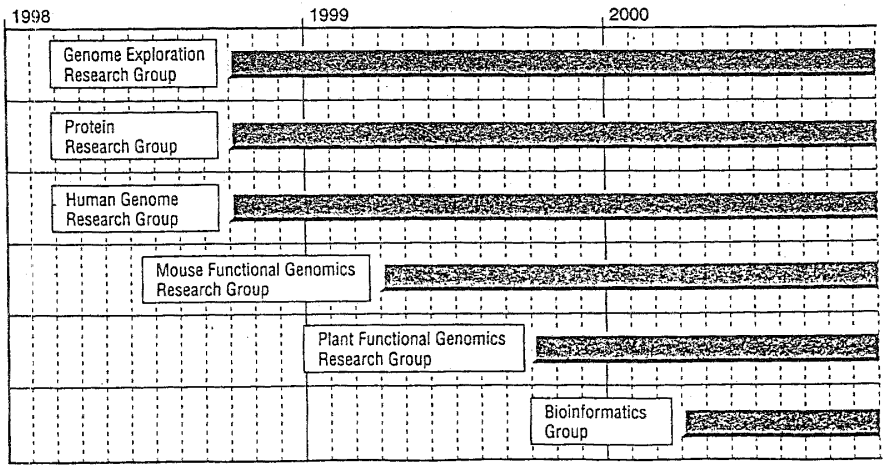
<Number of Patents Applications> : ●Between October 01, 1998 and March 31, 1999:
02 / Domestic Patent Applications
00 / International Patent Applications

●Between April 01, 1999 and March 31, 2000:
15 / Domestic Patent Applications
05 / International Patent Applications

●Budget transition

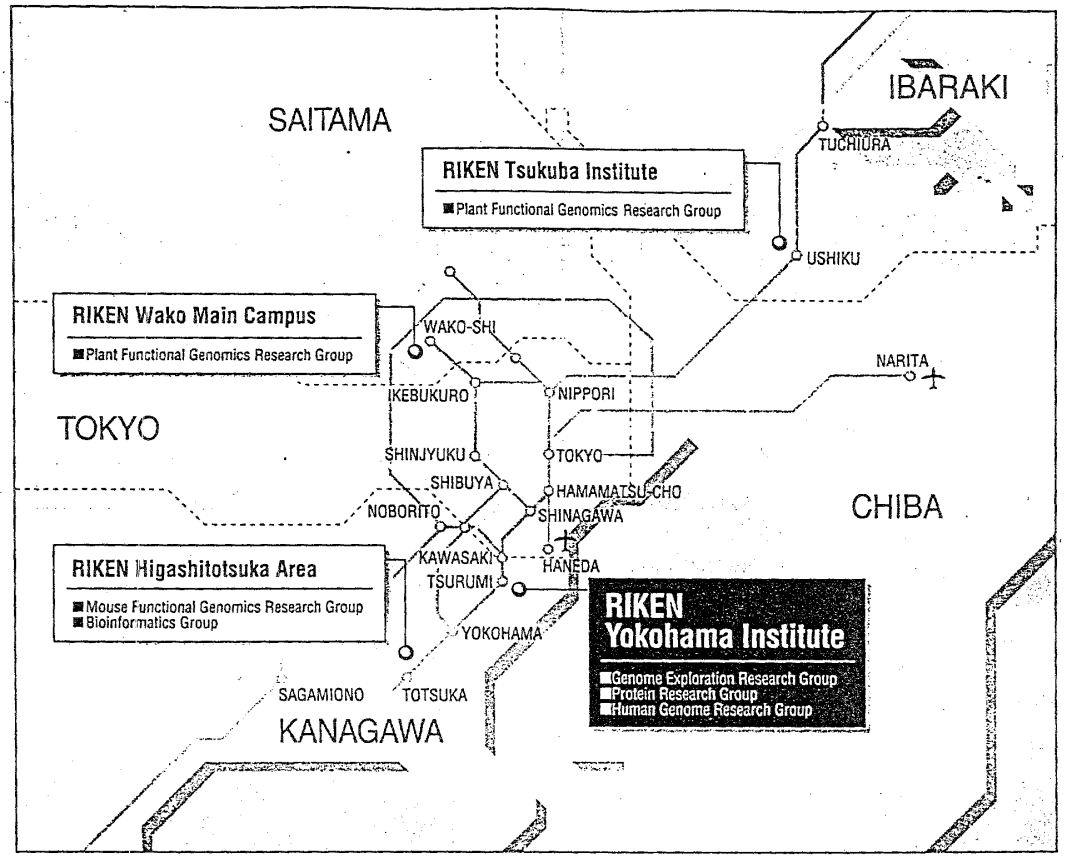


●History of GSC



Recent Media Releases

TITLE	Publication	Date
Genome Exploration Research Group		
RIKEN Develops Sugar-Utilizing Method: Enzyme Response Speed Increased Tenfold; Heat-Resistance Increased	Nihon Keizai Shimbun	Jan. 04, 1999
RIKEN Publishes Index of Mouse Genome Encyclopedia on Internet	Nikkei Sangyo Shimbun	Jan. 12, 1999
Japan Creates Mouse DNA Encyclopedia (Vol. 397, pp. 98-99)	Nature	Jan. 14, 1999
RIKEN Posts Gene Encyclopedia on Home Page	Sankei Shimbun	Jan. 16, 1999
RIKEN Publishes Mouse Genome Dictionary on Internet	Asahi Shimbun	Jan. 18, 1999
Hunting Mouse Genes (Vol. 283, p. 455)	Science	Jan. 22, 1999
RIKEN Mouse Genes Published by DDBJ	Kagaku Kogyo Nippo	Jul. 16, 1999
DDBJ: RIKEN Mouse Genome Encyclopedia Lists 175,000 Entries	Japan Industrial Journal	Jul. 19, 1999
Genome Research: 180,000 Items of RIKEN Mouse Genome Data Published Simultaneously	Nikkan Kogyo Shimbun	Aug. 06, 1999
Study of Disease-Causing Genes: RIKEN and U.S. Universities Use Mice in Quest to Develop DNA Microarray	Nihon Keizai Shimbun	Sept. 06, 1999
RIKEN and Shimazu Corporation Develop High Speed DNA Analysis Equipment	Nihon Keizai Shimbun	Oct. 09, 1999
RIKEN / Shimazu Corporation Machine Speeds up DNA Analysis Fourfold	Japan Industrial Journal	Oct. 10, 1999
RIKEN / Shimazu Corp. Develop High-Speed DNA Base Sequence Analysis: Processes 384 Specimens Simultaneously	Nikkan Kogyo Shimbun	Oct. 11, 1999
Gathering of Mouse Genes Accelerates - Existence of Full-Length cDNA - Towards Proving 140,000-Variety Prediction	Kagaku Kogyo Nippo	Oct. 13, 1999
RIKEN, JST Isolate Transient Diabetes Gene in Human Newborns with Independently-Developed RLGS System	Japan Industrial Journal	Feb. 29, 2000
RIKEN, Others Discover Genetic Cause of Diabetes in Newborns	Nihon Keizai Shimbun	Mar. 04, 2000
Lesson in Economics - Opening up the New Millenium - Era of Integration and Acceleration in the Arbor of Life - Cross-Sectional Research Holds Key - View of Techno	Nihon Keizai Shimbun	Apr. 03, 2000
The Rise of the Mouse, Biomedicine's Model Mammal	Science	Apr. 14, 2000
RIKEN Obtains DNA from 20,000 Mouse Genes; Supplies to U.S. Essentially Free of Charge	Asahi Shimbun	May 08, 2000
Exhibition of 21st Century Dream Technology - Scientists' Three Greatest Dream Technologies - Gaining Control over the Three Most Serious Diseases, Including Cancer	Nihon Keizai Shimbun	Jun. 19, 2000
Protein Research Group		
Technology for Developing the 21st Century Marketplace: Towards Full Understanding of Genomic Information	Nihon Keizai Shimbun	Oct. 18, 1999
Beyond the Genome, Protein: the Age of Determining Large Number of Protein Structures	Asahi Shimbun	Dec. 10, 1999
1000 Different Protein Folds: The Greatest Challenge After the Human Genome in the Analysis of the Three-Dimensional Structure of Proteins	Yomiuri Shimbun	Jan. 24, 2000
21st Century Prelude: The Genome Cannot be Understood Without Understanding of Protein and Protein Structure	Asahi Shimbun	Mar. 22, 2000
Protein Structure Group Seeks to Draft Common Ground Rules (Vol. 403, 691)	Nature	Feb. 17, 2000
Human Genome Research Group		
Rejection of Genetically Modified Foodstuffs: Information Regarding Safety Must Be Made Public	Nihon Keizai Shimbun	Oct. 04, 1999
Decoding of the "Human Blueprint" to be Completed as Early as Next Spring - Tremendous Impact - Genetic Revolution - Human Genome Project	Mainichi Shimbun	Dec. 31, 1999
Aera Journalists Choose Japan's Top 50 Key People (p. 52, p. 59) Dr. Yoshiyuki Sakaki	Aera	Dec. 1999 - Jan. 2000
Human Profile: Mr. Yoshiyuki Sakaki, a leader of the Human Genome Project	Asahi Shimbun	Jan. 01, 2000
Decoding of Chromosome 21to be Completed Next Month - Japanese/German Human Genome Research Team - Hope Raised for Understanding Intractable Diseases	Yomiuri Shimbun	Jan. 10, 2000
A Glimpse of the 21st Century Through the Decoding of the Human Genome (p. 28? p. 29)	Foto	Mar. 15, 2000
Decoding Chromosome 21 - Understanding of Downs Syndrome Gains Momentum - Japanese/German Research Team Releases Findings on Internet	To-o Nippo	May 09, 2000
Decoding Chromosome 21 - RIKEN/Keio University/German Joint Research Team - Understanding of Downs Syndrome Gains Momentum	Yamagata Shimbun	May 09, 2000
Decoding Chromosome 21 - Understanding of Downs Syndrome and Other Genetic Diseases Gains Momentum - Japanese/German Research Team Discovers 98 New Genes	Kyoto Shimbun	May 09, 2000
Decoding Chromosome 21 - RIKEN and Others in Japan/Germany Joint Research - Light in the Future for Cancer and Downs Syndrome Cures	Asahi Shimbun	May 09, 2000
Decoding Chromosome 21 - Japanese/German Research Team - Hope for Downs Syndrome Cure	Sankei Shimbun	May 09, 2000
Decoding Chromosome 21 - Japanese/German Research Team - Path to Unraveling Causes of Intractable Diseases	Nihon Keizai Shimbun	May 09, 2000
Decoding Chromosome 21 - Joint Japanese/German Research Team - Understanding of Downs Syndrome Gains Momentum	Tokyo Shimbun	May 09, 2000
Chromosome 21 Completed, Phase Two Begun (Vol. 288, p. 939)	Science	May 12, 2000
Recounting a Genetic Story (Vol. 405, pp. 283-284)	Nature	May 18, 2000
The DNA Sequence of Human Chromosome 21 (Vol. 405, pp. 311-319)	Nature	May 18, 2000
RIKEN Begins the World's First Comparison of Human and Chimpanzee Brain Genetics: Exploring the Secrets of Intelligence	Yomiuri Shimbun	Jun. 23, 2000
Celera Announces Completion of Human Genome Decoding - Life Science Hold High Hopes - International Team Also Nears Completion	Nihon Keizai Shimbun	Jun. 27, 2000
Joint International Team Announces Completion of Human Genome Description: 90% Decoded, Research Accelerates	Yomiuri Shimbun	Jun. 27, 2000
Decoding of Human Genome "Almost Complete": Joint Project of Japan/U.S. Governments and U.S. Private Enterprises	Sankei Shimbun	Jun. 27, 2000
Japan/Europe/U.S. Complete Decoding of Human Genome - U.S. Private Enterprise Also Makes Announcement - Step Towards Diagnosis and Treatment of Genetic Diseases	Mainichi Shimbun	Jun. 27, 2000
85% of Human Genome Description Published - U.S. President Announces Reading of Genetic Code - Official Collaboration to be Discussed	Asahi Shimbun	Jun. 27, 2000
90% of Human Genome Decoded - Next Step is Practical Application - Research Accelerates Through Competition - High Expectations for Medical Applications - Concern for Discrimination in Everyday	Tokyo Shimbun	Jun. 27, 2000
The Human Genome Project Gallops Towards a Revolution of Life and Medicine: Decoding of Chromosomes 21 and 22 Completed (July Issue, p. 12? p. 17)	SCIaS	Jul. 01, 2000
Study Compares Chimps and People (Vol. 406, p. 4)	Nature	Jul. 06, 2000
ON THE GENE TRAIL: How a research team in Japan mapped chromosome 21 (July 7, 2000)	Asiaweek	Jul. 07, 2000
Mouse Functional Genomics Research Group		
RIKEN Begins Systematic Development of Point Mutations in Mice	Nikkei Biotech	Dec. 06, 1999
Plant Functional Genomics Research Group		
Identification of Large Number of Genes that Respond to Early-Stage Dry Stress	InterLABO	Jul. 2000
Bioinformatics Group		
Using Computers in Quest to Unravel Mystery of Gene Functioning	Yomiuri Shimbun	Apr. 17, 2000



The RIKEN Genomic Sciences Center (GSC)'s Genome Exploration Research Group, Protein Research Group, and Human Genome Research Group began research in the new facilities at the RIKEN Yokohama Institute in Tsurumi-ku, Yokohama on October 1, 2000. The Mouse Functional Genomics Research Group and Bioinformatics Group are conducting research in RIKEN Higashitotsuka Area. The Plant Functional Genomics Research Group is using facilities at the RIKEN Tsukuba Institute and RIKEN Wako Main Campus. These research groups will gradually integrate with the RIKEN Yokohama Institute.

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●Mouse Functional Genomics Research Group ●Bioinformatics Group	214 Maeda-cho,Totsuka-ku,Yokohama City,Kanagawa, 244-0804,JAPAN
●Plant Functional Genomics Research Group	3-1-1 Koyadai,Tsukuba City,Ibaraki,305-0074,JAPAN 2-1 Hirosawa,Wako City,Saitama,351-0198,JAPAN

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