Protein 3000 Project to Increase International Contribution and Competitiveness of Japan

Objectives and Framework

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Background

The international project team on human genome sequencing announced the draft sequence in 2002, propelling life sciences research into a new era. The human genome was officially completed in 2003, and the following year saw the completion of the precise decoding of the rice genome, too. The announcement of the decoding of the human genome marked the start of the post-genome era in life sciences research, and thrust proteins, the functional elements of cells, into the limelight.

Genome projects have worked on fully decoding genetic information of a variety of organisms, and in light of this, post-genomic research's key strategic goal at present is the exhaustive analyses of proteins, the products of genetic expression. This has given rise to the emergence of a new field of study called Structural Genomics.

Nucleic acid and proteins, which are types of biomacromolecules, can be likened to computer hardware and software. Genetic DNA is a polymer made up of four nucleotides with similar physicochemical properties, and thus genetic DNAs can be manipulated in the same way. This means, for example, that any kind of DNA can be extracted and purified using the same protocol. This is the same as being able to use the same operating system software on any type of computer.

In contrast to this, proteins — the functional elements — are highly diversed, and even proteins with the same function may present in different ways in different organisms. This is the same as different model computers having different types of keyboards even though they all use Windows. In the same way, structural genomics cannot follow in the footsteps of human genome projects, and a more specific strategy is required given the wide variety of proteins to be examined.

Objectives

For proteins, a strategy of exhaustive analysis, like that applied for the human genome, may not necessarily be effective. The structural classification of proteins has been studied for many years now, where, for example, secondary structural topologies of proteins for which 3D structures had been determined have been explained. At the very beginning of the age of structural genomics, it was believed that all pro-

teins found in the living organisms could be classified in 10,000 basic structures.

Structural genomics is thus working on elucidating all of these basic structures. As the basic structure is associated with the primary sequence, if all the basic structures can be solved, then we should be able to speculate 3D structure of a protein from it's genetic information. And, as function is based on structure, it will be possible to predict both function and structure of a protein of interest from the gene sequence. This has given rise to the idea that we should promote international collaboration to identify all the basic structures of proteins, as was seen in the genome age.

The Protein 3000 Project, in the wake of these international academic trends, is so named because of Japan's aim to identify one-thirds, that is 3000, of the total number of basic protein structures.

However, when this project was first put together, Japan was making around a 7% contribution to protein structural analysis, and so achieving this goal would require Japan starting with basic research infrastructure upgrades in this area. The Protein 3000 Project thus incorporates initiatives aimed at improving and expanding the research environment through the upgrading of research equipment for protein structure and functional analysis, the development of research techniques and methods, and the training of personnel. Though Japanese contribution to the structural determination of proteins was low, Japan has been the world first rate country in terms of NMR-based structural analyses. In addition, we have constructed the most advanced synchrotron radiation facilities for protein structural studies including the SPring-8 radiation facility and those of the High Energy Accelerator Research Organization (KEK) (See Photos).

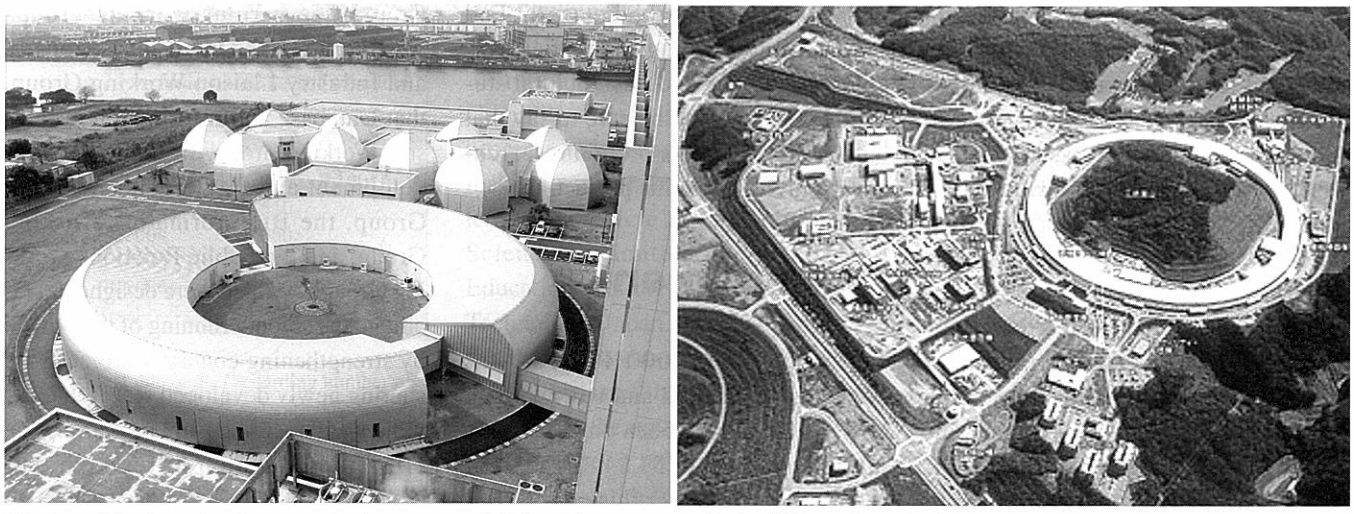
Although this project called for massive sums of research funding, it was also expected to lead to a strengthening in the international competitiveness of Japanese industry, as the analysis outcomes are to be used to foster new industries, such as drug design. As such, the analysis of 3000 new proteins is not the sole aim of this project.

Research framework

Since the early planning stages, "All Japan" was a key phrase used as part of the Protein 3000 Project, as the project aimed to harness the collective abilities of protein research scientists around Japan to achieve the project objectives. Research scientists affiliated with other ministries and agencies, as well as research organizations under the umbrella of the Ministry of Economy, Trade and Industry, are also part of the committee that drew up the project. This committee also includes representatives from industry as well.

The Japan Science and Technology Agency (JST) has also gotten on-board through their Core Research for Evolutional Science and Technology (CREST) projects and other projects, launching projects complementary to the Protein 3000 Project, such as the "Protein Structure and Functional Mechanisms" project. The CREST Project got underway in the same financial year as the Protein 3000 Project. The JST project aims to analyze proteins and protein complexes of particular biological significance and to develop revolutionary research techniques and methods associated with the structural and functional analyses of proteins (See Table 1).

The Protein 3000 Project consists of two parts; exhaustive analyses and more specific analyses (See Table 2). The exhaustive analyses are headed up by RIKEN Yokohama's Genomic Sciences Center, and the more specific analyses of proteins are handled mainly by university research laboratories and national research institutes. Specific protein analysis is further broken up into



Photos: Project background: Japan established largest-scale facilities ahead of therst of the world
(left: RIKEN large-scale nuclear magnetic resonance (NMR) facility; right: Large-scale synchrotron radiation facility, "SPring-8")

Table 1: Selected themes and principal investigators in CREST "Protein Structure and Functional Mechanisms"

Selection fiscal year	Principal investigator	Role / Affiliation	Research themes
FY2001	Kazuhiro Iwai	Prof., Osaka City Univ.	Analysis of the Ubiquitin-Mediated Regulation of Protein Functions
	Masatsune Kainosho	Visiting Prof., Tokyo Metropolitan Univ.	Developing a New Approach for High-throughput, High-accuracy NMR Structural Analyses of Genomic Proteins
	Yuji C. Sasaki	Chief Scientist, SPring-8 / JASRI (Japan Synchrotron Radiation Research Institute)	Analysis of Dynamical Function/Structure of Protein Molecules From Single-Molecular Experiment With X-rays
	Yoshinori Shichida	Prof., Kyoto Univ.	Structural and Functional Analyses of G Protein-Coupled Receptors Using Rhodopsin as a Model Receptor
	Kazuhiro Nagata	Prof., Kyoto Univ.	Quality Control Mechanism of Newly Synthesized Proteins in the Endoplasmic Reticulum
	Toshio Hakoshima	Prof., Nara Institute of Science and Technology	Structural Basis of Protein Functions and their Regulation by Dynamic Complex Formation
FY2002	Hidenori Ichijo	Prof., Univ. of Tokyo	Molecular Mechanisms of Recognition and Conversion of Stress Signaling
	Koreaki Ito	Prof., Kyoto Univ.	Principles and Regulatory Devices that Govern the Dynamic Behaviors of Proteins in the Cell
	Yuji Goto	Prof., Osaka Univ.	The Molecular Pathogenesis of Amyloidosis
	Hiroyuki Sorimachi	Department Head, The Tokyo Metropolitan Institute of Medical Science	Elucidation of Physiological Functions of Intracellular Modulator Proteases
	Akihito Yamaguchi	Prof., Osaka Univ.	Studies on the Structure and Function of Xenobiotic Efflux Proteins
	Tamotsu Yoshimori	Prof., National Institute of Genetics	Intracellular Traffic System Organized by Proteins and Membranes
	Kazuyoshi Yonezawa	Prof., Kobe Univ.	Identification and Functional Analysis of Proteins Mediating Cell Growth Control
FY2003	Hiroyuki Araki	Prof., National Institute of Genetics	Structure and Function of the Protein Complexes in the Synthesis of Nucleic Acids
	Noriyuki Sagata	Prof., Kyushu Univ.	Analysis of the Structure and Function of Cell Cycle and Checkpoint Regulators
	Masashi Suzuki	Group leader, National Institute of Advanced Industrial Science and Technology	DNA-recognition and Ligand-binding by the Feast/Famine Regulatory Proteins, FFRPs
	Teizo Fujita	Prof., Fukushima Medical Univ.	Analyzing Interaction among Protein Molecules in Host Defense and the Mechanism to Exert Function
	Mutsuhito Ohno	Prof., Kyoto Univ.	Remodeling of RNA Export Pathway for RNA/Protein Complex
	Hideki Sumimoto	Prof., Kyushu Univ.	Control Mechanism for Superoxide-Producing NAD(P)H Oxidase

seven bioreaction-specific areas: development and differentiation, transcription and translation, post-translational modifications, the formation of higher-order structures, signal transduction, the brain and nervous systems, and metabolic systems. After a call for experts in each of these fields, a research framework was established that included participating researchers headed up by a selected, central research body. Through this process of selection, two core research bodies were selected for one of the research areas — transcription and translation — bringing the total number of core research bodies to nine, including RIKEN Yokohama as well. These nine organizations co-operate with some 90 other participating research organizations and over 800 research scientists (excluding graduate students). If we compare this to membership of the Protein Science Society of Japan (PSSJ) that there are around 1,150 people working in this field, including graduate and postdoctoral students, then it would be safe to say that almost all of Japan's protein researchers are involved in this project.

Management

The Protein 3000 Project was launched in FY2002 and will wrap up in FY2006, having been on the receiving end of a total of 57.8 billion yen of research funding over this period (See Table 3).

The Protein 3000 Project Promotion Committee has overseen and managed the project, as well as formulated basic project policies. Under the Promotion Committee various working groups were set up — the Intellectual Property and Industry Liaison Working Group, that Database and Information Disclosure Working Group, the Equipment Development and Engineering Working Group, the Bioinformatics Working Group, and the Public Relations Working Group — which were designed to facilitate the smooth running of the project by strengthening contact with industry, sharing newly developed research techniques and methods, and promoting the effective utilization of research outcomes. A Project Secretariat was also set up to handle the administration of the Project. The Project Secretariat was

Table 2: Framework of Protein 3000 Project

Research category	Principal investigator / Core institute	Associated institutes	Extent of analysis (5-year targeted)
I. Large-scale Analysis Program (Program for integrated analysis of basic protein structure)			
—	Shigeyuki Yokoyama RIKEN Genomic Sciences Center	Regarding functional analysis, collaborating with universities, private firms, etc. (joint research, etc.)	2,500
II. Targeted Analysis Programs (Programs for targeted analysis of protein)			
Development and differentiation of organisms and replication and repair of DNA	Masaru Tanokura Graduate School of Agricultural and Life Sciences, Univ. of Tokyo	Univ. of Tokyo, Mitsubishi Kagaku Institute of Life Sciences, Tokyo Metropolitan Univ., Tokyo University of Pharmacy and Life Science, National Institute of Agrobiological Sciences, Nippon Medical School, Takara Bio Inc., Ehime Univ., Gunma Univ., Kyushu Univ., Chiba Univ., Tokyo Institute of Technology, Chemical Biology Institute	500
Transcription and translation*	Isao Tanaka Graduate School of Science, Hokkaido Univ.	Hokkaido Univ., National Institute of Advanced Industrial Science and Technology (AIST), Univ. of Tokyo, Niigata Univ., Ochanomizu Univ., National Institute of Genetics, Nippon Institute for Biological Science, Osaka Univ., Kyushu Univ., Kumamoto Univ., Tokyo Institute of Technology	
Transcription and translation*	Yoshifumi Nishimura Graduate School of Integrated Science, Yokohama City Univ.	Yokohama City Univ., Toyama Medical and Pharmaceutical Univ.,Univ. of Tokyo, Biomolecular Engineering Research Institute, Kyoto Univ.	
Posttranslational modification and transport	Soichi Wakatsuki Institute of Materials Structure Science, High Energy Accelerator Research Organization (KEK)	Institute of Materials Structure Science, High Energy Accelerator Research Organization, Osaka Univ., Kyoto Univ., Institute of Physical and Chemical Research, Nagaoka University of Technology, Univ. of Tokyo, Nagoya City Univ., Showa Univ., Japan Atomic Energy Agency (JAEA), AIST, Nara Institute of Science and Technology, Tokyo Institute of Technology, Tokyo Metropolitan Institute of Gerontology, Kyoto Sangyo Univ.,	
Protein higher-order Structure formation	Kunio Miki Graduate School of Science, Kyoto Univ.	Kyoto Univ., Osaka Univ., Hokkaido Univ., Tokyo Univ. of Agriculture and Technology, Nagoya Univ., Tokyo Institute of Technology, Kyushu Univ., JAEA, Toyama Medical and Pharmaceutical Univ., Univ. of Hyogo, Kyoto Institute of Technology	
Intracellular signal transduction	Fuyuhiko Inagaki Graduate School of Pharmaceutical Sciences, Hokkaido Univ.	Hokkaido Univ., SAIL Technologies Inc., Nara Institute of Science and Technology, Kyushu Univ., Univ. of Tsukuba, Univ. of Tokyo, National Institutes of Natural Sciences	
Brain and nervous system	Atsushi Nakagawa Institute for Protein Research, Osaka Univ.	Osaka Univ., Nagoya Univ., Univ. of Tokyo, Univ. of Tokushima, Okayama Univ., Univ. of Hyogo, Kansei Gakuin Univ., Hiroshima Univ., National Institutes of Natural Sciences, Ehime Univ., Japan Synchrotron Radiation Research Institute (JASRI)	
Metabolic systems	Seiki Kuramitsu Graduate School of Science, Osaka Univ.	Osaka Univ., AIST, Osaka City Univ., Univ. of Tokyo, Tokyo Institute of Technology, Chiba Institute of Technology, Univ. of Tokushima, Nagoya Univ., Kagawa Univ., Okayama Univ., Hiroshima Univ., Saga Univ., Nagasaki Univ., Kyoto Univ., Univ. of Tsukuba, Fukui Prefectural Univ., Tokushima Bunri Univ.	
Total			3,000

* Yokohama City University will mainly conduct analysis of protein related to Transcription while Hokkaido University will mainly conduct analysis of protein related to Translation, respectively as the core institute.

Table 3: Outline of Protein 3000 Project

- **Project realization duration:**
  FY2002 ~ FY2006
- **Research Object:**
  Analyze basic structures and functions for over 3,000 types of proteins
- **Budget (Unit: ¥ million):**

FY2002	11,770	(9,100*)
FY2003	9,510	
FY2004	9,050	
FY2005	9,770	
FY2006	8,600	
Total	57,800	

- **Results:**
  See Table on P. 7 regarding number of protein structures determined.
- **Participating institutions/personnel:**
  9 groups, 90 institutions and 813 people (as of May, 2005)

* Other supplementary budget (this is included in the total budget.)

initially located within the Mitsubishi Research Institute, but is currently located within the Faculty of Agriculture at the University of Tokyo.

In addition to this, an Evaluation Committee was also set up to evaluate progress and management each year and make recommendations accordingly. Interim reports were also made by the Life Science Committee, the Ministry of Education, Culture, Sports, Science and Technology, Japan. The management of the Project has been reviewed based on the outcomes of these evaluations each year, while the outcomes of evaluations have also been reflected in the allocations of research funding to the various research bodies.

The Protein 3000 Project is an international research project, as outlined above, and has been undertaken with cooperation from the International Structural Genomics Organization (ISGO) as well, which assigned two representatives to Japan. The Project has also involved bi-lateral conferences being held between Japan and the UK and Japan and France to promote information sharing, and has thus been managed in such a way so as to coordinate with other countries as well.

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