

Preface

Genome Science: today and tomorrow

A special research project "Genome Science from now on"

This is the collection of papers presented at the Uehara Memorial Symposium 2002, "Genome Science: towards a new paradigm?"

The aim of the symposium was primarily to make a progress report of the special research project carried out by 21 groups of researchers supported by the Uehara Memorial Foundation for the years 2000-2002. The project is named as "Genome Science from now on" (Korekano Genomu Kakagu, in Japanese). The aim of the project was to promote the biological research of various organisms from bacteria to human and at various levels, from cells, tissues to whole body, based on the whole genome information that is becoming available rapidly. The experimental and theoretical technology developed for the functional analysis of a vast amount of genome information has made it possible to study both cellular and multi-cellular functions in terms of genome wide expression of genes. Through these studies we expect to develop a new concept of life based not on genes but on the whole genome. In other words, "gene as the unit of life (the basic concept of molecular biology)" will change to "genome as the unit of life (the basic concept of genome science)". This is what I call a paradigm shift. There were serious and intriguing discussions at the symposium on whether the future Genome Science brings about a new paradigm or just is the old paradigm with a new technology. Obviously it was too premature to draw any conclusion on this important subject by the end of the symposium, but all participants agreed that it was the first of many efforts to seek for a new paradigm of biology that encourages the students of next generation to join in the study of life science.

Uehara memorial symposium 2002

The symposium consisted of four themes. The first was "Genomic view of the cell" where we dealt with the progress made in understanding the universality and diversity of cellular functions based on genomic information. Transcriptome, proteome and metabolome of bacteria, yeast, organelle of eukaryotes and lymphocytes were of primary interest. The second "Genomic view of development" dealt with characteristic features of multi-cellular organisms. In particular we focused on developmental biology that is by far the most quickly advancing field following the complete sequencing of genomes of the nematode and fruit fly. The current aim is to construct a comprehensive database for temporal and spatial genome expressions during the early stage of development. The third theme was "Evolution and genome diversity" where we adopted theories and experiments concerning genome rearrangement, mutation and diversity that are involved in specific genome functions. In addition, new aspects of evolution based on comparative genomics were discussed. The last was "Functional analysis of human genome" where we explored technologies both for experimental and computational analyses of polymorphism and genome imprinting in order to apply the knowledge of human genome to the future medicine and pharmacology. Each session boasted a presentation by one or more leading scientists in each field who had been invited from home and abroad in order to help understand the current state and future trends of Genome Science in the world and to make critical discussion on the papers presented by researchers of this project. Many of the invited speakers have kindly contributed their papers to this proceeding.

Genome is replacing gene: from molecular biology to genome science

The symposium dealt with a variety of topics, differing in organisms (from bacteria to human), in levels (from organelle to whole body) and in biological phenomena (metabolism, cell cycle, development, neuron function, evolution, etc.). One may wonder how such a varied symposium can possibly attract experts on various fields of biological sciences. We once experienced a similar situation in 1960-1970 at the beginning of molecular biology when structure and function of DNA and genes attracted the interests of biologists in many fields. Later the study of genes has deeply permeated into many fields of life science, and as the study became more specific and more in detail, the molecular biologists are separated into many meetings common in either organisms (i.e. *E. coli*, *Drosophila* etc.) or in phenomena (i.e. replication, immunology etc.). Now history is repeating itself as "Genome" is replacing "Gene". Researchers assembled in this symposium shared many common interests in spite of differences in topics they study.

First, they shared technology, experimental, theoretical and computational, for the analysis of structure and function of numerous genes in Genomes. The technology developed in the study of small genomes, bacterial and yeast genomes, is applicable for the analysis of nematode, fly and human genomes. Furthermore, the comparative genomics is the most powerful method to identify structure and function of genes of your interest. The concept of homologs, paralogs, and invader genes by horizontal transfer, is established by the comparative study of many microbial genomes. This concept is now expanded to higher eukaryotes and is used as a tool for identifying new genes including their regulatory regions for transcription and translation.

Second, they shared the concept of the gene set and its net work that perform reactions (sequential, cyclic or of cas-

cade) to give rise to complex phenomena such as metabolism, cell cycle, signal transduction and embryonic development. The technology involved in the analysis of multiple gene functions is under developing to solve various biologically important phenomena characteristic for each organism. A new technology developed in a given phenomenon of a given genome can be directly applicable to any other phenomena of any other genomes. The theoretical and computational analyses are particularly important in understanding complex features of interactions among multiple genes. A proper simulation of gene net works by computation may be able to predict appropriate experiments to perform. At present such an attempt is limited with simulation of a simple cell function such as metabolic pathways, but will eventually develop many model cells (Electronic cells) that perform more complex functions. The present research project and hence the symposium was one of the first attempts to stimulate close interaction between the experimental biologists and information/computation scientists.

Genomic view of diversity and evolution was the third topic that was shared by all participants, as it is the fundamental issue of Genome Science. Although diversity is the most important principle of the biology, it has never been studied seriously in molecular level due to the lack of technology. Similarly, study of molecular evolution has been limited to phylogenetic analysis by using specific homolog such as rRNA genes. The theory proposed by S. Ohno on the evolution and diversification of genetic information by gene duplication was one of a few contributions by molecular biology to the evolution. Ohno's theory is now extensively studied in many microbial genomes whose entire sequences have become available. Not only the evolution of genes and gene systems but also evolution and diversification of organisms are emerging by genome scale comparison of closely related species. For example, origin and diversity of microbial pathogenesis are becoming clear by comparative study of pathogens with harmless close relatives. Similar studies are now extending to higher organisms, nematodes and flies to clarify specification of these groups of organisms. The ultimate goal of such studies would be to understand how humans have evolved from the common ancestor of primates. Worldwide consortia including Japanese groups have initiated the comparative studies between human genome with those of close relatives, chimpanzee and other primates.

A paradigm shift?

The symposium, hence this proceeding covers most of the important issues of the today's Genome Science, thanks to the contributions by the guest speakers as well as project leaders. Is there any paradigm shift in Genome Science today? Or is there still the old paradigm of Molecular Biology equipped with new technologies? The mere fact that a new type of assembly of researchers differing from previous biological meetings could have held an active three days meeting seems to be a good indication of a paradigm shift. What is then Genome Science tomorrow? The major change will be the role of information/computation sciences (in silico science) compared with experimental biology in the structure/function analysis of genomes. At present the weight of experiment is heavier than the "in silico science" that supports the analysis of numerous data produced by the experiments. In future the weight will reverse to render the experiments to a supporting role for "in silico science" that predicts proper experiments to perform in order to prove or disprove the models or simulations proposed by "in silico" analysis. The meetings of the Genome Science tomorrow may constitute mostly of information/computation scientists, and the experimental biologists will go back to their own fields to do more practical work on medicine, agriculture, environmental biology etc.

Human genome

Finally I should mention the human genome. Undoubtedly, understanding of human is an ultimate goal of Genome Science tomorrow. Comparative genomics between human and chimpanzee (and other primates) would describe from where humans have come, what are humans and where will they go. The entire human genome sequence will be read within a couple of years, but understanding the instruction written in the sequence would require decades of functional analysis. There is so much to do until the differences in brain function between human and chimpanzee will be revealed by the differences in genomic information that have accumulated during several million years of evolution. For the time being, human genome research will focus on the gene hunting of multifactor diseases that have become the most serious problem in developing countries as life-style related diseases. The genome wide analysis of sequence polymorphism in world scale not only helps identify disease sensitive genes but also detects characteristic features for each individual as to the sensitivity to various multifactor diseases. Furthermore, studies on multi-gene functions, net works and gene systems, in cell, tissue and organs will reveal the mechanism of the occurrence of multifactor diseases and their pathogenesis. Consequently, we expect that the medicine (treatment and prevention) tomorrow will be based on logical assessment of genome function depending on individual's genomic polymorphism. You may find reports of the initial phase of genome based medical researches in this proceeding.

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