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Session 6: Pharmacogenomics: Impacts-Clinical & Regulatory Implication of New Genetic Science (Future for Tailor-made Therapy)

Pharmacogenomics: Implications for Post-Genome Science (Future for Tailor-made Medicine)

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The advances in life science research has led, at the dawn of the new century, to analysis of human genome sequence and a variety of gene technologies which opened a gateway to a new paradigm for health care and medical practice. Combining with new generations of computing power, it has become possible to decipher genomic messages, to make genetic diagnoses for a wide variety of disorders/diseases, to discover and create geneand protein-based new drugs, and to identify individual susceptibility and efficacy for drugs. Other possibilities include embryonic stem (ES) cells for cell and tissue re-generation and reengineering, cloning of organs and even whole organisms including humans. Ethical issues will became critical for the society with participation of professionals in different disciplines, scientists, the public and the policymakers. The national policy for research and development investment must be implemented carefully, wisely, and strategically as the resources are limited and the return could be unpredictable, but could be more than significant. International competition has become even harder as the results of life science research could become a significant component of national economic power and health care policy. I will discuss some key issues in these and other aspects of life science research and policies in Japan and elsewhere.

Introduction

There are three major issues we could address here today. One is human genome project and the national consortium against a venture company; second is the genetic basis of diseases; and third is new drug discoveries based on genetic. These issues probably have been discussed by previous speakers. Therefore, I would like to touch upon the genetic basis of disease and the genome analyses with SNP and microsatellite and how to identify disease-related genes that could be a basis for new drug discovery and disease diagnosis. Because of the time frame, I would like to focus not on genetic and environmental factors; disease specific gene abnormalities, the SNP and microsatellite analyses, but instead first focus on the case of deCODE, from which we could learn something.

1. Strategy of deCODE

DeCODE is a biotech-venture company and its strategies are to identify disease-specific or disease-related genes and the company targeted to Iceland. Why Iceland? Obviously, the company's major aim was to analyze genes in some families and disease-related genes, which "Bridging Strategies and Pharmacogenomics." (デジタルプレス)、2002/05/01、PP.211-218

could become targets of new drugs combining functional genomics, pharmacogenomics and bioinformatics. These combinations could lead to drug discovery and support health care and health informatics (Fig. 1). Everybody is thinking about such an endeavor, but what is unique



Fig. 1 deCODE's business

about the company is that they targeted Iceland. They worked together with the medical information database of the Iceland Health Department, which has a massive family database and disease database. Somehow, people in Iceland like to keep all the records. They don't want to throw away anything and Iceland has a population of only 260,000. There is an agreement that not

everybody has to participate, but those who are willing to sign a well-informed consent before they participate will allow the company an access to their medical records and their genome analyzed.

The unique resource of Iceland and for the deCODE Company is a medical information database filed and kept in the health care department (Fig 2). Medical information of at least

1HD=Icelandic Health Sector Database (Medical Information Database owned by government) Generation of MegaDatabase Acquisition of Royalties Discovery of disease specific genes by linking these three sets of Databases.

Fig. 2 deCODE's resources

five generations could be incorporated into the computer and any royalty gained from any discovery through deCODE could become an assets to the people of Iceland and the nation. Eventually some new drugs may be discovered and then the people in Iceland can benefit from these drugs with special arrangements incorporated

in the contract. In this plan, you don't need to analyze the massive data, but three sets of databases, that of family medical records, databases of individual medical records and genome analyses. Thus, this is a more prioritized cost-effective and well-targeted strategy. In Iceland, there is family history database of five generations available. The limited mobility of the people in Iceland is another advantage. Thus, it is a smart move to study the people of Iceland and build a genome database. Everybody is trying to generate the genome databases but the medical information and the family database are important elements to identify and relate specific genes to some diseases or common diseases. Discovery of disease-specific or disease-related genes by linking these three sets of megadatabase are the key for the deCODE strategy. deCODE's product and services are also shown here. One is new drug development and collaboration with research and development with pharmaceutical companies. Obviously that is necessary once you identify candidates disease-specific or related genes. Next step is to create some platform which allows to the discovery of new lead compounds, perhaps through high throughput systems, then to new drugs and new diagnostic tools. In addition to the pharmacogenomics, responder/nonresponder, side effect prediction, and so forth to drugs could be developed. This is a very important way to deal with this massive database. Some major companies have been investing already on this deCODE venture. Further, an income would be generated from patents and licensing and offering the database and the software to those who are interested in. In addition, genome based medical information could be implemented to improve the healthcare in Iceland and elsewhere.

2. Development of Post-Millennium Project

Learning from this deCODE adventure and the possible development of post-millennium projects-or just post-genome-will be important in the near future. Some of the discovery is based through biotechnology ventures, and some research results to industrialization. Return of the public investment, ie, tax money to the public is important. So far, microsatellite and SNP analyses, gene hunting to functional analysis. DNA chips, antibody, full-length cDNA and proteome, all these things have been individually done, which is just fine. Identification of target molecules and target pathways and understanding of pathophysiology of diseases are the components of the so-called translational research but more importantly, to support such an entire scheme of post-genome projects is not only about the genome but also in silico target hunting, discovery and identification of lead chemical compounds, in silico evaluation of chemical reactions, which is a sort of a screening system of any new candidate compounds.



Fig. 3 Development of post millennium project

These are critical components of drug discovery (Fig. 3). The process then is more like a real development in large pharmaceutical industries, but to identify these each step effectively from genome to clinical application requires a gigantic mega-database may be necessary. For example, if you identify some SNPs, how do you know it is related to some common disease? For this, you need a high quality patient database, based on at least 1000 patients, or 2000, and then normal humans. With this database, you can analyze drug relations and co-relations. Without such database, relating one SNP to a disease would be very difficult. For microsatellite analyses, you may need only hundreds of patients to analyze the correlations but SNPs, you need a more massive database. Securing family databases as shown in this example of deCODE would be an advantage.

These are the basic technologies for functional genome analysis, but the key is how to utilize them. We have to prioritize the mission, and then we must plan strategies and draw proper roadmaps. All these processes are very, very important. SNP and microsatellite analyses have advantages and disadvantages. You have to understand these. Then the action tank should be made perhaps contemporary and lead to the database and these are the gene-hunting protein analysis into translational research and discovery (Fig. 3).

3. Strategies for Biotechnology Research, and National Investment

All researchers are interested in identifying disease-specific genes. That is fine, but ultimately we would like to utilize such information into clinical settings. We are looking at new diagnostic tools, drug development, improvement in health care. Research requires financial support, which mostly comes from the public money or taxpayers money or the national investment.

It is important as science policy of a nation that how cost effectively the national investment should be prioritized and implemented with a defined strategy, with a vision. Further, public and private investment in partnership with academic research institutes and corporations be developed.

Thus, there are roles of ventures, incubations and creation of strategic platforms for each major disease category. People in academic sector have to pursue high quality research and industry does so for profit, which is fine, but there are certain risks involved for both parties and there is a role of incubators and ventures, particularly in biotechnology and pharmaceutical industries.

4. Challenge to End-Stage Renal Disease (ESRD)

I would like to discuss with you some of the examples we are working on. Because I am a nephrologist, I am very much concerned about the growing health care burden of chronic renal disease and dialysis patients. We have a rapidly growing number of chronic dialysis patients in Japan, exceeding 200,000 and there are more than one million chronic dialysis patients world-wide. That costs a lot of money in each country, and developing countries cannot afford such an expensive treatment modality. End-stage renal disease (ESRD) statistics in Japan and the USA show the prevalence of more than 200,000 in Japan and to more than 300,000 in US: the number of chronic dialysis patients is 200,000 in Japan and 240,000 in US and

transplant recipients are 5,000 in Japan and almost 100,000 in US. There are about 30,000 new patients entering ESRD programs in Japan each year: in US it is 80,000. The total annual health cost is roughly \$10 billion in Japan and \$17 billion in US and it is still increasing. The problem with chronic renal disease is a lack of defined target molecule and also, the lack of defined, well-established animal models. Target cells involving the progressive nature of chronic renal disease are multiple, but glomerular mesangial cells are the most upstream in the progress of most of chronic renal disease, including diabetes. In fact, renal disease of diabetes has become a number one cause of ESRD in many developed countries including US, Japan, Korea, and elsewhere. This is because of changing lifestyle and urbanization, which include less caloric expenditure.

We have identified the five new genes that are almost exclusively or predominantly expressed in the human glomerular mesangial cells. One such gene is megsin, a new member of serine protease inhibitor superfamily (Fig, 4). In many diseases like IgA nephropathy-the



Fig. 4 Megsin structure

second most common cause of chronic renal diseasejust second to diabetes, and in diabetes, there is an increase in mesangial cells in number and mesangial matrix, respectively.

In both instances, megsin gone and protein are both overexpressed or up-regulated as compared with normal control, suggesting the cause/effect relation of this single gene.

Obviously, to prove this point, we had to produce human megsin transgenic mouse which demonstrates a typical feature of chronic glomerule disease, with expansion of the mesangial cell area and the increased mesangial cell compared to normal controls. This is interesting because this expression is limited to renal glomerular mesangial cells. Because this is a serine protease inhibitor, we can envision the presence of a serine protease which is a target of megsin, a serine protease inhibitor. Such serine protease inhibitor is likely to work as a clearance machinery of the immune complex and the mesangial matrix protein. Therefore, the upregulation of megsin would result in predictable phenomena, seen in mesangial cells in human diseases and in the transgenic mice. We now could offer you several opportunities (Fig. 5). One is that we identify this new gene and gene protease. Thus, we can provide in vitro screening systems which allow screening for potential new lead compounds. Also, there is transcriptional factor(s) we are now working to identify, and this could be an additional in vitro screening system regulating this megsin gene. These systems will function as screening systems for low molecular weight

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inhibitory compounds which may lead to discovery of new drug development specific for chronic renal disease. As I told you already, there is a lack of proper animal models for ESRD, but this megsin transgenic mouse could now become a very useful animal model for progressive chronic renal disease.

Fig. 5 Future strategy for renal drug development with megsin as a target molecule Therefore, we would have

not only an in vitro screening systems, but when we identify some lead compound, we could offer an in vivo screening systems in animal models. Also, drugs currently available and also in the developmental stage could be tested in this in vivo system and then that would lead to an evaluation of effective drugs and discovery of new drugs. That I see as a responsibility of any investigator working primarily in the kidney disease area.

Conclusion

At this dawn of the new century, we face a new challenge, but we also have been given a great opportunity for adventure and competition that we will enjoy. Thus, we are given enormous opportunities for greater scientific advances and achievements and, more importantly, we have an opportunity for greater service to the public and the mankind.

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