Overview of Current State of Affairs and Perspectives on Toxicogenomics.

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In the field of toxicology, recent advances in genomics research has led to the development of toxicogenomics, a novel research field enabling us to analyze chemical toxicities or side-effects at the level of gene expression. While participating in public toxicogenomics projects, we are also concentrating on in-house toxicogenomics studies to establish novel and efficient toxicological screening methods and to clarify the mechanisms of toxicants. Here, we will review current trends and perspectives on toxicogenomics, including examples from our own research.

This paper is translated from R&D Report, "SUMITOMO KAGAKU", vol. 2004-I.

Introduction

Recent progress in genomics research has permitted the compilation of substantial amounts of genome information from laboratory animals such as rats and mice as well as from humans. Therefore, use of methodologies that incorporate genome technology has increased in the field of toxicology. Conventionally, research has been conducted on the activity of a single or small number of genes, in order to analyze the mechanism of toxicity for particular chemicals. However, an enormous amount of genome information has accumulated in recent years and DNA chips (also referred to as DNA microarrays) have been developed for global analysis of gene activity. This progress has made it possible to perform analysis at higher dimensional levels completely different from those conventionally carried out. These technological innovations have opened up a new field of toxicology called "toxicogenomics."

In our laboratory, we are also undertaking toxicogenomics studies in collaboration with Genomic Science Laboratories, Sumitomo Pharmaceuticals Co., Ltd., aiming primarily at establishing screening systems applicable to efficient development of pharmaceutical compounds and agrochemicals. A further intent of our joint studiesis elucidating the mechanisms of toxicity for specific chemicals, with the ultimate goal of this research being to increase both the breadth and the speed of safety assessment for such chemicals. Additionally, we have established a consortium with several other organizations and are actively participating in toxicogenomics projects implemented by an independent government corporation, the New Energy and Industrial Technology Comprehensive Development Organization (NEDO). In this paper, we introduce some of the projects currently being undertaken by our laboratory and discuss international perspectives and aspects of toxicogenomics research.

Toxicogenomics

1. Definition of Toxicogenomics

Toxicogenomics is a term coined by combining "toxicology" and "genomics," and it refers to the study and analysis of toxicity and the side effects of chemicals adversely affecting specific organs and tissues in living organisms, at global gene expression levels.[1] In a broader sense, the term toxicogenomics occasionally refers to the study of toxicity in biochemical fields that utilize the suffix "-omics," such as "proteomics" (the comprehensive study of protein composition and dynamics) and "metabonomics" (the comprehensive measurement and understanding of the dynamic behaviors of metabolic responses in living systems). Multiple reactions occur continuously in the bod-

ies of living organisms. Tracing these reactions back to their origins leads to the determination of the quantitative behavior of genes, in other words, gene expression changes. In order to respond to environmental changes and sustain life, a living organism must control the reactions that occur internally through changes in gene expression. If a living organism is exposed to a chemical, the organism will be affected by the chemical and gene expressions will change (**Fig. 1**). Since living organisms have highly reproducible patterns of response to stimuli, the hypothesis is that exposure of an organism to similar influences will result in similar changes in gene expression.[2] Under this hypothesis, the concept behind toxicogenomics is that toxicity for specific chemicals can be detected based on similarities in gene expression.

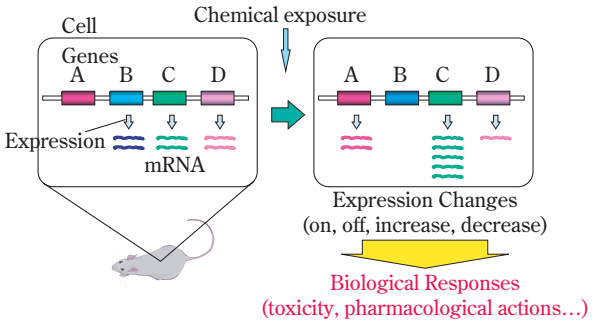


Fig. 1 Gene Expression Changes after the Treatment with Chemicals

2. Methods for Conducting Toxicogenomics Research

The primary methodology used in toxicogenomics research is pattern recognition, which makes it unnecessary to always have prior understanding of the actual function of the genes being analyzed. A group of genes is first selected to characterize the toxicity or side effects of a particular chemical, and it is then sufficient just to get a grasp of the patterns. There is another research field called "pharmacogenomics" that can be utilized to analyze the pharmacological activity of a particular chemical substance from the resulting gene expression. There are no methodological differences between these two. The only difference between toxicogenomics and pharmacogenomics is whether the resulting effects being studied will be classified as toxicity or pharmacological activity. The actual procedures employed within toxicogenomics research can be explained as follows: First, gene expression patterns are studied for many different chemicals having a variety of toxic effects, with a database compiled to contain the information. The test subjects may be laboratory animals, such as rats, or any in vitro cell culture. Next, the gene expression patterns that occur in response to exposure to new chemicals are studied under the same experimental conditions. These resulting gene expression patterns are then compared to those of the known chemicals in the database (**Fig. 2**). Finally, the toxicity of the particular chemical is estimated, based on similarities in the data. Furthermore, many of the gene characteristics have already been identified from the literature. Therefore, even under circumstances in which no database information is available, it may still be possible to determine the toxicity of specific chemicals, as long as the gene characteristics that indicate changes in expression are studied and their significance is understood.

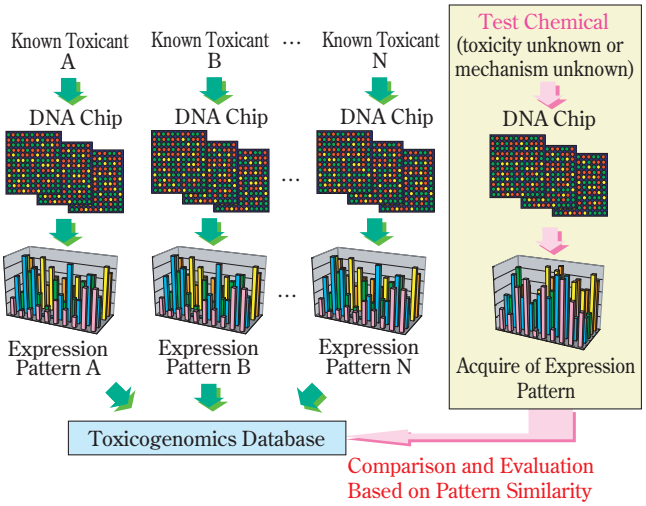


Fig. 2 Representative Method for Toxicogenomics

3. Applicability of Toxicogenomics Research and Supporting Technology

Applications of toxicogenomics research include: (1) discovering the marker genes that characterize toxicity in specific organs and tissues; and (2) utilizing these marker genes to create screening systems that can be used to predict the toxicity of chemicals. Moreover, toxicogenomics research can be used to (3) study genes where expression changes to elucidate the mechanisms of toxicity for a chemical where the toxicity has not yet been

identified. The technologies that support toxicogenomics research are various methods for comprehensive gene expression analyses, with one typical example being DNA chips. For details on DNA chip procedures, see earlier reports.[3, 4] The amount of data used in toxicogenomics research is enormous. In addition, the performance of pattern recognition methods, and identification and extraction of similar patterns, are essential operations for toxicogenomics research. Therefore, this research requires the application of systematic information science-based procedures to perform the required compilation, recording and interpretation of such data. These different disciplines make toxicogenomics a field of research based on a combination of genomics and information science in addition to conventional toxicology.

General Trends in Toxicogenomics Research

In the past, traditional research on gene expression changes was conducted to elucidate the mechanisms of toxicity for specific chemicals. As a result, it was discovered that chemicals possessing certain toxicities would induce typical gene expression changes in living organisms. Later, the invention of DNA chip technology resulted in a profound shift from the mere study of simple gene expression to the comprehensive investigation and analysis of global gene expression profiles. In the midst of this transition, the US National Institute of Environmental Health Science (NIEHS) and several US venture companies that specialize in gene expression analysis became the first organizations to pay serious attention to the utility of comprehensive gene expression analysis and to initiate its application to toxicological research. An overview of current trends in toxicogenomics research is provided below.

1. Activities of Public and Non-Profit Research Institutions

NIEHS is a public research institution administered under the US National Institutes of Health (NIH) as its environmental toxicology division. In early 2000, NIEHS developed a DNA microarray, called the ToxChip, which was used for toxicological studies and subsequently used to initiate a program of formal toxicogenomics research. Based on this, NIEHS established the National Center for Toxicogenomics (NCT) in September 2000.[5] NCT not only compiles and organizes the results of toxicogenomics research conducted within NIEHS, but also conducts joint research with external organizations, serving to promote toxicogenomics research throughout the US. Currently, the NCT has obtained 37 million dollars in research funding from NIH and, along with 5 other public US research institutions, has established a consortium to conduct joint toxicogenomics research. Through this research consortium, NCT is aiming to accomplish the following objectives: the standardization of methods for gene expression testing and analysis; development of analytical tools; evaluation of both species-specific and dose-responsive gene expression patterns specific to toxic chemicals; discovery of toxic markers; and creation of a toxicogenomics database. In the U.S. there is also the National Center for Toxicological Research affiliated with the Food and Drug Administration (FDA) and involved in joint pharmaceutical-related toxicogenomics research. Many universities utilize toxicogenomics methods in their own toxicity research programs in accordance with each area of study.

In Europe, the Fraunhofer Institute of Toxicology and Experimental Medicine, a German research institute, is currently undertaking a toxicogenomics project. The project is funded by state governments and other organizations. The purpose of this project is to create a database by collecting gene expression data for in vitro primary human and rat hepatocytes and in vivo rat tissues, all for use in applications for pharmaceuticals, agrochemicals and typical toxicants. During 2002, data was already obtained for more than 30 chemicals.[6]

The International Life Science Institute (ILSI) is an international NGO that acts to facilitate collaboration among the industrial, governmental and academic sectors. The ILSI, , has established a genomics application research committee (popularly known as the Genomics Research Committee) in its Environmental and Health Sciences Institute for applying genomics to risk assessment, based on toxicogenomics analysis. It has also initiated a joint international toxicogenomics research program. Three different types of toxicities are subjects for this joint research: hepatotoxicity, nephro-

toxicity and genetic toxicology. A working group was organized for each type of toxicity and a microarray testing has been carried out. At present, the initial stage of experimentation and subsequent data analysis has been completed, with the results having been released recently in a scientific research journal.[7] Furthermore, ILSI is working with the European Bioinformatics Institute (EBI) to develop a database and analysis tools. Details about the planned database will be released in the near future. The special feature of the ILSI joint research project is that the various DNA microarray/DNA chip systems currently used by each research institution will be integrated into a single database to accommodate multiple platforms.

Today, the importance of toxicogenomics research is also increasingly recognized in Japan. The projects described below, which are actively being conducted by NEDO and the Ministry of Health, Labor and Welfare seem to be moving in advance of those conducted in Europe and the US.

2. NEDO Toxicogenomics Project

(1) Project Objectives

It is important to assess the chemical hazards from the perspective of comprehensive chemical management. In evaluating the hazard posed by a certain chemical, it is critical to investigate chronic toxicity (i.e., carcinogenicity, teratogenicity, etc.). However, this type of study has enormous costs (approximately 200-300 million yen for a single chemical), requires a long period of time (approximately 3 years for a single chemical) and expends the lives of numerous laboratory animals. Therefore, increasing the speed and reducing the cost of such hazard assessments have now become pressing needs. The objectives of the NEDO toxicogenomics project are to develop DNA microarrays and experimental procedures for evaluating carcinogenicity through toxicogenomics research and low-cost and accurate methods for predicting carcinogenicity in shorter periods of time. Specific goals are developing novel prediction methodologies that reduce the cost of hazard assessment by a factor of 100 and reducing the time required by a factor of 50-60, compared with today's requirements for conventional chronic toxicity testing.

(2) Organization and Administration

The NEDO toxicogenomics project is a five-year plan started in 2001. The project is conducted by a research consortium including the Chemicals Evaluation and Research Institute, Japan; Mitsubishi Chemical Safety Institute, Ltd.; and Sumitomo Chemical Co., Ltd. (**Fig. 3**), coordinated by project leader Professor Tomoyuki Shirai, Nagoya City University. A Hazard Assessment System Development Promotion Committee has been established in the Toxicogenomics R & D Head Office (Chairman: Nobuyuki Ito, Honorary Professor, Nagoya City University). The committee receives advice from a variety of experts in related research fields.

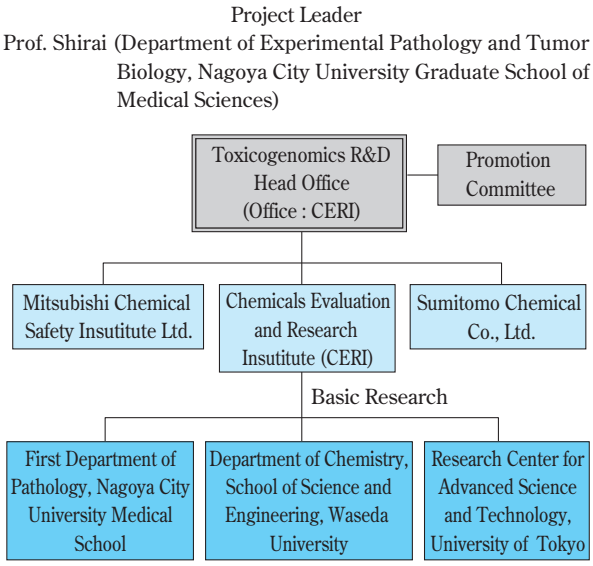


Fig. 3 Organization of NEDO Project

(3) Research Overview

The objective of this project is to determine the gene expression patterns and specific marker genes peculiar to carcinogenic substances through the compilation and analysis of gene expression profile data on chemicals having known mutagenicity and carcinogenicity. For this purpose, NEDO has created a proprietary DNA microarray and a standard protocol for methods used in administration and organ sampling and freezing. Based on this protocol, the test chemical is repeatedly administered to rats over a period of 28 days, samples are collected at several points in time and then gene expression analysis is performed. NEDO has set a goal of establishing a methodology for assessing and estimating the carcinogenicity of unknown chemicals by compiling gene expression

profile data for approximately 90 chemicals. This data will then be subjected to comprehensive analysis in conjunction with the results from blood biochemistry tests and histopathological examinations. Furthermore, NEDO is conducting fundamental research on the analysis of protein expression (proteomics) and performing comparisons of gene expression profiles using human and rat hepatocytes to collect supplemental information for the corroboration of hazard assessments.

3. Ministry of Health, Labour and Welfare Toxicogenomics Project

(1) Project Objectives

Prior to the actual administration of new pharmaceuticals to humans, the level of safety is carefully verified through a variety of non-clinical tests. Even so, unexpected side effects may occur with actual administration to humans. In addition, certain side effects may not be detected at all during clinical trials due to administration on a comparatively small scale and the low frequency of side effects. In such cases, these side effects may only be discovered once the product is on the market. From this perspective, the objective of the Ministry's toxicogenomics project is to establish a safety assessment/risk prediction system that enables the manufacture of pharmaceuticals having fewer side effects by studying how particular types of chemicals affect and interact with particular genes, with hepatotoxicity and nephrotoxicity as subjects for the study because they represent the most frequently reported side effects in humans.

(2) Organization and Administration

Due to the high cost (capital investment) and long periods of time involved, it is difficult for a single research institution, university or pharmaceutical company to create a large-scale database for use in safety assessments for pharmaceuticals on its own. Therefore, the National Institute of Health Sciences, along with 17 pharmaceutical companies, has begun collaborating on a 5-year toxicogenomics project by combining expertise, human resources and funding. Sumitomo Pharmaceuticals Co., Ltd. is one of the participants in this project, which commenced in 2002. The project is conducted through a system of collaborative operations, including a company responsible for the information technology and bioinformatics parts of the project (**Fig. 4**).

(3) Research Overview

This project involves the use of microarrays to assess the effects of chemical exposure on rats, primary rat and human hepatocytes. The results are subjected to comprehensive analysis to ascertain the chronological gene expression profiles for the target tissues. In addition, the project also involves the measurement of conventional toxicity markers. The primary target tissues used in the project are the liver and the kidney. A toxicity database will

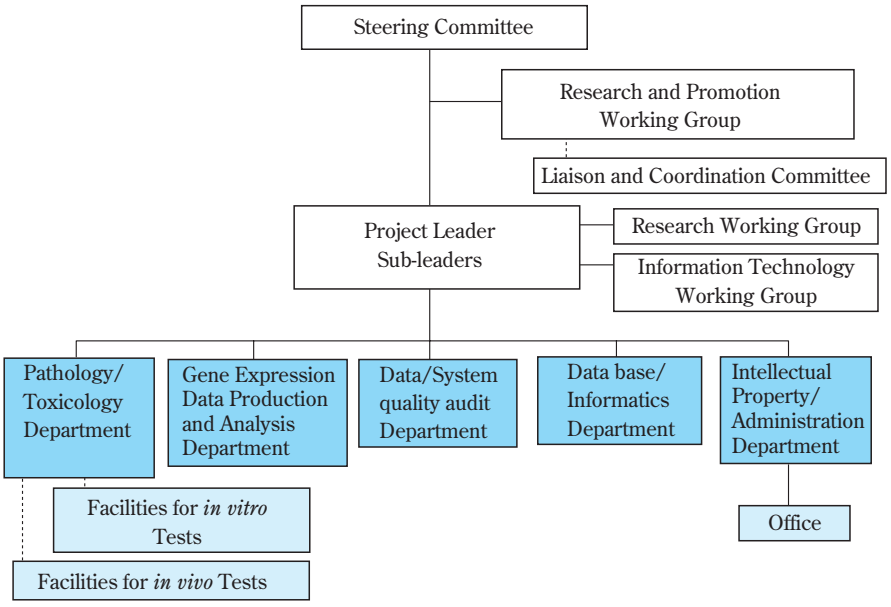


Fig. 4 *TGP* Project Organization Chart

be created based upon this information. The two concepts behind the creation of the databaseare: the elucidation of mechanisms for toxicity through analysis of changes in gene expression profiles associated with toxic changes and the prediction of toxicities for unknown chemicals through comparison with changes in gene expression for known toxic substances. As a specific goal, experiments are currently planned for approximately 150 chemicals, including pharmaceuticals. Using informatics technology, the goal is to develop a system for assessing and predicting the safety of pharmaceutical candidates, at the earliest possible stage of pharmaceutical development (**Fig. 5**).

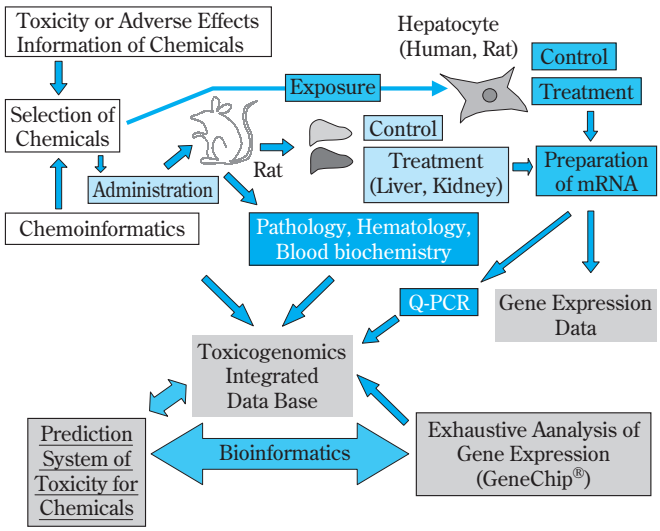


Fig. 5 Schematic Overview of the Project

4. Pharmaceutical Companies and Venture Companies

While projects carried out by public organizations are advancing, a variety of venture companies that specialize in gene expression analyses, particularly in the US, are expanding their toxicogenomics businesses. Typical examples include Gene Logic and Iconix Pharmaceuticals. Both companies have created their own specialized toxicogenomics databases and are using them to conduct toxicity prediction businesses (**Table 1**).

Leading pharmaceutical companies in the US and Europe are introducing toxicogenomics research into pharmaceutical development, either as independent projects or as joint projects with the venture companies above. Toxicogenomics research with in vitro cells is being used in the early stages of screening as a rough shakeout for pharmaceuticals. In addition, it appears that in vivo toxicogenomics assessment systems with rats are used in the later stages of lead optimization, to select the best compounds for development. At this stage, for example, toxicogenomics is used to exclude any compounds showing gene expression patterns similar to those of compounds previously known to exhibit toxicity problems. The primary interest here lies in predicting whether certain chemicals may cause hepatotoxicity and nephrotoxicity. Through the use of toxicogenomics, these companies are aiming to correctly select compounds that have a high probability of success with no dropouts and to reduce the costs associated with the development of pharmaceutical candidates.

Table 1 List of Bioventures concentrating on Toxicogenomics Businesses

Company	Gene Expression Platform	Toxicogenomics Database/Prediction	Features
CuraGen	GeneCalling®	Predictive Toxicogenomics Screen (PTS)	Hepatotoxicity prediction services and contract gene expression profiling
Gene Logic	Affymetrix GeneChip	ToxExpress/ ToxSuite/ ToxScreen	Reference database subscription and contract prediction services
Iconix	Amersham CodeLink	DrugMatrix	Profiling of structurally-related pharmaceuticals and toxicants (total 2000)

5. Status of Database Creation

Since a critical aspect of toxicogenomics research is the analysis of gene expression patterns, the key to successful research lies in the quality of the gene expression database used as a reference for comparing chemicals. Therefore, each research organization has created its own database according to the needs of its area of research. At the same time, public databases, which can be considered to be the basic infrastructure of toxicogenomics research, have also been enhanced gradually (**Table 2**). Databases currently with public access include the Gene Expression Omnibus (GEO)[8] of the National Center for Biological Institute (NCBI) and the EBI Array Express.[9] These have been created based on general gene expression data collected from public research sources. Although these databases were not compiled specifically for toxicogenomics, they

Table 2 List of Public Toxicoegnomics Databases

Constructor	Database	Aim of database construction	Current state
NIEHS	Chemical Effects in Biological Systems (CEBS)	Evaluation for environmental pollutants	Under development
NCBI	Gene Expression Omnibus (GEO)	General gene expression database repository	Open for public through website
EBI	ArrayExpress	General gene expression database repository	Open for public through website
ILSI/ HESI	ILSI Microarray Database (IMD)	Multiplattform, for ILSI toxicogenomics project	Available near soon
NCTR	ArrayTrack	Pproprietary researches at NCTR	Limited access
Fraunhofer Institute	ToxSAYS	Prediction of pharmaceutical toxicity	Under development
NEDO	(No name)	Carcinogenicity prediction	Under development
MHLW	(No name)	Hepato- and nephrotoxicity prediction	Under development

do include some data pertaining to toxic chemicals. Other databases are currently under development and are scheduled for public release in the future.

6. Fish Toxicogenomics

Hitherto, toxicogenomics research has been primarily concerned with toxicity studies conducted on mammals; particularly rodents, such as rats and mice. However, in recent years a new trend has developed, in which toxicogenomics research is conducted using fish to study environmental and developmental toxicity. Among all fish species, the zebra fish is considered to be one of the most promising experimental subjects for toxicogenomics research because a large number of individual subjects can be obtained easily; in vitro fertilization is relatively easy to perform; since the embryo is transparent, the developmental process and any toxic changes can be easily monitored. A zebra fish toxicogenomics project called the Embryo Array System has already been initiated, under the leadership of Professor Tanaka of Mie University, with support from the Ministry of Economy, Trade and Industry. Venture companies, such as Excelixis and Phylonix are currently embarking upon zebra fish genomics projects. Furthermore, the US Environmental Protection Agency (EPA) has also started genomics research using the fathead minnow for aquatic environmental impact assessments. In addition, some UK organizations use flounder for genomics research on environmental pollutants.[10)]

7. Regulatory Approaches

Since the area of toxicogenomics is still a developing field, the gene expression data for agrochemicals or pharmaceuticals cannot be immediately utilized for regulatory purposes at present. However, regulatory agencies have recognized the usefulness of toxicogenomics and are currently examining methods for evaluating its use for regulatory data.

On June 25 of 2002, the US EPA released the Interim Policy on Genomics as its thinking on genomics research.[11)] Details of the policy include: (1) although the utility of genomics methodologies has been acknowledged, the relationships between changes in gene expression and adverse effects are unclear at this time,so genomics data alone are insufficient as a basis for decisions; (2) for risk assessment purposes, genomics data must be considered on a case-by-case basis; and (3) prior to the acceptance of genomics data, adequacy regarding the quality, representativeness and reproducibility of the data must all be reviewed.

Likewise, on November 3, 2003, the US FDA released a draft guidance for pharmacogenomic data submissions and subsequently collected opinions.[12)] This draft guidance also covers toxicogenomics research. Details include: (1) any toxicogenomics data used in decision making in an animal safety trial or during clinical development in a human trial must be submitted upon application for the particular medicine; (2) if a toxicogenomics study is intended for medicine label description purposes such as for restrictions on drug usage, such data must still be submitted; and (3) although there is no obligation to submit data if a toxicogenomics study is conducted for exploratory or research purposes, other than those described above, voluntary submission of data is encouraged. The intent behind this draft guidance is to obtain as many data as possible from the general public, in order to evaluate both the data characteristics and the methods used to determine and handle such data. The FDA also conducts collaborative research with several DNA chip manufacturers such as Affymetrix and Agilent Technologies, and on the other hand, it is aggressively gathering

information itself and has concluded agreements with database companies such as Gene Logic and Iconix Pharmaceuticals.

Other regulatory bodies, including domestic regulators, have not yet released any opinions pertaining to toxicogenomics.

Specific Examples of Toxicogenomics Research

In addition to participating in projects conducted by the Ministry of Economy, Trade and Industry, our laboratory is currently conducting joint toxicogenomics research with Genomic Science Laboratories, Sumitomo Pharmaceuticals Co., Ltd. This joint research involves the utilization of the gene expression database and toxicity prediction services provided by Gene Logic. Through this database and associated services, we aim to increase the efficiency and speed of research concerning the safety of medicines in the area of pharmaceutical development. Two specific examples of gene expression analyses for chemicals that exhibit tissue-damaging characteristics are introduced below.

1. Identification of Marker Genes

Marker genes that characterize chemical toxicity for specific organs and tissues can be discovered by using the toxicogenomics methodologies as described in the above sections. It is thought that the study of marker gene expression changes will enable the detection of toxicities that have never been easy to assess in the past due to a lack of appropriate markers, thus leading to a faster and more accurate understanding of toxicity than by using existing toxicity markers. We have investigated gene expression changes in genital organs dosed with several toxicants (**Fig. 6**). As a result, we have discovered a gene where expression was changed in relation to changes in the hormonal concentration brought about by a chemical toxicity (Gene 5 in the figure). This particular gene is expected to be a desirable candidate for a marker gene useful in evaluating the chemical toxicities.

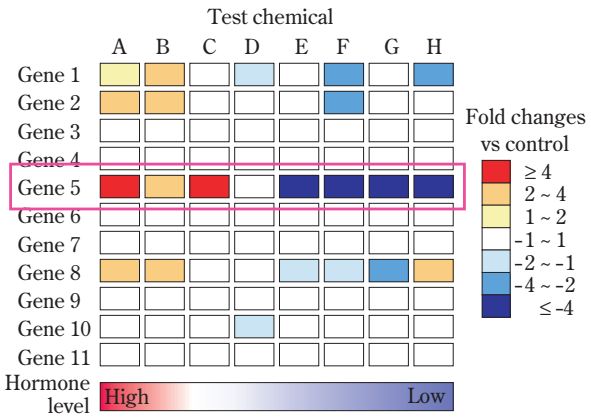
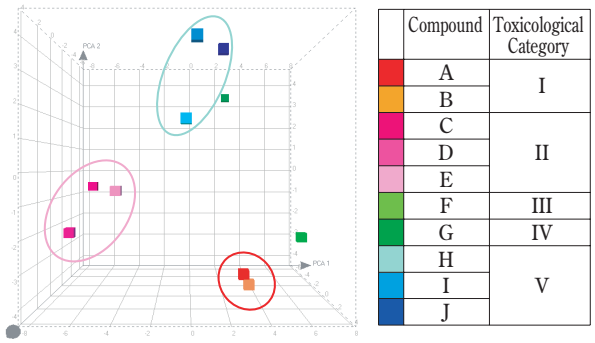


Fig. 6 Marker Gene Identification : Gene Expression Changes in Genital Organ

2. Evaluation Using Gene Expression for Chemicals Exhibiting Tissue-Damaging Characteristics

In the event that tissue damage (to liver, kidney, heart or lung) is recognized in laboratory animals such as rats during the development of pharmaceuticals or agrochemicals, the mechanism of toxicity must be elucidated in order to determine a policy for the development of such compounds, or to provide feedback for information used for the creation of successor compounds. Toxicogenomics methodologies are extremely effective in illuminating clues for determining the mechanism of toxicity. We administered several chemicals possessing tissue-damaging properties to rats and obtained the resulting gene expression data. Subsequently, we investigated similarities in gene expression patterns using a mathematical method called principal component analysis (PCA), based on the gene expression data from these gene groups (**Fig. 7**). In PCA, similar data tends to be located close together within in the 3-dimensional space spanned by the first three principal components as shown in Figure 7. As a result of the analysis, the data from chemicals with similar tis-



	Compound	Toxicological Category
	A	I
	B	
	C	II
	D	
	E	
	F	III
	G	IV
	H	V
	I	
	J	

Fig. 7 Evaluation of Organ Toxicity with a Toxicogenomic Method
–Principal Component Analysis of Gene Expression Data–

sue-damaging characteristics showed a tendency to cluster together when plotted in the 3-dimensional PCA space. Thus, we found that gene expression data from chemicals exhibiting the same tissue-damaging characteristics are also highly similar. These results suggest that tissue-damaging characteristics can be categorized based on gene expression data.

Challenges Faced by Toxicogenomics Research

As toxicogenomics is still a developing area of research, there are a number of challenges and problems yet to be overcome. Some of these potential problems are described below.

1. Data Compatibility

One problem is that there may be some differences in data characteristics, depending on the method used to obtain the gene expression data. More specifically, it has been discovered that there may be deviations in the data, depending on the type of DNA chip used. Therefore, additional caution must be employed when comparing data obtained using different methods or different types of DNA chips. Furthermore, there are no data exchange standards yet for exchanging data with other parties, further complicating the lack of compatibility and creating another major problem. However, an international organization known as the Microarray Gene Expression Data Society (MGED) has proposed a data exchange compatibility standard called, MIAME-Tox,[13] which may form the basis for a future international data exchange standard.

2. Data Analysis Methods

Current methods for data analysis are inadequate for dealing with the large volumes of data that are generated through the use of microarray technology. In addition there are currently a great number of genes that have not even been named, as well as genes with functions that remain unknown. Therefore, it is currently impossible to determine the significance of expression changes for these unknown genes, making it necessary to conduct analyses using advanced methods from the field of information science.

3. Evaluation Methods

At present, no methods have yet been established for evaluating gene expression data in terms of toxicity. There are no established theories pertaining to the definition of particular gene expressions of toxicological significance. Moreover, there is only a limited amount of information pertaining to the correlation between gene expression and present toxicology, which includes the concept of a no observable effect level. It is possible that gene expression changes currently considered as nonharmful in terms of unknown functionality and toxicology may later be found to possess some degree of correlation with severe toxicities. Under these circumstances, we will face the problem of how to ensure the safety of chemicals under actual conditions where the amount of available gene information is not substantial. To utilize toxicogenomics data as application and registration data for regulatory purposes, the problems mentioned above must be solved one by one, including the establishment of appropriate evaluation methods.

Conclusion

We have described the international trends in toxicogenomics research, including the current activities conducted by our own laboratory. Although we are facing the various challenges and issues described above, toxicogenomics remains a very promising area of research. It is highly regarded as a novel and efficient method for predicting toxicity of chemicals at an early stage. It is also expected to be an effective method for elucidating the mechanisms of toxicity. Furthermore, through its common language, the gene itself, we may overcome the problems we are currently facing in the toxicological field, such as species specificity and the bridging of data between pre-clinical tests and clinical tests . At present, only minimal toxicogenomics data has been released to the public , because a lot of time is required to create databases and also because private companies usually maintain confidentiality by not disclosing proprietary information. Thus, expectations are greater than practical usage indicates. However, it is expected that the technical challenges and problems pertaining to evaluation methods will gradually be solved as research progresses in the

future. In addition, it is expected that toxicogenomics research will be further popularized as the cost of analytical systems, DNA chips and microarrays continues to decrease. At the same time, it is expected that public databases will be created through current ongoing public projects, as well as through other planned projects. Thus, it appears that a public information infrastructure will gradually be established.

Recently, the concept of systems biology, which refers to the understanding of a variety of vital phenomena at a systems level, rather than at a molecular level, is rapidly gaining attention.[14] By integrating data from proteomics and metabonomics with comprehensive gene expression analysis (i.e., toxicogenomics in a narrower sense), we expect to be able to apply a systems approach to toxicology. In this situation, the experimental procedures and techniques taken from information science will be enhanced further, enabling us to conduct more comprehensive studies on adverse effects on living organisms, resulting in tremendous growth for the field of toxicology. Our company will continue its proactive participation in current and future national toxicogenomics projects. We shall also carry out internal toxicogenomics research for application to safety assessments for chemicals, including pharmaceuticals and agrochemicals.

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