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Full Research in Society, for Society

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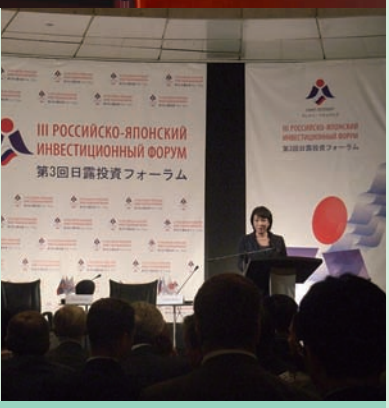

MESSAGE

On the Occasion of the AIST Open Lab

FEATURE

Medical Glycoscience

– Strategy for pioneering the post-genome era in Japan: glycoproteomics –

Research Hotline

UPDATE FROM THE CUTTING EDGE（October–December 2008）

In Brief

On the Occasion of the AIST Open Lab

Dr. Hiroyuki Yoshikawa
President
National Institute of Advanced Industrial Science and Technology (AIST)

1. Accomplishments from eight years of *"Full Research"*

The AIST Open Lab held on October 21 and 22, 2008 at the AIST Tsukuba was a truly significant event. Besides exhibiting the current AIST research projects to the public, in particular to people from industries in which the results might be used, this was an occasion to put in front of the world the accomplishments from our eight years of what we like to call *"Full Research."*

Back in 2001 when the new AIST began operations, besides carrying out a major restructuring of the organizations that existed under the former Agency of Industrial Science and Technology, we resolved to conduct *Full Research* in each of the newly formed research units. To this end, we created research units that integrate the functions of *Type 1 Basic Research, Type 2 Basic Research,* and *Product Realization Research*. This represented a brand new approach for researchers, who had been used to conducting these different types of research separately, while also taking the heads of each research unit into uncharted territory. Implementing this approach was fraught with problems, but everyone involved from researchers to staff of management-related divisions addressed the challenge of *"Full Research"* with enthusiasm. As the problems were being solved, I believe we have managed to produce solid accomplishments.

The AIST Open Lab presented an opportunity to put these achievements in public view. At the same time, it was an occasion for us to reflect on what we ourselves have been doing up to now, and to consider once again the directions to be taken as we go forward. The research units as well as the divisions and departments in AIST have had a chance to think about our future directions. Even though they have their own individual viewpoints, common to all of them is one major issue. It has to do with how we go about actually getting our accomplishments out into the society, and to industry. That has, of course, always been an issue since AIST went into operation, and in the last few years it has gradually come to be a major topic for discussion. It was also the purpose for holding the AIST Open Lab. Since the nature of the issue differs somewhat from one research field to another, its discussion cannot be summarized neatly under a single heading. Still, I believe it is necessary on this occasion for us to share it throughout AIST as a common theme across all

research fields.

The reason is our recognition that the process of getting results out into the world is not a separate act. The definition of research needs to include the concept that research results are used by society based on a general understanding of them, which is an essential part of today's research. In that way, scientific research is able to acquire social significance. Put another way, the concept of "*Full Research*" becomes complete only when it includes the notion of having the results used by society.

This overlaps with the experience of many researchers that, even when the potential is shown in *Type 2 Basic Research* that new knowledge resulting from research can find actual use and become of value to society, and furthermore *Product Realization Research* is completed indicating a model for application to existing industry, industry still does not attempt to make use of these results. It in turn corresponds to the observation (by Ichimura, Full Research Workshop, July 17, 2008) that a fourth type of research, "*Substantiating Research*" is necessary.

We are already aware that there are many issues to be overcome, through our experience with applying research results to industrial use, that is, through our actual efforts to "socialize" *Full Research*. These include legal and institutional issues concerning public finance and patents, issues relating to corporate administrative thinking and risk assessment standards for introducing new technology, and also such issues as social practices and communication between science and society. As one would expect, the final decision of industry is made from an economic standpoint. What must not be forgotten here as well is that in this process, research results undergo a trial, through which technology becomes refined, in parallel with changes in society itself, for the sake of winning public acceptance.

In the course of these experiences, we become aware of one thing. These issues, as noted above, do not get solved within the scope of the science and technology which we are researching. The object of the researches is the achievement of science and technology, but the process of dealing with it is a social one. Laws, economy, business management, customs, and communication, are different issues from the science and technology we deal with in our researches. Accordingly, if we solve these issues not only by coming up with individual approaches matched to the special nature of each of the scientific and technological issues we handle, but also by seeking to treat them as something general, the common underlying framework must be of social science and humanities. This is where social technology makes its appearance.

2. Sustainable technological progress

In writing about social technology elsewhere,[1] I have defined it as technology having its foundation in social science. This definition parallels the notion that "scientific technology" means technology having its foundation in natural science. If we are going to talk about the socialization of research based on this definition, we will need to go into more detail here. The reason is that we need to extract here some issues that come about when thinking about social science, which traditionally may not have had much to do with technology, along with natural science, which today has become deeply involved with technology. Both of these happen to be features of the present age, but my starting premise is that both for social science and for technology, these are not representative of their original, underlying nature. I believe, in other words, that the knowledge of social science ought to be used by actual society as technology, while as the foundation of technology, social science is equally as important as natural science.

What I would like to emphasize first of all is that for technology, the natural science and social science forming its foundation differ only in that the object of one is nature and of the other is society; inasmuch as they both share the scientific method by which they create knowledge, there ought not to be any particular difference in how their knowledge is used. In this regard, the course of history has taken some surprising turns. To take a typical example of social technology, those of us in the world of science and technology (engineering) look with wonder at how knowledge created by dialectic materialism came to form notions of actual society and find actual use in society. In fact, its use not only did not succeed but left behind major losses. To those of us in science and technology, using one theoretical system (containing no contradictions) to design actual society as a whole and applying that to society is something that not only cannot but must not be done. We know that even a highly complete theory for understanding the natural world, such as Newtonian mechanics, no matter how splendid a theory, cannot by itself be used to create actual nature. And now the issue for us is that we have come to realize the need for *Full Research*, a means of original knowledge production, as a process for applying scientific knowledge to reality. We recognize that in order to create existing (artificial) things, we need the type of thought that crosses different areas, called *Type 2 Basic Research*. Moreover, since our work inevitably involves dealing with elements that have not yet been scientifically explained, creation of new knowledge will certainly be necessary. Therefore both the creators of scientific knowledge and its users must have the humility to acknowledge that a complete solution does not exist.

An active attempt to realize this as a mechanism in society, in addition to being humble, is the information cycle,[2, 3] which makes "sustainable progress" possible. What can be said about both natural science and social science is that, if they are to go beyond simply explaining phenomena and become used by actors in society and exert influence on the social situation, the producers and users of knowledge must fulfill their respective roles toward knowledge production as a whole, and must act responsibly. This can be illustrated as in Fig. 1.

Society has many actors, who impact society or nature by their actions. That impact is accepted if it does not disrupt the sustainability of society, but correction is required in case it is disruptive. These days there are many actors in society who claim scientific knowledge as the basis for their actions. If that is true, then whether their actions are good or bad depends on the underlying scientific knowledge and how it is used. This is where knowledge creators and users are joined together, and where each fulfills their roles of advising and decision-making aimed at action. The assessment of actions is carried out by observational scientists. Based on whether the results are good or not, the design scientists create new advice and send it out to society. This becomes the basis on which actors act. The information cycle functions in such a way. The cycle corresponds to the mechanism clarified by Ferdinand de Saussure[4] by which language evolves through circulation, and the knowledge possessed by society likewise evolves by means of this cycle. This mechanism operates without anyone leading and directing the action. The mechanism is driven by the ideas and thinking of individual people. It takes place by abduction, which Charles Sanders Peirce[5] described as central to the process by which human beings create knowledge. The result of abduction is a theory, which becomes proven by this cycle. The scientific knowledge and wisdom accumulated over the long history of mankind through this repeated cycle are assets common to the human race, on which people base their actions, rather than being instructed by specific individuals. Scientific knowledge is possessed by scientists, experts who are responsible for it, while wisdom is what everyone relies on as a guide. As a result, even though progress in some cases occurs in a leap, basically it takes place continuously, a little at a time. This is what makes possible sustainable progress, and also promises that progress will become a continuous chain.

In Fig. 1, so-called observational scientists are not limited to the natural science fields, but generally exist also in the social sciences. In fact, explaining phenomena through observation is what social science is really about. When we think about the information cycle, what we should pay careful attention to are the design scientists. In the case of natural science, this means engineers in the broad sense; but engineers are closely linked to the knowledge obtained in physical science, where observationalists play a central role. With the social sciences, on the other hand, the problem is that there is not necessarily a close link between the two. As we noted earlier, with the social sciences there is the possibility that one academic theory depicts one fixed image of society, whose realization then becomes a categorical imperative for the scientists associated with that theory. When this happens, the analytical results by observational scientists reach actors on a one-way flow,

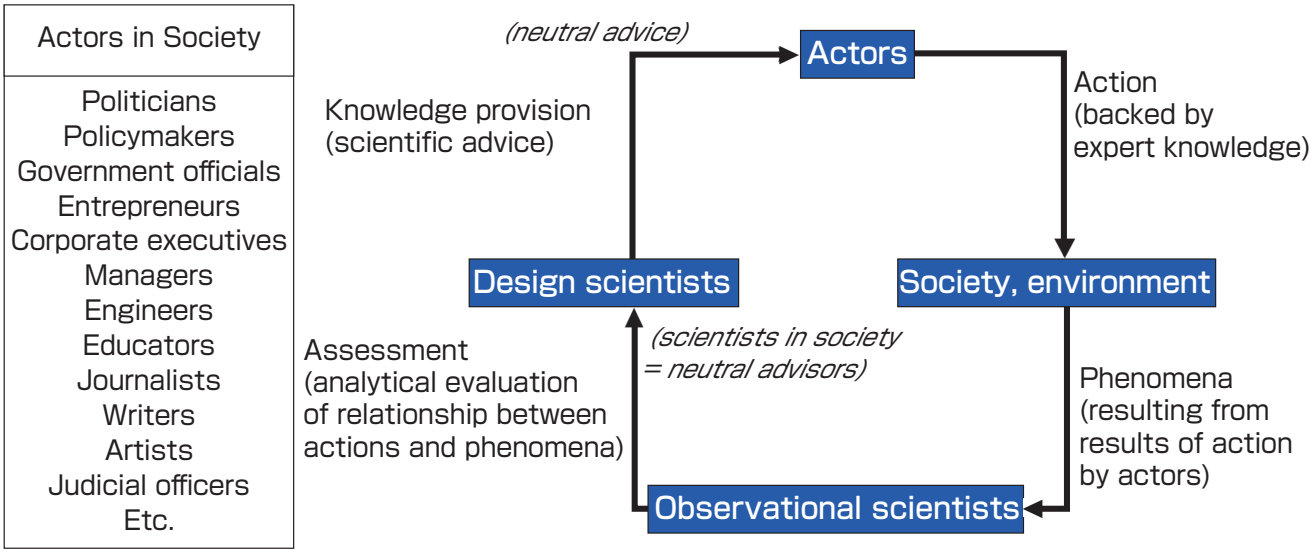

Fig. 1 Information Cycle for Sustainable Progress

so that the effects resulting from their actions based on these analyses are never returned to the observational scientists. The information cycle does not exist; accordingly, sustainable progress is not possible.

This is where we encounter the "piecemeal engineering" pointed to by Karl Popper in his critique of historicism.[6] Popper criticized the tendency of historicism to offer policy proposals that are holistic and utopian. He stressed that the only way of bringing meaningful results to society, such that people's behavior is beneficial to real society as a whole, is by exerting effort in improving existing technology, which is the method actually adopted by engineers. While listening to criticisms from outside and keeping people's welfare as the major goal, this approach does not try to come up with policies that will solve all problems at once.

The reason for bringing Popper into this discussion is that he called this approach incremental "social engineering," or social technology. His definition of social technology is not necessarily identical in all respects to our definition, which we shall talk about later, but has many points in common. In criticizing those who interpret social technology as a holistic application of social theory, he points to something that is important to us as well. He insisted that the technology in social technology, as well as the technology in scientific technology, should have a characteristic incremental nature. What Popper was saying already in 1957 is today considered anew as having important meaning. In the following, I would like to look briefly at some matters that are necessary for making use of the concept of social technology.

3. Scientific technology and social technology

When thinking, for example, about installing railways, fundamental to this is railway technology. The making of various facilities and selecting locations where they can be installed are things that can be done with scientific technology. While these are necessary conditions, however, when it comes to deciding whether or not to go ahead with the installation or what kind of railway to install and where, such matters are decided based on social conditions. In deciding the specifications for building the railway, it is necessary to think in detail about such matters as how to use the resulting railway, how to make it useful for society, and how to create economic benefits. What is necessary for this analysis is social scientific knowledge. As this example makes clear, the knowledge from scientific technology is a necessity for the construction, and social scientific knowledge is the sufficient condition. Accordingly, the issues cannot be treated accurately if these are considered in juxtaposition. For the sake of strictly analyzing these issues, let us give some thought to the following classification, even though it is somewhat different from what we are used to.

A classification of scientific knowledge based on Peirce is shown in Fig. 2. Peirce noted that the phenomena, the objective reality from which knowledge is extracted, are divided into physical existence and human existence in science. The examples here are actions; the customs to be followed, and the materials used when making things, are taken up and abstracted

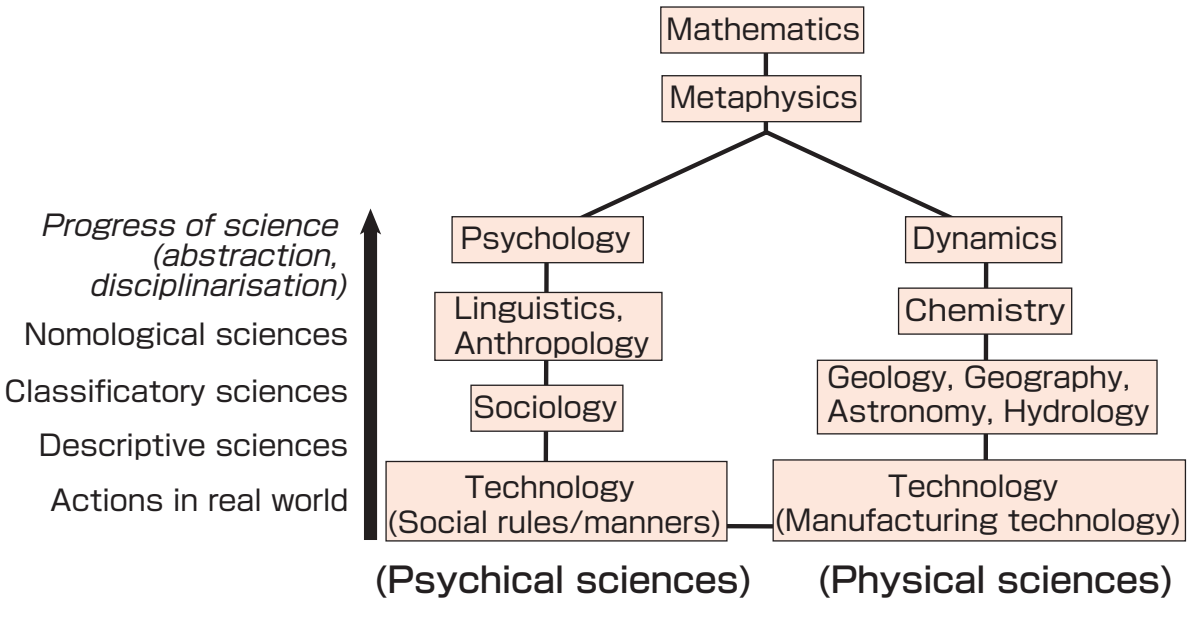

Fig. 2 Peirce's Classification of the Sciences

by means of description, classification, and nomology. The abstract system of customs is called psychical science, while the abstract system of materials is called physical science. Although each of these makes up an independently complete science, in reality they are deeply interrelated. Peirce does not use this example, but let us think about a knife and fork. There are certain manners decided for their use, and these manners are the object of sociology. Manners are a kind of language, and more fundamentally they no doubt have a psychological base. As for the making of knives and forks, this is done by forging and polishing, which are methods having their foundation in material properties. The methods are based on description, classification (chemistry), and nomology (physics). In such a way, technology exists historically independent of science; but the basis of its existence becomes rationally valid by means of science as abstracted general knowledge, with this abstraction being in accordance with Peirce's approach. Technology thus backed by scientific knowledge is the technology of today. According to Peirce, psychical science and physical science become metaphysics through a process of convergence, and knowledge becomes complete when it arrives at mathematics; but for now we shall stop short of considering the metaphysics or mathematics of knives and forks.

Of interest here is the fact that, when we attempt to offer actual technological results created using modern technology and what we earlier called abstracted knowledge, both knowledge belonging to psychical science and that belonging to physical science become necessary at the same time. Even in my, not Peirce's, simple example of a knife and fork, in order to provide these correctly to users, we need to make them using manufacturing technology, and also teach people how to use them. For a more refined provision, theories of physics and psychology might be used. Inasmuch as this provision is a social phenomenon, the technology on which basis it rightfully takes place can suitably be called social technology. In this way social technology is seen as technology with its foundation in both psychical science and physical science. To make this correspondence clear, here we are using the term psychical technology to refer to technology having psychical science as its foundation, and physical technology to refer to technology with a physical science foundation. In general parlance, however, the former may be said to correspond to "policy technique" and the latter to scientific technology.

In this way, social technology (within the scope of a linear analysis) can be understood as a merging of psychical technology based in psychical science and physical technology based in physical science. A conceptual drawing is given in Fig 3.

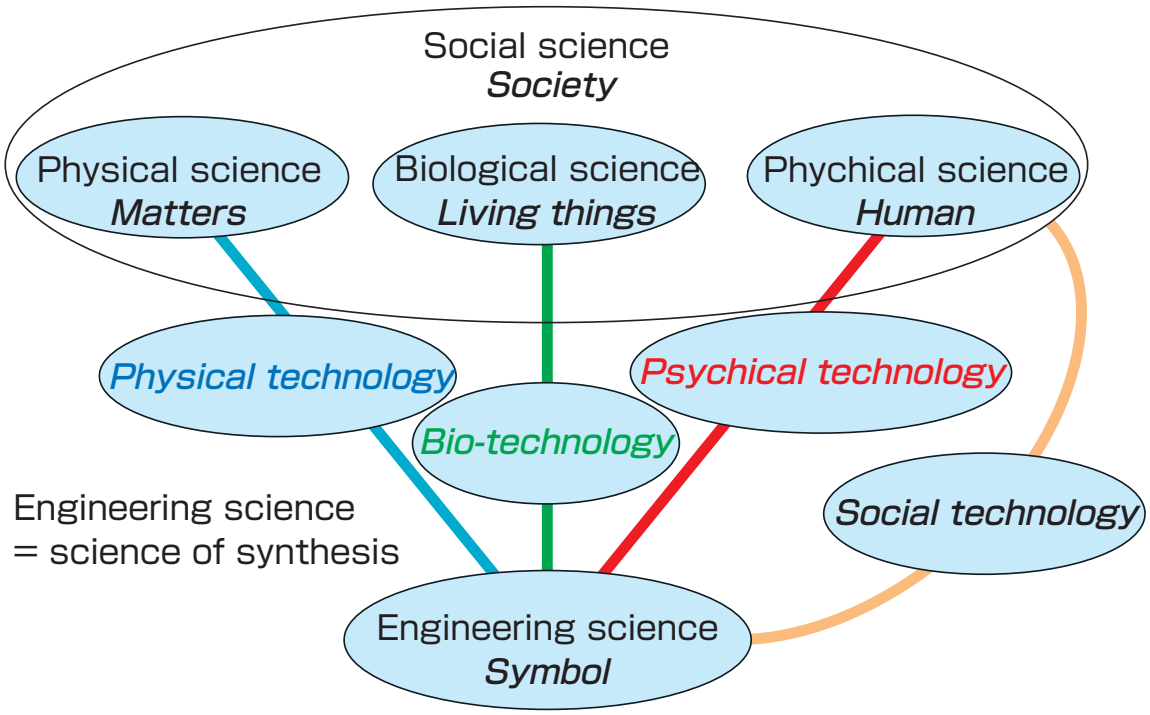

Fig. 3 Social Science and Social Technology

4. Actual status of social technology

For a more precise discussion, we need to consider additionally life-science technology having its foundation in life sciences, as indicated in Fig. 3; but here for the sake of convenience we shall think of life-science technology as being included in physical technology.

Assuming that social technology is the convergence of psychical technology and physical technology, what is its status in reality? To start with the conclusion, since physical science has progressed too far out of balance with psychical technology, the situation today is that a proper social technology has not been established.

Here we have used a rough definition of psychical technology as having its foundation in psychical science. Accordingly, what we are calling psychical science includes such disciplines as sociology, anthropology, linguistics, and psychology, as given in Fig. 2, and is thus science dealing with the psychical side of human beings. It has a long history and has had major accomplishments. What we notice here, however, is that when we look at physical technology as constructional activity based in physical science, and psychical technology as constructional activity based in psychical science, the two differ in terms of the relationship between their foundation and constructional activity. Constructional activity based in physical science, that is, the production of significant physical artifacts, at least historically has brought safety and abundance to the human race. On the other hand, when we look at constructional activity based in psychical science, which would be the creation of psychologically significant psychical artifacts grounded in psychical science, it is more difficult to come up with abundant examples of things in general use. Educational psychology is a field whose systematization has progressed; but compared, for example, to progress in physics resulting in highly advanced materials technology, we have to admit that educational psychology has seen only limited use in the classroom. Interestingly, we are more likely to think of things like hypnosis, opinion manipulation, ethnic cleansing or other abnormal misuses. Ideologically based social revolution, mentioned earlier, also fits in this category. This is not how it was supposed to be. The increase in knowledge was supposed to bring good things to the human race. In looking for the cause, perhaps we need to think about whether there are basic problems in the way knowledge is used. I would therefore like to proceed with an analysis based on the following approach.

We all have experience with industrial products being accepted by society and going on to become progressively advanced in their performance. Industrial products are artifacts created by physical technology having its foundation in physical science. They are able to bring safety and affluence to human beings because the loop of sustainable progress is working. Industrial products, in other words, appear on already established markets and are selected by consumers. Ordinary industrial goods are characterized by having markets that are sufficiently mature, having gained public consent, and being recognized as economic mechanisms. The processes by which consumers select products and by which products are used are made clear by surveys of sales performance, consumed products and so on. This information is sent to the designers of industrial products, and is fed back into design changes and new products. This is sustainable progress.

Does sustainable progress also occur in the case of the "products" created by psychical technology based in psychical science? For the sake of convenience, we shall here call these "cultural products," which can include education, learning assistance, expert advice, psychological care, artistic works, entertainment and the like. We need to consider whether there is for these cultural products, as with their industrial counterparts, an "information cycle driven by piecemeal abduction." My conclusion is that in the case of these cultural products, it is still underdeveloped.

Thinking, for example, about attempts to assess the quality of education provided at the university level, it cannot yet be said that evaluation by public mechanisms making continuous efforts matches the evaluation as seen by those receiving education. University rankings and the like are also one-sided. Evaluation in elementary and secondary education is difficult. The markets that play the important role of driving the cycle in the case of industrial products are underdeveloped in the education field. Even so, we must not be fooled by silly proposals like the voucher system that try to imitate the industrial product evaluation system. That would be the folly of making education subject to economy, and would be a problem also for economy. In education, based on the full awareness that the results will appear in society as a whole many years down the line, a specifically designed evaluation is needed in cooperation between educators and learners (or their guardians), while receiving the support of society. This has nothing to do with economy. Educational economics is of course necessary, but this must not be tied to the assessment of individual educational efforts. Reform based on this evaluation must be carried out not according to a complete theory, but piecemeal by

participation of the people involved. Moreover, a condition of reform is that it must be proposed by the participants, that is, by abduction. I will not go into further detail here, but none of these conditions can be considered as having been adequately met.

The immaturity of cultural products is evident not only in terms of the evaluation that is central to a selection mechanism and important for sustainable progress, but also from the standpoint of piecemeal action and abduction.

Looking beyond education to such cultural products as works of art and entertainment, the establishment of social mechanisms for the proper advancement of arts and entertainment has not taken place and we await mechanisms specific to each.

One more thing needs to be pointed out. It is my view that the technology enabling the markets that are an important factor toward sustainable progress of the industrial products mentioned above belongs not to physical technology but to psychical technology. Accordingly, the completion of the markets results from psychical technology. We noted that the market for cultural products, which are the result of psychical technology, is still underdeveloped. Yet the market for industrial products, which are the result of physical technology, is mature even though the market itself is based on psychical technology. There is much we can learn from this point.

Since social technology is the convergence of psychical technology and physical technology as discussed in section 3, what we need to do next is to extract the issues for social technology from both their statuses. What we can say based on the discussion so far is that the maturity of psychical technology is far below that of physical technology. Let us consider next what the resulting problems are for social technology and how these can be solved.

5. The socialization of full research

We have not yet come to the point of talking about social technology in general. I believe the only way is to clarify this through the process of solving the issues that we face. Looking back over history, we find other examples of engineering that developed through a similar process, with the theory becoming completed as real problems were solved, and the technology becoming systematized. This development approach can thus be taken here as well. Accordingly, rather than immediately thinking about a systematic "social engineering," we shall apply our thought here to social technology based on actual examples such as its form, effects, and elements; and if possible, we shall think about a general systematization in parallel with this analysis.

A reality-based issue here is the socialization of *Full Research,* as noted earlier. Through *Full Research,* we created sciencific and technological knowledge usable by industry. But we also realized that it would not be easy to go beyond the stage of simply meeting the necessary condition of usability and fulfill the sufficient condition of bringing about actual use by industry. The point of our discussions here is the idea that these necessary and sufficient conditions can be created by social technology. Physical technology is used to meet the necessary conditions, and psychical technology is used to meet the sufficient conditions. In fact, the two are not independent but intricately related. For the sake of simplicity, however, we shall use the following analysis.

Let us assume that the research results of AIST are based in physical technology. Since ours is *Full Research,* by no means is it limited to just the physical side of things. We are thinking about actual application to industry in *Type 2 Basic Research* and in *Product Realization Research,* and we are also already considering various psychological aspects. However, since in the socialization that follows *Type 2 Basic Research* and *Product Realization Research* the main aspect can be said to exist in psychical technology, there is a broad tendency (by thinking linearly) to lump psychical technology and socialization together. One result is that the contents of all our researches are not clearly known; not only that, we are faced with the issue of achieving socialization by means of a psychical technology that is immature also from the standpoint of sustainable progress.

Here we need to remind ourselves that the market for industrial goods has become mature thanks to psychical technology. We have been calling the fruits of *Full Research* "products," but are these industrial products or cultural products? Here we come up against a logically difficult issue, so let us put off discussing it for now. In either case, the important thing to note here first of all is that products resulting from *Full Research* are new artifacts, and at the very least there is no established market for them of which society is aware. The fate of arriving on a market that is not yet recognized is unavoidable given the intrinsic nature of *Full Research* with its quality of newness, like nothing that has come about before.

From this we can draw our conclusion. Namely, the socialization of *Full Research* has the same kind of problem as that of offering to society cultural products for which a market has not yet been established. Moreover, this must be a piecemeal process and done by abduction.

Simply put, the socialization of *Full Research* will not take

place by an existing, general approach, which only has to be followed to succeed. Rather, the approach must be created in each individual case. This is the kind of effort already being made today, not only by researchers but in cooperation across industry, academia, and government, and by research-related departments dealing with intellectual property, venture capital and so on. The problem, therefore, is that those efforts as individual, special undertakings are not cumulative, but are destined to evolve as they are carried out on each occasion. To enable success, we need to understand the nature of the problem, establish a method for accumulating efforts, and create a realistic organization. This is a process that needs the participation of all AIST members.

Considering that service engineering is a typical example of social technology, I believe the Center for Service Research established last year is particularly called upon to play an important role toward the socialization of *Full Research*. If we were to neglect this important and most immediate issue we face and simply pursue a broad range of external social issues, we would end up making the same mistake as the former Center for Technology and Society.

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Medical Glycoscience

Strategy for pioneering the post-genome era in Japan: glycoproteomics

Glycoproteomics and Medical Glycoscience

The Genome Project which started in 1980s achieved its goal to identify human genome sequences faster than expected. After that, proteomic researches have started utilizing genome data as their basis. The technological development of analysis made these researches possible. It is however difficult to understand the whole picture of the biological system just by analyzing proteins. A protein shows its function after various modifications, and the modification associated with sugar chains is thought to be most important and to be difficult to analyze. The focus of research is now changing from genome to proteome and further to glycome. We believe that research activity will be recognized for its potential for human use. We inform researchers worldwide who study lifescience the significance of glycoproteomics, and expand and promote industrial technologies required for the development of domestic glycoscience. As a start, we will focus on finding the biomarkers of practical use by applying the fundamental technologies we have gained so far. In the course of identifying the biomarker, we expect to find drug seeds. We hope that our research will eventually lead to the well-being of mankind.

Director
Research Center for Medical Glycoscience
Hisashi Narimatsu

Establishment of Glyco-innovation and Industrial Technology (GLIT)

In the lifescience field, research subjects are shifting from genes to proteins with the development of medical and pharmaceutical applications. Actually, more than a half of proteins of eukaryotes possess sugar chains, and as a form of glycoproteins, they are known to have various functions in living organisms. For example, the functions of sugar chains are deeply involved in cancer, cellular differentiation, development, infectious diseases, brain, reproduction, receptor proteins, etc. Domestic organizations including research institutes such as AIST, universities and companies retain world leading knowledge and technologies in the areas of glycogene resources, structural and functional analyses and sugar chain synthesis. However, the system which provides the knowledge and technologies efficiently for the utilization in the related researches as well as for industrial applications is not well developed and organized. Therefore, by sharing the technologies, resources and information with researchers from a variety of sections, and also by assisting human resource development through education, we think we can create an intellectual creation cycle which contributes to acceleration of industrial application, especially to the development of novel diagnoses methods and drug discovery. To this end, we have established GLIT: Glyco-innovation and Industrial Technology, which is comprised of members not only from universities and research institutes but also from companies, medical agencies, and governments.

Research Center for Medical Glycoscience
Yoh-ichi Shimma

Biological Function of Glycans

● Search for glycan biomarker of hepatocellular carcinoma

Chronic Hepatitis(CH), liver cirrhosis(LC), hepatocellular carcinoma (HCC)

Hepatitis C-type virus (HCV) transmission were caused by administration of blood products, whose patients with CH have been certified to take aids for curative treatment since April 1, 2008. Based on results from epidemiological studies, HCV infection is known to cause CH, resulting in LC and HCC that are the significant sequelae at 20～30 years after HCV infection. The iatrogenic HCV transmission had occurred in the patients in 1980s', whose risk of LC and HCC comes higher day by day. Regarding

For inquiries about this page : Research Center for Medical Glycoscience http://unit.aist.go.jp/rcmg/ci/

current aspects of HCV associated disease, committee for strategic hepatitis treatment of Ministry of Health, Labour and Welfare proposed to develop detection markers for LC and HCC with high sensitivity as soon as possible. The one reason is that present detection markers for either evaluation of LC or early detection of HCC have not been good enough to serve this purpose.

New pathological knowledge of the hepatic disease and novel techniques for medical care innovate medical intervention.

New knowledge and novel techniques for medical care have altered basic approaches of medical diagnosis and intervention for not only for liver cancer but also esophageal and gastric cancer. Inflammatory reaction and fibrosis in LC and CH are also exemplary. Though fibrosis used to be considered an evidence for wound healing in general, fibrotic change associated with HCV infection is currently deemed worse prognostic marker for the liver disease. Moreover, it is pointed out that detection and treatment against fibrosis would play an important role to cure this disease.

Additionally, novel techniques such as radiofrequency ablation (RFA) have altered not only the treatment approach but also diagnostic criteria for HCC. Generally, HCC arises from LC at 7~8 % and CH at 3~4 % per year, small foci of which used to be difficult for surgical pathologist to diagnose because of the weak atypism on the histological appearance. RFA therapy is as effective as surgical resection for less than 2 cm diameter tumor in spite of less invasiveness than surgery, emergence of which drastically changed such situation. As a consequence, such lesion is now classified in well differentiated HCC, and exclusively treated by RFA therapy.

Future vision on medical care for liver disease

By intensive cooperation, we attempt to explore suitable biomarkers for clinical utilities on diagnosis and treatment of CH, LC, and HCC in Research Center for Medical Glycoscience of AIST. As lectin micro-array method can sensitively and comprehensively evaluate alterations of carbohydrate structures of proteins derived from hepatocytes, it is expected to improve estimation methods for not only LC but also early detection of HCC. Furthermore, through the studies to determine carbohydrate structures on alpha-fetoprotein (AFP) from HCC and placenta as a surrogate cancer antigen, we have established techniques to distinguish cancer associated AFP from placental AFP based on the differential glycosylation pattern. Taken such new technologies together, we are exploring further specific carbohydrate biomarkers that are used clinically in liver disease.

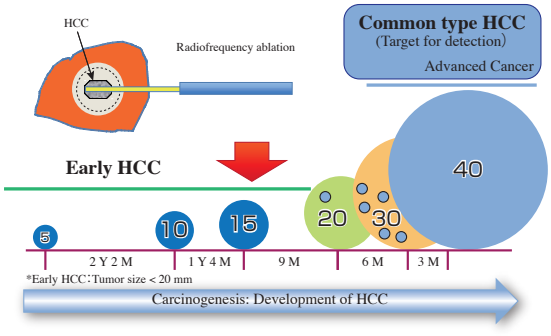


Fig.1 Radiofrequency ablation and Hepatocellular Carcinoma: Novel techniques such as radiofrequency ablation (RIA) have altered not only the treatment approach but also diagnostic criteria for HCC.

New biomarkers in our research goals

New biomarkers are expected to reduce overall burden of medical care by decreasing frequency of liver biopsy, and to cut health care costs by decreasing frequency of computed tomography (CT) scan and Fibroscan test. Additionally, new biomarkers are expected to be useful in foreign countries as BRICs where the prevalence of HCV infection is as high as, or higher than in Japan. We predict the improved sanitation of the societies and long-term follow up of HCV infected patients in these countries due to the economical development, where outcome of HCV is going to be noticed as social problems. Our biomarkers that are developed must be effective to help for overcoming the disease in these countries as well as in Japan.

Research Center for Medical Glycoscience
Yuzuru Ikehara

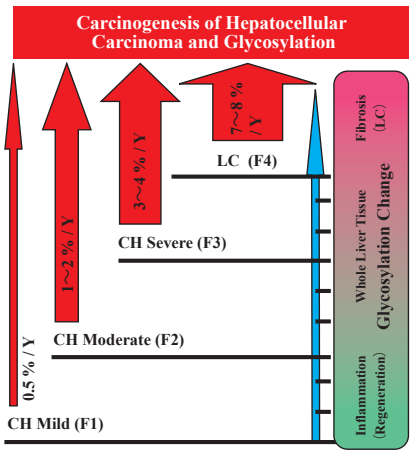


Fig.2 Liver Fibrosis and Hepatocellular Carcinoma (HCC) risk: HCC arises from Liver Cirrhosis (LC) at 7~8 % and Chronic Hepatitis (CH) at 3~4 % per year. Glycosylation pattern of liver tissues changes with development of fibrosis.

Glycoengineering of FGF proteins

What are FGF proteins?

FGF stands for fibroblast growth factor protein family that is composed of 22 members in the human body. The FGF proteins are expressed by and act on various types of the cells in our body. They modulate a variety of physiological processes through regulating cellular proliferation, differentiation and other activities. Thus, smart usage of FGF proteins would enable treatment of many pathological conditions and utilization of biological functions outside our body.

Why do we need to put glycans on proteins?

Many proteins in our body are naturally modified with various glycans. The glycans mediate molecular interations and protect proteins from degradation. Thus, artificially modifying recombinant proteins with glycans is a promising approach to gain biologically active proteins equipped with these functions.

Modification of FGF with heparan sulfate.

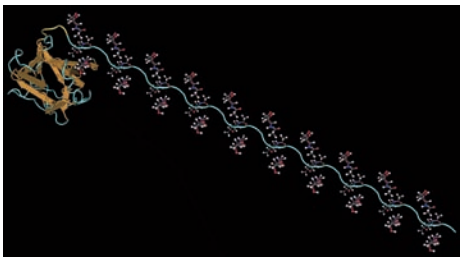
Heparan sulfate is a class of long sugar chain composed of repetitive units, resides on cell surfaces and in extracellular matrices, and is involved in cellular communication. By the aide of heparan sulfate, FGF proteins are stabilized and transduce their signals through FGF receptors on cell surface. We developed a technology to modify a FGF protein itself with heparan sulfate sugar chains by utilizing glycosynthesis ability of animal cells. The modified FGF, PG-FGF1, demonstrates augmented activity as well as improved stability, and is expected to be applicable to various clinical purposes (Table).

FGF1 protein modified with heparan sulfate (PG-FGF1) has many advantages over natural FGF1 as a therapeutic agent.

		PG-FGF1	FGF1 (aFGF)	FGF2 (bFGF)	FGF10 (KGF2)	PDGF
target tissue	epithelium	+	+	–	+	–
	dermis	+	+	+	–	+
stability	protease resistance	+	–	–	–	–
	heat resistance	+	–	–	–	–
	acid resistance	+	–	–	–	–
	alkaline resistance	+	–	–	–	–
activation in wound fluid		+	–	–	–	–
adsorption loss		low	high	high	high	high
effective concentration		low	high	high	na	na
total cost		low	high	high	na	na

Modification of FGF with O-glycans

The *O*-linked (mucin type) glycans, rather short sugar chains, modify proteins in clusters to form a shape resembling that of a brush. They affect interaction with water molecules as well as with other molecules. We developed a technology to modify a FGF protein with cluster *O*-glycans by utilizing glycosynthesis ability of animal cells (Figure). The *O*-glycan modified FGF showed elongated half life in circulating blood. Furthermore, elimination of the terminal sialic acids of the *O*-glycans made its half life even shorter than that of natural FGF.



Proposed structure of a FGF protein modified with cluster O-glycans.
[Drawn by using structures of FGF1 and a mucin peptide generated by Cn3D software (http://www.ncbi.nlm.nih.gov)]

Perspectives

The FGF proteins modified with glycans demonstrate high specificity, augmented activity, enhanced stability and controlled half life. These features would make them safer and more effective therapeutic agents than the natural FGF proteins in clinical applications. A technology for expressing such glycoproteins with uniform glycan structures in large amounts will be the subject of future research and development.

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Biological function analysis of mice lacking a glycogene which synthesizes polylactosamine chains

Glycans that regulate immunity

Over the past few years, we have been isolating and characterizing many glycogenes including glycosyltransferases. We are attempting to elucidate the function of carbohydrate chains (glycoconjugates). We analyzed glycogene (especially glycosyltransferase)-deficient mice to investigate *in vivo* function of carbohydrate chains. In order to generate many strains of glycogene-deficient mice, we selected the target genes which are thought to be disease-related and biologically important.

Here, I would like to present our research findings on the phenotype of polylactosamine synthase (β1,3-*N*-acetylglucosaminyltransferase 2, β3GnT2)-knockout mice which is one of the strains of knockout mice we have created. Polylactosamine containing the repeating units of *N*-acetyllactosamine (LacNAc) (Gal[galactose]β1-4GlcNAc[*N*-acetylglucosamine]β1-3)$_n$, is a fundamental structure of carbohydrates carried on glycoproteins (*N*-, and *O*-glycans) and glycolipids (Fig. 1). Polylactosamines are further modified by the addition of different carbohydrate antigens such as Lewis antigens and other blood group antigens. We investigated *in vivo* function of polylactosamines using β3GnT2-knockout mice. We first analyzed immunological responses in the knockout mice. The results from flow cytometry analysis, LEL lectin-blot analysis and radioisotope metabolic labeling analysis, showed that the amount of polylactosamine chains on *N*-glycans was greatly reduced in the tissues of the knockout mice (Fig. 1). Furthermore, we screened polylactosamine-carrying molecules of wild-type mice by lectin microarray analysis, and found that polylactosamine was present on CD28 and CD19, both known as immune co-stimulatory molecules in T cell receptor signal transduction (T cells) and B cell receptor signal transduction (B cells), respectively (Fig. 2). Polylactosamine levels on these molecules were reduced in the knockout mice. Knockout T cells were more sensitive to the induction of immune signals such as intracellular calcium flux, on stimulation with anti-CD3ε/CD28 antibodies, and proliferated more vigorously than wild-type T cells. Knockout B cells also showed hyperproliferation on BCR stimulation. These results indicated that polylactosamine chains on glycoproteins are important regulatory factors, presumably suppressing excessive responses during lymphocyte activation.

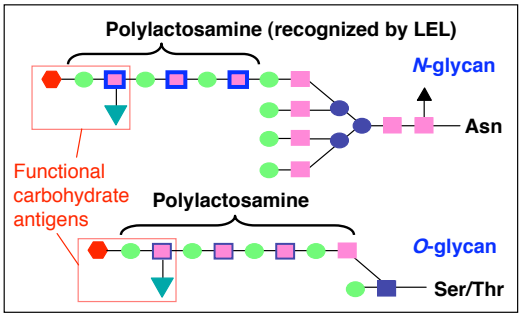

Fig.1 Examples of carbohydrate structure containing polylactosamine
galactose
N-acetylglucosamine
GlcNAc transfered by β3GnT2

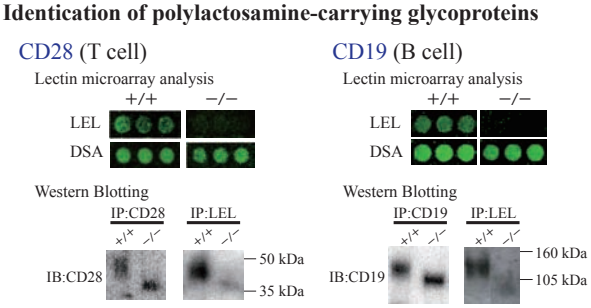

Fig.2 Glycan analyses of immunoprecipitated glycoproteins by lectin microarraying (above). We analyzed receptor proteins on cell surfaces. The LEL signals which indicate polylactosamine chains were decreased on immunoprecipitated glycoproteins. **Western blot analyses of immunoprecipitated glycoproteins (below).** This mobility shift of CD28 and CD19 was observed in knockout mice. These results are consistent with the reduction of molecular weight of the decreased polylactosamines. +/+: wild-type mice, -/-: homozygous null mice, IP: immunoprecipitation, IB: Immuno-blot.

Future prospects

Through the analyses of phenotypes of glycogene-deficient mice along with the identification of structural alterations of glycans and glycan-carrying molecules, we believe that these studies will contribute to a better understanding of the regulatory mechanisms of glycoconjugates. In addition, it is expected that such analysis of molecular mechanism using glycogene-deficient mice enables us to gain further insights into the biological function of carbohydrate chains (glycoconjugates). We will continue investigating the *in vivo* functions of glycoconjugates using glycogene-deficient mice.

These works were supported by "Medical Glycomics: MG" project in New Energy and Industrial Technology Development Organization (NEDO) in Japan.

Research Center for Medical Glycoscience
Akira Togayachi

Structural Analysis of Glycoproteins

● Structural and quantitative analysis of glycoproteins using mass spectrometry

Using glycogenes that have been massively cloned from human genome, we have created a glycan library and a multistage tandem mass spectral (MS^n) database of glycans. Structural analysis of glycans by a simple sequencing is quite difficult due to their structural complexities such as positional isomers, stereo-isomers and branching structures. In spite of the structural complexity, as each glycan has its own characteristic spectral pattern in the MS^n spectra, we can analyze the glycan structures by a method similar to finger print matching of their MS^n spectral patterns. We built a prototype of the glycan analysis system using the MS^n spectral database of glycans in 2006, and we are working toward its practical use[1]. Furthermore, this MS^n database of glycans will be opened to the public soon through RIO-DB (http://riodb.ibase.aist.go.jp/riohomee.html).

Applying the analytical techniques for glycan structures, we are searching for glycan biomarkers which may be useful in early detection of cancers and in selection of the best medical treatment for particular patients. A great challenge for glycan biomarker discovery is "enrichment". Cancer biomarkers secreted from cancerous tissues to serum are expected to be exiguous (typically ng/mL order in concentration). Therefore, structural analysis of glycans of the cancer biomarkers can not be performed unless the biomarkers are enriched in some way. We are aiming to discover novel glycan biomarkers by developing a simple method for enrichment of mucins which are the major constituents of epithelial mucus and have long been implicated in health and in disease.

In addition to mucins, other serum glycoproteins carrying cancer-specific glycans are thought to be good biomarkers. If their core proteins are originated from particular tissue cells, they must have higher tissue specificity. Therefore, we are now trying to discover such biomarker target, *i.e.,* tissue-specific protein having cancer-specific glycans and detectable label in serum, under the close cooperation amongst outside medical institutions and the research teams of Research Center for Medical Glycoscience. Potential glycoproteins are captured from the culture media of a series of cancer cell lines with specific probe lectins or anti-glycan antibody-immobilized column, and their core proteins are identified comprehensively by liquid chromatography / mass spectrometry (LC/MS)-based proteomic approach called "IGOT method"[2]. Using stable isotope-labeling, the change of their label can be analyzed quantitatively. Many biomarker candidates have been identified from the media of hepatocellular carcinoma (liver cancer) and other cancer cells. Now their validation studies are underway and the discovery of novel cancer serobiomarkers is expected.

Research Center for Medical Glycoscience
Akihiko Kameyama, Hiroyuki Kaji

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● Glycan profiling by means of lectin microarray

Development of lectin microarray as a high sensitive glycan profiler

Lectin microarray system is an emerging technique for analyzing glycan structures based on the glycan profiling concept utilizing a group of glycan-discriminating proteins, lectins. This technology mainly comprises of a lectin array slide and a microarray scanner, both of which we originally developed in collaboration with Moritex Co during the NEDO SG project (2002-2005). The former includes spots of over 40 plant lectins with different binding specificities for multiplex detection of glycan-lectin interactions, through which detailed features of glycan modifications and branching patterns will be obtained (Fig.1). For the latter, we adopted an evanescent-field fluorescent-assisted detection principle, whereby no glass washing process is required [1]. In general, the glycan-lectin interaction is relatively weak in comparison with antigen-antibody interactions for example. Thus, some glycans once bound to a lectin on the array may dissociate during the washing process. This should result in significant reduction in the signal intensity.

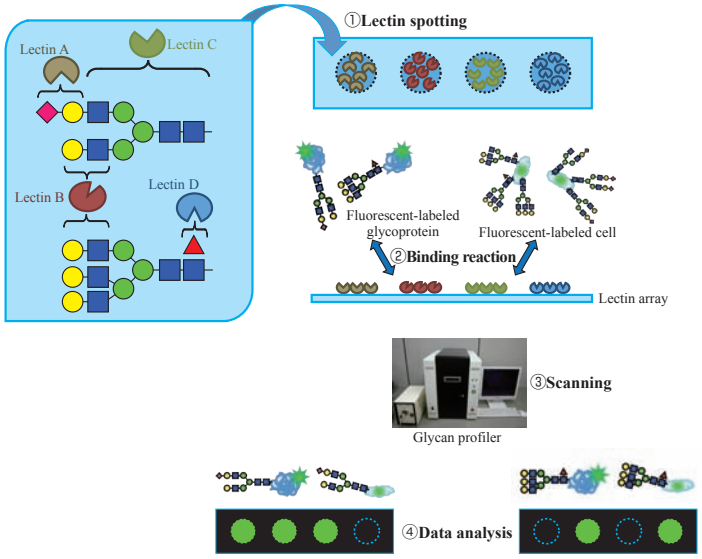

Fig. 1 Lectin array is a practical approach to profile glycans expressed on proteins and cells by means of lectins, as decoder molecules, each which shows different sugar-binding specificity. Thus, distinct sugar-binding patterns will be obtained for different cells and glycoproteins.

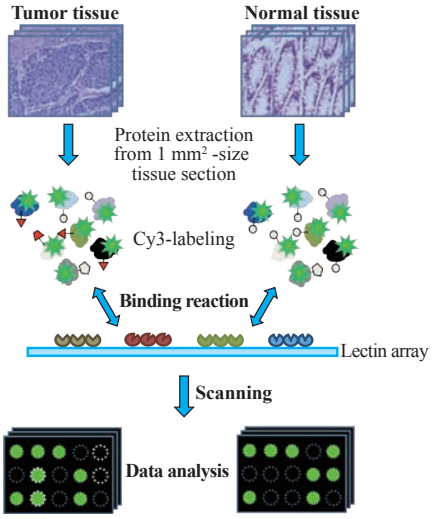

Fig.2 As a result of comparison, it is clear that some lectin signals (circled with *broken lines*) show significant changes, which are attributed to those in glycan structures (shown in red).

While most of the conventional microarray scanners need the washing process, our scanner is unique in getting rid of this problem. Furthermore, our continuous improvement in the array platform achieved an analysis of a glycoprotein structure with the highest sensitivity in 2008 (only 10 picogram of protein is required for assay) [2].

Discrimination of stem cells on the basis of differential cell glycomics

It is said that over a hundred of glycosyltransferases cooperatively act to synthesize/maturize glycans. Glycosylation pattern should reflect alteration of gene expression levels of individual glycosyltransferase during cell differentiation and proliferation. Therefore, cell separation becomes possible by means of differential profiling targeting cell surface glycans (Fig.1). Due to extremely high sensitivity and accuracy, the developed glycan profiling system is considered to best fit the purpose of "stem cell reader", which contributes to regenerative medicine in terms of quality control of stem cells, *e.g.,* before transplantation. In this regard, we have already constructed systematic manipulation protocols including preparation of fluorescent-labeled glycoproteins from only ten-thousands of cells and data-mining procedures, such as for gain-merging and max-normalization[3]. Now, we can discriminate mouse embryonic stem cells from their differentiated forms with retinoic acid. Our group also developed a skilled technique for direct analysis of live cells[4]. Since this method does not require undesirable cell fragmentation, but internally labels the cells, it represents a novel, direct procedure for profiling cell surface glycans.

Lectin microarray should accelerate glycan-related biomarker discovery

There have been enormous advances in the findings of glycosylation alterations in the process of oncogenesis. Therefore, novel tumor-specific glycoproteins accompanying substantial structural changes in glycan moieties will become potential biomarkers with higher specificity than those established previously. For this reason, we developed an extremely feasible methodology enabling differential glycan analysis targeting restricted areas of tissue sections using an ultra-sensitive lectin microarray[5]. In fact, the developed method is sufficient to detect glycoproteins derived from approximately 1,000 cells derived from tissue sections (1.0 mm^2 and 5 μm in thickness). With this system, tumor-related glycan alterations can be clearly detected as signal differences in appropriate lectins on the array (Fig.2). Obviously, the developed technology is straightforward and comprehensive, and thus should accelerate discovery of a series of novel disease-associated glyco-biomarkers under the concept of glycoproteomics.

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Glycan synthesis

● Human glycoprotein production in yeast

Therapeutic glycoproteins and production host

Protein therapeutics, such as antibody therapeutics and cytokine administration, are now known as the largest class of new candidates developed by the pharmaceutical companies. Although most of these glycoproteins are produced in mammalian cells, there is concern for inadequate bovine serum supply and the risk of bovine spongiform encephalopathy. We are constructing a mammalian-type glycoprotein expression system in yeast because manufacturing costs are cheaper than mammalian cells and yeast is virus-free.

Strategy of human glycoprotein production in yeast

Yeasts have a drawback of inability to attach mammalian-type sugar chain for the production of therapeutic glycoproteins for human use. We have cloned and analyzed yeast-specific glycosyltransferases genes for more than ten years. Based on the knowledges, we disrupted the genes involved in hypermannosylated modification. Next, we introduced the genes responsible for the sugar-nucleotide synthesis, the transport of sugar-nucleotide from cytosol to Golgi lumen, and the transfer and hydrolysis of sugars. In the above, the introduced genes are not limited to mammalian ones if the encoded enzymes share the same substrate specificity. We have already reported the production of the human antibody and lysosomal enzyme for enzyme replacement therapy of lysosomal diseases. In the case of the lysosomal enzymes, *in vitro* glycosidase digestion technique was combined to the *in vivo* expression system in yeast, because uncovering of mannose-6-phosphate residues in yeast is so complicated.

In contrast, the engineering of *O*-glycosylation has not been attempted in yeast because *O*-mannosylation is one of the specific modifications in yeast and is vital for yeast cells. We have also succeeded in making both *O*-GalNAc peptide and mucin-type glycoprotein in yeast by introducing three responsible genes encoding *Bacillus* UDP-GlcNAc 4-epimerase, human UDP-Gal/GalNAc transporter 2, human ppGalNAc-T1 and *Drosophila* β-1,3 GalT (Fig. 1). Combined usage of a compound inhibiting yeast protein *O*-mannosyltransferase (PMT) suppressed yeast-specific *O*-mannosyl modification, and increased mucin-type glycoprotein production. We also succeeded in the secretion of human podoplanin (aggrus), which is known as a platelet-aggregating factor on cancer cell, with core 1 structure in the yeast strain. After *in vitro* sialylation, the podoplanin induced platelet aggregation. Interestingly, substitution of ppGalNAc-T1 for ppGalNAc-T3 caused loss of platelet aggregation activity of the podoplanin whereas sialylated core1 structure was also detected by lectin microarray. We have already reported that a sialylated core 1 structure at Thr52 in PLAG domain of podoplanin is essential for platelet aggregation, and our results indicated ppGalNAc-T1 recognized the Thr52 of it and transferred GalNAc residue in the yeast.

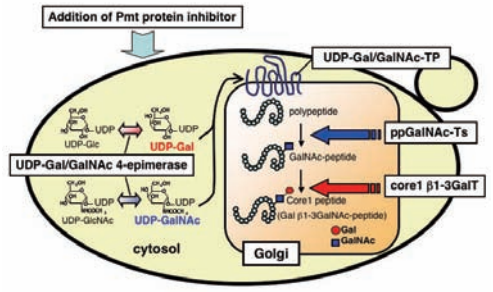

Fig. 1 Strategy for production of mucin-type glycoprotein in yeast.
This strategy consists of "shut-down" of the genes related to yeast-specific sugar modification and "knock-in" of the genes for humanized glycoprotein production.

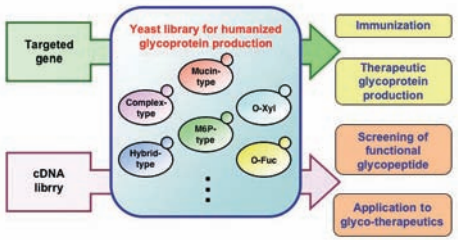

Fig. 2 Application of yeast library for functional analysis of humanized glycoprotein

Future plans

Based on the development of yeast system to produce mammalian *N*- and *O*-glycosylated sugar chains, it is reasonable to say that the production of therapeutic glycoproteins and glycopeptides by yeast has now become a good candidate in any manufacturing process. This yeast system has potential for both functional analysis of mammalian-type glycan and production of mammalian-type glycoprotein for pharmaceutical use. We expect that expression of the targeted gene or cDNA library in our system leads to finding more functional glycopeptides (Fig. 2) and glycoproteins for development of therapeutics.

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Development of effective production methods for therapeutic glycoproteins in yeast using a novel mutagenesis technique

Problems with glycoprotein production in yeast

Although therapeutic glycoproteins containing a mammalian-type *N*-linked oligosaccharides have been produced by disrupting genes responsible for the biosynthesis of the outer chain of mannan, this approach led to a growth defect as well as decreased protein productivity in these yeast strains. The production of glycoproteins using yeast cells has been attempted by many groups. However, the decreased protein productivity in engineered yeast strains was an obstacle to the development of efficient glycoprotein production in yeast. For economic reasons and for effective production of such glycoproteins in yeast, development of appropriate strains is highly desirable. We applied to yeast a novel mutagenesis technique, based on the disparity theory of evolution, which was developed by Neo-Morgan Laboratory Inc., for producing glycoproteins with mammalian-type *N*-linked oligosaccharide.

Development of yeast strains for effective production of humanized glycoprotein

With this novel mutagenesis technique, it is now possible to induce extensive non-lethal mutations in the yeast genome. This technology could increase the error threshold without losing genetic information, and hence could produce a large number of advantageous mutants. The DNA polymerase δ variant, with defective proofreading function, encoded by the *pol3-01* gene of the yeast *Saccharomyces cerevisiae* is known to act as a strong mutator. Here, we constructed a yeast expression plasmid designated YEplac195-*pol3-01*, containing the *pol3-01* gene and capable of introducing multiple mutations due to dominant negative expression of the *pol3-01* gene. We used

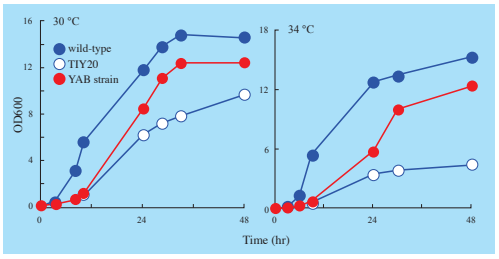

Fig.1 Growth curves. Yeast cells, as indicated in the plot, were grown at 30 °C and at 34 °C. At the indicated time points, OD600 of each culture was measured to monitor cell growth.

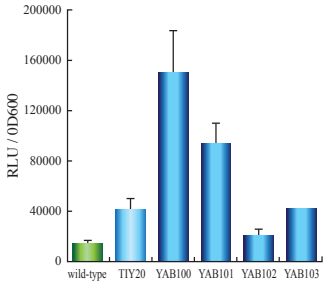

Fig.2 Luciferase activity in culture medium. Luciferase activity (in RLU) in each culture was normalized to optical density at 600 nm, and expressed as RLU/OD600.

this plasmid to transform the *S. cerevisiae* TIY20 strain, which is deficient in the outer chain of yeast mannan type *N*-glycan due to the disruption of three genes *(och1Δ mnn1Δ mnn4)* [1]. TIY20 manifests a temperature-sensitivity and cannot grow at 37.5 °C. The volume of the YEplac195-pol3-01 transformant cultures was increased stepwise in order to promote cell division. This was necessary to accumulate mutations in the yeast genome. We selected 4 colonies (designated YAB100, YAB101, YAB102 and YAB103) which grew at 37.5 °C. The growth kinetics of these strains at 30 °C and 34 °C are shown in Figure. 1. At 30 °C or 34 °C, all YAB strains steadily proliferated, whereas TIY20 was greatly inhibited. These observations suggested that the YAB strains not only suppressed the ts-phenotype but also overcame the growth defect. We also investigated the structure of the *N*-linked oligosaccharides in the W303-1B (wild-type), TIY20 and YAB strains. While those from the W303-1B strain revealed several peaks corresponding to $Man_8GlcNAc_2$ to $Man_{14}GlcNAc_2$, the oligosaccharides from the TIY20 and YAB strains showed only one peak corresponding to $Man_8GlcNAc_2$. Furthermore, we analyzed how efficiently the YAB strains would secrete a foreign protein, namely the reporter protein CLuc, a natural secretary luciferase from *Cypridina noctiluca*. Surprisingly, CLuc secretion was approximately 10 times better in one of these mutants (YAB100) than the wild-type strain (Fig. 2)[2]. This suggests that this strain developed here is suitable for the production of humanized glycoprotein.

Future prospects

We succeeded in isolating useful yeast strains for the production of glycoproteins by using a novel technique that accelerates the evolution of microorganisms. Using the isolated yeast strains, we will develop a new yeast strain which can produce human glycoproteins containing complex-type and hybrid-type *N*-linked oligosaccharides, and aim to provide useful human glycoproteins for therapy.

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Chikashi Shimoda (Department of Biology, Graduate School of Science, Osaka City University)

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Glycoinformatics, Database

● Computational structural analysis for saccharides : fragmentation and interaction analyses

Empirical and/or theoretical rules for the fragmentation of oligosaccharides would be of considerable assistance in the development of novel tools for the structural analysis of oligosaccharides for use in glycomics. We focused on the sodiated saccharides, and fragmentation mechanisms were simulated according to proposed reaction mechanisms in order to find the general rules of glycan fragmentation. Several computational methods, such as molecular mechanics calculations, semi-empirical calculations, and electron orbital calculations, were used to interpret and analyze the experimentally observed fragmentations. We explore, by theoretical calculations, the reasons why sodium-adduct ions of oligosaccharides produce certain characteristic fragment patterns.

We have developed a web-based tool named SGCAL (Structural Glycomics CALculations). SGCAL (Fig. 1) is capable of building a 3D structure from oligosaccharide sequence information and of visualizing the calculated results and the experimental mass spectra, thereby supporting investigations on correlations between the structure of oligosaccharides and their fragmentation patterns[1]. All collision-induced dissociation (CID) spectra were obtained from sodium adduct ions by using a mass spectrometer, and the observed fragment ions were recorded as lists of peaks in SGCAL.

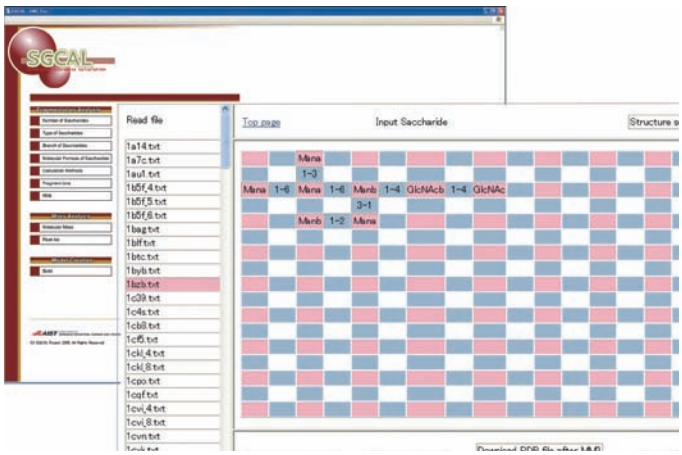

Fig.1 Fragmentation analysis for oligosaccharides (SGCAL: http://sgcal.cbrc.jp)

Theoretical calculations were performed for the oligosaccharides and the results were compared with those obtained experimentally to provide information on structure-reactivity relationships[2,3]. SGCAL also has a mass-analysis function for searching through calculated results and experimental data: when mass values with an allowable mass range are entered into a search box, the mass-analysis function will retrieve lists of parent and fragment ions that meet the search criteria.

We develop algorithms/software to analyze the recognition mechanism of biological macromolecular complexes and simulate protein-protein docking, molecular dynamics, quantum mechanics calculations on the complex molecules using Grid computing environment (Fig. 2). Theoretical calculations using computational chemistry-based methods can be useful in the analysis of experimentally obtained data. Theoretical rules for the fragmentation and recognition mechanism of saccharides can be a novel tool for the structural analysis of oligo- and poly-saccharides in glycomics.

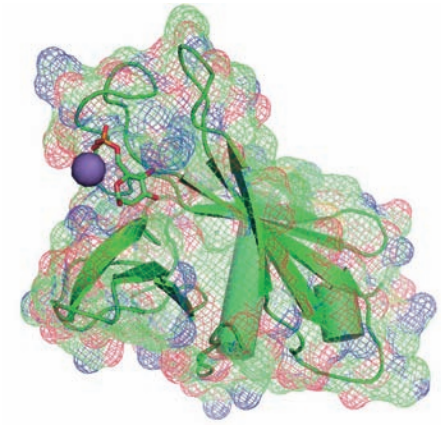

Fig. 2 Docking simulation for lectin-saccharide

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Kazuhiko Fukui

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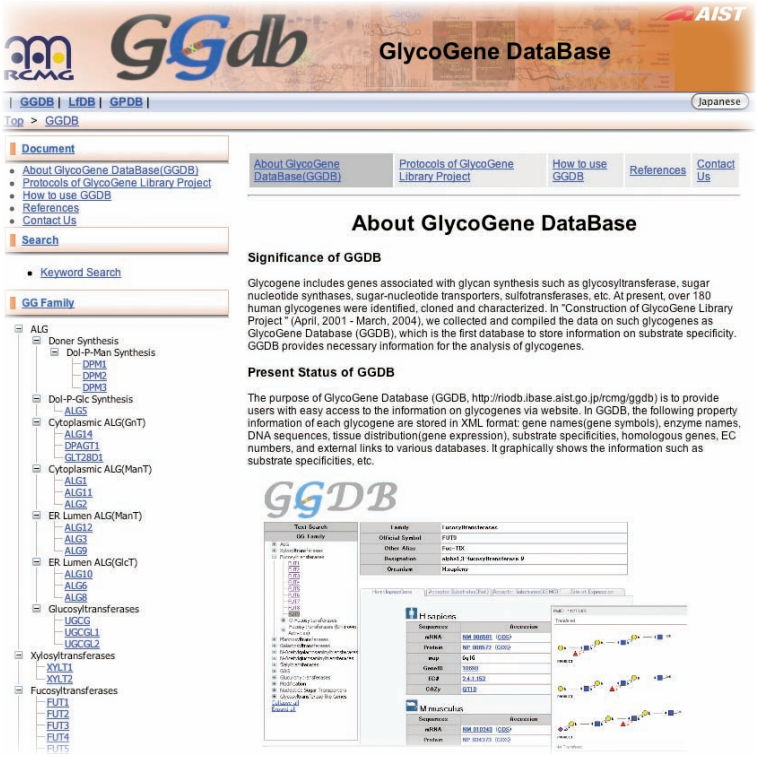
● Integration of glycodatabases

There are various sugar chain related databases in Japan. For example, KEGG Glycan stores the information on sugar chain structures reported in journals. GlycoEpitope has various information of antibodies which recognizes sugar chain epitopes including antigenic sugar chain structures. GALAXY determines a sugar chain structure from the results of HPLC analysis. LipidBank compiles glycolipid structures and their biological activities in conjunction with the structural analysis data of glycans. AIST published the following databases on the Web which were constructed based on the results of the NEDO project. Glyco-Gene database (GGDB) stores the compiled information on human glycogenes. Lectin database (LfDB) presents general information of lectins along with the interaction data between the lectins and standard sugar chains. Glycoprotein database (GlycoProtDB) exposes the actual glycosylation sites of glycoproteins identified by IGOT method, and mass spectral database (GMDB) shows images of fragmentation pattern of sugar chains resulted from mass spectral analysis.

Each database has its own way of use so that users need to learn how to use each database to retrieve necessary information individually, which is time consuming and inconvenient. Research Center for Medical Glycoscience of AIST is now constructing an integrated glycodatabase in which users can search information stored into the databases with a single query using a cross-searching service, and is also developing a system which allows access to other databases used in the field of lifescience. It is also important to provide information on glycoscience, especially those related to sugar chains such as cancer, immunology, infectious diseases, with researchers of other fields in order to bring more understanding to glycoscience.

To this end, we have been constructing the integrated glycodatabase (JCGGDB) as a part of the lifescience integrated database project directed by the coalition of 4 ministries. We are planning to expand and improve the database which covers a wide range of information, from basic to specialized information, and to create a user friendly interface, in the near future.



GlycoGene DataBase (http://riodb.ibase.aist.go.jp/rcmg/ggdb/)

Research Center for Medical Glycoscience
Toshihide Shikanai

Research Hotline

UPDATE FROM THE CUTTING EDGE

Oct.-Dec. 2008

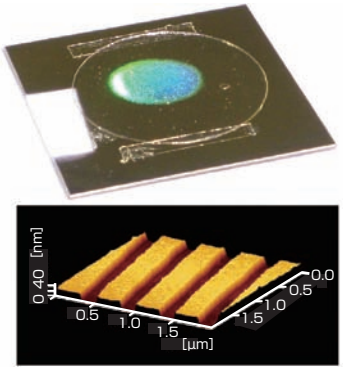
The abstracts of the recent research information appearing in Vol.8 No.10-12 of "AIST TODAY" are introduced here, classified by research area.
For inquiry about the full article, please contact the author via e-mail.

Life Science and Biotechnology

Enhanced fluorescence biochips with sub-wavelength periodic structure

Application for a sensitive fluorescence microscope and biosensor

Surface plasmon resonance is recently familiar as a detection tool for a bio-sensor or a biochip. On the other hand, surface plasmon-field enhanced fluorescence spectroscopy (SPFS) is studied as a powerful technique to detect a small number of molecules at an interface and the application of SPFS to bio-related research and medical field is expected. In this study, metal-coated substrates with sub-wavelength periodic grating pattern are fabricated, and the chips are applied to the grating coupled-surface plasmon resonance (GC-SPR) possible to provide the strong photon-molecule coupling field without complicated optical system using prisms. The fluorescence enhancement of fluorescence-labeled protein bound to the chip surface was more than 20 times compared with that on the a normal slide glass. We apply the GC-SPR to a fluorescence microscope system possible to obtain a surface-selective enhanced fluorescence image and to a biochip system for clinical diagnosis.



A photograph of a fabricated chip with the sub-wavelength periodic grating pattern (upper) and a scanning probe microscope image measured (bottom)

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AIST TODAY Vol.8, No.12 p.20 (2008)

Connection of micro-pad array by nano-plating technique

Application of the failure in electroless plating process to nano-fabrication technique

We have developed a method of connecting micro-pad electrodes by nano-plating technique. Chip-to-substrate connection is a very important technology for developing high performance electronic instruments. We have investigated a method of pad-connection using electroless plating. Generally, it is known that electroless plating, especially electroless NiB deposition, can occur not only on metal surface but also on resist surface. The phenomenon of "bridge" formation by the so-called "extraneous deposition" was utilized as a novel technique to perform selective deposition on organic resist. The behavior of extraneous deposition was controlled by adjusting deposition conditions. Thus, we developed connection of the facing pads to form the metal films deposited on the area between the pads. This method was applied successfully to interconnecting the 5 µm-width pads forming an array with a pitch of 20 µm. This method is a candidate as high-density chip-to-substrate connection for high performance electronic instruments in the field of electronic packaging.

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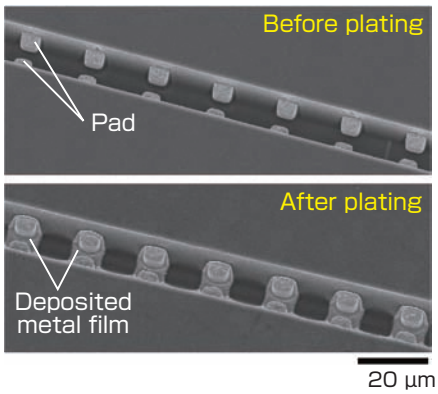
AIST TODAY Vol.8, No.12 p.21 (2008)

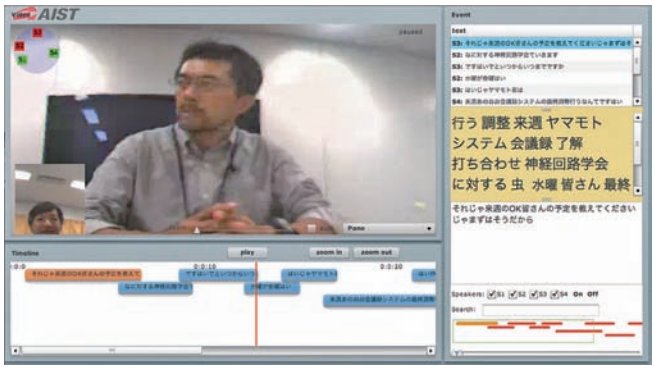


Realized connection of micro-pad electrodes using this technique

An efficient browsing system for multi-media meeting recordings

A simple and efficient way of searching topics in meeting recordings

We have developed MArc , a system for browsing multi-media recordings of small-party meetings. In this system, meetings are recorded by an input device consisting of an omni-directional camera and a microphone array. By applying audio signal processing and automatic speech recognition to the recordings, speakers are automatically identified and the keywords in their speech are detected. Using the obtained information as tags for speech events, a topic of interest can easily be searched by users. The newly developed browser visualizes the outline of recordings based on the tag information.



Browser which shows the contents of meeting recordings

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AIST TODAY Vol.8, No.12 p.22 (2008)

Development of tungsten oxide nanotubes

Visible-light-driven photocatalyst for indoor application

We have developed a facile and economical method to produce nanoporous-walled WO_3 nanotubes in a large scale. These WO_3 nanotubes are monodispersed near 300-1000 nm in diameter and 2-20 μm in length. These nanotubes possess larger specific surface areas than commercial WO_3 particles. The platinum-loaded WO_3 nanotubes show a visible-light-induced photocatalytic activity in the degradation of acetaldehyde about three and eight times greater than those of commercial WO_3 particles and nitrogen doped TiO_2, respectively. Such a large activity enhancement probably arises from the nano-porous tubular structure, which results in a larger effective surface area, higher mobility of the charge carriers and more absorbed photons. This work provides a new scheme to design multicomponent photocatalysts to improve the photocatalytic activity as well as it offers a new material platform for solar cells, nanodevices, and other applications.

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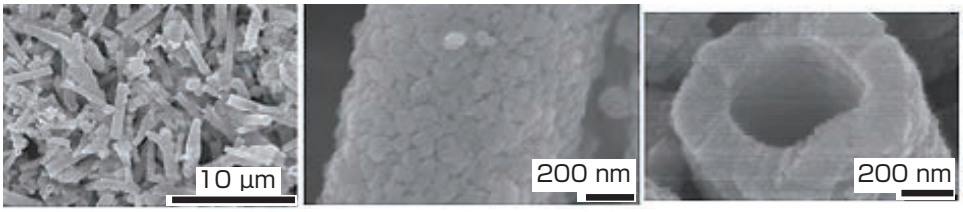
AIST TODAY Vol.8, No.11 p.20 (2008)



Scanning electron micrograph of tungsten oxide nanotube

New magnesium alloy sheet with high formability at room temperature

High stretch formability comparable to aluminum alloy sheets

Magnesium alloys have the high potential for improving fuel efficiency of vehicles and reducing CO_2 emission because of their light weight and high specific strength. For their greater applicability, it is necessary to develop rolling technologies for the mass production of high-performance magnesium alloy sheets. Critical requirements for the magnesium alloy sheets are not only high strength, but also high formability at room temperature for commercial applications. However, rolled magnesium alloy exhibits poor formability at room temperature due to strong texture formation. We have developed a new magnesium alloy sheet with excellent stretch formability at room temperature comparable to aluminum alloy sheets. The new magnesium alloy sheet is processed from hot rolling, and composed of magnesium-zinc binary alloy with dilute addition of rare earth (such as cerium). The excellent formability is attained by a modification of texture resulting from the dilute rare earth addition in magnesium-zinc alloy.

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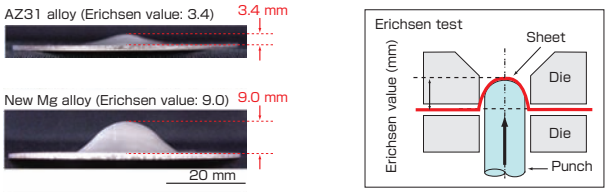
AIST TODAY Vol.8, No.12 p.23 (2008)



Results of Erichsen tests for the AZ31 alloy and the new Mg alloy

A flexible CIGS solar cell with energy conversion efficiency of 17.7 %

Enabling development of a sticker-type high-performance solar cell

We have developed a technique for dramatical improvement of the energy conversion efficiency of flexible solar cells that utilize CIGS, a non-silicon semiconducting material made from copper (Cu), indium (In), gallium (Ga), and selenium (Se). Using this technique, high-performance solar cells with a variety of flexible substrates such as metal foils, ceramics sheets, and polymers are fabricated. The thickness of the CIGS photoelectric conversion layer is very thin in the order of several micrometers. Owing to this feature, lightweight and flexible solar cells that can be installed on a curved surface and portable solar cells are expected to be realized. It has been difficult to develop high-performance flexible CIGS photovoltaic cells so far. By the development of a new controlled alkaline addition technique and a new polymer substrate handling technology, the energy conversion efficiency of the flexible CIGS solar cells is dramatically enhanced. Using this technique, an energy conversion efficiency of 14.7 % has been demonstrated using a polyimide substrate with the use of a low temperature (400°C)-grown CIGS absorber layer. In addition to this, 17.7 % efficiency has been demonstrated using a flexible zirconia ceramics sheet substrate (the CIGS absorber layer was grown at 550°C).

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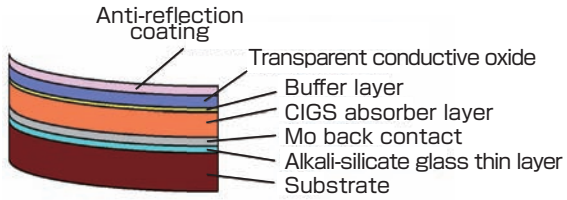
AIST TODAY Vol.8, No.10 p.20 (2008)



Schematic of the structure of the flexible CIGS solar cell developed in the present work

Development of a visible light responsive photocatalyst using tungsten oxide

Complete oxidative decomposition of various volatile organic compounds under visible light

We have developed a tungsten oxide (WO_3) visible light responsive photocatalyst that can be activated to a high enough level to enable the complete oxidative decomposition of various volatile organic compounds (VOCs) under visible light illumination including fluorescent lighting indoors or in vehicles, where little ultraviolet (UV) light exists. Complete oxidative decomposition means completely oxidizing an organic substance by decomposing the substance into carbon dioxide (CO_2) and water, and detoxifying it. We have succeeded in complete oxidative decomposition of VOCs including formaldehyde, acetaldehyde, formic acid, acetic acid, and aromatic compounds such as toluene, which are known as a persistent substances. This photocatalyst has been realized by adding newly developed high-performance promoters, namely metallic palladium (Pd) and copper (Cu) compounds, to a WO_3 semiconductor photocatalyst. Activity improves dramatically simply by mixing promoter particles into the WO_3 powder. In acetaldehyde decomposition under visible light irradiation, the Pd added WO_3 photocatalyst showed an oxidative decomposition activity more than seven times that of a typical photocatalyst, titanium oxide (TiO_2).

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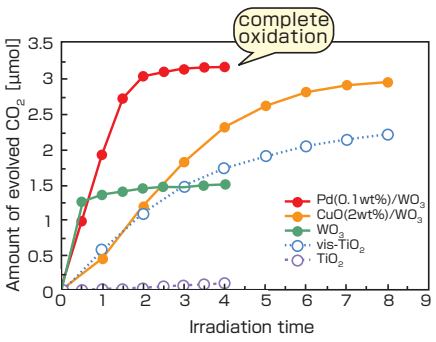
AIST TODAY Vol.8, No.10 p.21 (2008)



Time courses of CO_2 formation during photocatalytic degradation of acetaldehyde (ca. 1.6 μmol) under visible light irradiation (λ> 400 nm).
TiO_2: commercial powder.
vis-TiO_2: visible-light-active TiO_2.

Fabrication of robust superhydrophobic surfaces

Superhydrophobic surfaces of polytetrafluoroethylene by a simple process

We report an efficient, facile and inexpensive process for large area fabrication of robust hydrophobic surfaces with tunable water contact angle up to >150°. The process is essentially a template-based hot-imprinting procedure. We choose wire mesh as the template and polytetrafluoroethylene as a substrate. Compared with other imprinting methods, the advantages in choosing wire mesh as the template are: (1) the shapes and sizes of the features are tunable via changing wire mesh; (2) wire mesh can be fixed on either flat or tubular surfaces, and applicable to various substrate shapes; (3) such templates are easily peeled off from the substrate simply by lifting without any additional step; (4) the templates are robust and can be used repeatedly; (5) wire mesh is commercially available at low cost from industrial batch-processing, and is woven with various weave methods and can cover large areas.

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AIST TODAY Vol.8, No.10 p.22 (2008)

A: Photo of thin polytetrafluoroethylene film placed on the letters "AIST" before thermal transfer and water contact angle(110°)
B: Photo after thermal transfer and water contact angle(154°)

Real-space observation of Li extraction/insertion in positive electrode material for Li-ion batteries

Toward developing the advanced positive electrode materials for Li ion batteries

We achieved real-space direct observation of the extraction and insertion behaviors of Li ions by using a spectrum-imaging method based on scanning transmission electron microscopy (STEM) and electron energy-loss spectroscopy (EELS). It was found that the Li ions were firstly extracted from Fe-rich $LiFeO_2$ nanodomains and subsequently extracted from Mn-rich Li_2MnO_3 nanodomains to extend to the whole region of the particle in a high-capacity positive electrode material, $Li_{1.2}Mn_{0.4}Fe_{0.4}O_2$ (Li_2MnO_3–$LiFeO_2$). After discharge, Li ion insertion was confirmed by the Li mapping images. These results indicate the role of nanodomain structures in activating both $LiFeO_2$ and Li_2MnO_3 domains, which are each inactive in pure bulk form.

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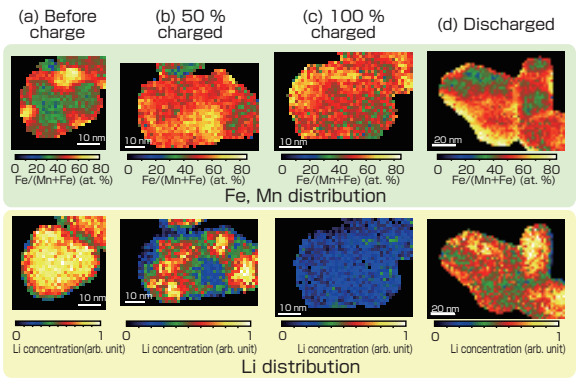
AIST TODAY Vol.8, No.11 p.21 (2008)

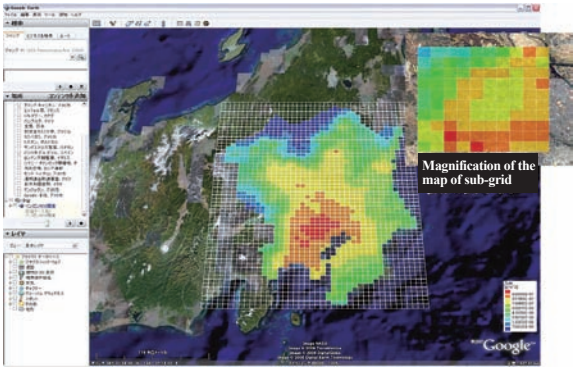


Observation of Li extraction and insertion by STEM-EELS spectrum imaging. Fe/(Mn+ Fe) maps (upper column) and corresponding Li concentration maps (lower column)

Release of enhanced "Atmospheric Dispersion Model for Exposure and Risk Assessment (ADMER Ver. 2.5)"

Creation of a map of the atmospheric concentration of chemical substances on Google Earth™

We have developed ADMER Ver. 2.5, a model to estimate extensive atmospheric concentrations of chemical substances, and distribution of exposed population. ADMER Ver. 2.5 may be freely downloaded at http://www.aist-riss.jp/software/admer/ from August 5, 2008. AIST's Atmospheric Dispersion Model for Exposure and Risk Assessment (ADMER) is free software that can be used to calculate atmospheric concentrations of chemical substances in each area of Japan from data on emissions and meteorological conditions. The newly released, upgraded version makes it possible to display concentrations maps on satellite photos in Google Earth™. In addition, it has such features as enhanced calculation speeds through parallel processing, improved user-friendliness, and an in-built function to download Automated Meteorological Data Acquisition System (AMeDAS) data of the Japan Meteorological Agency. U.S. EPA (Environmental Protection Agency) began releasing atmospheric concentrations data using Google Earth™ in 2007, but this is a first for Japan.



An example of displaying atmospheric benzene concentration map on Google Earth™

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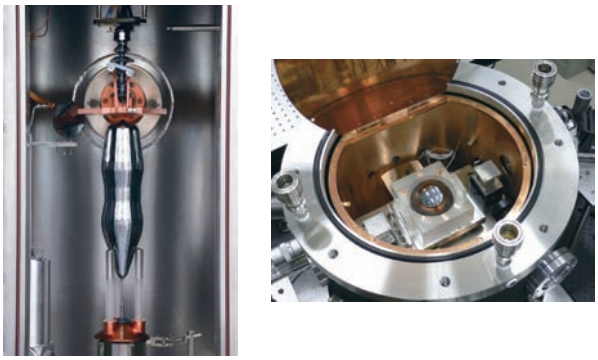
AIST TODAY Vol.8, No.11 p.22 (2008)

The International Avogadro Coordination Project entering its last phase of measurement

Redefinition of the kilogram by ^{28}Si

In order to redefine the kilogram, the only SI base unit still defined by material artifact, the International Avogadro Coordination (IAC) Project was organized by the International Committee for Weights and Measures (CIPM) in 2004. Seven national metrology institutes and the International Bureau of Weights and Measures (BIPM), including the National Metrology Institute of Japan (NMIJ) of AIST, are involved in this project. We hope that the new silicon crystal made of pure ^{28}Si produced in the project will achieve fundamental reduction of uncertainty in the determination of the Avogadro constant. In May 2007, a 5 kg of ^{28}Si crystal with an enrichment factor of 99.99 % was successfully grown by the cooperation with the Russian and German institutes. After two 1 kg spheres were polished from the crystal, one of the spheres came to NMIJ in April 2008 for its density measurement. The project has entered its last phase of measurement, and final results will be available by the end of 2009.



5 kg of ^{28}Si crystal (left) with enrichment factor of 99.99 % grown with float-zone (FZ) method, and laser interferometer (right) which measures the diameter of 1 kg of silicon sphere made from this crystal. Measurement of the diameter of the sphere is done with nanometer precision in a vacuum of strictly-controlled temperature by radiation shield.

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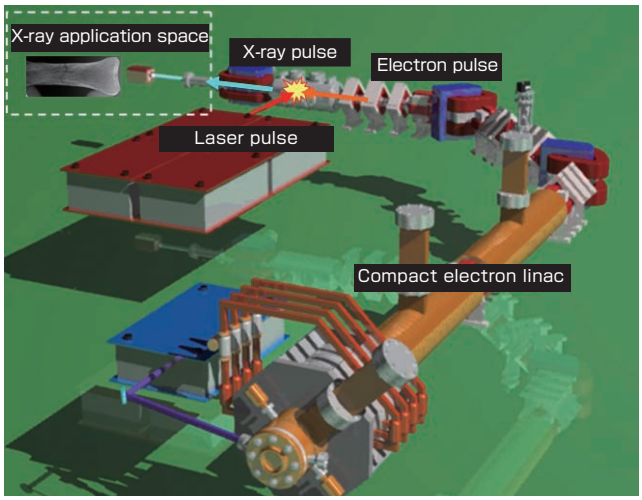
AIST TODAY Vol.8, No.10 p.23 (2008)

Development of linac based X-ray source via laser Compton scattering

Expansion to medical applications using quasi-monochromatic X-ray

Short pulses of quasi-monochromatic X-ray in 10–40 keV have been generated via the laser Compton scattering (LCS) of an ultra-short laser pulse with a high density electron pulse. The LCS hard X-ray source consists of a compact S-band 40 MeV linac and a Ti:sapphire laser system. It has been developed at AIST in order to be applied to medical uses. The refraction contrast imaging of a biological specimen has been successfully demonstrated with the LCS hard X-ray. The LCS X-ray source will be a powerful tool for advanced medical diagnosis.



Laser Compton scattering X-ray source

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AIST TODAY Vol.8, No.11 p.23 (2008)

Thailand National Science and Technology Fair 2008

AIST has signed comprehensive agreements respectively with NSTDA (National Science and Technology Development Agency) and TISTR (Thailand Institute of Scientific and Technological Research), and has strengthened the ties through such events as collaborative workshops. As part of the collaboration with the two Thai research organizations, AIST participated in Thailand National Science and Technology Fair 2008 which was held from August 8 to 22, 2008. The fair which is held in August every year, is a large-scale event attended by about a million people, mainly student groups from elementary schools to universities, and AIST has participated every year since 2005.

Within the NSTDA area, AIST exhibited therapeutic robots, "Paro," a CIGS solar cell, and a thermoelectric generation module, with the help of NSTDA staff. We also presented an overview of the collaborative research with NSTDA with panels on such topics as biofuels and the Biomass Asia project.

Many people visited the fair every day, and our interactive demonstrations of Paro and others especially attracted many visitors and were eagerly received. Moreover, Her Royal Highness Princess Maha Chakri Sirindhorn and H.E. Wutipong Chaisang, then Minister of Science and Technology, visited the AIST booth. These exhibits highlighted the presence of AIST and proclaimed its collaboration with Thailand.

Paro, popular also in Thailand

Japan-Russia Investment Forum

The 3rd Japan-Russia Investment Forum hosted by the Ministry of Economy, Trade and Industry (METI) of Japan and the Ministry of Economic Development and Trade (MEDT) of Russian Federation was held from September 4 to 6 in Sankt Peterburg, Russia. At the sectorial session "Cooperation in Innovation Area: Information and Communication Technology, Industry-Academia Collaboration", AIST Vice-President/Innovation Architect Junji Itoh gave a lecture titled "AIST Innovation Strategy". He presented the overview on AIST, its mission as an innovation hub, and its collaborative efforts with industry, academia and government, citing actual examples.

Keynote address by METI Vice-Minister Takaichi

This forum was organized based on an agreement reached at a meeting in November, 2005 between H.E. Toshihiro Nikai, METI Minister, and H.E. German Oskarovich Gref, then MEDT Minister of Russia. The first forum was held in September, 2006 in Sankt Peterburg, and the second in February, 2007 in Tokyo, and representatives of the governments and businesses of both Japan and Russia have assembled. The forums have played important roles for information exchange and personal interactions. Each event attracted over 500 participants. Ms. Sanae Takaichi, METI Vice-Minister, representing Japan attended this third forum.

At the attached exhibition room, AIST exhibited panels of its research results and the therapeutic robot, "Paro".

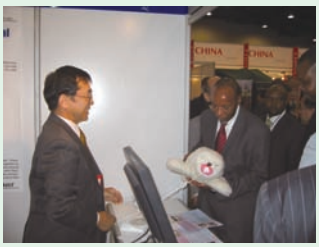
INSITE08 Held in South Africa

International Science, Innovation & Technology Expo (INSITE08) hosted by the Department of Science and Technology (DST) of South Africa was held from September 15 to 17, 2008 in Johannesburg.

The exposition is held every two years, and this was its third event. AIST, upon the request of the Embassy of South Africa in Japan, participated for the first time, and exhibited mainly two collaborative projects concerning mineral resources of South Africa, and the therapeutic robot, "Paro".

Many junior high school, high school and university students visited the AIST booth. VIPs including H.E. Mosibudi Aaron Mangena, Minister of Science and Technology of South Africa, and the Japanese Ambassador to South Africa came to our booth, and the Minister held Paro and showed great interest in the research of AIST.

Furthermore, using this opportunity, with the help of the Embassy of South Africa of Japan, AIST representatives visited the DST Hydrogen Group and other notable research organizations of South Africa, namely National Mineral Research Organisation (MINTEK), University of Witwatersrand, Council for Scientific & Industrial Research (CSIR), and Council for Geoscience (CGS). They surveyed the research institutions and discussed widely on such topics as the possibilities of research collaboration and training for young researchers.



DST Minister Mangena holding "Paro" at AIST booth

Sudanese Minister of Science and Technology to AIST Tsukuba

On October 9, 2008, Dr. Ibrahim Ahmed Omar, Minister of Science and Technology of the Republic of Sudan, visited AIST Tsukuba, accompanied by Mr. Hamza Elamin Baau, Sudanese Ambassador to Japan, Dr. Eis Ibrahim El Gaali, Senior Research Scientist, and Mr. Abdalla Mohammed Ali Alawad, Special Secretary to the Minister.

On the day of the visit, they received welcoming greetings from AIST Senior Vice-President Akira Ono, and were given an overview of AIST by the International Affairs Department. Research Coordinator Yoshiro Owadano gave an overview of the research of AIST in the fields of environment and energy which was followed by an exchange of views.

Minister Omar explained that, under the Ministry of Science and Technology, there are 10 research centers concerning such fields as agriculture, livestock, industry, and energy, and various efforts are underway. Especially in the field of energy, there is a strong interest in renewable energy such as solar energy which they have in abundance, windpower and biodiesel. Much interest was shown in the MEGA-SOLAR photovoltaic system of AIST.

This visit by the minister is expected to trigger a wide range of research collaboration including personal exchange.

Minister Ibrahim Ahmed Omar (second from left)

5th Workshop with VAST, Vietnam

The 5th Workshop with Vietnamese Academy of Science and Technology (VAST), a core research institution of Vietnam, with which AIST has signed a comprehensive agreement, was held from November 3 to 4 in Ho Chi Minh City.

From the Vietnamese side, several dozens of representatives participated including VAST President Chau Van Minh, Vice-President Nguyen Khoa Son, and directors of research institutes. From the Japanese side, 26 people participated including AIST Senior Vice-President Akira Ono and 15 other researchers, and 10 members of the Dyeing Wastewater Treatment Project, funded by New Energy and Technology Development Organization (NEDO) representing industry, university and NEDO. At this workshop, sessions were divided into "biomass", "IT", "environment (wastewater treatment)", "GEO Grid and geology", for research reports, exchange of views and discussions on future plans. At the same time, the NEDO Project Promotion Committee was held, and there was intensive discussion, with a tour at the wastewater treatment installations of the dyeing factory in Ho Chi Minh City.

At the end, the priority collaborative themes of the future were presented in each session, and there were active exchange of concrete ideas for areas that seek outside funds to reinforce the research collaboration. It was agreed that the next 6th workshop will be held in 2010.

Opening ceremony of the 5th VAST-AIST Workshop
Front row, third from left to right: Mr. Shoji Kukita, Director General for Asian Region, NEDO, VAST President Minh, AIST Senior Vice-President Ono, VAST Vice-President Son

Cover Photos
Above: Message from President (p. 2)
Below: Keynote address by METI Vice-Minister Takaichi (p. 27)

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