Striving to combine creativity, flexibility and leadership in research to meet the challenges of a new age.

This center was originally founded in April 1, 2002 at the Tohoku University Graduate School of Medicine as the Center for Translational and Advanced Animal Research (CTAAR). Its establishment as an educational and research institution was initially designed to advance post-genomic research with particular emphasis on the elucidation of genome (gene) functions in experimental animals. These objectives have now been largely fulfilled.

Nevertheless, trends in post-genomic research have rapidly progressed over time. In order to promote advanced interdisciplinary research, it is crucial to integrate diverse knowledge from traditional disciplines (e.g., biology, structural biology, clinical medicine, chemistry, pharmacology, and computer engineering) and create new, innovative research areas. In the meantime, it is equally important to place greater emphasis on "clinical applications of research outputs", that is, "translational research". In terms of operation, we think that the conventional form of industrial-academic cooperation, which routinely involves "one-way transfer of research outputs from individual researchers to corporate firms", is not practical and effective. Instead, a paradigm shift now calls for research based on "open innovation" to be extensively pursued among the academia and industry, as well as rapid synthesis of basic research findings into clinical applications. To better serve these new missions, our center has been officially reorganized (in April 1, 2010) with new missions and research directions.

In the new setup, the United Centers for Advanced Research and Translational Medicine (hereafter ART) will serve as research vectors for "core centers", which are ART subsidiary units devoted to cross-disciplinary projects among researchers (teams) who share common missions and research vehicles. Rather than acting as vertically structured instructional units, these core centers are project-oriented and organized in a creative and flexible way. In order to meet the challenges of a new age, ART will make every effort to facilitate the use of personnel and research material resources (as open resources) and to build strong research teams that transcend conventional disciplinary boundaries. We hope that the core centers will function as project units that produce world-class research and scientists, and ultimately serve as a future Center of Excellence for the Tohoku University specializing in cross-disciplinary and integrative research in life sciences.

As of April 1, 2010, ART comprises nine unique core centers (Advanced Medical Research and Incubation Core Center, Neurosciences Core Center, Oxygen Medicine Core Center, Human Disease Epigenome Core Center, Prion Diseases Core Center, Metabolic Diseases Core Center, Cancer Medicine Core Center, Integrated Gynecology Research Core Center, and Advanced Integrated Nephrology Core Center), with a research staff of 172. With the core centers, there is a host of training possibilities for investigation and education spanning basic research and clinical practice in the abovementioned fields.

ART has strived to become a leading research institution with a vision for the future, and will continue to do so by upholding Tohoku's University's intellectual philosophies, namely, "Research First", "Open-Door Policy", and "Practitioner-Oriented Research and Education".

ART stands out as operating a system that is optimized for active research by young scientists. With ART's research infrastructure and support network, young investigators will have an advantage with regard to engaging in highly productive research and to finding ways to rapidly translate their research findings into clinical applications. It is our sincere hope that young scientists blessed with the creativity and flexibility to take on future challenges will come to ART and call it home!
“Striving to combine creativity, flexibility and leadership in research to meet the challenges of a new age”

Originally established in 2002 as the Tohoku University Graduate School of Medicine’s Center for Translational and Advanced Animal Research (CTAAR), the Center underwent a major restructuring in April of this year and was renamed as “the United Centers for Advanced Research and Translational Medicine (ART)”. After fulfilling its original aim as an educational and research institution to advance post-genomic research with a particular emphasis on the elucidation of genome functions in experimental animals, ART is now promoting advanced interdisciplinary researches in response to the need to integrate diverse knowledge from traditional disciplines (e.g., biology, structural biology, clinical medicine, chemistry, and computer engineering) and create innovative research fields, as well as the increased need to emphasize clinical applications of research outputs known as “translational research”. Specifically, ART integrates nine ‘core centers’ that serve as research units for projects involving researchers from different disciplines who share common missions and research objectives. This organization emphasizes the formation of teams and the use of personnel and resources in a manner that transcends conventional disciplinary boundaries, and establishes an operational framework that provides opportunities to young researchers. It is anticipated that young researchers will leverage this organization to conduct creative research that may lead to the accelerated clinical application of research outcomes. Setting its sights on human applications, ART is eagerly pursuing the relatively new area of ortho/endorlated drug discovery, thus ensuring that its future operations will be closely watched. To that end, we invited the Dean of Tohoku University’s Graduate School of Medicine Dr. Masayuki Yamamoto, Chairman of Tohoku University hospital (TUh) Dr. Susumu Satomi, and ART Director Dr. Toshio Miyata to participate in a wide-ranging discussion about the reorganized center.

Yamamoto: Firstly, I feel that the Graduate School of Medicine has changed dramatically from the days when it was considered that universities could no longer be ivory towers, around the time that Japan’s national universities all became corporations in 2004. We have been actively collaborating with industry to apply research outcomes for the benefit of society. For instance, we conducted the Tohoku University Biomedical Engineering Research Organization (TUBERO) Project and established the Graduate School of Biomedical Engineering (BME). When promoting collaboration between industry and academia, we established an organization for translational research (TR) and disseminate research outcomes to society so. In that regard, we have established one of Japan’s seven TR centers (i.e., the Center for Innovation of New Biomedical Engineering; INBEC) here at Tohoku University. Still, we have learned that simply creating the TR Center was not enough to attract research “seed” (i.e., technology, resources, and ideas). We realized that in order to connect these seeds—which exist in university laboratories like diamonds in the rough—to the TR Center we had to think about what type of structure was required. That’s why we decided to reorganize ART to give it the added function of an incubation center. Seed creation is obviously important, so we had Dr. Miyata design a center that would both incubate and connect these seeds to the TR Center. The resulting concept incorporates plenty of new ideas about how a university should operate, Dr. Miyata. Can you provide us with an outline of your concept?

Miyata: The aims of the restructuring were: to provide a forum for integrated, interdisciplinary research or, in other words, the efficient fusion not only of the Graduate School of Medicine but also various other fields such as pharmacology, engineering, and computer science, and to change the organization into one focused on the practical application of research outcomes (growing outcomes back into medical care). It was also necessary to consolidate new ways of managing a university research organization. The greatest challenge was how to build a framework that would maximize our limited human resources to instead of a vertical cost-cutting structure (e.g., courses A, B, and C with each a professor, associate professor, etc.) in the exactly same fields, we sought to build a challenge-oriented, flexible, cross-cutting research organization and focused on ‘human resources’ (leaders) and ‘projects’ (identifying aims and deadlines). I believe that a research organization which attracts numerous open-minded researchers like a magnet and features an operating structure with leaders and project management that can systematically promote research despite human resource time and budgetary constraints, is one which can perform well.

Our translational research activities are based on the underlying concept of ‘open innovation’ to allow for development while providing a point of contact for various industries and researchers including those from other universities. Instead of the conventional closed model that directs individual outcomes straight to the pharmaceutical industry, our major premise has been the open-source model focusing on shared human and research resources, and this is an advantage of academic research. In the pharmaceutical industry, outcomes and
"We have realized that, in order to connect research seeds existing in university laboratories like diamonds in the rough to the Translational Research Center (TRC), we have to create a novel structure of organization."

(2) Masayuki Yamamoto

The most important thing is to create a free-flowing process by raising awareness about the TRC so that research seeds from both inside and outside the university find clinical applications via the ART and through clinical research and trials conducted by Tohoku University Hospital (TUH).

(2) Sato

resources exist within a closed system and are incapable of spurring new ideas.

The new institute (ART) has been reorganized into nine "core centers": those focusing on specific "seed research" in neurology, cancer, oxygen metabolism, metabolic syndrome, kidney disease, and obstetrics and gynecology, etc., and those developing research seeds into medical treatments such as tumor-targeted drug discovery, cell therapy, and medical devices. Each core center has multiple projects, and forms part of a considerable research organization that currently employs 172 faculty members. The aim is to evolve each core center into a unique research community in which principal researchers (i.e., project leaders) that can exercise leadership skills regardless of their position or age achieve their objectives by motivating their associates. The declining popularity of research among young people is currently an issue, so we are also working to ensure that the core centers are operated in a way that enables successful people to come together and engage. In discussions without constraints, specifically, our core operating team also contains personnel who, despite holding a position below that of an associate professor, are capable of exercising leadership skills. In the future, we hope to achieve more efficient research outcomes by expanding our project management-based operation and consolidating systems for the support of research infrastructure (i.e., experts in regulatory matters and clinical development, etc.). For example, we have already established the "Regulatory Science Division" and even hired researchers who previously worked for the Pharmaceuticals and Medical Devices Agency (PMDA).

Yamamoto: Thank you very much, I find ART’s organization chart to be quite exciting and impressive in terms of university operation. Incidentally, Tohoku University has also established the TRC Center, which is officially known as the Center for Innovation of New Biomedical Engineering (CINBE). I would like to ask Dr. Sato, who is Director of the TRC Center and Chairman of TUH which has been closely involved in TRC’s founding and operation, to provide us with a basic introduction to the Center and describe how it will coordinate with ART in the future.

Sato: As previously indicated, although basic research is very well established in Japan, the system for clinical application of research outcomes is incomplete. As a result, Japan’s basic research ends up going overseas and returns in the form of specific applications. This represents a national loss to the health care industry and has been an issue for the past two decades; so resolving this situation has become a national project. Discussions began around 2002 and, after various developments, one of the leading TRC centers in Japan was established at Tohoku University in 2008. The TRC Center is equipped with three GMP-compliant cell processing centers (CPCs), making it possible to conduct three simultaneous research projects such as comei or islet transplants. It also features sufficient space for collaboration by university-based and other researchers. Because it functions as a support organization, the TRC Center has six divisions including an intellectual property division, a quality control investigation division, biostatistics division, and educational support division, each of which is staffed with recruited personnel.

Leveraging these organizations, a dozen or so research seeds have been initiated to date as support research.

The TRC Center’s support begins with researchers identifying their ultimate objectives, so it is important to organize intellectual property in the initial research stage when outcomes begin to appear and to create a research environment where the data required for IND/MDA drug review and so on is properly arranged. We also facilitate coordination with the private sector when it comes time to commercialize research outcomes, and make the necessary preparations for conducting clinical research coordinators (CRCs) and others for clinical trials and research.

SIR: It is difficult to generate a number of promising research seeds every year. The most important thing is to create a free-flowing process by raising awareness about the TRC Center so that research seeds from both inside and outside the university find clinical applications via the ART and through clinical research and trials conducted by TUH.

I think that the most important seeds derive from research conducted by the Graduate School of Medicine. The research being conducted by ART, in particular, is the closest to clinical applications, so this center continuously receives research conducted by ART, and it is our hope that it will translate into new diagnostic and therapeutic modalities.

The TRC Center is unique in that it was established with the strategy of promoting the TUBERO Project results and supporting TRX research on medical materials and devices. However, the University also has other relevant research seeds in the fields of drug discovery and biology, so we intend to enhance and support these in the future.

Als, we consider the modernization of TUBERO. It is important that the hospital functions as the last bastion of community health care by exploiting conventional diagnostic and therapeutic modalities. But I think that, in the future, about 20% of the hospital’s patients should be new clinical research or clinical trial patients associated with the University’s TR Center.

Yamamoto: Thank you very much. We can now see just how important ART is as a source of research seeds. I think that the Graduate School of Medicine and TUH have been consistently moving in the direction of supporting Sato’s research. Therefore, the Council for Science and Technology Policy has formulated the Health Science Research Promotion Council to promote health research, and the Council has issued its decision to use the academic knowledge accumulated from the research to help revitalize Japanese society. The Council has also announced policies on “green innovation” and “life innovation” towards the Implementation of the 4th Science and Technology Basic Plan in fiscal 2011.

As Dr. Sato mentioned, drug discovery initiatives pose some difficulties even from our perspective. I think that university-based drug discovery is a truly ambitious proposal. Dr. Miyata, I believe you are actively engaged in university-based drug discovery initiatives at ART. Could you give us a summary of academic-based drug discovery and clinical studies? In February of this year, the Ministry of Health, Labour and Welfare (MHLW) announced a new guideline in response to the new Window (W2) Guideline of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and I think that this guideline is recommending “exploratory clinical trials”. What do you think about this new trend?

Miyata: Drug development begins with the understanding of the disease, and compounds (seeds for drugs) are subsequently searched according to novel therapeutic concepts based on the pathological mechanism of the disease. Then, if a lead compound is fortunately obtained, thousands of its new derivatives are synthesized and optimized (i.e., for efficacy, pharmacokinetics, and safety). A final drug candidate is then selected, subjected to a full program of experiments to test the physical and toxicological properties (specifically, studies in animals) of a given molecule before proceeding to human clinical trials. Clinical trials conducted for the purpose of Shorin marketing approval applications are evaluated on the basis of clinical endpoints (efficacy). It is only after several more years have elapsed that the molecule is ready for studies in humans. And this is the point at which most compounds fail. Industry has to sink large amounts of money and time in developing molecules whose pharmacological impact does not comprehend in sufficient detail beforehand. This current framework carries significant risks right up until the end of the development process. So drug development requires a great deal of time and resources, and adoption in human clinical trials is also slow. This makes it impossible to develop many new drugs.

The key to reducing the time and costs involved in researching new molecules is to test the therapeutic hypothesis upfront, in man as soon as it is safe and practicable to do so, and to invest far more in creating a more holistic understanding of disease pathophysiology before embarking on expensive development programs. This is why proposals have been made to conduct drug discovery using more rational scientific processes and to fast-track administration in humans in order to evaluate the drug’s pharmacokinetics (using surrogate biomarkers as indicators) and efficacy. By identifying compounds that are withdrawn from development for pharmacokinetic reasons and valuable compounds that act on human physiology and morbidity faster, we are trying to reduce the time and money spent on drug development and find more potential drugs.

This is why the new guideline has been enforced, to accelerate practical application of drugs through measures such as microdose clinical trials and exploratory clinical trials. By administering compounds (whose safety has been confirmed in animals) in very small doses and evaluating their pharmacokinetics, and by selecting useful compounds using sensitive biomarkers in humans. It is possible to advance our understanding of disease and morbidity, and to reduce the inherent risks of compound development. At present, microdose clinical trials (pharmacokinetic) is being carried out under the initiative of the Graduate School of Pharmaceutical Sciences, but in the future I hope that the Graduate School of Medicine with its patients will also become involved, and that exploratory clinical trials evaluating effectiveness on physiology and morbidity will become the subject of active discussion.

Yamamoto: So you are saying that if a
“ART is re-organized to prove that academia is capable of undertaking the entire process, from performing pathophysiological research to identifying target molecules, in silico discovery of investigating new compounds, lead optimization, conducting preclinical studies, and eventually human clinical studies.”

Yamamoto: Yes, that’s right. It would not be a therapeutic dose, so the aim would be to determine the drug’s half-life, tissue distribution, and other pharmacokinetic properties. It would also be possible to evaluate tissue distribution to a specific organ in conjunction with a PET scan. In some cases, there should be a significant difference between the pharmacokinetics of a drug used on animals compared to when used on humans, so testing the drug in human in very small doses before conducting preclinical studies would allow us to eliminate unforeseen data. Also, it would fast-track our understanding of a drug’s effects on human physiology and morbidity using sensitive biomarkers. I think we would gain a major advantage in terms of new drug development. These so-called exploratory clinical trials enable even researchers in academia to easily access to human data without completion of a full program of expensive and time-consuming preclinical studies in animals. It should improve insights into human physiology/pharmacology and document the drug candidate’s characteristics and therapeutic target relevant to disease. Such an approach should alter the balance of risks dramatically, enable us to pursue many more promising compounds than is currently affordable, and develop them with a much greater probability of success.

Miyata: We are coordinating with TUI, which also makes it easy to conduct medical treatments on volunteers. So it is safe to say that university-based drug discovery is now a reality.

Yamamoto: We are coordinating with TUI, which also makes it easy to conduct medical treatments on volunteers. So it is safe to say that university-based drug discovery is now a reality.

Miyata: The clinical trial framework does not change, but we are able to obtain a considerable amount of information on human physiology and morbidity, and our basic research faculty can also contribute to clinical studies through the development and evaluation of biomarkers. Also, it may be possible to accelerate drug development for diseases where there is some reluctance to proceed from animal to human trials because of the steep hurdles posed by clinical trial endpoints. For example, the evaluation of endpoints in clinical studies of kidney diseases takes several years, meaning that new drug development is largely an arduous affair. However, if we could conduct an exploratory clinical study and confirm a drug’s distribution to the kidney as well as the physiological and pharmacological effects by using biomarkers in humans, we could accelerate the development of new drugs.

Miyata: Phase I clinical trials investigate the setting of doses that can be safely administered in healthy individuals as well as the pharmacokinetics. But if these trials could be conducted at university hospitals, it would likely be possible to effectively assess the investigational products’ physiological and pharmacological effects as well as its adverse effects by using biomarkers, because the latest diagnostic and analytical techniques would be available. If we are going to administer the drug to human subjects, we may as well obtain as much physiological and pharmacological information in human as possible.

Yamamoto: I think that the Graduate School of Medicine’s approach of actively undertaking early exploratory studies in cooperation with TUI in efforts to proceed to the development of drugs and research seeds is highly innovative. What do you think Dr. Satomi?

Satomi: I was reminded of the course of action that Dr. Miyata spoke of is consistent with the preparations being undertaken at TUI. The Pharmaceutical Affairs Law (PAL) is a major issue, so the TR Center has established a policy of recruiting experts from the INDA. At TUI, we are in the process of preparing hospital beds to cater for phase I and other clinical trials as well as clinical research. About 40 new hospital beds have been dedicated exclusively to this purpose, about 20 of which could be provided for use in exploratory health care; a plan we have started investigating for the near future. We have also increased the number of PET scanners to two, which allow for their use in clinical research as well as routine operations. We plan to facilitate clinical research by formulating provisions regarding the use of nuclides.

Miyata: Phase I clinical trials investigate the setting of doses that can be safely administered in healthy individuals as well as the pharmacokinetics. But if these trials could be conducted at university hospitals, it would likely be possible to effectively assess the investigational products’ physiological and pharmacological effects as well as its adverse effects by using biomarkers, because the latest diagnostic and analytical techniques would be available. If we are going to administer the drug to human subjects, we may as well obtain as much physiological and pharmacological information in human as possible.

Yamamoto: Searching for biomarkers and investigating pharmacokinetics and efficacy based on a profound knowledge of pathological conditions are our research specialities at the Graduate School of Medicine and TUI. I believe that we have created facilities that can be used in important aspects of drug discovery. This is a very good field for ART and the TR Center to venture into together.

Satomi: Yes, I agree. I anticipate that the University’s ability to realize this will act as a new enticement to young people and lead to the revitalization of TUI.

Yamamoto: Wonderful. That certainly adheres to Tohoku University’s stated goals of “Research First”, “Open-door” policy and “Practice-Oriented Research”. Finally, please describe your future ambitions for ART, the TR Center, and TUI from the perspective of this new trend in medical research.

Miyata: Specifically, that would be bringing two or three unapproved drugs to human clinical trial phases (microdose, exploratory clinical studies, Proof-of-concept (POC) studies on some diseases, etc.) independent of pharmaceutical industries. I want to prove that academia is capable of undertaking the entire process—from performing pathophysiological research to identifying target molecules, in silico discovery of investigating compounds, lead optimization, conducting preclinical studies, and eventually human clinical studies. There are still many areas that the pharmaceutical industry cannot commit to, like orphan diseases and kidney diseases. I think it would be highly significant to demonstrate that academia alone can reach such stages. Clinical studies do not necessarily have to involve a clinical trial conducted for the purpose of Shinsei marketing approval applications. Rather, it is important to select useful compounds which act on human physiology and pathology as exploratory clinical trials. Clinical studies can therefore enhance our understanding of physiology and morbidity, and provide the infrastructure (e.g., intellectual properties, promoting investigational new compounds, useful surrogate biomarkers) needed for full-scale development of new drugs by the pharmaceutical industry. The Institute of Physical and Chemical Research (RIKEN) has similar philosophy and approaches, and in April of this year, established the RIKEN Program for Drug Discovery and Medical Technology Platforms. Our Graduate School of Medicine is collaborating on this program based on a partnership agreement.

Satomi: I think that the TR Center’s leading priority is to experience success in providing research seed support. We are presently trying to coordinate several research seeds with the private sector to achieve commercial applications, and there are already 4-5 seeds for which this may happen. So we are holding progress meetings once a month towards that end, if we can realize the commercialization of a medical device or material, we would be setting a precedent within Japan. That would establish the TR Center as a pivotal facility in this field here. As mentioned earlier, establishing an environment to conduct early exploratory clinical studies would increase TUI’s appeal and bolster its activities, transforming it into a forward-looking hospital suited to the 21st century.

Yamamoto: Listening to the both of you is reassuring for me as the Dean of the Graduate School of Medicine. I would like to conclude today’s dialogue in the knowledge that the Tohoku University School of Medicine will continue its efforts into the future. Thank you for your time today.