Translational research in Japan: Opportunities and obstacles

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1. Introduction

First of all, I would like to express my pleasure to hold this very extraordinary and unique meeting - Franco-Japanese First Translational Research Initiative, today. I would also like to thank Mr. Roy and Mr. Higuchi for their great effort in bridging the relationship between Saint Louis Hospital and Kyoto University Hospital. Also, my great thanks go to Professor Calvo and Saint Louis Hospital Director Professor Lajonchere. This meeting was made possible by the quick decision-making of Professor Lajonchere when we visited Saint Louis Hospital last August and very friendly discussion with Professor Calvo. Many thanks.

This very unique Franco-Japan Translational Research Initiative reminds me of my visit to the United States some fifteen years ago when I met Dr. Charles A. Coltman, Jr. He is the chairman of Southwest Oncology Group, one of the biggest and the most active cancer clinical study group in the world. When we met in Houston, we agreed to start a 10-year program for the review and exchange of information about clinical trials on a broad range of cancer in each country. Fortunately for this year, we will have the 11th US-Japan Clinical Trial Summit Meeting. This meeting is focusing on multiple myeloma. This is a very unique and very important project not only for the two countries, US and Japan, but also for the whole world because we have determined a very unique and important prognostic factor for multiple myeloma. And this meeting will be organized by Dr. Takashi Uchiyama, the Director of the Kyoto University Hospital, and will be held on April 7-9, 2006 at Kyoto Miyako Hotel during the cherry blossom blooming season.

My talk today is about the national system and policy on translational research at academy and university hospital. My talk is relatively the same as those presented by Professor Lajonchere. When we plan to collaborate or harmonize with other countries, we must first understand and learn the healthcare systems which differ from country to country.

2. Healthcare system in Japan

This slide (Fig. 1) gives a short description of the healthcare system in Japan. Our system is very unique in the world. We have a universal insurance system. Patients under this system usually pays very small amount of money in co-payment compared to other countries. We have very unique point system of reimbursement. Under this point

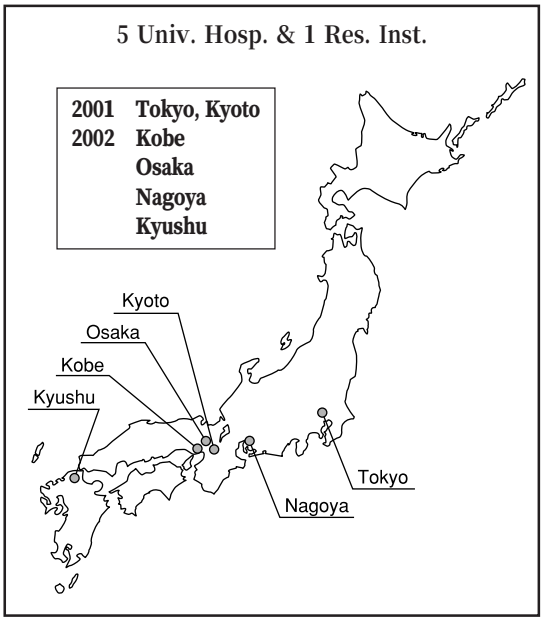
system, the Japanese government allocates equivalent points for each medical procedure in order to ensure equal opportunity for each patient and aiming for equal results. This is quite different other countries. We also have free access system meaning all doctors regardless of their specialty can treat see all patients. For example, gynecologists or internists can see children or surgeons can see dermatology patients. In the same vein, every patient can visit every doctor. Again this is quite different. This system guarantees diagnosis-oriented patient care and achieve early detection of diseases. Those systems allow Japanese patients to have opportunities detecting early stage diseases, For example, detection rates of stage Ⅰ cancers are substantially high. This is a very unique system. So I think it is important to learn the healthcare system of the country before discussing anything else.

Fig. 1 Health Care System in Japan

Japan
- Universal Insurance — small co-payment
- Dot System reimbursment
- Free Access

⇨ Diagnosis oriented
⇨ Early Detection increase stage Ⅰ

Fig. 2 Translational Research Centers in Japan -1 Established by MEXT



3. Translational Research Centers in Japan

In 2001, the Ministry of Education, Science, Culture and Sports (MEXT) built two translational research centers in Japan, one in Kyoto University and one in Tokyo University (Fig. 2). Following the year, four other translational research centers were built, in Osaka, Kobe, Kyushu, and Nagoya. Now, we have five university translational research centers and one institute. There are other universities which also challenge translational researches - Chiba University, Keio University and Tokyo University.

Each translational research center has different approach in clinical research and each TRC has its own collection of seed compounds in different stages of clinical development (Table 1). So quite frankly, the system is not well organized, but the five university translational research centers and one institute agreed to meet every year to hold discussions and exchange information. Each TRC has a cell processing center (CPC) but only Kobe TRC has a full GMP-level CPC. Unfortunately right now, Kyoto University Hospital CPC, which will be presented later on by Professor Maekawa, is not yet a full GMP-level CPC.

Table 1 TRC in Japan -2

1. Each TRC takes different approaches.
2. Each TRC has several seeds for clinical development.
3. Each TRC has Cell Processing CTR (CPC). TRC at Kobe has full GMP level CPC.

4. Kyoto University Translational Research Initiatives

Kyoto University Hospital has taken initiative to build infrastructure for translational research in terms of developing operational guideline of ethical committee, data center and basis for clinical practice (Table 2). This is a very important issue in Japanese university hospital, especially in our hospital. We have also taken initiative to carry out investigator-sponsored IND registered trial. This is really critical step to promote translational research in our country. In Europe and the United States, all translational research should be registered. Kyoto University Hospital has finally achieved breakthrough to carry out investigator-sponsored IND registered trial, with ongoing trials on Hepatocyte Growth Factor (HGF) and Prostaglandin-E Receptor 4 Agonist.

The Common Operational Guideline is a kind of an amendment of government-issued Ethics Committee regulation (Table 3). This was developed by TR Consulting Group, an autonomous governance initiative consisting of 5 leading university hospitals and one research institute which I mentioned you earlier. This guideline was activated in 2004 and is scheduled for revision either this year or next year.

Our hospital is currently undertaking many activities of new drug clinical development (Fig. 3). These activities include PGE analog and HGF which are IND-registered trials. We also have research on leptin, ghrelin and thioredoxin. Leptin and ghrelin are peptides and Phase 2 trials for these peptides are ongoing. We are also now preparing thioredoxin for IND-registered trial. bFGF is a regenerative medicine, and the results of trials in this area have been very successful. The six

Table 2 TRC at Kyoto Univ. Hospital takes initiative

▣ To build infrastructure for TR in terms of developing operational guideline of EC, data center and clinical practice basis.
▣ To carry out investigator sponsored IND registered trial. ex. HGF, and PGER4 agonist

Table 3 Common Operational Guideline for the Ethical Review of Translational Research

Developed by the TR Consulting Group an autonomous governance initiative consisting of 5 leading Univ. Hospitals and 1 Res. Inst.
Activated in 2004.4.1 Scheduled revision 2006.4.1

Fig. 3 Ongoing Translational Researches at KUHP

2006.1

class	species		No. of trials
• Chemical	1	PGE analog	1
• Hormone	2	leptin, ghrelin	3
• Biologics	3	thioredoxin, *HGF*, *FGF*	5
• Cellular	2	*BMC*, DC	2
Total	8		11

* □: IND Registered ** *color*: Regenerative Medicine

patients with peripheral artery obstructive disorder who received slow released bFGF treatment have already recovered. We also have the DC trial, which is a trial on anti-cancer immunotherapy. This is being conducted by Professor Uchiyama using bone marrow cell. It is also currently ongoing.

5. Kobe Translational Research Initiatives

Kobe city has a biomedical research institute and a translational research informatics center (Table 4). The mission of this center is to supervise 10 cancer translational research projects nationwide and to disseminate translational research methodology. These projects include cancer vaccine, cellular therapy, viral therapy and molecular targeting therapy. One of these projects is the gamma-delta T-cell project which is conducted by Professor Minato at the Kyoto University.

This photo shows the Kobe Translational Research Informatics Center built in 2002 (Fig. 4)

Table 4 Translational Research Informatics CTR at Kobe has responsibility

▣ To supervise nation wide 10 cancer TR projects including cancer vaccine, cellular therapy, viral therapy and molecular targeting therapy.
▣ To disseminate TR methodology.

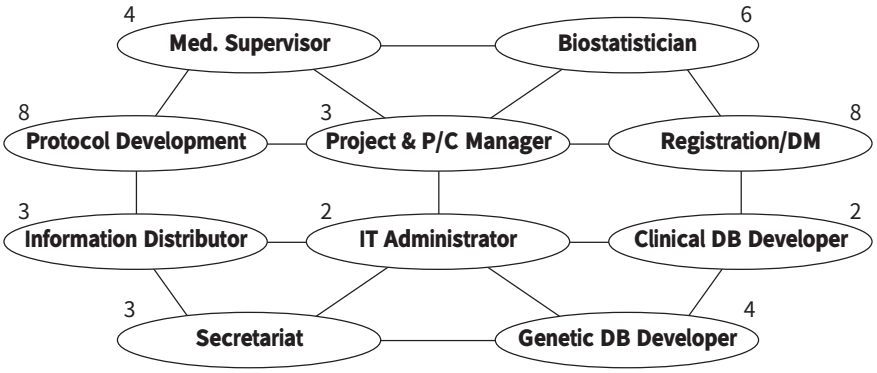
with the joint funding from MEXT and Kobe City.

This is the organization of the Translational Research Informatics Center at Kobe (Fig. 5). The center has 4 medical supervisors, 6 biostatisticians, 8 protocol managers, 3 project and P/C managers, 8 registration/data managers, 2 staff managing information distribution, 3 IT administrators (this is a very important position), and two IT specialists system engineers. We also have 2 clinical database developer, one genetic database developer, and 2 secretariats.

At the Institute, we conduct more than 70 trials including phase 1, 2 and 3 clinical trials and outcomes research, as well as genetic/biomarkers and diagnostic studies or PET scan projects (Table 5). Many of these projects are cancer trials.

Fig. 4 Translational Research Informatics Center at Kobe Founded in 2002

Fig. 5 TRI Kobe Operation Team



6. Major obstacles in translational research in Japan

We still have many obstacles to overcome to accelerate clinical research and promote translational research in Japan (Table 6). One major obstacle is the lack of legislation to protect human trial subjects. Also, we lack an established quality assurance in investigator-initiated clinical trials because many of these trials are non-registered trials. A solution to overcome these obstacles is to encourage investigator-sponsored IND-registered trial (Table 7). Therefore, we need to harmonize our translational research activities with those of the Europe and US.

7. Translational research - National strategy

In terms of national strategy (Table 8), to accelerate new drug development, we need to encourage investigator-sponsored registered trial, develop academia-industry complex as a new business scheme just as France is doing. But we need to establish our own business scheme which is different from EU and US because Japan's business culture is quite different from other countries. We also have to establish and enforce laws for protection of human subjects participating in clinical trials and establish quality assurance of medical practice. These last two points are very effective and if they are achieved, then Japan's translational research activities can be harmonized with the EU and the US. Thank you.

Table 5 Ongoing & Protocol developing Trials & Studies at KUTRC & TRI Kobe

	2005.1	
	Total	Cancer
Phase Ⅰ	2	2
Phase Ⅰ－Ⅱ	15	3
Phase Ⅱ	27	22
Phase Ⅲ	14	8
Outcomes	21	15
Genetic/Biomarker	6	6
Diagnostic	3	3
	88	59

Table 6 Major obstacles in Japan

- ▣ Lack of law which protect human subjects.
- ▣ Lack of quality assurance in investigator initiated clinical trial. (non-registered)

Table 7 Direction towards next 5 years

- ▣ Encourage investigator sponsored IND registered trial
  → harmonization of TR with EU & US

Table 8 TR－National Strategy

Which should be taken to accelerate new drug development.

- ▣ Encourage
  Investigator Sponsored Registered Trial
- ▣ Form Academia-Industry complex
  as New Business scheme
- ▣ Enforce Laws for
  - ■ Protection of Human Subjects
  - ■ Assurance of Medical Practice Quality

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