BENEFITS AND PROBLEMS OF THE USE OF HUMAN BIOMATERIALS IN NEW DRUG DEVELOPMENT IN JAPAN

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1. Introduction

Is it possible to extrapolate the animal data to humans in drug development?

As is well recognized, there are big differences in drug metabolism between human and animals (Table 1), leading directly to the difficulty of prediction of drug adverse effects in humans. The main reason for species differences is due to the differences in the drug metabolizing enzymes of human and animal livers. In addition to the species differences, it is well recognized that the individual and pharmacogenetic polymorphism are extremely important to predict the side effects and pharmacological efficacy of drugs.

What is the most useful way to predict the unexpected adverse effects of drugs?

The best way to solve the species differences in drug metabolism studies is to use the human biomaterials instead of animal tissues in *in vitro* experiments prior to clinical trials in new drug development. The use of human biomaterials leads to the decrease of the number of animals used for non-clinical studies,which is beneficial to animal right movement, and to conduct the clinical trials more rationally

2. International situations of the use of human materials

Is the recent situation on the use of human materials for drug development in Asia well harmonized with those of the U.S.A and European countries internationally?

In 1985, the Law of the use of human materials for drug development was approved in US Congress. Since that time, US FDA has required the data using human liver microsomes to identify the cytochrome P450 involved in the metabolism of the drug, and those data are essential for approval of new drugs. In pharmacokinetic studies the main purpose of the use of human liver specimens is to identify the cytochrome P450 isoform(s) which is responsible for the metabolism of drugs involved. Figure 1 shows a procurement newwork of human tissues. In the European countries, the contract industry named "*PHARMAGENE*" (Fig. 2) was established in April 1996 by suggestion of the Medical Research Council(MRC) of the government in the United Kingdom. Other European countries such as Germany and France are also trying to establish the organizations for this purpose. In 1994, the closed International Workshop entitled "The use of human materials in drug metabolism studies" was held in Utrecht, The Netherland. At the meeting, participants from the USA and European countries presented the excellent papers on the advantages of the human materials in drug metabolism studies. I was invited to the meeting to present the situation on this topic in Japan. At the meeting, productive suggestions regarding the cryopreservation of human liver and validation of drug metabolizing enzymes of human liver microsomes were presented. This

subject has not been officially discussed in Japan .

3. The recent situation in Japan

The public opinion on this subject in Japan is relatively conservative and sensitive to use human biomaterials because of emotional and ethical problems.

As a breakthrough of the current situations in Japan, Human and Animal Bridge Discussion Group(HAB), a non-profit organization, was established in 1994(Fig. 3). HAB has two memberships, i.e., individual members and corporative ones. The individual members consist of the researchers working for schools of medicine, pharmacy and veterinary medicine of various universities and drug industries. In 1994, HAB contracted the Internitonal Partnership with National Disease Research Interchnage(NDRI) in the U.S.A. NDRI is one of the non-profit organizations involved in the procurement of human tissues in the U.S.A. The tissues used for this purpose are mainly untransplantable tissues which are originally removed from brain death patients for organ transplantation. In 1996, Biomedical Research Institute(BRI) was formed as a research and procurement division of HAB. BRI has several activities such as the fundamental researches including the improved method of cryopreservation, possible use of S9 of human liver for Ames test and so on. The procurement service of human biomaterials to HAB corporative companies for reserach purpose only is also an important activity of BRI.

4. The main activities of HAB

The main activities of HAB are outlined as follows(Fig. 3).

1) Annual meeting. Scientific meeting takes place annually and at the meeting the distinguished speakers are invited nationally and internationally, talking about the recent advances and novel technical information in this field.

2) NEWSLETTER. The NEWSLETTER of HAB is published twice a year and the latest information are announced.

3) Procurement of human biomaterials in Japan. Human tissues such as liver and intestine are procured to the corporations and universities for research purpose only. The tissues involved are imported from NDRI monthly and procured them to the HAB members with invoice of handling money for only reserch purpose, not profitable works.

4) Collaboration program. HAB has advanced programs in collaboration with universities and drug industries. The researchers are welcome to BRI to investigate the drug metabolism of drugs under development using human biomaterials.

5. Future perspectives of human tissue procurement in Japan

In December 1997, Japanese Government formed the Working Group which discusses the practical guideline of the use of human biomaterials for drug development. This is extensively positive response of the Japanese Government to the progressive movements of HAB as well as other organizations because bureaucrat has usually stronger power than technocrat whenever new projects are considered in Japan. The final goal of HAB is to establish the non-profit organization sponsored by the Japanese Governmental and private sector, and this organization should be responsible for the tissue procurement nework to develop the incentive new drugs in Japan.

Table 1. Comparison of Liver Microsomal Drug Metabolizing Activities of Animals to those of Humans

Drugs	Human (11)	Dog (2)	Monkey (5)	Rat (10)
7-Ethoxycoumarin	100	197	194	61
Tolbutamide	100	5	50	136
s-Mephenytoin	100	394	718	334
Dibrisoquine	100	237	149	122
Diazepam*	100	1448	606	266
Diazepam**	100	142	167	155
Chlorozoxazone	100	53	76	171
Testosterone	100	27	150	65
Lauric acid	100	91	321	205

*:Demethylation of diazepam; **: Hydroxylation of diazepam

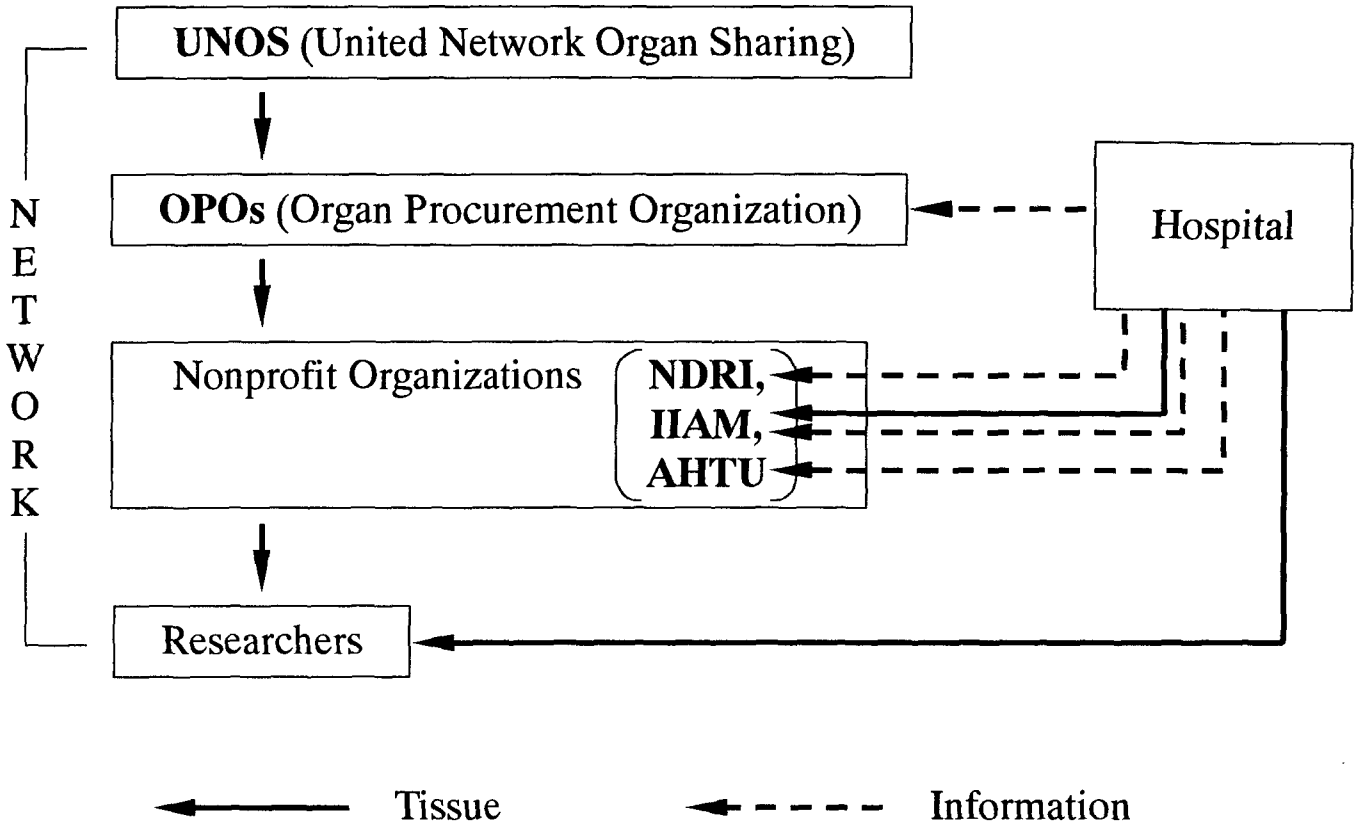
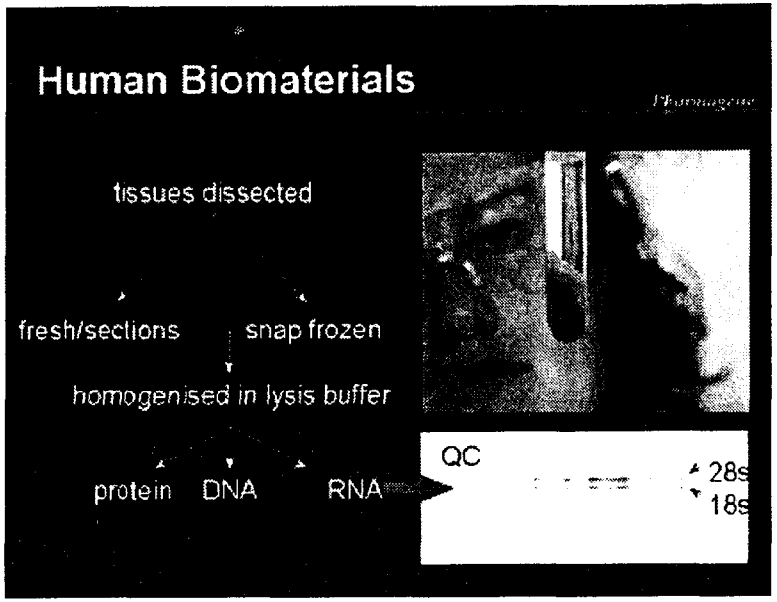


Fig. 1 Human Tissue Procurement Network in the U.S.A.

"Pharmagene"

In April 1996, Pharmagene raised equity funding of £1.4 million ($2.24m) from the founders, 3i Cambridge and Abacus Nominees Ltd.. These funds were used to establish the state-of-the-art facilities and to set up several collaborations for tissue supply. Pharmagene has also established one of the world's most comprehensive collections of human RNAs and proteins and the technologies with which to utilise this highly valued resource.



In July 1997, the Company raised a further £5 million ($8 million) from a group of investors led by 3i Cambridge, and Abacus (Nominees) Ltd.. This group includes Alta-Berkeley V C.V., Ivory and Sime Enterprise Venture Capital plc., Sosei & Co. Ltd., Enterprise Venture Capital Trust plc., Cambridge Quantum Fund Ltd., funds managed by Generics Asset Management, and Delta Equity Fund Limited Partnership. Directors and staff also made further investments.

Pharmagene also receives revenues received from its partnerships with biotechnology and pharmaceutical companies.

Fig. 2 Establishment of Pharmagene

URL: http://www.pharmagene.com/frames/menu/Funding.htm

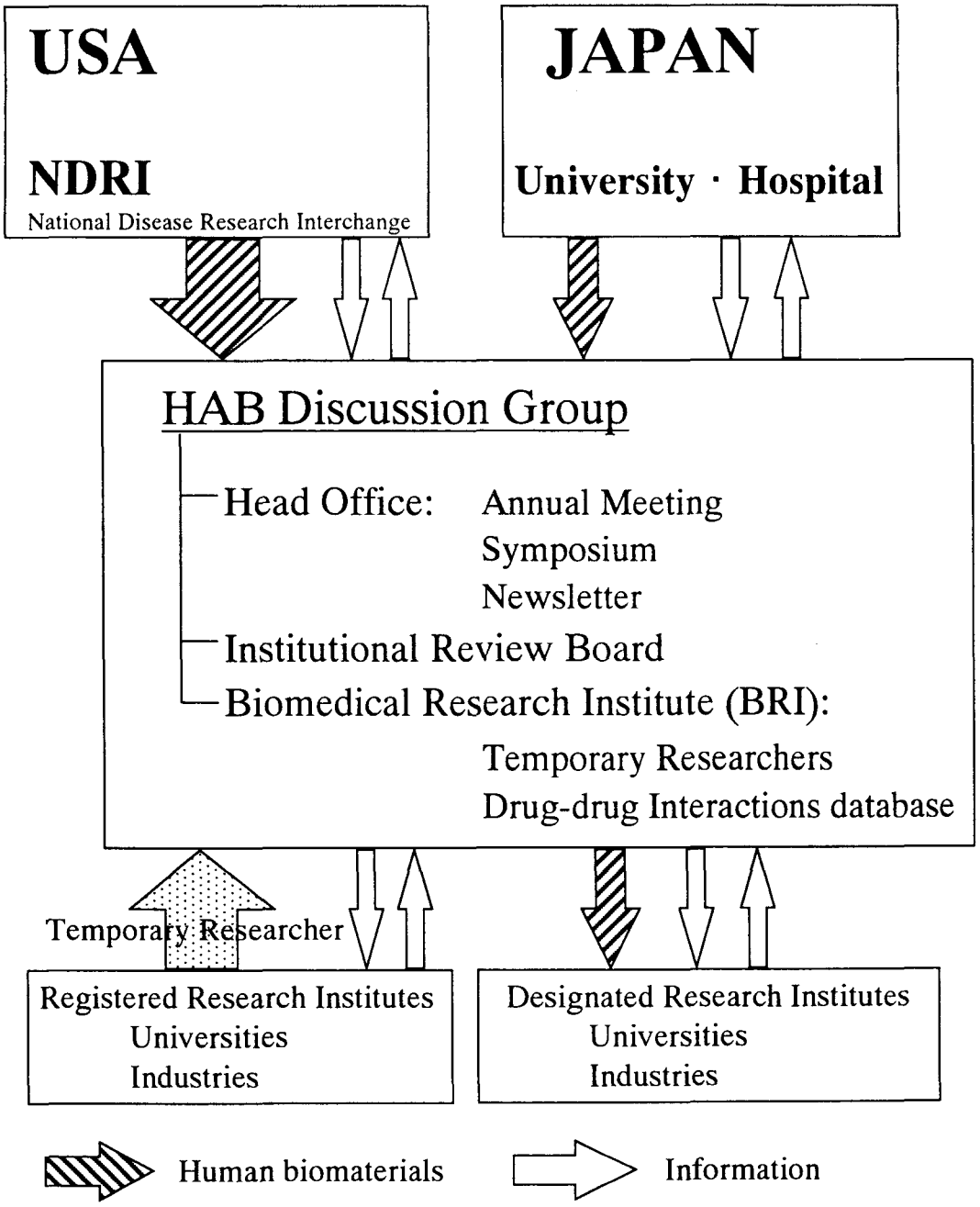


Fig. 3 Schematic Picture of HAB Activities