Current Status of Gene Therapy Products in Japan

Division of Cellular and Gene Therapy Products
National Institute of Health Sciences
Eriko Uchida, Ph.D.
**Gene Therapy**

- **Direct application of gene therapy products (in vivo gene therapy)**
  - Gene therapy products (vectors) carrying gene of interest
    - Viral vector
    - Non-viral vector
    - Naked DNA (plasmid)
    - Replicating recombinant Virus/bacteria

- **Genetically modified cells (ex vivo gene therapy)**
  - 1) Isolation of target cells (autologous, allogenic)
  - 2) Gene transfer
  - 3) Infusion of genetically-modified cells
Gene therapy clinical research

- Guideline for Gene Therapy Clinical Research (MHW Notice No.23)
  Published in 1994, Revised in 2004
  (Ministerial Notification of MEXT and MHLW; 2004 No.2)
  (Minor revision in 2008)

Gene therapy clinical trial

under the Regulation by Pharmaceutical Affairs Law (PAL)

- Guideline for Assuring the Quality and Safety of the Gene Therapy Products (MHW PAB Notice No.1062)
  Published in 1995
  (Minor revision in 2002 and 2004)
Evaluation System of Gene Therapy Clinical Study in Japan

Clinical Research

Head of the Institution

Submission of Protocol

Report

MHLW

Existence of new issues

YES

No

Report

Detailed Examination

Report within one month

Health Science Council

Guidelines for Gene Therapy Clinical Research

Clinical Trial under the Regulation by PAL

Manufacturer

Submission of Q/S Data

MHLW

Consultation

(3)

Report

Pharmaceuticals and Medical Devices Agency (PMDA)

Consultation/Advice

External Experts

(2)

Food and Pharmaceutical Affairs Council

Guidelines for Assuring the Quality and Safety of Gene Therapy Products

Consultation

(1)

Report

(5)

(4)
Summary of the Guideline for Gene Therapy Clinical Research (1)

● Chapter 1 : General Rules
  ï Target diseases
    Â Serious genetic diseases or life-threatening diseases such as cancer and AIDS
    Â Diseases which seriously damage the physical function of the patients
  ï Confirmation of Quality
    Â Genes and related materials transferred to the patients should be manufactured in accordance with GMP
  ï Genetic modification of human germ cells (including fertilized ovum and embryo) is prohibited
  ï Effectiveness and safety of the research can be predicted based on sufficient scientific knowledge
Summary of the Guideline for Gene Therapy Clinical Research (2)

- Chapter 2 : Protection of the Human Rights of Patients
  - Informed consent by document

- Chapter 3 : System of Research and Review
  - Tasks of the researchers, director, institution head, IRB

- Chapter 4 : Procedures for Conducting Clinical Research
  The director of the research should prepare a project protocol including,
  (1) The purpose, (2) Theoretical basis for the selection of the disease
  (3) Genes involved and the methods of transferring genes
  (4) Non-clinical research findings currently available
  (5) Safety evaluation from non-clinical studies
  (6) Basis for the conclusion that the research is feasible
  (7) Plan, (8) Suitability of institutions where the planned research will be conducted
  (9) Current situations of research related to the planned research
  (10) Professional records and list of publications of researchers

- Chapter 5 : Opinion of the Minister of MHLW
  - Responsibility of the Minister of MHLW

- Chapter 6 : Acts for Protection of Personal Information

- Chapter 7 : Miscellaneous Provisions
Guideline for Assuring the Quality and Safety of Gene Therapy Products

This guideline describes the major issues concerning the assurance of quality and safety of the gene therapy products and outlines the data and information to be addressed by manufacturers when filing an application with respect to the quality and safety of gene therapy products intended for clinical use.

- Chapter 1 General provisions
- Chapter 2 Manufacturing process
- Chapter 3 Specifications and formulation
- Chapter 4 Stability
- Chapter 5 Preclinical safety studies
- Chapter 6 Tests for effectiveness
- Chapter 7 Pharmacokinetics and pharmacodynamics
- Chapter 8 Manufacturing facilities and equipment
- Chapter 9 Ethical consideration
- Chapter 10 Miscellaneous provisions
Investigators, manufacturers or importers of gene therapy products of LMO (ex. Viral Vector) for Type I use*, have to evaluate the potential adverse effects of the products for other living organisms with the spread of the products in environment.

Approval of Type 1 Use Regulations is required before clinical study.

*Type 1 use: Use without preventing the dispersal of LMO into the air, water or soil outside facilities.
Current Status of Gene Therapy Clinical Study in Japan
<table>
<thead>
<tr>
<th>Region</th>
<th>Number of Protocols Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>29</td>
</tr>
<tr>
<td>USA</td>
<td>1034*</td>
</tr>
<tr>
<td>EU</td>
<td>480*</td>
</tr>
<tr>
<td>Others</td>
<td>112*</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1655</strong></td>
</tr>
</tbody>
</table>

*Data from Wiley Journal of Gene Medicine web site (2010) http://www.wiley.co.uk/genmed/clinical*
<table>
<thead>
<tr>
<th>Year of approval</th>
<th>Institution (hospital)</th>
<th>Target</th>
<th>Vector</th>
<th>Gene</th>
<th>Pts/cases (planned)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Hokkaido Univ.</td>
<td>ADA deficiency</td>
<td>Retrovirus</td>
<td>ADA</td>
<td>1</td>
</tr>
<tr>
<td>1998</td>
<td>Tokyo Univ.</td>
<td>Renal cell carcinoma</td>
<td>Retrovirus</td>
<td>GM–CSF</td>
<td>4</td>
</tr>
<tr>
<td>1998</td>
<td>Okayama Univ./ RPR Gencell</td>
<td>Lung cancer</td>
<td>Adenovirus</td>
<td>p53</td>
<td>9</td>
</tr>
<tr>
<td>2000</td>
<td>Jikei Univ./ RPR Gencell</td>
<td>Lung cancer</td>
<td>Adenovirus</td>
<td>p53</td>
<td>1</td>
</tr>
<tr>
<td>2000</td>
<td>Tohoku Univ./ RPR Gencell</td>
<td>Lung cancer</td>
<td>Adenovirus</td>
<td>p53</td>
<td>2</td>
</tr>
<tr>
<td>2000</td>
<td>Tokyo Medical Univ./ RPR Gencell</td>
<td>Lung cancer</td>
<td>Adenovirus</td>
<td>p53</td>
<td>3</td>
</tr>
<tr>
<td>2000</td>
<td>Chiba Univ./ RPR Gencell</td>
<td>Esophageal cancer</td>
<td>Adenovirus</td>
<td>p53</td>
<td>10</td>
</tr>
<tr>
<td>2000</td>
<td>Cancer Chemotherapy Center</td>
<td>Breast cancer</td>
<td>Retrovirus</td>
<td>MDR1</td>
<td>Cont.(3)</td>
</tr>
<tr>
<td>2000</td>
<td>Nagoya Univ.</td>
<td>Malignant Glioma</td>
<td>Liposome</td>
<td>IFN–β</td>
<td>5*2</td>
</tr>
<tr>
<td>2000</td>
<td>Okayama Univ.</td>
<td>Prostate cancer</td>
<td>Adenovirus</td>
<td>HSV–tk</td>
<td>9</td>
</tr>
<tr>
<td>2001</td>
<td>Osaka Univ.</td>
<td>Vascular disease</td>
<td>Plasmid DNA</td>
<td>HGF</td>
<td>22</td>
</tr>
<tr>
<td>2002</td>
<td>Tsukuba Univ.</td>
<td>Leukemia</td>
<td>Retrovirus</td>
<td>HSV–tk / ΔLNGFR</td>
<td>Cont. (10)</td>
</tr>
<tr>
<td>2002</td>
<td>Hokkaido Univ.</td>
<td>ADA deficiency</td>
<td>Retrovirus</td>
<td>ADA</td>
<td>Cont. (2)</td>
</tr>
<tr>
<td>2002</td>
<td>Tohoku Univ.</td>
<td>X–SCID</td>
<td>Retrovirus</td>
<td>γc chain</td>
<td>0 (5)</td>
</tr>
<tr>
<td>Year of approval</td>
<td>Institution (hospital)</td>
<td>Target</td>
<td>Vector</td>
<td>Gene</td>
<td>Pts/cases (planned)</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------</td>
<td>--------------------------</td>
<td>----------------------------</td>
<td>-----------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>2003</td>
<td>Kobe Univ.</td>
<td>Prostate cancer</td>
<td>Adenovirus</td>
<td>HSV-tk</td>
<td>6</td>
</tr>
<tr>
<td>2003</td>
<td>Shinsyu Univ.</td>
<td>Malignant melanoma</td>
<td>Liposome</td>
<td>IFN-β</td>
<td>5*2</td>
</tr>
<tr>
<td></td>
<td>Anges MG (Clinical trial)</td>
<td>Vascular disease</td>
<td>Plasmid DNA</td>
<td>HGF</td>
<td>41</td>
</tr>
<tr>
<td>2006</td>
<td>Kyusyu Univ.</td>
<td>Vascular disease</td>
<td>Sendai virus</td>
<td>FGF-2</td>
<td>9</td>
</tr>
<tr>
<td>2006</td>
<td>Jichi Medical Univ.</td>
<td>Purkinsson’s disease</td>
<td>Adeno associated virus</td>
<td>AADC</td>
<td>15</td>
</tr>
<tr>
<td>2007</td>
<td>Kitasato Univ.</td>
<td>Prostate cancer</td>
<td>Adenovirus</td>
<td>HSV-tk</td>
<td>Cont</td>
</tr>
<tr>
<td>2007</td>
<td>Sanofi–Aventis</td>
<td>Clinical limb ischemia</td>
<td>Plasmid DNA</td>
<td>FGF-1</td>
<td>Cont</td>
</tr>
<tr>
<td>2007</td>
<td>Takara Bio (Clinical trial)</td>
<td>Leukemia</td>
<td>Retrovirus</td>
<td>HSV-tk / ΔLNGFR</td>
<td>Cont.</td>
</tr>
<tr>
<td>2008</td>
<td>Okayama Univ.</td>
<td>Prostate cancer</td>
<td>Adenovirus</td>
<td>IL-12</td>
<td>Cont.</td>
</tr>
<tr>
<td>2009</td>
<td>Tokyo Univ.</td>
<td>Glioma</td>
<td>Oncolytic Herpesvirus</td>
<td></td>
<td>Cont.</td>
</tr>
<tr>
<td>2009</td>
<td>National Cancer Center</td>
<td>Leukemia</td>
<td>Retrovirus</td>
<td>HSV-tk / ΔLNGFR</td>
<td>Cont.</td>
</tr>
<tr>
<td>2009</td>
<td>Mie Univ.</td>
<td>Esophageal cancer</td>
<td>Retrovirus</td>
<td>Cancer antigen-specific TCR</td>
<td>Cont.</td>
</tr>
<tr>
<td>2009</td>
<td>Kyoto Prefectural Univ.</td>
<td>Renal cancer</td>
<td>Liposome</td>
<td>IFN-β</td>
<td>Cont.</td>
</tr>
</tbody>
</table>
Gene Therapy Protocols in Japan
- Target Diseases -

- **Neurological diseases** 1 (4%)
  - Parkinson’s disease

- **Genetic diseases** 2 (8%)
  - ADA deficiency

- **Peripheral artery diseases** 5 (19%)
  - Arteriosclerosis obliterans (ASO)
  - Critical limb ischemia (CLI)

- **Cancer** 18 (69%)
Gene Therapy Protocols in Japan
- Gene Delivery System -

- Adenovirus 9 (34%)
- Retrovirus 8 (30%)
- Liposome 3 (12%)
- Plasmid DNA 3 (12%)
- Herpes simplex Virus (replicating) 1 (4%)
- Sendai virus 1 (4%)
- Adeno-associated Virus 1 (4%)
Gene Therapy Protocols in Japan
- Type of Clinical Study -

Company-sponsored Clinical Trials
9 (35%)

Investigator's Clinical Researches
17 (65%)
Gene Therapy Protocols in Japan
- Product Development Stage -

Application for Marketing Authorization
1 (4%)

Beperminogen Perplasmid
(HGF-expressing plasmid DNA for ASO)
2008 Application
2010 Withdrawal → Global study (Phase III) is planned

Phase III (Global study)
1 (4%)

Riferminogen Pecaplasmid
(FGF-1-expressing plasmid DNA for CLI)

Phase I, I/II 24 (92%)
Recent trend for cancer gene therapy
- Oncolytic viruses -

Oncolytic viruses are intended to replicate selectively in tumour tissue and spread, destroying the tissue without causing excessive damage to normal tissues.

**Gene Therapy**

**Viral vector (replication incompetent)**

Effect of gene expression is limited only infected cells

**Oncolytic virotherapy**

**Conditionally replicating virus**

Effect of oncolytic viruses is expand peripheral and remote cancer cells

- Normal cell
- Cancer cell
- Infected cell
# Current status of oncolytic viruses developed in Japan

<table>
<thead>
<tr>
<th>Institution</th>
<th>Virus</th>
<th>Indication</th>
<th>Pts/cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical research</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nagoya Univ.</td>
<td>Naturally-attenuated Herpes simplex virus (HF-10)</td>
<td>Breast cancer</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic cancer</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head and neck cancer</td>
<td>3</td>
</tr>
<tr>
<td>Tokyo Univ.</td>
<td>Recombinant Herpes simplex virus (G47Δ)</td>
<td>Glioma</td>
<td>Continued (max 21)</td>
</tr>
<tr>
<td>Clinical Trial</td>
<td>Oncolys BioPharma</td>
<td></td>
<td>phase I finished (USA)</td>
</tr>
<tr>
<td></td>
<td>Recombinant Adenovirus (Telomelysin)</td>
<td>Solid tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naturally-attenuated Herpes simplex virus (HF-10)</td>
<td>Head and neck cancer</td>
<td>phase I continued (USA)</td>
</tr>
</tbody>
</table>
Recent trend for cancer gene therapy
- Live bacteria vector -

Necrotic areas of solid tumors are generally anaerobic and anaerobic bacteria naturally localizes and proliferates in an anaerobic environment. In Japan, recombinant non-pathogenic anaerobic bacteria *Bifidobacterium* modified to express the cytosine deaminase (CD) gene which convert prodrug 5-FC to 5-FU are developed for cancer therapy.

<table>
<thead>
<tr>
<th></th>
<th>Viral vector</th>
<th>Non-viral vector</th>
<th>Bacteria vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Efficacy</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cost</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Productivity</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Delivery</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Gene Expression</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>
Adoptive transfer of lymphocytes transduced with MAGE-A4-specific TCR gene for therapy-resistant esophageal cancer is being conducted in Japan.

From HP of Mie Univ.
Contribution to ICH GTDG Activity
ICH GTDG

ICH is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

ICH Steering Committee (SC) recognized that in the rapidly evolving area of gene therapy medicinal products, there is a need to continue to foster the exchange of information that may impact on the regulation of such products.

The Gene Therapy Discussion Group (GTDG) is established within the ICH in 2002 to lead these activities

- Sharing regional updates and monitoring regional emerging issues
- Proactively set out principles that may have a beneficial impact on harmonizing regulations of gene therapy products (ICH considerations)
GTDG ICH Considerations

GTDG ICH Considerations are documents developed by the GTDG to report specific scientific considerations. These documents are different from ICH Guidelines and do not undergo the formal ICH procedure and therefore do not require the ICH SC to signoff. However, the documents still require discussion and endorsement by the ICH SC.

ICH Considerations developed

- General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (October 2006)
- Oncolytic Viruses (2008, revised on September 2009)
- General Principles to Address Virus and Vector Shedding (June 2009)
ICH Considerations

General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors

This document identifies general principles for investigating and addressing risks for inadvertent germline integration and provides considerations to minimize this potential risk in humans enrolled in clinical trials.

This document applies to gene therapy vectors and could also apply to oncolytic viruses.

1. Introduction
2. Risk factors for inadvertent germline integration of gene therapy vectors
   2.1. Vectors
   2.2. Dose and route of administration
3. Non-clinical studies
   3.1 General considerations
   3.2 Biodistribution studies
4. Patient Monitoring
ICH Considerations: Oncolytic Viruses (OV)

This document identifies general principles for the clinical development of OV. The therapeutic potential of OV will need to be balanced against the risks associated with the use of virus that is replication competent.

1. Introduction
2. Product Characterization of OV
   2.1 Selectivity
   2.2 Molecular Variants
   2.3 Adventitious agent testing
3. Non-clinical studies
   3.1 Evaluation of Selectivity
   3.2 Selection and limitations of animal models
   3.3 Pharmacology / POC
   3.4 Biodistribution
   3.5 Viral Shedding Considerations
   3.6 Toxicology and safety studies
   3.7 Good Laboratory Practice (GLP) Studies
4. Clinical studies
   4.1 Pharmacokinetics, pharmacodynamics and biological activity
   4.2 Immunity and immune response
   4.3 Biosafety
ICH Considerations
General Principles to Address Virus and Vector Shedding

Shedding is defined as the dissemination of the virus / vector through secretions and/or excreta of the patient. Assessment of shedding can be utilized to understand the potential risk associated with transmission to third parties. The scope of this document excludes shedding as it relates to environmental concerns.
ICH Considerations
General Principles to Address Virus and Vector Shedding

The focus of this document is to provide recommendations for designing non-clinical and clinical shedding studies when appropriate. In particular, emphasis will be on the analytical assays used for detection, and considerations for the sampling profiles and schedules in both non-clinical and clinical studies.

1.0 Introduction
2.0 Biological Properties of the Virus / Vector
3.0 Analytical Assay Considerations
4.0 Non-Clinical Considerations
   4.1 Animal Species
   4.2 Dose and Route of Administration
   4.3 Sampling Frequency and Study Duration
   4.4 Sample Collection
   4.5 Interpretation of Non-Clinical Data and Transmission Studies
5.0 Clinical Considerations
   5.1 Sampling Frequency and Duration
   5.2 Sample Collection
   5.3 Interpretation of Clinical Shedding Data
6.0 Third Party Transmission
ICH M6 guideline:
Guideline on Gene Therapy Vector and Oncolytic Virus Shedding and Transmission (Draft 1)
This ICH guideline is under preparation based on Shedding Considerations.

ICH considerations under preparation:
General Principles to Address in preparation for First-in-Human Gene Therapy Studies (Draft 1)

The objective of this considerations is to highlight key points for preparing to conduct a first-in-human gene therapy clinical study. Additionally, this consideration will be useful to those investigators who have not previously conducted a gene therapy clinical study.
Infectivity PCR Method for Sensitive and Rapid Detection of Replication Competent Viruses

<Conventional infectivity assay>

Retrovirus vector
Adenovirus vector

Sensitive cells

Repeat x 5

1~9 days

3,4 days

RCV infection

Culture sup/cells

1~9 days

7 days

CPE/focus forming assay

Indicator cells

Extraction of virus genome

Virus concentration

Q-PCR

1 day

➢ Rapid
➢ Sensitive
➢ Quantitative

Application: RCV contaminated in gene therapy vectors, Virus/vector shedding, Viral safety of biological products
Thank you for your attention!

Contact Information

Eriko Uchida, Ph.D.
Laboratory 1 (Gene Therapy Products)
Division of Cellular and Gene Therapy Products
National Institute of Health Sciences
1-18-1 Kami-Yoga, Setagaya, Tokyo 158-8501, JAPAN

PHONE: 03-3700-1141 ext. 550
FAX: 03-3707-6950
E-MAIL: uchida@nihs.go.jp