Current Status of Gene Therapy Products in Japan

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

国立医薬品食品衛生研究所
National Institute of Health Sciences

Gene Therapy

Direct application of gene therapy products (in vivo gene therapy)

Genetically modified cells (ex vivo gene therapy)

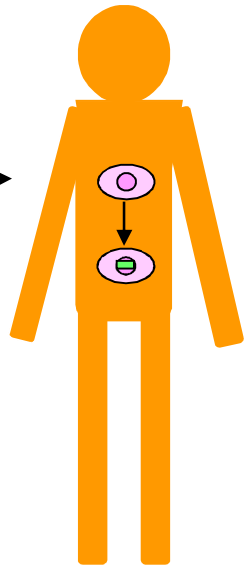
Gene therapy products (vectors) carrying gene of interest

Viral vector

Non-viral vector

Naked DNA (plasmid)

Replicating recombinant Virus/bacteria



1) Isolation of target cells (autologous, allogenic)

2) Gene transfer

3) Infusion of genetically-modified cells

2 Types of Gene Therapy Clinical Study and Related Guidelines in Japan

Gene therapy clinical research

・Guideline for Gene Therapy Clinical Research（MHW Notice No.23)

Published in1994, Revised in 2004

(Ministerial Notification of MEXT and MHLW; 2004 No.2)

(Minor revision in 2008)

Gene therapy clinical trial

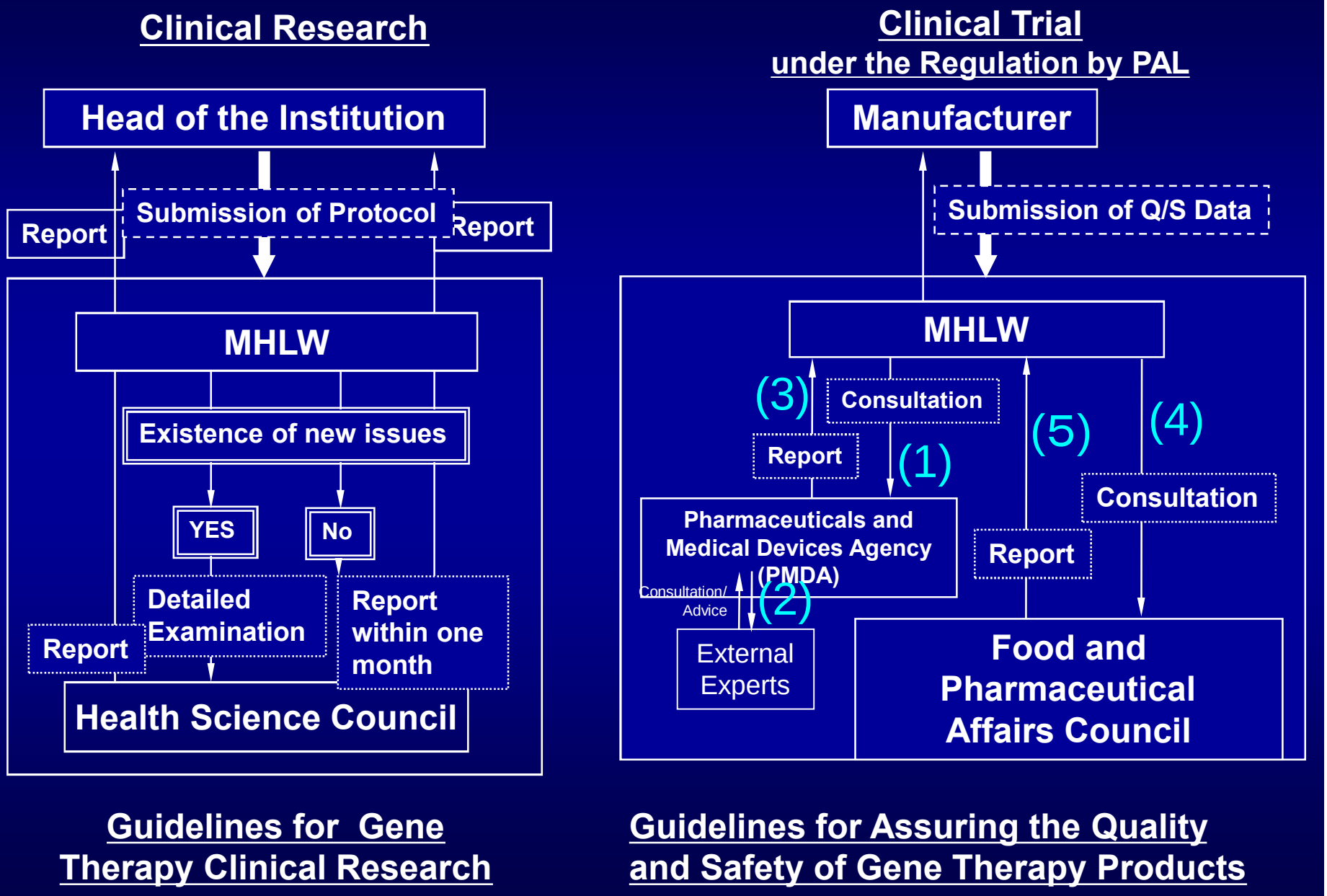
under the Regulation by Pharmaceutical Affairs Law (PAL)

・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



Guidelines for Gene Therapy Clinical Research

Guidelines for Assuring the Quality and Safety of Gene Therapy Products

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

- Chapter 1 : General Rules
  - ï Target diseases
    - Å Serious genetic diseases or life-threatening diseases such as cancer and AIDS
    - Å Diseases which seriously damage the physical function of the patients
  - ï Confirmation of Quality
    - Å 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
  - ï Informed consent by document
- Chapter 3 : System of Research and Review
  - ï 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
  - ï 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

Action of Japan for Cartagena Protocol on Biosafety to the Convention on Biological Diversity

Cartagena Protocol on Biosafety to the Convention on Biological Diversity (2002. 1)

Ÿ 2003. 6 Cartagena Protocol domestic low
ñLaw Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (LMO) ò（Law No. 97 of 2003）

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

Gene Therapy Experiences

Number of protocols approved

Japan	29
USA	1034*
EU	480*
Others	112*
Total	1655

*Data from Wiley Journal of Gene Medicine web site (2010) http://www.wiley.co.uk/genmed/clinical

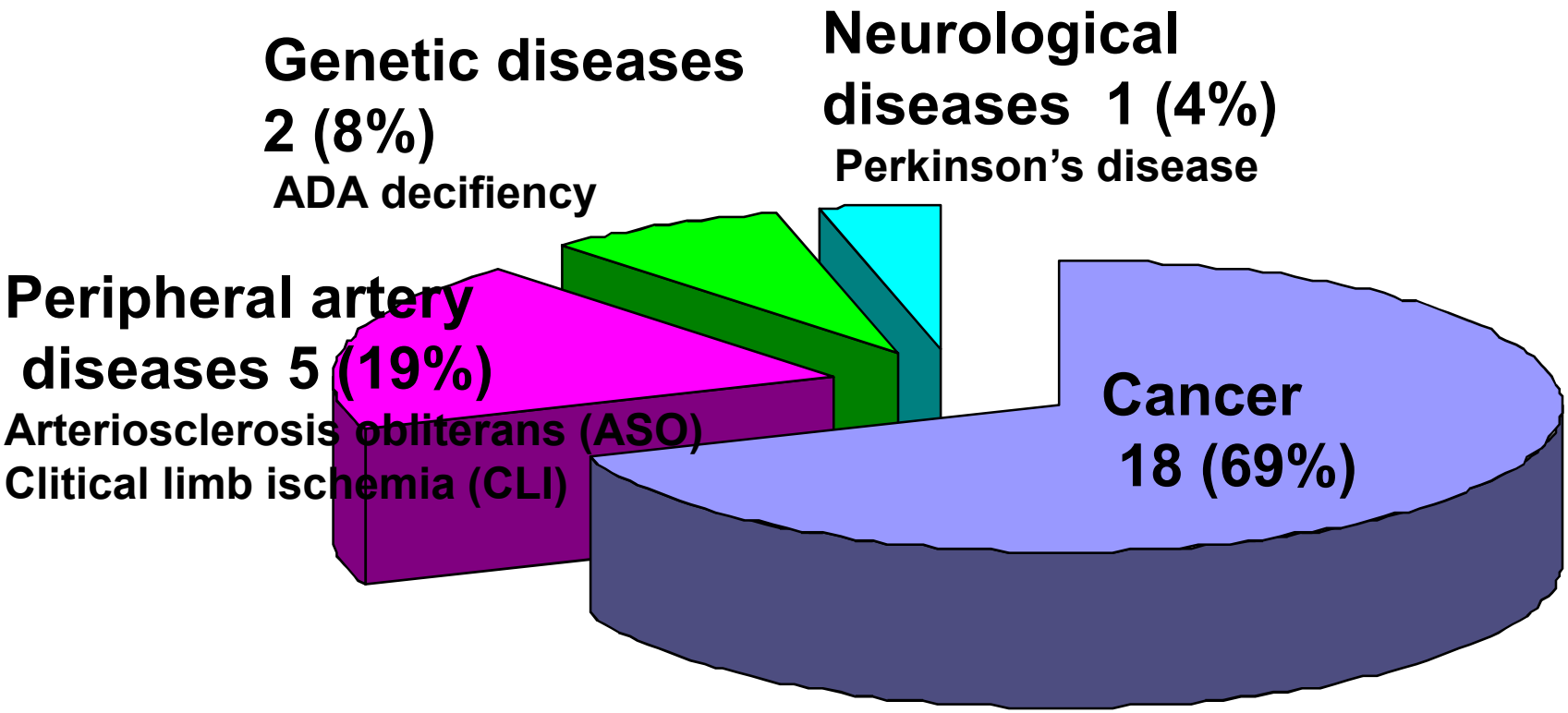
Gene Therapy protocols in Japan (1)

Year of approval	Institution (hospital)	Target	Vector	Gene	Pts/cases (planned)
1995	Hokkaido Univ.	ADA deficiency	Retrovirus	ADA	1
1998	Tokyo Univ.	Renal cell carcinoma	Retrovirus	GM-CSF	4
1998	Okayama Univ./ RPR Gencell	Lung cancer	Adenovirus	p53	9
2000	Jikei Univ./ RPR Gencell	Lung cancer	Adenovirus	p53	1
2000	Tohoku Univ./ RPR Gencell	Lung cancer	Adenovirus	p53	2
2000	Tokyo Medical Univ./ RPR Gencell	Lung cancer	Adenovirus	p53	3
2000	Chiba Univ./ RPR Gencell	Esophageal cancer	Adenovirus	p53	10
2000	Cancer Chemotherapy Center	Breast cancer	Retrovirus	MDR1	Cont.(3)
2000	Nagoya Univ.	Malignant Glioma	Liposome	IFN-β	5[#2]
2000	Okayama Univ.	Prostate cancer	Adenovirus	HSV-tk	9
2001	Osaka Univ.	Vascular disease	Plasmid DNA	HGF	22
2002	Tsukuba Univ.	Leukemia	Retrovirus	HSV-tk / ΔLNGFR	Cont.(10)
2002	Hokkaido Univ.	ADA deficiency	Retrovirus	ADA	Cont. (2)
2002	Tohoku Univ.	X-SCID	Retrovirus	γc chain	0 (5)

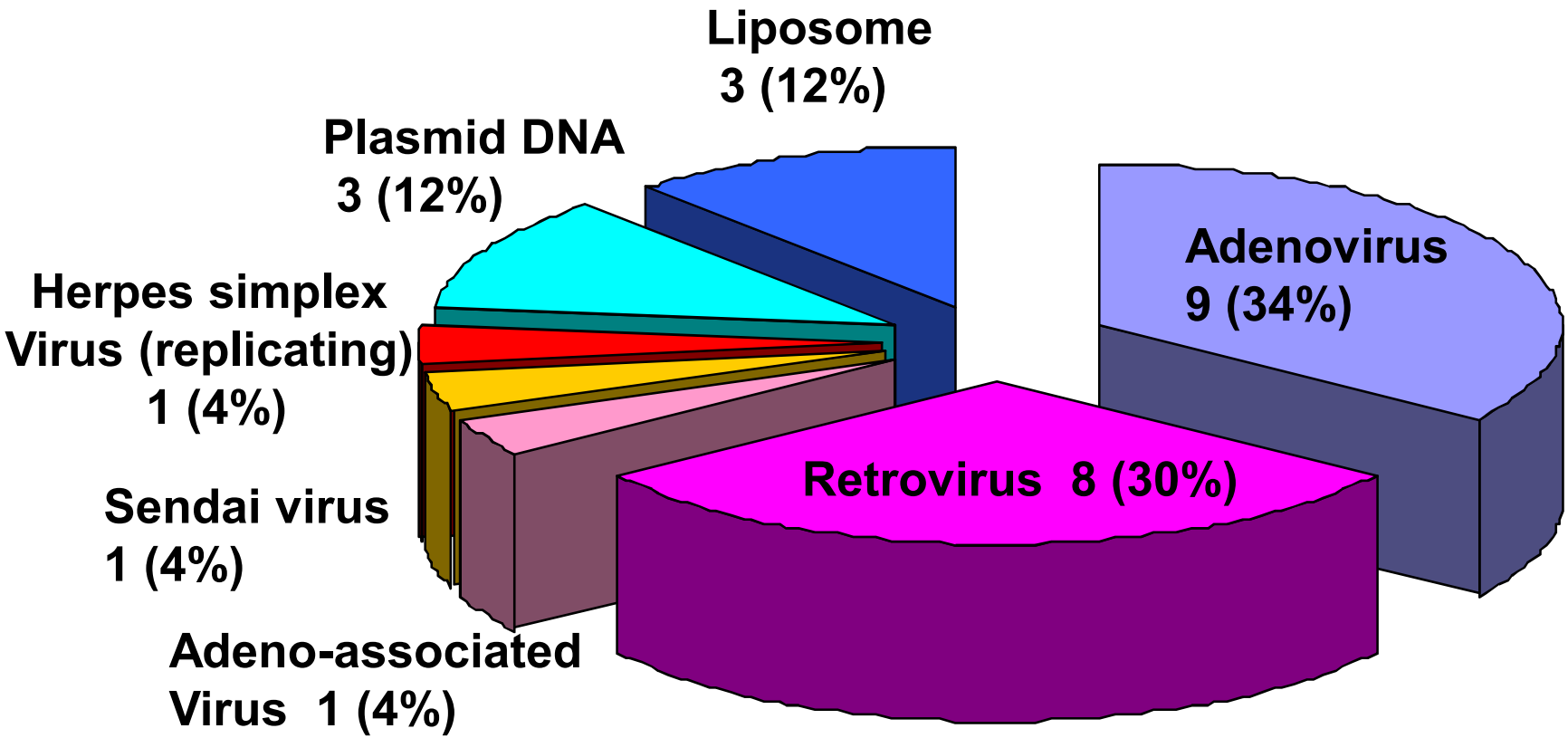
Gene Therapy protocols in Japan (2)

Year of approval	Institution (hospital)	Target	Vector	Gene	Pts/cases (planned)
2003	Kobe Univ.	Prostate cancer	Adenovirus	HSV-tk	6
2003	Shinsyu Univ.	Malignant melanoma	Liposome	IFN-β	5[#2]
2003	Anges MG (Clinical trial)	Vascular disease	Plasmid DNA	HGF	41 9
2006	Kyusyu Univ.	Vascular disease	Sendai virus	FGF-2	15
2006	Jichi Medical Univ.	Purkinson's disease	Adeno associated virus	AADC	6
2007	Kitasato Univ.	Prostate cancer	Adenovirus	HSV-tk	Cont
2007	Sanofi-Aventis	Clitical limb ischemia	Plasmid DNA	FGF-1	Cont
2007	Takara Bio (Clinical trial)	**Leukemia**	Retrovirus	HSV-tk / ΔLNGFR	Cont.
2008	Okayama Univ.	Prostate cancer	Adenovirus	IL-12	Cont.
2009	Tokyo Univ.	Glioma	Oncolytic Herpesvirus		Cont
2009	National Cancer Center	**Leukemia**	Retrovirus	HSV-tk / ΔLNGFR	Cont.
2009	Mie Univ.	Esophageal cancer	Retrovirus	Cancer antigen-specific TCR	Cont.
2009	Kyoto Prefectural Univ.	Renal cancer	Liposome	IFN-β	Cont.

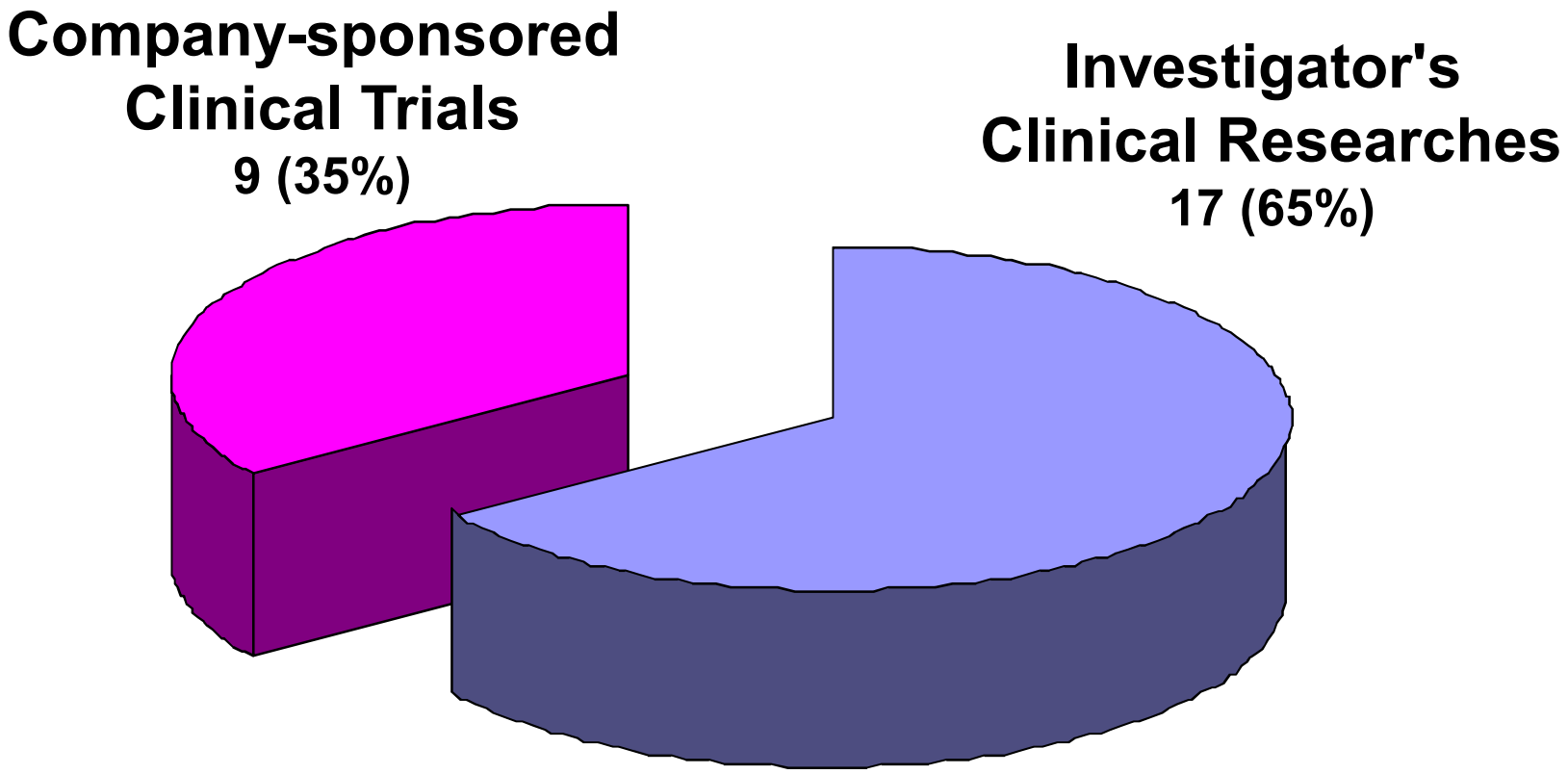
Gene Therapy Protocols in Japan
- Target Diseases -



Gene Therapy Protocols in Japan
- Gene Delivery System -



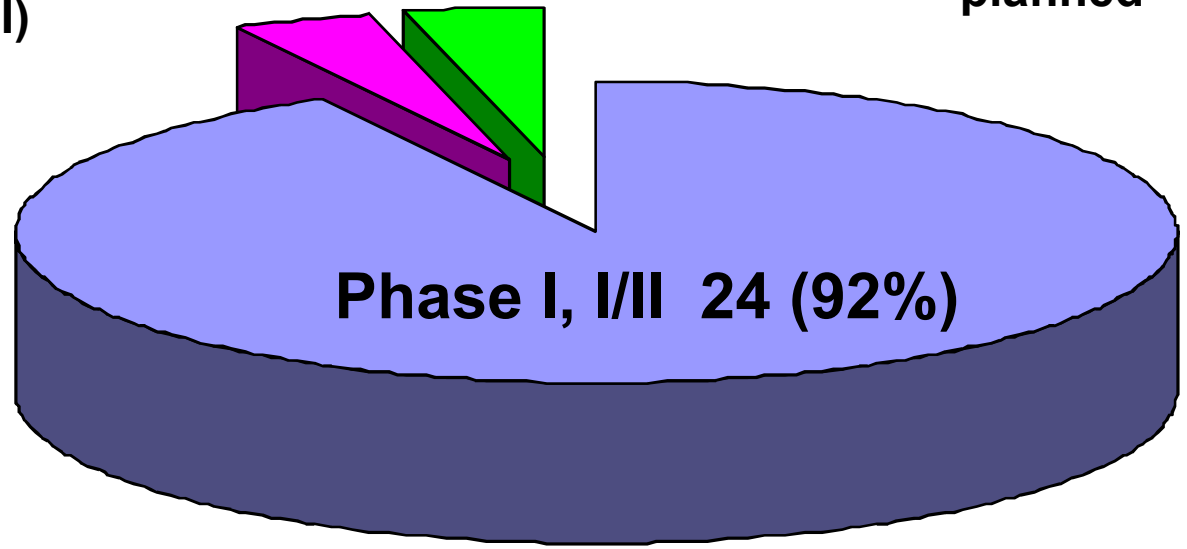
Gene Therapy Protocols in Japan
- Type of Clinical Study -



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)

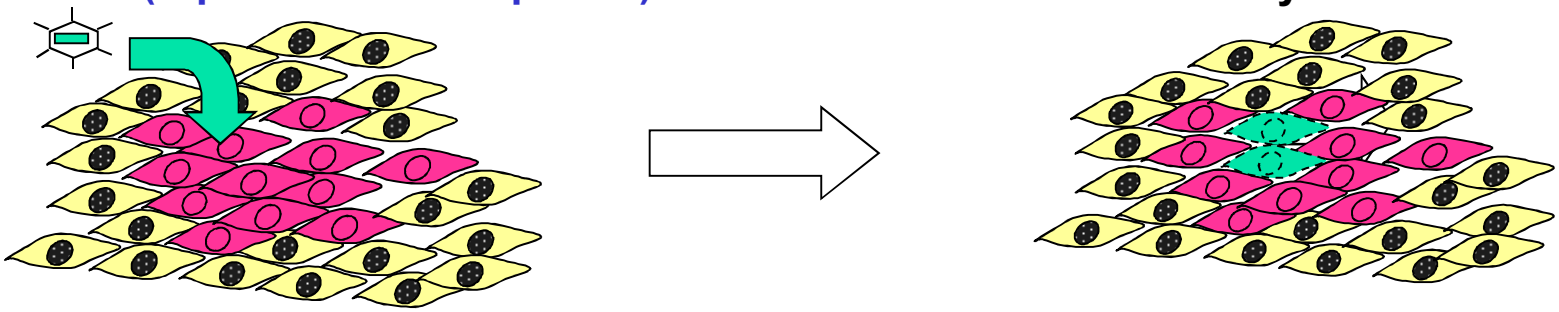


Recent trend for cancer gene therapy
- Oncolytic viruses -

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

Gene Therapy

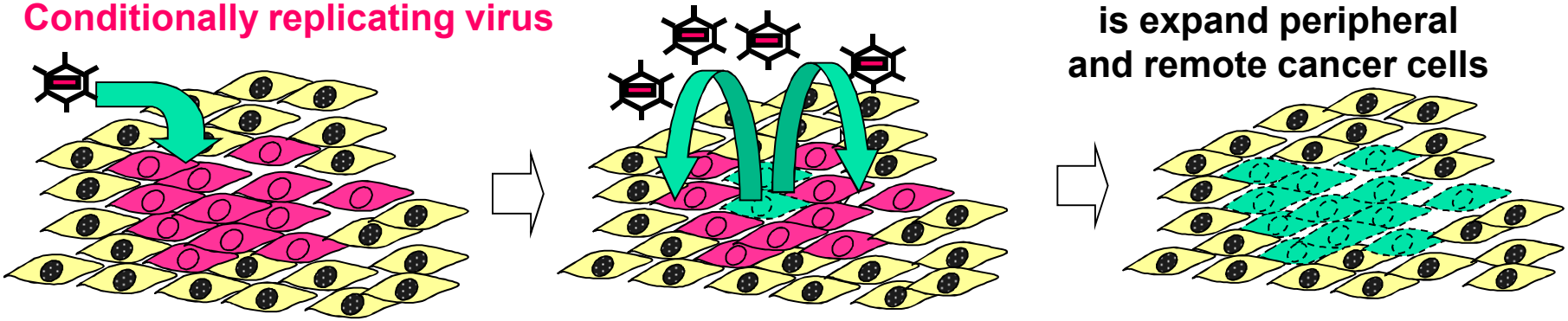
Viral vector (replication incompetent)



Effect of gene expression is limited only infected cells

Oncolytic virotherapy

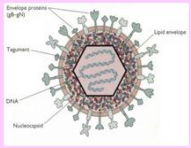
Conditionally replicating virus



Effect of oncolytic viruses is expand peripheral and remote cancer cells

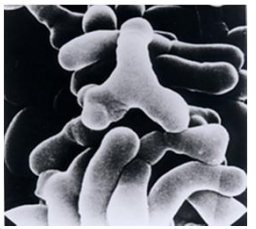
Normal cell **Cancer cell** **Infected cell**

Current status of oncolytic viruses developed in Japan

	Institution	Virus	Indication	Pts/cases
Clinical research	Nagoya Univ.	Naturally-attenuated Herpes simplex virus (HF-10) 	Breast cancer	6
			Pancreatic cancer	3
			Head and neck cancer	3
	Tokyo Univ.	Recombinant Herpes simplex virus (G47Δ)	Glioma	Continued (max 21)
Clinical Trial	Oncolys BioPharma	Recombinant Adenovirus (Telomelysin) 	Solid tumor	phase I finished (USA)
	M's Sciense	Naturally-attenuated Herpes simplex virus (HF-10)	Head and neck cancer	phase I continued (USA)

Recent trend for cancer gene therapy
- Live bacteria vector -

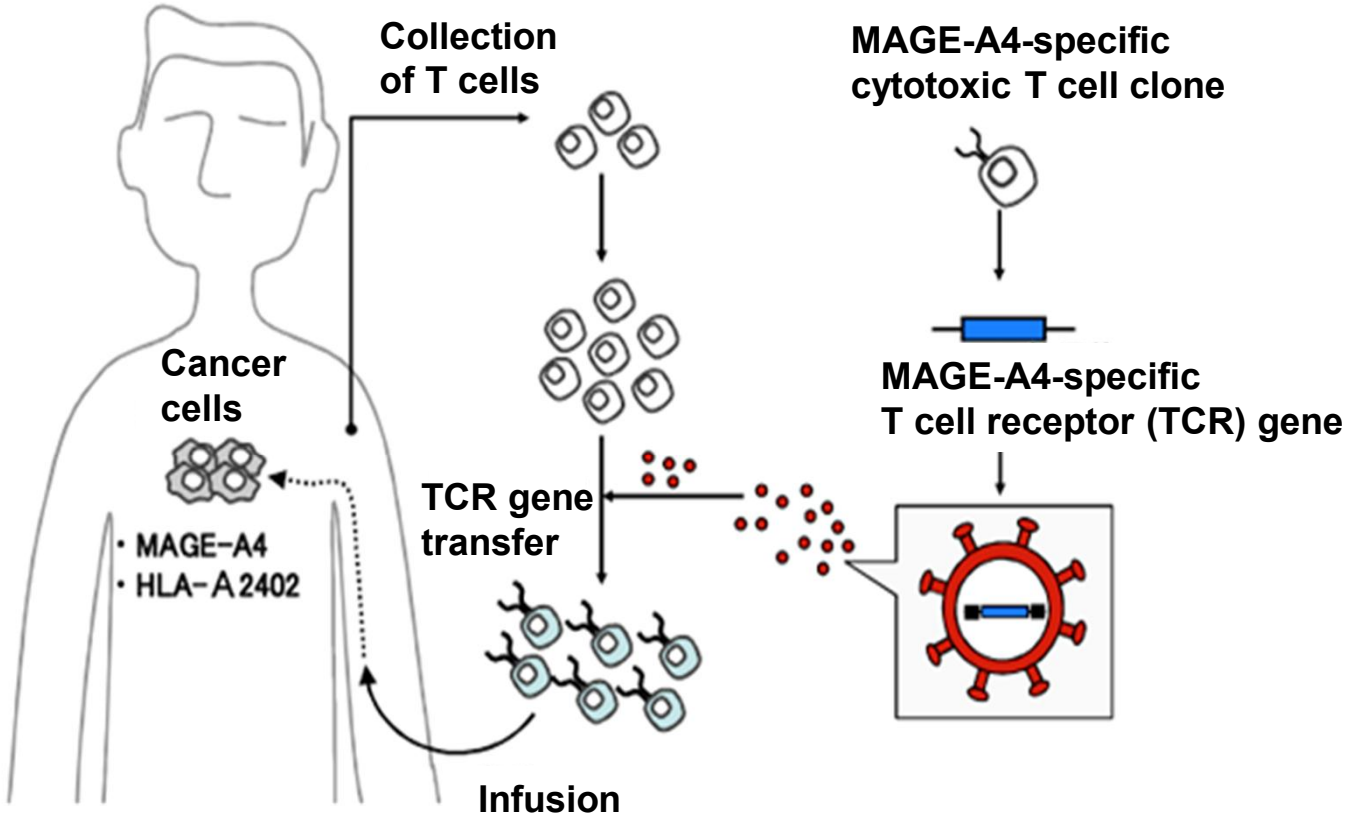
Necrotic areas of solid tumors are generally anaerobic and anaerobic bacteria naturally localizes and proliferates in an anaerobic environment. In Japan, recombinant non-pathogenic anaerobic bacteria *Bifidobacterium* modified to express the cytosine deaminase (CD) gene which convert prodrug 5-FC to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



	Viral vector	Non-viral vector	Bacteria vector
Safety	+	+++	+
Efficacy	+++	+	+
Cost	+	++	+++
Productivity	+	++	+++
Delivery	++	+	+++
Gene Expression	++	+	+++

Recent trend for cancer gene therapy
- Genetically-modified T cell Therapy -

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

ÅICH 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.

ÅICH 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.

ÅThe 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.

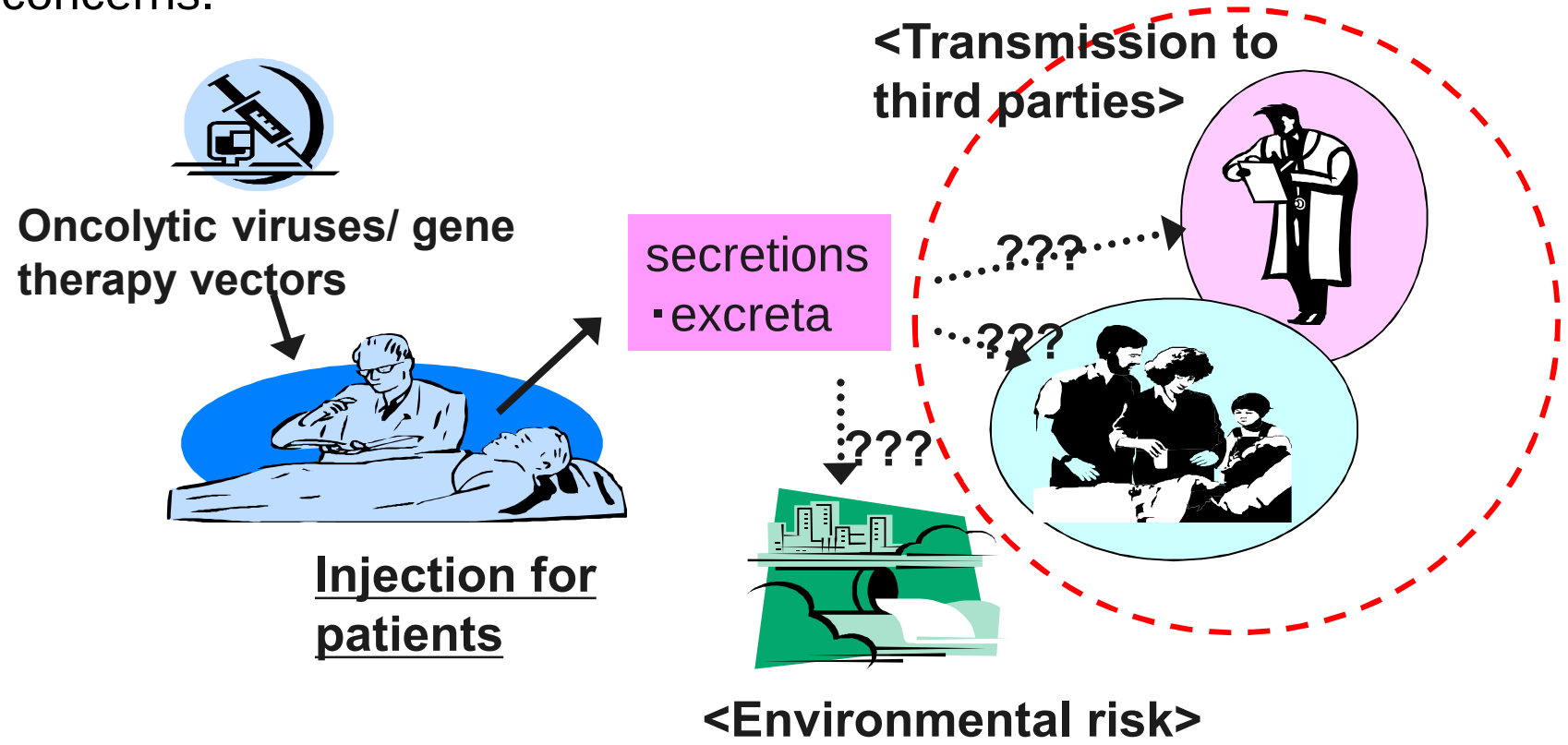
1. Introduction
2. Risk factors for inadvertent germline integration of gene therapy vectors
   - 2.1. Vectors
   - 2.2. Dose and route of administration
3. Non-clinical studies
   - 3.1 General considerations
   - 3.2 Biodistribution studies
4. Patient Monitoring

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.

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.

Current topic on ICH GTDG and M6 EWG

ICH M6 guideline:

Guideline on Gene Therapy Vector and Oncolytic Virus Shedding and Transmission (Draft 1)

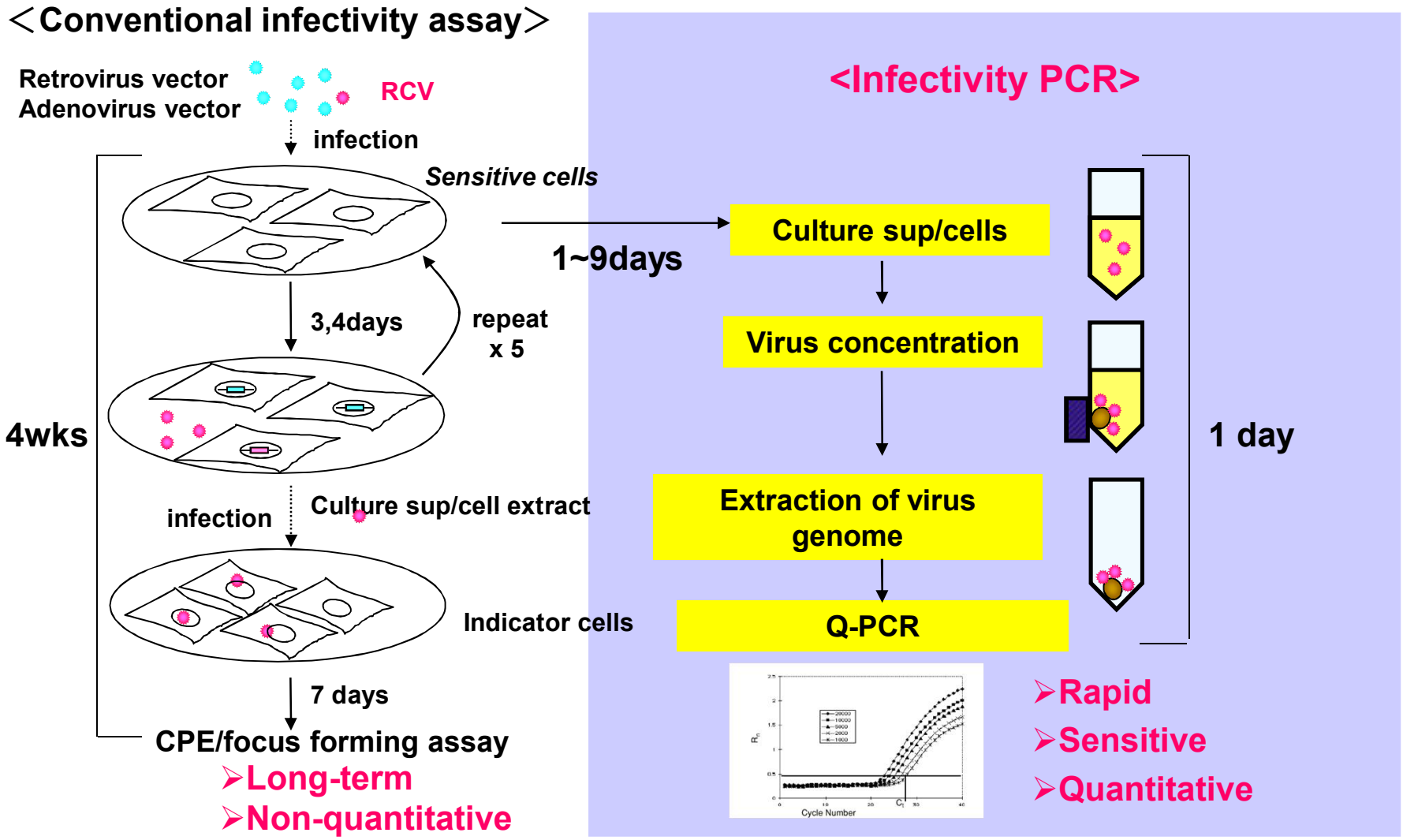
This ICH guideline is under preparation based on Shedding Considerations.

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



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