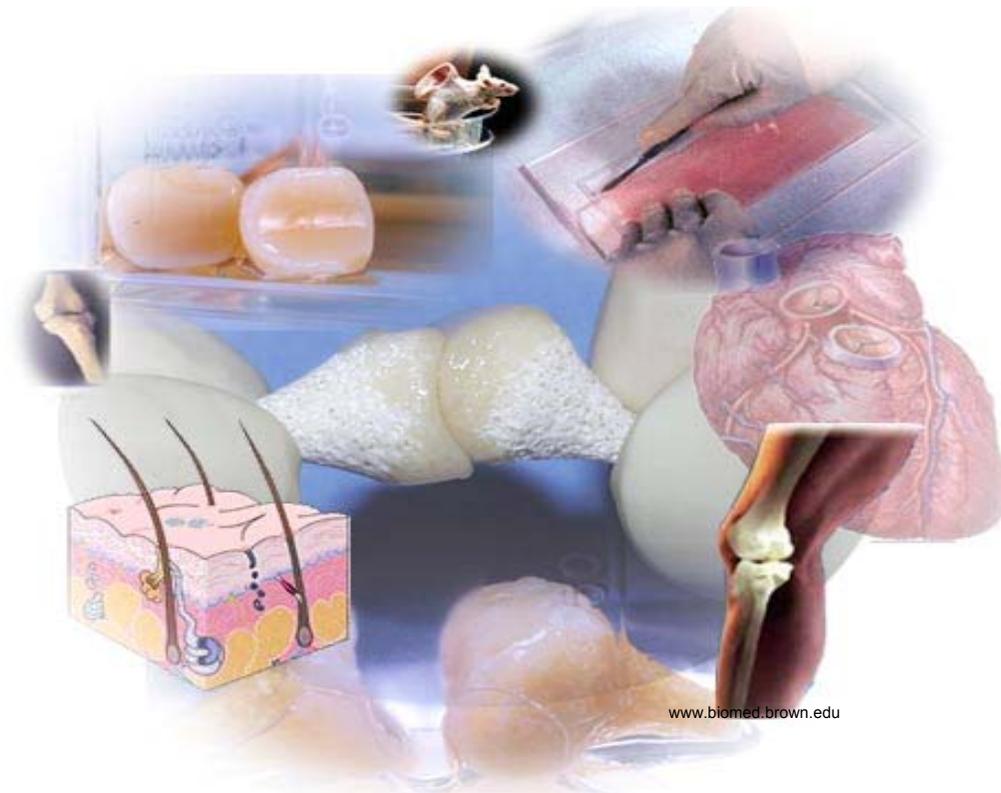


Overview of ICH GTDG Activities and Current Topics in Gene Therapy



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Disclaimer

The views expressed in this presentation are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the EMEA or one of its committees or working parties.



Agenda

1. Overview of GTDG activities in ICH
2. Exchange of information between ICH regions (Japan, US FDA, EU, Health Canada, EFTA)

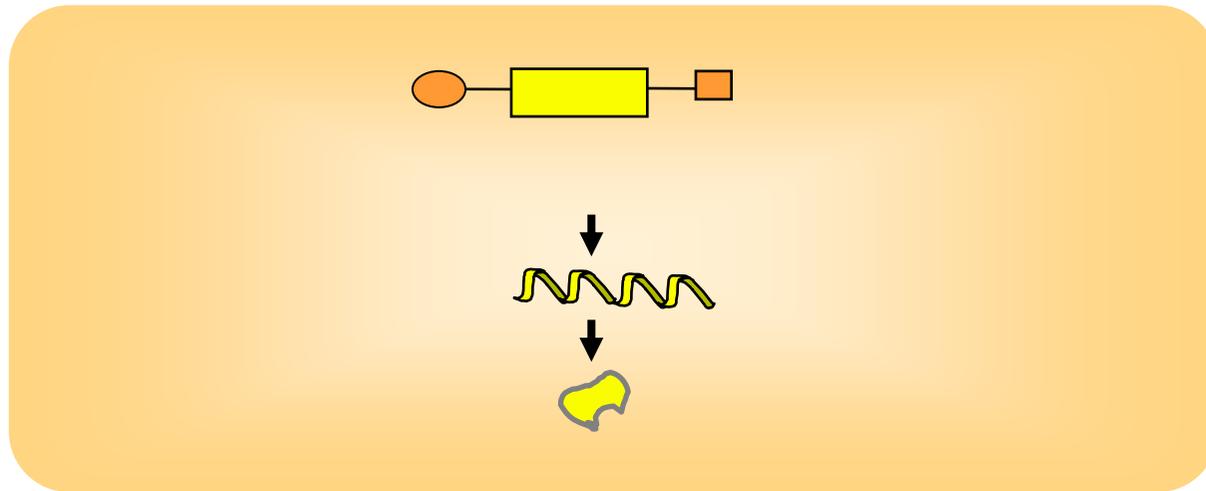
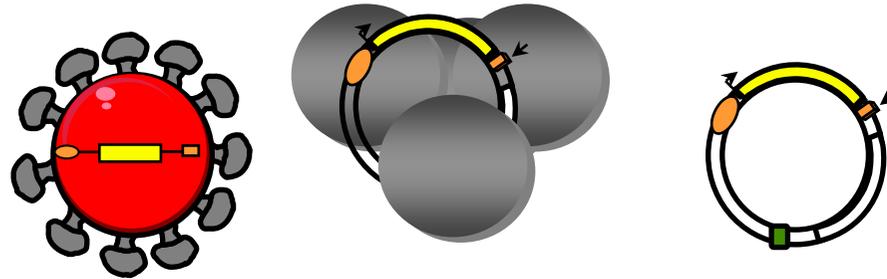


ICH

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Website: www.ich.org (-> GTDG)

Gene therapy: gene correction (future) or gene addition to restore cell function or provide new cell function



Genes are added to cells by gene delivery vehicles:

- replication-incompetent viral vector particles
- non-viral vector complexes
- naked DNA (naked nucleic acid) in bacterial plasmids
- related: oncolytic bacteria and viruses, DNA and live vector vaccines

ICH Gene Therapy Discussion Group

- 
- ✓ Medicines Agency and pharmaceutical industry representatives from the 3 ICH regions (Japan, USA, EU) and experts from the European Free Trade Association (EFTA), Health Canada and the WHO meet as the ICH Gene Therapy Discussion Group since 2001.
 - ✓ An observer from the Chinese SFDA attended meetings and has contributed a regional update.
 - ✓ Objectives:
 - Monitor emerging scientific issues
 - Proactively set out principles that may have a beneficial impact on harmonizing regulations of gene therapy products
 - Develop new ways of communication to ensure that the outcomes of ICH are well understood and widely disseminated such as
 - public ICH gene therapy workshops
 - public gene therapy press statements from the ICH SC
 - establish a publicly available ICH gene therapy web page

ICH Gene Therapy Discussion Group

- 
- ✓ Four public workshops held on topics such as
 - Workshop on Viral / Vector Shedding, Rotterdam, October 30, 2007
 - ICH Workshop on Oncolytic Viruses, Chicago, November 7, 2005
 - Presentations at ICH6, Satellite Session III on Gene Therapy, Osaka, November 15, 2003
 - Second Workshop on Gene Therapy - Satellite Session, Osaka, November 12, 2003
 - First Workshop on Gene Therapy, Washington, September 9, 2002

ICH Gene Therapy Discussion Group

- 
- ✓ GTDG Considerations documents:
 - General Principles to Address Viral / Vector Shedding (will be released in 2009 for comments)
 - Oncolytic Viruses (released in 2008 for comments, revised in 2009)
 - General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (2006)
 - General Considerations (2004) (SCID GT, long-term follow-up, HIV vaccination in healthy volunteers, replication-competent adenovirus in repl,-incomp. adv. vector preparations, germline transmission studies)

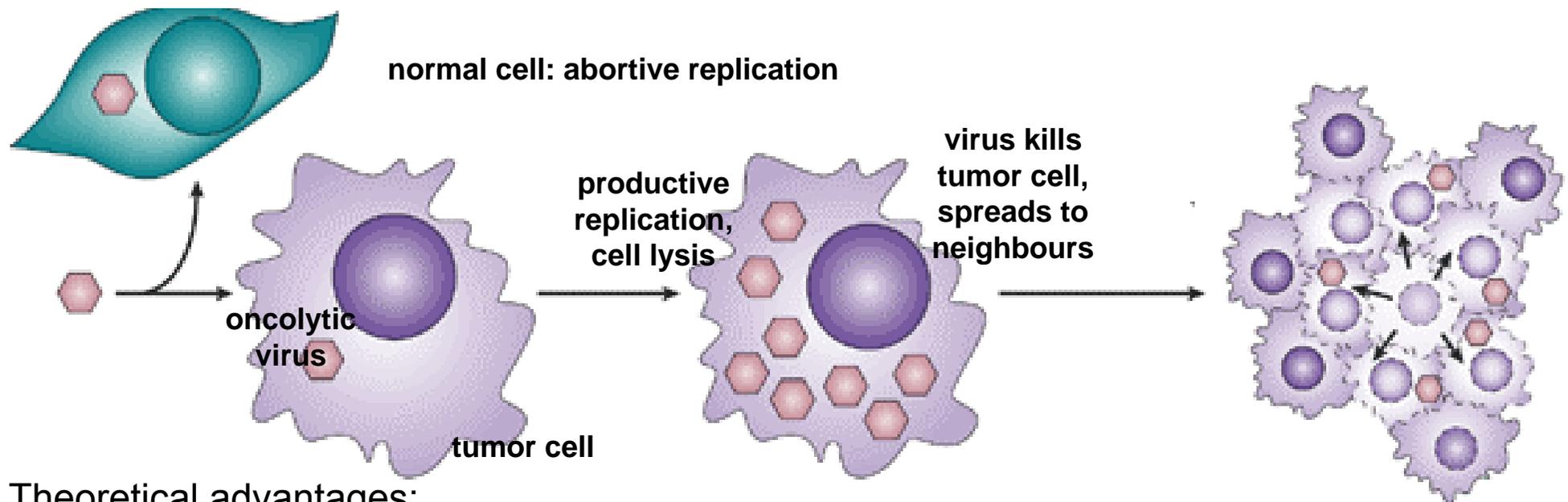
ICH Gene Therapy Discussion Group Report from Yokohama meeting 8-11 June 09

The scope of the ICH Gene Therapy Discussion Group (GTDG) meeting included:

- sharing regional updates,
- discussing the ICH Considerations on Viral / Vector Shedding,
- revising the ICH Considerations on Oncolytic Viruses,
- discussing and making plans for future activities (discussions on writing an ICH Guideline on Viral/Vector Shedding).

Conditionally replicating oncolytic virus

- Virus engineered to direct their cytotoxicity towards cancer cells



Theoretical advantages:

- viral replication within tumor mass allows infection of many cells
- lack of cross-resistance with standard therapies
- ability to cause tumor destruction by a variety of mechanisms



Theoretical risks:

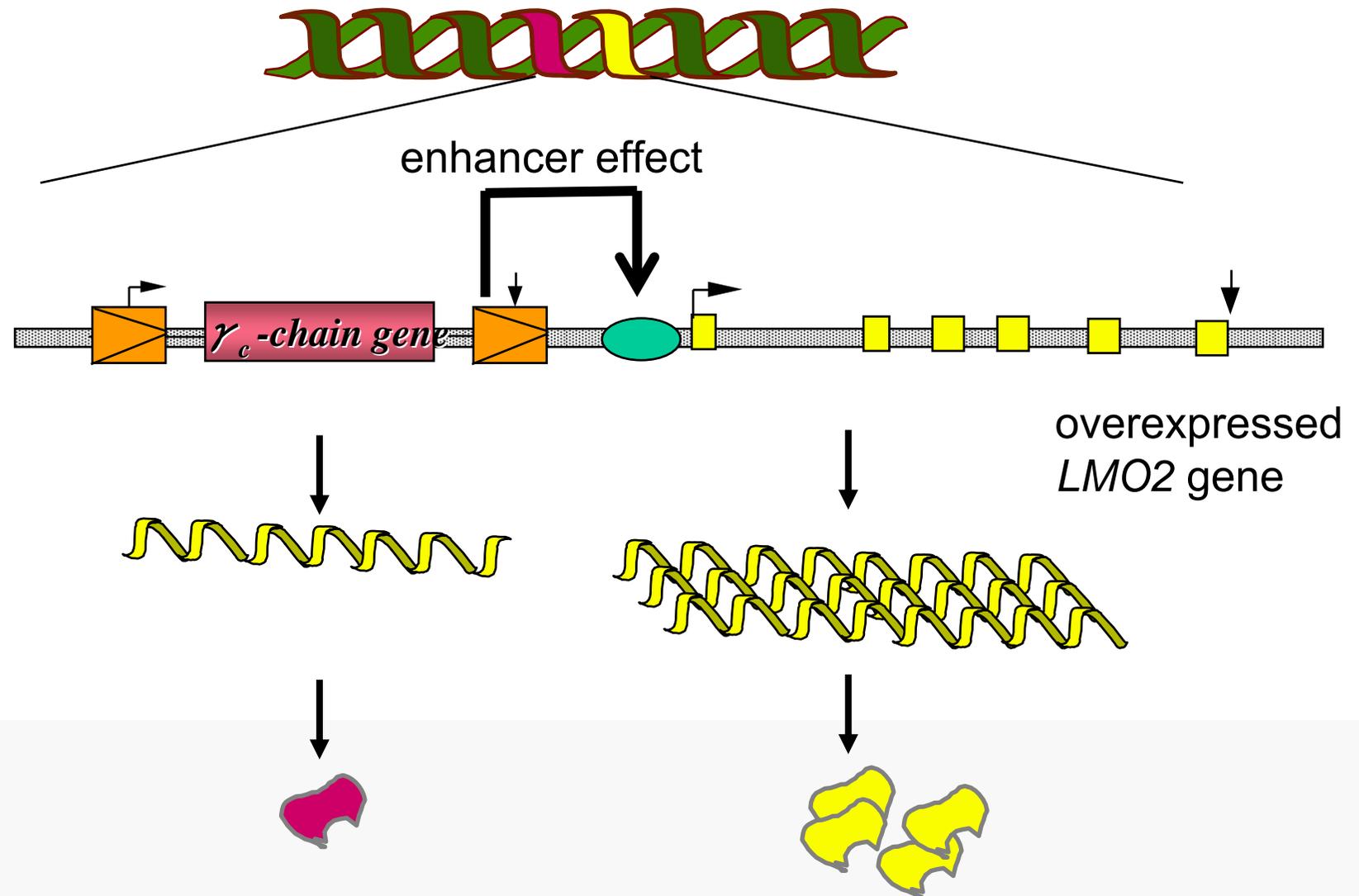
- chronic infection, introduction of new pathogens into the human population and adaptation

ICH Gene Therapy Discussion Group

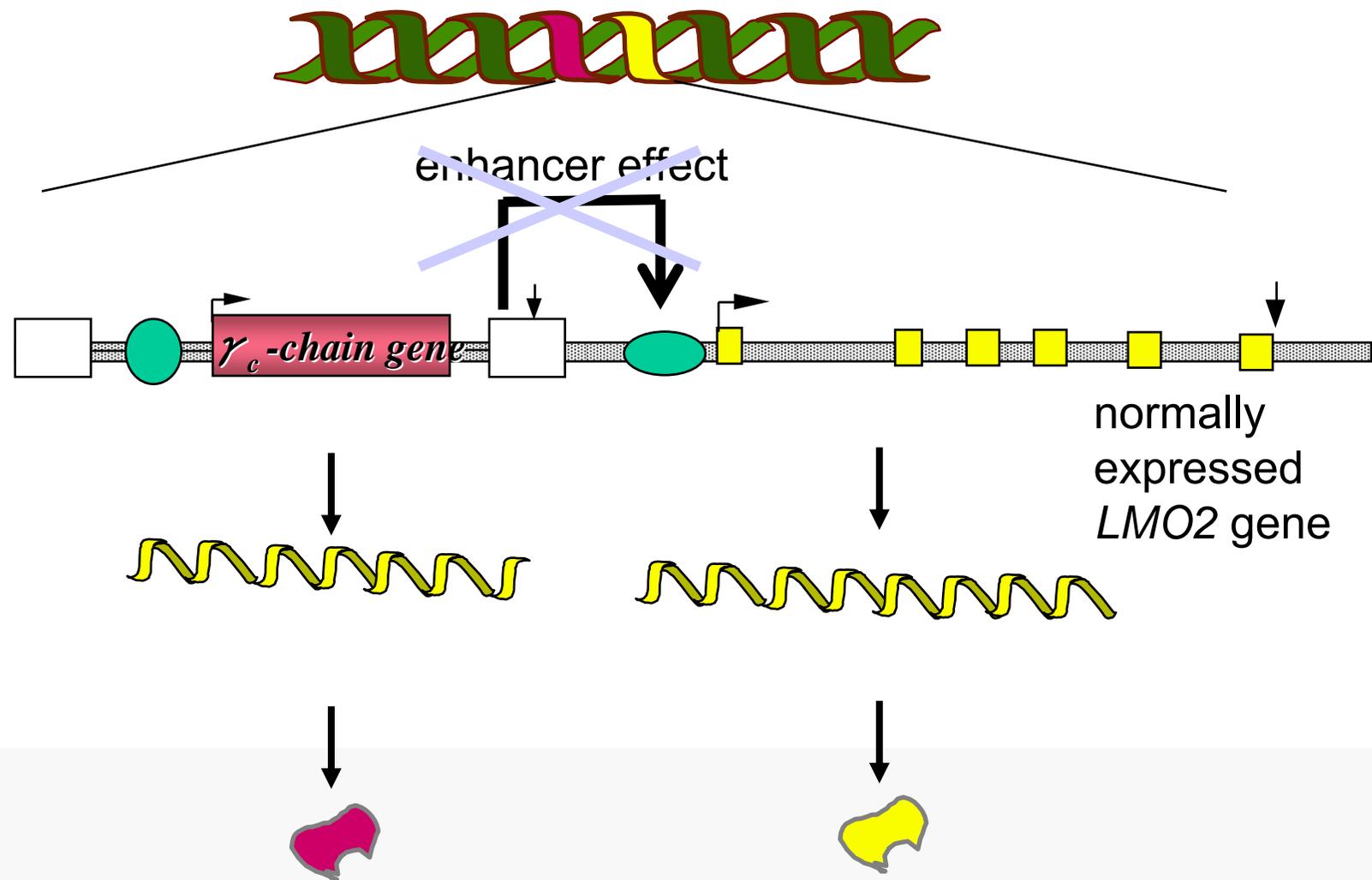
Interesting topics from regional updates

- 
- ✓ GTDG regional updates:
 - Gamma-retro- and lentiviral trials in EU leading to clonal cell dominance, sometimes oncogenesis (tumour development due to insertional mutagenesis; see next slide)
 - Autologous T bodies are potent mediators, severe adverse reactions in cancer patients observed
 - State of MAA applications in the EU: 3x applications under review
 - China: 2x gene therapy medicinal products on Chinese market, in vivo vectors in clinical trial, others in medical use

Insertional mutagenesis of integrating retroviral vectors: *p-onc* overexpression



SIN (self inactivating) vectors may reduce neighbouring *p-onc* overexpression



ICH Gene Therapy Discussion Group

Interesting topics from regional updates

- 
- ✓ Insertional mutagenesis/oncogenesis and clonal cell dominance:
 - Insertional oncogenesis previously observed in X-SCID trials using early generation retroviral vectors
 - From data analyses and field investigations next generation vectors developed to decrease oncogenic effect
 - Scientific data supported safety features
 - Next generation lentiviral vector was then used in β -Thalassemia *ex vivo* clinical trial
 - Clonal cell dominance as a possible precursor of oncogenesis observed
 - Clinical benefit seen
 - Defining appropriate benefit:risk balance
 - Discussion of inclusion criteria

ICH Gene Therapy Discussion Group Conclusions



As gene therapy development is global, products travel between Asia, America and Europe.

Sharing of information on benefits and risks observed with administered gene therapy medicinal products allows for measures to reduce risks for patients.

ICH Considerations and ICH Guidelines mediate harmonized approaches for product regulation and development.

Comments on ICH GTDG are welcome (www.ich.org).

Agenda

1. Overview of GTDG activities in ICH
2. New regulatory framework and new scientific committee at the EMEA:
the Committee for Advanced Therapies
3. Update on EMEA GTWP activities
4. State of gene therapy development



New legislation: EU Regulation on Advanced Therapies



- **Regulation on Advanced Therapies**
 - Regulation (EC) No. 1394/2007 of 13 November 2007
 - published on 10 December 2007
 - applicable since 30 December 2008
- For further reading:
<http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm>

Changes accrdg. to the EC ATMP Proposal

- Centralized licensing procedure for all ATMPs
 - Gene therapy products
 - Human somatic cell therapy products
 - Xenogeneic somatic cell therapy products
 - Tissue engineered products
- Autologous and directionally used medicinal products will undergo licensing
 - cell banks
 - industrially produced
- Tissue engineered products and somatic cell therapy products will undergo central licensing,
 - live (viable) and
 - substantially altered or engineered



New definition of GTMP

Gene therapy medicinal product means a **biological medicinal product** which has the following characteristics:

- (a) it contains an **active substance which contains or consists of a recombinant nucleic acid** used in or administered to human beings with a view to **regulating, repairing, replacing, adding or deleting a genetic sequence**;
- (b) its **therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence** it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall **not include vaccines against infectious diseases.**



Highlights from Regulation (3)

- Pre-authorisation requirements
 - Compliance with ‘Essential Requirements’ for products incorporating medical devices
 - Specific guidelines
 - on GMP (Good Manufacturing Practice) and
 - GCP (Good Clinical Practice)
 - Specific rules for labelling/packaging
- Post-authorisation requirements
 - **Follow-up of efficacy and adverse reactions**, and risk management: obligation for EMEA to inform relevant device/tissue national authorities
 - Traceability

Highlights from Regulation (4)

Incentives for industry:

- Scientific Advice:
 - 90% fee reduction for SMEs, 65% for others
- Scientific recommendation on advanced therapy classification: 60 days
- SMEs: Certification of quality and non-clinical data
- Additional fee reduction if applicant is SME or hospital and can prove there is a particular public health interest in the Community

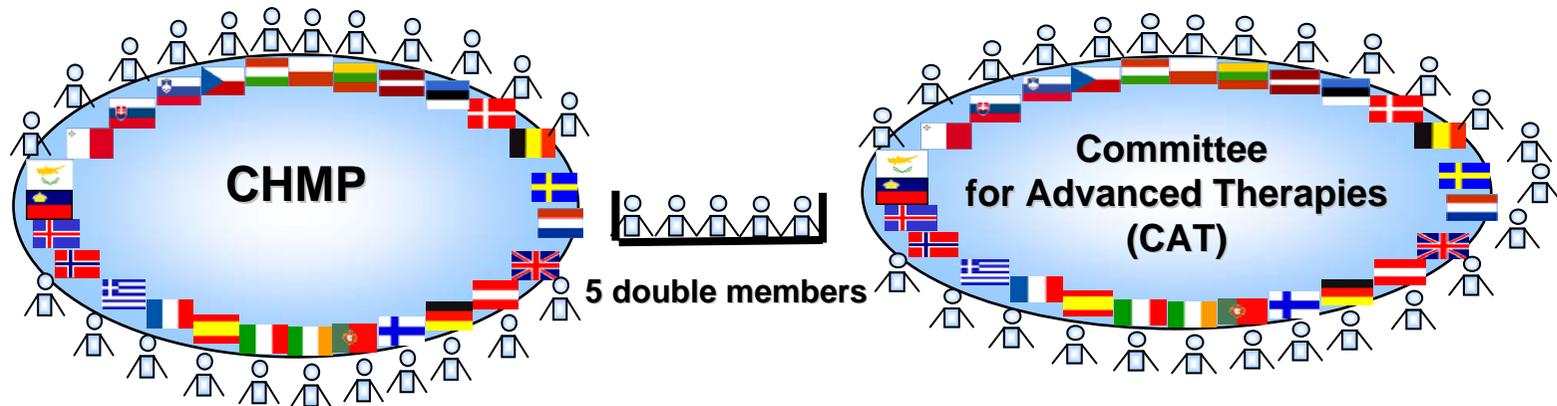
Revision of Annex I of EU Medicinal Product Directive (2001/83/EC)

What is in?

- Introduction: risk-based approach to determine the extent of Q/N-C and C data for MAA
 - in CTD Module 2
 - Description of methodology, nature of identified risks, implications of risk based approach for development programme
- New definitions of GTMP and sCTMP
- Specific requirements for GTMP / sCTMP + TEP

Publication to the EC Official Journal expected Q2/Q3 09

ATMP and Scientific expertise at EMEA



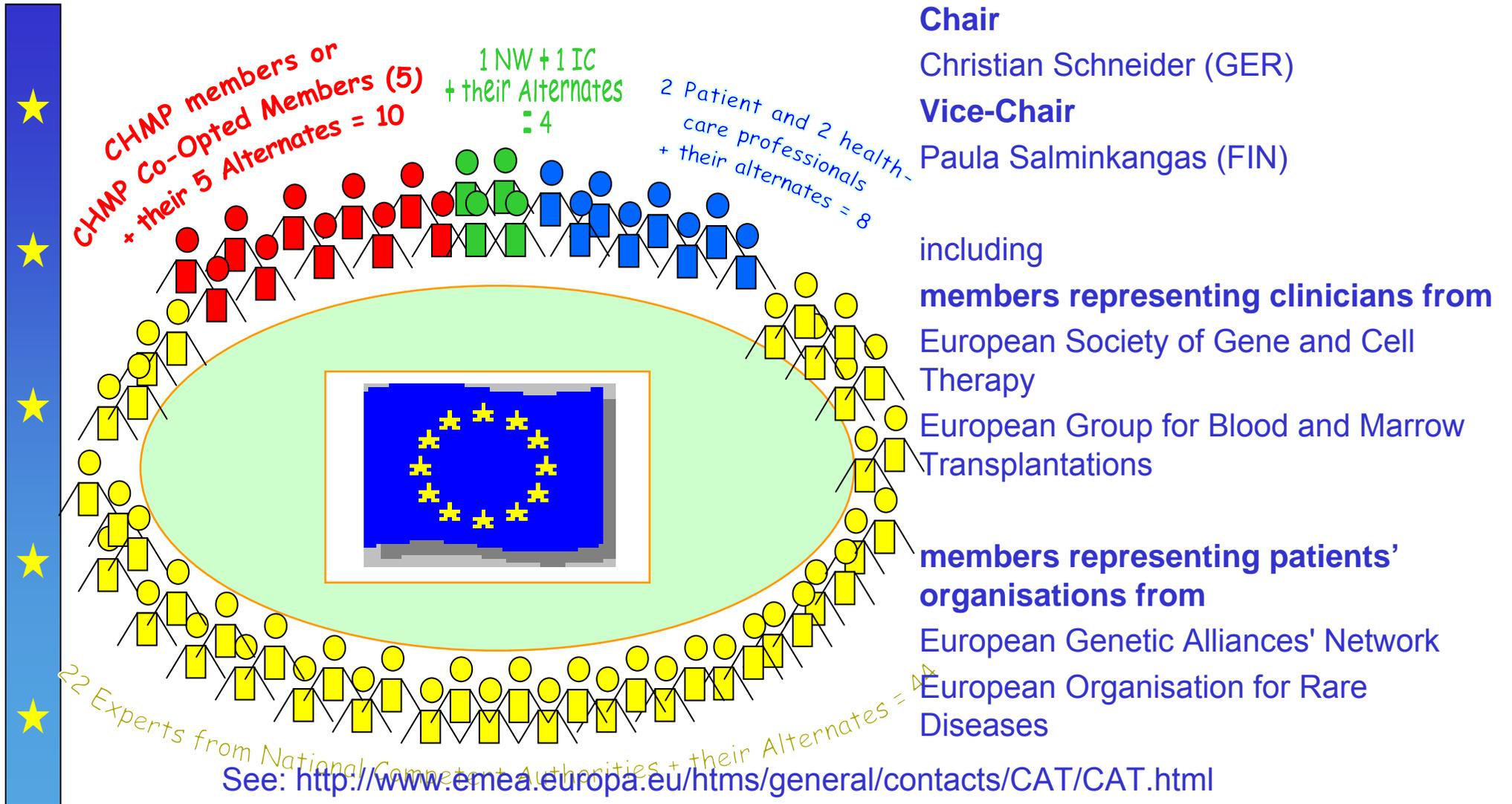
Working Parties
(i.e Gene Therapy, Cell-based
Product, Biological...)

Scientific Advisory Groups (i.e
Oncology, Diagnostics...)

Pediatric Committee,
Committee for Orphan
Medicinal Products

CHMP: Committee for Medicinal Products for Human Use

Composition of the CAT



Main Roles of the CAT

- 
- ✓ Contribution to EMEA **scientific advice** on ATMPs with Scientific Advice Working Party
 - ✓ ATMP **classification**
 - ✓ ATMP **certification** of quality/non-clinical data (Small and Medium Enterprise)
 - ✓ Draft **opinion on quality/safety/efficacy for ATMP Marketing Authorization Application** initial evaluation, re-examination, post-marketing activities.
 - ✓ Scientific expertise for ATMPs as requested

ATMPs on EMEA Website

The screenshot shows the EMEA website interface. The main content area features a news article titled "EMEA publishes report on supply shortage of radiopharmaceuticals" published on 10/03/2009. The article discusses a report on short-, medium-, and long-term aspects of the supply shortage of radiopharmaceuticals that occurred during autumn 2008. It provides an analysis of the situation and actions taken, along with recommendations for manufacturing and use. Links are provided for further details: [Report to the European Commission on the supply shortage of radiopharmaceuticals](#) and [Public statement on the current shortage of radiopharmaceuticals in the European Union](#).

Below the article is another news item: "EMEA work programme 2009 published" from 27/02/2009. It outlines the Agency's focus for 2009, including: further improving core activities, strengthening activities within the European medicines network, further improving safety-monitoring, implementing new legislation (Advanced Therapies Regulation), fostering transparency, and contributing to improved availability of medicines and innovation. A link is provided for [EMEA work programme 2009](#).

At the bottom of the main content is a "Latest Press Releases" table:

Latest Press Releases		See Press Office for archived press releases
13/03/09	PDCCO	Press Release from the 4-6 March meeting
13/03/09	CVMP	Press Release from the March meeting
10/03/09	MB	Press Release Management Board re-elects Vice-chair and starts budget discussions for 2010
10/03/09	EMEA	Report to the European Commission on the Supply Shortage of Radiopharmaceuticals
10/03/09	EMEA	Press Release Orion Corporation withdraws its application for an extension of indication for Stalevo (levodopa/carbidopa/entacapone)
20/02/09	EMEA	Press Release Review of field safety data by the European Medicines Agency finds a good safety record for inactivated bluetongue emergency vaccines

At the bottom of the page, there is a link to [See Press Office for archived press releases](#).

The right sidebar contains a "Fast track to a topic..." dropdown menu and a vertical list of product information categories. The "ADVANCED THERAPIES" category is highlighted with a red circle and a red arrow pointing to the main content area.

The left sidebar contains a navigation menu with sections: EMEA STRUCTURE, EMEA COMMITTEES, CONTACT & LOCATION, MEETINGS & EVENTS, RECRUITMENT, PUBLISHING SERVICES, and SEE ALSO.

http://www.emea.europa.eu/htmls/human/advanced_therapies/intro.htm

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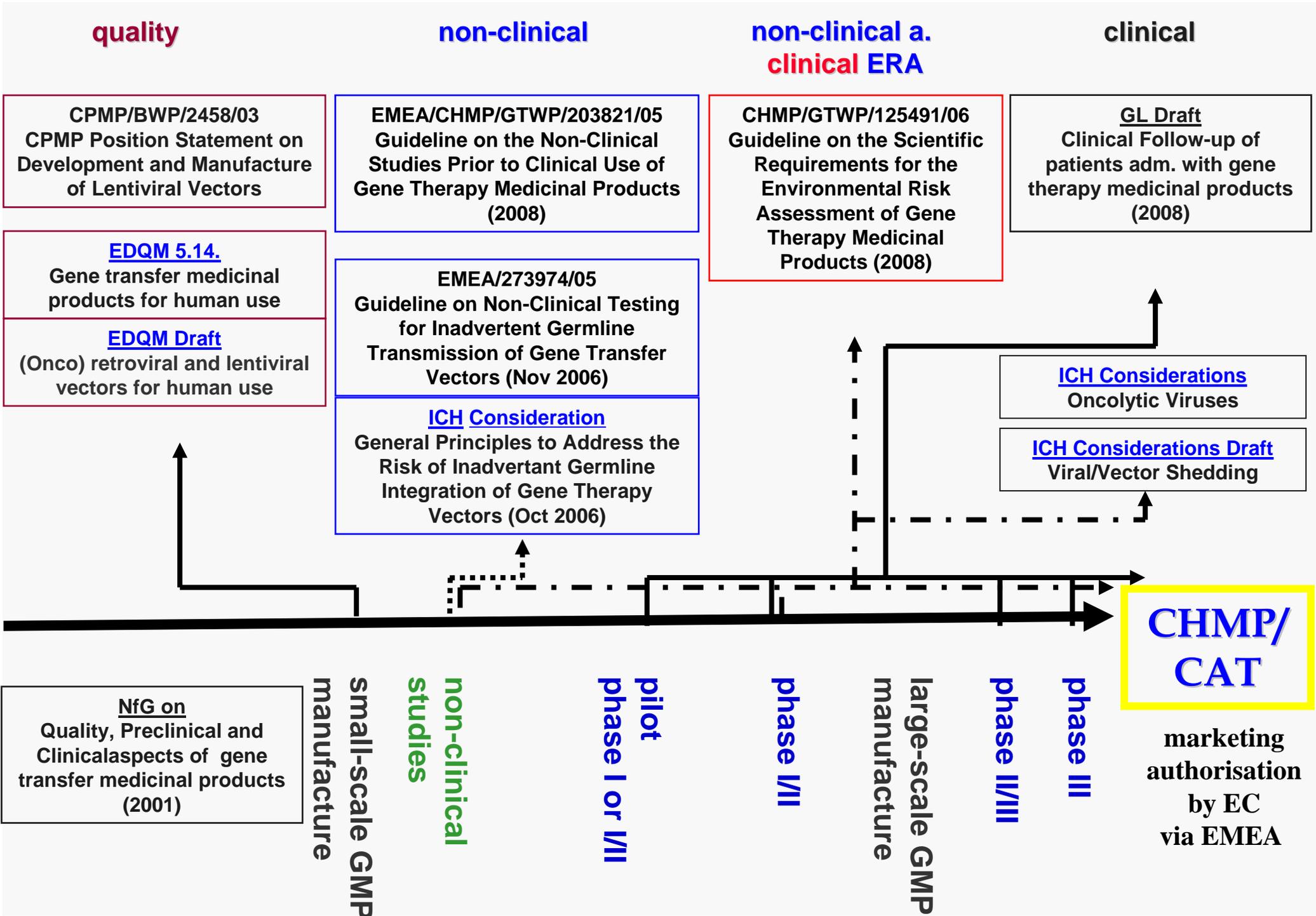
EMA/CHMP - Gene Therapy Working Party (GTWP)

Main Roles:

- ✓ Preparing, reviewing and updating guidelines
- ✓ Providing advice on product-specific matters relating to gene therapy medicinal products (e.g. scientific advice, marketing authorisation applications)
- ✓ Providing advice on issues relating to gene therapy
- ✓ Ensuring international cooperation on issues relating to gene therapy
- ✓ contributing to the organisation of workshops and training relating to gene therapy
- ✓ liaising with interested parties

EMEA/CHMP Gene Therapy Working Party Work Programme 2009

- 
1. **Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells**
 - Draft guideline
 2. **Guideline on follow-up of patients treated with gene therapy medicinal products**
 - Finalization
 3. **Guideline on Quality, non-clinical and Clinical aspects of live recombinant viral vectored vaccines**
 - Draft guideline
 5. **Reflection paper on quality, preclinical and clinical issues relating to adeno-associated viral vectors**
 - Released for **6-month public consultation by September 2009**
 6. **Note for Guidance on quality, preclinical and clinical aspects of gene transfer medicinal products**
 - Revision considered



Agenda

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EudraCT Clinical Trial Applications in the EU (3Q 2005 to 3Q 2008)

<i>Gene therapy/transfer MPs (trials / original products)</i>	<u>3Q 2005</u> (19 / 9)	<u>3Q 2006</u> (51 / 23)	<u>3Q 2007</u> (69 / 35)	<u>3Q 2008</u> (124 / 59)
cancer	4	13	20	29
cardio-vascular	2	3	4	6
metabolic diseases (diabetes)	–	–	–	1
autoimmune diseases	1	2	2	4
HIV vaccine	2	2	2	7
infectious disease (chronic Hepatitis C)	–	–	1	2
neuronal	–	1	3	5
vaccines (monovalent, combi-)	–	2	3	5
	9	23	35	59



EudraCT Clinical Trial Applications in the EU (3Q 2005 to 3Q 2008)

<i>Somatic cell therapy MPs (trials / original products)</i>	<u>3Q 2005</u> (25 / 13)	<u>3Q 2006</u> (73 / 59)	<u>3Q 2007</u> (132/112)	<u>3Q 2008</u> (213/171)
cancer immunotherapy	3	23	45	70
cardio-vascular	4	17	31	44
skin/liver/lung/eye/diabetes/ intestine/bone TE	5	12	28	48
neurological	1	4	5	6
lymphohistiocytosis (HLH)	–	1	1	1
AIDS	–	1	1	1
infertility	–	1	1	1
	13	59	112	171



History of gene therapy: understanding adverse reactions

- Jesse Gelsinger, 1999:
cytokine storm following administration of a very high dose of adenoviral vector to an OTC patient
- SCID-X1, 2002 and later:
lymphoproliferative disease
- ALT following AAV, 2004:
increased ALT levels following administration of AAV-F IX due to pre-existing immunologic memory cells directed against AAV
- CGD, 2005:
clonal cell dominance followed by myelodysplasia in a CGD patient and death due to loss of therapeutic gene expression in another CGD patient
- β -thalassemia clonal cell dominance, 2009:
lentiviral vectors including SIN-LTR, cell type-specific promoter and insulators used



History of gene therapy: indications of benefit

- With the aid of the Human Genome Project, more than 4,000 genetic diseases have been identified.
- first approved gene therapy procedure was performed in 1990, on four-year-old Ashanti DeSilva, who suffered from the rare genetic disease, severe combined immunodeficiency (SCID).
- ADA-SCID, SCID-X1 and CGD GT products have provided benefit to patients
- In Japan, a successful trial on vascular angiogenesis using bFGF has been completed. Benefit has been observed.
- Lentiviral vectors are being successfully used in Parkinson's disease, adrenoleukodystrophy and β -thalassemia.
- Congenital Leber amorosis trial has provided visual improvement to patients.
- 3x GT product MAA are under review in EU
 - Adv-HSV-tk (Cerepro)
 - Adv-p53
- 3x GT products are on Chinese/Philippine market.

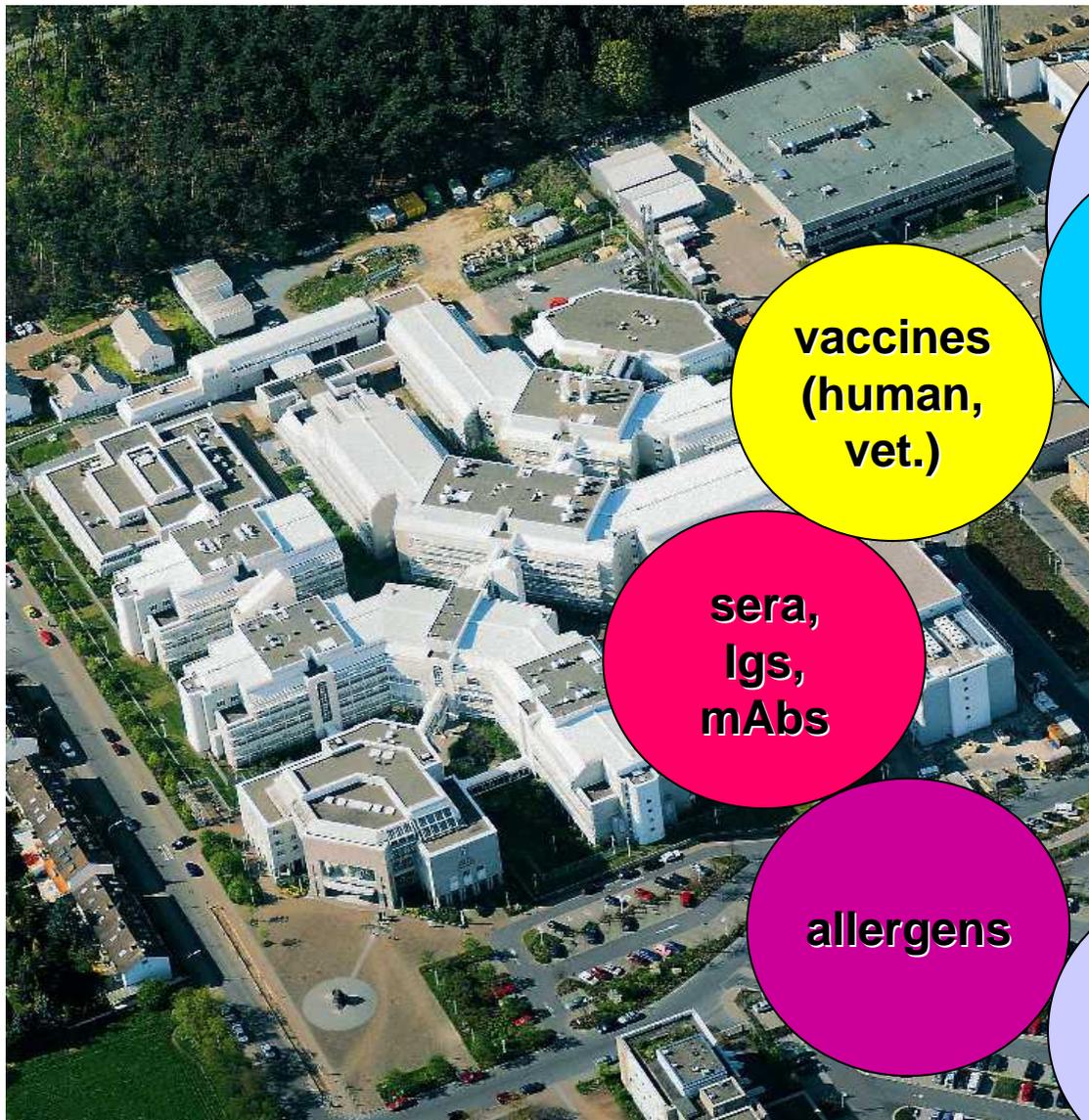




Acknowledgements

Marisa Papaluca Amati
Patrick Celis
Mayeul Boucaumont

Paul-Ehrlich-Institut: research on and regulation of vaccines and biomedicines



**vaccines
(human,
vet.)**

**sera,
Igs,
mAbs**

allergens

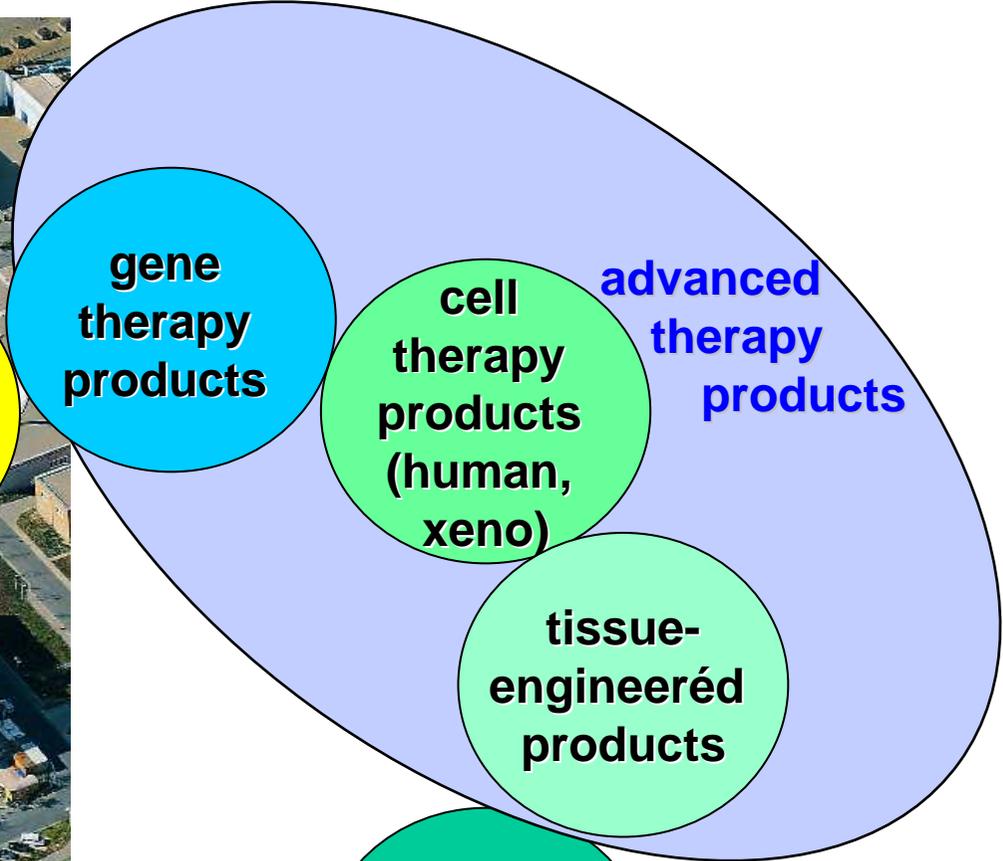
**gene
therapy
products**

**cell
therapy
products
(human,
xeno)**

**tissue-
engineered
products**

**blood a.
plasma-
derived
products**

**Classical
tissue
preparations**



**advanced
therapy
products**