# Regulatory Aspects of Gene Transfer Medicinal Products

- Introduction and Definition
- Regulatory Requirements
- State of the Art

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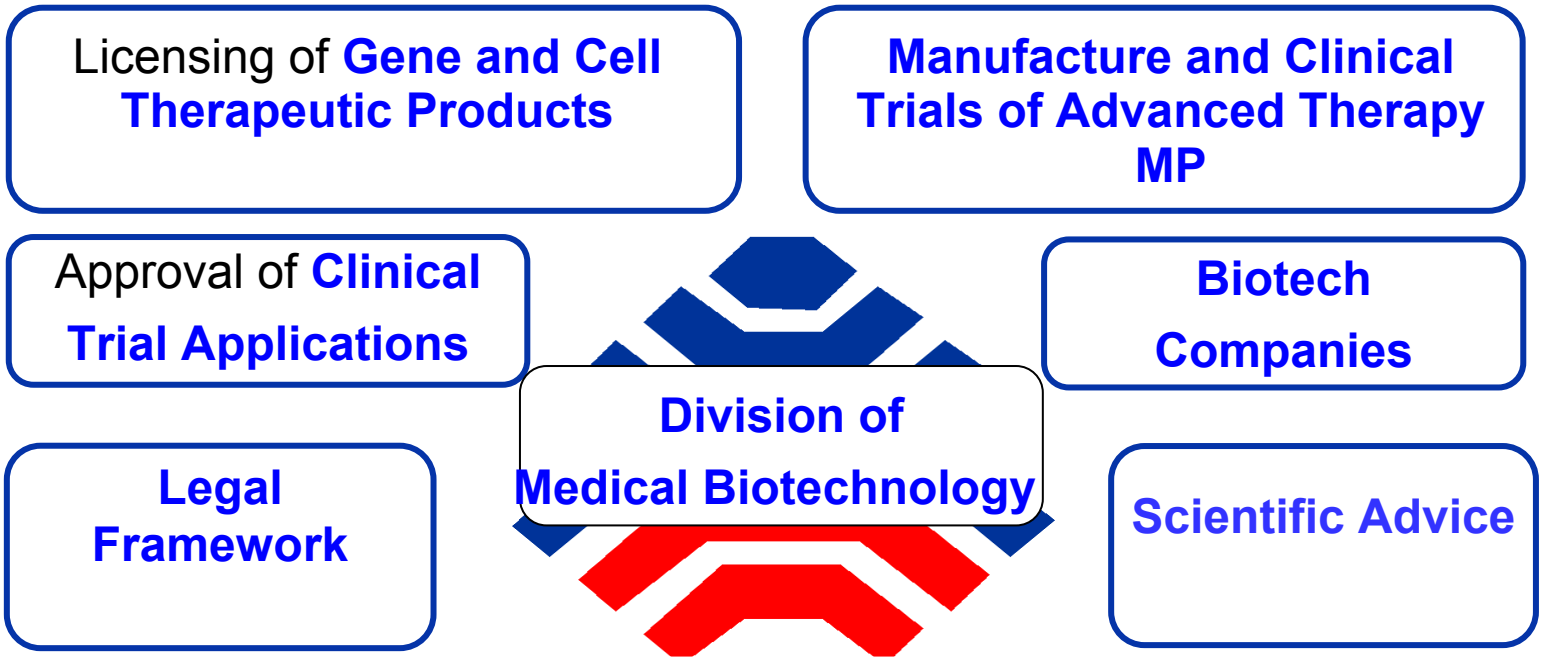
# Regulation & Research combined in the Divisions at PEI

- Safety
- Bacteriology
- Virology
- Immunology
- Vet. Medicine
- Allergology
- Med. Biotech.
- Hematology

# Activities in the Division of Medical Biotechnology



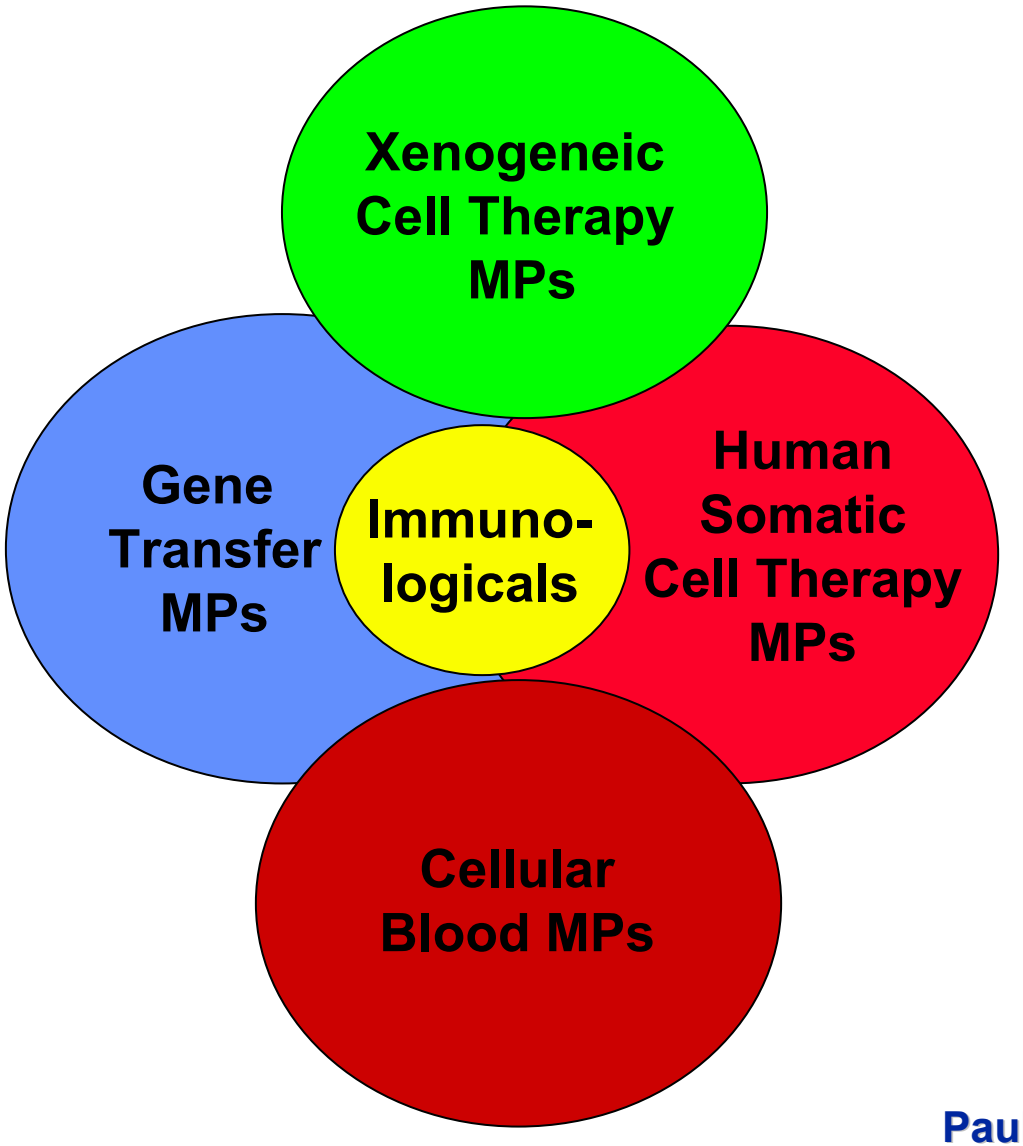

**Basic Research**

Retroviruses : HIV/ SIV and HERV/ PERV

Gene Therapy : AIDS and Tumour

Cell Therapy : Intracellular Signaling Pathways

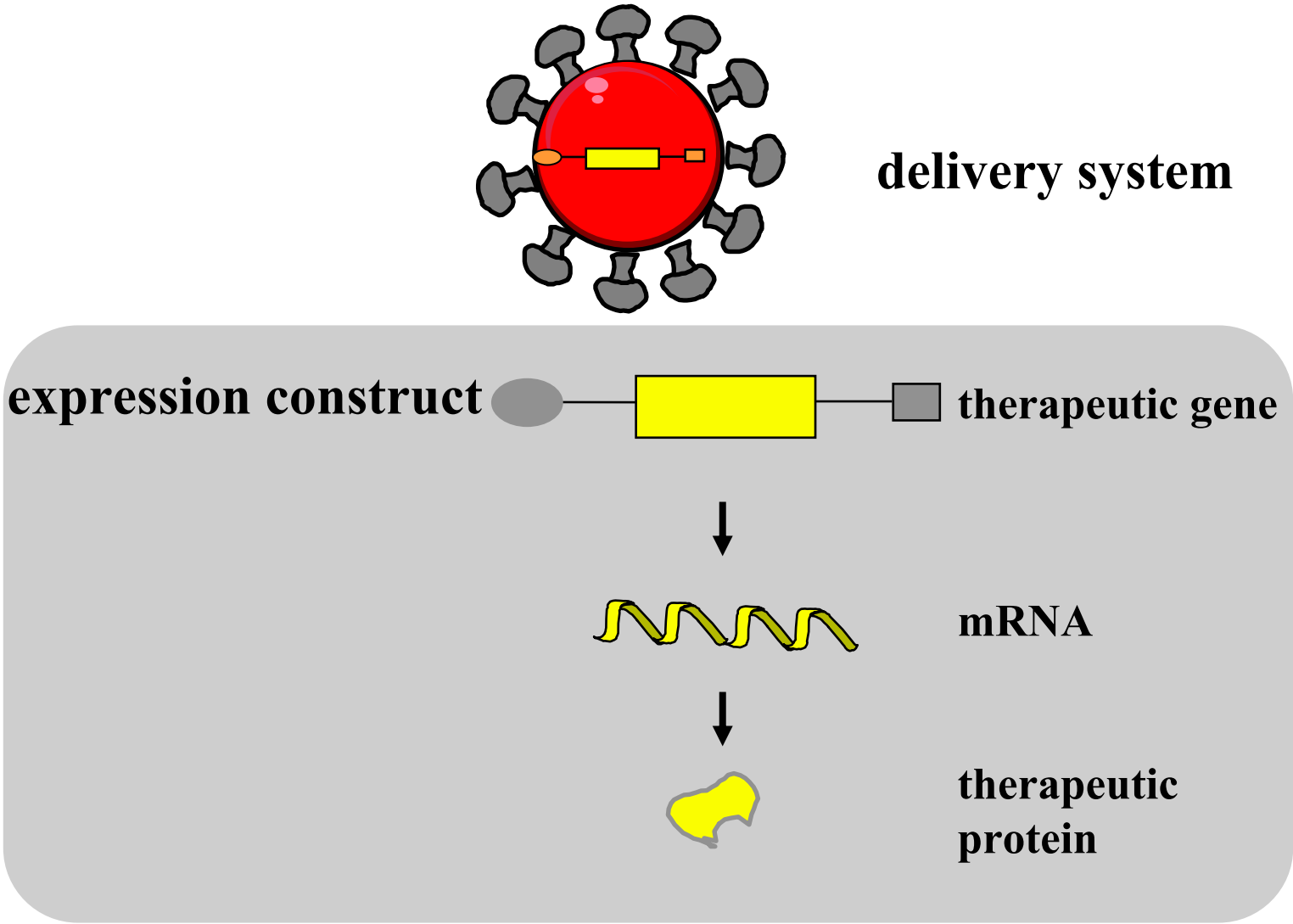
# Innovative biotechnology products



# Innovative biotechnology products

- Why are they special?
  - Mechanism of action is based on new insights into the molecular biology of cells and micro-organisms (molecular biology).
  - Use in medicine is evidence-based.
  - They pose new safety problems which are not generally foreseeable due to lack of experience in human use.
  - Experience is very limited, e.g. some adverse reactions may only be observed during use in a high number of patients.
  - Regulators and biomedical expertise to use them in clinical trials, to manufacture and to regulate them is very limited.

# Gene Transfer Medicinal Products (GT-MPs)



# Gene Transfer Medicinal Products

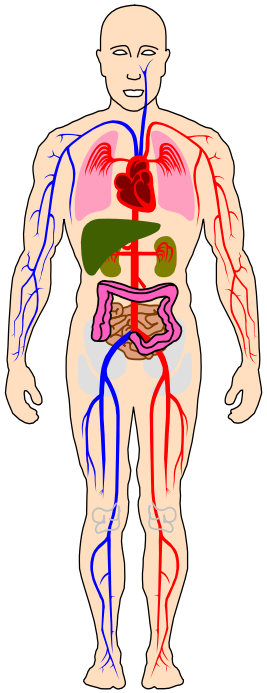
## (preventive, therapeutic, in-vivo diagnostic use)

***ex vivo***

Explantation of target cells

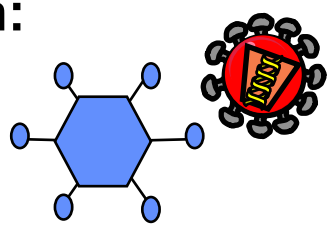
Gene transfer

Reinfusion of modified cells (autologous or allogenic)



***in vivo***

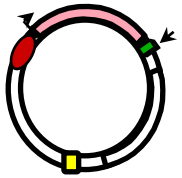
**Direct application:**



**viral vector**

**non-viral vector**

**naked DNA**



**microorganisms**

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# Genes used in gene transfer medicinal products

**Monogeneic inherited disease**

| | | |
|---|---|---|
| • normal cell | IL2R, ADA, gp55phox | SCID-X1, ADA-SCID, CGD |

**Cancer**

| | | |
|---|---|---|
| • cytokine | IL-2, GM-CSF | tumor vaccines (cells) |
| • tumor-specific antigens | tyr (melanoma) | therapeutic tumor vaccines |
| • tumor-suppr. | p53 | apoptose-induction (tumor cells) |
| • suicide | HSV-tk, CD | GvH/leukemia, donor lymphocte killing |

**Cardio-vascular disease**

| | | |
|---|---|---|
| • growth factor | FGF-4 | myocardium repair |
| • signaling | NOX | cell growth inhibitor |

**Infectious disease**

| | | |
|---|---|---|
| • ribozyme | Ri | HIV therapy |
| • antigenic | microbial (e.g. HIV) | preventive vaccines (inf. disease) |

# Legally required testing provisions for advanced therapy medicinal products (dossier for licensing application)

## Annex I
## of Directive 2001/83/EC

## as amended by Directive 2003/63/EC

- Technical requirements will have to be met with increasing stage of clinical testing and manufacture.
- CTD: Common Technical Document; simplified version for advanced biotechnology products.
- Establishment of the plasma (PMF) and the vaccine antigen master file (VAMF).

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# Gene therapy medicinal products

- Annex I Directive 2001/83/EC, Part IV.
  - For the purposes of this Annex, **gene therapy product shall mean**
    - **a product resulting from a set of processes aimed at the transfer, to be performed either *in vivo* or *ex vivo*,**
    - **of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of DNA),**
    - **to human cells and its subsequent expression *in vivo*.**
    - The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.
- Conditionally replication competent adenovirus included: viral genome is the therapeutic gene.
- Live virus vaccines not included, but DNA vaccines and vectored vaccines for preventive measures are included.

# Definition of innovative biotechnology products in the AMG

theoretisches Risiko

(21) Xenogene Zelltherapeutika sind zur Anwendung am Menschen bestimmte Arzneimittel im Sinne des § 2 Abs. 1, die genetisch modifizierte oder durch andere Verfahren in ihren biologischen Eigenschaften veränderte lebende tierische Körperzellen sind oder enthalten.

„(9) Gentransfer-Arzneimittel sind zur Anwendung am Menschen bestimmte Arzneimittel im Sinne des § 2 Abs. 1, die zur genetischen Modifizierung von Körperzellen durch Transfer von Genen oder Genabschnitten bestimmte nackte Nukleinsäuren, virale oder nicht-virale Vektoren, genetisch modifizierte menschliche Zellen oder rekombinante Mikroorganismen, letztere ohne mit dem Ziel der Prävention oder Therapie der von diesen hervorgerufenen Infektionskrankheiten eingesetzt zu werden, sind oder enthalten."

„(20) Somatische Zelltherapeutika sind zur Anwendung am Menschen bestimmte Arzneimittel im Sinne des § 2 Abs. 1, die durch andere Verfahren als genetische Modifikation in ihren biologischen Eigenschaften veränderte oder nicht veränderte menschliche Körperzellen sind oder enthalten, ausgenommen zelluläre Blutzubereitungen zur Transfusion oder zur hämatopoetischen Rekonstitution.

# Regulatory Requirements for GT-MPs

## Annex I
## of Directive 2001/83/EC

## European Note for guidance
## on the quality, preclinical and clinical aspects of gene transfer medicinal products
## (CPMP/BWP/3088/99)

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# Starting material and active substance: examples

- starting materials:
  materials from which the active substance is manufactured such as,
  - gene of interest,
  - expression plasmids,
  - cell banks and
  - virus stocks or non viral vector;

- active substance:
  - recombinant vector,
  - virus,
  - naked or complexed plasmids,
  - virus producing cells,
  - *in vitro* genetically modified cells.

# Technical requirements for licensing: expression, development genetics, sequences

- Information shall be provided on the relevant characteristics of the gene therapy medicinal product including
  - its expression in the target cell population

- Information concerning the
  - source, construction, characterisation and verification of the encoding gene sequence including its
  - integrity and
  - stability shall be provided

- The complete sequence shall be provided of the
  - therapeutic gene, (other genes)
  - regulatory elements and the
  - vector backbone

# Technical requirements for licensing: vector characterisation and source

- Information shall be provided concerning the characterisation of the
  - vector used to transfer and deliver the gene,
  - Its physico-chemical characterisation and/or
  - Its biological/immunological characterisation.
- For medicinal products that utilise a micro-organism such as bacteria or viruses to facilitate gene transfer (biological gene transfer), data shall be provided on the
  - pathogenesis of the parental strain,
  - tropism for specific tissues and cell types and the
  - cell cycle-dependence of the interaction.
- For medicinal products that utilise non-biological means to facilitate gene transfer,
  - the physico-chemical properties of the constituents individually and in combination shall be provided.

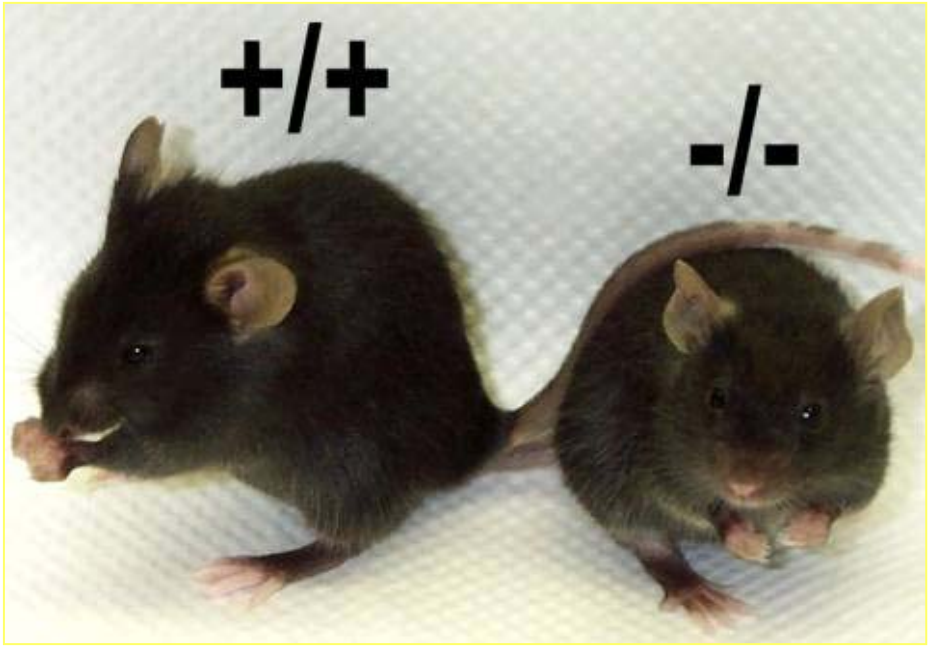
# Technical requirements for licensing: cell source and banking

- The principles for cell banking or seed lot establishment and characterisation shall apply to gene transfer medicinal products as appropriate.

- The source of the cells hosting the recombinant vector shall be provided and documented:
  - characteristics of the human source such as age, sex,
  - results of microbiological and viral testing,
  - exclusion criteria and
  - country of origin.

# Toxicity studies

- organ and tissue distribution of transgene, persistence, expression over time
- exclusion of germ line transmission and environmental risk
- physiological consequences of gene expression
- include functional end point *in vivo*
- it may be necessary to identify or develop new animal models.

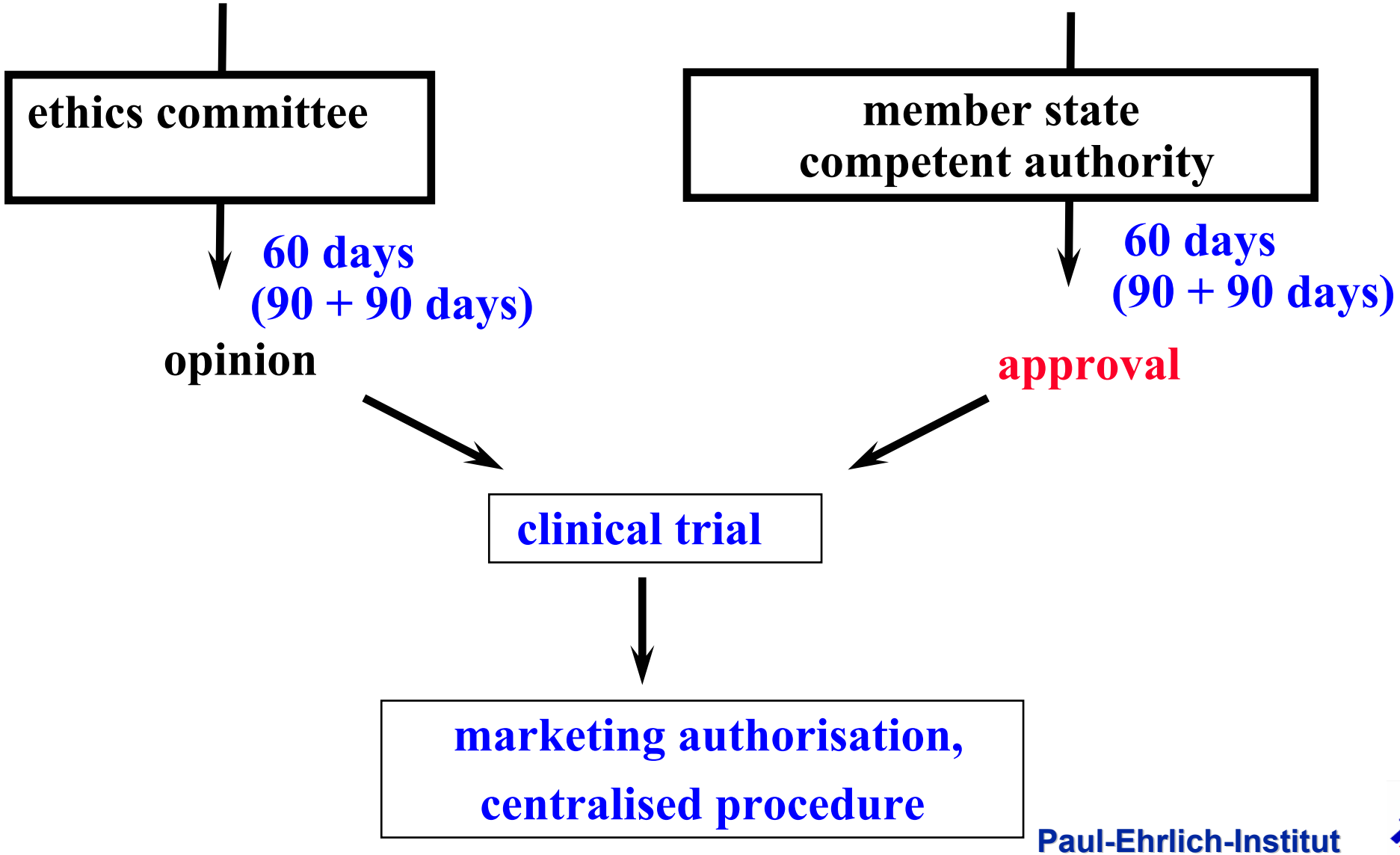


# Biological Monitoring

- absence of germ line transfer
- spread into other tissues
- antibodies against vector, vector-producing cell or genetically modified cell
- absence of replication competent vector-derived virus (shedding)

# Clinical trial approval

(after applying European GCP Directive )

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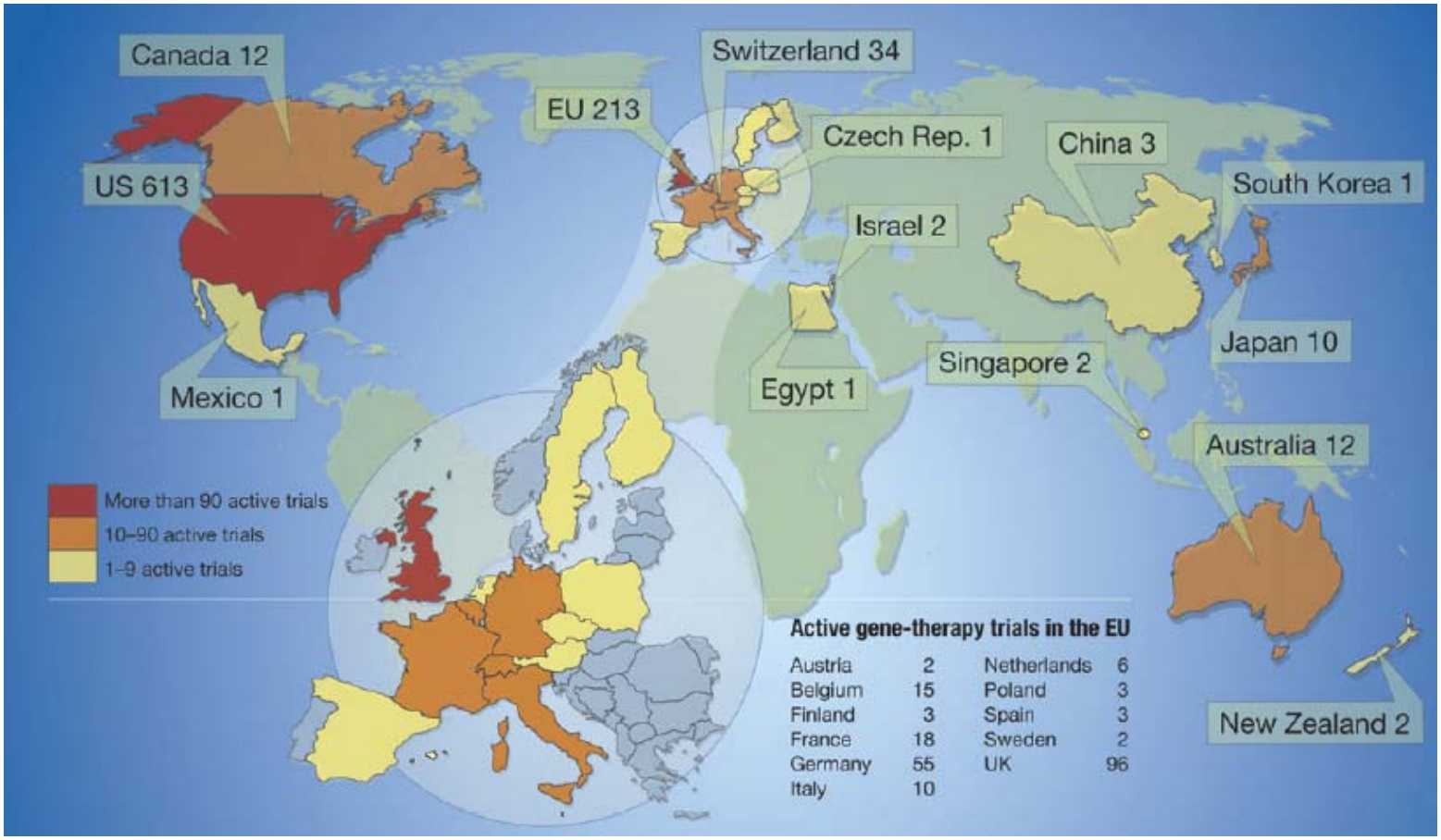
# State of the Art

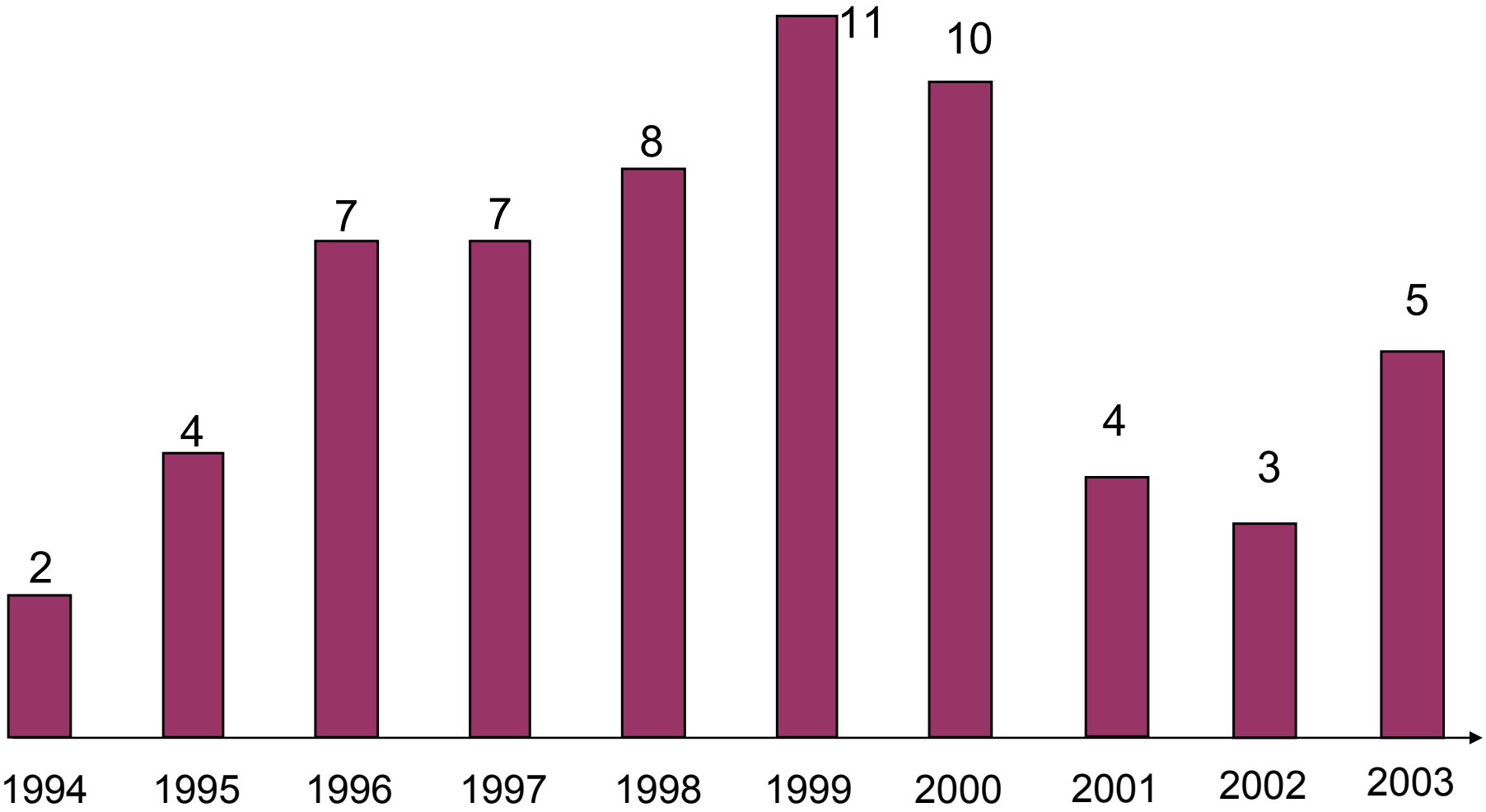
# ~ 4.000 patients have been treated with GT-MPs, about 600 in Europe (260 in Germany)



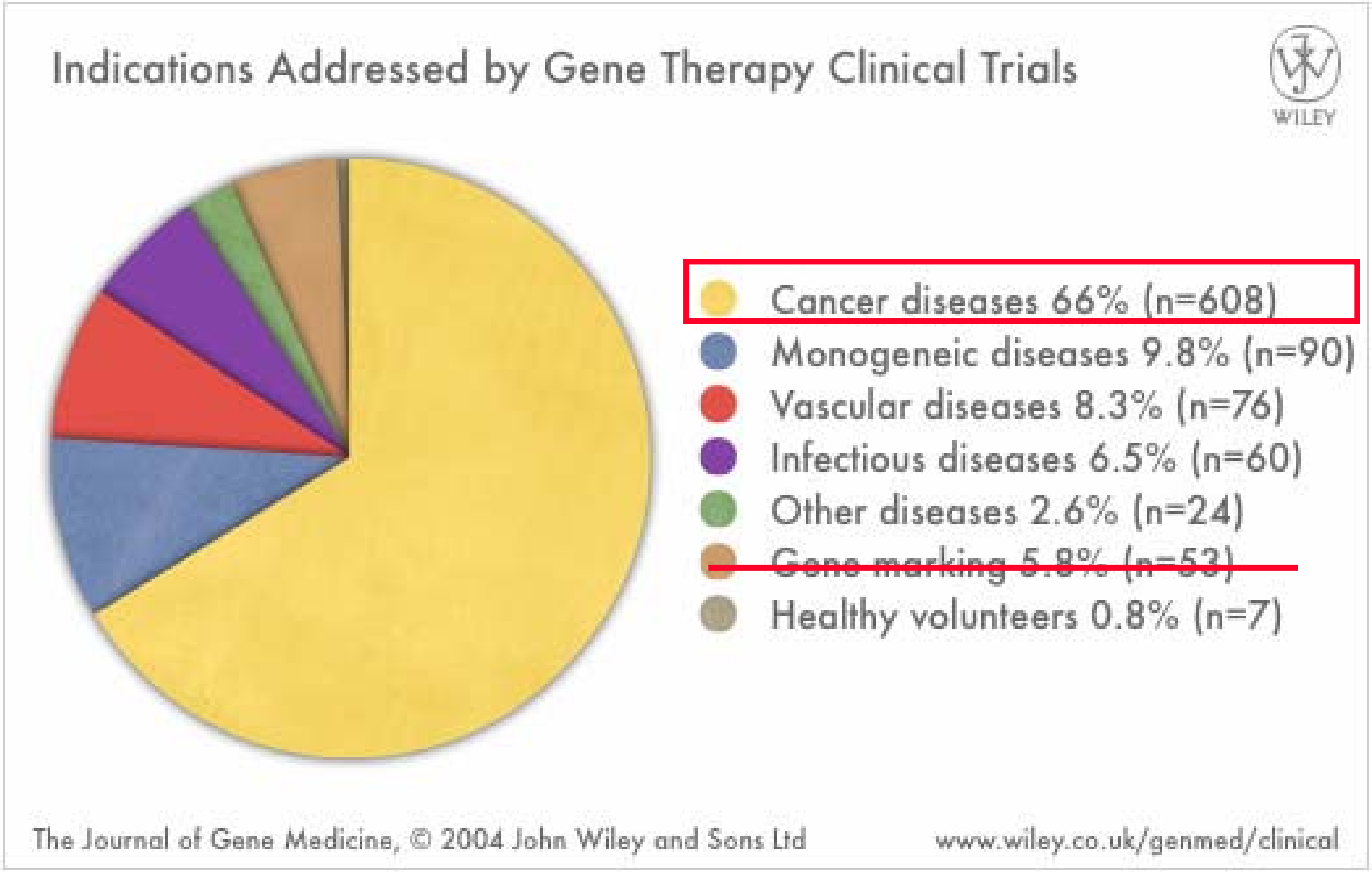
# Number of clinical GT trials in Europe: consolidation

(examplified by the development in Germany)

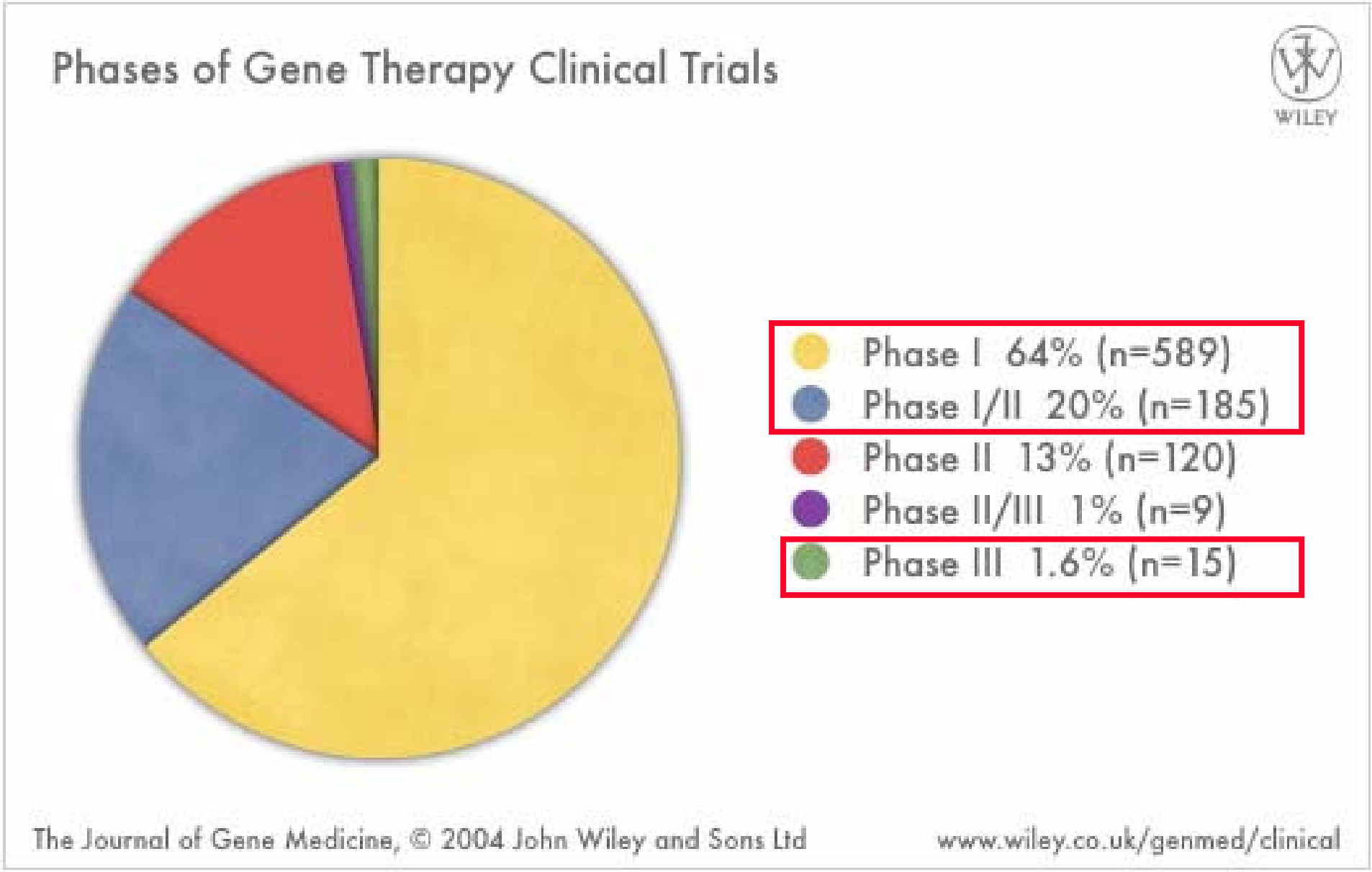
- general economic situation
- less industrial confidence in GT product success
- misinterpretation of regulatory action following SCID-X1 leukemias
- still constant clinical research in academia



# Cancer, cardio-vascular, monogeneic and infectious diseases are the main disease targets



# Most trials are phase I or I/II, few are phase III



# 69 clinical GT notifications were submitted, 58 clinical GT trials have been “approved” in Germany

| Disease or other application | No. |
|---|---|
| Cancer (immunotherapy) | 22 |
| Cancer (non immunotherapy) | 17 |
| Infectious disease (all HIV) | 7 |
| Monogenic inherited disorders | 1 |
| Cardio-vascular disease | 5 |
| Marker gene transfer | 5 |
| Others, e.g. rheumatoid arthritis | 1 |

**Deutsches Register für Somatische Gentransferstudien**
http://www.zks.uni-freiburg.de/dereg.html

# Gene therapy of cancer

| | Ex vivo | In vivo | Gamma-retroviral vector | Adenoviral vector | Naked nucleic acid | Packaged nucleic acid | Poxviral vector |
|---|---|---|---|---|---|---|---|
| Immuno-therapy | 14 | 7 | 3 | 1 | 2 | 12 | 3 |
| Non Immuno-therapy | 4 | 13 | 4 | 10 | | 3 | |

# Clinical progress in gene therapy

| | | | |
|---|---|---|---|
| • Adenosine deaminase deficiency | Adenosine deaminase gene (ada) | blood stem cells/ retroviral vector | 2 patients cured |
| • SCID-X1 | gamma-c-chain (IL-2R) | blood stem cells/ retroviral vector | 10 of 11 babies cured* |
| • Peripheral artery occlusive disease | Vascular endothelial growth factor (VEGF) | i.m./ plasmid DNA | improved vascularization |
| • Head and neck tumors | Conditionally replicating adenovirus, no transgene | tumor cells | local tumor regression |
| • Leukemia, graft versus host treatment | Herpes simplex virus thymidine kinase (HSV-tk) | T cells / retroviral vector | succesful graft versus host treatment |
| • Hemophilia B | Factor IX | i.m./ AAV vector | improved plasma levels |

*2 patients developed lymphoproliferative disease due to vector integration

# China approves first gene therapy

China became the first country to approve the commercial production of a gene therapy, and it is due to hit the market in early January. Despite technical hurdles and the wary attitude of regulatory authorities outside China, other countries are expected to soon follow suit.

On October 16, 2003, Shenzhen SiBiono GenTech (Shenzhen, China), obtained a drug license from the State Food and Drug Administration of China (SFDA; Beijing, China) for its recombinant Ad-p53 gene therapy for head and neck squamous cell carcinoma (HNSCC)—a cancer that accounts for about 10% of the 2.5 million annual new cancer patients in China. Sold under the brand name Gendicine, the world's first commercial gene therapy uses

"SiBiono's approach is not a trivial one," Jean-François Carmier, CEO of Transgene (Strasbourg, France) comments. "Introgen has been using a similar strategy for head and neck cancer and their product is showing encouraging results in Phase 3 trials" (see **Table 1**).

The success of SiBiono was in overcoming difficulties in developing the right system for delivering its adenoviral vector—considered an effective way of introducing a gene into tumor cells—without integrating the gene in the host cells' chromosomes and creating genetic alterations. SiBiono has addressed safety concerns by carefully dosing the injection (injecting a


Zhaohu Peng receives an approval certificate issued by China's State Food and Drug Administration for Gendicine, the world's first commercial gene therapy.

Nature Biotechnology, 2004

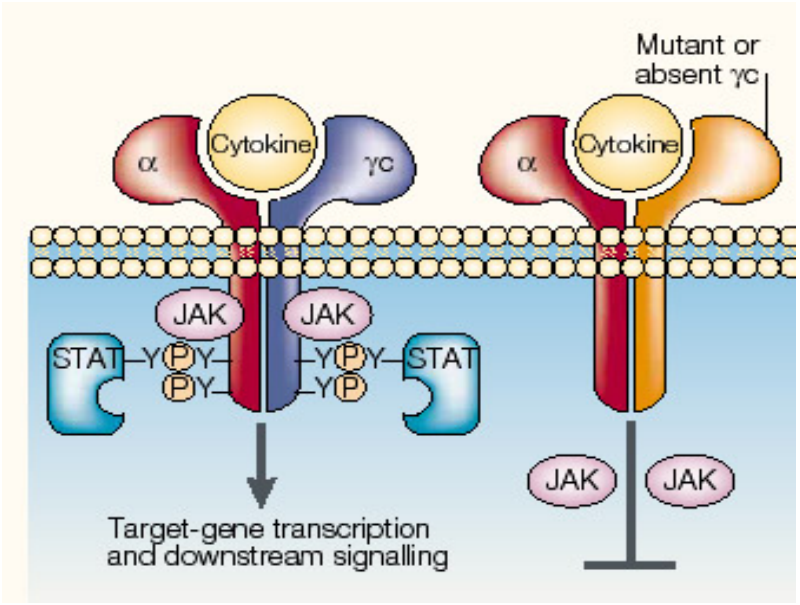
# Gene Therapy of X- SCID

**„Severe Combined Immunodeficency“**

- **defect in T- and B-cell development**
- **highly sensitive towards infections**

**Genetic defect in γC-chain**

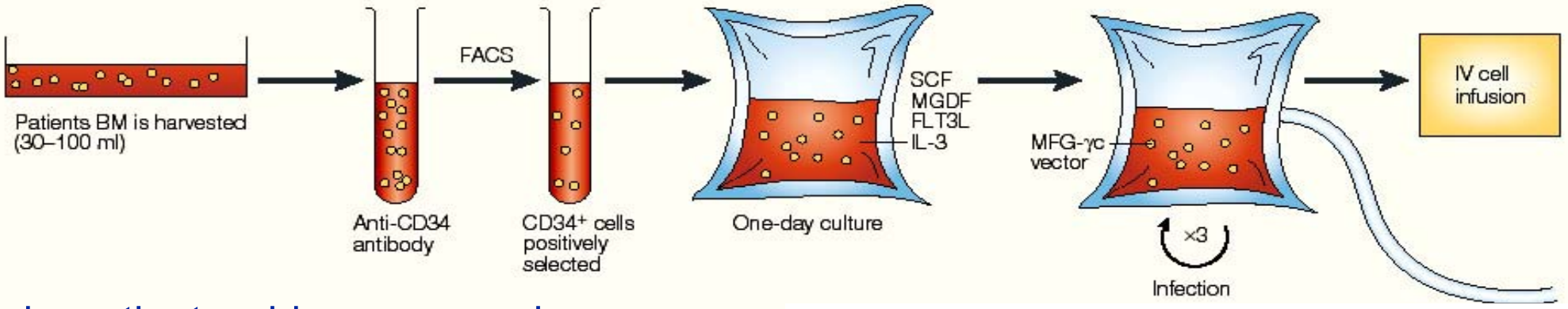
- **Cytokin receptor mutated or absent**
- **different ligands (IL-2, -4, -7, -9, -15, -21)**



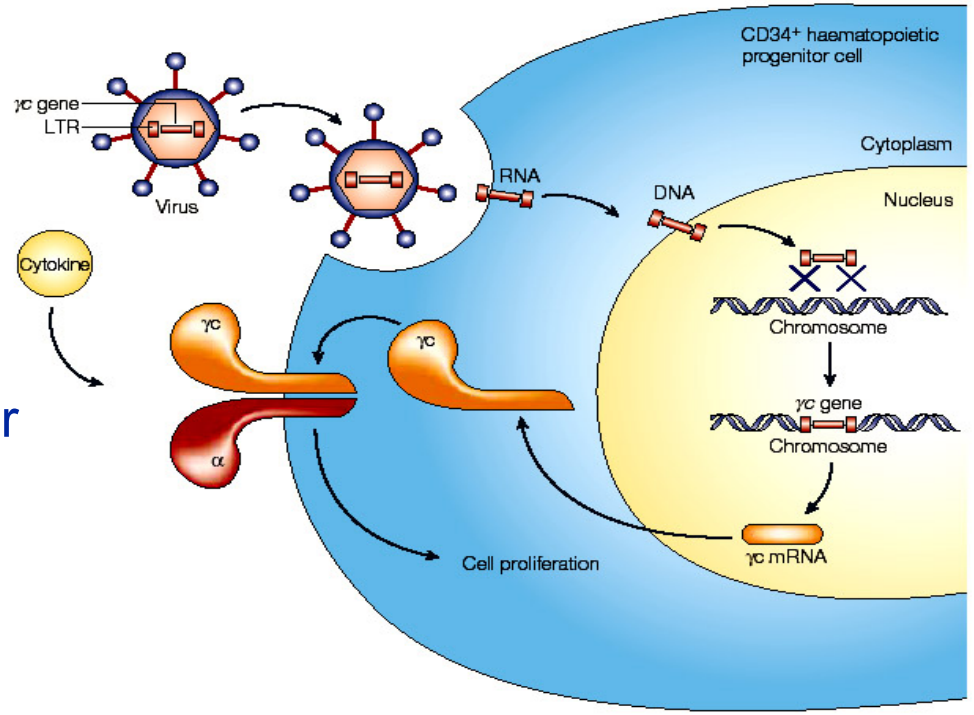

Fischer et al., 2002, Nature Rev Immunol. 2, 615

# Ex vivo gene transfer and SCID-X1 gene therapy

## Fischer et al., 2002

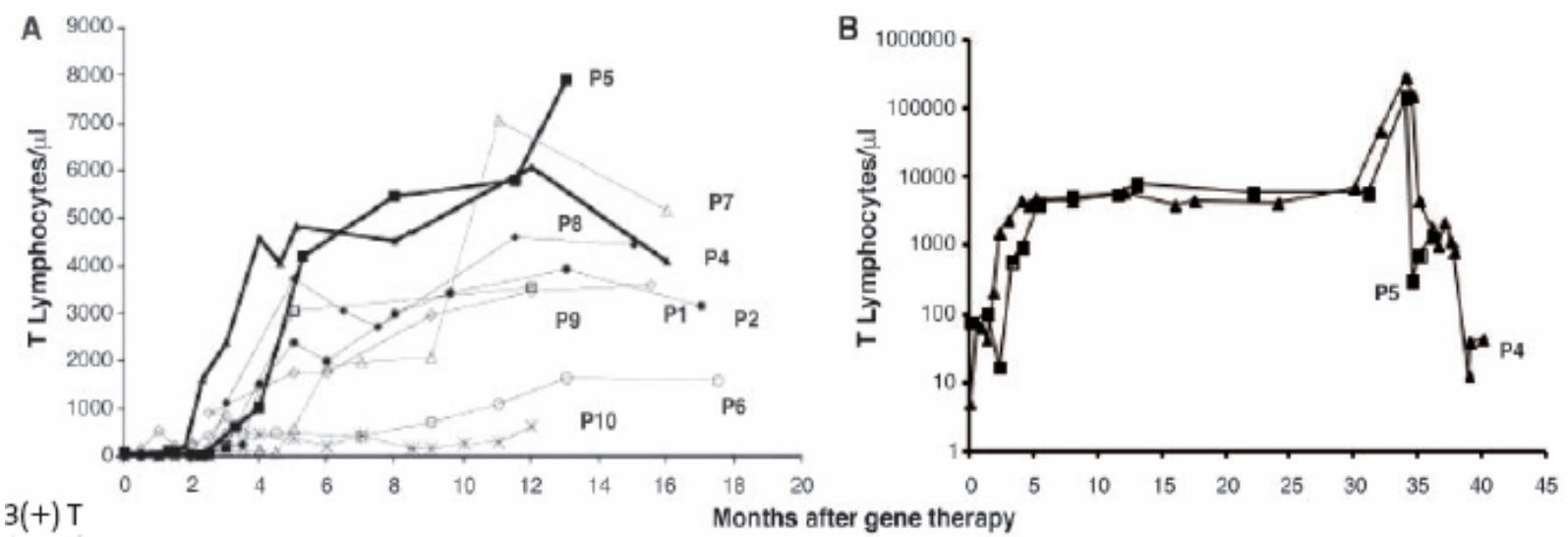



- investigator-driven approach
- mostly children < 1 year old
  with no available matched donor
- retroviral modification of CD34+
  bone marrow cells (~2x10$^8$ cells per kg)
- MLV-derived replication-incompetent vector
  (MLV(ampho) or MLV (GaLV))
- theoretical risk of insertional oncogenesis



9 of 10 patients but....

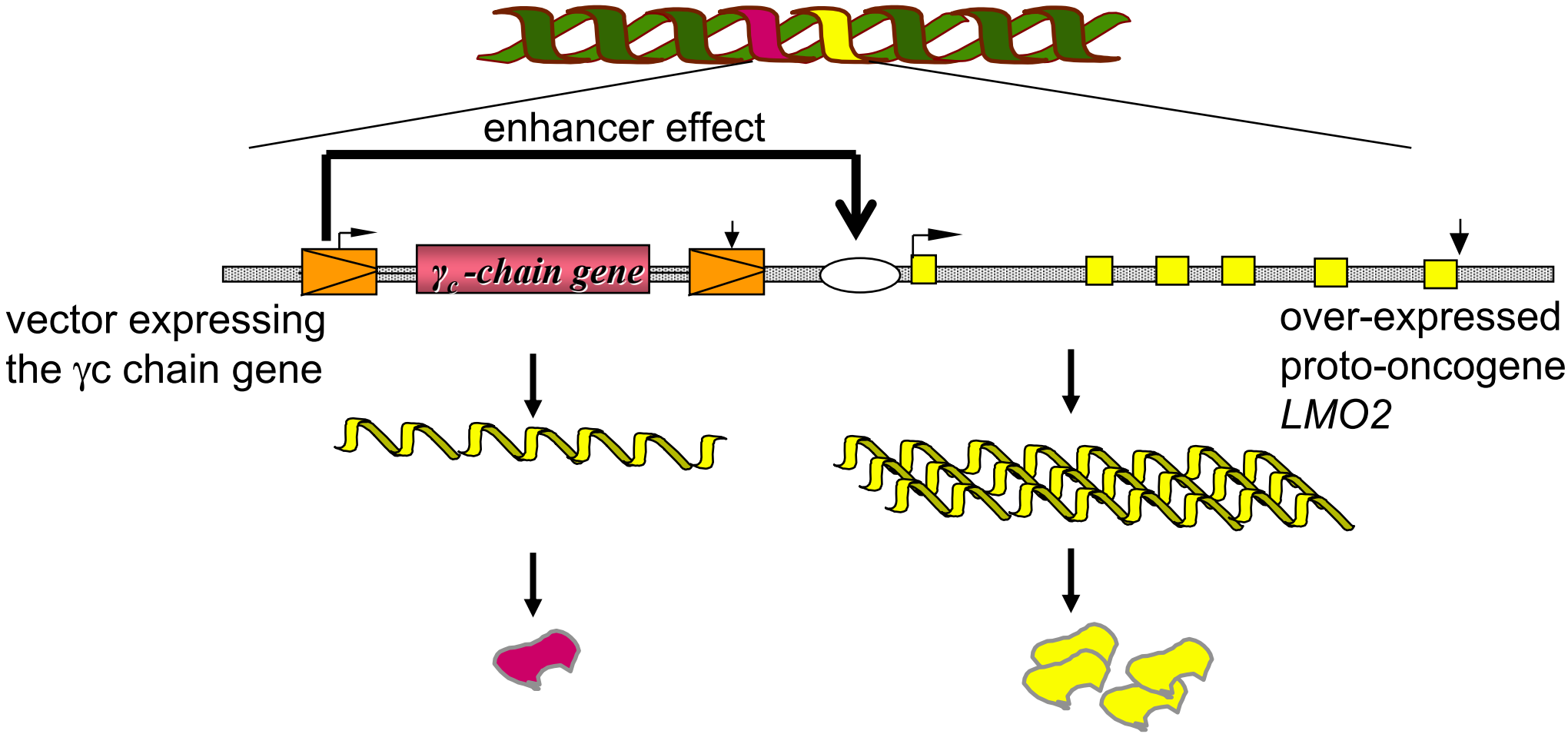
P4 and P5 treated at < 3 months of age developed lymphoproliferative disease




**Kinder mit Immunkrankheiten können die Außenwelt nur geschützt erkunden**

**Erfolg: vom Immundefekt SCID geheiltes Baby Shah Rayhman auf dem Arm seines Vaters**

# p-*onc* gene over-expression due to chromosomal integration of the retroviral expression vector



# Regulatory responses to leukemia-cases in 2002-2003

## United States

The FDA allows gene therapy trials for X-SCID if no other therapy is available. Clinical hold on other stem-cell gene therapy trials may be lifted after case-by case review.

- www.fda.gov/ohrms/dockets/ac/03/minutes/3924M2.doc

## United Kingdom

Approved clinical SCID trials are assessed on a case-by-case basis and are ongoing.

- www.doh.gov.uk/genetics/gtac/recommendationsGTAC-CSM.PDF

## France

After a temporary hold, the French reopened clinical studies for X-SCID in January 2004.

- afssaps.sante.fr

## Italy

Moratorium on any clinical trial involving the use of retroviruses until December 31, 2003. New ruling is currently awaited.

- www.iss.it/sitp/scf1/comu/index.html

## Germany

After a temporary hold on all trials involving retroviruses, gene therapy trials for SCIDs and other diseases restarted February 2003.

- www.bundesaerztekammer.de/30/Ethik/80Themen/85KomSomGen

## Europe

No Europe-wide regulations. Although experts argue that stem-cell gene therapy trials should be allowed for life-threatening disorders after careful risk-benefit evaluation.

- www.emea.eu.int/index/indexh1.htm

# Lessons learned from insertional oncogenesis

- **Seems to be a practical issue only for SCID-X1 gene therapy, not others.**

  (2 of 11 babies developed leukemias, whereas in more than 3000 other patients treated with retroviral vectors tumor induction was not observed)

- **Points at necessity to check absence or level of chromosomal integration for expression vectors able to enter the nucleus of cells.**

Remember:
10 of 11 babies cured!
Two leukemia babies successfully treated by chemotherapy!

# Interesting developments (and problems!) in human gene transfer (1)

- **Lentiviral vectors**
  - human, primate or others
  - manufacture (transient or stable vpcs)
  - level of RCV testing
  - prerequisites of first use in humans
- **Adenoviral vectors**
  - understanding toxicity (Gelsinger case!)
- **Plasmid DNA**
  - absence of resistance genes
  - increased dosage, absence of integration

# Interesting developments (and problems!) in human gene transfer (2)

- **Cell targeting vectors**
  - replicating cell targeting MLV
  - tumor cell ablation (repl. adenov.)
- **Tumors induced following LNGFR-expression via MLV-derived vector in CD34+ cells (mice)**
- **Insertional oncogenesis in SCID-X1 trial**
  - vector integration near *LMO2* gene
  - map integration sites for retroviral and AAV vectors

# Balancing risk and benefit in gene therapy

Calculated risk: the use of viral vectors to deliver corrective genes to a patient can cause side effects.

# Regulatory groups in clinical gene transfer

- National competent authorities
  (FDA, MCA, PEI, AFSSAPS, others)
- National central expert or ethics committees
  (RAC, GTAC, Commission of Somatic Gene Therapy, others)
- International groups
  - WHO Clinical Gene Transfer Monitoring Group
  - CPMP Gene Therapy Expert Group (GTEG) at EMEA
  - ICH Gene Therapy Discussion Group
  - WGs at NIBSC
  - Euregenethy
  - ASGT and ESGT Ethics Groups

# Scientific advice

- With a view to licensing via the centralized procedure:
  - EMEA
- In members states:
  - expert authorities
  - central ethics or expert committees