Challenges of Gene Therapy Medicinal Products

- Gene therapy medicinal products, a change of paradigm
- Gene therapy challenges
- EMEA/CHMP approach

Johannes Löwer
Klaus Cichutek
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Pre-ICDRA; “Improving World Health Through Regulation of Biological Medicines”
Seoul, 01-02 April 2006
A change in paradigm: nucleic acids as medicinal products

chemicals

\[
\begin{align*}
\text{Methotrexate} \quad & \quad \text{CH}_3 \quad \text{N} \quad \text{CH}_2 \quad \text{N} \quad \text{CH}_2 \quad \text{N} \quad \text{CH}_2 \quad \text{NH}_2 \\
\end{align*}
\]

recombinant proteins

\[
\begin{align*}
\text{EPO} \quad & \quad \text{COOH} \\
\text{EPObp2} \quad & \quad \text{EPObp1} \\
\end{align*}
\]

nucleic acids

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
A change in paradigm: nucleic acids as medicinal products

DNA → mRNA → Proteins

- Antisense Drug (Oligonucleotide)
- Traditional Drug

DISEASE

nucleic acids

oligonucleotides

siRNA

genomes

gene therapy
Using genes for the natural production of RNA or protein in somatic cells.
Gene Therapy Medicinal Products
(preventive, therapeutic, in-vivo diagnostic use)

vectors, nucleic acids, replicating micro-organism (not including live vaccines)

Direct application:
- viral vector
- non-viral vector
- naked DNA
- replicating rec. micro-organism (adenovirus, Salmonella)
Gene Therapy Medicinal Products
(preventive, therapeutic, in-vivo diagnostic use)

- genetically modified human cells
- vectors, nucleic acids, replicating micro-organism (not including live vaccines)

1) Isolation of the target cells (autologous or allogeneic)
2) Gene transfer
3) Re-Infusion of the genetically modified cells

Direct application:
- viral vector
- non-viral vector
- naked DNA
- replicating rec. micro-organism (adenovirus, Salmonella)

- cell line
- cell
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Principle issues in designing a successful gene therapy strategy

• Choice of gene/genetic strategy
  • gene correction
  • gene substitution
  • new function of cell
    • immunological
    • metabolical
    • pharmacological

• Delivery of the gene to the target cell
  • route of administration
  • proliferating or quiescent cells
  • Delivery into cytoplasm or nucleus

• Design of the expression vector
  • adequate duration of expression
  • adequate amount of gene product
  • absence of risks from expression vector, e.g., chromosomal integration, recombination etc.
Gene therapy

- Gene transfer medicinal products are diverse:
  - cells, viral vectors, non viral vectors, microbes or nucleic acid

- Applications include a variety of diseases:
  - monogeneic inherited disease,
  - cancer,
  - cardiovascular disease,
  - infectious disease.

- Specific scientific knowledge and regulatory expertise has to be available.

**Disease or other application**

- Cancer (Immunotherapy)
- Cancer (Non-Immunotherapy)
- Infectious disease (HIV, HBV)
- Monogeneic inherited disorders
- Cardio-vascular disease
- Marker gene transfer
- Others, e.g. rheumatoid arthritis
Adv-VEGF application for neovascularization

- angiogenic genes: FGF, VEGF, andere

- adenoviral vectors:
  - ΔE1, ΔE2, ΔE4
  - NO-inducing genes

risks:
- acute inflammatory reaction
- cancer (therapeutic gene)
- neo-angiogenesis (therapeutic gene)
Tumour vaccines

Theoretical risks:
- Inflammation
- Auto-immune disease
Conditionally replicating oncolytic virus: ICH Workshop Chicago (November 2005)

Virus engineered to direct their cytotoxicity towards cancer cells

Theoretical advantages:
- viral replication within tumor mass allows infection of additional cells
- lack of cross-resistance with standard therapies
- ability to cause tumor destruction by different mechanisms

Theoretical risks:
- introduction of new pathogens into the human population and adaptation
Retrovirally modified blood stem cells in SCID

benefit in 23 of 28 patients

3 leukemias in a SCID-X1 trial (P4, P5 und P10)

practical risk/side effect: insertional oncogenesis

new measures:
monitoring patients for delayed adverse events (longterm follow-up)
DNA and vectored vaccines

- plasmid DNA
- AAV
- MVA
- Vaccinia
- adenoviral vectors

theoretical risks:
cancer
auto-immune disease

clinical trials in healthy volunteers
Principle regulatory issues in gene therapy

- Replication-competent virus generated in helper cell
  - RCR initially detected, batches not released
  - RCA accepted to a certain extent in cancer
  - RCL discussion on-going
  - safer packaging cell lines in use

- Direct effects of vector particles
  - acute DIC induced by adv following systemic use of high titers
  - liver toxicity of AAV particles in seropositives due to immune effects

- Non-target effects of vector or gene product
  - biodistribution of vector after in vivo delivery
  - inadvertant germline transmission
  - retinal neoplasm by circulating FGF
  - retinal neovascularization by circulating VEGF
  - leukemia induced by vector insertions

- Complexity of the technology
  - various vectors (>6)
  - various genes (30,000)
  - various gene applications (3) (protein, antisense, ribozyme)
  - various disease applications (common and rare)
  - various treatment strategies
  - preventive, therapeutic, in vivo diagnostic
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EC/EMEA actions concerning gene therapy products

• Workshop on gene therapy 1998:
  • representatives from competent authorities in the Member States, patients organisations, European Commission, European Parliament

• Note for guidance on the quality, preclinical and clinical development of gene transfer medicinal products (CPMP/BWP/3088/99)
  • released for consultation in 2000 and finalised in April 2001

• CPMP Gene Therapy Expert Group/ CHMP Gene Therapy Working Party
  • formed “ad-hoc” in September 2001, established in January 2003
  • CHMP Gene Therapy Working Party since 2005

• CPMP Position Statement on Development and Manufacture of Lentiviral Vectors (CPMP/BWP/2458/03)

• Gene therapy product definition and technical requirements set out in the EU legislation 2003
  • Directive 2003/63/EC establishing the new Annex 1, Part IV (Advanced therapy products), to Directive 2001/83/EC
• Scientific Reports on Insertional Oncogenesis (January and June 2003, GTWP)
  • EMEA/CHMP/183989/04 Report from the CHMP Gene Therapy Expert Group Meeting 14-15 October 2004
  • EMEA/CHMP/127803/04 Report from the CHMP Gene Therapy Expert Group Meeting 17-18 June 2004
  • EMEA/CPMP/1879/04 Report from the CPMP Gene Therapy Expert Group Meeting 26-27 February 2004
  • EMEA/22880/03 Report from the Ad hoc meeting of CPMP Gene Therapy Expert Group 26-27 June 2003
  • EMEA/5382/03 Report from the Ad hoc meeting of CPMP Gene Therapy Expert Group 23-24 January 2003
  • One published as a scientific paper in J. Mol. Med.

• EMEA Training of Assessors in Gene Therapy (2004; GTWP)

• Consultations with external experts (regularly in 2003 – 2005; GTWP)

• Concept Paper on Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products (Released for Consultation November 2005) (GTWP) EMEA/CHMP/203831/05

• Concept Paper on the Development of a Guideline on the Non-Clinical Studies prior to Clinical use of Gene Therapy Medicinal Products (Released for Consultation November 2005) (GTWP) EMEA/CHMP/GTWP/203821/05

• Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products - Annex on Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors (Released for Consultation November 2005) (GTWP) EMEA/273974/05

• ICH Considerations. Workshops during ICH Conferences, ICH-GTDG
CHMP Gene Therapy Working Party (GTWP) members harmonize scientific views in gene therapy

- Core members
  - GTWP chair
  - MS regulators with GT expertise
  - CHMP WP representatives

- Consultation of gene therapy experts
  - from academia
  - from industry

- MS contact persons
  - form EU national competent authorities

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
Draft decision tree: non-clinical germline transmission studies prior to first use of vector/DNA in non-sterile patients/subjects

Studies resulting in a negative answer to the respective question listed in one of the squares should be followed by considering further testing as indicated. However, additional studies are not mandatory, but should be considered taking into account the parameters described in the text.
Medicinal product responsibility of the Paul-Ehrlich-Institut
Innovative biotechnology medicinal products

- Gene Transfer Medicinal Products: (vectors, DNA, gen. mod. cells, micro-org.)
- Somatic Cell Therapy MPs: (human cells; immunotherapy)
- Tissue Engineering MPs: (human cells incldg. stem cells)
- Xenogeneic Cell Therapy MPs: (xenogeneic cells)

Medical Biotechnology

- Licensing, scientific advice
  - Dev. of NfGs (EMEA)
  - Gene Therapy Expert Group (EMEA-GTEG)
  - WHO Clinical Gene Therapy Monitoring Group

- Clinical trial, manufacture
  - Commission of Somatic Gene Therapy
  - Clinical trial approval
  - Inspections

Basic scientific research

- Retrovirology: (HIV / SIV and HERV / PERV)
- Gene therapy: (AIDS and tumor gene therapy)
- Cell therapy/TE: (Signal transduction, stem cell diff.)
The End
First gene therapy product on Chinese market

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

“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

Zhaohu Peng receives an approval certificate issued by China’s State Food and Drug Administration for Gendicine, the world’s first commercial gene therapy.
Ark Therapeutics Grp - Regulatory Application

RNS Number: 29047
Ark Therapeutics Group PLC
28 October 2005

Cerepro™ Marketing Authorisation Application

Review Commences in Europe

- Dossier for potentially the world’s first gene therapy product 1 accepted by EMEA as ‘valid’ -

28 October 2005: Ark Therapeutics Group plc ('Ark') today announces that its Marketing Authorisation Application (MAA) for Cerepro™, a novel gene-based therapy for operable malignant glioma (brain cancer), has been filed with the European medicines regulatory authority, the EMEA, and that the application has been accepted for review.

The application for Cerepro™, a designated Orphan Drug, has met the submission requirements of the important validation stage, and formal review by the regulators has commenced. Earlier in the year, the Company announced that the EMEA had appointed Rapporteurs to review the MAA via the centralised regulatory process, which is the standard route for all biologics, and more recently Ark has announced that its Finnish manufacturing facility had received a licence to manufacture Cerepro™ for commercial supply. The Company is also announcing in a separate press release today that it has commenced a corroborative study of Cerepro™, Study 904, in up to 250 patients.
### Recent progress in gene therapy

- **SCID-X1** gamma-c-chain (IL-2R) blood stem cells/9 of 11 babies
- **PAOD** VEGF i.m./improved vascularization

- **MLV vector** cured, 2 cases of leukemia
- Plasmid DNA
Recent progress in gene therapy

- head and cell-dep. repl. adenovirus, tumor cells local tumor
  neck tumors no transgene regression

- leukemia, HSV-tk success ful GvH D
graft versus treatment leukemia
treatment

- hemophilia B Factor IX improved plasma
  vector levels

  T cells/ MLV vector

  AAV