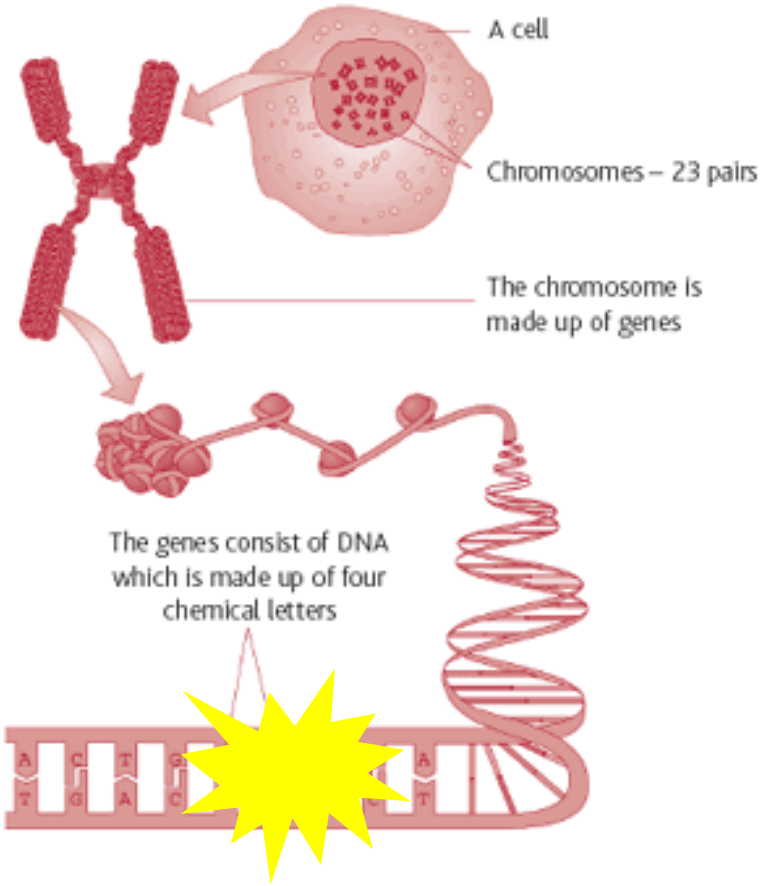
Gene and Cell Therapy entering Clinical Trials and Health Care

Gerard Wagemaker

Netherlands Society of Gene & Cell Therapy

V All-Russian Conference
"Current Issues of Pre-clinical and Clinical Trials of Drugs, Biomedical Cell Products and Clinical Tests of Medicinal Production"

Rare, inherited diseases



A single mutation in the code may have profound effects at the level of the organism

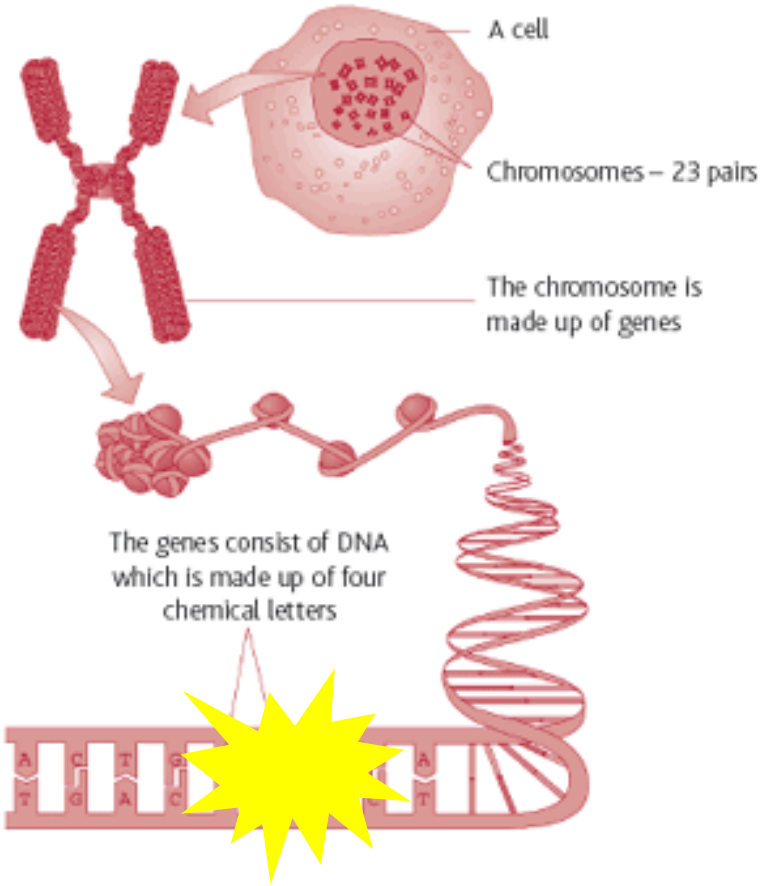
In humans, appr. 7,500 inherited diseases have been identified; the genetic defect has currently in about 40% been identified.

Although individually (very) rare, in total an estimated 24 million people in the European Union are affected by an inherited rare disease based on a genetic defect.

For most, a curative treatment is not available, treatment being symptomatic, with adaptations in living and work environments, and eventually intensive nursing and care.

Healthcare costs are excessive.

Rare, inherited diseases



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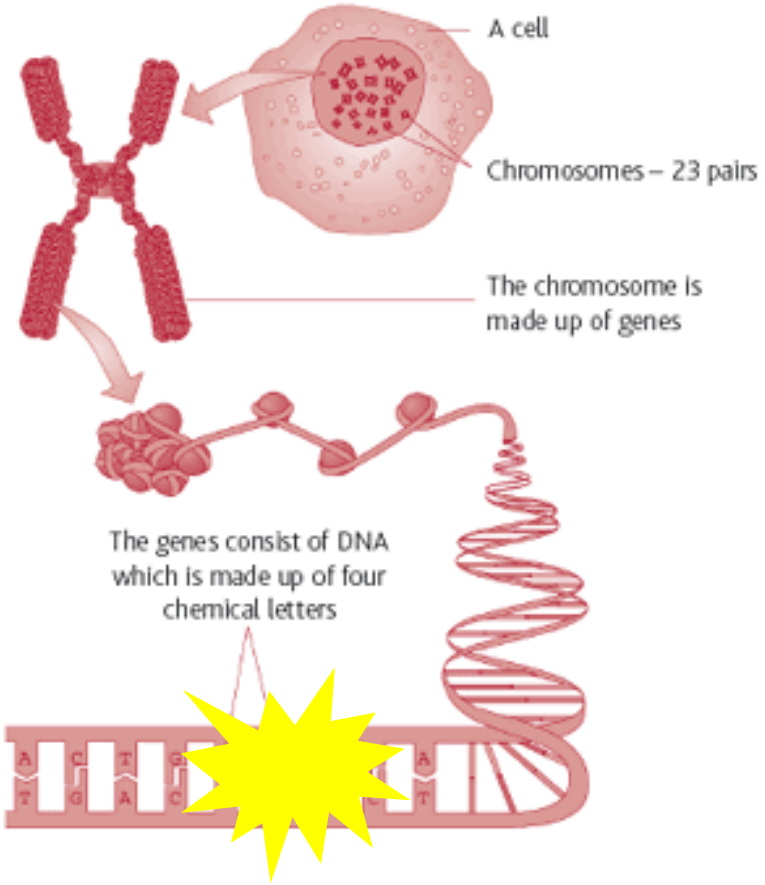
In humans, appr. 7,500 inherited diseases have been identified; the genetic defect has currently in about 40% been identified.

Approaches:

- *preconceptional, prenatal and postnatal diagnosis & genetic counseling – whole genome sequencing*
- *symptomatic therapy*
- *replacement therapy*
- ***correction of the defect: gene therapy***

Rare, inherited diseases



Current hematopoietic stem cell gene therapy development:

- ***Inherited immune deficiencies***
- ***Lysosomal storage disorders***
- *Selected mitochondrial disorders*
- *Sickle cell anemia*
- *Thalassemia*

- *Hemophilia, especially refractory F VIII deficiency (hemophilia A)*

A single mutation in the code may have profound effects at the level of the organism

Outline

- Historical background
- Preclinical efficacy and safety evaluation of stem cell gene therapy:
  - Primary immune deficiencies
  - Hurler syndrome
- Current developments in gene therapy
- Cellular therapies
- Regulatory issues

Some history: development of BMT for SCID

in collaboration with the Leiden University Dept. of Pediatrics

Dooren LJ, de Vries MJ, van Bekkum DW, Cleton FJ, de Koning J. Sex-linked thymic epithelial hypoplasia in two siblings. Attempt at treatment by transplantation with fetal thymus and adult bone marrow. J Pediatr. 1968 Jan;72(1):51-62.

THE LANCET

Volume 293, Issue 7608, 21 June 1969, Pages 1223–1227
Originally published as Volume 1, Issue 7608

ORIGINAL ARTICLES

TRANSPLANTATION OF BONE-MARROW CELLS AND FETAL THYMUS IN AN INFANT WITH LYMPHOPENIC IMMUNOLOGICAL DEFICIENCY

J. De Koning, D.W. Van Bekkum, K.A. Dicke, L.J. Dooren, J.J. Van Rood, J. Rádl

Some history: development of BMT for SCID

THE LANCET, NOVEMBER 8, 1986

BONE-MARROW TRANSPLANTATION FOR IMMUNODEFICIENCIES AND OSTEOPETROSIS: EUROPEAN SURVEY, 1968–1985

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First 162 SCID patients transplanted

Severe combined immune deficiency: SCID

“Bubble boy” (David Vetter)

- *Children born without cellular and humoral immunity*
- *Frequency (best estimate) 40-100 per year (USA)*
- *Treated since 1969 (Leiden, Minneapolis) by allogeneic bone marrow transplantation, currently medical standard treatment*
- *Problem: at present birth rate, 80-90% of the patients have no HLA matched sibling/family donor available*
- *Non-identical donors or mismatched family donors poor results, both in survival as well as in immune reconstitution:*

unmet medical need, gene therapy justified

Some history: development of BMT for SCID

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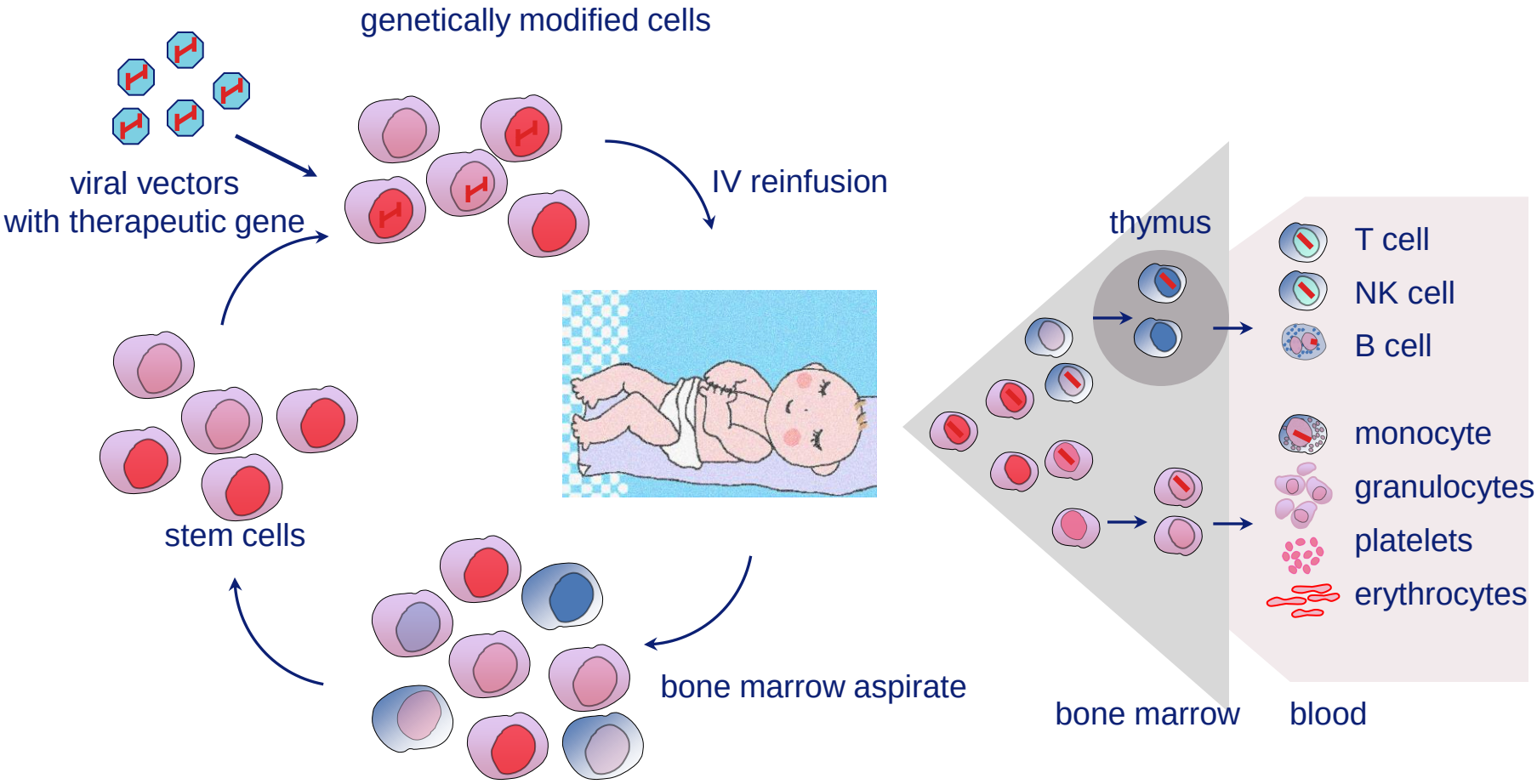
Seminal gene therapy trials X-linked SCID

Ex vivo stem cell gene therapy of autologous hematopoietic stem cells



X-SCID as a paradigm for HSC gene therapy development

- Results superior to allogeneic stem cell transplantation both in efficacy as well as in over-all survival
- But: autonomous T cell clones leading to leukemia in 5 patients

Pathogenesis of leukemia after HSC gene therapy

- Preferential integration of the retroviral vectors near proto-oncogenes, resulting in aberrant expression, driven by the retroviral promoter/enhancer of the therapeutic transgene, resulting in a preleukemic state

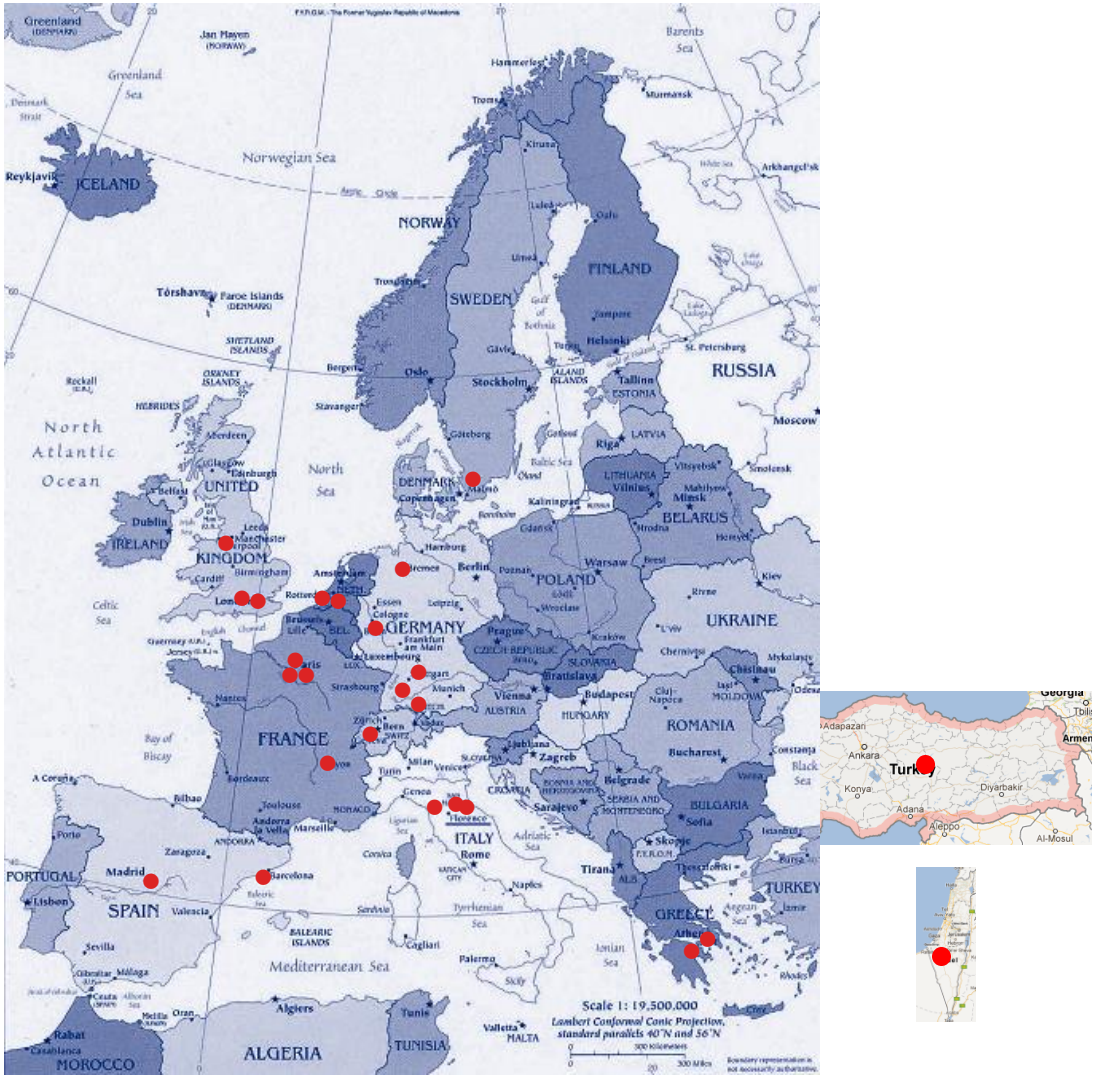
Remedy

- The original vectors, derived from *mouse leukemia retroviruses*, have been replaced by *self-inactivating (SIN) HIV-1 derived lentiviral vectors*, that do not have a preference for integration near proto-oncogenes.

Prospect

- Developed from 2002-2010, the lentiviral vectors are currently evaluated in clinical trials for Wiskott-Aldrich, X-linked SCID, ADA-SCID, adrenoleukodystrophy and metachromatic leukodystrophy.

Stem cell gene therapy for inherited disorders: EU collaboration 2002-2016



Sixth Framework Programme

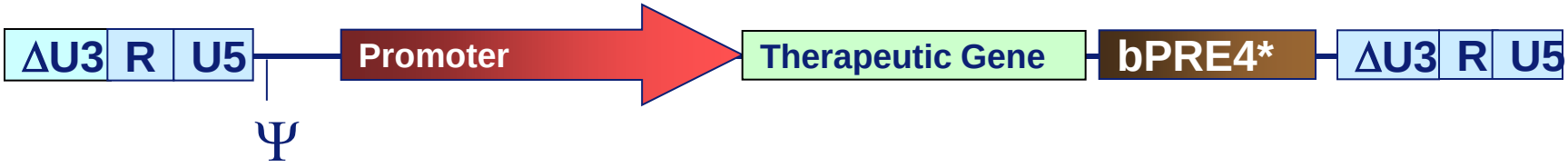
SEVENTH FRAMEWORK PROGRAMME

HIV-1 derived SIN lentiviral vectors

HIV-1 derived SIN lentiviral vectors display a reduced risk pattern

- Able to integrate into quiescent cells (short incubation time)
- Deletion of enhancer regions from the LTRs reduces risk of influencing neighbouring genes (SIN)
- Biased integration into actively transcribed genes but no bias towards transcription start sites or proto-oncogenes

Third generation SIN lentiviral vectors:

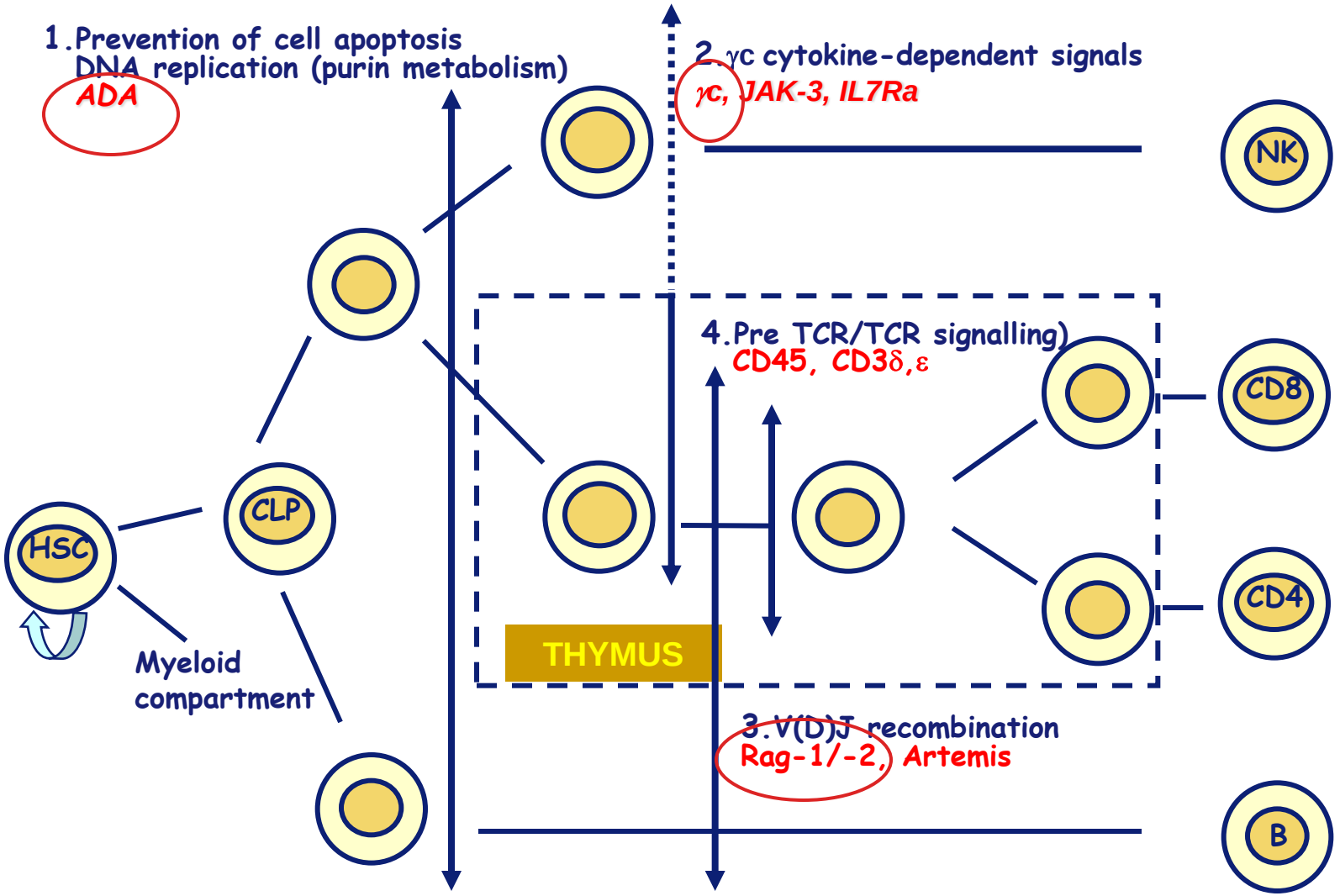


Essential: *Promoter choice* *Codon optimization*

Schambach A et al, Gene Ther. 2006

Development of lentiviral stem cell gene therapy for primary immune deficiencies

SCID diseases



Slide by A. Fischer

Efficacy and safety of lentiviral stem cell gene therapy

Conclusion:

- Codon optimization of the therapeutic transgene and appropriate promoter choice result in complete phenotype correction in X-linked SCID and RAG2 deficiency mice
- Both disease entities ready for clinical implementation: London, respectively Ankara

Marshall W. Huston, Niek P. van Til, Trudi P. Visser, Shazia Arshad, Martijn H. Brugman, Claudia Cattoglio, Ali Nowrouzi, Yuedan Li, Axel Schambach, Manfred Schmidt, Christopher Baum, Christof von Kalle, Fulvio Mavilio, Fang Zhang, Mike P. Blundell, Adrian J Thrasher, Monique M.A. Verstegen, and Gerard Wagemaker. Lentiviral gene therapy of murine hematopoietic stem cells using a native IL2RG promoter region and low-dose pre-transplant conditioning corrects the SCID-X1 phenotype. Mol Ther. 2011 Oct;19(10):1867-77

van Til NP, de Boer H, Mashamba N, Wabik A, Huston M, Visser TP, Fontana E, Poliani PL, Cassani B, Zhang F, Thrasher AJ, Villa A, Wagemaker G. Correction of Murine Rag2 Severe Combined Immunodeficiency by Lentiviral Gene Therapy Using a Codon-optimized RAG2 Therapeutic Transgene. Mol Ther. 2012 Jun 12.

Huston MW, Brugman MH, Horsman S, Stubbs A, van der Spek P, Wagemaker G. Comprehensive investigation of parameter choice in viral integration site analysis and its effects on the gene annotations produced. Hum Gene Ther. 2012 Nov;23(11):1209-19.

Development of lentiviral stem cell gene therapy for lysosomal enzyme deficiencies

Lysosomal storage disorders – gene therapy development

Some 40 lysosomal enzyme deficiencies known

Allogeneic HSC transplantation established or experimental:

Adrenoleukodystrophy (ALD)	*Paris (clin.trial)*
Hurler disease (MPS I)	*Milan/Utrecht/Rotterdam*
Krabbe disease (GLD)	*Milan*
Metachromatic leukodystrophy (MLD)	*Milan (clin.trial)*
(Gaucher disease	*Lund)*

Allogeneic HSC transplantation not effective:

Pompe disease	*Rotterdam*

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Allogeneic HSC transplantation not effective:

Pompe disease	*Rotterdam*

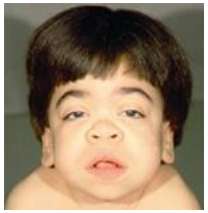
Hurler disease

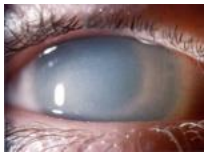
Mucopolysaccharidosis – storage of GAGs

MPS I **Hurler/Hurler-Scheie/Scheie disease**

α-Iduronidase (IDUA) deficiency

Storage of GAGs





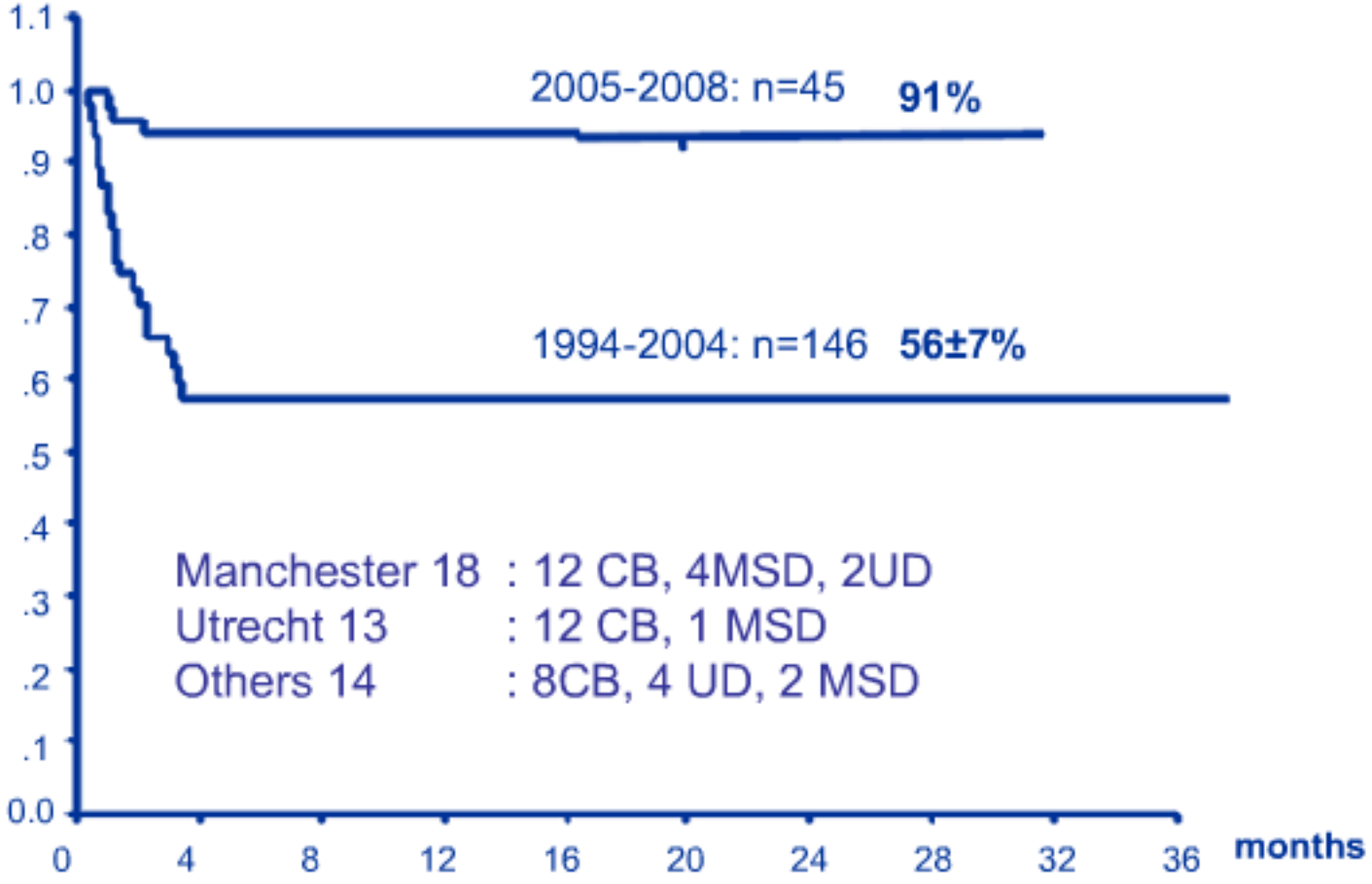
Current treatment - Hurler

▪ ***Enzyme replacement therapy (ERT)***	enzyme does not pass blood-brain barrier, insufficient to prevent skeletal deformities
▪ ***HSCT***	satisfactory results
▪ ***ERT- cord blood HSCT***	currently optimal with satisfactory outcome in survival but highly variable results in mental performance, and fails to alleviate skeletal deformities

EFS in Europe 2005-2008

After introduction of EBMT protocol

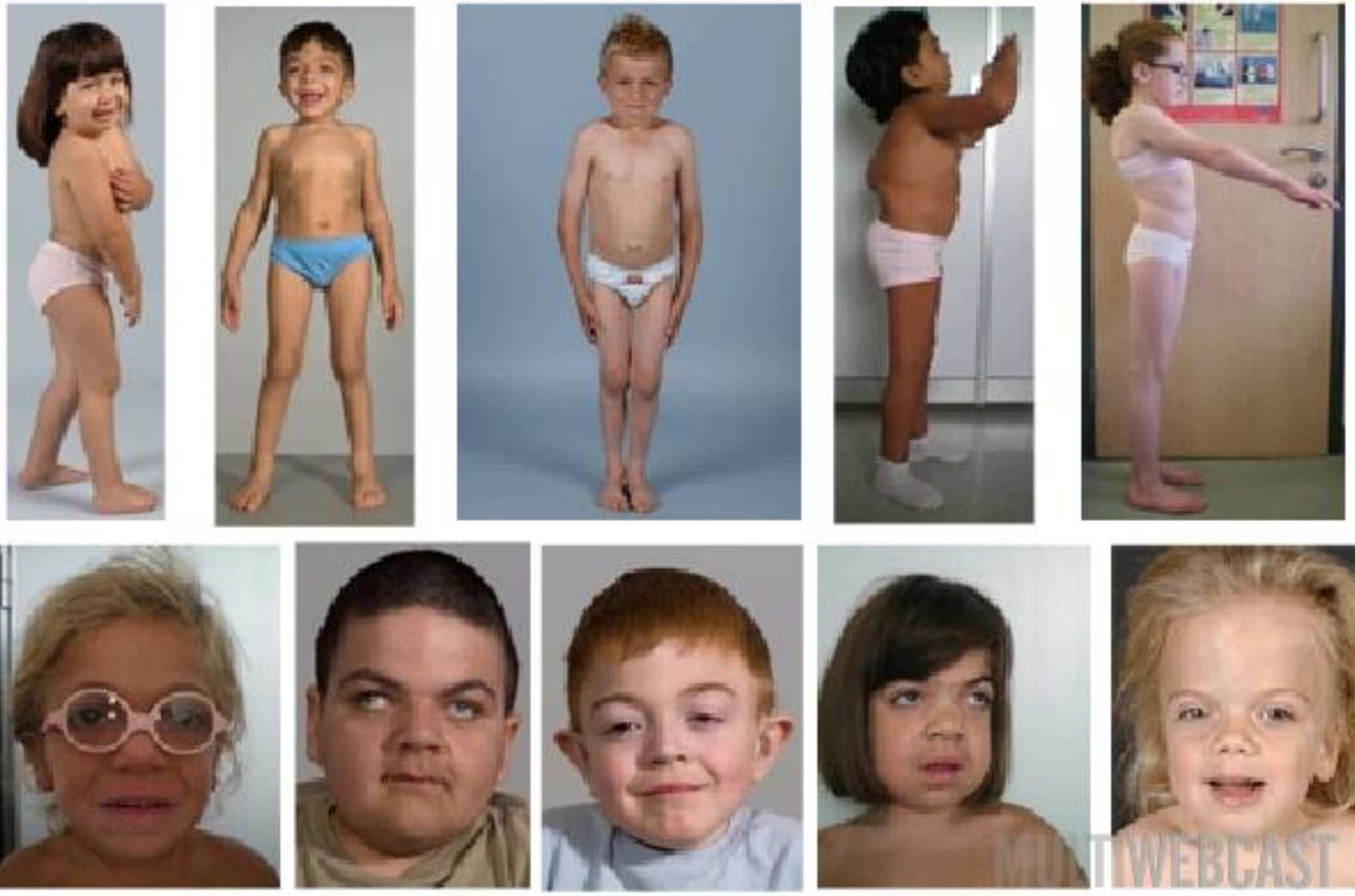
Universitair Medisch Centrum Utrecht



Hurler syndrome post-SCT

High variability! Residual Disease Burden

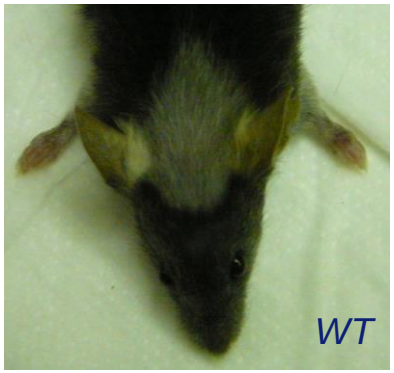
Universitair Medisch Centrum Utrecht

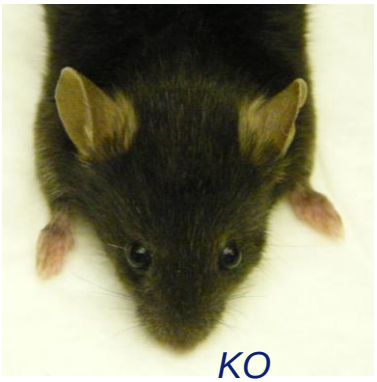


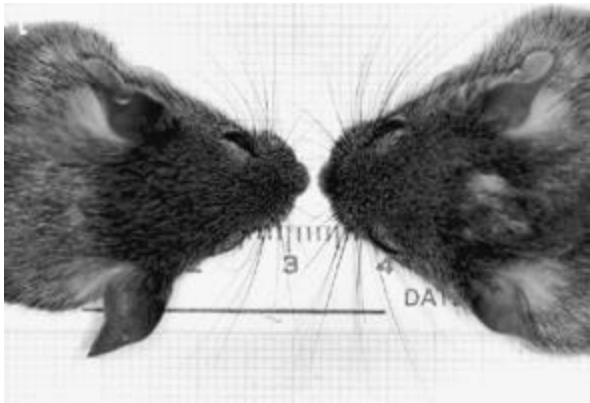
Slide: J.J. Boelens

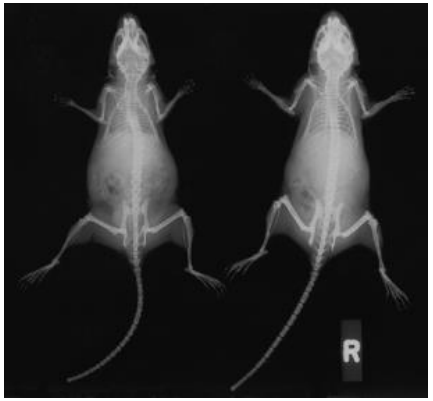
Stem cell gene therapy - Hurler (MPS-I) mouse

KO for IDUA gene
Symptoms visible at 4 weeks
Thickened paws
Closure of the eyes with some mucus
Broadened cranium, shortened
snout, protruding nasal bridge
and widely set eyes
Limited mobility
Reduced fertility
Early death, about 48 weeks
(wildtype 85 weeks)





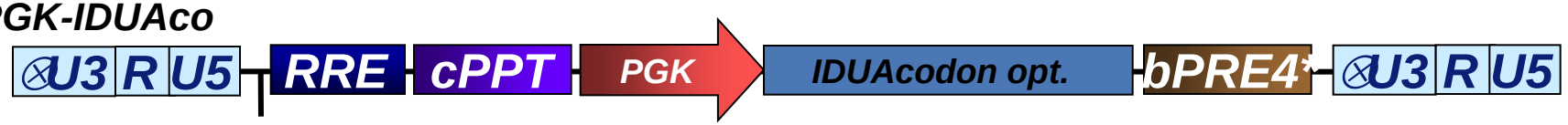




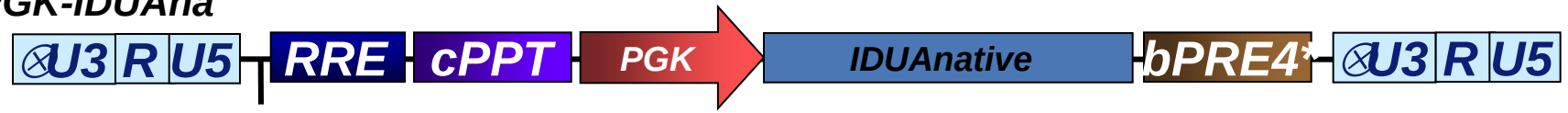
Ohmi, Neufeld, PNAS 2003

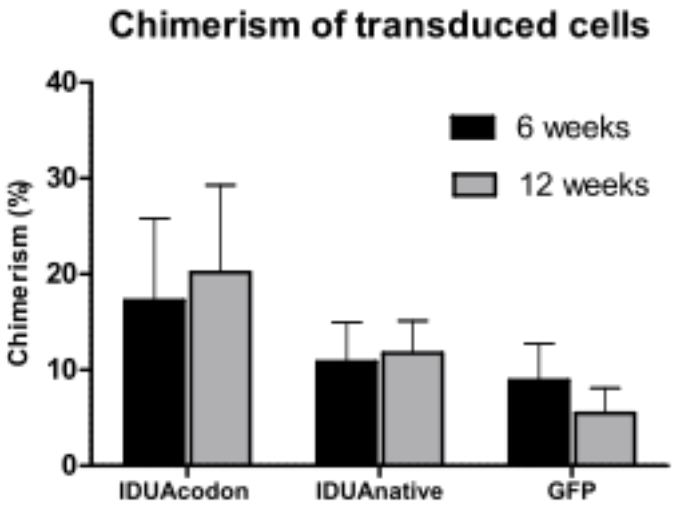
Comparison IDUA codon optimized and IDUA native (*in vivo*)

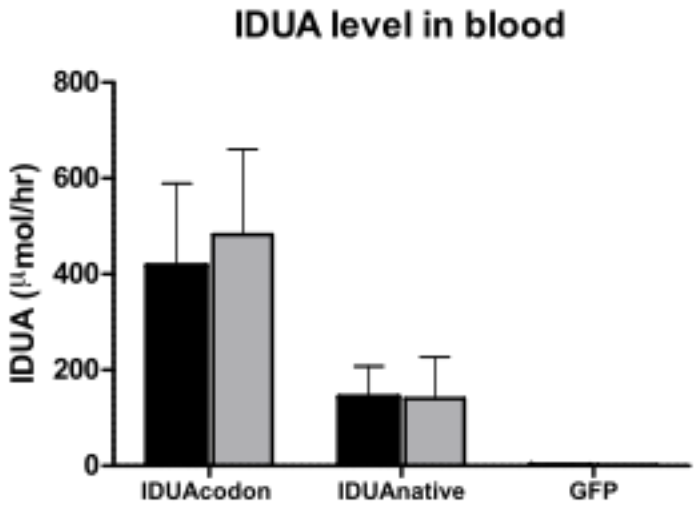
LV-PGK-IDUAco



LV-PGK-IDUAna

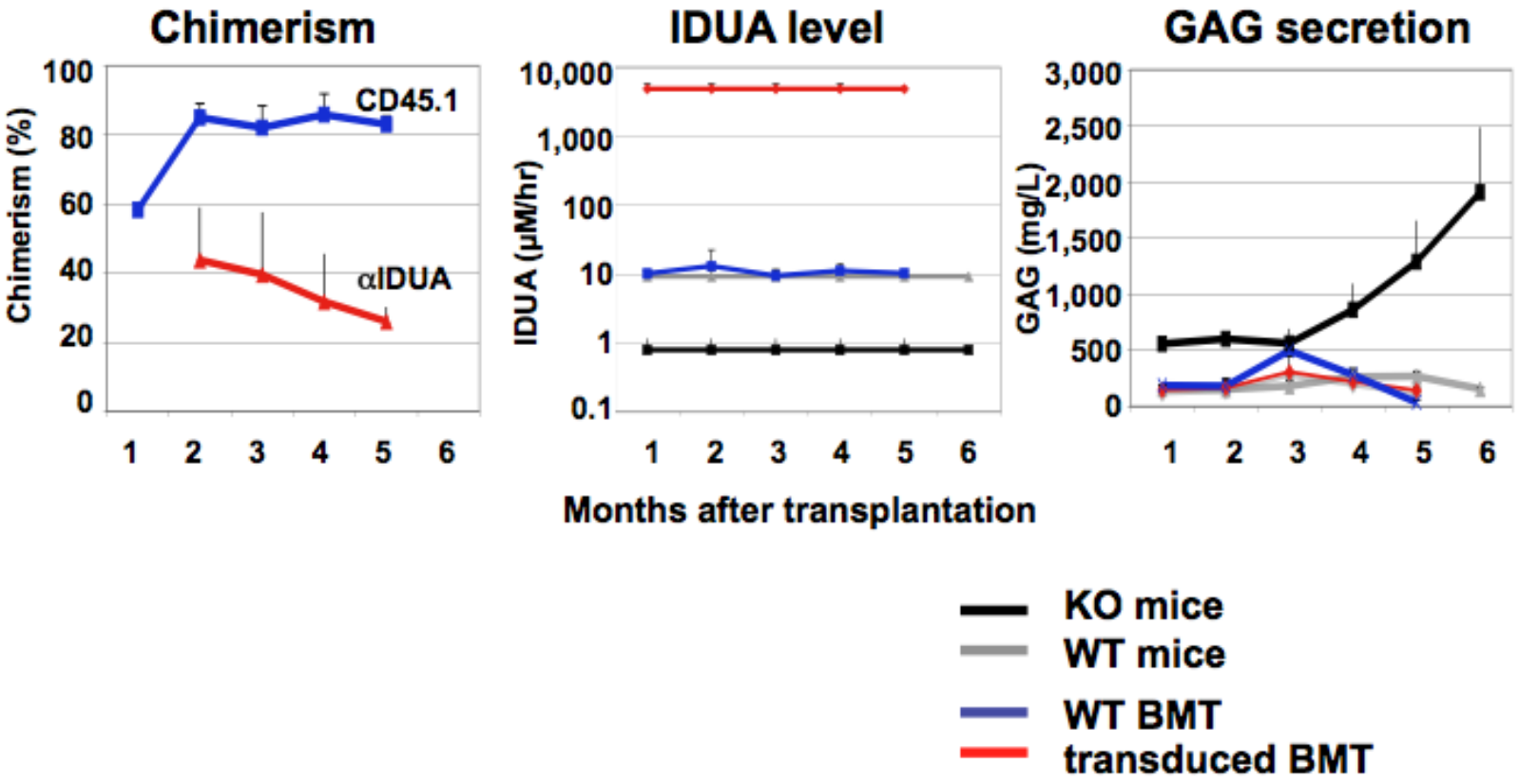






WT mice 10 ⁄mol/hr

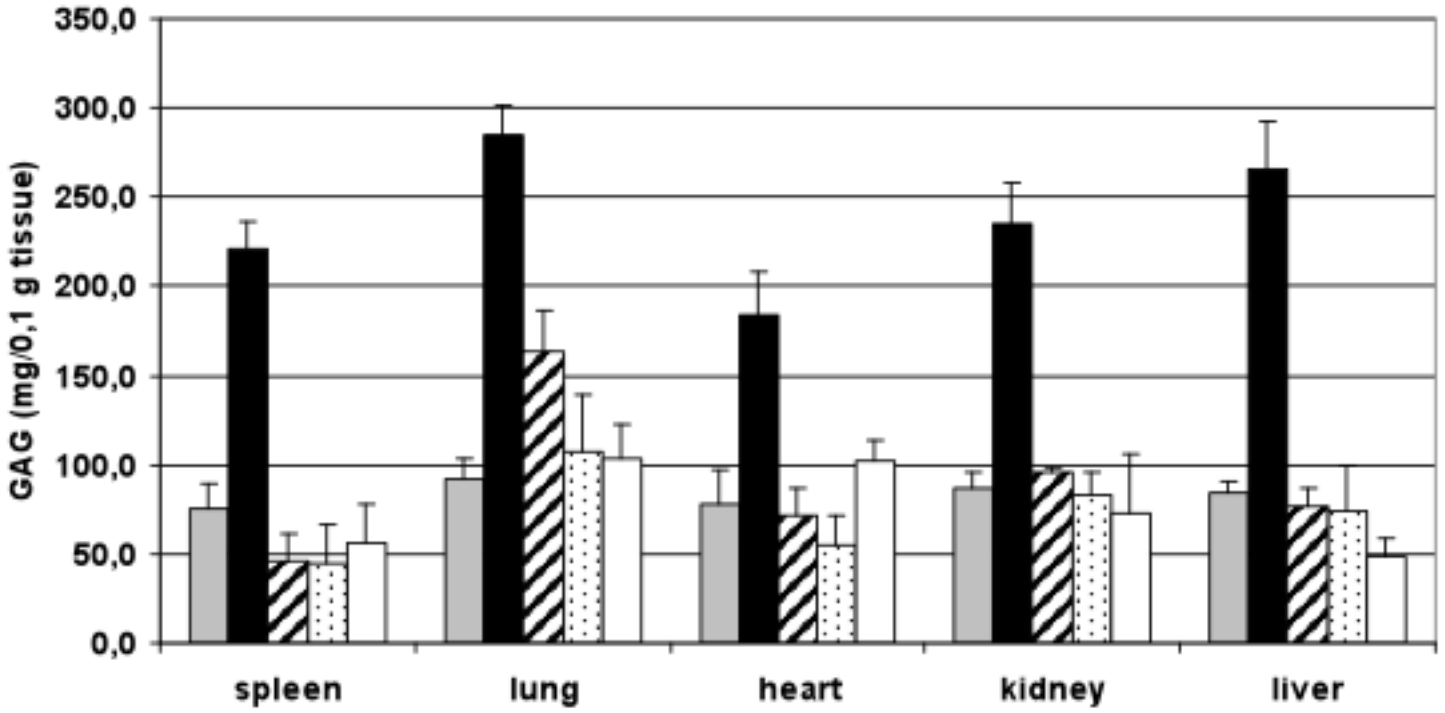
Results of stem cell gene therapy
3 wk old recipients, 6 Gy TBI



Rozemuller et al., manuscript in preparation

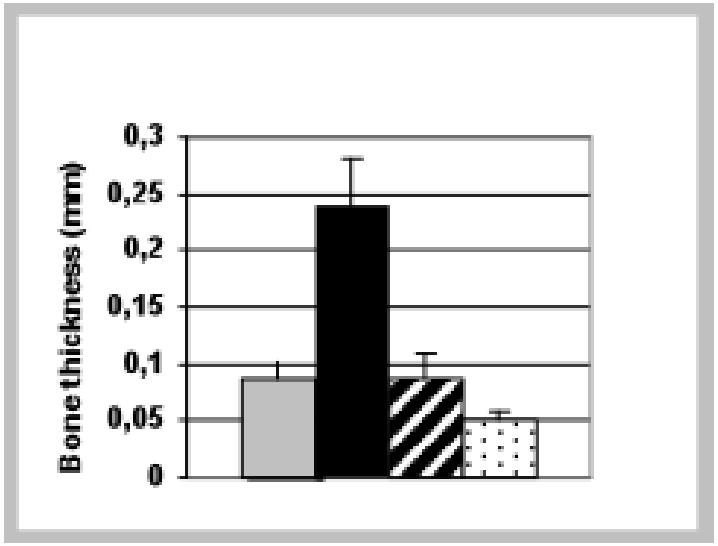
Gene therapy corrects GAG accumulation

3 wk old recipients, 6 Gy TBI

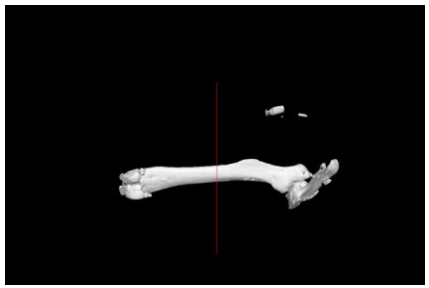


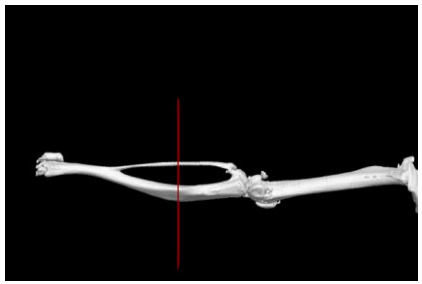
GAG accumulation was reduced in all organs for SF-IDUAco (dotted-bar), PGK-IDUAco (white bar), WT-BM (striped bar). As controls the WT mice are shown (grey bar) and the IDUA KO mice (black bar)

Gene therapy normalizes the skeletal phenotype



Bone thickness was reduced in femur for mice treated with transduced BM-cells and for standard BMT. SF-IDUAco (dotted-bar), WT-BM (striped bar). As controls the WT mice are shown (grey bar) and the IDUA KO mice (black bar)

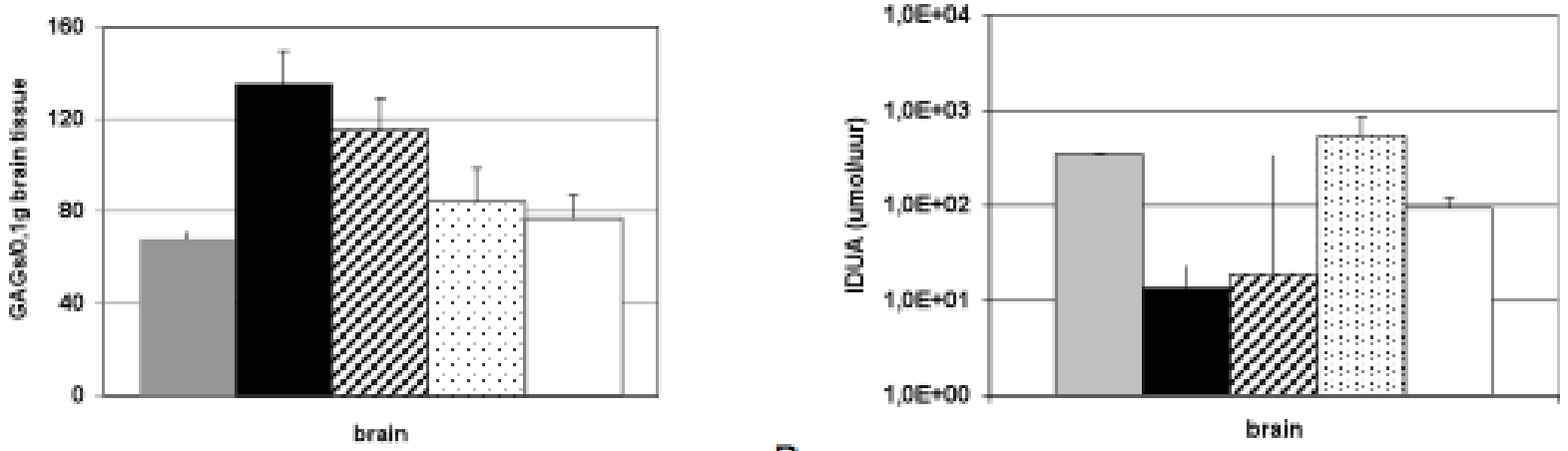




KO *gene therapy treated*

Gene therapy corrects enzyme and GAG levels in brain

3 wk old recipients, 6 Gy TBI



A B

GAG accumulation was reduced in brain for mice treated with transduced BM-cells and not for standard BMT (A), in accordance with high IDUA level in BM (B). SF-IDUAco (dotted-bar), PGK-IDUAco (white bar), WT-BM (striped bar). As controls the WT mice are shown (grey bar) and the IDUA KO mice (black bar)

Rozemuller et al., manuscript in preparation

Hurler HSC gene therapy

Appr. 20% - 30% of BM and blood cells express α-iduronidase, results:

- Very high level of production of α-iduronidase
- Restoration of α-iduronidase activity in tissues and full reduction of glycosaminoglycan storage
- Full correction of neuronal and skeletal phenotype
- No adverse effects observed
- Learning ability: likely prevented or disease progression halted
- Currently: procedure optimized, safety studies including integration pattern finalized, GMP grade clinical vector made.

Ready for implementation in a phase 1/2 clinical trial,

likely starting in Milan early 2018

Lentiviral stem cell gene therapy for inherited disorders: entering clinical trial

Lentiviral Hematopoietic Stem Cell Gene Therapy Benefits Metachromatic Leukodystrophy

Alessandra Biffi,* Eugenio Montini, Laura Lorioli, Martina Cesani, Francesca Fumagalli, Tiziana Plati, Cristina Baldoli, Sabata Martino, Andrea Calabria, Sabrina Canale, Fabrizio Benedicenti, Giuliana Vallanti, Luca Biasco, Simone Leo, Nabil Kabbara, Gianluigi Zanetti, William B. Rizzo, Nalini A. L. Mehta, Maria Pia Cicalese, Miriam Casiraghi, Jaap J. Boelens, Ubaldo Del Carro, David J. Dow, Manfred Schmidt, Andrea Assanelli, Victor Neduva, Clelia Di Serio, Elia Stupka, Jason Gardner, Christof von Kalle, Claudio Bordignon, Fabio Ciceri, Attilio Rovelli, Maria Grazia Roncarolo, Alessandro Aiuti, Maria Sessa, Luigi Naldini*

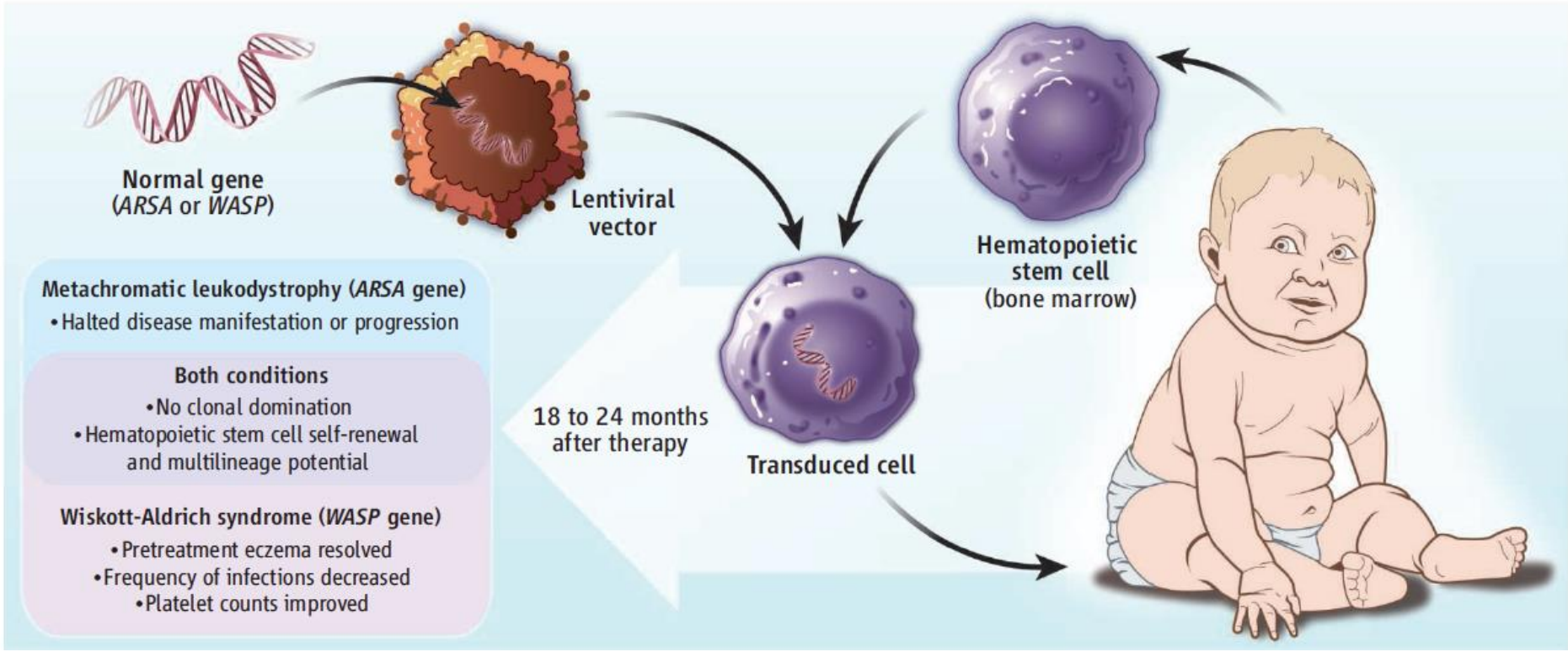
Lentiviral Hematopoietic Stem Cell Gene Therapy in Patients with Wiskott-Aldrich Syndrome

Alessandro Aiuti,* Luca Biasco, Samantha Scaramuzza, Francesca Ferrua, Maria Pia Cicalese, Cristina Baricordi, Francesca Dionisio, Andrea Calabria, Stefania Giannelli, Maria Carmina Castiello, Marita Bosticardo, Costanza Evangelio, Andrea Assanelli, Miriam Casiraghi, Sara Di Nunzio, Luciano Callegaro, Claudia Benati, Paolo Rizzardi, Danilo Pellin, Clelia Di Serio, Manfred Schmidt, Christof Von Kalle, Jason Gardner, Nalini Mehta, Victor Neduva, David J. Dow, Anne Galy, Roberto Miniero, Andrea Finocchi, Ayse Metin, Pinaki P. Banerjee, Jordan S. Orange, Stefania Galimberti, Maria Grazia Valsecchi, Alessandra Biffi, Eugenio Montini, Anna Villa, Fabio Ciceri, Maria Grazia Roncarolo, Luigi Naldini

23 AUGUST 2013 VOL 341 SCIENCE www.sciencemag.org

www.sciencemag.org SCIENCE VOL 341 23 AUGUST 2013
Published by AAAS

PERSPECTIVES



Current development of lentiviral stem cell gene therapy

Clinical trial/implementation for:

- *X-linked SCID (Milan, London)*
- *ADA-SCID (Milan, London)*
- *Wiskott-Aldrich syndrome (Milan, Paris, London)*
- *Adrenoleukodystrophy (Paris, Boston)*
- *Metachromatic leukodystrophy (Milan, Paris, London)*
- *Fabry disease (Toronto)*

In preparation for clinical trial:

- *RAG2 deficiency (Ankara)*
- *Chronic granulomatous disorder (Frankfurt, Milan)*
- *Hurler syndrome (Milan)*
- *Pompe disease (Rotterdam)*
- *Krabbe disease (Milan)*

Proof of principle:

- *Hemophilia A (F VIII deficiency)*
- *Several other lysosomal enzyme deficiencies*
- *Mitochondrial disorder MNGIE*

Summary current state of lentiviral stem cell gene therapy

- Ongoing clinical trials for X-linked SCID, Wiskott-Aldrich syndrome, adrenoleukodystrophy and metachromatic leukodystrophy, with currently tens of patients treated, reveal a high level of efficacy without gene therapy related adverse effects
- In preparation are multicenter clinical trials for Hurler (Milan) and Pompe (Rotterdam) diseases, as well as for RAG2-SCID (Ankara), Fabry disease (Toronto/Boston) and MNGIE
- HSC gene therapy is currently the only approach to achieve ***both robust immune tolerance to the transgene product* and effectively bypassing the blood/brain barrier by monocytes contributing to microglia*****

**van Til NP, Stok M, Aerts Kaya FS, de Waard MC, Farahbakhshian E, Visser TP, Kroos MA, Jacobs EH, Willart MA, van der Wegen P, Scholte BJ, Lambrecht BN, Duncker DJ, van der Ploeg AT, Reuser AJ, Verstegen MM, Wagemaker G. Lentiviral gene therapy of murine hematopoietic stem cells ameliorates the Pompe disease phenotype. Blood. 2010 Jul 1;115(26):5329-37*

***Hoogerbrugge PM, Suzuki K, Suzuki KU, Poorthuis BJHM, Kobayashi T, Wagemaker G, Van Bekkum DW. Science 1988, 239: 1035 - 1038.*

Current developments in gene therapy

Current developments in gene therapy

- Further viral vector development (e.g., “non-integrating “AAV, targeted integration of other viral vectors)
- Gene targeting and gene correction (CRISPR/Cas9)
- Oligonucleotide therapeutics
- Synthetic/molecular/physical methods of gene therapeutics delivery

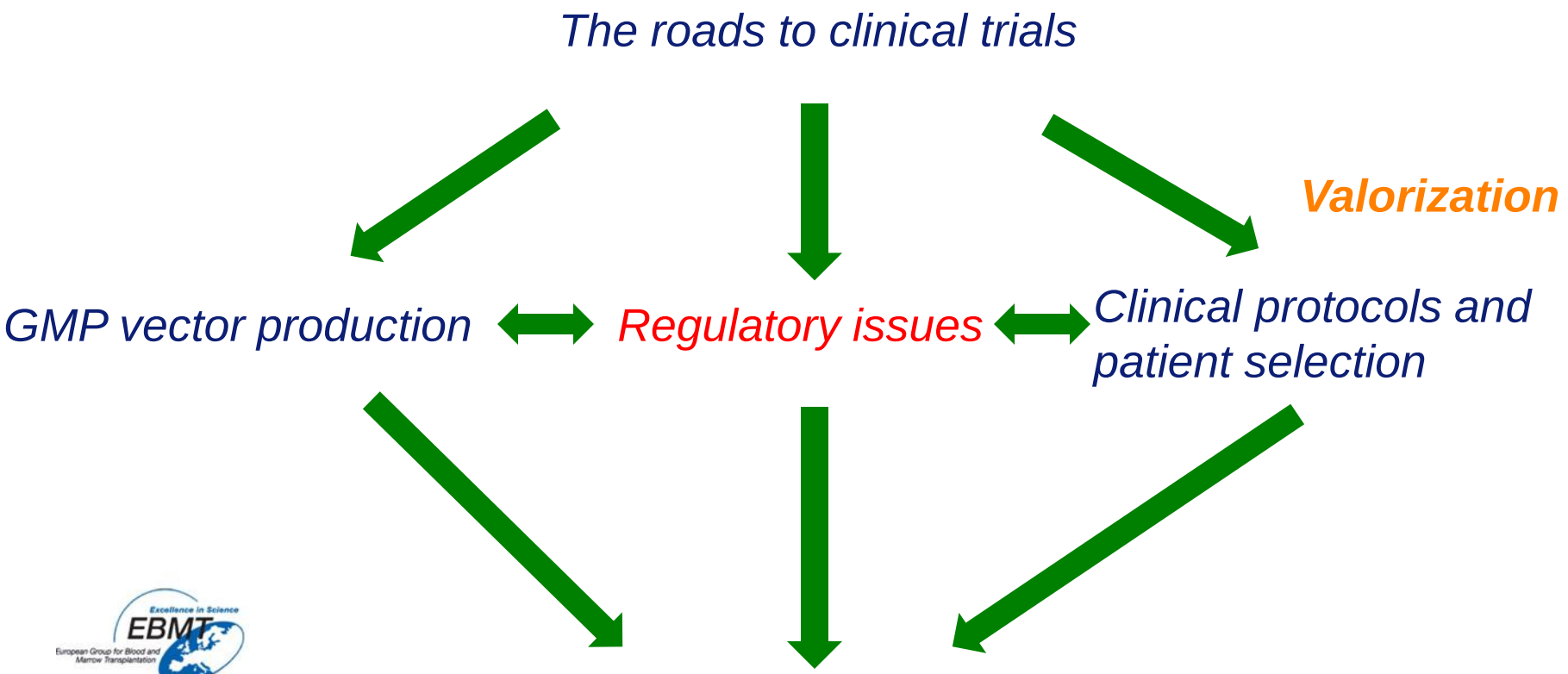
Cell Therapy

Cellular Therapy

- Cell Therapies:
  - Pluripotent
  - Hematopoietic
  - Endothelial
  - Beta Cells
  - Neural Cells
  - Mesangioblasts/pericytes
- Tissue Engineering: e.g., cartilage repair
- T-Cell Immunotherapy: CAR-T cells
- Somatic Stem Cell Therapies

Regulatory Issues

Gene therapy development

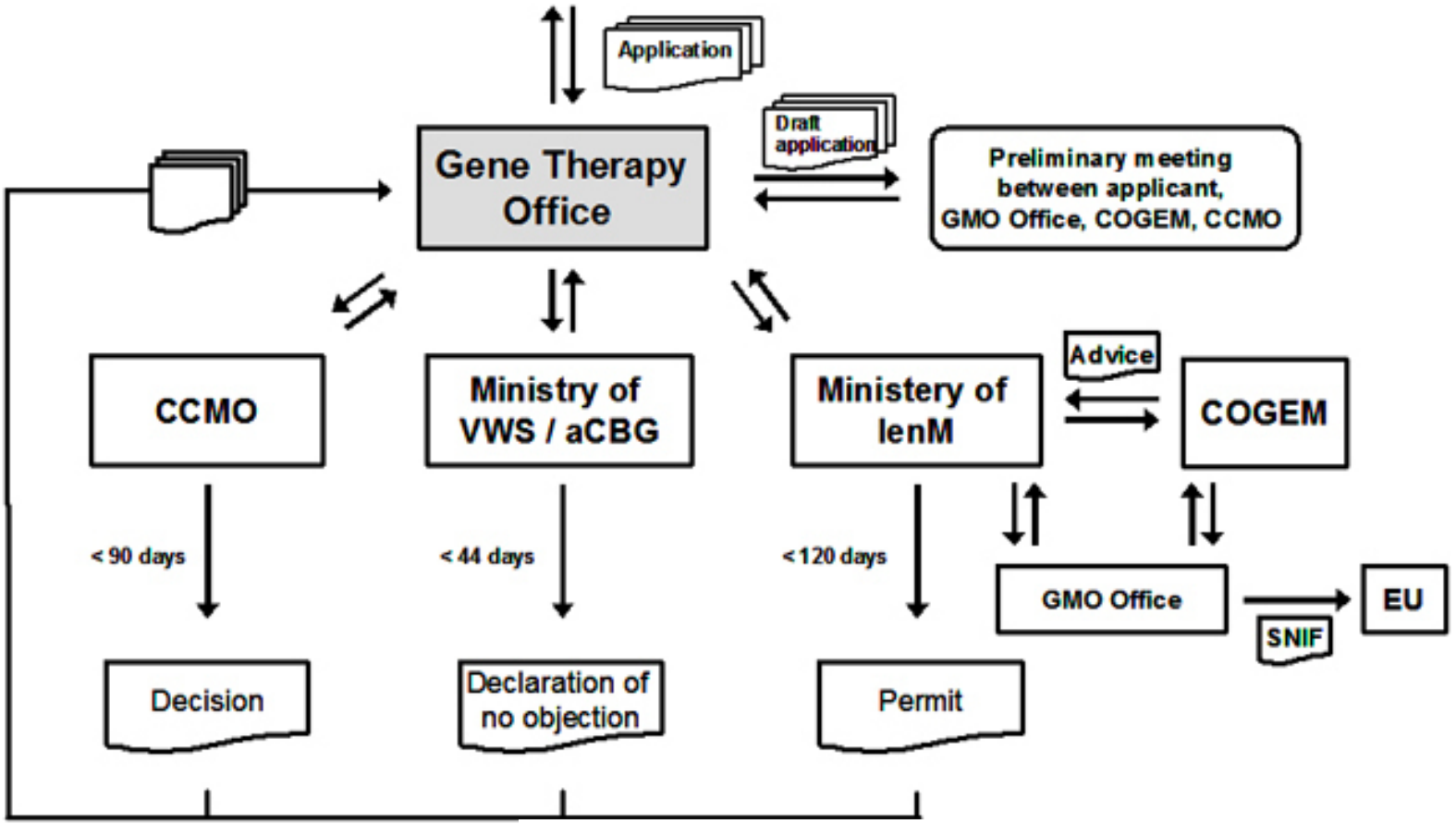


Working party inborn errors

Preclinical Efficacy and Safety Evaluation: GLP
Clinical Grade Vector Production: GMP

- Few preclinical research laboratories comply to Good Laboratory Practice. As a result the time consuming preclinical evaluation of gene & cell therapies in animal models need frequently to be repeated in specialized laboratories.
- Clinical grade lentiviral vector production requires Good Manufacturing Practice. The quality control under GMP conditions requires at least 2 years. Costs may amount up to 1 M€.

Obtaining a permit for a clinical trial using a genetically modified organism in The Netherlands



- The Central Committee on Research involving Human Subjects (CCMO)
- The Ministry of Health, Welfare and Sport (VWS/CBG)
- The Ministry of Infrastructure and the Environment (IenM) and the Office for Genetically Modified Organisms (GMO Office), which is responsible for processing permit requests, with additional advice in such processing provided by the Netherlands Commission on Genetic Modification (COGEM)

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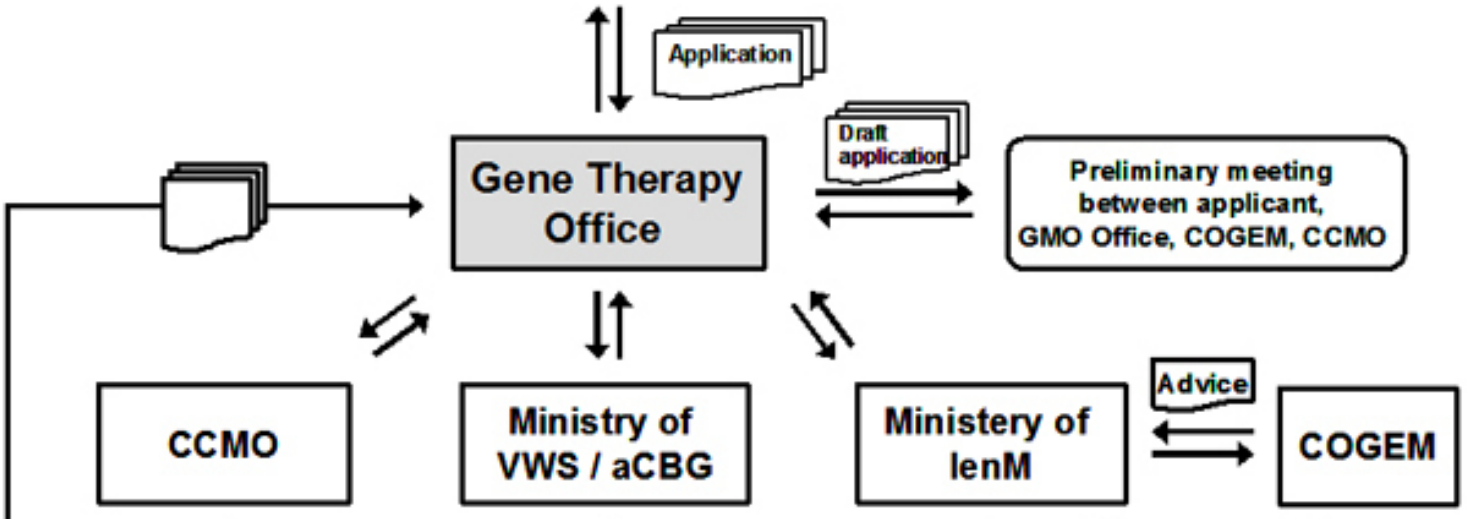

SNIF B Form

In accordance with European notification procedures, you must complete a Summary Notification Information Format (SNIF). Article 11 of Directive 2001/18/EC stipulates that there be exchange of information between the competent authorities and the European Commission. This means that the competent authorities must send a summary of the application form (SNIF form) to the Commission. The SNIF form can be found on the website of the Joint Research Centre of the European Commission (http://gmoinfo.jrc.ec.europa.eu/). Other Member States can then comment on it within 30 days. A Member State can also request to receive a copy of the full notification.

http://www.loketgentherapie.nl/en

Gene Therapy Office

search

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Application forms

- Viral vectors
- Bacteria
- Naked DNA (standard procedure IenM)
- Naked DNA (simplified procedure IenM)

Gene Therapy Office

The aim of the Gene Therapy Office is to streamline the licensing and permit granting procedures for clinical gene therapy studies in The Netherlands and to provide more insight into the procedures for investigators.

The Gene Therapy Office is primarily a service for professionals conducting clinical gene therapy research involving human subjects. Patients and interested public who want more information about gene therapy and/or participation in clinical trials can contact the Netherlands Society for Gene and Cell Therapy (NVGCT) or the CCMO, where information regarding gene therapy and clinical trials can be found.

Although there are currently various definitions of gene therapy, the Gene Therapy Office understands it to mean the following: '*Clinical research in humans either involving activities with genetically modified organisms (GMO), or whereby genetically modified cells can be created in the human body, or whereby changes are made to the genetic material of human cells.*'

Contact Information

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The Health Care Inspectorate

Inspectie voor de Gezondheidszorg
Ministerie van Volksgezondheid, Welzijn en Sport

In The Netherlands, it is forbidden by law to use medicines that are not registered -> EMA

www.ema.europa.eu

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- *Advanced Therapy Medicinal Products*
  multi-stakeholder expert meeting held on 27 May 2016:

  - Facilitating research and development;
  - Optimising regulatory processes for ATMPs;
  - Moving from hospital exemption to marketing authorisation;
  - Improving funding, investment and patient access.

We need more tailor made regulations

WORLD VIEW *A personal take on events*

Gene therapies need new development models

As with other medicines, the approval of gene therapies should hinge on a risk–benefit analysis for the patient, argues **Fulvio Mavilio.**

Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive

Romaldas Maciulaitis[1,2], Lucia D'Apote[3], Andrew E
Laura Pioppo[3,4] and Christian K Schneider[1,5,6]

Therapy in October 2011 (ref. 18). Clearly, the CAT must remain proactive to help further close the "translational gap" of ATMP development in the European Union.

www.ema.europa.eu

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- Orphan drug designation
- Marketing authorization
- “Hospital exemption”
- Compassionate use

Etc., etc.

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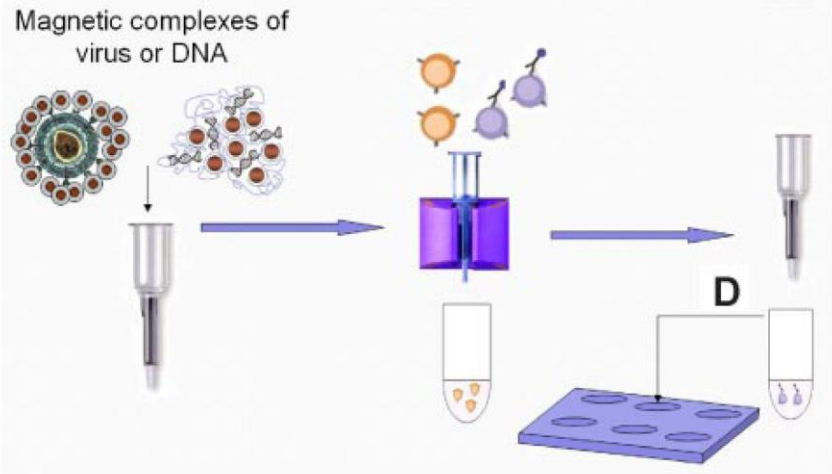
Once all these hurdles are taken, the Inspectorate:

- *Requires GMP facilities for gene and cell therapy, to be licensed only when is complied to all requirements, in addition a so-called Factory License with additional requirements*
- *Periodically inspects whether GMP is still correctly applied*
- *Decides whether the hospital exemption can be applied*
- *Monitors the results of the clinical trial*
- *Needs to be immediately informed on serious adverse effects*

Gene transfer closed system development

- Develop a system in which lentiviral vector transduction can be controlled resulting in one vector copy per cell.



Ultimate aim:

Stem cell selection, transduction and expansion in a single closed system

CliniMACS Prodygi
Miltenyi Biotec

*Sanchez-Antequera *et al*, Blood 2011

Finally

- The currently 28 member states of the European Union maintain 28 different procedures, including different medical end-points, for clinical trials with genetically modified organisms, which makes it impossible to organize a multicenter European clinical trial. Instead there are parallel trials for, e.g., a rare disorder, of which the results may or may not be combined.
- In addition, different countries use different EU directives for the use of genetically modified organisms

Attempts are being made to harmonize within the EU. It is expected that by October 2018 for medical/ethical aspects the national procedures will be replaced by a central procedure, based on the EU Clinical Trial Regulation (536/2014/EU)

Thank you for your attention

Acknowledgments: