Hematopoietic Stem Cell Gene Therapy: Two Decades of Development

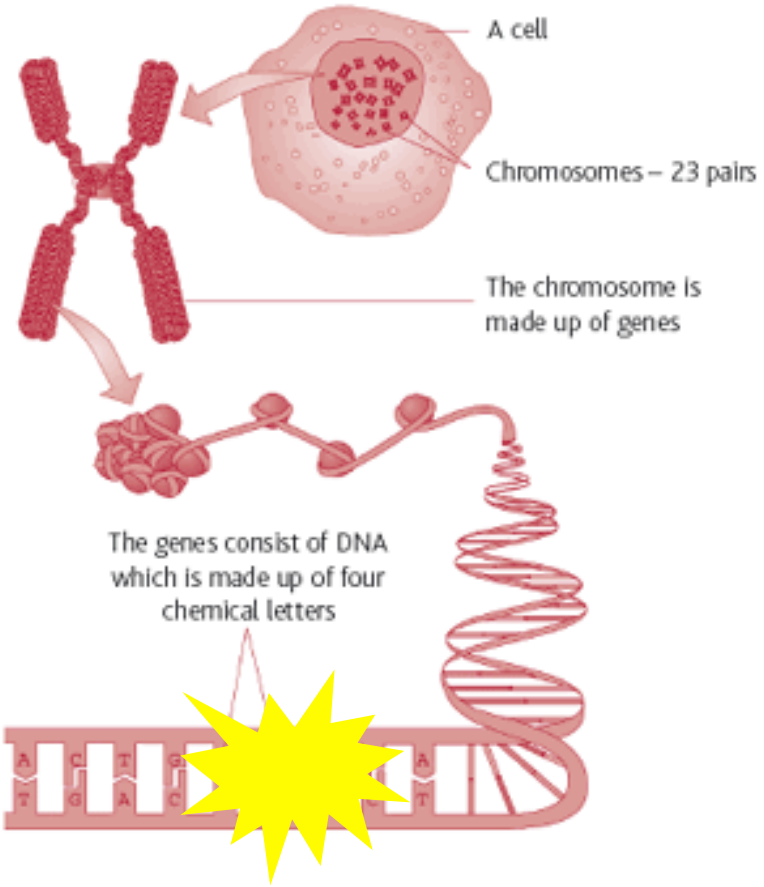
Gerard Wagemaker

Netherlands Society of Gene and Cell Therapy

NVGCT

ZonMw

Rare, inherited diseases



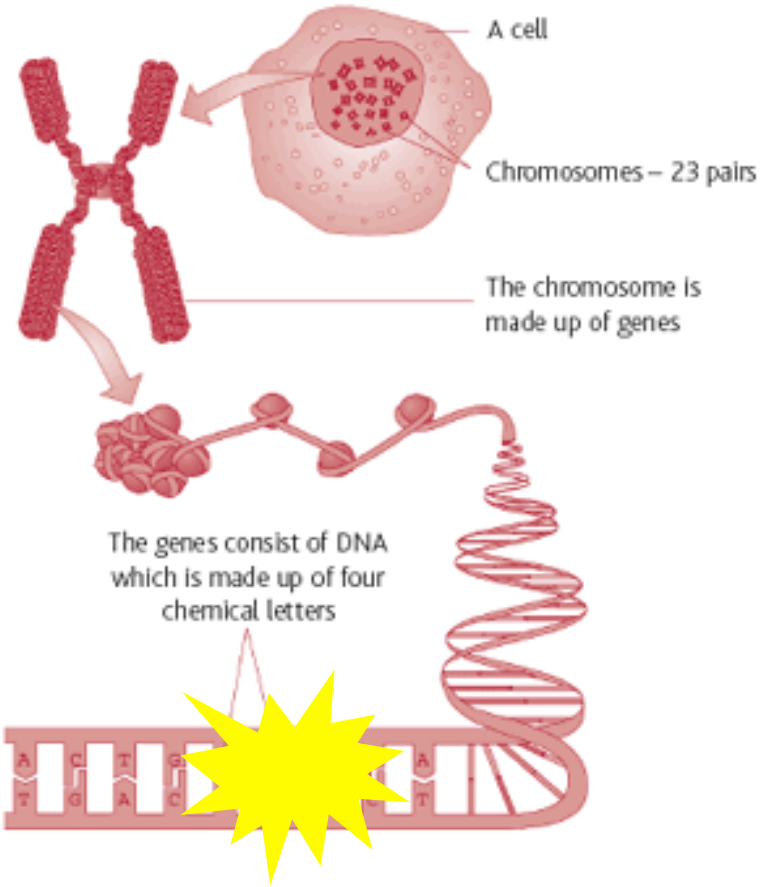
A single mutation in the code may have profound effects at the level of the organism

In humans, more than 7,500 inherited monogenic diseases have been identified; in around 40% the genetic defect has been identified.

Approaches:

- *prenatal diagnosis & genetic counseling*
- *symptomatic therapy*
- *replacement therapy*
- *correction of the genetic defect:* ***gene therapy***

Rare, inherited diseases



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In humans, more than 7,500 inherited diseases have been identified; in around 40% the genetic defect has been identified

Current hematopoietic stem cell gene therapy development:

- *Lysosomal storage disorders (Hurler, Pompe, Krabbe)*
- ***Inherited immune deficiencies***
- *Hemophilia (F VIII deficiency with inhibitor)*
- *Fanconi anemia*
- *Sickle cell anemia*
- *Thalassemia*

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
- *ADA-SCID additional problem: difficult to treat with BMT*

THE LANCET

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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

Treatment of Lymphopenic Hypogammaglobulinemia and Bone-Marrow Aplasia by Transplantation of Allogeneic Marrow — Crucial Role of Histocompatibility Matching

H.J. Meuwissen, M.D., R. A. Gatti, M.D., P. I. Terasaki, Ph.D., R. Hong, M.D., and R. A. Good, M.D.

N Engl J Med 1969; 281:691-697 | September 25, 1969 | DOI: 10.1056/NEJM196909252811302

THE LANCET, NOVEMBER 8, 1986

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

A. FISCHER[1] C. GRISCELLI[1]
W. FRIEDRICH[2] B. KUBANEK[2]
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Analysis of the first 162 patients treated

Currently > 1.000.000 patients treated with BMT

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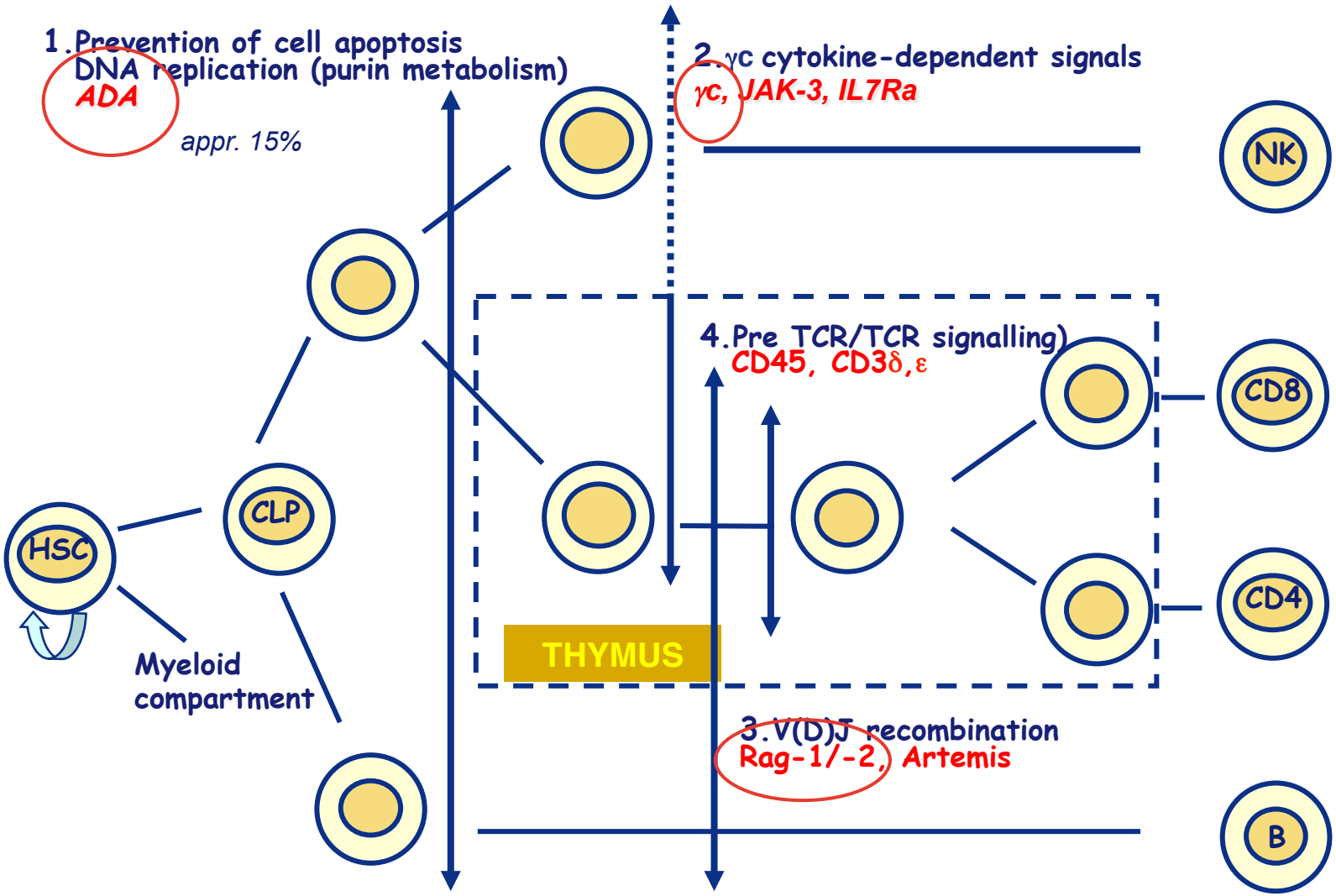
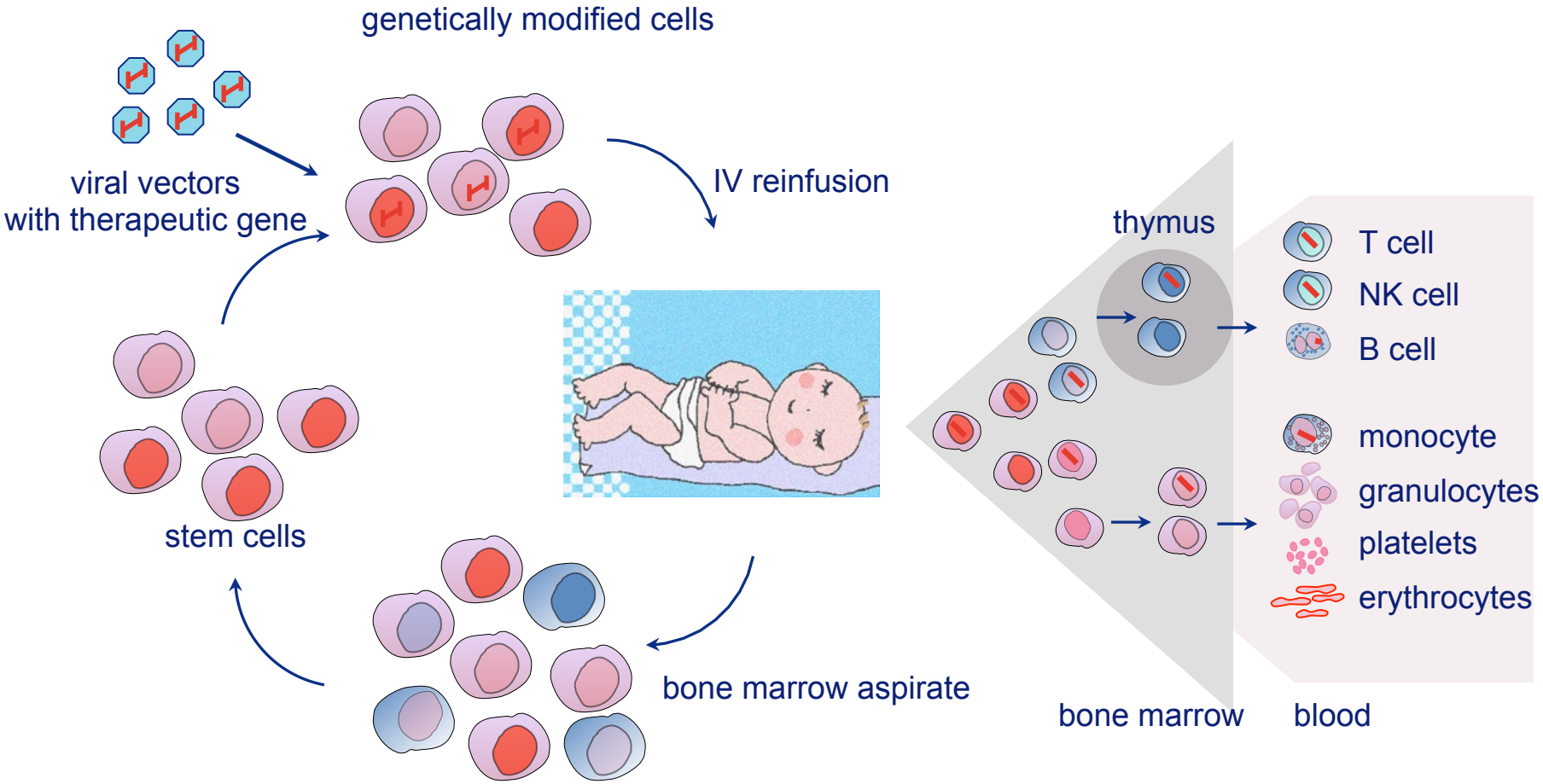
Seminal gene therapy trials X-linked SCID

SCID diseases



Slide by A. Fischer

Ex vivo stem cell gene therapy of autologous hematopoietic stem cells



Results first effective European clinical trials for immune deficiencies

X-Linked SCID **Paris, London**	**Disease free survival** **18/20 (90%)**	**Survival** **18/20 (90%)**
ADA SCID **Milan, London**	**Disease free survival** **19/26 (67%)**	**Survival** **26/26(100%)**

Overall survival: 44/46 = 96%

(Expected with available donor allogeneic stem cell transplantation: 25-50%)

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 HIV-1 derived lentiviral vectors, that do not have a preference for integration near proto-oncogenes.

Currently

- Developed from 2002-2010 in the context of “large scale collaborative projects” subsidized by the European Commission, the lentiviral vectors are currently evaluated in multicenter clinical trials.

Severe adverse effects following gammaretroviral stem cell gene therapy (strongly) co-dependent on disease phenotype

Disease phenotype	*Percentage severe adverse effects (leukemia)*
ADA-SCID	*0%*
X-linked SCID	*25%*
Wiskott-Aldrich	*75%*

References:

Aiuti A, Cassani B, Andolfi G, Mirolo M, Biasco L, Recchia A, Urbinati F, Valacca C, Scaramuzza S, Aker M, Slavin S, Cazzola M, Sartori D, Ambrosi A, Di Serio C, Roncarolo MG, Mavilio F, Bordignon C. Multilineage hematopoietic reconstitution without clonal selection in ADA-SCID patients treated with stem cell gene therapy. J Clin Invest. 2007 Aug;117(8):2233-40.

Biasco L, Ambrosi A, Pellin D, Bartholomae C, Brigida I, Roncarolo MG, Di Serio C, von Kalle C, Schmidt M, Aiuti A. Integration profile of retroviralvector in gene therapy treated patients is cell-specific according to gene expression and chromatin conformation of target cell. EMBO Mol Med. 2011 Feb;3(2):89-101.

Shou Y, Ma Z, Lu T, Sorrentino BP. Unique risk factors for insertional mutagenesis in a mouse model of XSCID gene therapy. Proc Natl Acad Sci U S A. 2006 Aug1;103(31):11730-5.

Braun CJ, Boztug K, Paruzynski A, Witzel M, Schwarzer A, Rothe M, Modlich U, Beier R, Göhring G, Steinemann D, Fronza R, Ball CR, Haemmerle R, Naundorf S, Kühlcke K, Rose M, Fraser C, Mathias L, Ferrari R, Abboud MR, Al-Herz W, Kondratenko I, Maródi L, Glimm H, Schlegelberger B, Schambach A, Albert MH, Schmidt M, von Kalle C, Klein C. Gene therapy for Wiskott-Aldrichsyndrome--long-term efficacy and genotoxicity. Sci Transl Med. 2014 Mar 12;6(227):227ra33.

Stem cell gene therapy inherited disorders: “CONSERT” Project

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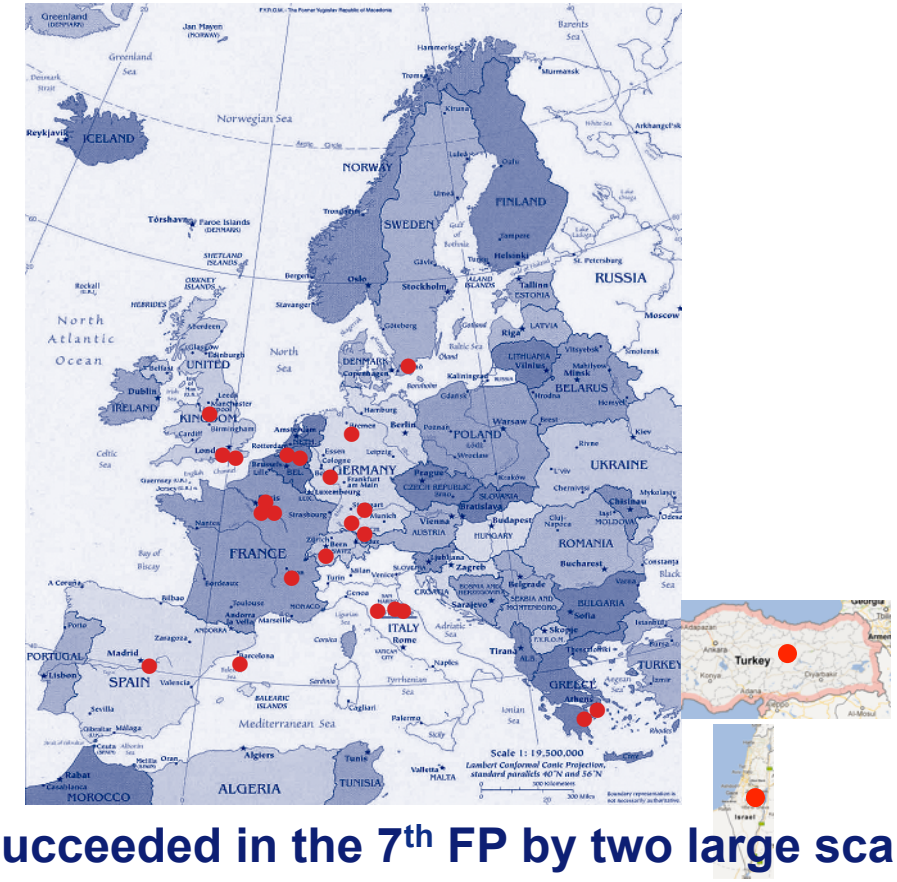
www.gene-therapy.eu

Stem cell gene therapy for inherited disorders: EU collaboration



CONSERT project succeeded in the 7th FP by two large scale integrated projects:

- ***PERSIST (2009-2013)****: Innovative technology including gene editing, selective expression for hemophilia and lysosomal enzyme deficiencies*
- ***Cell-PID (2010-2016)****: Clinical implementation for primary immune deficiencies*

Stem Cell Gene Therapy Development: EU consortium funding

EC:			
5th FP:	*"Inherinet" and "Lentivirus"*	*2001-2004*	*7 M€*
6th FP	*"CONSERT" project*	*2004-2009*	*11.4 M€*
7th FP	*"PERSIST" project*	*2009-2013*	*11.2 M€*
	"CELL-PID" project	*2010-2015*	*11.9 M€*
	"SUPERSIST" project	*2013-2016*	*3.0 M€*
	"NET4GCD" project	*2012-2016*	*6.0 M€*
HORIZON 2012			
	"SCIDNET" project	*2016-2019*	*7.0 M€*
Total EC contribution:			***57.5 M€***

Key collaboration: vector design and production, animal models, integration analyses, safety analyses, advanced stem cell biology, multicenter trials

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National:

United Kingdom : MRC
Germany: DFG
France: AFM, INSERM, CNRS
Netherlands: ZonMw, NWO
Italy: Telethon

Estimated total 2001-2016: > 200 M€ public funding

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

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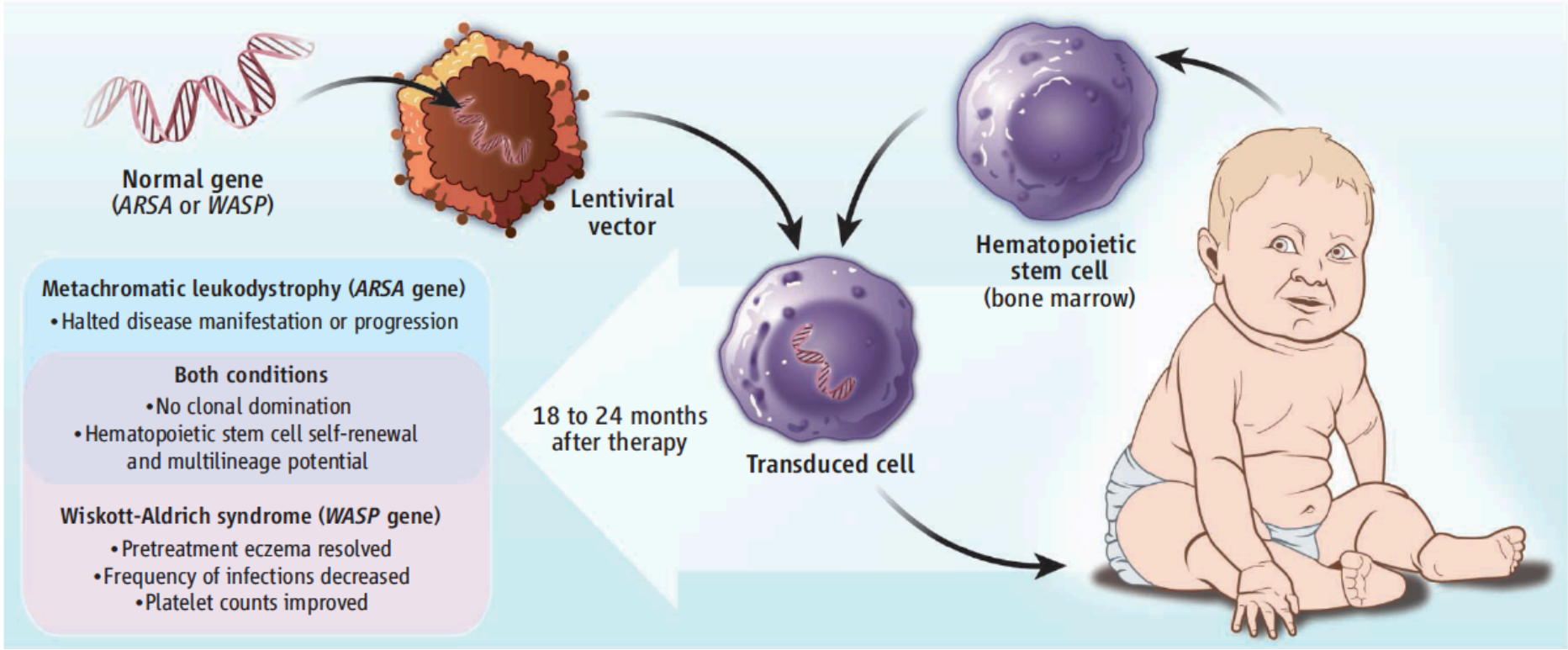
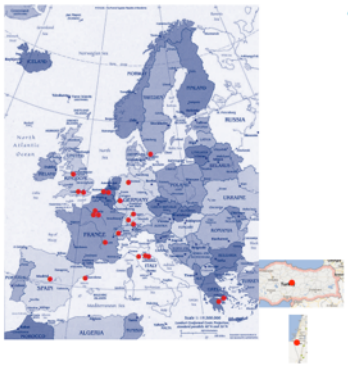
PERSPECTIVES



Current developments in stem cell gene therapy



Clinical 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)*

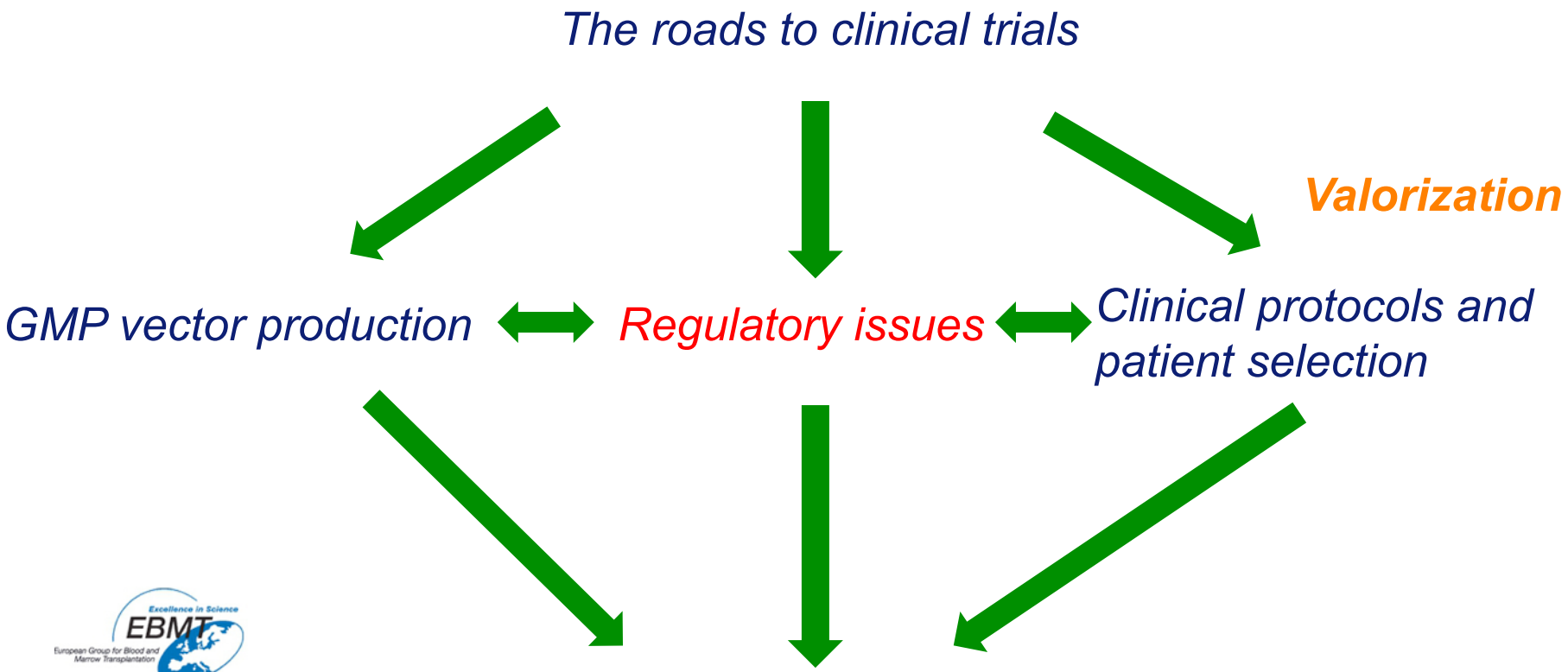
In preparation for clinical trial:

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

Proof of principle:

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

Gene therapy development



Working party inborn errors

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.

Costs of hematopoietic stem cell gene therapy as a single curative “medical standard treatment”

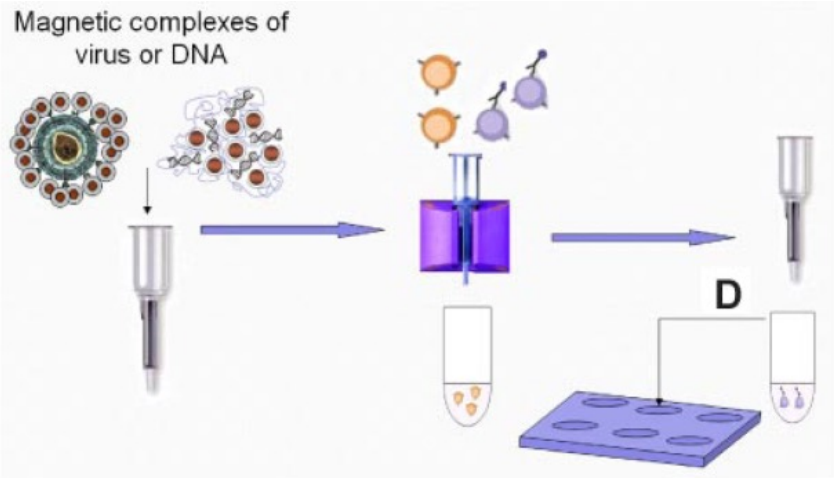
- Costs of autologous stem cell transplantation

+

- GMP vector
- GMP transduction facility
- Life-long monitoring

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

Gene Therapy brochures ready – Biomedinvo4all

http://www.biomedinvo4all.com/en/news/gene-therapy-brochures-ready

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Gene Therapy brochures ready – B...

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Roadmap to Treatment

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News

Home > News > Gene Therapy brochures ready

29 / 06 / 2009

Gene Therapy brochures ready

We have created two brochures on the patient view on the ethics of gene therapy, one for patients communities, one for public communities.The latter discusses more general aspects of gene therapy and aims to increase understanding what gene therapy can mean for patients. The one for patient communities discusses more ethical questions that might arise when you get involved with gene therapy as a patient.

Click here to go to the brochures

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Latest news

01 / 09 / 2009
- German brochures available

29 / 06 / 2009
- Gene Therapy brochures ready

27 / 05 / 2009
- PatientPartner: join the dialogue!

Latest calendar items

12 / 10 / 2009
- PatientPartner North-Western Europea ...

30 / 11 / 2009
- PatientPartner Central-Eastern Europ ...

24 / 03 / 2010
- PatientPartner Southern European reg ...

Directly to

- Medical Data- & Biobanks
- Clinical Trials
- Gene Therapy
- Stem Cell Therapy
- Medical Genetics
- Pharmacogenetics

TGO programma

Thank you for your attention

Acknowledgments: