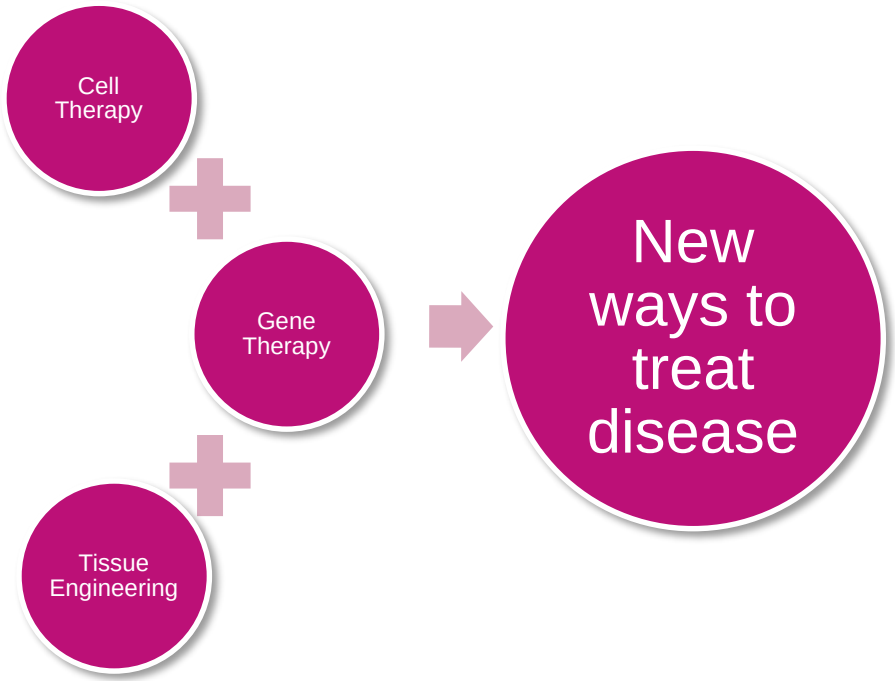
Cell therapies as medicines

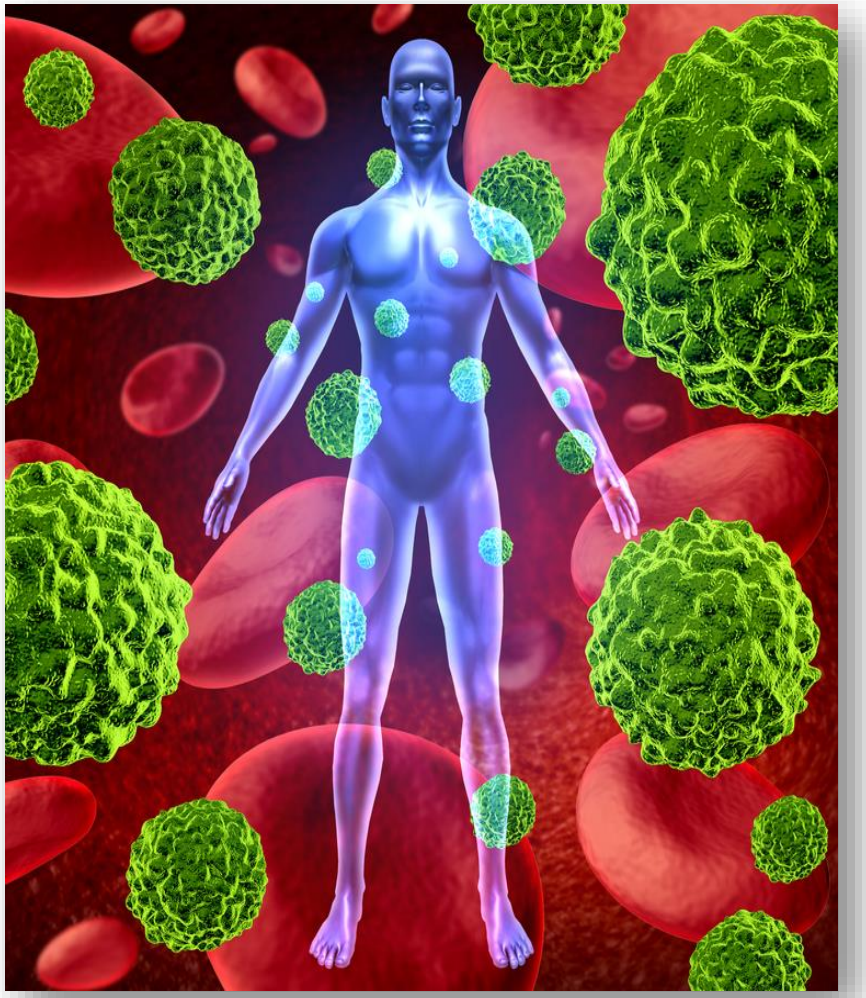
Sven Kili
VP & Head of Development
Gene Therapy, GSK

gsk
do more
feel better
live longer

The power of cells to treat diseases

We are now entering overlapping fields of biomedical research which can both repair the direct cause of genetic diseases in the DNA and cellular population respectively





Industry Overview

ARM Annual Report – 2015

Investment is growing in all areas

Total Financings:
$10.8 Billion 2015
Up 106% compared to 2014

Gene & Gene-Modified Cell Therapy: $6.8 Billion 2015
Up 84% compared to 2014

Tissue Engineering:
$806.8 Million 2015
Up 175% compared to 2014

Cell Therapy: $7.0 Billion 2015
Up 104% compared to 2014

**Total amount raised represents sector-wide figures; please note that some companies utilize technology from more than one technology group. As a result, the total financings amount does not equal the sum of the raises of the individual technology groups.*

Clinical Trials

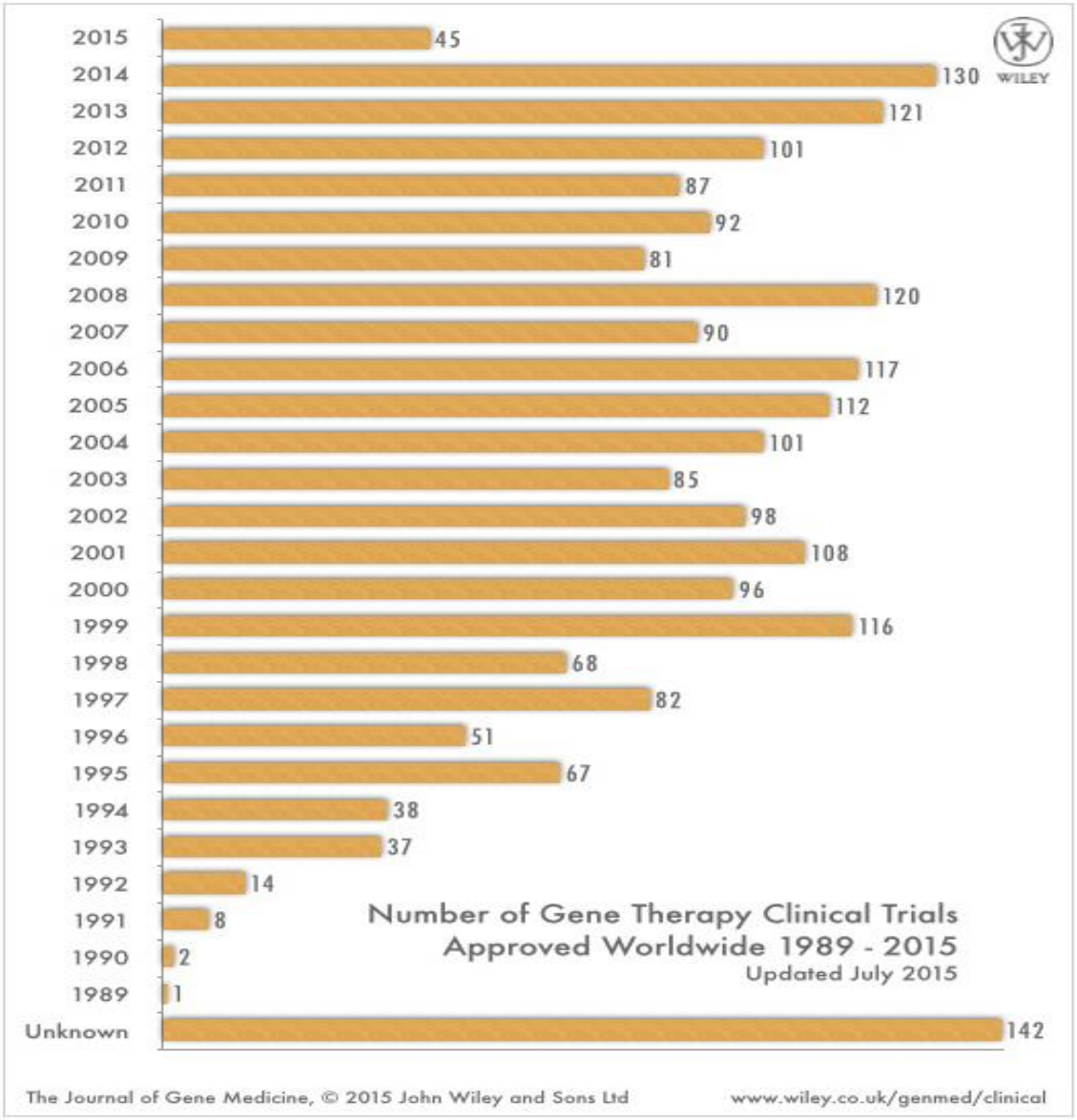
631 Clinical trials underway by year-end 2015

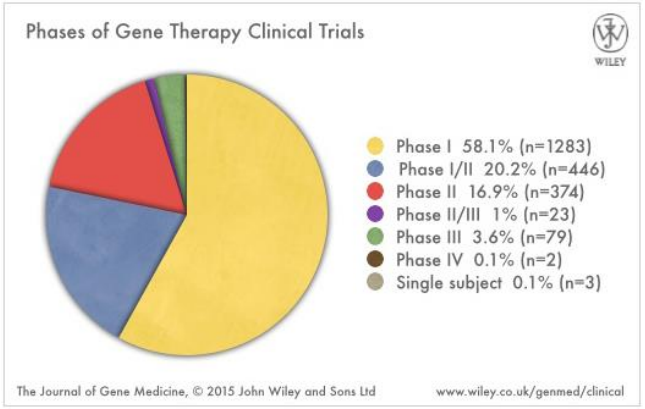
Ph. I: 192
Ph. II: 376
Ph. III: 63

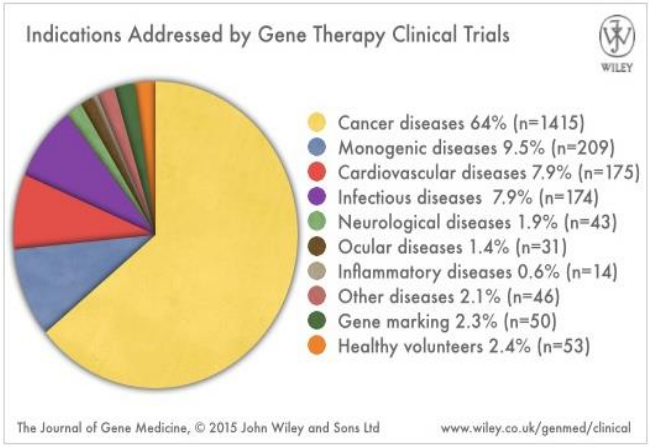
Clinical Trials by Therapeutic Category: Year-End 2015

- More than 40% of current clinical trials are in oncology
- More than 12% are in cardiovascular

Current hit-rate is still low....







There have been some successes.....

Carticel
(autologous cultured chondrocytes)

Apligraf
add life to healing

CHONDROCELECT

HOLOCLAR

PROCHYMAL

maci
matrix applied characterized autologous cultured chondrocytes

Epicel®
(cultured epidermal autografts)

BIODFENCE

In the news.....

GSK receives positive CHMP opinion in Europe for Strimvelis™, the first gene therapy to treat very rare disease, ADA-SCID

1st April 2016

The medicine is a stem cell gene therapy created for an individual patient from their own cells which is intended to correct the root cause of the disease.
The first life-saving gene therapy for children

Source:http:// http://www.gsk.com/en-gb/media/press-releases/2016/gsk-receives-positive-chmp-opinion-in-europe-for-strimvelis-the-first-gene-therapy-to-treat-very-rare-disease-ada-scid/

GSK is investing in Cell and Gene Therapies

Autologous gene therapy for rare diseases

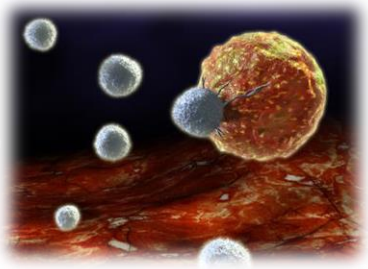
- Strategic alliance with the Telethon Institute of Gene Therapy (TIGET), Milan
- Alliance formed in 2010
- Targeting seven serious / life-threatening rare diseases, including:
  - Primary immune deficiencies
  - Lysosomal storage disorders
  - Blood disorders

Autologous gene therapy for Oncology

- Strategic collaboration with Adaptimmune Limited (Oxford, UK and Philadelphia, PA)
- Alliance formed 2014
- Targeting cancer indications including myeloma (AST, non-AST), melanoma, synovial sarcoma, ovarian cancer and breast cancer

GSK autologous gene therapy program in Oncology

- Strategic collaboration with Adaptimmune Limited (Oxford, UK and Philadelphia, PA) to develop and commercialize T-cell receptor (TCR) engineered T-cells to treat cancer
- Adaptimmune lead program with engineered TCR to the NY-ESO-1/LAGE-1 cancer testis antigen
- Follow-on programs in multiple cancer indications including myeloma (AST, non-AST), melanoma, synovial sarcoma, ovarian cancer and breast cancer
- Second T cell-based therapy to enter clinical trials in triple negative breast cancer in 2015, supported by a major grant from the UK's Technology Strategy Board



T cell (grey) killing a tumour cell (yellow)

Adaptimmune
TRANSFORMING T CELL THERAPY

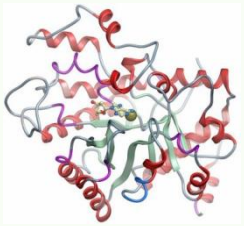
GSK gene therapy program overview

- The strategic alliance with the Fondazione Telethon and Ospedale San Raffaele, acting through their joint Telethon Institute for Gene Therapy (TIGET) was established to research and develop autologous *ex vivo* gene therapy for rare genetic disorders

Indication	Stage
ADA deficiency (ADA-SCID)	Positive CHMP opinion
Metachromatic leukodystrophy (MLD)	Ongoing trial in patients
Wiskott-Aldrich Syndrome (WAS)	Ongoing trial in patients
Beta-thalassemia	Ongoing trial in patients
Mucopolysaccharoidosis type I (MPS type I)	Pre-clinical
Globoid-cell leukodystrophy (GLD)	Pre-clinical
Chronic granulomatous disorder (CGD)	Pre-clinical

Targeting serious and life-threatening conditions

ADA-SCID



- **Severe, life-threatening deficiency of the immune system**
- HSCTs associated with a risk of GvHD; 60-90% survival
- Long-term ERT associated with a 78% survival over 20 years

Wiskott-Aldrich Syndrome (WAS)

- Life-threatening primary immune deficiency
- **Thrombocytopenia, autoimmune disease and blood malignancies**
- Risk of GvHD and graft rejection w/allogeneic HSCT; 60-90% survival

Chronic Granulomatous Disorder (CGD)

- Severe primary immune deficiency
- **Chronic fungi and bacterial infections and related complications**
- Risk of GvHD and graft rejection w/allogeneic HSCT; risk of mortality

Primary immune deficiencies

Beta- Thalassemia Major (BTM)

- **Severe anaemia & complications**
- Requirement for regular blood transfusions and iron chelation
- **Reduced life expectancy as a result of transfusion iron-overload and cardiac dysfunction**

Blood disorders

Metachromatic Leukodystrophy (MLD)

- Fatal lysosomal storage disease
- Late Infantile MLD, the most common form (~60% of patients)
- **Rapid loss in motor & cognitive function, followed by death**
- HSCTs with limited efficacy

Mucopolysaccharidosis type 1 (MPS-1)

- **Skeletal and connective tissues disorder, leading to obstructive airway disease, respiratory infections, or cardiac complications**
- Median survival 63-81% with HSCT, including bone marrow and cord blood transplants

Globoid-Cell Leukodystrophy (GLD)- Krabbe

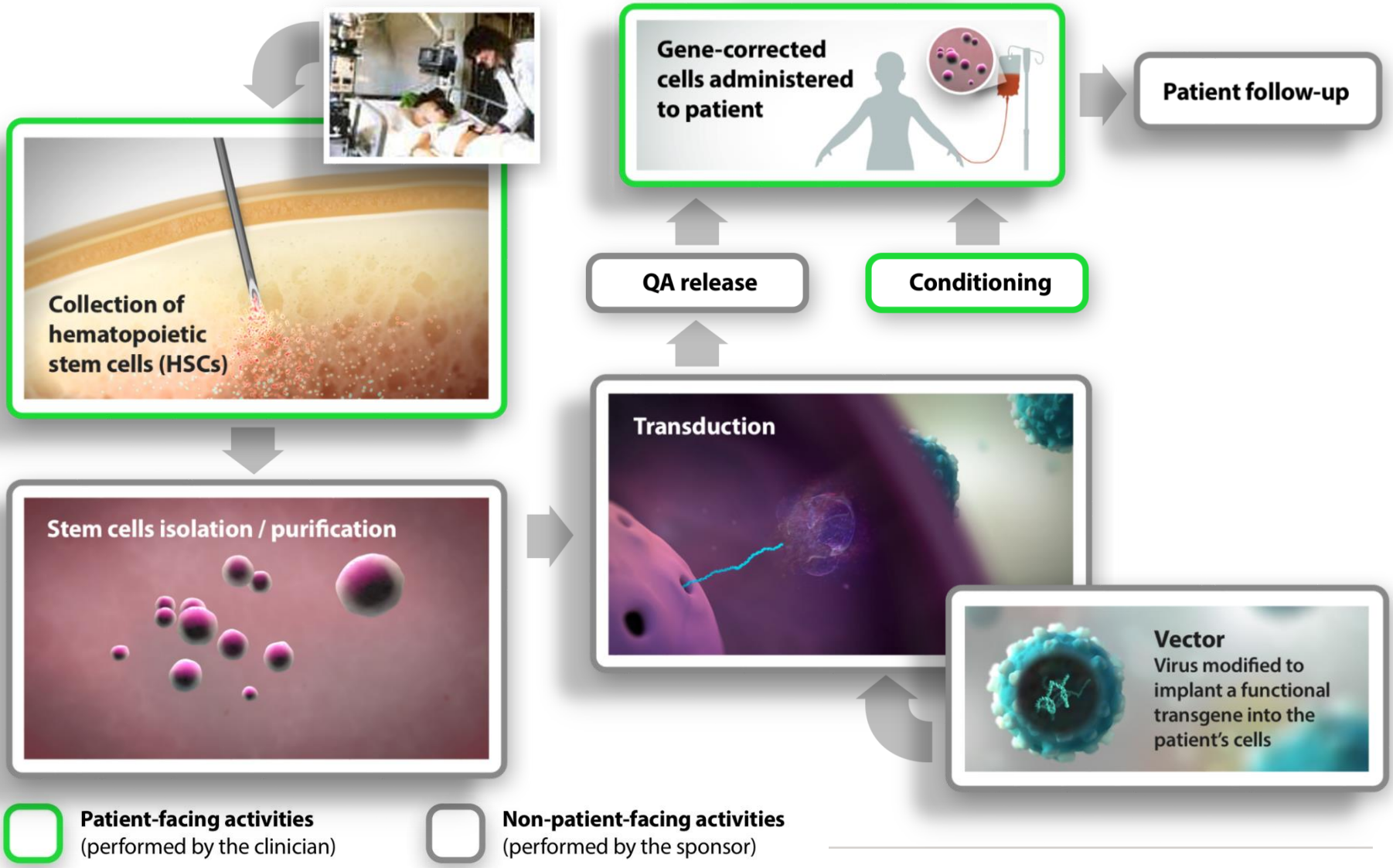
- Lysosomal storage disorder
- **Fever, limbs stiffness, seizures, feeding difficulties; slow mental & motor development**
- Median survival to 2-3 years of age in most common form

Lysosomal storage disorders

GvHD: graft-versus-host disease; ERT: enzyme replacement therapy; HSCT: hematopoietic stem cell transplant

Delivery of autologous gene therapy to the patient

Critical interface between clinician and manufacturer defines operating model more than logistics challenge of 'Hub and Spoke'



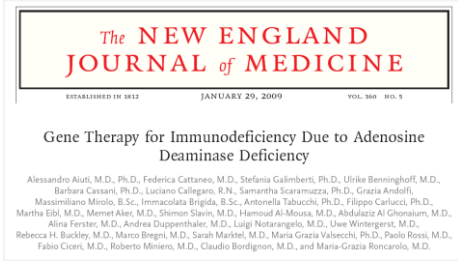
Autologous retroviral gene therapy for ADA-SCID (lead): Clinical data overview

- 18 patient reported in MAA submission Q2 2014[1]:
  - All patients alive after a median follow-up of > 7 years (100% survival)
  - Soc (matched unrelated SCT) <70% survival.

- Immune reconstitution:
  - 15/18 patients free from the need for long-term enzyme replacement or rescue Stem Cell Therapy
  - Gradual and sustained improvement in T-cell counts

- Reduced rate of severe infections[2]:
  - Reduction from 1.1 event per person-year of observation before GT to 0.43 events per person-year of observation after GT (0-3 year data; n=12 pivotal study)

- Overall favourable safety and AE profile:
  - No deaths to date
  - No leukaemia
  - SAEs & AE's consistent with the disease and HSCT intervention


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 29, 2009 VOL. 360 NO. 5

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

Alessandro Aiuti, M.D., Ph.D., Federica Cattaneo, M.D., Stefania Galimberti, Ph.D., Ulrike Benninghoff, M.D., Barbara Cassani, Ph.D., Luciano Callegaro, R.N., Samantha Scaramuzza, Ph.D., Grazia Andolfi, Massimiliano Mirolo, B.Sc., Immacolata Brigida, B.Sc., Antonella Tabucchi, Ph.D., Filippo Carlucci, Ph.D., Martha Eibl, M.D., Memet Aker, M.D., Shimon Slavin, M.D., Hamoud Al-Mousa, M.D., Abdulaziz Al Ghonaium, M.D., Alina Ferster, M.D., Andrea Duppenthaler, M.D., Luigi Notarangelo, M.D., Uwe Wintergerst, M.D., Rebecca H. Buckley, M.D., Marco Bregni, M.D., Sarah Marktel, M.D., Maria Grazia Valsecchi, Ph.D., Paolo Rossi, M.D., Fabio Ciceri, M.D., Roberto Miniero, M.D., Claudio Bordignon, M.D., and Maria-Grazia Roncarolo, M.D.

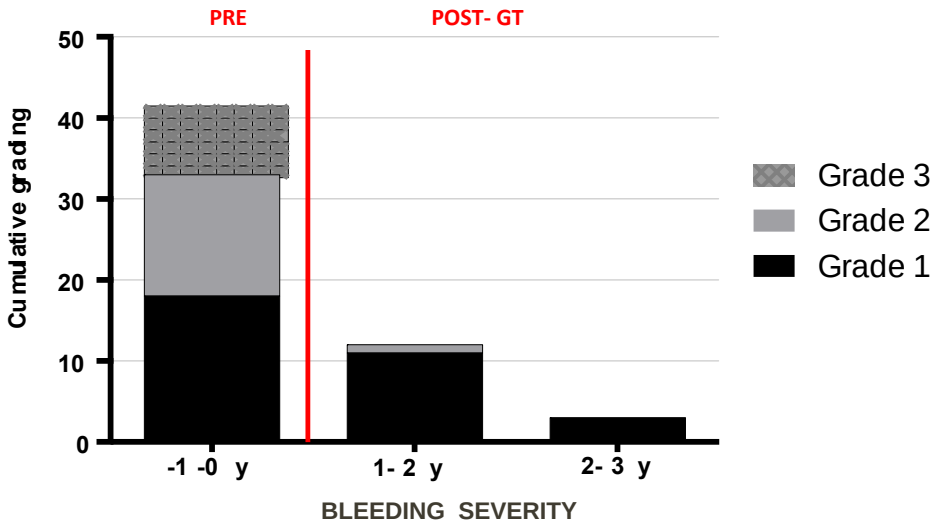
#1 including 12 patients treated in the pivotal study
#2 severe infection = infection requiring hospitalization or prolonging hospitalization
Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency (NEJM, 2009)

Gene Therapy for Wiskott-Aldrich Syndrome (WAS)

CD34+ cells transduced with LV encoding for *WASP* gene

WAS: improved immune function and platelet count

- 8 Patients treated so far
- All patients have shown improvements in:
  - WAS protein
  - Clotting (platelet count)
  - Severe Infections
  - Eczema (resolution)
- Good safety profile
  - 100% survival
  - No serious side effects related to GT
  - No abnormal clonal expansion

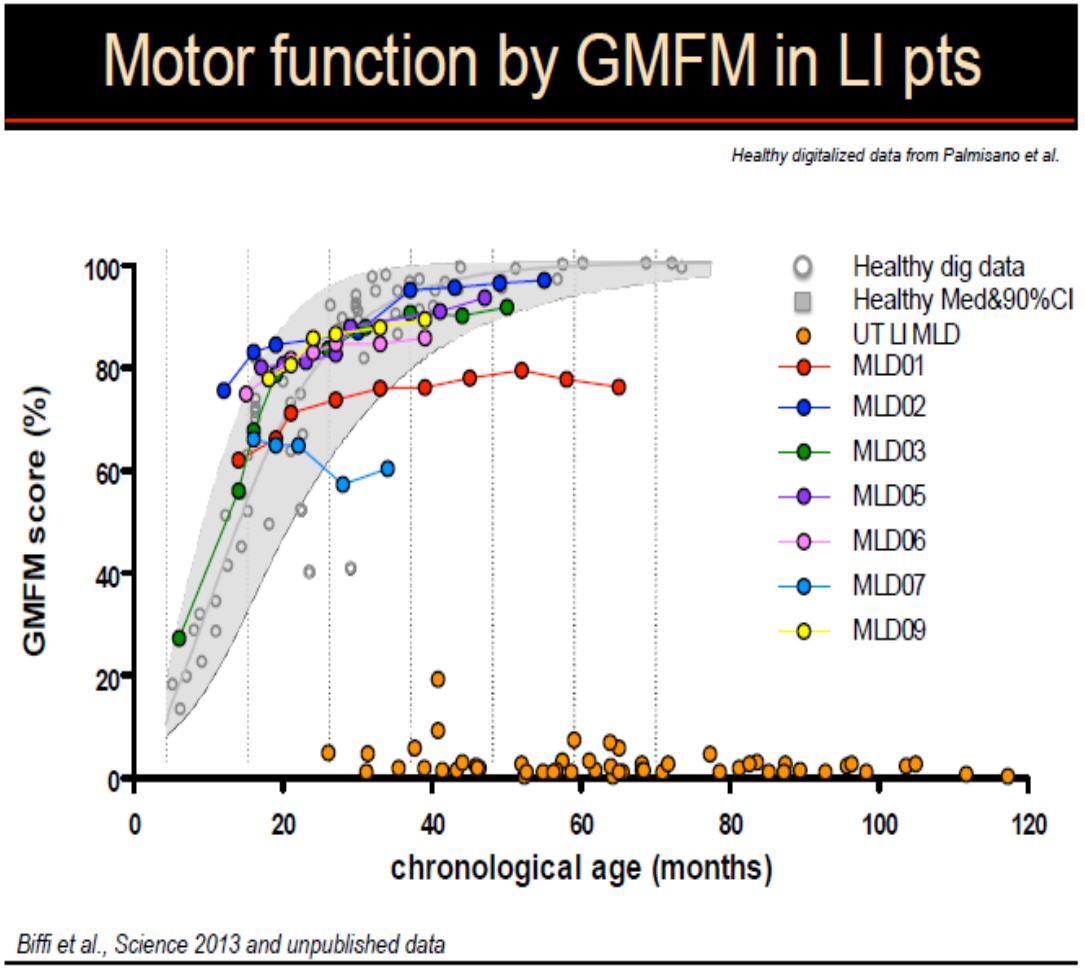


As of Jun 2014 (n=6)

Ferrua *et al*. Blood 2015

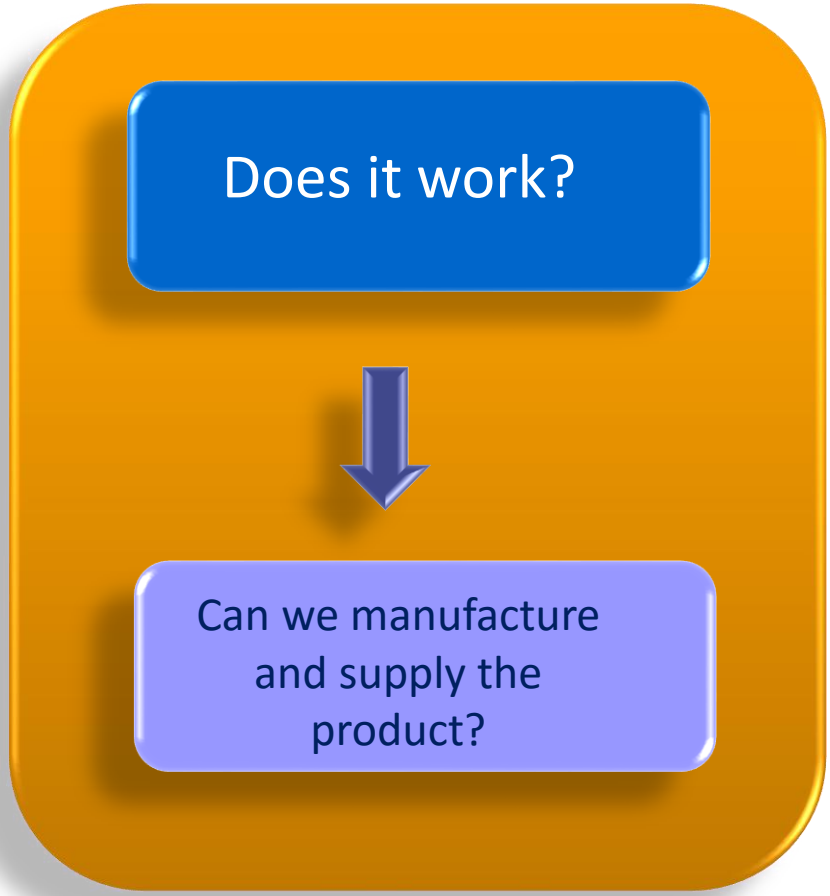
Gen Therapy for Metachromatic Leucodystrophy (MLD)

- Clinical study includes Late Infantile and Early Juvenile patients (n = 20)
- Total of 9 Late Infantile patients treated (7 shown)
  - 6 normal function
  - 2 sub-normal function
  - 1 low functional status
- All patients have survived past the death of their siblings
- 1 Fatality (unrelated to treatment)



A new kind of Challenge

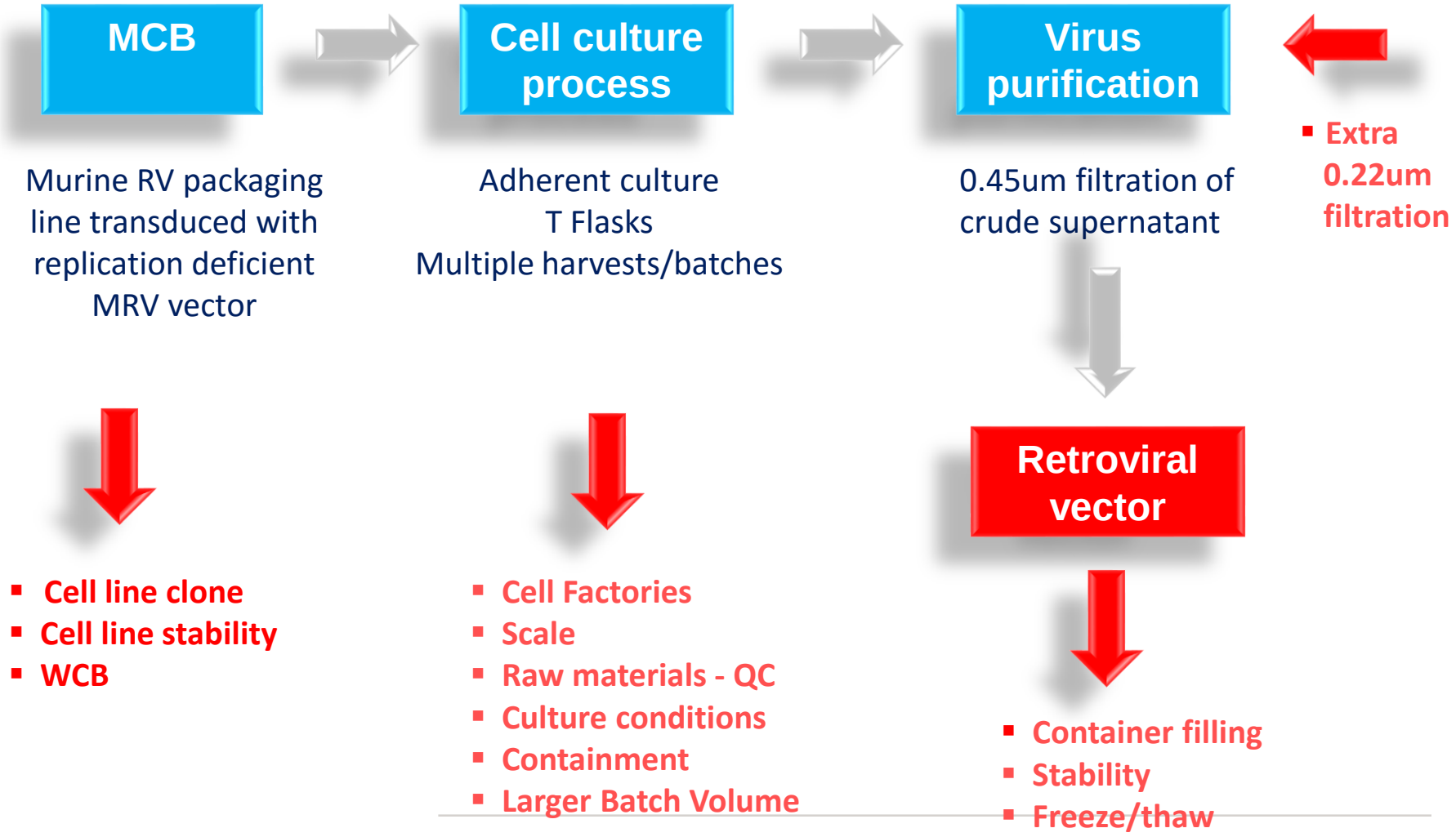
The historical project risk balance



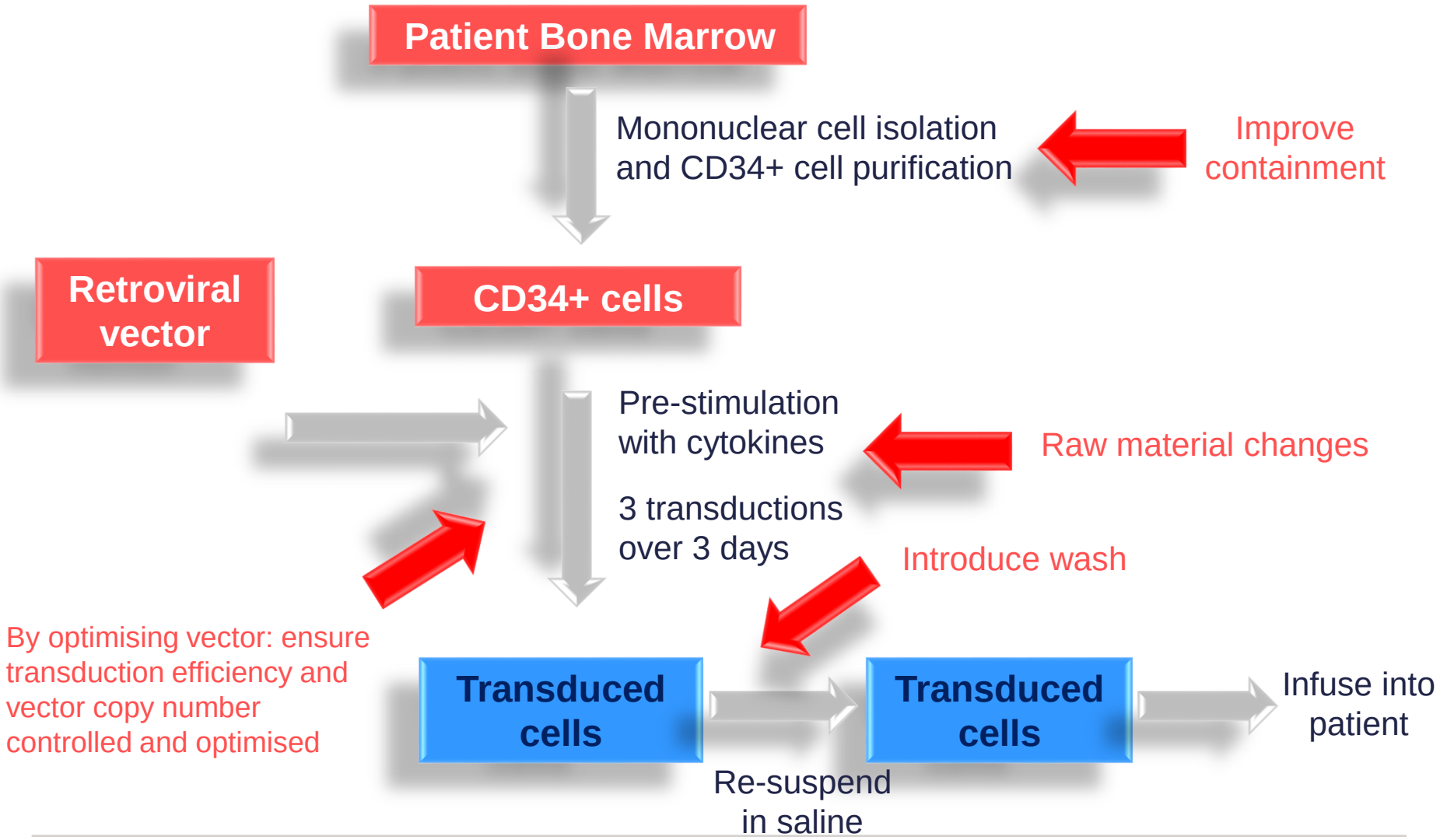
Risk balance for our lead programmes

Retroviral vector production – Scale up

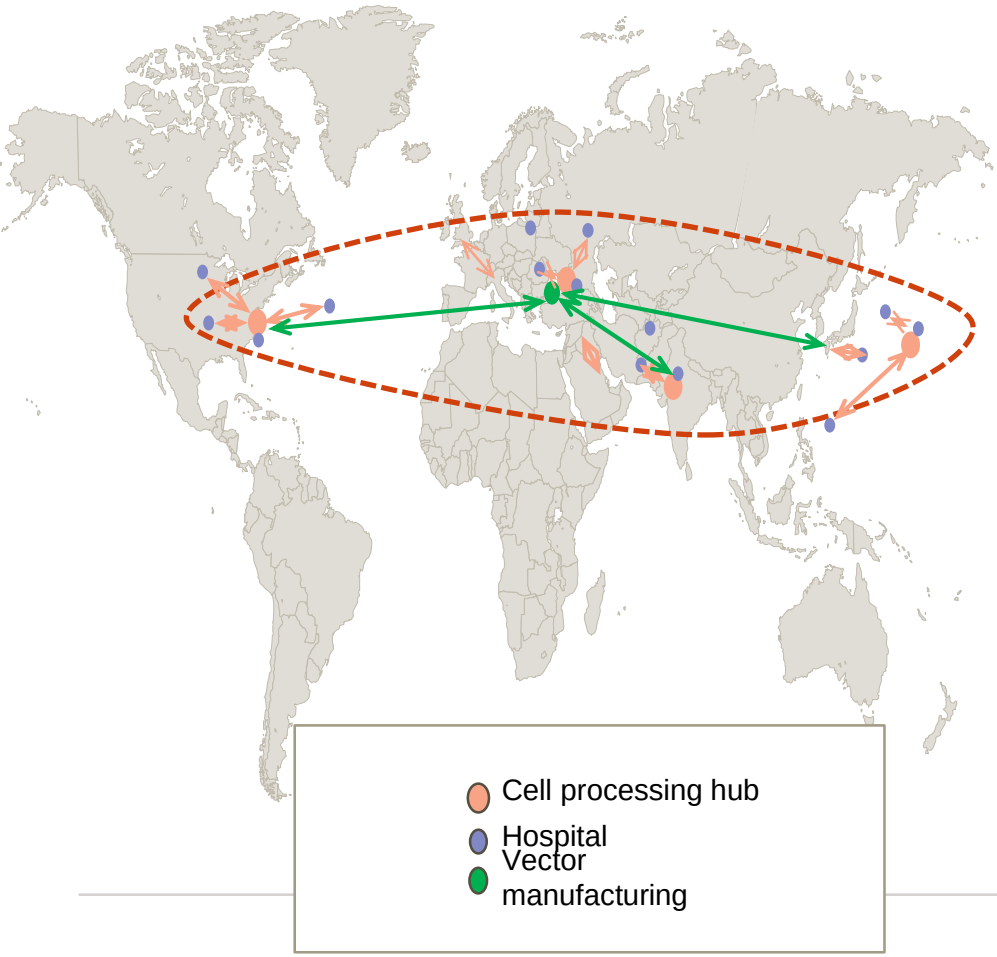
ADA-SCID



Cell Production changes



Planning the delivery of autologous gene therapy medicines globally



Vector manufactured in Italy (MolMed S.p.A.) and delivered to a global network of regional cell processing hubs

Regional hubs would serve a network of transplant centres of excellence

GSK investing in partnering options in the US and other regions:

- Partners for cell processing
- Partnering options with transplant centres to deliver gene therapy medicines
- Partners to provide logistics

Transforming patients' lives