Ensuring academic innovations reach patients

The story of a gene therapy for RAG1 deficiency

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Transforming lives with stem cell medicine

The Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW) is supported by a Novo Nordisk Foundation grant number NNF21CC0073729

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Disclosure

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reNEW The Novo Nordisk Foundation Center for Stem Cell Medicine

- Important Project of Common European Interest (IPCEI)

European Commission

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The opinions shared in this presentation reflect my personal views

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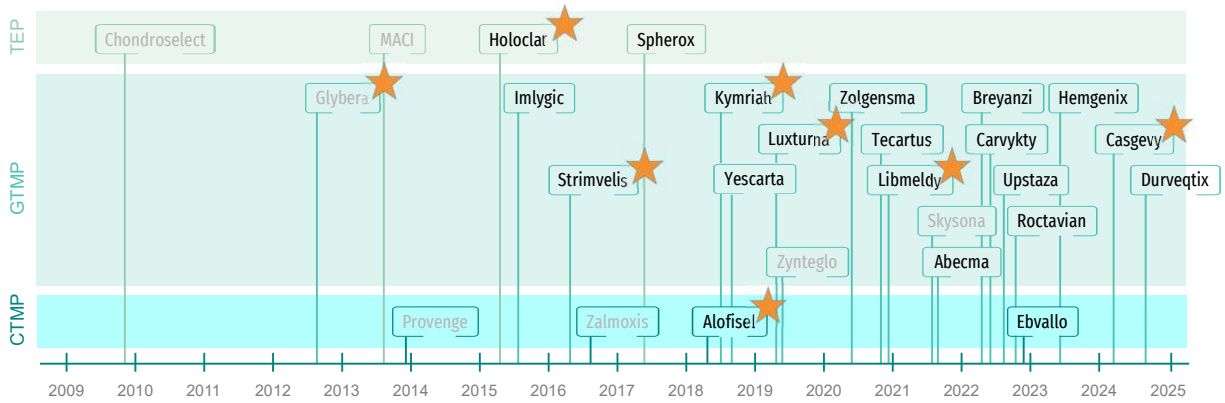
EMA approved ATMPs[1]
>30% have academic origin[2-4]

TEP: Tissue Engineered Product
GTMP: Gene Therapy Medicinal Product
CTMP: Cell Therapy Medicinal Product
Withdrawn/MA not renewed
★Academic origin[2]



1. EMA. CAT quarterly highlights and approved ATMPs (Novenber 2024). EMA/CAT/511673/2024. Last accessed: 04DEC2024. 2. Olesti *et al.* Cytotherapy. 2024;26(3):221-230. 3. Okuyama. *Drug Discov Today*. 2024;29(2):103866. 4. Kneller. *Nat. Rev. Drug Discov.* 2010;9:867–882.

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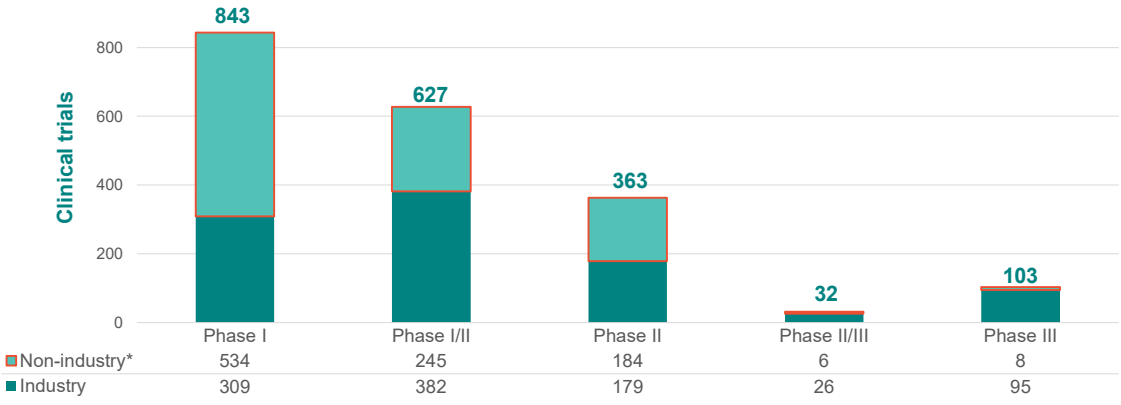
Academic development of advanced therapies
Mostly in non-clinical and early clinical development



1. Alliance for Regenerative Medicine. Q3 2024 Sector Data: Clinical Trials. Via: https://alliancerm.org/data. Last accessed: 10DEC2024

Non-industry: academic and government sponsors

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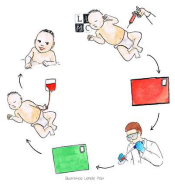
This research started 20 years ago…

First patient in the Netherlands successfully treated with stem cell gene therapy

22 June 2022 • *PRESSRELEASE*

Researchers at the Leiden University Medical Centre (LUMC) have successfully used stem cell gene therapy to treat a baby with the severe congenital immune disorder SCID. An important milestone: it is the first time stem cell gene therapy of Dutch origin is administered to a patient, and also the first time it is used to treat this particular form of SCID worldwide. The treatment was effective and the patient is doing well.



Molecular Therapy
Methods & Clinical Development
Original Article

Successful Preclinical Development of Gene Therapy for Recombinase-Activating Gene-1-Deficient SCID

Laura García-Perez,[1] Marja van Eggermond,[1] Lieke van Roon,[1] Sandra A. Vloemans,[1] Martijn Cordes,[1] Axel Schambach,[2] Michael Rothe,[2] Dagmar Berghuis,[1] Chantal Lagresle-Peyrou,[3,4,5] Marina Cavazzana,[3,6,7] Fang Zhang,[1] Adrian J. Thrasher,[1] Daniela Salvatori,[8,9,10,11] Pauline Meij,[8] Anna Villa,[10] Jacques J.M. Van Dongen,[1] Jaap-Jan Zwaginga,[1] Mirjam van der Burg,[1] H. Bobby Gaspar,[1] Arjan Lankester,[1] Frank J.T. Staal,[1] and Karin Pike-Overzet[1]

LUMC. Press release 22JUN2022. Eerste patiënt in Nederland succesvol behandeld met stamcelgentherapie. Via: https://www.lumc.nl/over-het-lumc/nieuws/. Illustration: Lieneke Post. Right photo: Getty Images

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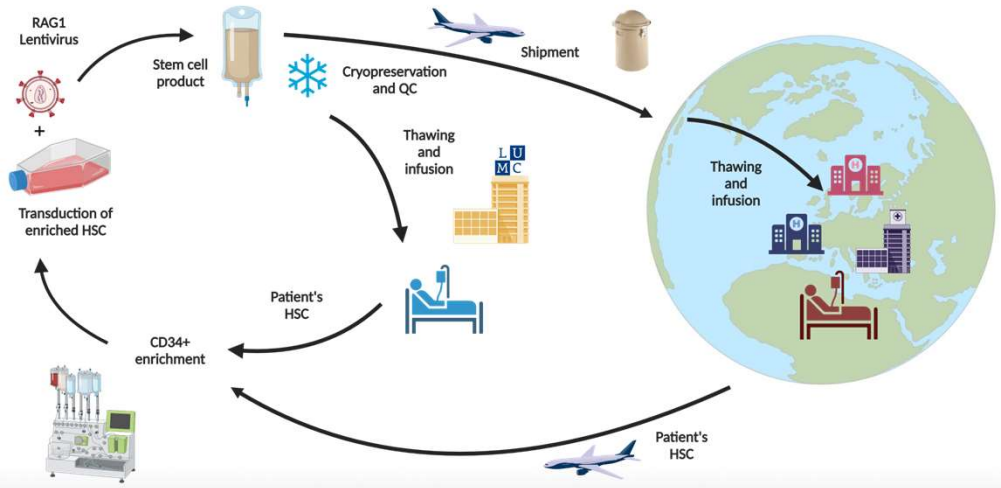
Cells travel, not the patient



Funding from the European Union's Horizon 2020 research and innovation programme under grant agreement 755170

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Recomb gene therapy

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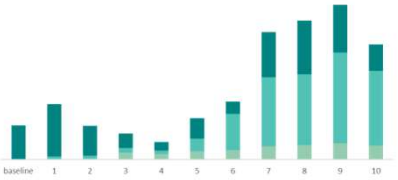
Where are we now…?

- Phase I/II trial sponsored by LUMC
- Inclusion criteria:
  - Rag1 deficient SCID as confirmed by genetic analysis
  - <2 years old
  - Peripheral blood T cells <300/µL and/or naive T cells <1/µL
  - Lack HLA-identical sibling or 10/10 Matched Unrelated Donor
- Exclusion criteria:
  - Omenn syndrome, hypomorphic RAG1 deficiency, previous allogeneic HSCT
- Approved clinical sites:
  - Spain, Poland, Italy, Turkey, Australia, UK
- Endpoints:
  - Feasibility: Successful generation of an IMP
  - Safety: Event free survival (EFS) after infusion
  - Overall survival, efficacy, clinical outcomes

- 5 patients included in the trial
- Good reconstitution of the immune system



- Clinically doing well
- First 2 patients (>1.5 year post HSCT) with normal vaccine responses

1. Study Details | Phase I/II Clinical Trial Stem Cell Gene Therapy in RAG1-Deficient SCID | ClinicalTrials.gov. 2. picture shown with consent

Funding from the European Union's Horizon 2020 research and innovation programme under grant agreement 755170

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Narrow evidence base
Pivotal trials for approved ATMPs (EMA)

Trade name	Pivotal study	Non-randomized	Non-controlled	Historical control	Intermediate endpoints	Population/no. of patients (enrolled)
Gene therapy medicinal products						
Kymriah (ALL)	Phase II	✓	✓	✓	✓	Children/92
Kymriah (DLBCL)	Phase II	✓	✓	✓	✓	Adults/147
Yescarta	Phase I/II	✓	✓	✓	✓	Adults/111
Tecartus	Phase II	✓	✓			Adults/105
Imlygic	Phase III				✓	Adults/437
Glybera	3 Phase II/III	✓	✓		✓	Adults/45
Strimvelis	Phase I/II	✓	✓	✓		Children/12
Luxturna	Phase III				✓	Children and adults/31
Zynteglo	Phase I/II and Phase III	✓	✓		✓	Children and adults/41
Zolgensma	Phase III	✓	✓	✓		Children/22
Libmeldy	Phase I/II	✓	✓		✓	Children/22
Skysona	Phase II/III	✓		✓		Children/32[a]
Abecma	Phase II	✓	✓	✓	✓	Adults/140

1. Iglesias-Lopez et al. Mol Ther Methods Clin Dev. 2021 Nov 11;23:606-618.

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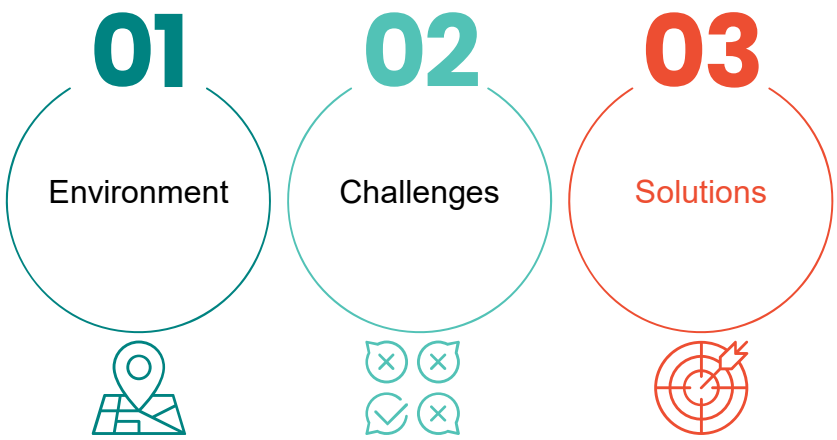

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Can academia do this alone?

…and should they?

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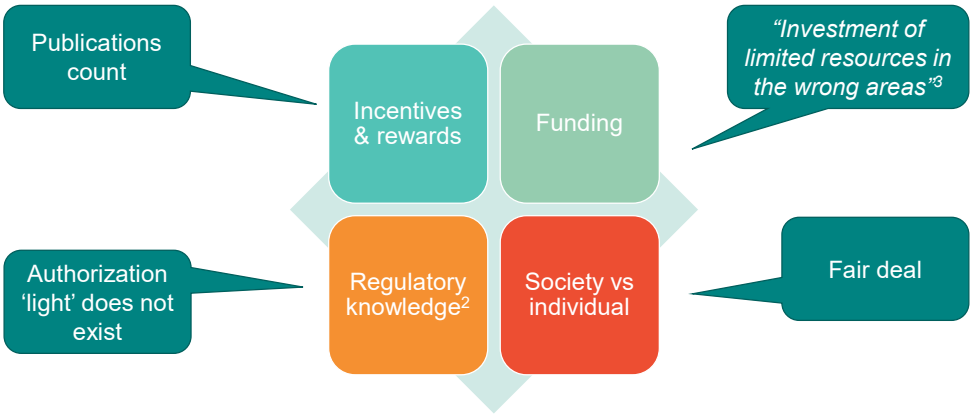
Well-positioned and well-equipped?
Challenges



1. Ogier et al. Translating academic discovery to patients' benefits: is academia ready to assume its key role? Swiss Academies Communications. 2019;14(1).
2. Hidalgo-Simon and Fibbe. Br J Clin Pharmacol. 2021;87(6):2412-2413. 3. Murray *et al. Drug Discovery Today*. 2024;29(4):103918.

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Academia is stepping forward: 2 examples

AGORA
Access to Gene Therapies for Rare Diseases

- Facilitating access to effective gene therapies for treatment of patients with ultra-rare diseases


Correspondence

Access to gene therapy for rare diseases when commercialization is not fit for purpose

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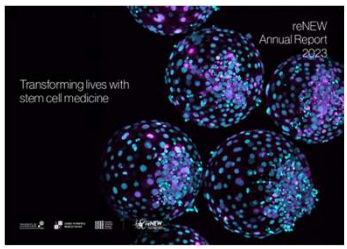
- Advance stem cell-based therapies
- Global collaborative network in targeted biomedical research



1. Fox et al. Nat Med 29, 518–519 (2023). 2. www.agoragenetherapy.org (last accessed: 17SEP2024) 3. www.renew.science.com. (last accessed: 17SEP2024)

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The landscape is changing…
First academic Marketing Authorization Holder

NEWS | 06 October 2023

Rescue of an orphan drug points to a new model for therapies for rare diseases

In a world-first, the Italian research charity Telethon will manufacture and distribute a gene therapy for an inherited immunodeficiency that was dropped by the industry.

Maria Cristina Valsecchi

Valsecchi MC. Rescue of an orphan drug points to a new model for therapies for rare diseases. Nature Italy. 06 October 2023. https://doi.org/10.1038/d43978-023-00145-1

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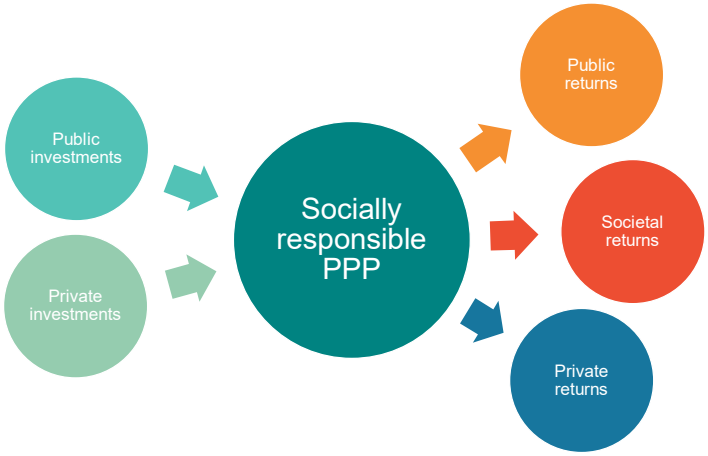
Socially responsible partnerships
A next step?



1. Rosenberg et al. J Inherit Metab Dis. 2023;46(5):806-816.

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Thank you for your attention

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