NVGCT Nederlandse Vereniging voor Gen- & Celtherapie

Program
ANNUAL CONFERENCE
June 25th and 26th 2026

Congrescentrum De Werelt

Westhofflaan 2, 6741 KH Lunteren

THURSDAY JUNE 25th 2026

9.00 **Registration and Coffee**

9.30 **Welcome and Opening Announcements**
Victor van Beusechem, President of the NVGCT

9.35 - 11.00 **SESSION I STEM CELLS & GENE EDITING**
Chair: Massimiliano Caiazzo

9.35 **FRANÇOISE CARLOTTI, LUMC**
Towards the next generation of beta cell replacement therapy for type 1 diabetes

10.05 **SANDER KOOIJMANS, UMC Utrecht**
Structural modification of short hairpin RNAs promotes siRNA delivery by biological vectors

10.30 **MAAIKE LENDERINK, UMC Utrecht**
Toward Scalable In Vivo Gene Correction for Mevalonate Kinase Deficiency and other Inherited Metabolic Diseases: A Platform-Based Preclinical Approach

10.45 **EVELINE ILCKEN, UMC Utrecht**
High throughput pegRNA screen for therapeutic prime editing of monogenic disorders

11.00 Coffee break

11.30 **EXHIBITOR PITCHES**
Chair: Fréderique de Graaf

Eurofins, Fujifilm Europe, Miltenyi en Sartorius

11.50 **ZonMw Young Investigator SpeedDate Challenge part 1**
Chair: Jan Theys

Presentation by 2025 winners: ***Despoina Trasanidou*** *(Sanquin)*
Tessa Prins *(ExoVectory)*

12.00 **STORYTELLING**
Chair: Niek van Til

MARLOES ten KATE, Take the Stage
Pitch Perfect

13.00-14:00 Lunch

13.30 - 14.30 **ZonMw Young Investigator SpeedDate Challenge part 2**
Chair: Jan Theys
Speed-dating (PIs & young investigators)

14.30 - 15.15 **KEYNOTE LECTURE**
Chair: Niek van Til
ZOLTAN IVICS, University of Leipzig, Germany
Going non-viral: genetic engineering of therapeutic cells with transposon technologies

15.15 Coffee break

15.45 - 17.00 **SESSION II RARE-NL – A PLATFORM FOR RARE DISEASES**
Chair: Karien de Rooij

15.45 **SIBREN van den BERG, RARE-NL & MIKE BROEDERS, FAST**
RARE-NL and ATMP-NL: building towards sustainable development and access for rare diseases and ATMPs

16.00 **GERTY SCHREIBELT & RENÉE RAAIJMAKERS, Radboudumc**
Therapy Accelerator for Rare Diseases: Advancing genetically corrected pericyte therapy for Myotonic Dystrophy type

16.15 **DIRK van ASSELDONK, Lenticure**
Challenges of a Social Enterprise

16.30 **JASMIJN KORPERSHOEK, UMC Utrecht**
IMPACT: autologous chondrons combined with allogeneic MSCs for treatment of cartilage defects

16.45 **DISCUSSION**

17.00 NVGCT General Assembly

17.30 **POSTER SESSION AND DRINKS**
See poster list on page 7.

19.00 Dinner

20.30 **LEGENDARY NVGCT PUBQUIZ**
Quizmaster: Jan Theys

FRIDAY JUNE 26th 2026

9.00 **Announcement Speed Date Finalists**

9.05 - 9.45 **KEYNOTE LECTURE**
Chair: Massimiliano Caiazzo
GABRIELE LIGNANI, University College London, UK
Reprogramming Brain Circuits: Towards On-Demand Gene Therapy for Neurological Disorders

9.45 - 10.45 **SESSION III NEURO & METABOLIC**
Chair: Annelot van Esbroeck

9.45 **KIMBERLY PIETERSZ, Netherlands Institute for Neuroscience**
Developing AAV-based gene therapy to target the catecholaminergic system in Parkinson's disease

10.05 **KIM WIJNANT, Radboudumc**
Mapping alternative splicing in iPSC-derived brain cells as a resource for therapeutic discovery

10.25 **ILMA REVERS, Amsterdam UMC**
Brain-directed gene therapy rescues a mouse model of neurodegenerative disease vanishing white matter

10.45 Coffee break

11.05 - 11.30 **Greiner Award for Best Thesis 2025**
Chair: Massimiliano Caiazzo

11.30 - 12.00 **ZonMw Young Investigator SpeedDate Challenge part 3**
Chair: Jan Theys

Pitches three finalists (5 minutes pitch, 5 minutes questions each)

12.00 Lunch

13.00 - 13.45 **SESSION IV REGULATORY**
Chair: Vera Kemp

13.00 **KATIA PAUWELS, Sciensano, Brussels, Belgium**
Can new gene therapies result in unintended germline modification?

13.15 **YUXI ZHAO, LUMC**
From guidance to study design: A risk-based regulatory strategy for an innovative in vivo gene editing therapy

13.30 **CHRISTINE van HATTEM, Utrecht University**
Patient access to cell and gene therapies through the European hospital exemption pathway in the Netherlands

13.45 **IMPORTANCE OF NEGATIVE DATA**
Chair: Karien de Rooij

STEFAN GAILLARD, Journal of Trial and Error
Failure as Fuel for Scientific Progress

14.15 Coffee break

14.45 - 15.45 **SESSION V GENE THERAPY FOR ONCOLOGY**
Chair: Enrico Mastrobattista

14.45 **DANIEL MATA, Princess Máxima Center**
Targeted Lipid Nanoparticles for the In Vivo Silencing of RUNX1::ETO in AML

15.00 **JELLA van de LAAK, Maastricht University**
Genetically modified bacteria as anti-cancer Trojan horse; in vivo anticancer effects of intratumoral immunotherapy producing Clostridium sporogenes

15.15 **JAIME FERNÁNDEZ BIMBO, Utrecht University**
Specificity and biodistribution of a T cell–targeted lipid nanoparticle for in vivo CAR-T generation

15.30 **TEREZA BRACHTLOVA, Amsterdam UMC/ORCA Therapeutics**
ORCA-010 Oncolytic Adenovirus Converts Immunologically Cold Tumors to Hot and Drives Durable Anti-Tumor Immune Responses: Phase I/IIa Results in Prostate Cancer

15.45 **NVGCT OUTSTANDING ACHIEVEMENT AWARD CEREMONY**
Chair: Victor van Beusechem

ROB HOEBEN, LUMC
Genetic modification and spontaneous mutation as complementary approaches for generating genetic diversity in oncolytic viruses

16.30 **Announcement Award Winners**
Jan Theys

16.45 **Closing remarks**
Victor van Beusechem, President of the NVGCT

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POSTER SESSION

Submitted abstracts and MSc students

P1 AXELLE LORIAUX, CELL SIGNALING TECHNOLOGY, USA
A Novel Monoclonal Antibody for the Detection, Enrichment, and Activation of Cells Expressing scFv-based Chimeric Antigen Receptors

P2 Madelon van Hoek, Leiden University
Progenitor-derived cDC platform to detect tumor antigen-specific T cells

P3 Manuela Lestón Cambeiro, University of Barcelona
Establishing a Reporter Cell Line to Detect SmD1–SmD2 Protein–Protein Interaction in Non-Small Cell Lung Cancer

P4 CLARA ALEMANY, ERASMUS MC
Ex vivo platform for personalized oncolytic virotherapy in glioblastoma

P5 Mariña Monteagudo Lago, Vrije Universiteit Amsterdam
Targeting of the Spliceosomal Protein SmD2 Suppresses Tumor Growth in Human Non-Small Cell Lung Cancer using Chicken Embryo Chorioallantoic Membrane (CAM) Tumor Model

P6 Angelique Versteegen, Leiden University / Leiden University Medical Center
The impact of oncolytic virotherapy on the Type-I Interferon response in pancreatic ductal adenocarcinoma (PDAC)

P7 PEIYU LI, AMSTERDAM UMC
Evaluation of SmD2 Gene Silencing to Treat Non-Small Cell Lung Cancer on Patient-Derived Tumor and Normal Airway Organoids in vitro and Xenograft Tumors in vivo

P8 Giulia Bovenga, Utrecht University
Brain targeting via lipid nanoparticles functionalized with an anti-HB-EGF nanobody

P9 MARTIJN KOPPENS, UMC UTRECHT
Mitochondrial genome editing to edit your favourite mutation in your cell model of choice

P10 JOSE CASTRO-ALPÍZAR, UMC UTRECHT
When Prime editing meets a difficult mutation: Lessons from MMUT

P11 THIJS RIETVELD, LUMC
Streamlining the transition of Advanced Therapies: an introduction to CORE-AMTP

P12 PIERRE SPRINGUEL, SARTORIUS
Evaluation of a novel all-in-one automated bioreactor for intensified autologous CAR-T cell manufacturing

P13 SIMON STAUBACH, SARTORIUS
Innovative Lipid-Based Delivery Solution: Unlocking New Opportunities in Manufacturing Genetically Modified Immune Cell Therapies

P14 GANESH RAMESH, UMC UTRECHT
Current Capacity and Gaps in Viral Vector Manufacturing: A Survey of Centers Associated with CTIWP of EBMT, NXTGEN-Hightech, DARE-NL, T2EVOLVE, and GoCART Coalition

P15 JORT ALTENBURG, UMC UTRECHT
ICAT, viral vector unit: accelerating clinical translation of advanced therapeutic medicinal products in an academic setting

P16 ALEXEY PINDYURIN, ANNOGEN BV
Safer and more effective gene therapies through high-throughput screening for precise, inducible, and cell-specific promoters

P17 Federica Tili, Utrecht University
Generation of human motor neurons via mRNA lipid nanoparticles

P18 GIORGIO GILIOLI, LUMC
Artificial thymic organoids can be used to study T-cell development from iPSC-derived hematopoietic stem cells

P19 Dewi Sprenkeler, Radboud University
Developing a Gene Therapy for Parkinson's Disease in a Mouse Model

P20 YUE CHEN, AMSTERDAM UMC
Developing a New Treatment for α-amanitin Poisoning

Submitted abstracts can be found below (page 31-44).

ABSTRACTS

NVGCT Outstanding Achievement Award Winner

ROB HOEBEN

Genetic modification and spontaneous mutation as complementary approaches for generating genetic diversity in oncolytic viruses

Rob C. Hoeben, Taco G. Uil, Iris J.C. Dautzenberg

Dept of Cell and Chemical Biology, Leiden University Medical Center, Leiden, The Netherlands

Adenoviruses and reoviruses are frequently used for oncolytic purposes. Whereas most oncolytic Ad-based vectors were generated through rational design, the reoviruses used were elected from a library of spontaneous mutants. Both strategies led to significant vector improvements. In adenoviruses, genetic modification-based strategies dominate but these approaches can be hampered by insufficient understanding of the viruses' intricate functions. In reoviruses, bioselection-based strategies lead the efforts on generation of new oncolytic variants. The difference between these viruses can be explained by the high-fidelity of adenovirus DNA replication, which results in a very low mutation rate (1.3×10^{-7} per base per cell infection cycle; Risso-Ballester et al., 2016). In reoviruses, there is no proofreading in the genome replication, leading to a mutation rate approximately 100- to 400-fold higher than that of adenoviruses.

Several years ago we generated a panel of adenovirus-polymerase variants harboring mutations in the domains involved in incoming base-selection, and the exonuclease function. As a consequence, the polymerases are error-prone and exhibit a decreased fidelity of DNA replication. The use of these mutants facilitates the bioselection of adenoviral phenotypes.

In my presentation, I will discuss the use of bioselection of spontaneous mutants with desired phenotypes that are useful for oncolytic-virus therapies.

Keynote Lecture

ZOLTAN IVICS

GOING NON-VIRAL: GENETIC ENGINEERING OF THERAPEUTIC CELLS WITH TRANSPOSON TECHNOLOGIES

Z. Ivics [1,2]

[1]Institute for Clinical Immunology, University of Leipzig, Germany; [2]Department of Clinical Gene Transfer, Fraunhofer Institute for Cell Therapy and Immunology, Leipzig, Germany

Transposons are jumping genes that have coevolved with their host genomes throughout evolution and are abundantly represented in all kingdoms of life. Nonetheless, only a small fraction of transposons are currently active in nature. Having recognized this, we have resurrected, by using molecular biology technologies, an active transposon from fish genomes that we named *Sleeping Beauty* (SB). SB is one of the first examples of synthetic biology in that it represents a gene that only exists in the laboratory. Very importantly, SB was the first transposon that has been demonstrated to be active in human cells, thereby opening the door for therapeutic applications. In the past 25 years we have characterized the basic mechanisms involved in SB transposition, and optimized its use for genetic engineering of human cells. Currently ongoing developments aim to clinically evaluate the system in the context of human lymphocytes engineered to express synthetic antigen receptors to treat cancer. We are currently evaluating the system for its applicability in hematopoietic stem cells, which would open the door for therapies of an entire array of inherited, monogenic diseases of the blood. Finally, we made significant progress in engineering the SB transposase with the goal of enhancing its activity and modifying its genome-wide insertion profile in human cells. These recent developments enable human clinical applications not only efficiently but at the same time at an advanced level of safety as compared to concurrent technologies.

Keynote Lecture

GABRIELE LIGNANI

Reprogramming Brain Circuits: Towards On-Demand Gene Therapy for Neurological Disorders

Gabriele Lignani[1]

[1]Research Department of Epilepsy, UCL Queen Square Institute of Neurology, London, UK

Disorders of the brain, from epilepsy to neuropsychiatric conditions, are increasingly understood as diseases of dysfunctional neural circuits rather than solely the consequence of single gene defects. While gene and cell therapies have transformed our ability to target the nervous system, most current strategies remain static, designed to replace, silence, or augment genes without adapting to the dynamic nature of brain activity. A central challenge therefore remains: how can we intervene with precision in circuits that are constantly changing, without disrupting the neural activity that underpins normal function?

In this work, we explore a new paradigm for gene therapy, one that is adaptive, activity-dependent, and intrinsically guided by the brain itself. We developed a strategy that selectively identifies and modulates overactive neurons in real time, operating in a closed-loop manner to suppress pathological activity only when it arises. Across multiple models of epilepsy, this approach achieves sustained seizure control while preserving normal behaviour, demonstrating the potential of therapies that act only where and when they are needed.

More broadly, this work points towards a shift from gene replacement to circuit reprogramming: from fixed interventions to responsive systems that restore balance within complex biological networks. By harnessing endogenous activity as both the trigger and the target of therapy, activity-dependent gene delivery opens the possibility of treating brain disorders independent of their underlying cause.

This emerging class of “on-demand” genetic therapies offers a conceptual and translational framework for precision medicine in the brain, with potential applications extending far beyond epilepsy to a wide range of neurological and psychiatric diseases.

MARLOES ten KATE

PITCH PERFECT

TaketheStage.nl | ScientificStorytelling.nl
Amersfoort, The Netherlands

Learn how to present your work clearly, engagingly, and convincingly.

As an expert in gene and cell therapy, you have likely experienced how difficult it can be to make highly technical information understandable, engaging, and impactful for others. Not only with doctors and patients, but also when collaborating with experts from other fields, speaking to policymakers, and sometimes even internally, it can be challenging to communicate your knowledge in an accessible way.

Scientific knowledge is inherently complex, so how can you make it accessible and easy to understand for others?

Marloes ten Kate is a presentation trainer and storytelling expert. In today's short session, she will introduce you to a simple yet highly effective communication model. This method helps you quickly prepare presentations that are engaging, clear, and impactful.

Participants will also have the opportunity to join a follow-up online training (in Dutch), to learn more insights and practical methods. So you can explore the approach in more depth and apply it to your own practice.

INVITED SPEAKERS

FRANÇOISE CARLOTTI

Towards the next generation of beta cell replacement therapy for type 1 diabetes

B. Rajaei[1,2], M. Tihaya[3], E. Steeneveld[1,2], L. Daleman[1,2], A Gasiunaite[3], M. Hanegraaf[1,2], A. de Leeuw[1,2], P. Meij[3], E.J.P de Koning[1,2], F. Carlotti[1,2]

[1]Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands; [2]Cure One, LUMC T1D research center, Leiden, The Netherlands; [3]Center for Cell & Gene Therapy, Leiden University Medical Center, Leiden, The Netherlands.

Type 1 diabetes (T1D) is a chronic disease in which insulin-producing beta-cells are destroyed by the immune system, leading to an inability to regulate blood sugar levels. There is currently no cure, and patients require life-long insulin therapy to survive. Beta-cell replacement therapy through pancreas or islet transplantation represents a functional cure for the most severely affected patients. However, this option is limited to a small group of patients due to a shortage of organ donors.
Pluripotent stem cell-derived pancreatic islets (SC-islets) hold great promise as next-generation beta-cell replacement therapy in patients with severe type 1 diabetes. Our lab developed a clinically-compliant, full 3D, multi-stage differentiation protocol to generate SC-islets, including an extensive characterization of the end product both *in vitro* and *in vivo*. We next engaged in translating our cell product toward clinical application, which requires adapting our processes to comply with Good Manufacturing Practices (GMP) and developing a manufacturing strategy that includes quality control and defined release criteria.
While the first clinical data from the field are very promising, key challenges remain to enable the long-term sustainability of such PSC-based therapies.

SANDER KOOIJMANS

Structural modification of short hairpin RNAs promotes siRNA delivery by biological vectors

Jarik M. Stoutjesdijk[1,2], Puck H. de Rooij[1,2], Lieke Velthuis[3], Olivier G. de Jong[4], Sander A.A. Kooijmans[1,2]

[1]Metabolic Diseases, Wilhelmina's Children's Hospital, University Medical Center Utrecht, Utrecht, 3584 EA, The Netherlands; [2]Regenerative Medicine Center Utrecht, Utrecht, 3584 CT, The Netherlands; [3]CDL Research, University Medical Center Utrecht, Utrecht, 3584 CX, The Netherlands; [4]Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

Biocompatible cell-derived vectors such as extracellular vesicles (EVs) and virus-like particles (VLPs) have gained increasing interest as next-generation delivery systems for therapeutic RNAs, including siRNAs. However, it remains challenging to load these vectors with siRNA at high concentrations. At the same time, after vector uptake by cells, encapsulated siRNA should efficiently be liberated in the cytoplasm. Here, we overcame these challenges by structurally modifying short hairpin RNAs so that they are actively loaded into EVs and VLPs, and converted to functional, gene-silencing siRNA after uptake by recipient cells.

To improve siRNA encapsulation in cell-derived nanoparticles, we inserted folded RNA structures (aptamers) in the backbone of enhanced green fluorescent protein (eGFP)-targeting short hairpin RNAs (shRNAs) at various locations. We expressed these shRNAs in HEK293T cells stably expressing Firefly luciferase or eGFP reporter genes, and found that shRNA gene silencing activity was strongly dependent on the location of the inserted aptamer. Northern blotting analysis demonstrated that activity of each shRNA correlated with its capacity to be processed into single-stranded siRNA by intracellular enzymes. Using ex vivo shRNA cleavage assays and gene knockout experiments, we confirmed that the cytosolic enzyme Dicer can process aptamer-modified shRNAs to active siRNAs, independent of the used siRNA sequence.

We next expressed modified shRNAs in HeLa or HEK293T cells and isolated EVs by tangential flow filtration and/or size exclusion chromatography. We observed high enrichment of unprocessed, aptamer-containing shRNAs in EVs when cells were engineered to overexpress canonical EV protein CD9 fused to an aptamer-binding protein (ABP). After uptake by cells, these EVs specifically reduced reporter gene expression in a dose-dependent manner. Gene silencing was further improved when EVs were engineered with the viral fusogen VSV-G, highlighting endosomal escape as a critical bottleneck for functional delivery. Finally, we showed that shRNA loading and functional delivery could be further potentiated when shRNAs were incorporated in MMLV-derived VLPs harboring ABP-modified Gag-pol proteins instead of CD9.

In conclusion, we have developed an engineering strategy to modify and efficiently load shRNAs into cell-derived delivery vectors and facilitate functional siRNA delivery to recipient cells. This platform technology is broadly applicable and reinforces development of novel, biocompatible siRNA therapeutics.

SIBREN van den BERG & MIKE BROEDERS

RARE-NL and ATMP-NL: building towards sustainable development and access for rare diseases and ATMPs

Van den Berg, S.[1], Broeders, M.[2], Stolwijk, N.N.[1,3]

[1.] RARE-NL Foundation, Amsterdam, the Netherlands; [2.] Centre for Future Affordable Sustainable Therapy development (FAST), Leiden, The Netherlands; [3.] Department of Endocrinology and Metabolism, Amsterdam UMC, Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Research Institute, Expertise Center for Inborn Errors of Metabolism, University of Amsterdam, Amsterdam, the Netherlands.

Drug repurposing and innovative therapies such as ATMPs and gene-based therapies, including RNA-based therapies (ATMP+), hold transformative potential for patients with high unmet medical needs. However, in the classic pharmaceutical model, the interests of companies, society, academic institutions and the government regularly conflict, leading to a system failure and sub-optimal progress in development of these innovations. Scientific, regulatory, organizational, and financial barriers frequently delay or prevent promising innovations from reaching patients, particularly in the rare disease field where expertise, patient populations, and resources are limited. To address these challenges, national initiatives such as RARE-NL and ATMP-NL have been established as “hubs” within the Centre for Future Affordable Sustainable Therapy development (FAST) ecosystem.

RARE-NL is a collaborative initiative in which university medical centres join forces and work with stakeholders in the field to support therapy development for rare diseases and drug repurposing. Embracing a 'case to system' approach, RARE-NL connects expertise, fosters collaboration and translates insights from individual cases into systemic solutions, with the ultimate goal of making effective therapies available to patients quickly, safely and responsibly.

ATMP-NL functions as an independent and connecting national platform aimed at strengthening the Dutch ATMP ecosystem and preparing the healthcare system for future innovations. ATMP-NL brings together stakeholders from across the full value chain, including academia, industry, regulators, payers, patient organizations, healthcare providers, and policymakers. Through strategic alignment, stakeholder representation, and co-creation of practical solutions, the platform aims to accelerate development, implementation, and sustainable patient access to ATMPs.

Together, RARE-NL and ATMP-NL represent complementary national coordination models that reduce fragmentation, strengthen collaboration, and contribute to a more sustainable and future-proof ecosystem for innovative therapies and patient access in the Netherlands.

GERTY SCHREIBELT & RENÉE RAAIJMAKERS

Radboudumc Therapy Accelerator for Rare Diseases: Advancing genetically corrected pericyte therapy for Myotonic Dystrophy type 1

R. Raaijmakers-Buurman[1], G. Schreibelt[2,4], K. Bos[2,4], K. Ruijtenbeek[4], M. Neefjes[4], M. Janssen[1,4], K. Mul[3], B.G.M. van Engelen[3], D.G. Wansink[2], H. van Bokhoven[1]

Department of Genetics[1], Medical BioSiences[2], Neurology[3], Therapy Accelerator for Rare Diseases[4], Radboud university medical center, Nijmegen, the Netherlands

Development of effective therapies for rare diseases faces significant scientific, regulatory, and economic challenges. The Therapy Accelerator for Rare Diseases at Radboudumc is a multidisciplinary team designed to overcome these barriers by fostering collaboration, innovation, and translational progress across the therapeutic development pipeline. Our team brings together expertise in clinical pharmacology, translational science, regulatory strategy, and patient-centered research to accelerate the journey from discovery to accessible, affordable, and available therapies.
A central objective is to identify and resolve translational bottlenecks within development programs. One such program focuses on a gene-edited stem cell therapy for Myotonic Dystrophy Type 1 (DM1), the most common adult-onset muscular dystrophy. DM1 is a multisystem disorder caused by an expanded CTG repeat in the *DMPK* gene, leading to progressive muscle weakness, cardiac abnormalities, endocrine dysfunction, cognitive impairment, and respiratory complications. With an estimated prevalence of 1 in 2,000–8,000 individuals and no curative treatment available, DM1 represents a compelling target for advanced therapeutic approaches.
We aim to use CRISPR/Cas9 technology to excise the pathogenic *DMPK* CTG trinucleotide repeat in autologous muscle precursor cells (pericytes), and transplant the corrected, edited cells back into the patient. The project is currently in the preclinical phase of the development of this stem cell/gene therapy for DM1 and we aim to move this project forward towards a first-in-human Phase 1 clinical trial.
The Therapy Accelerator supports this program by translating research protocols into GMP-compliant manufacturing and analytical methods for producing genetically corrected muscle precursor cells. In parallel, the team develops regulatory documentation, including a comprehensive product development plan. Insights gained through this collaboration will contribute to a broader ATMP development pipeline, enabling accelerated, cross-disease advancement of innovative cell and gene therapies.

JASMIJN KORPERSHOEK

IMPACT: autologous chondrons combined with allogeneic MSCs for treatment of cartilage defects

J.V. Korpershoek[1,2], L.A. Vonk[1,3], H. Stempels[1], N. van Egmond[1], D.B.F. Saris[1,2], R.J.H. Custers[1]

[1] Department of Orthopaedic surgery, UMC Utrecht, Utrecht, the Netherlands; [2] Department of Orthopaedic surgery, Mayo Clinic, Rochester, USA; [3] Xintela, Lund, Sweden

Aim and objective: The avascularity and low cellularity of articular cartilage prohibits spontaneous healing. For defects >2 cm², autologous chondrocyte implantation (ACI) is the clinical standard. While effective, it requires a first surgery to obtain a cartilage biopsy, followed by cell expansion, and a second surgery to implant the expanded cells. This imposes substantial burden on both patients and healthcare resources. IMPACT eliminates this patient-specific expansion by combining peroperatively isolated autologous chondrons with allogeneic bone marrow-derived mesenchymal stromal cells (MSCs), enabling single-stage intervention. Initial trial with 35 participants established safety profile, confirmed completely autologous hyaline-like tissue regeneration, and demonstrated patient-reported improvement maintained over 10 years. The current study aims to evaluate IMPACT's therapeutic efficacy compared with conservative management.
Methodology: Sixty symptomatic patients (aged 18-45 years) with cartilage defects 2-8 cm² participated in this crossover randomized controlled trial and were randomized to IMPACT or conservative therapy. Following randomization conservative therapy, participants could crossover after reaching the primary outcome at 9 months. The Knee Injury and Osteoarthritis Outcome Score (KOOS) served as the primary outcome, assessed at enrollment and months 3, 6, and 9. Secondary endpoints were 12- and 18-month KOOS, immunological response monitoring (anti-HLA antibody formation), adverse event tracking, and economic evaluation.
Results: At 6- and 9-month timepoints, IMPACT yielded statistically significant and clinically relevant KOOS improvements compared to conservative care ($p<0.05$). There were no serious adverse reactions. Immunological surveillance detected no donor-directed anti-HLA antibodies. The 25 patients who crossed over achieved similar improvement as patients randomized to IMPACT. Comprehensive cost-effectiveness analysis revealed IMPACT's cost savings from both healthcare system and societal perspective while delivering comparable quality-adjusted life years.
Conclusions: By combining autologous chondrons with off-the-shelf allogeneic MSCs, IMPACT offers autologous repair without the need for patient-specific cell expansion. IMPACT is a safe, effective, resource, and logistical attractive alternative to ACI.

DIRK VAN ASSELDONK

Challenges of a Social Enterprise

D.T.A. Dirk van Asseldonk[1], I. Isabel Gordaliza Alaguero[1], J.M.P. Hannerieke van den Hout[2,5] , N.A.M.E. Nadine van der Beek[3,5], W.W.M. Pim Pijnappel[1,2,4,5]

[1]LentiCure (100% affiliate company of Erasmus MC University Medical Center), Rotterdam, the Netherlands
[2]Department of Pediatrics, Erasmus MC University Medical Center, Rotterdam, The Netherlands.
[3]Department of Neurology, Erasmus MC University Medical Center, Rotterdam, The Netherlands.
[4]Department of Clinical Genetics, Erasmus MC University Medical Center, Rotterdam, The Netherlands.
[5]Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

Gene therapy is finally offering patients with severe, chronic hereditary disorders the prospect of halting the progression of their disease. In particular, lentiviral gene therapy is increasingly proving to be an effective treatment: a single administration with potentially a lifelong therapeutic effect. However, the first lentiviral gene therapies brought to market in recent years by the conventional pharmaceutical industry are priced at several million euros per patient. Such pricing is unsustainable for healthcare systems and represents a clear case of market failure. How are these prices determined? Which components drive these costs, and how can they be reduced?

LentiCure B.V. is a wholly owned subsidiary of Erasmus MC and therefore entirely publicly governed. This social enterprise aims to make lentiviral gene therapy for rare diseases accessible at the lowest possible cost. The company's initial focus is on Pompe disease, a severe metabolic and neuromuscular disorder.

In this presentation, the background of the company and of Pompe disease will be outlined as well as the pathway towards making this therapy accessible. The various obstacles and challenges along the way are identified and explained.

KIMBERLY PIETERSZ

DEVELOPING AAV BASED GENE THERAPY TO TARGET THE CATECHOLAMINERGIC SYSTEM IN PARKINSON'S DISEASE

K.L. Pietersz[1], T. Bracho[1], J. Rambow[1], B. Hobo[1], M. Romijn[1], V. Donega[2,3], B. Blits[6.], G. Scheefhals[5], F. De Winter[1], J. Verhaagen[1,4]

1. Laboratory for Regeneration of Sensorimotor Systems, Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences (KNAW), Amsterdam, The Netherlands.
2. Department of Anatomy & Neurosciences, CNAB, Amsterdam UMC, location Vrije Universiteit Amsterdam, De Boelelaan 1117, Amsterdam, The Netherlands
3. Amsterdam Neuroscience, Neurodegeneration, Amsterdam, The Netherlands
4. Department of Molecular and Cellular Neurobiology, Center for Neurogenomics and Cognition Research, Vrije Universiteit Amsterdam, Amsterdam, Netherlands
5. Syngle Therapeutics BV, www.syngletherapeutics.com, The Netherlands
6. Department of Metabolic Diseases, Wilhelmina Children's Hospital, University Medical Centre, Utrecht, The Netherlands

Aims: Adeno-associated viral (AAV)-mediated gene therapy offers a promising route for long-term disease modification in Parkinson's disease (PD). This study explores whether a single intravenous (IV) administration of an AAV vector can transform catecholaminergic neurons into "cellular factories" for therapeutic antibody production. By vectorizing the monoclonal antibody 26F1, we aim to establish a one-time minimally invasive strategy to selectively target pathological oligomeric forms of α-synuclein (α-syn). Methods: We first evaluated various Tyrosine Hydroxylase (TH) promoters to drive transgene expression specifically in catecholaminergic cells. Promoter constructs (luciferase or GFP) were packaged into AAV.PhP.eB, a vector capable of crossing the blood-brain barrier, and administered IV in mice. The most efficient promoter was then used to develop a PD model overexpressing α-syn A53T and the vectorized 26F1 antibody. Results: Screening of five candidate promoters identified a 2.5 kb sequence (Chan et al. 2017) as the most effective for our target regions. In an α-syn A53T overexpression model, this promoter-driven system resulted in a significant reduction of dopaminergic cells. Vectorized 26F1 antibody treatment exhibited a complex profile, characterized by acute motor impairment followed by significant long-term rescue from α-syn A53T-induced lethality. Conclusion: Our findings demonstrate that vectorized antibodies against α-syn can successfully prevent mortality in a relevant PD model. However, the cause of the initial motor decline for the vectorized antibody remains to be elucidated. Further studies are being undertaken to optimize the balance between safety and long-term neuroprotection.

KIM WIJNANT

Mapping alternative splicing in iPSC-derived brain cells as a resource for therapeutic discovery

Kim N. Wijnant, Imke M.E. Schuurmans, Annika Mordelt, Marina P. Hommersom, Lisenka E.L.M. Vissers, Nael Nadif Kasri

Radboudumc

Background:
Neurodevelopmental disorders (NDDs) present a significant therapeutic challenge, but antisense oligonucleotides (AONs) have emerged as a promising intervention. AONs can modulate alternative splicing to restore gene expression or protein function. For example, inhibiting nonsense-mediated decay (NMD)-sensitive splicing in heterozygous loss-of-function disorders can restore gene expression, while emerging strategies targeting homologous mutually exclusive exons allow therapeutic switching of exon usage to eliminate pathogenic variants in mutually exclusive exons.
Materials and Methods:
To explore the potential of these AON strategies for NDDs, we integrated long- and short-read RNA sequencing from iPSCs and iPSC-derived neurons, astrocytes, and microglia to systematically identify and characterize alternative splicing events, including their NMD-inducing potential, in cell types relevant to NDDs. We compiled these data into an online, cell type-resolved resource to facilitate therapeutic exploration.
Results:
Using this approach, we identified ~65,000 alternative splicing events, of which 62% were novel. Querying known NDD genes, we nominated 60 abundant NMD events in underlying 42 autosomal dominant NDDs as promising therapeutic targets, including in *SCN1A*, *CHD2*, *EZH2*, and *NR4A2*, and a newly identified abundant NMD event in *PHIP*. We also identified 2,541 high-confidence mutually exclusive exon events, including 58 MXEs harboring NDD-associated variants, highlighting additional opportunities for therapeutic modulation.
Conclusion:
Our findings provide a comprehensive resource for prioritizing alternative splicing events, including NMD-sensitive exons and mutually exclusive exons, as targets for AON-based therapies. This framework expands the potential of splicing-targeting AON strategies across NDDs, offering a roadmap for modulation of gene expression and protein function in NDDs.

STEFAN GAILLARD

Failure as Fuel for Scientific Progress

S.D.M. Gaillard[1]

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Scientific progress is often presented as a continuous sequence of breakthroughs, yet much of research consists of failed experiments, rejected hypotheses, and inconclusive findings that remain unpublished. This talk examines the growing recognition that such “failures” are not obstacles to scientific advancement, but essential components of it. Using insights from the Journal of Trial & Error, the first multidisciplinary journal dedicated to publishing rigorous failures and negative results, the presentation explores the persistent gap between what is researched and what ultimately enters the scientific literature.

Despite increasing awareness of publication bias, negative and null results remain systematically underreported due to reputational concerns, limited incentives, and publication systems that prioritize novelty and positive outcomes. This selective reporting distorts perceptions of scientific success, impedes cumulative knowledge production, and can lead to unnecessary duplication of research efforts.

The talk highlights several benefits of publishing trial-and-error and negative findings. Sharing unsuccessful experiments can improve the efficiency of scientific research by preventing redundant studies and reducing wasted resources. It can also strengthen meta-analyses by providing a more representative evidence base and improve the quality of machine learning models through access to broader and less biased datasets. Examples from psychology, chemistry, and biomedical research demonstrate how failed or inconclusive studies often contain valuable insights that contribute to future discoveries.

By reframing failure as a productive and informative part of the research process, the presentation argues for a more transparent and comprehensive scientific culture. Greater openness about research struggles and unsuccessful outcomes can support a more accurate understanding of science, foster collaboration, and ultimately accelerate scientific progress.

SUBMITTED ABSTRACTS - ORAL PRESENTATIONS

MAAIKE LENDERINK

Toward Scalable In Vivo Gene Correction for Mevalonate Kinase Deficiency and other Inherited Metabolic Diseases: A Platform-Based Preclinical Approach

Maaike Lenderink[1], Jose Castro Alpízar[1], Emilia Nagyova[1], Sawsan Shehata[1], Eva Hoytema van Konijnenburg[1], Joris van Montfrans[2], Joost Frenkel[2], Erika van Nieuwenhove[2], Sander Kooijmans[1], Sabine Fuchs[1]

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Mevalonate kinase deficiency (MKD) is a rare autosomal recessive metabolic disease caused by pathogenic variants in the *MVK* gene, leading to systemic autoinflammation and early mortality in severe cases. Current treatment relies on lifelong anti-inflammatory therapy. Although allogeneic hematopoietic stem cell transplantation can be curative, it carries significant risks, underscoring the need for alternative approaches. Genome editing, particularly base editing, offers the potential for precise, single-variant correction. While recent proof-of-concept demonstrates clinical feasibility, major challenges remain in extending these approaches beyond the liver and developing scalable strategies for broader clinical application.

We developed an *in vivo* gene correction strategy for MKD targeting both hematopoietic stem cells (HSCs) and hepatocytes. In parallel, we establish MKD as a model for a modular, scalable preclinical framework adaptable across *MVK* variants and extendable to other metabolic and hematopoietic diseases.

Two clinically relevant *MVK* variants were selected. Editing efficiency was evaluated in engineered Huh7 and K562 cell models carrying these variants, alongside reference controls to enable standardized benchmarking. Variant-specific adenine and cytosine base editing achieved high (up to 90-100%) on-target correction, comparable to clinically effective reference controls. Editing efficiencies of top-performing strategies were validated in patient-derived fibroblasts. For *in vivo* translation, we employ lipid nanoparticle (LNP)-based delivery systems, including a novel industrially developed HSC-directed approach, achieving >80% mRNA delivery *in vivo*. We are currently testing our strategies in mice with the *MVK* variants alongside reference variants in a Rosa26 locus. By using standardized rather than variant-specific models, multiple variants can be evaluated simultaneously while *in vitro-in vivo* correlations and shared experimental components can reduce the need for extensive animal testing.

Together, this work lays the foundation for a gene correction therapy for MKD and establishes a modular preclinical platform for scalable genome editing, accelerating clinical translation of personalized therapies across metabolic and hematopoietic diseases.

EVELINE ILCKEN

High throughput pegRNA screen for therapeutic prime editing of monogenic disorders

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Genetic diseases affect over 10,000 families in the Netherlands and are a major cause of childhood morbidity and mortality. Gene-editing technologies offer the potential for curative treatment by directly correcting disease-causing mutations. Prime editing is particularly promising, as it can, in principle, correct nearly any small genetic alteration. However, its efficiency is strongly constrained by the design of prime-editing guide RNAs (pegRNAs). PegRNA performance depends on multiple parameters, including primer binding site (PBS) length, reverse transcription template (RTT) length, and RNA secondary structure, which are highly dependent on the genomic context. Consequently, identifying optimal pegRNAs currently requires extensive empirical screening for each mutation, limiting scalability and slowing clinical translation. To address this, we developed a large-scale pegRNA screening approach. We designed a library of 37,894 pegRNAs targeting 34 clinically relevant mutations, with 200–2000 variants per mutation systematically varying PBS and RTT lengths. Editing efficiencies are assessed across six prime editors in both mismatch repair–proficient (K562) and deficient (HEK293T) cell lines, generating 454,728 unique editing conditions. Pilot data show a broad and biologically consistent range of editing efficiencies, confirming the sensitivity and robustness of the approach. We are integrating these data with public datasets, including PRIDICT and DeepPrime, to develop a predictive model for pegRNA performance. Using active learning, the model will be iteratively refined for new contexts, such as patient-derived cells with limited experimental data. This approach aims to enable efficient pegRNA design and accelerate the translation of prime editing toward clinical application.

ILMA REVERS

Brain-directed gene therapy rescues a mouse model of neurodegenerative disease vanishing white matter

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Vanishing white matter (VWM) is a rare, progressive neurological disorder characterized by the gradual loss of cerebral white matter. Mutations in the eukaryotic translation initiation factor 2B (*EIF2B1-5*) genes encoding for α to ε subunits of the eIF2B complex disrupt maturation and function of astrocytes and oligodendrocytes, which are essential for white matter development and maintenance. During the continuous white matter deterioration, patients experience a progressive loss of cognitive functions, motor skills, and coordination. There is no curative treatment available for VWM.
We investigated the therapeutic efficacy of an adeno-associated virus (AAV)-mediated gene therapy using the human *EIF2B5* coding sequence in a well-characterized VWM murine model (*Eif2b5*$^{R191H/R191H}$: VWM mice), with the aim to restore eIF2B activity within the CNS and mitigate disease symptoms. Healthy control and VWM mice were treated with two neurotropic AAV-PHP.eB or AAV9 vectors via intravenous injection at 10 weeks of age, and compared to saline injected controls. Effects on neuropathology and clinical signs were assessed by locomotor function tests. Proteomics analyses were performed to investigate molecular alterations associated with VWM pathology. Delivery of AAV-PHP.eB, but not AAV9 vectors, resulted in near complete correction of clinical symptoms as assessed by bodyweight and locomotor function including composite ataxia scores. Treatment with AAV-PHP.eB also restored disease specific proteomic changes in cerebellum. This preclinical study demonstrates correction of molecular and clinical signs in VWM mice highlighting the potential of CNS-directed AAV-based gene therapy for treating severe disabilities caused by biallelic pathogenic *EIF2B5* variants in VWM patients.

KATIA PAUWELS

Can new gene therapies result in unintended germline modification?

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Gene therapy offers transformative potential for the treatment of genetic and rare disorders, yet its expanding technological landscape has renewed attention to a critical safety concern: the possibility of unintended germline modification. Although current clinical approaches target somatic tissues, advances in delivery platforms—particularly non-viral systems—have prompted regulators and researchers to reassess whether germ cells may be inadvertently exposed to therapeutic agents. As intentional germline modification for reproductive purposes is explicitly prohibited under European Union legislation and international conventions, a clear understanding of the hazards and risks associated with inadvertent germline modification is essential.

The authors performed a study for the Netherlands Commission on Genetic Modification (COGEM) and the Central Committee on Research Involving Human Subjects (CCMO), evaluating the likelihood of inadvertent germline transformation arising from *in vivo* gene therapy applications. A systematic literature review across PubMed, Embase, and Web of Science identified 440 unique studies, complemented by expert consultations to contextualize findings and highlight knowledge gaps.

Across non-clinical and clinical data, no empirical evidence of unintended germline modification has been reported. Although certain viral and non-viral delivery systems can access gonadal tissues in preclinical settings, robust anatomical and physiological barriers— including the blood-testis, blood-epididymis, and blood-follicle barriers—substantially limit germ cell exposure. The analysis underscores the pivotal importance of biodistribution data in today's risk assessment and identifies methodological challenges, particularly for transient non-viral platforms and gene-editing systems.

Based on the findings the authors proposed a refined, risk-based framework that integrates delivery system characteristics, cellular localization, and cargo properties. Enhanced transparency, improved analytical sensitivity, and harmonized regulatory guidance are essential to support proportionate risk-benefit evaluation and to foster responsible innovation in the rapidly evolving field of gene therapy.

YUXI ZHAO

From guidance to study design: A risk-based regulatory strategy for an innovative *in vivo* gene editing therapy

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Academic institutions play a central role in advancing innovative cell and gene therapy programs toward clinical application. However, the transition from proof-of-concept (PoC) to first-in-human (FIH) studies remains a critical bottleneck. This challenge arises not only from scientific complexity, but also from insufficient integration of regulatory strategy into early development, resulting in misalignment between exploratory research and regulatory expectations. Early integration of a risk-based regulatory strategy can guide non-clinical study design, inform key development decisions, and accelerate progression toward FIH studies.

This presentation demonstrates how embedding regulatory strategy at early stages enables a fit-for-purpose, risk-based development approach. Using a non-viral, CRISPR-based in vivo gene editing approach for Duchenne Muscular Dystrophy (DMD) as a case study, this work builds on ongoing PoC and non-clinical studies to address key regulatory challenges in advanced gene therapy development. Particular emphasis is placed on how EU regulatory guidance can be translated into actionable, risk-based development decisions on model selection, biodistribution assessment and off-target evaluation. These decisions are further strengthened through strategic regulatory engagement, including EMA Innovation Task Force (ITF) briefing meeting and scientific advice. Together, these inputs directly inform the design of a fit-for-purpose non-clinical package in preparation for FIH studies.

In addition, the role of institutional regulatory expertise is highlighted, not as supportive infrastructure, but as an embedded capability that enables developers to shape a coherent development plan, from early study design to defining the therapy they ultimately aim to deliver to patients.

Through this case study, we show that early integration of regulatory strategy functions as a key mechanism to de-risk development, improve efficiency and ensure non-clinical evidence is aligned with clinical study design. This approach provides a practical framework for scientists to move beyond exploratory research toward robust, regulatory-ready development pathways for gene editing therapies.

CHRISTINE VAN HATTEM

Patient access to cell and gene therapies through the European hospital exemption pathway in the Netherlands

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The European hospital exemption (HE) is a regulatory pathway that allows patients access to unauthorised cell and gene therapies. We performed a retrospective cohort study of HEs in the Netherlands (2008-2024) to investigate the pathway's relevance for patient access. We collected data from the national competent authority's documents on product characteristics and associated medical conditions, three key assessment criteria (*unmet medical need, non-routine use, level of evidence*), and the number of patients granted for and treated under HE.
All 23 products were cell or tissue therapies, of which 19 were granted an HE. These were primarily granted and used for patients with cardiac diseases, allogeneic transplantation complications, or oncological diseases. Criteria were assessed more explicitly over time, particularly the unmet medical need. HEs were granted for and used on a non-routine basis for 10 patients/year (range 1-50). Submitted evidence concerned high-level clinical trial data (n=21/23, 91%). Fewer patients were treated than HEs were granted for (323 versus 779, 41%), all with products from academic hospitals. In conclusion, our findings indicate that the HE in the Netherlands constitutes a distinct regulatory pathway for cell and gene therapies; it enables access to non-routinely prepared products for relatively few patients with an unmet medical need, generally 10 patients/year, based on limited clinical data.

JELLA VAN DE LAAK

Genetically modified bacteria as anti-cancer Trojan horse; *in vivo* anticancer effects of intratumoral immunotherapy producing *Clostridium sporogenes*

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In recent years, cancer immunotherapy has revolutionized; there is ongoing growth in novel immunotherapeutics to treat various cancer types. Despite remarkable successes, adverse effects due to systemic exposure and ineffective treatment delivery remain major challenges. Tumour-targeting strategies are investigated to tackle these limitations and increase therapeutic efficacy. Most solid cancers contain areas of necrosis, which are associated with poor prognosis. Strikingly, this necrotic environment is specific for neoplasia and provides an opportunity for targeted therapy. We study the use of the anaerobic bacteria *Clostridium sporogenes* as tumor-specific delivery vehicle. Upon spore injection, this species selectively penetrates necrotic tumor areas and germinates into vegetative bacteria. We have "armed" *C. sporogenes* with immunotherapeutic genes and hypothesize this can act as intratumoral immunotherapeutic producing and secreting vehicle; a Trojan horse strategy.
The immunotherapeutic gene murine interleukin (mIL)-2 was inserted into the chromosome of *C. sporogenes* using CRISPR-Cas9 techniques. Immunotherapeutic production/secretion and biological activity were assessed using ELISA and cellular assays. *In vivo* studies were executed to assess therapeutic efficacy of *C. sporogenes-mIL-2* alone or combined with radiotherapy.
Using spheroid models, we verified that genetic insertions did not affect germination, growth, or colonization abilities of *C. sporogenes-mIL-2*. ELISA results showed successful secretion of mIL-2 up to 3400 pg/mL and cytotoxic T cell proliferation assays confirmed biological activity. Results of *in vivo* studies showed therapeutic effects of *C. sporogenes-mIL-2* by reduced tumor volumes in both *C. sporogenes-mIL-2* and *C. sporogenes-mIL-2*+radiotherapy treated tumors, compared to controls.
Our results show that *C. sporogenes-mIL-2* can grow and secrete immunotherapy specifically in necrotic tumor area. Furthermore, our results show *in vivo* anticancer effects of our Trojan horse clostridium, alone or combined with radiotherapy, highlighting the potential of this strategy.

TEREZA BRACHTLOVA

ORCA-010 Oncolytic Adenovirus Converts Immunologically Cold Tumors to Hot and Drives Durable Anti-Tumor Immune Responses: Phase I/IIa Results in Prostate Cancer

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Most solid tumors are immunologically "cold", lacking T cell infiltration required for response to immune checkpoint inhibitors (ICIs) or other immunotherapies. Converting cold tumors into immunologically active microenvironments represents a critical unmet need. Oncolytic adenoviruses (OAds) are equipped to address this challenge through their direct facilitation of cancer cell lysis and virus-induced immune activation. Here we report Phase I/IIa results of ORCA-010, a potency-enhanced OAd, in treatment-naïve high-risk localized prostate cancer (NCT04097002).

The Phase I dose-escalation study enrolled patients across three dose levels, establishing a safety profile of ORCA-010 up to the highest tested dose 1.5×10^{12} vp. The Phase IIa study enrolled 12 patients who received two intraprostatic injections of ORCA-010 at 1.5×10^{12} vp each, two weeks apart. Nine patients underwent radical prostatectomy eight weeks after the final dose; three patients were followed for one year.

ORCA-010 was well tolerated with no dose-limiting toxicities and only Grade I/II adverse events. Treatment induced a profound and durable remodeling of the tumor immune landscape. Peripheral blood analysis demonstrated a significant post-treatment increase in activated and proliferating $CD8^+$ T cells, with $CD8^+$ and $CD4^+$ T cells expressing IFN-γ and TNF-α upon challenge with prostate tumor-associated antigens; evidence of sustained systemic immune priming. Prostatectomy specimens showed marked intratumoral $CD8^+$ T cell infiltration without rise in $FoxP3^+$ Treg cells; and strikingly, focal accumulation of $CD8^+PD\text{-}1^+$, $CD8^+GrzB^+$ and $CD8^+Ki67^+$ T cells within the tumor microenvironment (TME), hallmarks of cold-to-hot tumor conversion.

These findings establish ORCA-010 as a potent immune activator in the TME. This immune remodeling, by itself sufficient to drive meaningful anti-tumor responses, positions ORCA-010 as a critical enabler for cold tumor indications where current immunotherapies have failed. This strongly suggests that, when combined with standard backbone regimens, ORCA-010 has potential to unlock immunotherapy responses in patient populations that today have no effective options.

DANIEL MATA

Targeted Lipid Nanoparticles for the In Vivo Silencing of RUNX1::ETO in AML

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Chromosomal abnormalities are a hallmark of pediatric Acute Myeloid Leukemia (AML). Among them, the RUNX1::ETO fusion gene is the most common and is a key driver of leukemogenesis, making it an attractive therapeutic target. However, current treatments cannot selectively inhibit this oncogene and are associated with long-term side effects.
siRNA-based therapeutics, delivered by lipid nanoparticles (LNPs), offer a precise approach to silence disease-driven transcripts while sparing healthy cells. Nonetheless, their clinical use is limited due to their poor endosomal escape, undesired immune activation and liver accumulation. To overcome these limitations, we developed a novel LNP formulation that replaces conventional lipids by integrating the biodegradable PEG alternative, polysarcosine, the endosomal escape agent β-sitosterol, and the VLA-4 targeting ligand Bio1211 for targeted delivery to hematopoietic and leukemic cells.
Compared to the benchmark Onpattro formulation, the optimized LNP achieved enhanced knockdown following a single 150nM siRNA dose, resulting in the complete loss of RUNX1::ETO protein expression in patient-derived leukemic cells. After repeated dosing and long-term *ex vivo* co-culture, stem cell frequency was reduced by more than threefold compared with controls. In addition, the LNPs maintained their physicochemical properties and knockdown potency after one month of storage at 4°C. In NSG mice transplanted with patient-derived AML cells, repeated siRNA treatment resulted in 70% reduction of the RUNX1::ETO fusion 24h, and importantly, the treatment also impaired AML engraftment and sustained the low RUNX1::ETO levels for 10 days *ex vivo*.

Our results highlight the importance of fine-tuning the LNP composition for effective RNA delivery. Rational selection of lipid components, combined with a targeting moiety, enabled the development of a stable and low-immunogenic siRNA carrier with robust gene-silencing efficacy. Preclinical evaluation demonstrated the therapeutic potential of this approach, representing a step toward the development of a targeted alternative to conventional chemotherapy.

JAIME FERNÁNDEZ BIMBO

Specificity and biodistribution of a T cell–targeted lipid nanoparticle for in vivo CAR-T generation

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Chimeric antigen receptor (CAR)-T cell therapy has shown remarkable clinical efficacy in B cell malignancies; however, ex vivo manufacturing remains complex, costly, and limits patient accessibility. In vivo CAR-T generation represents a promising alternative, but efficient and specific delivery of genetic cargo to T cells remains a major challenge. Lipid nanoparticles (LNPs) are a leading platform for systemic nucleic acid delivery, yet their application in immune cell targeting is constrained by pronounced hepatic tropism following intravenous administration.

To address this limitation, we developed NCtx, a T cell–targeted LNP incorporating CD3/CD7-directed binders and co-delivering CD19 CAR minicircle DNA together with SB100x transposase mRNA. We previously demonstrated that NCtx enables efficient in vivo CAR-T generation and potent antitumor activity. Here, we present a comprehensive evaluation of biodistribution, functional delivery, and persistence using reporter LNP surrogates in humanized mouse models.

At reduced therapeutic dose, untargeted NCtx exhibited markedly decreased hepatic accumulation and expression compared to a benchmark LNP. Incorporation of targeting moieties redirected distribution toward T cell–rich organs, particularly spleen and lungs, enhancing functional mRNA delivery while maintaining low liver expression. Long-term studies with integrating minicircle DNA constructs showed sustained and expanding transgene expression exclusively in animals treated with targeted NCtx, predominantly localized to the spleen. Untargeted formulations did not yield detectable DNA-derived signal, indicating that functional delivery depends on active targeting.

Integration site and histopathological analyses further confirmed that transgene expression was primarily restricted to lymphocytes, with minimal off-target expression. Collectively, these findings demonstrate that NCtx overcomes hepatic tropism and enables targeted, functional in vivo delivery to T cells, supporting its development for systemic CAR-T engineering.

SUBMITTED ABSTRACTS - POSTER PRESENTATIONS

THIJS RIETVELD

Streamlining the transition of Advanced Therapies: an introduction to CORE-AMTP

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The first administration in humans is a pivotal step in advanced therapy development, but remains a hurdle for developers to overcome. Challenges that developers face in the run-up to First-in-Human (FIH) trials relate to translating product interactions and determining the FIH dose. CORE-ATMP (Cutting-edge Optimization and Research Enhancement for Advanced Therapy Medicinal Products) connects academia (LUMC) and a clinical research organization (CHDR), supported by regulatory bodies (CBG-MEB and CCMO) in a quest to streamline translation of advanced therapies to FIH trials. Specifically, the partners aim to develop 1) a general methodology for the selection of (surrogate) potency assays for cell-based therapies, and 2) a tool that evaluates non-clinical data packages to de-risk clinical trials. EMA, FDA and TGA guidelines will be analyzed to identify common and diverging non-clinical data requirements, generating an overview of the regulatory landscape. Additionally, key product characteristics, best practices, and common pitfalls in product development will be based on aggregated and public information of products that hold marketing authorization or entered clinical trials. To ensure that the developed frameworks are regulator-informed and align with the current needs, interviews will be conducted with regulators and experts in the field. The tools will be validated through real-world cases, assuring scientific robustness and adherence to harmonized legislation. To maximize the project's impact, CORE-AMTP strives to actively engage with stakeholders to foster synergy and knowledge exchange within the ATMP community. Ultimately, CORE-AMTP aims to de-risk FIH trials and accelerate the translation of advanced therapies through the development of novel methodologies.

AXELLE LORIAUX

A Novel Monoclonal Antibody for the Detection, Enrichment, and Activation of Cells Expressing scFv-based Chimeric Antigen Receptors

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Chimeric Antigen Receptor (CAR)-T cell therapy is a highly innovative form of immunotherapy that has proven to be successful in the treatment of B cell malignancies and multiple myeloma. As this treatment modality continues to evolve toward the targeting of novel tumor antigens and engineering of CAR constructs that enhance cell persistence, there is a need for reagents that can be leveraged to selectively interrogate multiple aspects of CAR-T cell biology. Here, we report on a novel and highly versatile recombinant rabbit monoclonal antibody raised against the Gly4Ser peptide linker, which is commonly integrated into single-chain variable fragment (scFv)-based CARs. This antibody can be leveraged for flow cytometry-based CAR detection, magnetic bead-based CAR-T cell enrichment, and selective activation of CAR transduced cells.

MARTIJN KOPPENS

Mitochondrial genome editing to edit your favourite mutation in your cell model of choice

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Our group aims to establish a platform for gene editing of any mitochondrial DNA variant in any cell model of interest. We use mitochondrial base editors such as DdCBE and mitochondrial adenine base editors, as CRISPR-based approaches cannot edit mitochondrial DNA. Our goals are twofold: 1) to build novel disease models ranging from metabolic disorders to cancer, and 2) to develop gene-correction therapies for patients with mitochondrial disease.
We have applied mitochondrial gene editing across a broad range of cultured cell types, including patient-derived cells, induced pluripotent stem cells (iPSCs), cardiomyocytes, myotubes, fibroblasts, and human organoids from multiple tissues. To advance toward clinical translation, we are developing delivery strategies using virus-like particles (VLPs) and lipid nanoparticles (LNPs).
We established protocols that allowed for efficient mitochondrial genome engineering in diverse organoid systems, iPSCs, and iPSC-derived lineages. Functionally, we showed that gene correction improved mitochondrial activity in patient-derived cells. We further achieved gene editing through DdCBE delivery by LNPs and VLPs.
Together, this platform supports robust mitochondrial genome editing in a variety of cell types, enabling the creation of novel disease models and assembling key components required for mitochondrial gene-correction therapy. These advances have formed the foundation for our current efforts towards developing gene-correction strategies for kidney tubulopathy, cardiomyopathy, and MELAS, and towards generating novel cancer models driven by mitochondrial DNA mutations.

PIERRE SPRINGUEL

Evaluation of a novel all-in-one automated bioreactor for intensified autologous CAR-T cell manufacturing

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Despite the significant clinical breakthroughs enabled by chimeric antigen receptor (CAR) T cell therapies, manufacturing bottlenecks continue to limit patient accessibility. Existing CAR-T manufacturing platforms are predominantly designed for the production of a unique dose for a single patient, driving reliance on scale-out strategies to increase production capacity which increases cleanroom footprint, manual operator requirements and overall costs. Automated and parallelised bioreactor platforms that enable multi-batch processing and bioprocess intensification are required to improve manufacturing efficiency and reduce costs. This study aimed to evaluate the Eveo Cell Therapy Platform (Sartorius), a novel automated, closed, multi-parallel system, and to assess critical process parameters to intensify autologous CAR-T cell production. Processes were initiated with 50 million CD3+ T cells which were activated, transduced using lentiviral vector, and expanded within the Eveo Platform using serum-free medium. The impact of critical process parameters, including agitation rate, gassing, concentration steps, and perfusion, was assessed based on measurements of CAR-T cell viability, growth, metabolism, phenotype, transduction efficiency and cytotoxicity. An optimised process was evaluated using three healthy donors across three bioreactors to assess process reproducibility. Volume reduction prior to transduction, combined with optimised mixing and perfusion, achieved 130-fold expansion and 60–70% CAR+ cells without transduction enhancers, representing a seven-fold improvement over industry-standard static controls. This enabled production of a first dose of 200 million CAR+ cells within 3.5 days, a two-day acceleration compared with static controls, and more than 20 total doses within seven days. Harvested CAR-T cells maintained >90% viability, a predominantly central memory phenotype, low levels of exhaustion, and potent in vitro cytotoxicity. These findings demonstrate that optimisation of process parameters on the Eveo Platform enables significant improvements in transduction efficiency and cell expansion, supporting rapid and scalable manufacture of autologous CAR-T cells within a compact footprint.

ALEXEY PINDYURIN

Safer and more effective gene therapies through high-throughput screening for precise, inducible, and cell-specific promoters

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Advances in gene and cell therapy increasingly depend on precise control of transgene expression, whether stable, cell type-specific, or dynamically regulated. Here, we showcase how gene therapies can be made safer and more effective using our SuRE™ (Survey of Regulatory Elements) technology, a high-throughput platform for discovering and optimizing finely tuned promoters. Leading biopharma companies use promoters generated with SuRE™ technology, which are also employed in clinical trials. The technology combines genome-wide screening, combinatorial shuffling, iterative selection, high sensitivity and in vivo evaluation.

We first applied SuRE™ to engineer promoters that drive expression exclusively in T-cells, ensuring that in vivo CAR-T applications have transgene expression restricted to the intended cell type. Through multiple rounds of screening, we identified constitutive promoters with strong T-cell specificity that achieve expression levels approaching those of widely used ubiquitous promoters, while maintaining minimal off-target activity across more than 15 cell types. In parallel, by contrasting activated and non-activated Jurkat T-cells, we developed inducible promoters that respond robustly to T-cell activation. These promoters outperform industry-standard promoter NFAT, exhibiting 10–1000-fold induction depending on stimulation, while returning to baseline in the absence of signals. Such inducible promoters enable advanced designs, including context-dependent “armor” (e.g., IL-12) expression restricted to tumor environments, to prevent exhaustion of immunotherapies.

In addition, we generated inflammation-responsive promoters for CNS-targeted gene therapies. Genome-wide screening followed by large-scale combinatorial testing (>50,000 hybrid promoter variants) enabled the identification of candidate elements activated by neuroinflammatory signals. The lead promoter demonstrates strong and specific induction in an in vivo model of neuroinflammation, supporting its utility in therapies targeting diseases such as multiple sclerosis.

Together, Annogen’s SuRE™ platform enables the creation of both cell type-specific and conditionally inducible promoters, enabling precise, tailored and durable expression essential to ensure the safety and effectiveness of next-generation gene and cell therapies.

CLARA ALEMANY

Ex vivo platform for personalized oncolytic virotherapy in glioblastoma

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Glioblastoma (GBM) is an immunologically cold and aggressive brain tumor with very poor prognosis. Oncolytic virotherapy represents a promising treatment modality; however, clinical responses are only observed in a small subset of patients. Because of the complex tumor microenvironment and interpatient heterogeneity, personalized functional screening systems need to account for the interactions between tumor cells and the patient's own immune cells.
We previously showed that patient-specific tumor responses to different oncolytic viruses can be quantified in *in vitro* cocultures by measuring differences in IFNγ production. To improve the predictive value and clinical relevance of such assays, we have developed an ex vivo patient-specific tumor–PBMC co-culture model based on freshly resected GBM explants, where cell interactions occur in autologous serum. This system preserves more effectively the native tumor microenvironment, including immune cells and stromal components such as macrophages, endothelial cells, and microglia. The platform enables the testing of oncolytic viruses and immunomodulatory agents, with readouts obtainable in under three weeks. Our findings indicate that our new approach captures clinically relevant heterogeneity and may serve as a practical screening tool to support therapeutic decision-making.

GIORGIO GILIOLI

Artificial thymic organoids can be used to study T-cell development from iPSC-derived hematopoietic stem cells

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Genetic mutations in *RAG1* cause a spectrum of severe immunodeficiencies, ranging from severe combined immunodeficiency (SCID) to hypomorphic forms with residual but abnormal T cell development. We previously demonstrated, using artificial thymic organoids (ATOs), that T-cell development from RAG1-SCID patient-derived HSPCs can be restored by lentiviral gene therapy. However, the scarcity of hematopoietic stem and progenitor cells (HSPC) from patients with rare genetic mutations remains a major obstacle for studying the effect of these mutations on T-cell development and preclinical testing of new gene therapy strategies. To overcome this, we successfully generated hematopoietic stem cells (iHSCs) from induced pluripotent stem cells (iPSCs) carrying RAG1 null or patient-specific hypomorphic mutations.
Flow cytometric characterization confirmed that iHSCs are homogenous and express typical $CD34^+$ HSPC surface markers ($CD45RA^-$ $CD34^+$: 99.6%; $CD38^-$ $CD34^+$: 98.9%; $CD90^+$ $CD34^+$: 90.0%). Moreover, wild-type iHSCs supported T-cell development in ATO cultures ($TCR\alpha\beta^+CD3^+$ cells: WT 12.9%). In contrast, RAG1 null iHSCs failed to generate T cells, while hypomorphic RAG1 mutation resulted in reduced T-cell output compared with isogenic wild-type controls ($TCR\alpha\beta^+CD3^+$ cells: RAG1 null 0.06%; R975Q 4.36%). These findings recapitulate defects observed in mouse models and patients with RAG1 mutations. In a preliminary experiment, transduction of RAG1-mutant iHSCs with a lentiviral vector encoding codon-optimized RAG1, currently under investigation in a clinical trial for RAG1-SCID (NCT04797260), restored T-cell development in ATOs ($TCR\alpha\beta^+CD3^+$ cells after lentiviral transduction: WT 47.7%, RAG1 null 7.73%; R975Q 25.9%).Together, our results suggest iHSC-derived ATOs could be used as a disease model to investigate rare genetic mutations affecting T-cell development and to test gene therapy strategies. Moreover, this platform provides first preclinical evidence in a human model that lentiviral gene therapy could benefit patients with hypomorphic RAG1 mutations, who have been excluded from the current RAG1-SCID trial.

YUE CHEN

Developing a New Treatment for α-amanitin Poisoning

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Introduction:
Amanita phalloides (death cap) causes most fatal mushroom intoxications due to its resemblance to edible species. Its main toxin, α-amanitin, binds to and inactivates RNA polymerase II (RNAPII) blocking gene transcription leading to cell death (1). Although other organs are affected, the acute liver failure caused by α-amanitin is the primary cause of death. Current treatments aim to inhibit toxin uptake via hepatocyte transporters, especially OATP1B3, or block α-amanitin binding to RNAPII, using silibinin. Mouse studies showed that to be beneficial, these treatments have to be started within 4 hours after intoxication. However, patients usually reach the hospital after 12 to 24 hours, which is too late for effective treatment.

Aim: RNA based therapy.
Cells expressing a mutant RNAPII, not binding to α-amanitin, are resistance to this toxin (2). LNP mediated delivery of RNA encoding the resistant mutant can restore the RNAPII activity to restart gene transcription in the liver. In combination with supportive current treatments, this may prevent liver failure and/or stimulate recovery.

Methods:
mRNA encoding the resistant mutant RNAPII generated by in vitro transcription using T7 polymerase. Lentiviral vectors encoding this RNAPII were generated to establish α-amanitin resistance in cell lines, including the human hepatocyte-like cell line HepaRG.

Results:
Transfection of mRNA encoding resistant mutant RNAPII up to 4 hours after α-amanitin resulted in partial rescue of cell viability based on WST-1 assays. Although the effects were small, in these in vitro experiments, the mRNA transfection proved more effective than silibinin treatment, the current treatment option.

Conclusion:
Although the efficacy of transfection of mRNA encoding resistant mutant RNAPII was limited in vitro, it proved more effective than the currently used drugs such as silibinin, warranting further in vivo testing.

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SIMON STAUBACH

Innovative Lipid-Based Delivery Solution: Unlocking New Opportunities in Manufacturing Genetically Modified Immune Cell Therapies

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Gene-modified cell therapies, such as engineered T cells or Natural Killer (NK) cells expressing chimeric antigen receptors (CARs), are among the most promising treatments for cancer and autoimmune diseases. Traditionally, these therapies rely on lentiviral vectors to transfer the gene of interest; however, this approach is associated with lengthy manufacturing timelines, high costs, and potential safety risks. To overcome these limitations, our research focuses on lipid-based solutions as a promising alternative for producing CAR-T and CAR-NK cells.
In this study, innovative lipid-based solution LipidBrick®Cell Ready was employed first for transient protein expression with the production of functional ex vivo mRNA-based CD19CAR-T cells and then for stable cell modification through the delivery of genetic engineering tools such as CRISPR using Cas9 mRNA and sgRNA targeting the TRAC gene. Optimization of T cell transfection was initially performed in 96-well plates before scaling up to a T25 flask. To demonstrate the versatility of this solution, diverse nucleic acid payloads (mRNA, plasmid DNA and nanoplasmid) and various cell types (T cells, NK cells, monocyte-derived dendritic cells and hematopoietic stem cells) were successfully transfected with our LipidBrick®Cell Ready reagent. Finally, we've shown that our ready-to-use solution LipidBrick®Cell Ready could be efficient to generate functional CD19 CAR-NK cells.

PEIYU LI

Evaluation of SmD2 Gene Silencing to Treat Non-Small Cell Lung Cancer on Patient-Derived Tumor and Normal Airway Organoids *in vitro* and Xenograft Tumors *in vivo*

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Background: Non-small cell lung cancer (NSCLC) has a poor prognosis; there is an urgent need for more effective therapies. Previously, we identified the Sm gene family, core components of the RNA splicing machinery, as promising cancer-selective therapeutic targets. This study evaluates the therapeutic potential of targeting SmD2, one of the Sm genes, using human NSCLC xenografts on fertilized chicken eggs and patient-derived organoids.

Methods: Human NSCLC cell lines (A549, H460) were inoculated onto fertilized chicken eggs and established tumors were injected with an adenoviral vector expressing a short hairpin silencing SmD2 (AdV-shSmD2) or a non-targeting control (AdV-NT). Tumor engraftment, SmD2 knockdown efficiency, and tumor growth were analyzed. Patient-derived tumor and normal airway organoids were established from 10 patient lung tumor resections. Organoids were characterized using cell type-specific markers. Organoid cultures were transduced with AdV-shSmD2 or AdV-NT and cell viability was quantified using CellTiter-Glo 3D.

Results: In the xenograft tumor models, AdV-SmD2 silenced the SmD2 gene and significantly suppressed tumor growth compared to AdV-NT. Patient-derived organoids were established with a high success rate (>80%) from adenocarcinoma and squamous cell carcinoma resections. Normal airway organoids contained the major lung epithelial cell types, including basal cells, ciliated cells, club cells, goblet cells, and type-1 and 2 alveolar cells. Transduction with AdV-SmD2 reduced viability in tumor organoids of most patients ($p<0.01$). In contrast, non-malignant airway organoids remained viable and intact following the same treatment.

Conclusions: Our findings demonstrate that the vulnerability of NSCLC cells to Sm gene silencing was confirmed *in vivo* and cancer-selective cell killing was validated in patient-derived organoid cultures. This study provides strong preclinical evidence supporting in particular SmD2 as a candidate for therapeutic gene silencing in lung cancer.

JOSE CASTRO-ALPÍZAR

When Prime editing meets a difficult mutation: Lessons from MMUT

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Prime editing is a versatile CRISPR/Cas9-based genome editing technology that enables precise DNA modifications without introducing double-strand breaks or donor DNA templates, making it a promising approach for gene correction in monogenic diseases. Here, we aimed to develop a personalized prime editing therapy for methylmalonic acidemia (MMA), which is a rare and severe metabolic disease caused by mutations in the *MMUT* gene. Moreover, given that the MMUT gene exerts its function mainly in the liver, we explored whether prime editing components could be delivered using lipid nanoparticles (LNPs).
In initial experiments using our fluorescent reporter system (fluoPEER) we identified several promising prime editing guide RNAs (pegRNAs), suggesting that editing MMUT gene would be feasible. However, when selected prime editing components were applied at the genomic MMUT locus in primary cells carrying the mutation, limited editing efficiencies were observed. We therefore implemented an iterative optimization strategy to improve editing efficiency for this hard-to-edit target. Using fluoPEER and evolving bioinformatic prediction tools, we optimized pegRNA design across various prime editor variants. The best-performing configurations were subsequently evaluated at the genomic level using lentiviral cell lines harboring the *MMUT* target region in K562 and HUH-7 cells, where editing efficiencies increased up to ~50% after enrichment of edited cells. These results demonstrate the importance of pegRNA design and editor selection for efficient prime editing at the MMUT locus. Finally, as delivery remains a major bottleneck for *in vivo* prime editing, we optimized formulation of prime editor-encoding mRNA and pegRNAs in LNPs and achieved robust editing in multiple cell types. Currently, we are evaluating efficiency of these LNPs *in vivo*.
Overall, this work highlights important considerations for disease target selection and prime editing optimization and represents an important step toward in vivo prime editing therapies for liver-dominant metabolic diseases such as MMA.

GANESH RAMESH

Current Capacity and Gaps in Viral Vector Manufacturing: A Survey of Centers Associated with CTIWP of EBMT, NXTGEN-Hightech, DARE-NL, T2EVOLVE, and GoCART Coalition

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Advanced therapy medicinal products (ATMPs) hold great potential for treating complex diseases, and viral vectors are mainly used for producing them. Several viral vector–based ATMPs have been approved globally, particularly for cancer. Among these, chimeric antigen receptor (CAR) T-cell therapies represent the most established application, with all approved products engineered using lentiviral or γ-retroviral vectors. However, large-scale production of GMP-grade viral vectors remains a significant bottleneck. Most academic institutions and hospitals rely on contract development and manufacturing organizations for vector supply, which delays research and clinical translation.
To assess current practices and challenges in viral vector production for ATMPs, we conducted a survey among facilities affiliated with the EBMT, NXTGEN Hightech, DARE-NL, T2Evolve, GoCART Coalition,

and commercial ATMP developers. The survey was distributed to academic, non-profit, and commercial ATMP facilities. It collected data on viral vector usage, production technologies, and manufacturing practices. Respondents were also asked to identify technological needs to guide future innovation.
A total of 92 valid responses were received, representing centers across 33 countries. Development stages of viral vector–based gene therapies ranged from laboratory research to pre-GMP, clinical trials, and commercial production. Thirteen facilities reported in-house viral vector manufacturing, mainly for ex vivo cell modification (n=10), with lentiviral vectors (n=9) and HEK293 derivatives (n=11) being most commonly used.
We will report during the conference on reported key advantages and limitations of current upstream production technologies, along with areas requiring improvement. We also report on mapping results of downstream processing methods and current or desired online/offline process parameters.
The survey highlights the growing role of academic and hospital-based facilities in viral vector production, particularly for autologous therapies. It demonstrates broad geographic engagement in cell and gene therapy development and reinforces the central role of viral vectors in advancing ATMPs across both academic and clinical settings.

JORT ALTENBURG

ICAT, viral vector unit: accelerating clinical translation of advanced therapeutic medicinal products in an academic setting

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Advanced Therapy Medicinal Products (ATMPs), including gene therapies, engineered T cell therapies, and tissue-engineered products, have demonstrated transformative potential in oncology and regenerative medicine. Academic research institutes are crucial in the development of these innovative therapies, however, translating an ATMP from research to clinical trials requires specialized, translational expertise to bridge the gap between research-grade products and Good Manufacturing Practice (GMP) compliant production processes, as well as to build robust regulatory files for clinical testing.

To address these challenges, embedded within the University Medical Center Utrecht, the Innovation Center for Advanced Therapies (ICAT) was established. Part of ICAT is the viral vector unit, which focusses on the development, optimization and upscaling of viral vector production processes.

These processes are designed with the end goal in mind: production under GMP in the in-house, state-of-the-art GMP facility. Viral vector process development can be conducted using a range of possibilities. Upstream (= cell & viral vector production) development can be executed using adherent or suspension cells for the production of different types of viral vectors, using transduction or through producer cell lines. Downstream (= purification) processes are developed using a variety of techniques, including, but not limited to, clarification, tangential flow filtration, and various chromatography methods. These processes can be executed on a range of production scales, from lab bench to full production scale. The developed processes will be fully GMP compliant, and designed to be compatible to the in-house GMP facility. Therefore, they can easily be transferred to the GMP facility to produce viral vectors to be used for clinical trials.

By integrating innovation, translation and clinical production ICAT enables a smooth transition from bench to bedside and beyond. ICAT's trans- and multidisciplinary approach is designed to overcome the critical barriers in the bench-to-bedside translation of ATMPs.