ASGCT 2025 Clinical and AI / ML Preview

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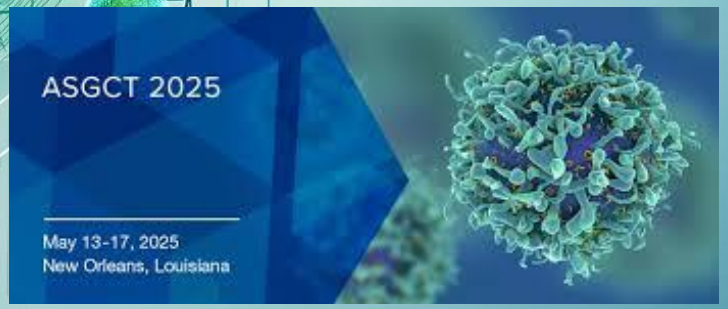

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ASGCT 2025 Preview – Table of Contents

ASGCT 2025 – General Overview

- **Record-Breaking Abstract Volume Expected:** Over 1,300 abstracts covering discovery, translational, and clinical research
- **Largest Clinical Program to Date:** Expanded late-stage data presentations, signaling the field's readiness for broader patient impact
- **New Focus on Real-World Evidence:** Dedicated sessions to explore long-term safety, durability, and patient-reported outcomes
- **Increased Regulatory Dialogue:** Live panels with FDA, EMA, and global agencies expected to address evolving regulatory frameworks
- **Cross-Platform Technology Integration:** Synergies between gene editing, mRNA, viral vectors, and cell-based therapies to be highlighted
- **Manufacturing and CMC Challenges in Focus:** Sessions on standardizing analytics, scale-up, and regulatory-compliant manufacturing processes
- **Emerging Digital & AI Applications:** Early applications of AI in vector optimization, biomarker discovery, and trial design will be expected

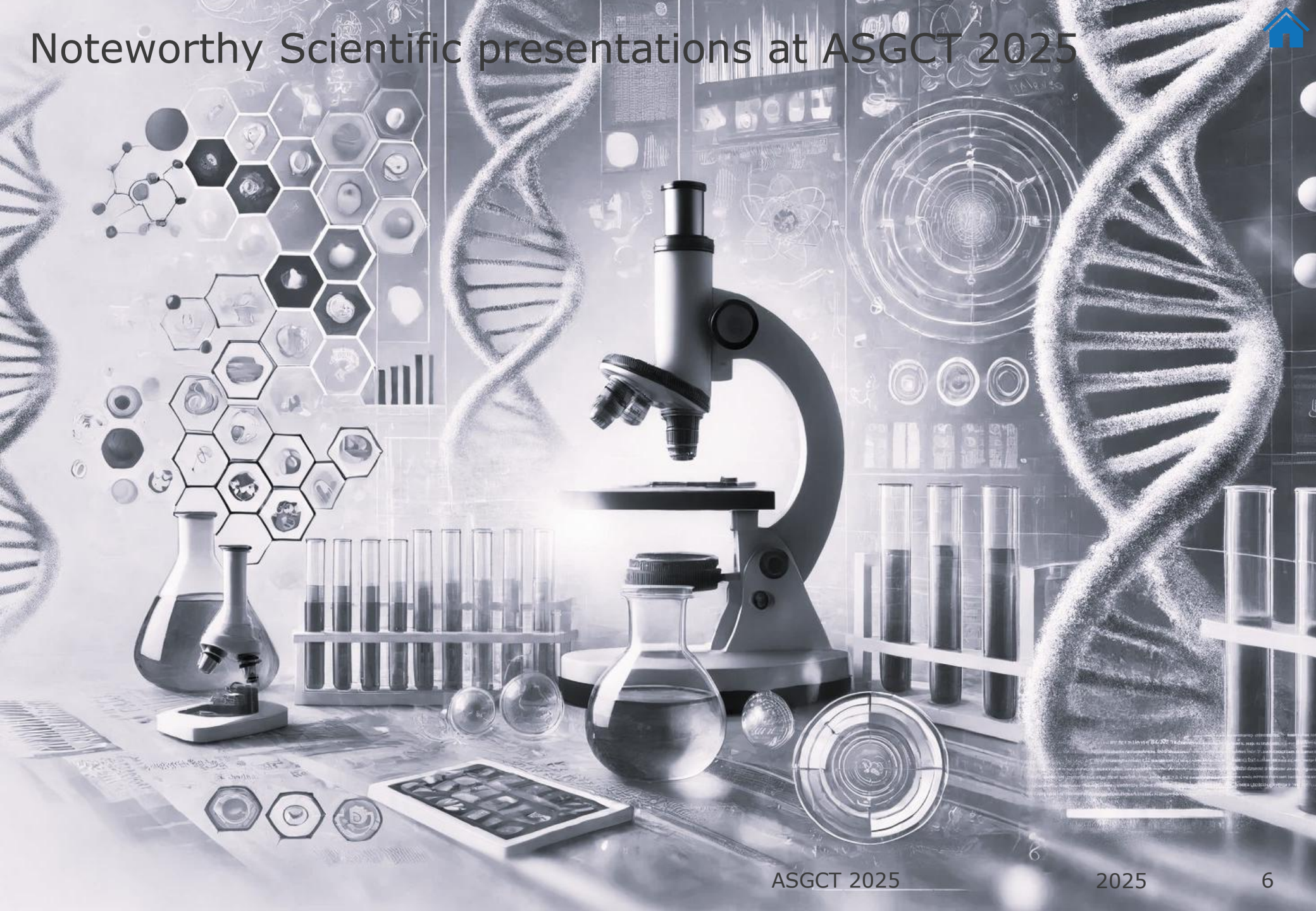
ASGCT 2025– Conference Themes (1/2)

- **Ophthalmology Front and Center:** Phase 1/2 data on retinal gene therapies for RPGR, RS1, and VEGFA to draw significant attention
- **Breakthroughs in Neuromuscular Disorders:** New clinical data on DMD, SMA, and MECP2 therapies advancing toward regulatory submissions
- **First-Ever Liver-Directed Gene Insertion Data:** Landmark OTC deficiency program poised to deliver transformative outcomes in neonates
- **Solid Tumor CAR-T Momentum Building:** First-in-human results on mesothelin, GD2, and EPHB4 CAR-Ts expected to expand cell therapy's reach
- **Advances in Base and RNA Editing:** Next-gen CRISPR and Cas13 programs entering preclinical and early clinical stages across multiple diseases

ASGCT 2025– Conference Themes (2/2)

- **AAV Vector Engineering Updates:** Efforts to reduce immunogenicity and increase specificity to be prominently featured
- **New Data on Immune-Modulating Cell Therapies:** Results on regulatory T cells and NK cell therapies in autoimmunity and neurodegeneration
- **Preclinical to Clinical Manufacturing Translation:** Insights on analytical method transfer, lot release testing, and process validation to be shared
- **Global Access and Health Equity Discussions:** Panels to address affordability, supply chain, and patient access in underserved regions

Noteworthy Scientific presentations at ASGCT 2025



Key Topics From Notable Presentations (1/9)

- **Neurology & Neuromuscular Disorders:** Sessions will showcase how CRISPR, AAV, and ASO-based therapies will be transforming treatment prospects for complex neurological and neuromuscular disorders, moving closer to clinical translation

  - Gene Therapy Advancements in Neurodevelopmental & Neurodegenerative Diseases: Promising preclinical and early clinical findings from CRISPR-Cas13 RNA-editing (HG204) for MECP2 Duplication Syndrome and RM-201 gene editing for Parkinson's disease

  - AAV and Oligonucleotide Strategies for Neuromuscular Disorders: Multiple programs including LTS-101 for CLN2 Batten disease, INS1201 and EXG001-307 for Duchenne and SMA, and allele-specific ASOs targeting A53T mutation in Parkinson's

  - Clinical Pipeline Expansion with New Trial Designs: Ongoing trials like HERO (HG204 for MDS), MUSCLE (HG302 for DMD), PROPEL (SBT101 for ALD), and ASCEND (INS1201 for DMD) are advancing gene therapies from preclinical to clinical stages

Key Topics From Notable Presentations (2/9)

- **Oncology (CAR-T, Gene and Virotherapies) :** ASGCT 2025 will spotlight how rationally designed CAR-T and virotherapies often in combination with immunomodulators, will be breaking through long-standing barriers in solid tumor treatment

  - Next-Generation CAR-T Designs Targeting Solid Tumors: Innovations include GITRL co-expression, PD-1 retention blockade, and novel constructs (e.g., anti-GD2, anti-DLL3, anti-MSLN, and anti-EPHB4) to overcome exhaustion and immunosuppressive microenvironments

  - Combination Strategies Enhancing Immunotherapy: Combining CAR-T with checkpoint inhibitors (e.g., αPD-1, αCTLA-4), oncolytic viruses, or ALK inhibitors like Alectinib shows additive efficacy in hard-to-treat tumors like glioblastoma, neuroblastoma, and MSS colorectal cancer

  - Viral and Vector-Based Therapies in Solid Tumors: DNG64 retroviral gene therapy and novel adenoviral vectors (AdVs) for HNSCC demonstrate tumor-specific lysis, immune priming, and efficacy when combined with immunotherapy or chemotherapeutics

Key Topics From Notable Presentations (3/9)

- **Infectious Disease & Immunology:** Experts will discuss how gene-encoded antibody therapies, including plasmid DNA and AAV vectors, will be redefining infectious disease treatment by enabling durable, in vivo biologic production
  - Synthetic DNA-Encoded Monoclonal Antibodies (DMAbs): Phase 1 trials demonstrate long-term in vivo antibody production using plasmid DNA electroporation, with over 72 weeks of durable SARS-CoV-2 neutralizing activity and no major safety concerns
  - Gene-Encoded Antibodies as Biologic Alternatives: DMAb platforms encoding Evusheld-like antibodies validate a recombinant protein–free approach, offering scalable, long-acting solutions for infectious disease prophylaxis
  - AAV-Delivered bNAbs for HIV Suppression: Co-delivery of PD-L1 with AAV-bNAbs prolongs antibody expression and sustains SHIV viremia suppression in macaques post-ART, paving the way for functional HIV cure strategies

Key Topics From Notable Presentations (4/9)

- **Metabolic & Rare Diseases:** Presentations are set to address gene editing and AAV therapies that will rapidly redefine the treatment landscape for rare metabolic diseases, moving toward functional cures with durable clinical benefit
  - Gene Therapies Targeting Urea Cycle Disorders (UCDs): ECUR-506 and DTX301 demonstrate promising safety and efficacy in OTCD through both gene editing and AAV-based gene transfer, with early success in neonates and durable response in adults
  - Emerging Treatments for Fabry Disease: ZS805 and 4D-310 show improved α-Gal A activity and reduced Lyso-GL3, with new insights on AAV neutralizing antibodies supporting broader patient eligibility in gene therapy trials
  - Innovative Approaches in Other Rare Genetic Conditions: AAV and CRISPR/Cas9 strategies in PKU (GS1168), cblB MMA, GSD Ia, and Gaucher disease (LY-M001) show robust preclinical and early clinical success in enzyme restoration and metabolic correction

Key Topics From Notable Presentations (5/9)

- **Autoimmune & Inflammatory Diseases:** ASGCT 2025 will feature a paradigm shift in autoimmune treatment, with autologous CAR-T and NK cell therapies demonstrating promise for long-lasting remissions beyond conventional immunosuppression
  - CD19 CAR-T Therapies for Autoimmune Indications: Rese-cel (CABA-201) shows consistent B cell depletion and sustained clinical improvement across SLE, systemic sclerosis, and inflammatory myopathies, supporting drug-free remission potential with ongoing RESET trials
  - Mesenchymal Stem Cell-Based Therapy in Crohn's Disease: TH-SC01, an allogeneic umbilical MSC therapy, achieved 50% remission in refractory perianal fistulas at 24 weeks in Phase 2, with no serious adverse events reported
  - Innate Immunotherapy Targeting Neuroinflammation: Troculeucel, a non-engineered autologous NK cell product, demonstrated anti-inflammatory activity and clearance of pathogenic aggregates in preclinical neurodegenerative models

Key Topics From Notable Presentations (6/9)

- **Clinical Operations, Safety & Data Science:** Discussions expected to emphasize the integration of real-world data, genomic monitoring, and immunogenicity profiling to optimize gene and cell therapy trial design, patient selection, and long-term safety oversight

  - Real-World Risk Profiling in CAR-T Therapy: National inpatient analyses reveal HLH and CKD significantly increase complications and length of stay, emphasizing the need for early identification and tailored CAR-T strategies in high-risk populations

  - Understanding CAR-T Cell Persistence and Integration Sites: Longitudinal monitoring links specific integration sites (e.g., PACS1, RPTOR) to durable remission, highlighting the importance of integration analysis in post-infusion surveillance

  - Impact of pre-existing Immunity in Gene Therapy Trials: ICM-203 shows favorable safety and disease modification in osteoarthritis, with efficacy dependent on pre-treatment NAb status, supporting stratified enrollment in AAV gene therapy trials

Key Topics From Notable Presentations (7/9)

- **Cardiology (Cardiac Gene Therapies and CAR-T) :** AAV and CRISPR platforms will be unlocking curative potential in cardiology, targeting structural, electrical, and lipid-related drivers of cardiovascular disease with unprecedented precision will be discussed
  - MYBPC3 Gene Replacement in Hypertrophic Cardiomyopathy (HCM): FT-017, an AAV9 vector, restored cMyBP-C expression, reversed pathology, and improved cardiac function in preclinical models, supporting its advancement toward clinical evaluation for MYBPC3-related HCM
  - CaMKII Inhibition as a Novel Strategy in Atrial Fibrillation (AF): AAV-mediated CaMKII gene silencing reduced AF burden and corrected electrophysiological instability in murine models, demonstrating therapeutic potential for rhythm control in AF
  - CRISPR-Based PCSK9 Editing in HeFH: ART002 achieved up to 91% PCSK9 and 68% LDL-C reductions with a single IV dose in HeFH patients, positioning it as a game-changing, durable gene-editing therapy for ASCVD risk reduction

Key Topics From Notable Presentations (8/9)

- **Gene & Cell Therapy Platforms & Delivery Technologies:** Conference will spotlight how innovations in capsid purification, immune evasion, magnetically guided delivery, and analytical assay design will optimize gene and cell therapy platform development for clinical scalability
  - Advanced AAV Capsid Purification and Standards Adoption: Ultragenyx and consortium-led studies confirm DGEUC and IDXUC outperform AEX in enriching full capsids, with validated AAV8 standards supporting global assay harmonization
  - Assay Innovation for Vector Quantification and Biodistribution: Axovia's ddPCR and ABL's p24 ELISA kits enable accurate quantification of AAV and LV vectors, especially at low titers—critical for early-stage preclinical and clinical development
  - Next-Gen Vector Targeting Technologies: Magnetic nanoparticle-conjugated lentiviral vectors enhance airway transduction, while synchrotron imaging validates precision targeting—advancing delivery for respiratory gene therapy
  - Scalable Manufacturing and Immune-Evasive Engineering: Process analytics from Andelyn Biosciences refine yield predictors, while AAV-PD-L1 co-expression strategies prolong therapeutic expression by mitigating host immune responses

Key Topics From Notable Presentations (9/9)

- **Ophthalmology (Retinal and Ocular Gene Therapies):** Discussions set to highlight the maturity of retinal gene therapy with robust clinical gains in diverse disorders, while also emphasizing immune tolerance and inclusive research practices in ophthalmic innovation
  - CRISPR and AAV-Based Retinal Therapies Advance Clinical Development: HG202 and FT-002 showed promising safety and structural/functional improvement in nAMD and XLRP, supporting gene-based disease modification in previously untreatable inherited retinopathies
  - Robust Outcomes in Pediatric and Late-Stage Retinal Diseases: Subretinal gene therapies (scAAV8-hRS1 for XLRS and ZM-02 for advanced RP) improved visual acuity, retinal structure, and microperimetry, confirming clinical utility across age and disease severity spectra
  - Gene Therapy Resilience Against Immune Barriers: KH631 maintained efficacy despite pre-existing neutralizing antibodies and anti-drug responses, reinforcing the immunological advantage of subretinal AAV delivery in CNV models
  - Increasing Trial Momentum and Patient-Centered Access: Global trial mapping revealed LHON dominance in optic neuropathy programs, and the use of audio consent tools in iPSC trials improved accessibility for visually impaired participants

Focus of Key Industry Sponsored Sessions at ASGCT 2025 (1/6)

- **REGENXBIO:**
  - Focus Areas: AAV-Based Gene Therapy for Rare Neurological Disorders
  - Presentations will cover RGX-121 for neuronopathic MPS II and novel AAV capsid variants for targeted brain delivery
- **Entrinsic Bioscience:**
  - Focus Areas: Oligonucleotide Therapeutics for Neuromuscular Disorders
  - Sessions will highlight ENTR-601-44, an EEV-conjugated PMO therapy in clinical development for Duchenne Muscular Dystrophy
- **Verve Therapeutics:**
  - Focus Areas: Cardiovascular RNA-Based Therapeutics
  - Discussions will address WISPER LncRNA-targeted therapies aimed at reversing cardiac fibrosis in heart failure models

Focus of Key Industry Sponsored Sessions at ASGCT 2025 (2/6)

- **Sanofi / Translate Bio:**
  - Focus Areas: Self-Amplifying mRNA Vaccine Platforms
  - Presentations will explore pioneering self-amplifying mRNA technologies for next-generation infectious disease prevention
- **Biogen:**
  - Focus Areas: Neurodegenerative Disease Gene Silencing
  - Updates will include preclinical and translational data on BIIB080, a tau-targeting antisense oligonucleotide for early Alzheimer's Disease
- **Ionis Pharmaceuticals:**
  - Focus Areas: RNA-Based Therapy for Huntington's Disease
  - Preclinical pharmacology and projected clinical dosing data will be shared for IT di-siRNA targeting mutant Huntingtin protein

Focus of Key Industry Sponsored Sessions at ASGCT 2025 (3/6)

- **Neurogene:**
  - Focus Areas: Gene Therapy for Rett Syndrome
  - Insights from Neurogene's START pilot program will cover the development and regulatory progress of NGN-401 for Rett Syndrome
- **Sangamo Therapeutics:**
  - Focus Areas: TfR1-Mediated Oligonucleotide Delivery
  - Sessions will discuss translational pathways from preclinical to clinical development for neuromuscular disease therapies using TfR1 delivery systems
- **Novartis:**
  - Focus Areas: CD19 CAR-T and Engineered Tregs for Autoimmune Disease
  - Data will be presented on CAR-T and Treg-based strategies to manage autoimmune diseases while balancing risk-benefit profiles

Focus of Key Industry Sponsored Sessions at ASGCT 2025 (4/6)

- **Adaptive Biotechnologies / Genentech:**
  - Focus Areas: Engineered Treg Therapies
  - Presentations will detail novel Treg cell engineering approaches for treating autoimmune disorders
- **Beam Therapeutics**
  - Focus Areas: Fully Programmable RNA Medicines
  - Pioneering presentations will focus on the design and deployment of programmable RNA-based therapeutic platforms
- **Intellia Therapeutics:**
  - Focus Areas: In Vivo Immune Cell Engineering
  - Data will be shared on the use of targeted nanoparticles for immune cell programming in vivo

Focus of Key Industry Sponsored Sessions at ASGCT 2025 (5/6)

- **Sana Biotechnology:**
  - Focus Areas: Hypo-Immune Cell Platforms
  - Presentations will explore engineering cells to evade immune detection to improve allogeneic cell therapy outcomes
- **BlueRock Therapeutics / Bayer:**
  - Focus Areas: Autologous iPSC-Derived Neuron Replacement
  - Data will focus on neuron replacement therapies for Parkinson's Disease using autologous iPSC-derived cells
- **AskBio / Bayer:**
  - Focus Areas: Universal AAV Gene Therapy for Solid Tumors
  - Presentations will introduce SRN-101, a universal AAV gene therapy strategy targeting solid tumors

Focus of Key Industry Sponsored Sessions at ASGCT 2025 (6/6)

- **MeiraGTx:**
  - Focus Areas: HSV-1 Vector Platforms for Pulmonary Genetic Diseases
  - Data will showcase HSV-1 vectors designed for respiratory tissue targeting in genetic pulmonary disease
- **Alliance for Regenerative Medicine (ARM) / Industry Panels:**
  - Focus Areas: Global Regulatory, CMC, and Clinical Development Best Practices
  - Industry-led sessions will address global lifecycle management, CMC streamlining, and regulatory differences across jurisdictions
- **General Science & Communications**
  - Focus Areas: Scientific Communication and AI for Therapeutic Design
  - Sessions will cover best practices for science communication on social media and AI-driven promoter and transgene design

Notable Presentations at ASGCT 2025

Notable Presentations at ASGCT 2025
Neurology & Neuromuscular Disorders (1/5)

Date	Title	Author	Summary
13 May 2025	A Non-GLP Dose Range Finding Study in Cynomolgus Macaques Evaluating the Biodistribution, Expression, and Safety of LTS-101, a Novel Preclinical Gene Therapy Candidate for the Treatment of CLN2 Batten Disease	David E. Leib	• **Introduction:** Latus Bio is developing LTS-101, a gene therapy for CLN2, a form of Batten disease caused by TPP1 deficiency. LTS-101 uses AAV-Ep+, a novel capsid for ICV delivery to ependymal cells, producing TPP1 in the CSF. • **Methodology:** xA dose-range finding study in juvenile macaques evaluated LTS-101's biodistribution, transgene expression, and safety at low, mid, and high doses, administered via ICV. • **Results:** LTS-101 showed dose-dependent TPP1 expression in the CSF, with the mid dose being the maximum tolerated dose. High doses caused transient motor deficits. • **Conclusions:** LTS-101 demonstrated favorable safety, strong TPP1 expression, and low systemic exposure, suggesting its potential for treating CLN2 with a single ICV dose.
13 May 2025	HG204 CRISPR-Cas13 RNA-Editing Therapy for MECP2 Duplication Syndrome: Preclinical Success to First-in-Human Study	Alvin Luk	• **Introduction:** MECP2 duplication syndrome (MDS) is a severe neurodevelopmental disorder caused by MECP2 gene gain-of-function. HG204, a CRISPR-Cas13-based RNA-editing therapy, targets MECP2 to reduce protein levels and reverse disease phenotypes, with preclinical studies demonstrating its safety and efficacy. • **Methodology:** Preclinical studies in non-human primates (NHPs) assessed the editing efficiency and safety of HG204, delivered via intracerebroventricular (ICV) injection. The HERO clinical trial is evaluating HG204's safety and therapeutic potential in MDS patients. • **Results:** Preclinical data showed effective MECP2 editing, reduced protein levels, and sustained effects. HERO trial data indicated favorable safety, with early improvements in adaptive behaviors. • **Conclusions:** HG204 shows promise as a transformative treatment for MDS, with ongoing clinical evaluation and orphan drug designations supporting its potential.

Notable Presentations at ASGCT 2025
Neurology & Neuromuscular Disorders (2/5)

Date	Title	Author	Summary
13 May 2025	A 4-Week Study of Rodent Multiple Sclerosis (MS) Model	Mele Avilla	• **Introduction:** Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by myelin loss, leading to symptoms like paralysis. The study aims to establish a reproducible rodent model of MS to replicate human disease pathology and immune activity. • **Methodology:** MS was induced in C57BL/6J female mice using myelin oligodendrocyte glycoprotein (MOG), Complete Freund's Adjuvant (CFA), and pertussis toxin (PTX). The study evaluated four groups: control (PBS) and test groups with varying doses of MOG/CFA and PTX. Locomotor activity, histology, serum chemistry, and cytokine analysis were performed. • **Results:** The model successfully induced MS-like symptoms, with alterations in ambulation and immune responses. • **Conclusions:** This rodent MS model is effective for evaluating new therapies, offering insights into autoimmune treatments for MS.
13 May 2025	Initial Safety Results from the PROPEL Trial Evaluating SBT101 as a Potential Gene Therapy for Spinal Cord Disease in Adult Males with X-linked Adrenoleukodystrophy	Lawrence Hayward	• **Introduction:** X-linked adrenoleukodystrophy (ALD) is a neurodegenerative disorder caused by ABCD1 gene mutations, leading to VLCFA accumulation and neurological damage. Adrenomyeloneuropathy (AMN) lacks treatments, causing progressive disability. SBT101, an AAV9 vector encoding ABCD1, shows promise in preclinical models for restoring ABCD1 expression and halting disease progression. • **Methodology:** PROPEL is a Phase 1/2 study evaluating SBT101 in adult males with AMN, focusing on safety and efficacy across two dose cohorts. Secondary endpoints include clinical assessments and biomarkers. • **Results:** Eight patients were dosed with no serious adverse events related to SBT101. Early transduction evidence and encouraging biomarkers were observed. • **Conclusions:** SBT101 is well tolerated, with promising early data supporting its development as a gene therapy for AMN.

Notable Presentations at ASGCT 2025
Neurology & Neuromuscular Disorders (3/5)

Date	Title	Author	Summary
14 May 2025	CRISPR-hfCas12Max Genome Editing Therapy Demonstrates Preclinical Efficacy and Early Clinical Benefit in Duchenne Muscular Dystrophy	Alvin Luk	• **Introduction:** Duchenne muscular dystrophy (DMD) is a severe X-linked disorder causing muscle degeneration. Current therapies, like antisense oligonucleotides and AAV-micro-dystrophin gene therapies, are limited by low dystrophin restoration and adverse events. HG302, a CRISPR-based gene-editing therapy, aims to restore dystrophin expression with minimal off-target effects. • **Methodology:** Preclinical studies in humanized DMD mice and non-human primates (NHPs) assessed HG302's editing efficiency, dystrophin restoration, and safety. The ongoing MUSCLE trial evaluates its clinical efficacy and safety in ambulant DMD boys. • **Results:** HG302 achieved efficient exon skipping, restoring dystrophin to 70% of wild-type levels in mice and improving motor function. NHPs showed effective editing with no liver or kidney abnormalities. Early MUSCLE trial data indicated improved motor function post-treatment. • **Conclusions:** HG302 offers a transformative, one-time therapeutic approach for DMD, with promising preclinical and early clinical results.
14 May 2025	Next-Generation AAV-Based Gene Therapy for Spinal Muscular Atrophy: Safety and Efficacy of EXG001-307 in Clinical Trials	Zhenhua Wu	• **Introduction:** Gene therapy has revolutionized spinal muscular atrophy (SMA) treatment. Onasemnogene abeparvovec (Zolgensma) provides significant benefits but carries risks, including liver failure. EXG001-307, an AAV-based gene therapy, aims to enhance neuronal expression and reduce toxicity. • **Methodology:** A Phase 1/2 open-label, dose-escalation trial evaluated the safety and efficacy of EXG001-307 in Type 1 SMA patients. • **Results:** Thirteen patients showed rapid motor improvements. In the high-dose cohort, 100% had CHOP-INTEND scores >40, and 44% could sit independently. Two patients developed thrombotic microangiopathy, likely linked to concurrent infections. • **Conclusions:** EXG001-307 demonstrated remarkable efficacy, achieving critical motor milestones in Type 1 SMA patients, offering a promising therapy with targeted benefits.

Notable Presentations at ASGCT 2025
Neurology & Neuromuscular Disorders (4/5)

Date	Title	Author	Summary
14 May 2025	Design of the Phase 1 ASCEND Study to Investigate the Safety and Biodistribution of INS1201 Gene Therapy in Males With Duchenne Muscular Dystrophy	Mark Stahl	• **Introduction:** INS1201 is an AAV9-based gene therapy delivering micro-dystrophin for Duchenne muscular dystrophy (DMD), showing preclinical efficacy in mice and nonhuman primates. Delivered intrathecally, INS1201 targets skeletal and cardiac muscles effectively at lower doses compared to intravenous administration. • **Methodology:** To present the design of the ASCEND Phase 1 study assessing the safety and biodistribution of INS1201 in ambulatory DMD boys aged 2-5 years. • **Results:** The study evaluates 12 participants across two cohorts to determine the recommended Phase 2 dose (RP2D), with primary endpoints focused on safety, and secondary endpoints measuring micro-dystrophin expression and motor function. • **Conclusions:** The ASCEND study aims to identify the RP2D of INS1201, with long-term safety data to follow in an extension study.
15 May 2025	Design of the Phase 1 ASCEND Study to Investigate the Safety and Biodistribution of INS1201 Gene Therapy in Males With Duchenne Muscular Dystrophy	Mark Stahl	• **Introduction:** INS1201 is an AAV9-based gene therapy delivering micro-dystrophin for Duchenne muscular dystrophy (DMD), showing preclinical efficacy in mice and nonhuman primates. Delivered intrathecally, INS1201 targets skeletal and cardiac muscles effectively at lower doses compared to intravenous administration. • **Methodology:** To present the design of the ASCEND Phase 1 study assessing the safety and biodistribution of INS1201 in ambulatory DMD boys aged 2-5 years. • **Results:** The study evaluates 12 participants across two cohorts to determine the recommended Phase 2 dose (RP2D), with primary endpoints focused on safety, and secondary endpoints measuring micro-dystrophin expression and motor function. • **Conclusions:** The ASCEND study aims to identify the RP2D of INS1201, with long-term safety data to follow in an extension study.

Notable Presentations at ASGCT 2025
Neurology & Neuromuscular Disorders (5/5)

Date	Title	Author	Summary
15 May 2025	First in Class ASO Targeting A53T Allele: Preclinical Efficacy	Christina Tyner	• **Introduction:** The A53T missense mutation in SNCA is a major risk factor for early-onset Parkinson's disease (PD). This study proposes an antisense oligonucleotide (ASO)-based allele-specific strategy to target the mutant A53T allele, reducing α-synuclein production without affecting the wild-type allele, ensuring healthy α-syn levels are maintained. • **Methodology:** An 18-mer PS-MOE ASO was designed to specifically target the A53T allele. HEL cells were treated with the A53T-specific ASO, and the knockdown of SNCA expression was assessed. • **Results:** ASO treatment reduced SNCA expression by 40%, with minimal off-target effects. iPSC-derived models are being used to further assess the therapy. • **Conclusions:** This novel ASO strategy selectively targets the mutant allele, offering potential for improved PD treatment by preserving normal α-syn levels while reducing pathological accumulation.

Notable Presentations at ASGCT 2025
Oncology (CAR-T, Gene and Virotherapies) (1/5)

Date	Title	Author	Summary
13 May 2025	Alectinib Enhances Anti-tumor Efficacy of Disialoganglioside 2 Chimeric Antigen Receptor T Cells in ALK-Mutated Neuroblastoma by Suppressing Programmed Death-Ligand 1	Yuya Sugitatsu	• **Introduction:** High-risk ALK-mutant neuroblastoma (NB) is challenging due to drug resistance and an immunosuppressive tumor microenvironment (TME). GD2 CAR-T cell therapy shows promise, but its efficacy is limited by immune evasion, particularly through PD-L1 upregulation. Alectinib, an ALK inhibitor, may enhance CAR-T cell efficacy by inhibiting PD-L1 expression. • **Methodology:** GD2 CAR-T cells were generated and their efficacy assessed in co-culture assays with ALK-mutant NB cells. Alectinib's effects on ALK signaling and PD-L1 expression were studied, and in vivo efficacy was tested in an ALK-mutant NB xenograft model. • **Results:** Alectinib reduced PD-L1 expression, enhanced CAR-T cell activity, and significantly improved tumor growth suppression and survival in vivo. • **Conclusions:** Alectinib enhances GD2 CAR-T cell efficacy by blocking PD-L1-mediated immune evasion, offering a promising approach for ALK-mutant NB treatment. Further clinical investigation is warranted.
13 May 2025	GITRL Coexpression in Anti-GD2 CAR-T Cells Results in Persistent Antitumor Activity and Exhaustion Resistance in a Glioblastoma Model	Izadora Furtado	• **Introduction:** CAR-T cell therapy for solid tumors faces challenges due to the tumor microenvironment, which limits cell infiltration and persistence. GITR engagement on T cells and Tregs has been shown to enhance T cell function and reduce immunosuppressive activity, potentially improving CAR-T cell efficacy. This study investigates the antitumor efficacy of anti-GD2 CAR-T cells coexpressing GITRL in a glioblastoma model. • **Methodology:** CAR-T cells coexpressing GITRL or CAR alone were tested in vitro and in vivo. Tumor cell lysis, IFNγ secretion, exhaustion marker expression, and in vivo antitumor activity were assessed. • **Results:** CAR.GD2/GITRL cells showed enhanced cytotoxicity, reduced exhaustion marker expression, and better persistence in vitro compared to CAR.GD2 cells. In vivo, both CAR-T cells showed similar tumor regression and survival benefits. • **Conclusions:** GITRL coexpression in CAR-T cells improves resistance to exhaustion, enhancing functional activity, and persistence, with potential applications for other CAR constructs.

Notable Presentations at ASGCT 2025
Oncology (CAR-T, Gene and Virotherapies) (2/5)

Date	Title	Author	Summary
13 May 2025	Trial in progress: Phase I study of non-viral gene-modified CAR-T cell therapy for malignant solid tumors with expression of EPHB4 receptor（CARTiEr）	Chikako Funasaka	• **Introduction:** EPHB4 is overexpressed in various tumors, including malignant bone and soft tissue tumors. AP8901, a CAR-T cell targeting EPHB4-expressing tumors, is developed using genetic techniques to prevent T cell exhaustion. Preclinical studies showed therapeutic efficacy in rhabdomyosarcoma models. • **Methodology:** This Phase I, single-center, single-arm study evaluates the safety, tolerability, pharmacokinetics, and antitumor activity of AP8901 in patients with Ewing's sarcoma or solid tumors expressing EPHB4. A dose-escalation design (3+3) is used, with key inclusion criteria including confirmed metastatic disease and EPHB4-positive tumor cells. • **Results:** Safety and efficacy outcomes will be measured, focusing on dose-limiting toxicities and preliminary antitumor activity. • **Conclusions:** AP8901 may provide a targeted treatment for EPHB4-expressing metastatic solid tumors, with the study designed to assess its safety and preliminary efficacy.
13 May 2025	Phase I Open-label Single-arm Study to Evaluate the Safety, Tolerability and Preliminary Efficacy of CHT102, an Allogeneic Mesothelin-targeted CAR-T Cell, in Patients with Advanced Solid Tumors (CHAPTER)	Zhigang Gu	• **Introduction:** CHT102 is an allogeneic CAR-T therapy targeting mesothelin (MSLN) in advanced solid tumors, enhanced by proprietary ROBUS-T technology. Preclinical studies demonstrated high specificity, cytotoxic efficacy, and persistence. This Phase I trial evaluates its safety and efficacy. • **Methodology:** The study included patients with advanced MSLN-expressing tumors, progressive disease, and ECOG status ≤1. Patients underwent lymphodepletion followed by CHT102 infusion. Dose escalation was performed using a 3+3 design with four cohorts (3×10^8 to 18×10^8 CAR+ T cells). • **Results:** 7 patients were enrolled, with six completing infusions. No dose-limiting toxicities were observed. Common treatment-related adverse events were hematologic. At median follow-up of 56 days, 83.3% of patients showed disease control, with some tumor reduction. • **Conclusions:** CHT102 demonstrated a favorable safety profile and encouraging efficacy, especially in pancreatic cancer patients, with an 83.3% disease control rate. Further investigation is warranted.

Notable Presentations at ASGCT 2025
Oncology (CAR-T, Gene and Virotherapies) (3/5)

Date	Title	Author	Summary
14 May 2025	Using primary cell culture models to study adenoviral vectors for virotherapy of head and neck squamous cell carcinoma	Eric Ehrke-Schulz	• **Introduction:** Adenoviral vectors (AdVs) are being explored for oncolytic therapy (OAdV) and tumor gene therapy (TGT) in head and neck squamous cell carcinomas (HNSCC). Given the heterogeneity of HNSCC, including HPV positivity, we aimed to improve AdV efficacy by identifying novel AdV serotypes that enhance tumor lysis and gene delivery. • **Methodology:** Primary patient-derived HNSCC cell cultures were transduced with a library of reporter gene-expressing AdV serotypes. The most effective AdV serotypes were armed with the hTert promoter and death proteins and their oncolytic properties were evaluated in vitro. • **Results:** AdV serotypes 4, 21, 34, 35, and 37 outperformed AdV5 in transduction efficiency and tumor cell viability reduction, showing 10-100 fold improved tumor killing. • **Conclusions:** New AdV serotypes armed with death proteins show promising potential for improving OAdV and TGT in HNSCC. This approach could personalize treatment based on tumor characteristics, enhancing therapy effectiveness.
14 May 2025	Preclinical Study of Combination therapy of GUCY2C CAR-T with Immune Checkpoint Inhibitors for Metastatic Colorectal Cancer	Yanping Ding	• **Introduction:** CAR-T cell therapy has shown success in hematologic cancers but faces challenges in solid tumors due to immunosuppressive microenvironments. GUCY2C-targeted CAR-T cells have shown promise in microsatellite stable (MSS) metastatic colorectal cancer (mCRC), but combining them with immune checkpoint inhibitors (ICIs) may enhance efficacy. • **Methodology:** GUCY2C CAR-T cells were developed and tested in vitro and in vivo using a mouse model of MSS mCRC. Mice received CAR-T cells and ICIs (αPD-1, αCTLA-4) in various combinations, with tumor growth and survival analyzed. • **Results:** Combination therapies, particularly with αPD-1 and αCTLA-4, significantly inhibited tumor relapse and improved survival compared to CAR-T monotherapy. • **Conclusions:** Combining GUCY2C CAR-T cells with ICIs, especially αPD-1 and αCTLA-4, improves treatment efficacy in MSS mCRC, offering a potential strategy for overcoming immune evasion in solid tumors.

Notable Presentations at ASGCT 2025
Oncology (CAR-T, Gene and Virotherapies) (4/5)

Date	Title	Author	Summary
15 May 2025	Phase 2 Study Using Talimogene Laherparepvec, Nivolumab, and Trabectedin for Advanced Leiomyosarcoma and Liposarcoma (NCT03886311)	Jason Ballon	• **Introduction:** This Phase 2 study evaluated the combination of Trabectedin (T), Nivolumab (N), and Talimogene Laherparepvec (TVEC) for advanced leiomyosarcoma (LMS) or liposarcoma (LPS), aiming to enhance efficacy beyond chemotherapy alone. • **Methodology:** The study assessed progression-free survival (PFS) and other secondary endpoints in patients with advanced LMS/LPS using a combination of T, N, and TVEC. Treatment was given over a defined schedule, with TVEC administered intratumorally. • **Results:** The study showed promising efficacy, with a median PFS of 8.0 months and a disease control rate of 83.3%. The 6-month PFS and OS rates were 62.5% and 87.5%, respectively. • **Conclusions:** The combination therapy demonstrated significant improvement over Trabectedin alone, with manageable toxicity, suggesting a randomized trial is needed to confirm these findings.
15 May 2025	DLL3-targeting CAR co-deletion of PD1 results in enhanced T cell cytotoxicity and persistence in a pre-clinical model for small cell lung cancer.	Hua Zhang	• **Introduction:** Small cell lung cancer (SCLC) is a high-grade neuroendocrine cancer with limited treatment options. DLL3, a protein highly expressed in SCLC, is an ideal target for CAR-T therapy. • **Methodology:** A VHH antibody targeting DLL3 was engineered into a second-generation CAR-T format with and without PD1 intracellular retention. Both versions were compared for in vitro activity and in vivo efficacy using a subcutaneous SHP77 tumor model. • **Results:** The PD1-retained CAR-T showed superior long-term cytotoxicity and tumor suppression compared to the unmodified CAR-T, with enhanced T cell persistence and faster tumor regression. • **Conclusions:** PD1-deleted DLL3 CAR-T demonstrated improved efficacy and persistence in preclinical models, suggesting its potential for clinical development in SCLC treatment.

Notable Presentations at ASGCT 2025
Oncology (CAR-T, Gene and Virotherapies) (5/5)

Date	Title	Author	Summary
15 May 2025	Novel Humanized anti-CD20 CAR-T cells Demonstrate Robust Efficacy in B-cell Lymphoma in Preclinical Studies.	Ambalika Chowdhury	• **Introduction:** Anti-CD19 CAR-T therapies are effective for relapsed/refractory B-cell lymphomas (r/r B-NHL), but CD19 loss causes 60% of relapses. Anti-CD20 therapies like Glofitamab show efficacy post-CAR-T failure, but high costs limit access. This study aimed to develop a CD20-targeted CAR-T therapy to complement our CD19 CAR-T (Tali-cel) for better durability in r/r B-NHL. • **Methodology:** Two humanized anti-CD20 CAR constructs (h1CAR20 and h2CAR20) were designed from murine anti-CD20 scFv. CAR-T cells were generated via lentiviral transduction and tested for cytotoxicity, cytokine release, and repeat stimulation. In vivo studies were conducted in NOD/SCID mice with CD20+ Raji cells, monitored by bioluminescent imaging (BLI). • **Results:** CAR-T cells achieved 50% transduction efficiency and 40-60-fold expansion. h2CAR20-T cells showed robust efficacy even against low CD20-expressing tumor cells. Cytokine release was similar to mCAR20-T cells. In vivo, h2CAR20-T cells showed better tumor suppression and survival than mCAR20 and h1CAR20 ($p = 0.0399, 0.0352$). h2CAR20-T cells had no toxicity, unlike mCAR20-T and h1CAR20-T cells. • **Conclusions:** h2CAR20-T cells demonstrated strong efficacy and safety in preclinical models, showing promise for combination therapy in r/r B-NHL.
15 May 2025	Analysis of Clinical Benefit for a Phase 2 Basket Study Using DNG64 Cyclin G1 Inhibitor Gene Vector + Immunotherapy for CCNG1 Oncogene Expressing Tumors Predicts Successful Efficacy Endpoints (NCT04091295)	Sant Chawla	• **Introduction:** DNG64, a retroviral vector targeting Cyclin G1 (CCNG1) expression, induces apoptosis in cancer cells and primes the tumor microenvironment by reducing stroma production. It is being evaluated in combination with immunotherapy for advanced sarcoma, pancreatic cancer, and breast cancer in a Phase 2 basket study. • **Methodology:** The study evaluates clinical benefit rate (CBR), overall response rate (ORR), and correlation between CCNG1 expression and efficacy in 40 patients using DNG64 plus an FDA-approved drug. Tumor specimens are analyzed for CCNG1 expression. • **Results:** Among 8 patients treated, 50% had partial responses (PR), with a 75% CBR at month 4. The highest response rates were observed in patients with high CCNG1 expression. • **Conclusions:** DNG64 combined with immunotherapy shows promising efficacy, meeting the Simon 2-stage design threshold, and warrants further evaluation in a randomized Phase 2 study.

Notable Presentations at ASGCT 2025
Infectious Disease & Immunology (1/2)

Date	Title	Author	Summary
13 May 2025	Expanded Analysis of in vivo-delivered SARS-CoV-2 Plasmid DNA-encoded Monoclonal Antibodies (DMAb) in a Phase 1 Clinical Trial in Healthy Adults	Ami Patel	• **Introduction:** This Phase 1 clinical trial evaluates the safety, tolerability, and pharmacokinetics of a synthetic plasmid DNA-encoded monoclonal antibody (DMAb) cocktail, targeting SARS-CoV-2 variants. The DMAb cocktail uses in vivo electroporation technology for muscle-expressed monoclonal antibodies. • **Methodology:** A sensitive ELISA and bead-based isolation were developed to distinguish DMAb from naturally occurring antibodies. Functional analyses included binding assays and pseudovirus neutralization assays. • **Results:** DMAb serum demonstrated binding to SARS-CoV-2 variants and neutralized the ancestral virus with IC50 values consistent with Evusheld. Durable expression was detected for over 72 weeks. • **Conclusions:** DMAb demonstrates durable expression and biological activity, supporting its further development as a gene-encoded biologic drug for SARS-CoV-2 prevention.
13 May 2025	A FIH dose-escalation trial of the safety and pharmacokinetics of anti-SARS-CoV-2 DNA-encoded monoclonal antibodies (DMAb) formulated for delivery by CELLECTRA in healthy adults	David B. Weiner	• **Introduction:** This first-in-human Phase 1 trial evaluates a synthetic plasmid DNA (pDNA) platform for in vivo production of monoclonal antibodies (mAbs), offering an alternative to recombinant protein technology. The trial tests a pDNA cocktail encoding the SARS-CoV-2 neutralizing mAb cocktail Evusheld. • **Methodology:** Participants received intramuscular pDNA injections encoding AZD5396 and AZD8076, delivered via electroporation. The study assessed pharmacokinetics, durability, anti-drug antibody (ADA) responses, and SARS-CoV-2 neutralization activity. • **Results:** DMAbs were detected in all participants, with stable levels over 72 weeks. Functional assays confirmed receptor-binding and neutralization activity. No serious adverse events occurred. • **Conclusions:** This study demonstrates the feasibility of synthetic pDNA DMAb technology, showing durable in vivo production of functional antibodies, with potential applications for treating various diseases.

Notable Presentations at ASGCT 2025
Infectious Disease & Immunology (2/2)

Date	Title	Author	Summary
14 May 2025	Therapeutic efficacy of AAV-delivered HIV-1 bNAbs to prevent SHIV rebound in rhesus macaques	Priya Dhole	• **Introduction:** ART is the standard treatment for HIV-1 but does not eliminate the viral reservoir. The use of broadly neutralizing antibodies (bNAbs) delivered via AAV vectors is being explored, though host immune responses limit their efficacy. • **Methodology:** This study investigates co-delivery of PD-L1 with AAV-expressed bNAbs to suppress immune responses and sustain bNAb expression in rhesus macaques, aiming to maintain SHIV viremia suppression after ART interruption. • **Results:** Co-administration of PD-L1 with bNAbs reduced immune responses and sustained bNAb expression, helping maintain SHIV suppression after ART cessation. • **Conclusions:** Combining PD-L1 with AAV-delivered bNAbs shows potential for long-term SHIV viremia suppression, advancing HIV cure strategies.

Notable Presentations at ASGCT 2025
Metabolic & Rare Diseases (1/5)

Date	Title	Author	Summary
13 May 2025	Initial clinical results from OTC-HOPE, the first in vivo, liver directed, AAV-mediated gene insertion study in neonatal OTC deficiency: complete clinical response observed in first male infant to receive ECUR-506 and complete 24-week Phase 1/2 study	Julien Baruteau	• **Introduction:** Ornithine transcarbamylase deficiency (OTCD) causes hyperammonemia due to OTC deficiency. Current therapies are insufficient, and liver transplantation is often required. ECUR-506, a gene-editing product using dual AAV vectors, targets the PCSK9 gene and delivers a codon-optimized human OTC gene for neonatal OTCD treatment. • **Methodology:** The OTC-HOPE clinical trial (NCT06255782) assesses ECUR-506 in male infants with neonatal OTCD. Data from the first participant are reported. • **Results:** After receiving ECUR-506 at 6.5 months, the participant showed improved ammonia levels, increased BUN and urinary nitrogen, with no further hyperammonemia events. • **Conclusions:** ECUR-506 shows potential in restoring OTC function, supporting further trials.
13 May 2025	Durable Efficacy and Safety of DTX301: Long-term Follow Up (LTFU) of a Phase 1/2 Trial in Adults with Ornithine Transcarbamylase Deficiency (OTCD	Cary Harding	• **Introduction:** OTCD is an X-linked urea cycle disorder causing episodic hyperammonemia and severe health risks. DTX301, an AAV8 vector with the OTC gene, is being studied as treatment. This report presents long-term follow-up (LTFU) data of 11 adults with late-onset OTCD who received DTX301 in the Phase 1/2 trial (NCT02991144). • **Methodology:** The Phase 1/2 trial was a global, multicenter, open-label study evaluating DTX301's safety and efficacy over 52 weeks, with up to 7 years of LTFU. Complete Responders discontinued ammonia-scavenger meds and protein restriction. • **Results:** No serious adverse events related to DTX301. Most patients showed increased ureagenesis and decreased plasma ammonia AUC. 7 patients showed meaningful responses, with 3 achieving Complete Responder status. • **Conclusions:** DTX301 shows manageable safety and durable improvements. A Phase 3 trial (NCT05345171) is underway to further evaluate its efficacy.

Notable Presentations at ASGCT 2025
Metabolic & Rare Diseases (2/5)

Date	Title	Author	Summary
13 May 2025	rAAV Gene Therapy for Classic Fabry Disease: ZS805 Results from An Ongoing Investigator-Initiated Clinical Trial	Biao Dong	• **Introduction:** ZS805, an AAV5-based gene therapy with the GLA gene, was evaluated for treating Fabry disease. This study assessed safety, efficacy, and immunogenicity in patients with anti-α-Gal and anti-AAV5 antibodies. • **Methodology:** Dose escalation was conducted with 1.0×10^{13} vg/kg (low dose) and 2.0×10^{13} vg/kg (high dose). Eleven participants were enrolled, with ten receiving prednisone prophylaxis. Primary endpoints were safety, tolerability, and efficacy. • **Results:** α-Gal A activity significantly increased, and Lyso-GL3 and GL-3 levels decreased by 20-67%. ZS805 was well-tolerated, with no dose-limiting toxicity. Vector DNA cleared from blood, urine, saliva, and semen over weeks. • **Conclusions:** ZS805 shows promising efficacy and safety, supporting further evaluation for Fabry disease.
14 May 2025	OTC-HOPE: The first in vivo, liver directed, AAV-mediated, gene insertion clinical trial in infants	Gabriel Cohn	• **Introduction:** Despite aggressive treatment, recurrent hyperammonemia often necessitates liver transplantation. ECUR-506 is an investigational gene therapy for OTCD, aiming to provide a long-term solution by integrating a functional OTC gene into the liver genome. • **Methodology:** ECUR-506 consists of two AAVrh79 vectors: one encoding a meganuclease (M2PCSK9) for targeted editing of the PCSK9 gene, and the other carrying a codon-optimized OTC gene. This dual-vector approach allows targeted integration of the OTC gene into the hepatocyte genome. Preclinical studies in a murine OTCD model assessed the effectiveness of gene integration. • **Results:** Gene integration with ECUR-506 resulted in stable OTC expression and significantly improved survival in mice, outperforming gene addition therapy. This approach provided more durable results and better outcomes than gene addition. • **Conclusions:** ECUR-506 shows promise as a treatment for OTCD by enabling durable gene expression and enhancing survival in preclinical models. Gene integration may offer a more stable and effective solution for OTCD patients.

Notable Presentations at ASGCT 2025
Metabolic & Rare Diseases (3/5)

Date	Title	Author	Summary
14 May 2025	AAV-mediated Gene Knock-down and Replacement Therapy for PKU was Effective with High Efficacy and Low Dosage	Tenghui Yu	• **Introduction:** Phenylketonuria (PKU) is caused by mutations in the PAH gene, impairing phenylalanine (Phe) metabolism. Standard treatment requires strict dietary restrictions, which patients often struggle to follow. Gene therapy trials have had limited success. Restoring PAH in 10-20% of hepatocytes normalizes plasma Phe in mice, but most PKU mutations are missense, not null. It was hypothesized that reducing endogenous mutant PAH while introducing wild-type (WT) PAH could improve therapy. • **Results:** In PKU mouse models, dual expression of WT PAH and RNAi-mediated silencing of mutant PAH reduced Phe more in ENU2 than in PAH-KO mice. GS1168, an AAV vector, showed therapeutic effects at 3E11 vg/kg in ENU2 mice. Toxicology studies in mice and NHPs confirmed safety. • **Conclusions:** x GS1168 offers promising AAV-based gene therapy for PKU, improving patient quality of life by addressing both mutant and functional PAH.
14 May 2025	AAV9 -Mediated Gene Therapy of MMAB Deficiency: Preclinical Efficacy in Mouse models of Cobalamin B Type Methylmalonic Acidemia	Eun-Young Choi	• **Introduction:** Cobalamin B-type methylmalonic acidemia (cblB MMA) is a severe inborn error caused by MMAB gene mutations, leading to elevated MMA levels and liver transplants. Current treatments are limited, and no established therapies exist for MMAB deficiency. • **Methodology:** We studied 17 MMAB-deficient patients and created hypomorphic mouse models with severe mutations. AAV vectors expressing MMAB were tested for in vivo efficacy. • **Results:** AAV gene therapy rescued lethality, normalized growth, and reduced MMA levels. sc AAV vectors outperformed ss vectors at low doses. • **Conclusions:** AAV-mediated gene therapy effectively reduced MMA levels and improved survival, offering a potential therapeutic strategy for MMAB deficiency.

Notable Presentations at ASGCT 2025
Metabolic & Rare Diseases (4/5)

Date	Title	Author	Summary
15 May 2025	Long-Term Efficacy of Genome Editing in Infant Mice With Glycogen Storage Disease Type Ia	Elizabeth J. Brooks	• **Introduction:** Glycogen storage disease type Ia (GSD Ia) is caused by a deficiency in glucose-6-phosphatase (G6Pase), leading to severe hypoglycemia, hyperlipidemia, and a long-term risk of liver tumors. Gene replacement therapy using AAV vectors has limitations, motivating the development of genome editing to integrate a therapeutic transgene for G6Pase expression. • **Methodology:** G6pc -/- mice with a combination of Donor and CRISPR vectors were treated, or Donor-only for gene replacement. The efficacy was evaluated after 52 weeks. • **Results:** Genome editing showed the highest survival rate (81%) and improved blood chemistry, including reduced alanine aminotransferase and cholesterol levels. It also significantly decreased hepatomegaly compared to gene replacement therapy (78% survival). • **Conclusions:** Genome editing with CRISPR/Cas9 provides better long-term efficacy than gene replacement therapy, offering a promising approach for early treatment of GSD Ia.
15 May 2025	Evaluation of Clinical Safety and Efficacy of LY-M001: A Phase I/II Trial of AAV8-Mediated Gene Therapy for Gaucher Disease Type I	Fengkui Zhang	• **Introduction:** Gaucher disease (GD), caused by mutations in the GBA1 gene, leads to glucocerebrosidase (GCase) deficiency. LY-M001, an AAV8-based gene therapy, delivers a codon-optimized GBA1 gene to express modified GCase. The Phase I/II dose-escalation trial (CTR20241092) investigates LY-M001's safety and efficacy in GD patients. • **Methodology:** The Phase I/II trial includes naive and pre-treated GD1 patients who discontinued standard care for at least two weeks before receiving LY-M001. Primary objectives include assessing safety and efficacy with monitoring for 38-52 weeks, followed by long-term follow-up. • **Results:** Four participants received LY-M001. The treatment was well tolerated, with mild liver enzyme increases resolved with immune modulation. GCase activity normalized within a week, peaking at 8-16 weeks, reducing Lyso-GL1 levels. No anti-drug antibodies were detected. Improvements were observed in hemoglobin (9-41 g/L), platelets (10-41 × 10^9/L), and organ volumes. Participants also reported better quality of life with reduced abdominal distension and fatigue. • **Conclusions:** LY-M001 is a promising AAV8-based therapy for Gaucher disease, showing favorable safety and efficacy. Enhanced GCase expression leads to improved disease symptoms and quality of life.

Notable Presentations at ASGCT 2025
Metabolic & Rare Diseases (5/5)

Date	Title	Author	Summary
15 May 2025	Low Pre-existing AAV-Neutralizing Titers Detected Using a Cell-Based Assay Did Not Impact 4D-310 Safety or Efficacy in Fabry Cardiomyopathy Patients	Brian Long	• **Introduction:** 4D-310 is an investigational genetic medicine for Fabry disease cardiomyopathy, using a novel AAV capsid (C102) to deliver the human GLA transgene to cardiomyocytes for alpha-galactosidase (AGA) production. The INGLAXA Phase 1/2 study followed 6 participants for up to five years after receiving 4D-310. • **Methodology:** Participants were tested for neutralizing antibodies (NAb) against the C102 capsid using a cell-based transduction inhibition assay and a ligand-binding total anti-drug antibody (ADA) assay. • **Results:** Three of the 6 participants had detectable neutralizing factors at baseline, while all were negative for C102 capsid-binding total antibodies. Despite pre-existing neutralizing factors, efficacy and safety outcomes at Week 52 were similar across both groups. • **Conclusions:** Cell-based assays may overestimate pre-existing AAV neutralizing antibodies. The ligand-binding ADA assay minimizes the risk of excluding potential candidates for AAV gene therapy.
16 May 2025	A First-in-Human Double-Blind, Placebo-Controlled Single and Multiple Ascending Dose Study (SAD, MAD) in Healthy Volunteers to Evaluate the Safety and Tolerability of an Investigational Antisense Oligonucleotide Therapy (CMP-CPS-001) for the Treatment of Urea Cycle Diseases (UCDs): Interim Safety Readout	Yuri Maricich	• **Introduction:** UCDs are rare genetic disorders caused by defects in enzymes or transporters in the urea cycle, leading to ammonia buildup. Symptoms range from irritability to severe issues like seizures and coma. Current treatments include low-protein diets, nitrogen scavengers, and liver transplants. CMP-CPS-001, an antisense oligonucleotide targeting CPS1's regulatory RNA, aims to restore urea cycle function in OTC deficiency and other UCDs. • **Methodology:** CMP-CPS-001 targets the CPS1 gene's regulatory RNA to enhance CPS1 activity. Clinical trials assess its efficacy in OTC deficiency and other UCDs. • **Results:** CMP-CPS-001 restored CPS1 activity in preclinical models, improving urea cycle function. In clinical trials, it showed positive safety and efficacy outcomes, particularly in OTC-deficient patients, with improved ammonia metabolism. • **Conclusions:** CMP-CPS-001 presents a novel treatment for UCDs, particularly OTC deficiency. It offers a promising alternative to liver transplants and could improve quality of life for patients.

Notable Presentations at ASGCT 2025
Autoimmune & Inflammatory Diseases (1/3)

Date	Title	Author	Summary
14 May 2025	Use of Expanded Non-genetically Modified Natural Killer Cells (Troculeucel) with Enhanced Cytotoxicity in Patients with Alzheimer's Disease. Preliminary Clinical and Biomarker Results.	Paul Song	• **Introduction:** Misfolded protein deposits in neurodegenerative diseases trigger neuroinflammation and damage. Recent studies show that simply removing these proteins isn't enough to address the underlying pathology. Natural Killer (NK) cells can reduce neuroinflammation by eliminating activated T cells and degrading protein aggregates. Troculeucel, an autologous, non-genetically modified NK cell product, enhances cytotoxicity and activating receptor expression, offering potential therapeutic benefits. • **Methodology:** Troculeucel was produced from autologous NK cells with enhanced cytotoxicity and receptor expression. Its ability to reduce neuroinflammation, target activated T cells, and degrade protein aggregates was tested in preclinical models of neurodegenerative diseases. • **Results:** Troculeucel showed increased cytotoxicity and over 90% activating receptor expression. It effectively targeted activated T cells, degraded protein aggregates, and induced anti-inflammatory cytokine production, demonstrating potential for reducing neuroinflammation. • **Conclusions:** Troculeucel is a promising therapeutic candidate for neurodegenerative diseases. Its ability to reduce neuroinflammation and degrade protein aggregates warrants further clinical evaluation.
14 May 2025	RESET-SLETM: Clinical Trial Evaluating Rese-cel (Resecabtagene Autoleucel), A Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Non-Renal SLE and Lupus Nephritis: Correlative Findings	Jason Stadanlick	• **Introduction:** Current SLE treatments aim to control disease but often require chronic immunosuppressants. Rese-cel (CABA-201) is an autologous anti-CD19-CAR T cell therapy designed for durable, drug-free remissions by transiently depleting CD19+ B cells. The RESET-SLETM trial (NCT06121297) evaluates rese-cel in non-renal SLE and lupus nephritis (LN). • **Methodology:** This Phase 1/2 trial involves non-renal SLE and LN cohorts, with patients receiving a one-time infusion of rese-cel (1x10^6 CAR T cells/kg). • **Results:** xSix patients (4 SLE, 2 LN) were dosed. Therapy was well-tolerated with mild CRS in two. One N patient had ICANS, resolving with treatment. B cell depletion occurred, and autoantibodies decreased. All patients showed clinical improvement and significant SLEDAI reductions. • **Conclusions:** Rese-cel shows promising pharmacokinetics and efficacy, supporting its potential for drug-free remissions in SLE and LN. The RESET-SLETM trial continues.

Notable Presentations at ASGCT 2025
Autoimmune & Inflammatory Diseases (2/3)

Date	Title	Author	Summary
14 May 2025	RESET-SScTM: Clinical Trial Evaluating Rese-cel (Resecabtagene Autoleucel), A Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Systemic Sclerosis: Correlative Findings	Zachary Vorndran	• **Introduction:** Rese-cel, an autologous 4-1BB anti-CD19-CAR T cell therapy, targets durable responses in systemic sclerosis (SSc) without chronic immunosuppression. The Phase 1/2 RESET-SScTM trial evaluates its safety and efficacy in patients with severe skin or organ involvement. • **Methodology:** Patients receive a one-time infusion of 1x10^6 CAR T cells/kg after preconditioning with fludarabine and cyclophosphamide. • **Results:** One patient (SSc-Skin-1) completed 3 months of follow-up, experiencing grade 2 cytokine release syndrome (CRS), resolving with fluids. CAR T cells peaked at 2 weeks, undetectable by day 29. B cell depletion occurred, with reconstitution at 8 weeks. Autoantibodies decreased, and the patient maintained a drug-free clinical response. • **Conclusions:** Rese-cel induced B cell depletion and supported durable remission in SSc patients, with ongoing evaluation in the RESET-SScTM trial.
15 May 2025	Safety and Efficacy of Umbilical Cord-Derived Mesenchymal Stem Cells (TH-SC01) in Patients with Perianal Fistula in Crohn's Disease: Phase 1 and 2 Clinical Trials	Zixuan He	• **Introduction:** Evaluate the safety and efficacy of intralesional TH-SC01, an allogeneic umbilical mesenchymal stem cell product, for perianal fistula in Crohn's disease (CD). • **Methodology:** Phase 1: Open-label, single-arm study (2022-2024). Phase 2: Randomized, placebo-controlled, double-blinded study (2023-2025). Adult patients with treatment-refractory perianal fistulas were enrolled. • **Results:** Nine patients in Phase 1 and 40 in Phase 2 (median age 26.5 years) were enrolled. Recommended RP2D: 120 million cells. In Phase 2, combined remission at 24 weeks was 50% in the TH-SC01 group and 10% in the placebo group. Significant improvements were observed in disease activity indices and quality of life. No serious adverse events. • **Conclusions:** Intralesional administration of 120 million TH-SC01 cells shows potential for treating refractory perianal fistulas in CD, warranting further Phase 3 investigation.

Notable Presentations at ASGCT 2025
Autoimmune & Inflammatory Diseases (3/3)

Date	Title	Author	Summary
16 May 2025	RESET-MyositisTM: Clinical Trial Evaluating Rese-cel (Resecabtagene Autoleucel), A Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Idiopathic Inflammatory Myopathies: Correlative Findings	Samik Basu	• **Introduction:** Rese-cel (formerly CABA-201) is an autologous 4-1BB anti-CD19 CAR T cell therapy for idiopathic inflammatory myopathy (IIM), targeting CD19+ B cells with a one-time infusion. RESET-MyositisTM (NCT06154252) is a Phase 1/2 trial assessing rese-cel in IIM patients with immune-mediated necrotizing myopathy (IMNM), dermatomyositis (DM), antisynthetase syndrome (ASyS), and juvenile IIM (JIIM). • **Methodology:** Three IIM patients (IMNM-1, IMNM-2, DM-1) received rese-cel. The primary objectives were safety and efficacy, focusing on immune response, B cell depletion, and autoantibody levels. • **Results:** Rese-cel was well-tolerated with no serious adverse effects. CAR T cells peaked between days 8-15, with rapid B cell depletion observed by 15 days. After 8 weeks, repopulation of transitional B cells occurred. Myositis-specific autoantibodies decreased, and total improvement scores increased in all patients. • **Conclusions:** Rese-cel shows potential for durable, drug-free remissions in IIM patients. Evaluation continues in the RESET-MyositisTM trial.

Notable Presentations at ASGCT 2025
Clinical Operations, Safety & Data Science (1/3)

Date	Title	Author	Summary
13 May 2025	A United States Population-Based Study on the Epidemiology and Impact of Hemophagocytic Lymphohistiocytosis on In-Hospital Outcomes in Patients Receiving Chimeric Antigen Receptor T-Cell Therapy	Adamsegd Gebremedhen	• **Introduction:** Hemophagocytic Lymphohistiocytosis (HLH) is a severe inflammatory syndrome with uncontrolled immune activation, leading to organ failure and death. In CAR-T patients, HLH is known as immune effector cell-associated HLH-like syndrome (IEC-HS). This study evaluates the epidemiology and impact of HLH on outcomes in CAR-T patients using U.S. data. • **Methodology:** CAR-T therapy patients with NHL, B-cell ALL, and MM from 2018 to 2021 using the National Inpatient Sample were annalyzed. The cohort was stratified by HLH status, comparing outcomes such as mortality and complications using multivariate regression. • **Results:** 4,120 adults received CAR-T, 50 with HLH (1.2%). HLH patients had higher mortality (20% vs. 3%, $p < 0.05$) and worse outcomes, including shock (aOR 6.3), coagulopathy (aOR 21.6), and hemorrhage (aOR 51.3). They also required more intensive care and had longer stays (32.4 vs. 16.8 days, $p < 0.05$). Charges were similar between groups. • **Conclusions:** HLH in CAR-T patients is linked to higher mortality, complications, and longer stays. Early identification and management are essential to improve outcomes and reduce healthcare burden.
14 May 2025	Exploring the Impact of Chronic Kidney Disease on In-Hospital Outcomes in Patients Receiving Chimeric Antigen Receptor T-Cell Therapy: Insights From a United States Population-Based Study	Adamsegd Gebremedhen	• **Introduction:** CAR T-cell therapy, approved since 2017, revolutionized cancer treatment for NHL, ALL, and MM. However, it can cause cytokine release syndrome and tumor lysis syndrome, leading to kidney injury. This study evaluates the impact of chronic kidney disease (CKD) on CAR T-cell outcomes using national data. • **Methodology: A**dults with ALL, NHL, and MM from the National Inpatient Sample who received CAR T-cell therapy between 2018-2021 were analyzed. The cohort was stratified by CKD status, comparing sociodemographics, comorbidities, and outcomes using multivariate regression models. • **Results:** Out of 4,120 patients, 370 (9.0%) had CKD. CKD patients were older (64.8 vs. 60.2 years, $p<0.05$) and had more comorbidities. CKD patients had higher odds of acute kidney injury (adjusted OR 2.9), but no significant differences in mortality or other complications. Mean hospitalization cost was $1,196,413, with a length of stay of 17 days. • **Conclusions:** CKD patients on CAR T-cell therapy are more likely to experience acute kidney injury but not higher mortality. These findings inform tailored approaches for CKD patients receiving CAR T-cell therapy.

Notable Presentations at ASGCT 2025
Clinical Operations, Safety & Data Science (2/3)

Date	Title	Author	Summary
14 May 2025	Long-term Dynamics and Integration Site Analysis of CAR-T Cell Therapy in Relapsed/Refractory Lymphoma and Multiple Myeloma: A Retrospective Study	Zhihan Chen	• **Introduction:** CAR-T therapy is effective for relapsed/refractory lymphoma and multiple myeloma, but the link between CAR-T cell persistence and efficacy is unclear. Integration sites in T cells may influence persistence and oncogenesis. This study analyzes 18 patients to explore CAR-T cell dynamics, clinical outcomes, and integration site risks. • **Methodology:** 18 patients (8 lymphoma, 10 myeloma) received various CAR-T products. CAR-T cell levels were monitored by ddPCR, and integration sites were analyzed with LAM-PCR and sequencing. • **Results:** All lymphoma patients are in remission. In myeloma, 7 of 10 remain in remission, 3 relapsed. Relapsed patients had significantly lower CAR-T cells at 6 months ($p < 0.05$). Integration sites were enriched in 11q13, with PACS1 and RPTOR genes showing persistence in lymphoma. No dominant clones or secondary malignancies were observed. • **Conclusions:** Certain integration sites may enhance CAR-T efficacy, with low risk of secondary malignancies. Long-term studies are needed to confirm these findings.
14 May 2025	SAFETY AND EFFICACY OF THE THERAPY WITH CD4+CD25HIGHCD127 - T REGULATORY CELLS – 12 YEARS AFTER ADMINISTRATION	Piotr Trzonkowski	• **Introduction:** CD4+CD25highCD127- T regulatory cells (Tregs) are being tested as immunotherapy for type 1 diabetes (T1DM). This study assessed long-term safety and efficacy after Treg therapy in children with T1DM. • **Methodology:** 51 T1DM patients treated with Tregs, 7.5 to 12 years post-treatment were re-examined . Patients were grouped into Tregs+anti-CD20 (N=9), Tregs 1 dose (N=10), Tregs 2 doses (N=8), and a standard of care (SoC) control (N=24). Over 700 variables were analyzed, including diabetes tests and safety evaluations. • **Results:** The Tregs+anti-CD20 group showed better C-peptide secretion, insulin independence, and remission duration compared to the SoC group. No significant differences were found in other tests. Importantly, no severe adverse effects occurred. • **Conclusions:** Treg therapy, especially with anti-CD20, shows long-term safety and efficacy and should be considered for newly diagnosed T1DM patients.

Notable Presentations at ASGCT 2025
Clinical Operations, Safety & Data Science (3/3)

Date	Title	Author	Summary
15 May 2025	Interim Analysis of a Phase 1/2a Study of ICM-203 AAV Gene Therapy for Osteoarthritis	Dae-Won Kim	• **Introduction:** An interim analysis of the low-dose cohort in the phase 1/2a trial of ICM-203, an AAV vector expressing truncated human Nkx3.2, was conducted to assess safety, immunogenicity, and activity. • **Methodology:** Eight patients with grade 3 osteoarthritis received ICM-203 or placebo. Safety was evaluated through TEAEs, and immunogenicity via NAb titers and T-cell responses. Efficacy was assessed using KOOS, WOMAC, and MRI-based imaging (MOAKS). • **Results:** Six ICM-203 and two placebo patients were treated. No significant safety concerns; mild arthralgia was common. Three ICM-203 patients had positive baseline NAb responses. ICM-203 subjects without baseline NAb showed improved KOOS and WOMAC scores, and imaging, compared to placebo. No efficacy was seen in NAb-positive patients. • **Conclusions:** ICM-203 was well tolerated, showing greater efficacy in NAb-negative patients. It shows promise as a DMOAD, with ongoing studies on higher doses.

Notable Presentations at ASGCT 2025
Cardiology (Cardiac Gene Therapies and CAR-T) (1/2)

Date	Title	Author	Summary
13 May 2025	Preclinical Efficacy and Safety Evaluation of FT-017: a Novel AAV-Based Gene Therapy for MYBPC3-associated Hypertrophic Cardiomyopathy	Zhong-Dong Shi	• **Introduction:** Hypertrophic cardiomyopathy (HCM), frequently caused by MYBPC3 haploinsufficiency, disrupts sarcomeric function. Restoring cMyBP-C protein levels offers a rational therapeutic strategy. • **Methodology:** FT-017, an AAV9 vector carrying codon-optimized MYBPC3 under a cardiac-specific promoter, was tested in vitro (C2C12 cells) and in vivo (Mybpc3-KO mice and NHPs) across developmental stages. Doses ranged from 1×10^{13}–3×10^{14} vg/kg. • **Results:** FT-017 restored cMyBP-C expression to wild-type levels, reversed myocardial pathology, improved LV function, and reduced cardiac biomarkers. In NHPs, it showed excellent biodistribution and minimal transient hepatotoxicity. • **Conclusions:** FT-017 demonstrated potent, durable cardiac rescue and safety, supporting clinical advancement in MYBPC3-related HCM.
13 May 2025	Gene Therapy Targeting Atrial Fibrillation Using Mouse Models: A Novel Approach to Cardiac Rhythm Regulation	Sofia Maria De La Serna Buzon	• **Introduction:** Atrial fibrillation (AF) is a widespread arrhythmia linked to stroke and heart failure. CaMKII hyperactivation drives calcium overload and atrial remodeling, making it a compelling gene therapy target. • **Methodology:** While not fully detailed, the study employed AAV-based gene delivery to inhibit CaMKII activity in two murine AF models, aiming to reverse pro-arrhythmic signaling and structural remodeling. • **Results:** Gene therapy effectively reduced AF burden by correcting CaMKII-mediated calcium dysregulation and electrophysiological instability, indicating restored atrial function. • **Conclusions:** AAV-CaMKII inhibition shows strong therapeutic promise for AF, supporting continued preclinical optimization toward clinical translation.

Notable Presentations at ASGCT 2025
Cardiology (Cardiac Gene Therapies and CAR-T) (2/2)

Date	Title	Author	Summary
13 May 2025	Efficacy and Safety of ART002, a Single-dose Gene Editing Therapy, in Patients with Severe Heterozygous Familial Hypercholesterolemia	Yongzhong Wang	• **Introduction:** Severe HeFH poses high ASCVD risk; current treatments (statins, PCSK9 inhibitors, siRNA) offer suboptimal efficacy or adherence. ART002 uses CRISPR/LNPs to permanently inactivate hepatic PCSK9 in vivo. • **Methodology:** An open-label, single-arm trial (N=6) administered single-dose ART002 (0.3–1 mg/kg) IV in HeFH patients. Primary endpoint: safety; secondary: plasma PCSK9 and LDL-C reduction at 24 weeks. • **Results:** ART002 was well-tolerated (no SAEs or ≥Grade 3 toxicities). PCSK9 levels dropped up to 91% (mean 73–86%), LDL-C up to 68% (mean 56–62%). 83% achieved ≥50% LDL-C reduction, including difficult-genotype cases. • **Conclusions:** ART002 shows transformative potential as the first durable, single-dose PCSK9-editing therapy, offering major clinical impact in HeFH management.

Notable Presentations at ASGCT 2025
Gene & Cell Therapy Platforms & Delivery Technologies (1/4)

Date	Title	Author	Summary
14 May 2025	Development of a ddPCR Assay to Quantify AXV-101 Levels for a Mouse Biodistribution Study	Victor Hernandez	• **Introduction:** AXV-101, an AAV9-based BBS1 gene therapy, requires precise biodistribution analysis. Axovia developed an in-house ddPCR assay to establish detection limits and baseline levels in naïve mouse tissues. • **Methodology:** Tissues from C57BL/6j mice were processed post sub-retinal injection. DNA was extracted and quantified; ddPCR was performed with controls and virus-spiked samples. Dilution series optimized assay sensitivity and addressed matrix effects, especially in eye tissue. • **Results:** Naïve tissue showed signal comparable to non-template controls. Spiked samples yielded measurable viral DNA. High DNA concentrations (>35 ng/µL) introduced signal error. A dilution factor of 8.80E+07 was optimal for spiking. • **Conclusions:** The validated ddPCR assay distinguishes naïve from AXV-101-exposed tissue, supporting its application for preclinical biodistribution studies.
14 May 2025	Use of Statistical Analyses for Evaluating Large Historical Datasets of AAV Productions to Assess Process Parameters – A Case Study	John Ketz	• **Introduction:** Andelyn Biosciences evaluated its Curator™ adherent AAV platform, used in over 450 GMP clinical batches, to identify critical process parameters influencing viral yield and recovery for Serotypes A and B. • **Methodology:** Historical GMP production data (n=118 sublots) were analyzed using Pearson correlation matrices, assessing variables like titer, BSA levels, pressures, and confluency. Linear regression was applied where $r \geq 0.7$ or $p \leq 0.05$. • **Results:** IDX had the lowest recovery (~50%). Few parameters showed strong correlation. TMP during TFF and concentration factor impacted process efficiency and recovery, especially at IDX. • **Conclusions:** Despite low correlation trends, the process is robust. TMP and concentration factor warrant monitoring to further enhance consistency and yield.

Notable Presentations at ASGCT 2025
Gene & Cell Therapy Platforms & Delivery Technologies (2/4)

Date	Title	Author	Summary
14 May 2025	A Comparative Study of Full Adeno-Associated Virus 8 (AAV) Capsid Enrichment Platforms	Shaofeng Wang	• **Introduction:** Ultragenyx evaluated capsid purification technologies—AEX, IDXUC, and DGEUC—for AAV8, aiming to minimize empty/partial capsids that reduce efficacy and pose safety concerns. • **Methodology:** AAV8 affinity pool was purified using the three methods. Post-processing, qPCR quantified genomic copies; AUC assessed capsid composition; and cell-based assays measured GOI expression potency. • **Results:** All methods yielded similar GC recovery (40–50%). DGEUC produced 96–99% full capsids and 175% relative potency. IDXUC yielded 55–65% full capsids (160% potency), AEX 25–32% (87%). • **Conclusions:** Density-based methods (IDXUC, DGEUC) enriched for full capsids, enhancing potency, underscoring method choice as critical for therapeutic AAV quality.
14 May 2025	Quantification of Full, Empty, and Partial Particles of AAV8 Reference Standards From Multi-Lab Study	Anthony Blaszczyk	• **Introduction:** AAV gene therapy growth is hindered by the lack of well-characterized empty/full capsid standards, limiting innovation in analytical method development. • **Methodology:** Publicly available AAV8 Empty and Full Capsid standards were analyzed across six orthogonal platforms (AUC, SEC-MALS, CD-MS, cryo-EM, Mass Photometry, UV-vis) by five labs. Complementary assays (NGS, dPCR, CGE, peptide mapping) evaluated identity, purity, aggregation, genome content. • **Results:** All methods confirmed capsid identity; AUC, CD-MS, and Mass Photometry also quantified partials. Broader analyses provided quantitative data on titer, genome integrity, and aggregation. • **Conclusions:** These validated standards will support adoption and cross-validation of novel AAV analytical technologies, aiding development and commercialization across gene therapy platforms.

Notable Presentations at ASGCT 2025
Gene & Cell Therapy Platforms & Delivery Technologies (3/4)

Date	Title	Author	Summary
15 May 2025	Optimising Magnetic-Guidance of Lentiviral Vectors for Improved Airway Gene Therapy Efficacy	Martin Donnelley	• **Introduction:** Gene therapy for cystic fibrosis requires improved airway targeting and vector retention. Magnetic nanoparticles (MNPs) conjugated to vectors may enable guided delivery via external fields. • **Methodology:** Rat basal epithelial cells were transduced in vitro using lentiviral GFP vectors conjugated to CombiMag or ViroMag MNPs across a range of MNP:LV ratios and co-incubation times, with/without magnetic fields. GFP expression was measured via flow cytometry. Synchrotron X-ray imaging assessed in vivo MNP behavior on tracheal surfaces. • **Results:** Magnetic field exposure enhanced GFP expression significantly. Increasing MNP:LV ratios improved expression up to 200:1. Co-incubation time had no impact. A Halbach-array magnetic wheel optimized in vivo MNP manipulation. • **Conclusions:** Magnetic targeting enhances vector delivery efficacy. Optimized MNP:LV ratio (200:1) and magnetic setup will inform in vivo CF gene therapy trials.
15 May 2025	ABL's HIV p24 ELISA Kit: a Solution for Lentivirus Quantification in Industrial Processes	Shanshan Zhu	• **Introduction:** ABL, leveraging decades of HIV expertise, evaluated its HIV-derived p24 ELISA kit for lentiviral vector (LVV) quantification, addressing inconsistencies between RNA-based and protein-based titers in early-stage, low-concentration samples. • **Methodology:** In-process LVV samples were analyzed using the ABL® kit and four competitor kits (B–E); p24 levels (ng/mL) and genomic titers (vg/mL) were quantified via ELISA and qRT-PCR, respectively, with correlation and performance compared across kits. • **Results:** The ABL® kit demonstrated superior reliability, particularly in detecting low-titer LVV samples, outperforming competitors in consistency and correlation. • **Conclusions:** ABL® kit offers robust, cGMP-compatible LVV quantification, supporting broad industrial and clinical gene therapy applications.

Notable Presentations at ASGCT 2025
Gene & Cell Therapy Platforms & Delivery Technologies (4/4)

Date	Title	Author	Summary
16 May 2025	"AAV-vectored PD-L1 Co-Expression as a Strategy to Enhance AAV-Delivered bNAb Efficacy	Michael Kuipa	• **Introduction:** Immune responses limit the efficacy of rAAV-vectored broadly neutralizing antibodies (bNAbs) for HIV-1. Leveraging PD-L1's immunosuppressive role, AAV9.PD-L1 co-delivery was previously shown to enhance 10-1074 durability and protection in nonhuman primates; here, the strategy is extended to the more immunogenic 3BNC117. • **Methodology:** Five groups of macaques received various AAV9 combinations encoding PD-L1, 10-1074, or 3BNC117. Humoral and cellular immune responses were assessed by ELISA and ELISpot. SHIV-AD8 challenge assessed protective efficacy; biodistribution and immunomodulation analyses are ongoing. • **Results:** PD-L1 co-delivery enhanced sustained bNAb expression and protection from SHIV. Animals with durable expression exhibited reduced anti-drug antibody and T cell responses. • **Conclusions:** AAV9.PD-L1 co-expression suppresses host immunity, enabling prolonged bNAb expression and antiviral protection—broadly applicable to vectored immunotherapies.

Notable Presentations at ASGCT 2025
Ophthalmology (Retinal and Ocular Gene Therapies) (1/4)

Date	Title	Author	Summary
13 May 2025	CRISPR-Cas13 Gene Editing Therapy Targeting VEGFA Demonstrated Early Efficacy in Neovascular Age-Related Macular Degeneration	TJ Cradick	• **Introduction:** nAMD is driven by VEGF-A overexpression; current anti-VEGF treatments, while effective, require frequent injections, leading to adherence challenges. HG202, a CRISPR-Cas13 RNA-editing therapy, aims to durably suppress VEGF-A. • **Methodology:** In the SIGHT-I trial (NCT06031727), nine patients with active nAMD received subretinal HG202 via AAV in three escalating doses. Safety (AEs/SAEs) and preliminary efficacy (BCVA, CRT, injection frequency) were evaluated. • **Results:** No drug-related toxicity observed. CRT reduction (13–88 μm) and anti-VEGF need decreased up to 100%. Visual changes correlated with cataract status, not therapy toxicity. • **Conclusions:** HG202 shows early promise as a safe, durable, one-time treatment for nAMD.
13 May 2025	12-Month Safety and Efficacy Evaluation of Subretinal Gene Therapy (FT-002) for the Treatment of RPGR Gene Mutation Associated X-linked Retinitis Pigmentosa	Xinyan Li	• **Introduction:** XLRP, driven by RPGR mutations, leads to early-onset blindness with no current therapy. FT-002 delivers a codon-optimized RPGRORF15 gene via AAV5 to rescue photoreceptor function. • **Methodology:** In a Chinese open-label, dose-escalation study (NCT05874310), 18 males (18–45 years) received subretinal FT-002 (5×10^{10} to 20×10^{10} vg/eye). Safety, immunogenicity, and efficacy were assessed over 12 months. • **Results:** FT-002 showed good tolerability; 44% experienced manageable inflammation. No RPE atrophy or significant EZ loss occurred. Microperimetry improvements (up to 1.32 dB) and ≥7 dB gains in ≥5 loci in 33–50% support functional benefit. • **Conclusions:** FT-002 is safe, preserves retinal structure, and may improve function in RPGR-related XLRP.

Notable Presentations at ASGCT 2025
Ophthalmology (Retinal and Ocular Gene Therapies) (2/4)

Date	Title	Author	Summary
13 May 2025	Initial Results from Gene Therapy for X-linked Retinoschisis via Subretinal Delivery of scAAV8-hRS1 in Pediatric Patients	Lu Fang	• **Introduction:** XLRS, caused by RS1 mutations, is the leading cause of macular degeneration in boys. This study evaluates scAAV8-hRS1 gene therapy via subretinal delivery in pediatric XLRS patients. • **Methodology:** In a single-center trial (ChiCTR2300076682), nine patients (ages 5–18) received unilateral subretinal scAAV8-hRS1. Safety (TEAEs) was primary; BCVA and SS-OCT were secondary endpoints over 26 weeks. • **Results:** No drug-related or severe TEAEs were observed. Treated eyes improved 9.3–10 letters BCVA. Schisis resolved by week 13 with no recurrence; CRT reduced ~430–480 µm. Seven of nine restored outer retinal layers. • **Conclusions:** scAAV8-hRS1 safely restored structure and function in XLRS pediatric patients, supporting further clinical development.
13 May 2025	Safety and Efficacy of ZM-02 Optogenetic Gene Therapy Clinical Study for Advanced Retinitis Pigmentosa	Wenhui Zhou	• **Introduction:** Retinitis pigmentosa (RP), the most common inherited retinal disease, has no current treatment. ZM-02, an AAV-delivered optogenetic therapy encoding PsCatCh2.0, aims to restore vision via intravitreal injection in advanced RP. • **Methodology:** In the MOON trial (NCT06292650), eight severely visually impaired RP patients were randomized to high-/low-dose ZM-02 or sham. Safety (AEs, SAEs, DLTs) was primary; visual function (BCVA, MLTs) was secondary. Follow-up extended up to 12 months. • **Results:** No DLTs or SAEs occurred. 83.3% receiving ZM-02 improved in BCVA (mean gain: 0.54 logMAR), all improved in MLTs, and unexpected color vision gains were observed. • **Conclusions:** ZM-02 demonstrated strong safety and functional visual improvement, supporting its potential for advanced RP therapy.

Notable Presentations at ASGCT 2025
Ophthalmology (Retinal and Ocular Gene Therapies) (3/4)

Date	Title	Author	Summary
13 May 2025	Gene Therapy Clinical Trials Targeting Optic Neuropathies and Other Ocular Diseases until 2024	Niranjana Kesavamoorthy	• **Introduction:** Gene therapy offers novel therapeutic options for optic neuropathies, historically deemed untreatable. This study comprehensively evaluated all clinical trials in ocular gene therapy registered up to 2024. • **Methodology:** A multi-registry search across 14 international databases identified trials involving gene therapy for ocular diseases, including optic neuropathies. • **Results:** Among 260 ocular trials (1998–2024), 12% targeted optic neuropathies—mostly Leber's hereditary optic neuropathy. Retinal disorders dominated (85%). AAV vectors were used in 61% of trials; most employed gene augmentation strategies. Trial activity peaked in 2023. Industry-sponsored trials comprised 77%. • **Conclusions:** LHON remains the primary optic neuropathy target. Overall, ocular gene therapy trials are rising, reflecting strong industry engagement and scientific momentum.
13 May 2025	Evaluating the impacts of pre-existing NAb and ADA in rhesus monkeys on the efficacy of subretinal injection of KH631	Qiang Zheng	• **Introduction:** AAV-based gene therapies are challenged by anti-AAV neutralising antibodies (NAbs) and anti-drug antibodies (ADAs), which may compromise tissue transduction or therapeutic protein stability. This study assesses whether such immune responses affect KH631 efficacy. • **Methodology:** Rhesus monkeys (26 eyes) received subretinal KH631 (3E9–5E11 vg/eye). Serum NAbs and ADAs were measured on days 0 and 27. CNV lesions were induced on day 28 and assessed via FFA on days 42 and 56. • **Results:** Despite pre-existing NAbs (3 monkeys) and ADA development (5 monkeys), 100% grade-4 CNV lesion suppression was maintained at both assessment points. • **Conclusions:** KH631 retained full efficacy regardless of NAb or ADA presence, supporting the immunological resilience of subretinal AAV gene therapy delivery.

Notable Presentations at ASGCT 2025
Ophthalmology (Retinal and Ocular Gene Therapies) (4/4)

Date	Title	Author	Summary
15 May 2025	Supporting the Informed Consent Process in Clinical Trials of Induced Pluripotent Stem Cell–Derived Corneal Epithelium Transplantation	Kayo Takashima	• **Introduction:** In ophthalmic iPSC trials, especially those involving retinal and corneal diseases, visually impaired participants face challenges in understanding written consent materials. This study evaluated the effectiveness of audio materials co-developed with visually impaired individuals to enhance informed consent. • **Methodology:** Semi-structured post-trial interviews were conducted with four participants in an iPSC-derived corneal epithelium transplantation trial. Interview data mentioning audio materials were analyzed qualitatively. • **Results:** Participants reported four experiences: (1) easy comprehension, (2) understanding after repetition, (3) difficulty understanding, and (4) comprehension with family support. Audio aids also helped facilitate family discussions about trial participation. • **Conclusions:** Audio materials improved accessibility and supported informed decision-making. Post-participation interviews offered a valuable method for evaluating such patient-centered initiatives, highlighting the need for reasonable accommodations in clinical research for visually impaired populations.

Key Industry Sponsored Sessions Information

ASGCT 2025 Key Industry Sponsored Sessions Information (1/5)

Date	Sponsor	Title
14 May 2025	Latus Bio	Novel AAV Capsid Variants for Targeted Brain Delivery
14 May 2025	REGENXBIO Inc.	RGX-121 (clemidsogene lanparvovec) : an investigational AAV Gene Therapy for the Treatment of Neuronopathic Mucopolysaccharidosis Type II
14 May 2025	Genetic Alliance	Genetic Testing in 202 – Rare Disease and preventative routine screening
14 May 2025	Dyne Therapeutics	TfR1-mediated delivery of oligonucleotides for the treatment of neuromuscular diseases: translating research into clinic
14 May 2025	Entrada Therapeutics Inc	Clinical Trial of ENTR-601-44, an Endosomal Escape Vehicle (EEV)-conjugated PMO, for the Treatment of Duchenne Muscular Dystrophy

ASGCT 2025 Key Industry Sponsored Sessions Information (2/5)

Date	Sponsor	Title
14 May 2025	HAYA Therapeutics	A WISPER from the Heart: Targeting a Cardiac Myofibroblast-specific LncRNA to Treat Cardiac Fibrosis
15 May 2025	Cabaletta Bio	Clinical & Translational Findings Following Resecabtagene Autoleucel Anti-CD19 CAR T Cell Therapy in Autoimmune Disease
15 May 2025	Atalanta Therapeutics	IT di-siRNA for the treatment of Huntington's disease: preclinical safety and pharmacology with clinical dose projections
15 May 2025	Biogen	BIIB080: the development of a tau-targeting antisense oligonucleotide in early AD
15 May 2025	AskBio	AI use for promotor and transgene design

ASGCT 2025 Key Industry Sponsored Sessions Information (3/5)

Date	Sponsor	Title
15 May 2025	Neurogene Inc.	Neurogene's experience with the START Pilot Program in advancing their NGN-401 product for Rett Syndrome
16 May 2025	Convey Bio	Communicating Complex Science on Social Media
16 May 2025	Orchard Therapeutics	Developing and delivering hematopoietic stem cell gene therapies to patients with rare neurometabolic diseases
16 May 2025	Kriya Therapeutics	The pathway to bringing gene and cell therapies from bench to bedside
16 May 2025	Takeda	Introductory overview of some of the key differences across global jurisdictions (e.g. raw materials, donor eligibility, facility design)

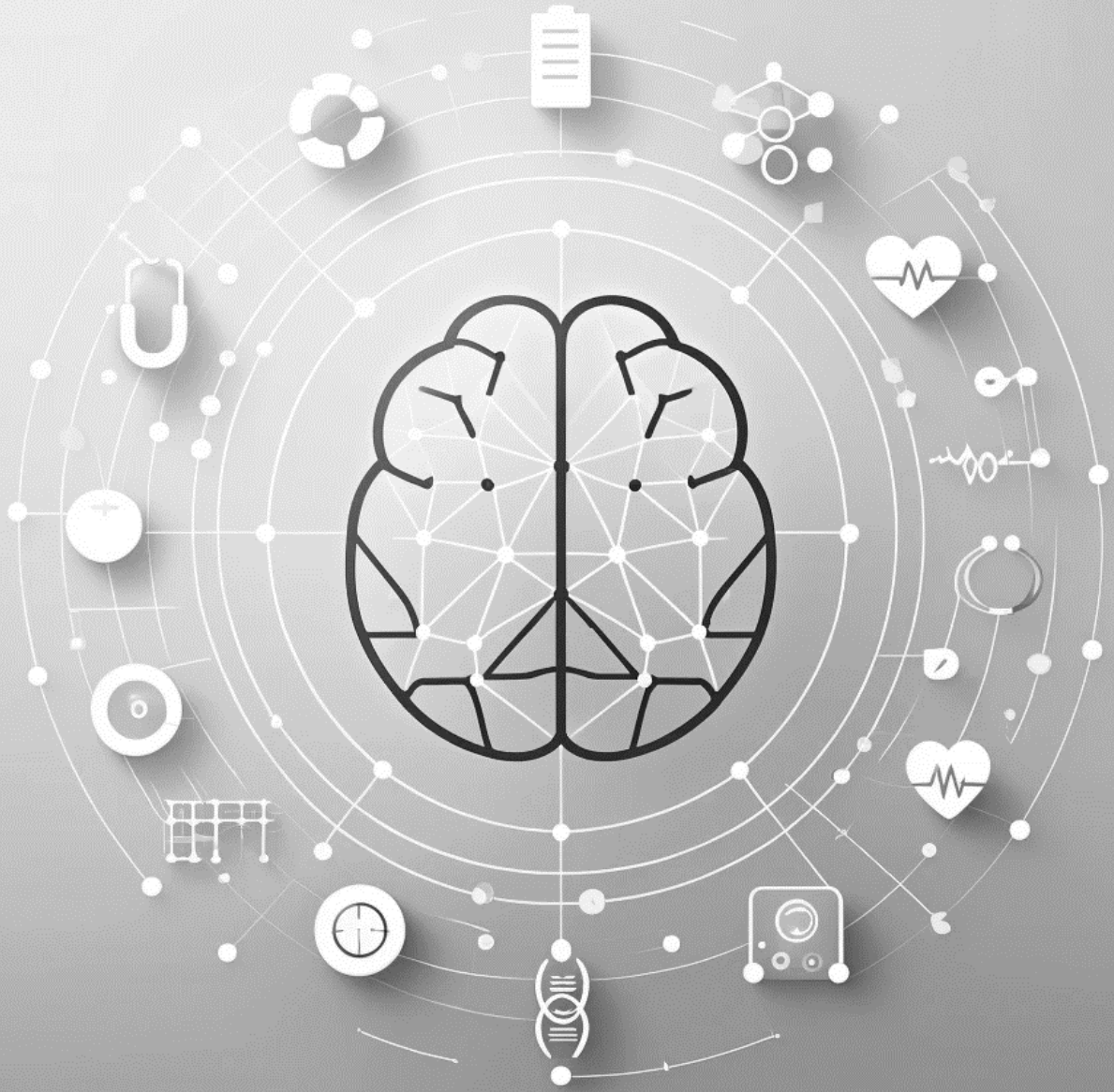
ASGCT 2025 Key Industry Sponsored Sessions Information (4/5)

Date	Sponsor	Title
16 May 2025	Bristol Myers Squibb	Navigating the Curves: Global Lifecycle Management Experiences in a Commercial Cell Therapy Product
16 May 2025	Artiva Biotherapeutics	Streamlining Global Cell Therapy Clinical Studies: Strategies for CMC Content and Structure
16 May 2025	Sana Biotechnology	Next Generation Strategies For Evading Immunity In Stem Cell Therapies (Organized by the Stem Cell Committee)
16 May 2025	Aspen Neuroscience	Autologous iPSC-Derived Neuron Replacement for Parkinson's Disease
16 May 2025	Sail Biomedicines	Pioneering the design and deployment of fully programmable RNA medicines

ASGCT 2025 Key Industry Sponsored Sessions Information (5/5)

Date	Sponsor	Title
16 May 2025	Capstan Therapeutics	In vivo immune cell engineering using targeted nanoparticles
17 May 2025	Arcturus Therapeutics	Self-Amplifying mRNA Vaccines: Pioneering a New Era in Infectious Disease Prevention
17 May 2025	Cabaletta Bio	CD19 CAR-T for Autoimmune Disease: insights to risk-benefit
17 May 2025	Sonoma Biotherapeutics	Engineered Treg therapies to treat Autoimmune Diseases
17 May 2025	Siren Biotechnology	SRN-101 universal AAV gene therapy for solid tumors
17 May 2025	Krystal Biotech	HSV-1 as a vector system for targeting respiratory tissues in genetic pulmonary disease

Noteworthy AI / ML presentations at ASGCT 2025



Themes from key AI / ML presentations at ASGCT 2025 (1/2)

- **At ASGCT 2025, role of AI and machine learning will be discussed in reshaping gene and cell therapy by driving advancements in gene editing optimization, personalized drug discovery, scalable cell expansion, and precise genome quantification leveraging AI-driven models, microfluidic systems, and cutting-edge technologies to enhance therapeutic efficacy and clinical outcomes**
- Check out the key AI / ML themes at ASGCT 2025 below:
- **CRISPR-GEM for MSC Chondrogenesis:**
  - CRISPR-GEM utilizes machine learning to identify effective CRISPRa targets, improving MSC differentiation for cartilage repair. Key genes like PRG4 and BMP2 were activated, enhancing chondrogenic potential.
- **AI-Driven Drug Discovery Platforms:**
  - AI was employed to design high-quality, diverse candidate libraries for drug discovery. The new platform outperformed traditional methods by 100–1000× in diversity, significantly advancing discovery pipelines
- **Scalable Treg Expansion Using G-Rex Technology:**
  - AI-based optimization of G-Rex technology enables robust, scalable Treg expansion, supporting clinical manufacturing with high viability (up to 93%) and expansion rates (7.9-fold).

Themes from key AI / ML presentations at ASGCT 2025 (2/2)

- **Nanoneedle-Assisted AAV Genome Quantification:**
  - AI-assisted quantification of AAV genomes using Tessie platform resolves discrepancies in genome integrity profiles, offering precise, non-misclassified assessments crucial for gene therapy vector quality.
- **AI-Optimized AAV Capsids for Tissue Targeting:**
  - Machine learning models optimized AAV capsid design, significantly improving tissue-specific targeting. In vivo kidney-targeting screens achieved >200× preference for kidney transduction over liver.
- **Long-Term Therapeutic Delivery with NT-501:**
  - AI-enhanced real-time aging studies validated NT-501 implant's long-term stability and its ability to provide sustained protein delivery for chronic retinal diseases, supporting its therapeutic viability.
- **Microfluidics for Stem Cell Gene Editing:**
  - AI-powered microfluidic platforms offer a low-toxicity, high-efficiency alternative for HSC gene editing, improving transfection efficiency (>95%) and reducing reagent use, enhancing clinical-grade gene therapies.

Noteworthy AI / ML presentations at ASGCT 2025

Notable Presentations at ASGCT 2025
AI / ML (1/5)

Date	Title	Author	Summary
13 May 2025	Machine Learning-Informed CRISPR Screening for Enhanced MSC Chondrogenesis	Tomas Gonzalez Fernandez	• **Introduction**: Cartilage injury repair is limited by poor MSC chondrogenesis and phenotype instability. The study aims to validate CRISPR-GEM, a machine learning model predicting effective CRISPRa targets for enhancing MSC differentiation. • **Methodology**: CRISPRa was delivered via RALA peptide complexes with dCas9-VPR mRNA and gRNAs. qPCR quantified gene activation, while SOX9-GFP knock-in reporters enabled functional screening. • **Results:** Six top genes (e.g., PRG4, BMP2) showed significant activation. SOX9 reporter assays confirmed strong responses, with a 15.7-fold SOX9 increase. • **Conclusions:** CRISPR-GEM effectively predicts chondrogenic regulators. The non-viral, high-throughput system enables scalable functional validation and broad therapeutic applicability
13 May 2025	A Novel Method For Generating Unprecedented, Unbiased, Ultra-High-Sequence Diversity Libraries Of Plasmids And Recombinant Viruses (With Validation) For High-Throughput Screening, data for machine learning (AI) And Targeted Therapy.	Praveensingh B. Hajeri	• **Introduction**: High-quality, high-diversity candidate libraries are critical for drug discovery, yet current methods overstate diversity, lacking rigorous NGS validation. AI design is limited by biased training datasets. • **Methodology**: A novel library-generation platform was developed and validated using stringent NGS metrics, outperforming existing methods by 100–1000× in sequence diversity and uniformity. • **Results:** Libraries of plasmids and recombinant adenoviruses (e.g., Fiber variants) were successfully constructed and benchmarked for diversity, duplication, and scalability. Screening against a cancer-specific target demonstrated functional relevance. • **Conclusions:** This platform creates superior libraries enabling unbiased, AI-ready datasets or even bypassing AI. It advances discovery pipelines via robust experimental foundations.

Notable Presentations at ASGCT 2025
AI / ML (2/5)

Date	Title	Author	Summary
13 May 2025	G-Rex (Gas Permeable Rapid Expansion) Technology used for T regulatory Cell Culture	Dana Margittai	• **Introduction**: Scalable, GMP-compliant culture of Tregs is vital for cell and gene therapy. G-Rex technology, which uses convection for nutrient/gas exchange, may outperform diffusion-based methods like flasks or WAVE bioreactors. • **Methodology**: Tregs from four donors were cultured in G-Rex 24-well plates across seeding densities (0.5–4 × 10^6 cells/cm^2) with IL-2 and CD3/CD28 stimulation. X-VIVO™ 15-based medium supported expansion over 5 days. • **Results:** Optimal expansion and viability were seen at 1–2 × 10^6 cells/cm^2 (up to 7.9-fold expansion, >93% viability). G-Rex matched or outperformed tissue culture plastic. • **Conclusions:** G-Rex enables robust, scalable Treg expansion, supporting its clinical manufacturing potential.
13 May 2025	Improved Quantification of Adeno-Associated Virus (AAV) Viral Genome Using Nanoneedle Technology for Enhanced Molecular Specificity	Qimin Quan	• **Introduction**: AAV heterogeneity complicates accurate genome quantification. Standard assays struggle to discriminate full-length from long partial genomes, impacting vector quality assessments. • **Methodology**: A novel nanoneedle-based assay on the Tessie platform was developed to specifically quantify 4.3 kb full-length and 3.9 kb left-truncated genomes. Tessie was benchmarked against ELISA, ddPCR, AUC, and electrophoresis using a heterogeneous AAV reference sample. • **Results:** AUC overestimated full genomes; electrophoresis indicated <11% true full-lengths. Tessie resolved these discrepancies, accurately quantifying full, partial, and empty capsids, aligning results across all methods. • **Conclusions:** Tessie provides precise genome integrity profiling, correcting misclassifications by legacy assays and enabling improved AAV product characterization for clinical-grade gene therapies.

Notable Presentations at ASGCT 2025
AI / ML (3/5)

Date	Title	Author	Summary
13 May 2025	Artificial Intelligence Enables Rapid and Efficient Identification of Adeno-Associated Vectors with Improved Transduction of Target Tissues	Leszek Lisowski	• **Introduction**: Current AAV capsids are suboptimal for tissues like brain, kidney, and lung, limiting therapeutic reach and requiring high doses with associated risks and costs. • **Methodology**: Sendatu combines proprietary peptide display, AAV engineering, and AI-driven peptide optimization. Their ML model scores 120M peptides using packaging, entry, and expression data to design capsids with specific tissue tropism and functionality. • **Results:** In HuH-7 cells, all 10 ML-designed capsids outperformed wild-type and physical-screened variants. In vivo kidney-targeting screens yielded capsids with >200× kidney:liver transduction preference. • **Conclusions:** The AI-augmented platform enables rapid, cost-effective discovery of functionally enhanced, tissue-specific AAV capsids, addressing key limitations in gene therapy vector design.
15 May 2025	NT-501 Capsule Stability and Encapsulated Cell Technology Platform Capabilities	Lovisa Selander	• **Introduction**: The NT-501 implant delivers CNTF to treat Macular Telangiectasia type II using encapsulated cell technology (ECT). Given its long-term intraocular placement, capsule material stability and delivery flexibility require validation. • **Methodology**: Real-time and accelerated aging studies in saline simulated in vivo conditions. Material integrity assessed via pressure-decay leak tests, HPLC-MS for HMDA, and H&E staining. Modified ECT capsules tested for enhanced protein delivery via ELISA. • **Results:** Capsules maintained structural and functional integrity over two years. Modified capsules showed significantly higher therapeutic protein secretion in vitro. • **Conclusions:** NT-501 demonstrates long-term material stability and tunable therapeutic delivery, validating its potential as a durable, modifiable platform for chronic retinal diseases.

Notable Presentations at ASGCT 2025
AI / ML (4/5)

Date	Title	Author	Summary
15 May 2025	Encapsulated Cell Technology Enables Steady State Delivery of a Wide Range of Therapeutic Targets	Ian McHugh	• **Introduction**: Neurotech's ECT enables sustained intraocular delivery of therapeutics via genetically engineered human retinal pigment epithelial (RPE) cells within a semi-permeable capsule, overcoming limitations of repeated injections. • **Methodology**: RPE cells were engineered to express and secrete therapeutic proteins using signal peptide elements. Expression was confirmed via immunoassays; cell identity and stability were assessed through phenotypic and immunofluorescence profiling. • **Results:** ECT enabled expression of diverse proteins (20–185 kDa), including CNTF, antibodies, and peptides. Clones showed stable protein production with unchanged cell phenotype. • **Conclusions:** ECT is a robust, customizable platform for long-term intraocular protein delivery, with clinical validation supporting its therapeutic viability.
15 May 2025	Robust Gene Editing of CD34+ Hematopoietic Stem Cells Using a Microfluidics-Based Gene Delivery Technology	Seyeon Bae	• **Introduction**: Hematopoietic stem cell (HSC)-based therapies face challenges from cytotoxic delivery methods; microfluidics offers a gentler, more efficient alternative for gene editing. • **Methodology**: Researchers used a microfluidic mechanoporation system to deliver EGFP-mRNA and CRISPR/Cas9 RNPs targeting B2M into CD34+ HSPCs. Metrics evaluated included viability, gene-editing efficiency, recovery, and differentiation, compared to electroporation. • **Results:** The workflow achieved >95% transfection efficiency, >90% viability, and >80% B2M knockout. It required 4× less RNP than electroporation and enabled same-day post-thaw editing while preserving stemness. • **Conclusions:** This microfluidic platform offers a low-toxicity, scalable, and effective alternative for clinical-grade HSC gene editing, improving yields and reducing reagent use.

Notable Presentations at ASGCT 2025
AI / ML (5/5)

Date	Title	Author	Summary
15 May 2025	Deep Learning Algorithm-Guided Optimization of a Natural Ligand-based CAR-T against CD70 in Acute Myeloid Leukemia	Amrik Kang	• **Introduction**: AML remains a high-mortality cancer; CD70 is a promising, selective target. Natural ligand (NL) CAR-Ts using CD27 show promise but lack optimization strategies. • **Methodology**: Deep learning (ProteinMPNN) and Rosetta were used to design CD27 variants. CARs were integrated into T-cells via AAV/CRISPR at TRAC. In vitro assays tested cytotoxicity, cytokine secretion, and binding affinity. In vivo efficacy was assessed in NSG mouse models. • **Results:** Variant "N88A" exhibited enhanced cytokine release, cytotoxicity, and in vivo tumor clearance versus wildtype. It had ~3× improved CD70 binding affinity (Kd = 110 nM vs. 350 nM WT). • **Conclusions:** Deep learning-enabled optimization of NL CARs can substantially improve AML CAR-T therapies through better target engagement and tumor control.

Strategic Insights and Strategy Development is our focus