EVALUESERVE

ASGCT Annual Meeting 2023

Post-Conference Overview

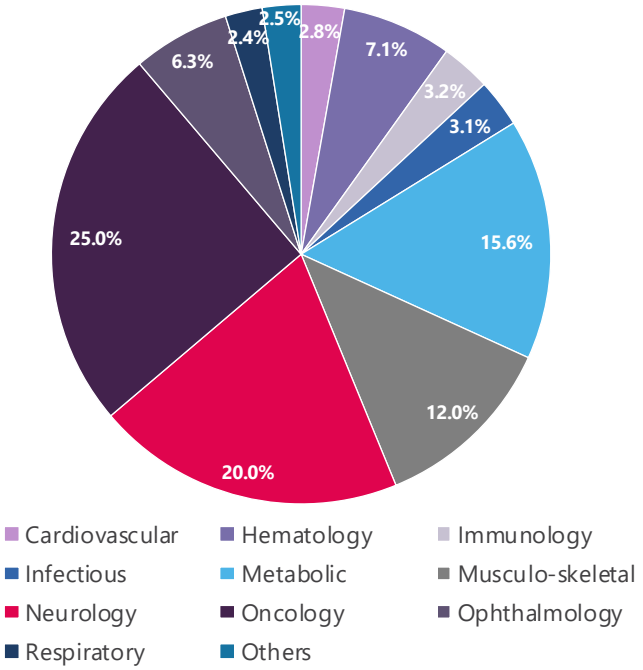
Prepared by: Evalueserve

June 2023

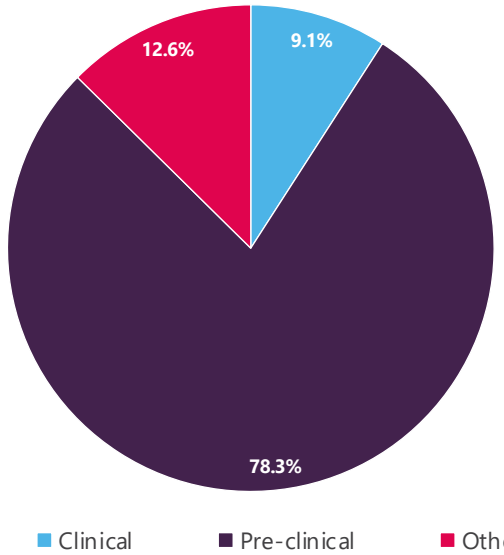
Overview of Conference

Distribution of abstracts by Therapeutic Area, Status of Study presented and Sponsor Type

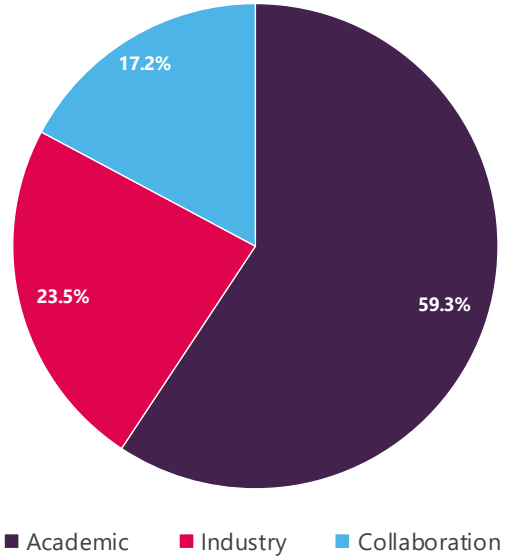
Therapeutic Area



Status of Study Presented



Study Sponsor Type

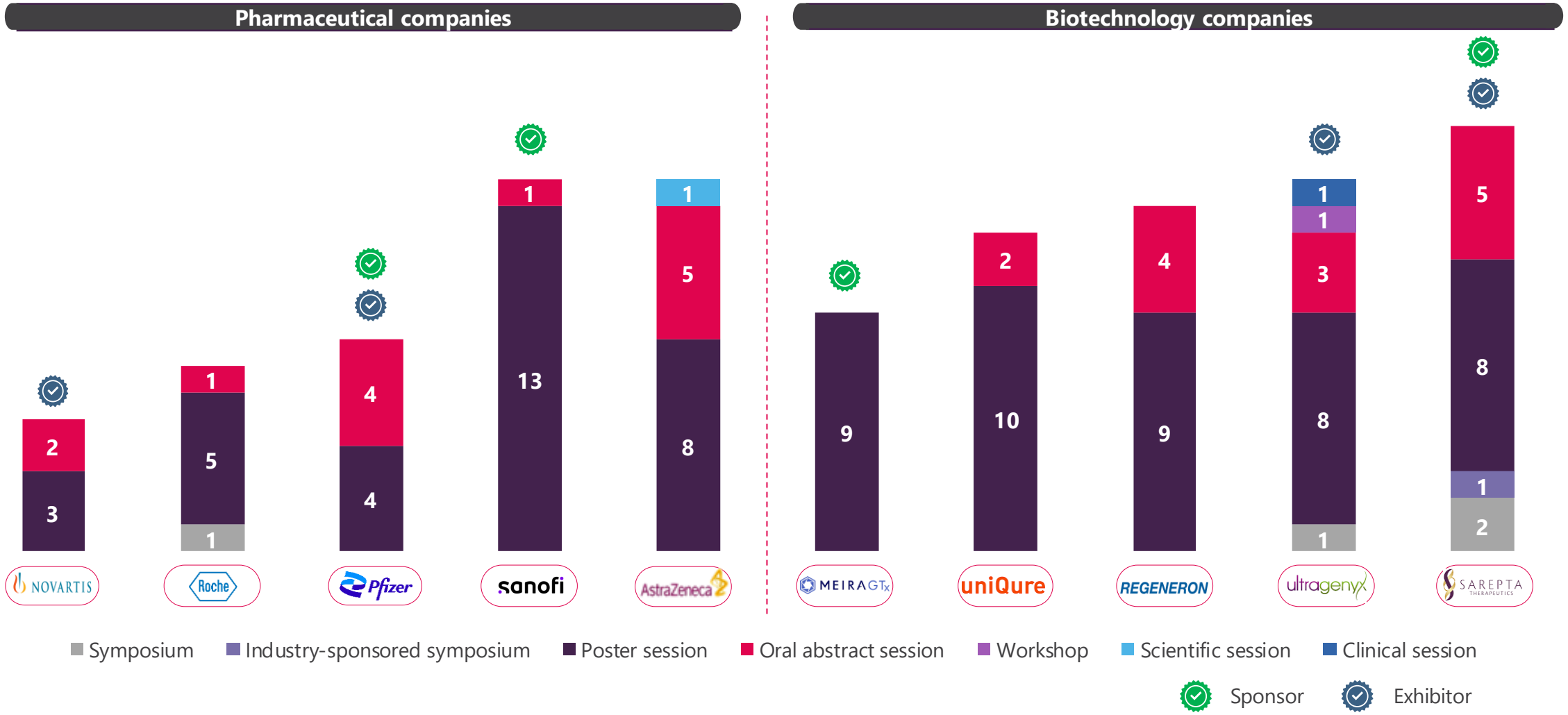


- Most abstracts were presented in the therapeutic areas of **Oncology (25%) and Neurology (20%)**, followed by **rare Metabolic disorders (15.6%) and Musculo-skeletal disorders (12%)**
- In Oncology, there were **25 clinical data read-outs**, of which **56% were for solid tumors**, and the rest for hematological cancer, indicating a **shift in focus of researchers** to develop efficient, safe and durable therapies for solid tumors by addressing its current limitations. Most of these assets were cell therapies (CAR-Ts), oncolytic viruses and few gene therapies
- **Pre-clinical studies represented around 73%** of total indication-specific abstracts, which mainly focused on addressing unmet needs in certain patient populations, with a focus on innovation and novelty of platform, technology or target, and has certain advantages over current treatments or practices
- As expected, the studies were mainly **sponsored by academic institutions or hospitals (59.3%),** as they control most of the CGT innovations, however, **collaborations between industry and academia is on the rise**, and with biotech players and big pharma companies joining the race, it is expected to accelerate innovation, clinical and commercial development in the CGT landscape and in turn, make these personalized therapies more accessible worldwide

Sources: Molecular Therapy journal (05/23)

Share of Voice by Top Competitors

Sarepta, Ultragenyx, Sanofi, AstraZeneca are the top four companies with the most participation, mainly in poster & oral abstract sessions



Sources: 1. ASGCT 2023 website, 2. Molecular Therapy journal (05/23)

ASGCT'23 Highlights from Four Broad Themes & Key Abstracts

Breakthrough early assets

Next-generation early-stage assets with accelerating innovation, driven by novel MoAs and better understanding of unmet needs in certain disease areas

- #1118: LYL119, a CAR-T with potential to target solid tumors with high unmet needs, ROR1+ TNBC or NSCLC
- #1543: SKG0201, next-gen gene therapy for SMA to mitigate tolerability & toxicity issues related to ZOLGENSMA (SoC)

Novel approaches

Innovative and novel approaches with potentially significant impact on reducing disease burden, addressing unmet needs and accelerating non-viral delivery platforms

- #53: UV-VV200 + TumorTags, a novel approach to overcome CAR-T failure, especially in FR+ solid tumors
- #966: ceDNA non-viral vector, curbs the barriers of short $t_{1/2}$ of ROCTAVIAN (SoC) & limited cargo capacity of rAAV vectors

Key clinical data read-outs

Potential curative CGTs under clinical trials with proof-of-concept, long term safety and efficacy data, that outperforms current SoCs with high chances of regulatory approval

- #01: exa-cel, first CRISPR-Cas9-based cell therapy to provide cure for TDT & SCD & eliminate need of blood transfusions
- #354: delandistrogene moxeparvovec, first gene therapy for DMD with potential approval in H2 2023

Novel technologies

Elevated insights around novel platforms and manufacturing techniques concerning off-the-shelf approaches, scalable AAV production and cost-effective gene delivery

- #1441: VivoVec, off-the-shelf lentiviral platform producing polyfunctional CAR-Ts, to address current CAR-T limitations
- #411: TESSA technology, produces safe, high quality, cost effective, scalable AAVs, eliminating need for plasmid transfection

Sources: Molecular Therapy journal (05/23)

Abbreviations: CGT: cell and gene therapy; SoC: standard of care; TDT: Transfusion-dependant beta thalassemia; SCD: Sickle cell disease; DMD: Duchenne muscular dystrophy; MoA: mechanism of action ; TNBC: triple-negative breast cancer; NSCLC: non-small cell lung cancer; AAV: Adeno-associated virus; CAR: chimeric antigen receptor; F": folate receptor; $t^{1/2}$: half life; rAAV: recombinant adeno-associated virus

Post-conference analysis across key themes

- Key Clinical Data Read-outs
- Breakthrough Early Assets
- Novel Approaches
- Novel Technologies

Highlights of Key Presentations

Key clinical data read-outs at ASGCT 2023

Asset	Summary	Expert Views
Exagamglogene autotemcel	**CLIMB THAL-111; CLIMB SCD-121 (Ph 2/3):** elimination of transfusions in pts with TDT & VOCs with SCD, significant increase in HbF & total Hb; CRISPR/Cas9-edited *BCL11A* alleles stable after >1 y, indicated successful editing of long-term HSCs	Exa-cel is an *ex vivo*, non-viral autologous CD34+ HSPC cell therapy. Results indicated **potential to be the first CRISPR/Cas9 therapy to provide a one-time cure for TDT and severe SCD**
DTX401	**NCT03517085; NCT03970278 (Ph 1/2):** Significant reduction in cornstarch needs with mean total daily cornstarch intake reduction was 70% at Week 52 ($p<0.0001$) and 65.6% at 4 years ($p<0.0001$). All patients experienced TEAEs, unrelated to study drug	DTX401 is an AAV8 expressing human *G6PC* gene, which showed a **positive efficacy and safety profile in all treated Glycogen storage disease type Ia (GSDIa) pts, sustained for four years**
RP-A501	**NCT03882437 (Ph 1):** Pts had stabilized/improved BNP, troponin and LV wall thickness and NYHA Class, findings persisted up to 36 months; resulted in cardiomyocyte transduction, LAMP2B expression & improved clinical parameters of HCM	RP-A501 is an AAV9 encoding a normal copy of the human LAMP2B isoform (AAV9.LAMP2B). It was safe and the **data supports activation of a Ph 2 trial in Danon disease**
RP-L102	**NCT04069533; NCT04248439 (Ph 2):** RP-L102 showed phenotypic correction via sustained increase in BM CFC MMC resistance, genetic correction, sustained engraftment & hematologic stabilization with ≥1y follow up, in absence of conditioning	**RP-L102 is a potentially curative therapy for Fanconi anemia-related bone marrow failure**, which affects 80% of these pts. Can be administered without transplant conditioning-related toxicities
huMNC2-CAR44	**NCT04020575 (Ph 1/2):** Efficacy observed at low dose with best response at Day 28. 4/7 patients had Stable Disease and 1 patient had Partial Metabolic Response; No evidence of on-target or off-tumor toxicities	**MUC1* is a new cell therapy for solid tumors like breast cancer. huMNC2-CAR22 to outperform CAR44** due to high persistence, reduced CRS & ability to kill low antigen expressing cancer cells
Delandistrogene moxeparvovec	**NCT03375164 (Ph 1/2a):** Mild to moderate TRAEs, no SAEs, discontinuations, or AEs associated with complement activation; All DMD pts demonstrated clinically meaningful improvement on NSAA, improved muscle strength & ambulation ability at three years	**Safety profile and enduring response provide proof-of-concept** for continuation of clinical trials assessing delandistrogene moxeparvovec using single dose gene therapy in DMD patients

Cell Therapy Gene Therapy

Sources: 1. Molecular Therapy journal (05/23); 2. CT.gov

Abbreviations: Pts: Patients; TDT: Transfusion Dependent β-Thalassemia; VOC: Vaso-occlusive crisis; SCD: Sickle Cell Disease; HSC: Hematopoietic stem cell; HbF: Fetal hemoglobin; HSPC: hematopoietic stem and progenitor cells; TEAE: Treatment-emergent adverse event; BNP: B-type natriuretic peptide; LV: left ventricle; NYHA: New York Heart Association; HCM: Hypertrophic cardiomyopathy; BM CFC: Bone marrow colony-forming cells; MMC: mitomycin-C; NSAA: North Star Ambulatory Assessment; DMD: Duchenne muscular dystrophy; TRAE: Treatment-related adverse event; SAE: Serious adverse event; AE: adverse event

Exa-cel is proving to be an efficient, safe and cost-effective therapy, set to be the first CRISPR/Cas9-based therapy to provide a one-time functional cure for TDT and SCD

VERTEX

Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Transfusion Dependent β-Thalassemia (TDT) and Severe Sickle Cell Disease- (SCD)

ASGCT'23 data spotlight

- Efficacy and safety data from the ongoing pivotal Phase 2/3 trials of exagamglogene autotemcel (exa-cel) in patients with TDT and severe SCD: CLIMB THAL-111 and CLIMB SCD-121
- Patients: First 75 patients dosed with exa-cel (TDT: 44; SCD: 31)

Efficacy:

- 42/44 TDT patients stopped RBC transfusions (0.8-36.2 months)
- 2 remaining patients had 75% and 89% drop in transfusion volume, respectively
- HbF increased and mean total Hb was >11 g/dL at month 3

- SCD patients (100%) no longer had severe VOCs (2.0-32.3 months)
- Mean proportion of HbF was >20% by month 3, increased to ~40% at month 4
- Mean total Hb was >11 g/dL after month 3
- Both TDT and SCD patients with ≥1 year follow-up had stable proportions of CRISPR/Cas9-edited *BCL11A* alleles

Safety:

- 2 TDT patients had SAEs related to exa-cel, both resolved
- No SCD patients had SAEs
- No deaths, discontinuations, or malignancies

Implications

- **Exa cel was successful in eliminating transfusion needs** in all TDT patients **and VOCs** in all SCD patients
- Long-term HSCs successfully edited, evident through stable proportions of *BCL11A* alleles after 1 year
- On 3 Apr 2023, **Vertex and CRISPR completed submission of rolling BLA to the US FDA**, basis results from pivotal CLIMB-111, CLIMB-121 and CLIMB-131
- At ISPOR 2023, Vertex presented an economic evaluation suggesting that **exa-cel can improve survival and QoL, reduce TDT-related complications and substantially lower disease-related costs vs. current SOC**
- **Cost-effective prices for exa-cel** is expected to range from **~USD 2.8 - 4.1 million**

Cell Therapy

Sources: 1. ASGCT 2023 website, 2. Molecular Therapy journal (05/23) – Abstract #01; 3. Vertex PR (04/23); 4. Vertex ISPOR 2023

Abbreviations: RBC: red blood cell; Hb: haemoglobin; VOCs: vaso-occlusive crisis; HbF: fetal haemoglobin; SAE: serious adverse events; HSC: hematopoietic stem cell; BLA: Biologics License Application; QoL: quality of life

Long-term safety, tolerability and enduring response of delandistrogene moxeparvovec supports its POC for further clinical trials in DMD, with anticipated US approval in H2 2023

SAREPTA THERAPEUTICS

Phase 1/2a Trial of Delandistrogene Moxeparvovec in Patients with Duchenne muscular dystrophy (DMD): 4-year Update

Gene Therapy

ASGCT'23 data spotlight

- Safety data from a Phase 1/2a open-label trial of systemic delivery of delandistrogene moxeparvovec ($2.0x10^{14}$ vg/kg) in patients with DMD
- Patients: Four ambulatory patients with DMD (≥4 to <8 years old)

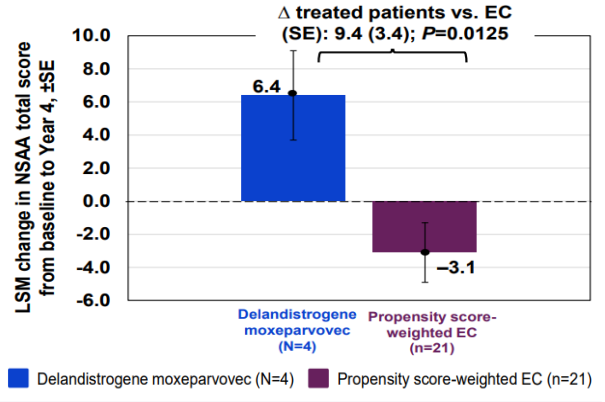
Efficacy:

- NSAA showed long-term overall improvements in motor function maintained over 4 years, a durable response and evidence of stabilization of function, mostly accompanied by TFT improvements
- In a post hoc analysis, a significant and clinically meaningful difference in NSAA total score seen in treated vs. EC patients (LSM Δ=9.4; p=0.0125)

Safety:

- After 4 years, no new safety signals seen; safety data consistent with its wider clinical trial program
- TRAEs were mild to moderate, mostly during first 90 days of treatment, all resolved
- Reinforced an overall long-term acceptable safety profile

Change in NSAA total score from baseline to Year 4 in treated patients vs. EC (least-squares mean [LSM])



	Change from baseline to Year 4				Mean
	Patient 1	Patient 2	Patient 3	Patient 4	All patients
Age at Year 4, (years)	9.7	8.8	10.1	8.1	**9.2**
NSAA total score	+4	+11	+6	+7	**+7.0**
Time to Rise, (sec)*	+0.7	−0.3	−0.7	0	**−0.1**
4-Stair Climb, (sec)*	−0.7	−1.7	+0.7	−2.6	**−1.1**
100m, (sec)*	−4.1	−10.1	−0.1	−13.5	**−7.0**
10m run, (sec)*	−0.7	−0.8	+0.3	−0.1	**−0.3**

Implications

- Delandistrogene moxeparvovec is a rAAV gene transfer therapy to compensate for missing dystrophin in DMD
- **Encouraging safety and tolerability profile and enduring response** after 4 years of treatment provide **proof-of-concept for continuing clinical trials**
- **Sarepta has filed a BLA to the US FDA** which is currently under review, expected to be **completed by 22 June 2023**
- It will be potentially granted an **initial accelerated approval** for use in ambulant DMD patients aged 4-5 years
- Top-line data from the **Phase 3 EMBARK trial** (expected in Q4'23) will potentially be confirmatory for a **non-age-restricted label expansion** of the drug
- Analysts predict that this one-time treatment will cost **USD 2 million**

Sources: 1. ASGCT 2023 website, 2. Molecular Therapy journal (05/23) – Abstract #354; 3. Sarepta PPT; 4, Sarepta PR (05/23); 5. Nature (06/23)

Abbreviations: TFT, timed function test; NSAA: North Star Ambulatory Assessment; EC: external control; LSM: least-squares mean

Highlights of Key Presentations

Key early-stage asset presentations at ASGCT 2023

Asset	Summary	Expert Views
AVB-202	**Friedreich's Ataxia mice model (Preclinical):** Dose-dependent extension of lifespan and improvement in cardiac abnormalities; Well tolerated, favorable safety profile & robust transgene expression across multiple doses and RoA in NHPs	**AVB-202 is a novel AAV9 gene therapy to prevent progression of cardiac and CNS manifestations in Friedreich's Ataxia**, by restoring frataxin and ameliorating FA-related cardiomyopathy
MAGE-A4 TCR	**Xenograft mice models (Preclinical):** T cells co-expressing MAGE-A4 TCR and CTBR12 controlled tumors with doses eliciting minimal responses & exhibited superior durability of response; can safely enhance T cell potency in intractable solid tumors	**MAGE-A4 is a cancer/testis Ag with robust intracellular expression in solid tumors**. Trial planned to evaluate efficacy & safety of **enhanced MAGE-A4 TCR + CTBR12 in solid tumors**
EG-70	**Ovarian cancer mice model (Preclinical): :** Well tolerated, IL-12 expression robust and reversible, increased IFNγ production, significant reduction of tumor burden, has potential to remodel TME, bridge innate & adaptive anti-tumor immune responses	**EG-70 is a plasmid** expressing two non-coding RNA products, using **novel DDX non-viral gene therapy platform**, to deliver it safely to peritoneal cavity for **ovarian** and **bladder cancer** (Ph 1/2)
LYL119	**H1975 *in vivo* model (Preclinical):** Durable function, prolonged cytotoxicity and cytokine production, significant improvement in tumor control ($p<0.0001$), CAR-T cell expansion ($p<0.0001$), effective & durable CAR T-cell activity in ROR1+ solid tumors	**LYL119 is a ROR1-targeted CAR-T cell therapy that incorporates four novel T-cell reprogramming technologies** to overcome limitations of effective cell therapies for **solid tumors**
ABO-503	***Rs1* mutant mice model (Preclinical):** Robust RS1 expression in retina, improvement in density and function observed in cone photoreceptors, no observable immune response, future para-retinal administration in NHP to support clinical development	**ABO-503 is a novel AAV gene therapy** that delivers *RS1* gene to photoreceptors for **potential treatment of X-Linked Retinoschisis,** whose **current SoC is limited to palliative care**
SKG0201	**SMNΔ7 mice model, NHPs (Preclinical):** rapid and long-lasting correction of functional SMN levels, improvement in body weight & lifespan, safe and well tolerated, stronger potency, no liver toxicity, long-lasting improvements in motor functions	ZOLGENSMA (Novartis) is associated with liver & blood toxicity. **SKG0201**, with improved safety profile & better efficacy represents a **new, novel, new generation gene therapy for SMA patients**

Cell Therapy Gene Therapy

Sources: 1. Molecular Therapy journal (05/23); 2. CT.gov

Abbreviations: RoA: Route of administration; NHP: non-human primates; CNS: central nervous system; Ag: antigen; TCR: T cell receptor; TME: tumor microenvironment; DDX: arginine-glucose derivatized-oligomeric chitosan; CTBR12: chimeric TGFβ-IL12 switch receptor; SMA: Spinal Muscular Atrophy; SMN: survival motor neuron; SoC: standard of care

LYL119 can be a potential answer to addressing CAR-T challenges by targeting ROR1, a highly expressed cell surface antigen present on multiple aggressive solid tumors

Lyell

Preclinical Development of LYL119, a ROR1-Targeted CAR T-Cell Product Candidate Incorporating Four Novel T-Cell Reprogramming Technologies to Overcome Barriers to Effective Cell Therapy for Solid Tumors

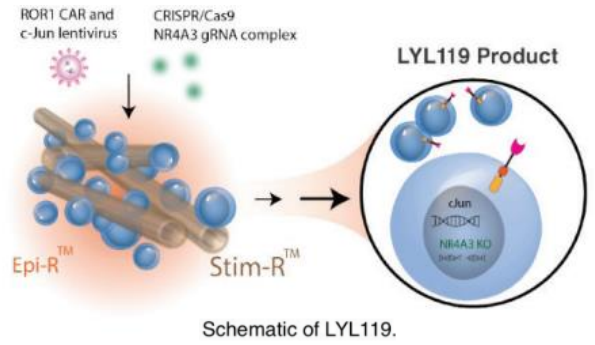
ASGCT'23 data spotlight

LYL119, a CAR-T with four stackable reprogramming technologies to address challenges of using cell therapies in solid tumors –

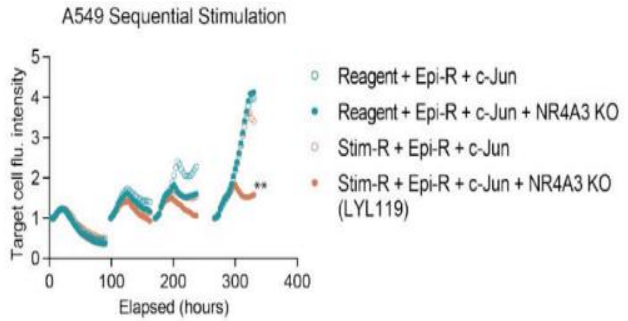
- Genetic overexpression of AP-1 family c-Jun to reduce CAR-T exhaustion & improve functionality
- *NR4A* gene knockout (KO)
- Epi-R™ manufacturing protocol to promote stem-like characteristics
- Stim-R™ technology. that presents anti-CD3 & anti-CD28 to optimize T-cell activation

Manufacturing process and preclinical data:

- **NR4A3 KO + c-Jun (Epi-R) -** robust anti-tumor efficacy with activity at a 7-fold reduced CAR-T cell dose ($p<0.005$), CAR T-cell expansion (>20-fold) [H1975 model], improved tumor control ($p<0.0001$) [difficult-to-treat A549 model]
- **Stim-R and Epi-R -** improved tumor control ($p<0.0001$), CAR-T cell expansion (31-fold, $p<0.0001$), and overall survival ($p<0.0001$) [H1975 model]
- **NR4A3 KO + c-Jun (Stim-R + Epi-R) -** additive benefits to prolong cytotoxicity using A549 tumor cells *in vitro*



Schematic of LYL119.



LYL119 demonstrates prolonged cytotoxicity in vitro (1 of 3 donors shown).

Implications

- There are multiple limitations due to which cell therapies (specially CAR-Ts) have not been successful in solid tumors
- Some of these barriers include T-cell exhaustion, immunosuppressive tumor microenvironment and tumor heterogeneity
- **Lyell Immunopharma focuses on genetic and epigenetic reprogramming** to target solid tumors with high unmet needs like ROR1+ TNBC or NSCLC
- **LYL119 is a ROR1-targeted CAR-T** that can **limit CAR-T exhaustion** and provide **effective and durable functionality** in patients with ROR1+ solid tumors
- **IND submission expected in H1 2024**

Sources: 1. ASGCT 2023 website, 2. Molecular Therapy journal (05/23) – Abstract #1118; 3. Lyell pipeline

Abbreviations: CAR: chimeric antigen receptor; AP-1: activator protein 1; NR4A: nuclear receptor subfamily 4A; TNBC: triple-negative breast cancer; NSCLC: non-small cell lung cancer; IND: investigational new drug

To mitigate the tolerability and toxicity issues associated with ZOLGENSMA, SKG0201 can be a potential alternative novel AAV gene therapy with better efficacy and safety profile

Skyline THERAPEUTICS

SKG0201: A Next Generation Gene Therapy for Spinal Muscular Atrophy with Better Efficacy and Safety Profile

ASGCT'23 data spotlight

SKG0201 is a novel AAV-mediated gene replacement product, comprising of an optimized human SMN1 cDNA under the control of a unique human promoter, optimized to fully attain SMN restoration

Preclinical data (SMNΔ7 mice):

- A single IV administration of SKG0201 resulted in a rapid and long-lasting correction of functional SMN levels, significant improvement in body weight gain & lifespan extension
- Stronger potency
- No liver toxicity vs. reference vector (scAAV9-CMVen/CB-hSMN1), suggesting lower dose can be used in clinical trials, further enhancing its safety profile
- Lasting efficacy in improving motor function deficits, preventing NMJ breakdown and increasing axon conductivity
- The vector manifested a strong anti-inflammatory and neuroprotective effect in the CNS, and anti-fibrosis and protective roles in the heart and liver

Preclinical data (NHP):

- In a pilot study in neonatal cynomolgus monkeys, high hSMN levels in the CNS suggested robust and long-term expression
- The vector was safe and well tolerated

Implications

- **Novartis' ZOLGENSMA** is marketed for the treatment of SMA, but it has **tolerability issues**, significant liver & blood toxicity, due to high vector doses
- Thus, there is a **need for a new AAV gene therapy for SMA** that confers better safety and efficacy at low doses
- **SKG0201 has a potentially superior efficacy and safety profile**, and represents a **new generation of AAV gene therapy for SMA patients**
- These preclinical results validate the potency of **Skyline's proprietary capDRIVE® AAV technology platform** for capsid discovery, transgene design and vector engineering
- A 26-week toxicology and biodistribution study in NHP is ongoing

Sources: 1. ASGCT 2023 website, 2. Molecular Therapy journal (05/23) – Abstract #1543; 3. BioSpace PR (05/23)

Abbreviations: SMA: Spinal muscular atrophy; AAV: Adeno-associated virus; SMN: survival motor neuron; cDNA: circular DNA; CNS: central nervous system; NHP: non-human primates

Highlights of Key Presentations

Novel approaches presented at ASGCT 2023

Approach	Summary	Expert Views
UB-VV200 (Umoja Biopharma)	**NSG mice model (Preclinical):** UB-VV200 efficiently generated TagCAR T cells in non-activated PBMC-humanized NSG mice bearing FRα+ tumors, proliferated in an antigen-dependent manner with UBTT170 and cleared established tumors; no acute toxicities	Tumor heterogeneity & immunosuppressive TME are the key challenges limiting CAR-T feat in solid tumors. **UB-VV200 + UB-TT170 can facilitate cytolytic & expansion of TagCAR T cells**
NTPT-hGAA (Pfizer)	**Gaa$^{-/-}$ mice model (Preclinical):** Fusion of NTPT derived from IGF-II to hGAA- created chimeric protein NTPT-hGAA, that enhanced enzyme uptake, cleared glycogen, fixed autophagic defects in muscle & brain, restored muscle function; well tolerated	Efficacy of rhGAA enzyme replacement therapy for Pompe disease is limited due to hepatic clearance. **NTPT-hGAA is a novel & safe strategy to deliver liver-expressed hGAA to muscles & CNS**
CD8-targeted fusosome (Sana Biotechnology)	**Nemestrina macaques (Preclinical):** Confirmed specific CAR expression in human and NHP CD8+ effector T cells, specific CD19+ or CD20+ target cell engagement and cell killing; *in vivo* administration possible for this fusosome for CAR-T therapies	**Novel gene therapy platform to deliver CAR transgenes directly to T cells** via **fusosome** (novel integrating viral vector with alterable target specificity), to overcome barriers of *ex vivo* CAR-Ts
***FIX* program** (Regeneron / Intellia Therapeutics)	**Rodents, primates (Preclinical):** Expression of FIX via insertion was durable & stable in multiple models of rapid liver growth, candidate demonstrated robust, dose-responsive human FIX expression in both rodents & primates, rescued hemostasis in mice	**CRISPR/Cas9-based targeted gene insertion platform technology** is advantageous over AAV episome-based therapies. **FIX gene insertion program is a novel treatment for Hem B pts**
Hybrid gene therapy (Poseida Therapeutics)	**OTC-deficient mice (Preclinical):** Gene therapy platform used super piggyBac® DNA insertion system that enabled integration of the therapeutic human *OTC* gene into the genome, entailing complete survival & biomarker normalization of urea cycle function	There is an **unmet need for reducing disease burden in Ornithine Transcarbamylase deficiency (OTCD)** patients to whom liver transplant is the only current corrective option
Novel non-viral vector (sanofi)	**Hemophilia A mice model (Predinical):** Novel vector FVIIIXTEN ceDNA persistently produced ~200% of normal FVIII levels for >6 mos at 20x lower dose of all DNA forms tested; can be a potential non-viral gene therapy for chronic diseases like Hemophilia A	**Limitations of AAV-mediated gene therapy** like pre-existing neutralizing Ab, inability to treat pediatric pts and a limited cargo capacity (<5 kb) **can be mitigated by novel non-viral vectors**

● Cell Therapy ● Gene Therapy

Sources: 1. Molecular Therapy journal (05/23)

Abbreviations: FIX: Factor 9; PBMC: peripheral blood mononuclear cell; FR: Folate receptor ; TME: tumor microenvironment; NTPT: N-terminal peptide tag; IGF: Insulin-like growth factor; rhGAA: recombinant human acid-alpha-glucosidase; CNS: central nervous system; NHP: non-human primate; pts: patients; Hem B: Hemophilia B; OTC: Ornithine Transcarbamylase; Ab: antibody, Pts: patients; mos: months; FVIII: Factor 8

To overcome CAR-T failure in solid tumors, UV-VV200 + TumorTags is a novel approach that can generate, expand and direct TagCAR T cells specifically to FR+ solid tumors

Umoja BIOPHARMA

UB-VV200 is a Novel Surface-Engineered Lentiviral Product Candidate for In Vivo Engineering of Universal TagCAR T Cells for the Treatment of Solid Tumors

ASGCT'23 data spotlight

- Integrated platform with a surface-engineered lentiviral vector drug, UB-VV200, designed specifically to express a universal anti-fluorescein CAR (TagCAR) & a synthetic cytokine receptor (anti-CD3 scFv) for high avidity, selective *in vivo* expansion of TagCAR T cells
- Used in combination with TumorTags like UB-TT170, targeting folate receptors (FRα and β), to simultaneously target the tumor and TME

Preclinical data (PBMC-humanized NSG mice):

In vitro:

- UB-VV200 activated T cells to facilitate efficient transduction in a dose-dependent manner
- TagCAR T cells mediated antigen-specific cytolytic activity and cytokine release against FRα+ MDA-MB-231 tumor cells, when cocultured with UB-TT170

In vivo:

- UB-VV200 efficiently generated TagCAR T cells in non-activated PBMC-humanized NSG mice bearing FRα+ MDA-MB-231 tumors, which proliferated in an antigen-dependent manner in the presence of UBTT170 and cleared established tumors
- TagCAR T cells alone did not exhibit expansion or anti-tumor activity
- No acute toxicities were associated with its administration

Implications

- Some key challenges that limit CAR-T success in solid tumors are tumor heterogeneity, immunosuppressive TME, complex *ex vivo* manufacturing and need for lymphodepletion
- **UV-VV200 is specifically engineered to overcome these barriers**, in combination with TumorTags (UB-TT170)
- It was successful in engineering TagCAR T cells and UB-TT170 can direct these cells s to eliminate FRα+ tumor cells
- These data support development of **UB-VV200 in combination with TumorTags as a new therapeutic approach against solid tumors**
- **Folate receptors are expressed in epithelial cancers** like breast, cervical, colorectal, renal, nasopharyngeal, ovarian, and endometrial

Cell Therapy

Sources: 1. ASGCT 2023 website, 2. Molecular Therapy journal (05/23) – Abstract #53

Abbreviations: CAR: Chimeric antigen receptor; scFv: single-chain variable fragment; FR: folate receptors; TME: tumor microenvironment; PBMC: peripheral blood mononuclear cell

Novel ceDNA vector can be a potential non-viral gene therapy for Hem A, as it curbs the barriers of short half-life in current SoC as well as limited cargo capacity of rAAV vectors

sanofi A Novel Vector for Non-Viral Gene Therapy of Hemophilia A

Gene Therapy

ASGCT'23 data spotlight

- Baculovirus-insect cell system (BICS) was used to develop a novel platform technology including, a versatile baculovirus shuttle vector "BIVVBac" bacmid, for non-viral vector production, in a form of closed-end DNA (ceDNA)
- ceDNA vector has no packaging constraints due to limited space within the viral capsid, unlike rAAV vectors

Preclinical (Hemophilia A mice model):

Aim:

- To understand feasibility of BIVVBac system for ceDNA production by using hFVIII along with regulatory elements like liver-specific promoter, intron, transcriptional enhancer, and XTEN to enhance circulating half-life in Hemophilia A patients
- Efficacy of several parvoviral ITRs in driving long-term persistence expression of FVIIIXTEN in Hemophilia A mice

Results:

- FVIIIXTEN ceDNA persistently produced up to 200% of normal physiological level of FVIII for more than 6 months at 20x lower the dose of other DNA forms tested by the systemic administration
- Confirms the feasibility of novel vector (ceDNA) for the non-viral gene therapy of Hemophilia A

Implications

- Current SoC for Hemophilia A is prophylaxis to increase FVIII levels and the only gene therapy, BioMarin's ROCTAVIAN
- Although effective, they have **short half-life** and require frequent IV infusions, invoking need for effective gene therapy
- Most used **AAV vectors have certain limitations like limited cargo capacity**. To overcome this, **non-viral gene therapies are gaining traction**
- **Novel ceDNA vectors were able to produce high levels of FVIII, sustained for >6 months,** confirming its potential to be a **non-viral gene therapy for Hemophilia A**
- **Sanofi's ALTUVIIIO (efanesoctocog alfa) is the latest FVIII replacement therapy to be approved in the US**

Sources: 1. ASGCT 2023 website, 2. Molecular Therapy journal (05/23) – Abstract #966; 3. Sanofi PR (02/23)

Abbreviations: Hem A: Hemophilia A; SoC: standard of care; rAAV: recombinant adeno-associated virus; hFVIII: human factor 8; FVIII: factor 8

Highlights of Key Presentations

Novel technologies presented at ASGCT 2023

Technology	Summary	Expert Views
TESSA™ platform (WuXi Advanced Therapies)	TESSA™ (tetracycline-enabled self-silencing adenovirus) technology developed to meet the growing demand for AAV manufacture, (upstream and downstream processes), integrated with intricate testing capabilities that increases efficiency & reduces cost	**TESSA™ technology is a competitive solution for AAV production** & scale-up; significant improvement on vector yield vs. plasmid-based methods; to boost product approval timeline
Next-CAP platform (AaviGen)	AAV capsid engineering platform prepared proprietary novel heart-specific AAV capsids, that enabled systematic development of optimal therapeutic capsid-promoter-transgene ensembles for further dose-expression, -efficacy and -toxicity assessment	**Next-CAP is an efficient and versatile platform to produce next-generation AAV capsids for heart-specific gene therapy** of uncurable rare and common cardiac diseases like Heart Failure (HF)
mAAVRx process (AstraZeneca)	mAAVRx manufacturing process achieved increased product yield and quality, more potent AAV vectors in scalable suspension HEK293 cells, it generated higher titers than Expi293F+FectoVIR production systems, significant reduction in packaged plasmid DNA	**mAAVRx has the potential to be applied successfully to different production systems** as increase in vector titers & vector purity can **reduce the cost of goods** & **improve product quality**
AAV retargeting platform (REGENERON)	A species-agnostic, modular AAV retargeting platform that utilizes rational capsid engineering and mAbs, to redirect viral particles to skeletal muscle and CNS via BBB crossing, enhanced on-target delivery and marked liver de-targeting vs. AAV9	**Modular antibody-based AAV retargeting system** signifies a novel platform for **translatable, targeted gene delivery** for accelerating development of gene therapies for multiple diseases
Novel rAAV platform (ultragenyx)	A cost-effective and scalable rAAV production Pinnacle producer cell-line adenovirus helper platform, that eliminates the high cost of goods associated with transfection-based processes, achieved >3- fold increase in overall volumetric rAAV yield	**Novel platform significantly reduced cGMP batches required to initiate Phase I-II studies** vs. legacy process at a **significantly reduced cost** while meeting high dosing requirements in DMD
VivoVec platform (Umoja)	VivoVec is a novel off-the-shelf surface-engineered lentiviral vector platform for *in vivo* CAR-T cell generation. In humanized NSG mice, it generated substantial CAR-Ts (20-50-fold higher), potent and durable antitumor activity at low doses vs. lentiviral particles	Limitations of CAR-T include challenges to patient access, complex manufacturing, high cost. Novel **VivoVec particles have potential to efficiently create polyfunctional CAR-Ts cells *in vivo***

Cell Therapy Gene Therapy

Sources: 1. Molecular Therapy journal (05/23)

Abbreviations: AAV: Adeno-associated virus, rAAV: recombinant adeno-associated virus; mAb: monoclonal antibody; CNS: central nervous system; BBB: blood brain barrier; DMD: Duchenne muscular dystrophy ; cGMP: Current good manufacturing practices

VivoVec is a novel, off-the-shelf, lentiviral vector platform capable of generating polyfunctional CAR-Ts using co-stimulatory molecules to overcome current limitations

Umoja BIOPHARMA

Potent In Vivo CAR T Cell Generation and Durable Antitumor Activity in Preclinical Models Using VivoVec, a Surface-Engineered Lentiviral Vector Drug Product

ASGCT'23 data spotlight

- VivoVec is a novel off-the-shelf surface-engineered lentiviral vector platform for generation of CAR-T cells *in vivo*
- These particles are surface-engineered with cocal fusion glycoprotein and incorporate an anti-CD3 scFv and T cell costimulatory ligands to promote specific and efficient T-cell binding, activation, transduction

Preclinical (humanized NSG mouse model of B cell malignancy):

In vitro:

- CAR-T cells generated with VivoVec particles exhibited a less-differentiated, central memory-like phenotype and enhanced CAR-antigen-specific polyfunctionality, including cytokine production, proliferation and tumor cell killing
- VivoVec particles have high selectivity and avidity for T cell binding
- It enabled multiple RoA, including direct injection or delivery via extracorporeal gene delivery (ECGD) system

In vivo:

- VivoVec particles were successful in generating substantial amounts of CAR-T cells in the blood, and resulted in potent and durable antitumor activity at low doses
- 20-50-fold higher numbers of CAR T cells observed in blood and greater antitumor responses at lower VivoVec doses vs. lentiviral particles lacking T-cell costimulatory molecules

Implications

- CAR-Ts have major limitations like patient access, complex manufacturing, and high cost
- **VivoVec particles can efficiently generate highly functional CAR-T cells *in vivo***, following either direct injection or via ECGD system
- Incorporation of costimulatory molecules onto VivoVec's surface promoted **selective T-cell binding, activation and transduction**
- It resulted in **polyfunctional CAR-Ts that can rapidly clear a tumor** and provide protection against tumor re-challenge
- VioVec particles have the **potential to overcome limitations associated with current class of CAR-T cell therapies**

Cell Therapy

Sources: 1. ASGCT 2023 website, 2. Molecular Therapy journal (05/23) – Abstract #1441

Abbreviations: CAR-T: Chimeric antigen receptor T-cells; scFv: single-chain variable fragment; RoA: route of administration

TESSA™ heralds a new era of safe, high quality, cost effective, scalable AAV production, eliminating the need for plasmid-based transfection and its associated limitations

WuXi Advanced Therapies

Scaling-Up AAV-Manufacture GMP Production and Purification Using Innovative Plasmid-Free Technology

ASGCT'23 data spotlight

- **TESSA™ (tetracycline-enabled self-silencing adenovirus) is a plasmid-free technology** for high physical titer and infectivity, to meet the growing demand for AAV manufacture (increasing upstream productivities & recovery of downstream process)
- TESSA vectors uses dual phases of the adenoviral (Ad) lifecycle to produce AAV, & limits Ad contamination to 99.99%
- It includes co-infection with two adenovirus vectors: one encoding a GoI and the other encoding AAV's replicative (*rep*) and capsid (*cap*) genes

These AAV titre values were compared with values obtained using triple-plasmid transfection into WuXi ATU single clonal cell line from HEK293 parental cells

Results:

- Upstream production of AAV2 and AAV6 using TESSA platform was completed successfully in single use bioreactor
- Upstream GC titer of AAV2 was 20- fold and AAV6 was 10-fold higher with TESSA vs. triple plasmid transfection
- AAV2 and AAV6 overall recovery of 36% and 52% was achieved with 1.5E+14 total GC/L and >5.0E+14 total G/L of upstream production, final product obtained 88.2% and 88.4% of full capsids, respectively
- Thus, WuXi ATU had successfully scaled up AAV vector production using TESSA technology with the product demonstrating significant improvement on vector yield vs. plasmid-based methods

Implications

- **AAV vectors**, manufactured using plasmid-based transient transfection, **represent ~37% of CGT market**
- However, some challenges with working with plasmids on a large scale include cost, consistency and scalability
- **TESSA, a new transfection-free helper system ensures high-yield rAAV manufacturing**, raising the bar to produce **safe, high-quality viral vectors** at scale & eliminate need for plasmids
- TESSA is now **integrated with intricate testing capabilities**, that allows in-house assay development, biosafety, viral clearance, product release testing, **reduces costs and increases efficiency**
- **TESSA technology is a new paradigm that has the potential to accelerate product approval timeline**

Sources: 1. ASGCT 2023 website, 2. Molecular Therapy journal (05/23) – Abstract #411; 3. WuXi PR (03/22); 4. BioProcess International (10/21)

Abbreviations: AAV: Adeno-associated virus; GoI: Gene of Interest; GMP: Good Manufacturing Practice; GC: genome copies; HEK: human embryonic kidney; CGT: Cell and gene therapy; rAAV: recombinant AAV

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