Notable Recent Events in Gene Therapy Translation
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Clinical gene therapy has seen a lot of big wins and a lot of big setbacks over the past few years. To help myself keep track of important events in the field, I decided to write up this catalogue of key happenings. Though the landscape is ever-evolving, this resource should nonetheless be useful in the relatively near future and perhaps serve as a historical record later on. It has been fascinating to read up on the industry's dynamics! I hope any readers out there who encounter this page will find my catalogue similarly interesting and valuable.

BioMarin and Roctavian (AAV)

- **June 2023:** The FDA approved BioMarin's Roctavian, an AAV5 gene therapy for hemophilia A. It is the first AAV gene therapy for hemophilia [16].

Sarepta Therapeutics and Elevidys (AAV)

- **June 2023:** the FDA approved (Accelerated Approval pathway) Sarepta's AAVrh74 gene therapy for Duchenne's muscular dystrophy (DMD) in ambulatory of male patients 4-5 years old [1]. This treatment is known as Elevidys. It treats DMD by expressing a microdystrophin to replace the role of the defective endogenous dystrophin. The per patient cost of the one-time Elevidys treatment was listed at $3.2M [2]. It used a high AAV dose of 1.33×10^{14} vg/kg [3].
- **October 2023:** Sarepta's Elevidys failed to reach statistical significance for its primary endpoint (functional mobility) in a phase 3 clinical trial, though substantial evidence of secondary endpoint effects was reported by the company. A p value of 0.24 for the main functional mobility test was reported [4].
- **February 2024:** Despite its setbacks, the FDA still accepted an efficacy supplement to the Biologics License Application (BLA) of Elevidys, which removed age and ambulation restrictions from the treatment.
- **March 2025:** Sarepta reported a patient death due to acute liver failure after Elevidys treatment [5]. A recent cytomegalovirus infection was identified by the reporting physician as a possible contributing factor, but the main reason was probably the high AAV dose.
- **June 2025:** Sarepta reported another patient death due to acute liver failure after Elevidys treatment [6]. Both of the deaths were in non-ambulatory teenage boys.
- **June 2025:** Sarepta paused shipments of Elevidys to non-ambulatory patients. The FDA began investigating the Elevidys deaths. Sarepta also reported a third death (which had actually occurred in June), this time of a 51-year-old non-ambulatory patient in one of their clinical trials for limb-girdle muscular dystrophy (LGMD) [7]. This patient had been treated with an investigational gene therapy which leveraged the same AAVrh74 capsid as Elevidys [8].
- **July 2025:** The FDA issued a major action bundle which placed Sarepta's muscular dystrophy gene therapy clinical trials on hold, revoked AAVrh74's platform technology

designation, and made a voluntary request for Sarepta to immediately cease all Elevidys distribution [9]. Roche then paused shipments of Elevidys for non-ambulatory patients outside of the USA [10].

- **July 2025:** Sarepta initially resisted the request to stop distributing Elevidys. But after further consideration, Sarepta agreed to the FDA's request [7]. To mitigate financial losses, Sarepta performed major restructuring, laying off about 36% of their workforce (~500 employees) [11].
- **July 2025:** The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued an official negative opinion on the conditional marketing authorization (CMA) of Elevidys for ambulatory DMD patients of 3-7 years [12]. Roche noted that over 900 DMD patients (760 ambulatory) had received Elevidys, demonstrating a manageable safety profile.
- **July 2025:** The FDA began investigating the death of an 8-year-old boy who died in June after receiving Elevidys [13]. However, the treating physician deemed this death unrelated to the Elevidys treatment [14].
- **November 2025:** The FDA approved a new label for Elevidys which included a Boxed Warning, limited the indication to ambulatory DMD patients 4 years of age and older, and added new recommendations for safety and monitoring [15].

Vertex Pharmaceuticals, CRISPR Therapeutics, and Casgevy (*ex vivo* electroporation)

- **November 2023:** The United Kingdom MHRA (Medicines and Healthcare products Regulatory Agency) approved Casgevy (developed by Vertex Pharmaceuticals and CRISPR Therapeutics through a strategic partnership) for the treatment of sickle cell disease and transfusion-dependent beta thalassemia. Casgevy is the first CRISPR-Cas9 gene therapy applied in humans. It performs gene editing *ex vivo* on blood stem cells derived from the patient (via electroporation of Cas9) to knock out the erythroid-specific enhancer region of the BCL11A gene, disinhibiting production of fetal hemoglobin [17].
- **December 2023:** The FDA approved Casgevy to treat sickle cell disease [18]. Both the FDA and MHRA approvals represented the first regulatory authorization of a CRISPR therapy in the world.
- **January 2024:** The FDA approved Casgevy to also treat transfusion-dependent beta thalassemia [19].

Bluebird Bio and Lyfgenia (*ex vivo* lentivirus)

- **December 2023:** The FDA approved Bluebird Bio's Lyfgenia to treat sickle cell disease [18]. Lyfgenia is an *ex vivo* lentiviral gene therapy which delivers a copy of HbA^{T87Q} into blood stem cells derived from the patient. This hemoglobin behaves similarly to normal hemoglobin and thus treats the sickle cell condition. The one-time Lyfgenia treatment price is $3.1M.

Orchard Therapeutics and Lenmeldy (*ex vivo* lentivirus)

- **March 2024:** The FDA approved the Orchard Therapeutics gene therapy Lenmeldy to treat children with metachromatic leukodystrophy (MLD) [20], [21]. Lenmeldy is an *ex*

vivo gene therapy which uses a lentiviral vector to modify a patient's stem cells to add a functional copy of the ARSA (arylsulfatase A) gene. This gene encodes the ARSA enzyme and degrades harmful sulfatides. MLD patients possess mutations in their endogenous ARSA enzyme gene. Lenmeldy is the most expensive therapy in the world at $4.2M [21].

Krystal Biotech and Vyjuvek (topical HSV-1)

- **May 2023:** The FDA approved Krystal Biotech's Vyjuvek to treat dystrophic epidermolysis bullosa (DEB). It uses a herpes simplex virus 1 (HSV-1) vector to deliver normal copies of the COL7A1 (collagen type VII alpha 1 chain) gene into wounds caused by the disease [22]. A healthcare professional applies the vector topically to the patient's wounds once per week. The treatment costs $630,500 per year [21].

Abeona Therapeutics and Zevaskyn (*ex vivo* RVV + topical cell sheets)

- **April 2025:** The FDA approved Zevaskyn, a unique autologous cell sheet gene therapy, for treatment of recessive dystrophic epidermolysis bullosa (RDEB) [23]. Cells derived from the patient are collected and transduced with a replication-incompetent retroviral vector (RVV) carrying a copy of the COL7A1 gene [24]. These cells are used to grow sheets of skin which are grafted onto the patient's wounds. The treatment costs $3.1M and provides up to 12 cell sheets.

Pfizer and Beqvez (AAV)

- **April 2024:** The FDA approved Pfizer's Beqvez, an AAVRh74var vector encoding factor IX, for treatment of hemophilia B [25]. It was priced at $3.5M per patient [26].
- **May 2025:** Pfizer discontinued Beqvez due to lack of patients adopting the therapy (no patients had received the treatment outside of clinical trials) [26]. After discontinuing Beqvez, Pfizer was left with no gene therapies on the market or even in development, a setback for the gene therapy field.

Rocket Pharmaceuticals and RP-A501 (AAV)

- **May 2025:** During a phase II clinical trial for treatment of Danon disease with an AAV9 vector (6.7×10^{13} vg/kg), a patient died [27]. This led the FDA to put a clinical hold on the trial.
- **August 2025:** The FDA lifted its clinical hold on RP-A501 less than 3 months later [28]. They confirmed that Rocket Pharmaceuticals had addressed the issues relating to the clinical hold by changing the dose to 3.8×10^{13} vg/kg and modifying their immunomodulatory drug regime. Rocket Pharmaceuticals thus resumed the clinical trial.

Intellia Therapeutics and NTLA-2001 (LNP)

- **August 2024:** In a phase I clinical trial, Intellia Therapeutics demonstrated the first redosing data of an *in vivo* CRISPR therapy in humans [29]. This therapy treats transthyretin amyloidosis (ATTR) by knocking out the TTR gene in hepatocytes. It uses a lipid nanoparticle (LNP) delivery platform. It should be noted that further redosing

was not planned for NTLA-2001 specifically, but the data may be useful for future therapies from Intellia.

- **October 2025:** During the MAGNITUDE-2 phase III clinical trial for NTLA-2001, a patient experienced a grade 4 liver adverse event and was hospitalized. As a result, the FDA placed the MAGNITUDE and MAGNITUDE-2 trials on clinical hold [30]. (The MAGNITUDE trial is for treating ATTR with cardiomyopathy and the MAGNITUDE-2 trial is for treating ATTR with polyneuropathy).
- **January 2026:** The FDA lifted its clinical hold on MAGNITUDE-2 [31].

UniQure and AMT-130 (AAV)

- **December 2024:** UniQure and the FDA reached an agreement for Huntington's disease gene therapy AMT-130 to enter the accelerated approval pathway [32]. AMT-130 uses an AAV5 vector encoding a miRNA which inhibits expression of the mutant Huntingtin protein [33]. The AAV5 is delivered directly to the brain via a micro-catheter [34].
- **September 2025:** UniQure showed a statistically significant 75% slowing of Huntington's disease progression in a phase I/II clinical trial for AMT-130, a major breakthrough [35].
- **November 2025:** Although UniQure had previously reached an agreement with the FDA for AMT-130 to enter the accelerated approval pathway (and had later presented the breakthrough data on slowing Huntington's disease progression by 75%), the FDA stated the data were insufficient to support approval due to the use of an external control group [36]. UniQure continues to work with the FDA in an effort to move AMT-130 forward despite this setback.

Capsida Biotherapeutics and CAP-002 (AAV)

- **September 2025:** In a phase I/II clinical trial (CAP-002 SYNRGY) intended to treat syntaxin-binding protein 1 (STXBP1) encephalopathy, Capsida Biotherapeutics used an AAV capsid which had been engineered to efficiently cross the blood-brain-barrier while exhibiting liver-detargeting. The first patient (a child) dosed with this treatment died [37]. The trial was placed on clinical hold.
- **January 2026:** After investigating, Capsida found that the patient's death was triggered by cerebral edema, but the root cause remained undetermined (i.e. no one knows whether the treatment had been directly responsible for the death) [38]. All of this has resulted in increased scrutiny on the field of blood-brain-barrier crossing AAVs.

Replimune and RP1 (HSV-1)

- **July 2025:** The FDA issued a Complete Response Letter (CRL) to Replimune's biologics license application (BLA) for treatment of advanced melanoma with RP1 [39], an oncolytic engineered herpes simplex virus 1 (HSV-1) equipped with a fusogenic protein that encodes GM-CSF (granulocyte-macrophage colony-stimulating factor). The CRL voiced concerns about the RP1 IGNYTE trial's design, interpretability, and inadequate controls, and the heterogeneity of the patient population. This represented a major (and highly publicized) setback for the company.

- **October 2025:** After presenting a revised trial design during a type A meeting with the FDA, Replimune's BLA resubmission was accepted [40]. This means that RP1 is cleared for further FDA evaluation towards possible approval for marketing in the U.S.

Beam Therapeutics, BEAM-302 (LNP), and BEAM-101 (*ex vivo* electroporation)

- **March 2025:** In a phase I/II clinical trial of its base editor formulation BEAM-302, Beam Therapeutics showed successful human proof-of-principle for treating alpha-1 antitrypsin deficiency (AATD) [41]. The formulation consists of a lipid nanoparticle (LNP) carrying guide RNA and an mRNA (the latter encodes the base editor).
- **March 2025:** The FDA cleared Beam's investigational new drug application (IND) for BEAM-302 to treat AATD [42].
- **December 2025:** Beam announced strong safety and efficacy data from its phase I/II clinical trial BEACON for their BEAM-101 *ex vivo* base editor therapy sickle cell disease therapy [43]. In BEAM-101, stem cells from a patient are electroporated with base editors which modify the promoter regions of HBG1/2 genes, preventing binding of the transcriptional repressor BCL11A. After reintroduction of the cells into the patient's bone marrow, this increases expression of fetal hemoglobin, combating the sickle cell disease.

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