Gene therapy at the crossroads

Two upcoming regulatory decisions represent a tipping point for commercial gene therapy, with implications for work on existing viral vectors and the pursuit of new ones.

Next month, the US Food and Drug Administration (FDA) will convene an advisory panel meeting to review two lentiviral gene therapies: Zynteglo (betibeglogene autotemcel) for β-thalassemia in patients requiring regular blood transfusions and Lenti-D (elivaldogene autotemcel) for patients with cerebral adrenoleukodystrophy. Much rests on the outcome. If these treatments fail, bluebird bio, a gene therapy flagship, will likely fail. Following a recent raft of problems for both lentiviral and adeno-associated viral (AAV) gene therapies, the sector needs a win — one that can provide continued industry momentum to invest in optimizing existing vector platforms and also spur research into new viruses that fill therapeutic niches currently out of reach.

For several years, gene therapy has been flying high, with 11 FDA approvals, including February's for Carvykti (ciltacabtagene autoleucel). After decades of research and thousands of human trials, the field finally attained commercial recognition, with a succession of stratospheric acquisitions by big pharma: Bamboo Therapeutics, AveXis, Spark Therapeutics, Nightstar Therapeutics, Audentes Therapeutics, Asklepios BioPharmaceutical, Juno Therapeutics and Kite Pharma brought asking prices that together totaled $41 billion.

Recently, however, a litany of setbacks has brought the field back to earth. An analysis from last year reported that, on average, 35% of 149 AAV gene therapy clinical trials were associated with treatment-emergent serious adverse events. This February, analysts at Jeffries attributed 40% of all clinical holds in 2021 to cell and gene therapies (although a portion of these related to manufacturing or quality issues rather than toxicity).

Last September, adverse events associated with AAV treatments were frequent enough to warrant a special FDA panel. The year before, the agency suspended a phase 1/2 trial of Audentes Therapeutics' AAV-8 encoding *MTM1* after two of three pediatric patients receiving a high dose experienced severe hepatotoxicity and died. Dose-limiting liver toxicities have also been observed in AAV trials carried out by Solid Biosciences, Sarepta Therapeutics, Pfizer and Homology Medicines.

The problems don't stop there.

Thrombotic microangiopathy — complement activation that causes platelet depletion and acute kidney injury — has been reported for AAV-9 gene therapies, first for Solid's Duchenne muscular dystrophy treatment SGT-001 and then in patients with spinal muscular atrophy receiving Novartis's Zolgensma (onasemnogene abeparvovec). And neuronal loss in the dorsal root ganglion of a patient with familial amyotrophic lateral sclerosis was found at autopsy following administration of AAVrh10 encoding a microRNA targeting *SOD1*.

AAV-induced cancer remains a worry, given reports of hepatocellular carcinoma (HCC) in AAV-treated newborn mice, non-malignant neoplasms observed in long-term AAV dog studies, and a possible link between wild-type AAV and HCC in humans — although HCC as a result of AAV human gene therapy has never been observed. Genotoxicity also remains a concern for lentiviral vectors: last August, the FDA suspended bluebird's Lenti-D phase 3 trial for adrenoleukodystrophy after a patient developed myelodysplastic syndrome.

The recurring theme is that elevated dosages of injected AAV vector can lead to bad outcomes. At low doses (10^{10}–10^{11} viral genomes per kilogram body weight (vg/kg)), AAV is tailor made for local delivery to the eye and the ear or for systemic applications (for example, hemophilia) with secreted proteins or encoded antibodies. But to reach targets like deep brain structures, motor neurons and muscle, doses reaching 2×10^{13} to 3×10^{14} vg/kg are required. Transduction inefficiencies are exacerbated by vector manufacturing deficiencies that lead to products containing empty capsids or translatable contaminating double-stranded DNA. As yet, the cause(s) of these toxicities remain unknown, but pre-existing immunity to the vector or cellular metabolic stress due to transgene overexpression likely plays a role).

A host of companies — including 4DMT, 64x Bio, Affinia Therapeutics, Capsida Biotherapeutics, Dyno Therapeutics, Generation Bio, StrideBio, VIVEbiotech and Vectalys — has sprung up to engineer capsids to address these issues. Rational design, ancestral sequence reconstruction or molecular evolution/shuffling of capsid libraries show promise for enhancing delivery to target tissues, improving evasion of neutralizing antibodies or increasing virus yield, with fitness data increasingly combined with machine learning to guide efforts. Also being investigated are hybrid or pseudotyped AAV vectors encapsidated in other virus shells, split vectors to overcome AAV capacity limits (~4.7 kb), and AAV cloaking in extracellular vesicles to avoid immune attack. Recent advances in virus-like particles, lipid nanoparticles and mRNA-encoded therapeutics are also likely to cross-fertilize the field.

Within the vector, the transgene construct continues to be optimized, with the inclusion of engineered inverted terminal repeats or circularized genome structures, epigenetic modulators and chromatin insulators, small-molecule gene switches, codon optimization and CpG depletion to reduce immunogenicity, synthetic promoters and enhancers, tissue-restrictive microRNAs and other regulatory elements. Yet there is still much to learn about the factors that lead to differing therapeutic responses from patient to patient.

Considering that 380 trillion viruses live on or inside our bodies, interest is growing in exploring the human virome for new vectors beyond AAV and lentivirus. For example, startup Ring Therapeutics is developing the human commensal anellovirus as a vector that can sidestep immunity; elsewhere, Krystal Biotech just published positive phase 1/2 results for its herpes simplex virus 1 vector (cargo capacity >30 kb) delivering *COL7A1* to patients with dystrophic epidermolysis bullosa; Amarna Therapeutics is exploring polyomavirus SV40's ability to induce tolerance to immunogenic transgenes; and Pfizer and the University of Iowa are collaborating on bocaviral/AAV hybrid vectors with an expanded transgene cargo capacity (5.2 kb) for cystic fibrosis.

All of this work will wither if funding runs dry. That could happen if adverse clinical readouts continue, reimbursement remains a puzzle and stock-market doldrums persist. Since December, bluebird, Amicus Therapeutics, Sigilon Therapeutics, Freeline Therapeutics, Gemini Therapeutics and Passage Bio have all been forced to cut jobs. With the commercial failures of Glybera (alipogene tiparvovec), Strimvelis and Zynteglo in Europe, let's hope that next month brings gene therapy better news. ❐

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