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ARTICLE | PRODUCT DEVELOPMENT

Suppressor tRNAs: Giving genetic medicines a broader reach

From preclinical therapies to David Liu's one-time approach, new tools aim to bypass stop codons across a wide range of diseases

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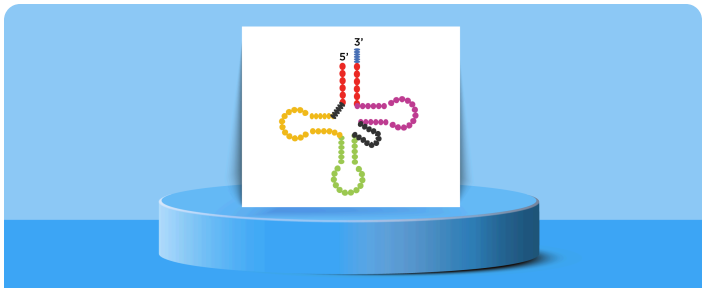

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While 2025 saw one tRNA biotech shut its doors, at least three others are still betting that engineered suppressor tRNAs can rescue protein production in patients with stop codon mutations.

The field has received a new boost from advances in other genetic disease modalities, novel research from academic labs solving some longstanding problems, and an injection of star power from base and prime editing pioneer David Liu who is turning his technology toward a one-and-done approach that he labels "gene-agnostic base editing." (Liu discussed this strategy, and others, with BioCentury in an October Q&A).

Gene editing's promise is highly precise treatment of rare diseases, but that precision often fragments the market and makes commercial models challenging. By contrast, the small field of engineered transfer RNAs (tRNAs), driven by a handful of companies and academic groups, aims to use a single modified tRNA to treat many different patients and diseases, using a "suppressor tRNA" therapy to override recurrent premature stop codons, inserting the desired amino acid instead.

Nonsense mutations introduce a premature termination codon (PTC) into a gene, causing translation to halt early and producing a truncated, usually non-functional protein. They are a common cause of genetic disease, as roughly 10% of pathogenic variants are nonsense mutations, and this group of genetic disorders is often referred to collectively as "stop codon diseases."

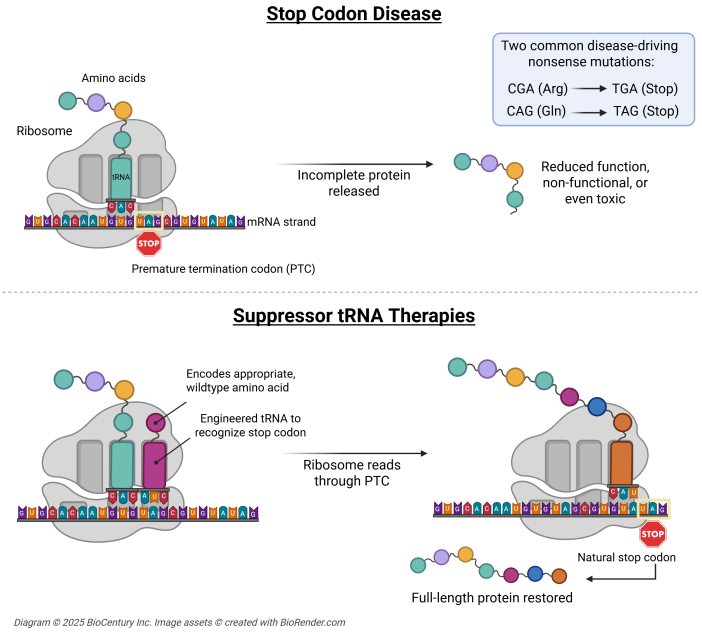
"Instead of having 10,000 of these different genetic conditions, we actually see a world where you simplify them into a few universal conditions, which can then be addressed using tRNAs that work across those common mutations," Alltrna Inc. CEO Michelle Werner told BioCentury.

Of the 19 possible single-nucleotide changes that create a PTC, the arginine (CGA)-to-TGA and glutamine (CAG)-to-TAG nonsense mutations together account for about 50% of all PTCs seen in patients. In principle, two suppressor tRNA medicines could cover a considerable fraction of all patients with stop codon disease.

Endogenous human tRNAs do not normally bind stop codons because release factors mediate termination.

Alltrna, Tevard Biosciences and Qixia Decode Biotechnology Co. Ltd. are all engineering suppressor tRNAs whose anticodons recognize PTCs and insert the appropriate amino acid, allowing the ribosome to bypass the stop and make full-length protein.

All three companies are still preclinical, with the most advanced, Alltrna, expecting to start clinical trials this year.



Company starts and stops

Alltrna is delivering its lead suppressor tRNA candidate, AP003, in lipid nanoparticles (LNPs) the company says are clinically validated, to protect the naked tRNAs from rapid degradation. A single dose of AP003 restored protein production to functional levels in transgenic mouse models of two stop codon diseases, methylmalonic acidemia and phenylketonuria, both caused by arginine-to-TGA PTCs. Alltrna presented the data at a Nature conference last December.

The company, backed by Flagship Pioneering, is preparing to enter the clinic this year through basket trials in patients with various diseases caused by the same PTC. "The hepatocytes are the most critical cells for the initial basket of diseases that we're addressing," said Werner, which she noted will likely comprise 10-12 rare diseases.

"Instead of having 10,000 of these different genetic conditions, we actually see a world where you simplify them into a few universal conditions."
Michelle Werner, Alltrna

Alltrna decorates its tRNAs with various chemical modifications to enhance therapeutic properties such as activity, potency and stability. The team is using machine learning and generative AI to design the tRNAs, since "when you look at both the sequence modifications as well as the chemical modifications, there are actually more tRNA patterns than there are atoms in the universe," said Werner.

hC Bioscience Inc. was focusing on designing natural tRNAs, a decision that co-founder and CEO Leslie Williams told BioCentury previously was based on the belief that delivering highly modified tRNAs carries a risk of triggering immunogenicity.

According to Werner, Alltrna has data showing its engineered tRNA oligonucleotides do not increase immunogenicity.

Williams told BioCentury in an email statement that hC Bio is no longer operating. "After completing key animal studies for our Hemophilia A program utilizing tRNA-based technology, we conducted a thorough assessment of the data. Given the challenges in targeted delivery and other factors, we made the difficult decision to discontinue development of the program," she said. hcBio, founded in 2021, had raised $40 million.

Engineered tRNA therapeutics companies
Designed to bypass premature stop signals

Company	Founded	Focus	Raised ($M)*	Delivery
Alltrna	2018	Stop codon diseases	$159	LNP
Tevard	2017	Cardiology, epilepsy, muscular dystrophies	$70	AAV
QiXia Decode	2021	Cancer, muscular dystrophies	ND	ND

Source: BCIQ, company websites • *Disclosed amount raised
ND = Not disclosed

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Tevard co-founder, president and CEO Daniel Fischer said his company's suppressor tRNA platform is well-suited for diseases "where you have a large gene that you couldn't deliver using an AAV vector or another method." Its first two programs target nonsense mutations in dystrophin (DMD) and titin (TTN), large genes responsible for Duchenne muscular dystrophy and dilated cardiomyopathy, respectively.

Tevard has raised about $70 million from dilutive and non-dilutive sources. It was previously partnered with Vertex Pharmaceuticals Inc. (NASDAQ:VRTX) on its DMD program in a 2023 deal with undisclosed financials, but Vertex terminated the program amid a reprioritization, returning the rights. About 15% of the DMD patient population could be treated with a suppressor tRNA.

In September, Tevard revealed data from the program showing AAV-delivered suppressor tRNAs targeting glutamine-to-TAA and arginine-to-TGA nonsense mutations restored, on average, 70% of full-length wild-type DMD levels *in vivo*. "With a 70% rescue in DMD levels, we're seeing functional rescue up to wild-type levels in mice," said Fischer.

This represents a massive leap from the company's previous results; during its Vertex partnership, DMD rescue levels increased from 1% to 6%. Since its September data, Tevard has pushed expression levels even higher, Fischer said. "Right after the collaboration terminated, we got 22%. Now we're at almost 90%."

In the dilated cardiomyopathy program, AAV-delivered arginine-to-TGA suppressor tRNAs drove full-length TTN production and restored proteomic homeostasis in the heart within six weeks *in vivo*.

Suppressor tRNA expression and protein rescue were sustained up to 12 weeks post-treatment. Fischer said the company hopes to nominate a development candidate for both programs this quarter, after completing non-human primate studies that will determine which AAV capsids to pair with the suppressor tRNAs.

"For us right now, the critical path is selecting the capsid," said Fischer. "We already have agreements with four different companies for novel myotrophic and cardiotrophic capsids." The capid will deliver a DNA construct that encodes the suppressor tRNA, offering the possibility of a one-and-done treatment.

Tevard's founders include Harvey Lodish, a pioneer in mRNA translation and founding member of the Whitehead Institute for BioMedical Research.

Beijing-based Qixia has also generated data in DMD. The company's 2021 paper in *Nature Biomedical Engineering* also showcased restoration of full-length DMD, but its most recent work focuses on overcoming nonsense mutations in key driver tumor suppressor genes, such as TP53.

Other companies that have reported tRNA programs include Cloverleaf Bio Inc., Recode Therapeutics Inc. and Shape Therapeutics Inc. Cloverleaf told BioCentury that its approach is not based on PTC readthrough because it does not believe the mechanism is feasible for oncology. In an email, Recode said it deprioritized its earlier tRNA program for cystic fibrosis in favor of the mRNA program, which performed better in preclinical studies. Shape has an RNAskip technology, but its website says it is currently focused on RNA editing. The company did not respond to a request for comment.

Academic drivers

Academic researchers have published several advances in the last two to three years that are finding translational applications.

Zoya Ignatova, a biochemist at the University of Hamburg, is credited with generating seminal *in vivo* data based on a generalizable engineered suppressor tRNA platform, published in *Nature* in 2023.

Ignatova's team is partnered with Arcturus Therapeutics Holdings Inc. (NASDAQ:ARCT), which has licensed two of the group's tRNA patents, to co-develop suppressor tRNA therapies for undisclosed indications. Arcturus supplies LNPs to encapsulate the tRNAs and enable *in vivo* delivery.

"We use prime editing to permanently convert a dispensable, redundant tRNA gene in our genome into a carefully engineered suppressor tRNA."
David Liu, The Broad Institute

While these methods are based on delivering an engineered tRNA, either in an LNP or encoded as DNA in an AAV vector, David Liu's most recent *Nature* paper proposes a prime editing approach to convert an endogenous tRNA into a suppressor tRNA.

Dubbed prime editing-mediated readthrough of premature termination codons (PERT), the technique makes a permanent change to the endogenous tRNA gene and offers one-and-done treatment potential.

"We use prime editing to convert a dispensable, redundant tRNA gene in your genome into a carefully engineered suppressor tRNA," Liu told BioCentury in October.

The team showed *in vivo* delivery of a single prime editor that converts an endogenous mouse tRNA into a suppressor tRNA rescued disease pathology in a model of Hurler syndrome.

A group led by John Lueck at the University of Rochester School of Medicine revealed in a *bioRxiv* preprint a tool to optimize AntiCodon-Edited tRNAs (ACE-tRNAs) to increase suppression efficiency for the most common cystic fibrosis-causing PTCs.

An important safety concern about these therapies is whether they can read through natural stop codons.

So far, that has not been the case, likely because of three features of native termination sites that are absent at premature stop sites: 1) Some native sites have several stop codons in tandem as a safeguard; 2) they are immediately followed by the mRNA's 3' UTR, a regulatory region of the transcript that does not get translated; and 3) they associate with a polyA binding protein that triggers release of the peptide chain. All of these features can be exploited as signposts to steer the tRNA therapies away from native stop codons.

As an alternative to creating suppressor tRNAs that read through PTCs, a Chinese group recently introduced an RNA base editor that installs a chemical modification at PTCs in mRNA, turning nonsense codons back into sense codons at the RNA level.

Using the system, dubbed RESTART v3, the authors of the *Nature Communications* paper installed pseudouridine at the PTC in OTOF mRNA, restoring OTOF expression from its endogenous locus in mice carrying a mutation equivalent to the one found in humans with profound deafness. The treatment improved inner hair cell function and significantly rescued hearing, with about 30% on-target editing and no detectable off-target RNA changes.