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hC Bio: restoring protein function with tRNA therapies

Its sights set on cancer and rare diseases, Boston-based hC Bioscience hopes to take its first engineered tRNA therapy into the clinic next year

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September 21, 2023 12:04 AM UTC

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hC Bio is among a small set of biotechs pioneering tRNAs as a new therapeutic modality to edit proteins and restore their function without the safety concerns of permanently editing the genome.

The technology behind hC Bioscience Inc. is rooted in a 2019 *Nature Communications* paper from a group led by co-founder Chris Ahern at the University of Iowa. Leslie Williams, who was an executive in residence at the university, told BioCentury she approached Ahern after reading the paper to argue "this could be a company."

Williams and Ahern officially founded hC Bio in February 2021, with Williams becoming president and CEO. A $40 million series A round followed in 2022; investors include Arch Venture Partners, Takeda Ventures, 8VC, Taiho Ventures, Panacea Venture and CureDuchenne.

The technology described in Ahern's paper, PTCX ("Patch"), has grown into hC Bio's lead platform. PTCX uses engineered tRNAs to recognize nonsense mutations in mRNA transcripts and suppress them by inserting the correct amino acid, restoring the protein to full length and function.

The job of tRNA, or transfer RNA, is to decode the mRNA sequence for protein synthesis. After the mRNA is created during transcription, specific tRNAs identify the amino acid that corresponds to a three-nucleotide mRNA codon, then transfer the amino acid to the growing polypeptide chain.

The complementary base pairing between the mRNA codon and the tRNA's anticodon ensures accurate matching between amino acid and tRNA.

If the mRNA harbors a nonsense mutation, it leads to a premature termination codon of either UAA, UAG or UGA, ending the amino acid sequence before a full protein is made. The result is loss of that protein's function.

"Nonsense mutations drive about 10-15% of all human diseases," said Williams. "What we're doing is overwriting the mutation and repairing the premature termination codon."

hC Bio engineers tRNAs that are able to find premature termination codons by making their anticodons complementary to UAA, UAG or UGA. But because the tRNAs are loaded with the amino acid normally found in the healthy protein, instead of stopping translation, the tRNA adds the good amino acid to the polypeptide chain, enabling protein synthesis to continue.

Williams said the approach is inherently safer than gene editing at the DNA level because the changes it creates aren't permanent. However, with the tRNA approach, therapies must be designed to target premature stop codons only and not native stop codons. To achieve this, hC Bio takes advantage of the physiological differences between native and premature stop codons, and conducts ribosome profiling to ensure that the tRNA therapies aren't interrupting mRNA translation at native stop codons.

Williams pointed to three features of native termination sites that are absent at premature stop sites. Native sites have several stop codons in tandem as a safeguard; they are immediately followed by the mRNA's 3' UTR, a regulatory region of the transcript that does not get translated; and they associate with a polyA binding protein that triggers release of the peptide chain. All of these features can be exploited as sign posts to steer the tRNA therapies away from native stop codons, said Williams.

hC Bio is also thinking beyond nonsense mutations, simultaneously developing a second tRNA-based platform called SWTX ("Switch") to target diseases caused by missense mutations, by marking the disease-causing proteins for destruction.

SWTX involves targeting rare codons in oncogenes with engineered tRNA that carry an incorrect amino acid. "The objective here is for oncolytic purposes, such that the cell expressing SWTX tRNA will display reduced viability and will also send 'non-self' protein messages extracellularly, thus promoting innate immune activation and protein degradation," said Williams.

The company aims to deliver its tRNAs encoded as DNA and packaged into lipid nanoparticles. A single tRNA therapy has the potential to treat many diseases, regardless of the gene or location of the mutation. However, it still has to reach the right tissue or cell type, and may require different carriers per indication.

"We're looking to potentially partner with companies with nanoparticles that target extra-hepatic tissues," said Williams. "But we're also looking beyond nanoparticles to things like conjugates. There's a lot of new, exciting delivery approaches that I think tRNA is very well-suited for."

hC Bio's lead programs are for colorectal cancer with liver metastasis and retinitis pigmentosa, and it is currently focused on testing dosing paradigms and durability in animal models. "In genetic disease, you have non-dividing cells and in cancer you have dividing cells, so the dosing paradigms will be different," said Williams.

The company presented preclinical data at the 2023 International Symposium of Aminoacyl-tRNA Synthetases showing its therapeutic tRNA candidate rescued expression of the tumor suppressor protein APC and activated downstream pathways to drive 75% tumor growth inhibition in an *in vivo* model of colorectal cancer.

Although hC Bio isn't the first company founded to create tRNA therapies, Williams said its plan to enter the clinic next year could make it first to start human testing. "This would be the first tRNA to be in humans, from what we know."

Flagship Pioneering launched Alltrna Inc. in 2018 with a tRNA platform that, like hC Bio's, can correct nonsense mutations. The company, which raised $109 million in series B financing on Aug. 9, has not disclosed its lead indications or timeline for entering the clinic.

One difference from hC Bio is that Alltrna uses AI to modify its tRNAs for stability and selectivity. "We believe that having many modifications has the potential to drive immunogenicity," said Williams. "That's where we see the differentiation. We're really focused on keeping this as natural or native as possible, with just engineering the anticodon."

Alltrna CEO Michelle Werner countered that certain modifications have been safely made across RNA modalities and that Alltrna has "generated data that shows we can leverage our platform to engineer modified tRNA oligonucleotides that do not increase immunogenicity."

Founded a year earlier, in 2017, Tevard Biosciences collaborated with Ahern's lab on methods to create tRNA therapies. Tevard is using viral delivery vectors rather than lipid nanoparticles and is pursuing Dravet syndrome and other genetic diseases.

A few other companies, such as Shape Therapeutics Inc., have previously said they are exploring tRNAs among other therapeutic modalities.

COMPANY PROFILE

hC Bioscience Inc.
Boston, Mass.
Technology: tRNA therapies to overwrite premature termination codons and restore protein expression or mark disease-causing proteins for destruction
Origin of technology: University of Iowa
Disease focus: Cancer, ophthalmic and rare diseases
Clinical status: Preclinical
Founded: 2021 by Leslie Williams and Chris Ahern
Academic collaborators: University of Iowa, University of Wisconsin-Madison, University of Rochester, University of Chicago
Corporate partners: CureDuchenne
Number of employees: 30
Funds raised: $40 million
Investors: Arch Venture Partners, Takeda Ventures, 8VC, Taiho Ventures, Panacea Venture and CureDuchenne
CEO: Leslie Williams
Patents: None issued