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DRUG DISCOVERY

Anima Biotech Heads for the Light with Up-to-$2.4B Takeda Partnership

Biotech draws pharma giants to platform aimed at developing small molecule drugs that control mRNA translation

By Alex Philippidis

Anima Biotech's discovery phase program to treat Huntington's disease is one of at least three preclinical programs being partnered with Takeda Pharmaceuticals through an up to $2.4 billion collaboration launched last week. Anima aims to selectively inhibit with small molecules the mutated protein in the HTT gene linked to the rare, inherited disorder. [Anima Biotech]

Anima Biotech gets its name from the Latin word for soul, the root of the word "animation," or bringing something to life, says co-founder and CEO Yochi Slonim.

Using its own technology that tags transfer RNA (tRNA) pairs repeating frequently during translation with fluorescent light, Anima identifies small-molecule drug candidates that selectively decrease or increase the translation of mRNA into proteins on ribosomes to modulate the levels of protein produced, then elucidate their mechanism of action in a target space.

Yochi Slomin, co-founder and CEO of Anima Biotech

One of Anima's key areas of interest is neurosciences, the subject of an ongoing, up-to-$1.49 billion collaboration with Eli Lilly. Last week, Anima doubled down on building its neuro pipeline by launching a second potentially 10-figure partnership with Takeda Pharmaceutical. The Japanese pharma giant agreed to work with Anima to discover and develop a new class of three to six small molecule drugs for genetically defined neurological diseases, through a partnership that could generate more than $2.4 billion for the seven-year-old biotech.

Anima and Takeda have disclosed one disease of interest, saying they plan to develop Anima's discovery-phase program to treat Huntington's disease (HD) by selectively inhibiting the aberrant protein produced by the mutant HTT gene that causes the rare, dominantly inherited disease. The companies will partner on discovery phase programs to develop

at least two other small molecule drugs against undisclosed neurological disease targets selected by Takeda.

In return, Takeda agreed to pay Anima up to approximately $120 million in upfront and preclinical research milestone payments, and up to $1.1 billion in payments tied to achieving clinical and commercial milestones, plus tiered royalties. Anima could reap another up to $1.2 billion, plus royalties, if Takeda exercises a time-limited option to develop treatments against another three targets of its choosing.

"What attracted Takeda to our platform is that we have demonstrated small molecules that are inhibiting only the mutant protein causing Huntington's disease, but are completely sparing the normal type of the protein. So it allows control over the broadest range of diseases, where the protein is under-expressed, overexpressed, or mutated," Slonim told GEN.

Meeting at J.P. Morgan

Slonim met Ceri Davies, Head of Takeda's Neuroscience Drug Discovery Unit, in January 2020 during the J.P. Morgan 38th Healthcare Conference, held in San Francisco, just weeks before the pandemic.

"I remember [Davies] saying, I can think of so many targets where this would be applicable," Slonim recalled. "Takeda got intrigued by two things: One, the results that Anima generated in the HD program. But they also went through a very deep dive into the platform itself, which made them want to make this collaboration much bigger than just one program. They saw the potential and the applicability to so many different diseases and targets that they're working on that are currently undruggable or untreatable with existing methods."

In announcing the companies' collaboration March 17, Davies stated: "By combining Anima's platform with our strength in translational medicine and clinical development, we aim to develop medicines that deliver greater benefits to patients with genetically-defined neurological diseases where there are non-existent or ineffective treatment options."

Anima isn't the only partner with which Takeda is targeting Huntington's disease.

Takeda holds an option to co-develop and co-commercialize three HD candidates through a potentially more than $2 billion collaboration launched in 2018. All three are allele-selective antisense oligonucleotides. On March 4, Wave said it expected to report significant data from Phase Ib/IIa trials assessing WVE-120101 and -120102 by month's end.

Also working to develop HD candidates is uniQure, which is expected to announce data from a Phase I/II trial (NCT04120493) by year's end on its gene therapy AMT-130, consisting of an AAV5 vector carrying an artificial micro-RNA specifically tailored to silence the HTT gene, leveraging the company's miQURE™ silencing technology.

The challenge of developing drugs against Huntington's disease surfaced anew on Monday, when Genentech, a member of the Roche Group, said that dosing of patients had been halted in the Phase III GENERATION HD1 trial (NCT03761849) evaluating tominersen, an antisense treatment licensed from Ionis Pharmaceuticals, and designed to reduce the production of HTT. Tominersen remains under study in Roche's Phase I GEN-PEAK trial and in a natural history study also overseen by the company.

Vaccinex continues to develop pepinemab (VX15/2503), which missed its co-primary endpoints of two cognitive assessments from the Huntington's Disease Cognitive Assessment Battery and Clinical Global Impression of Change (CGIC) in patients with early manifest and prodromal Huntington's disease in the Phase II SIGNAL trial (NCT02481674) in September 2020—though Vaccinex added that the results supported further development in mid-stage Huntington's disease patients with greater cognitive deficits, as well as in Alzheimer's disease.

Drugging the "Undruggable"

Anima specializes in treating targets long viewed as "undruggable" by targeting cellular mechanisms that regulate mRNA translation of proteins with specific biological roles in coordinating and regulating translation of individual mRNAs and pathways.

The company contrasts its approach with small-molecule drug developers that target mRNAs themselves. Since small molecules can reach everywhere in the body, if the targeted mRNA of a protein is in multiple tissues, it introduces the potential for severe systemic side effect for that drug, Anima reasons.

"We have taken a look at mRNA biology, not at the mRNA molecule. The molecule is there but it's not really a good target, in our view. The target is the biology that surrounds the mRNA and specifically the biology that translates mRNA into proteins," Slonim said.

The company's translation control therapeutics platform labels a target protein's signature transfer RNA (tRNA) pair with energy-donor or -acceptor fluorescent tags through Fluorescence Resonance Energy Transfer (FRET). When the two tRNAs come close together in the ribosome during the protein's translation, a light pulse is emitted. For 85% of known proteins, a signature tRNA pair can be identified that repeats with high frequency during translation but is relatively rare in the human gene expression background.

The company's translation control therapeutics platform features four key components:

- **Cerebio** applies bioinformatics algorithms to select a unique tRNA codon pair that is frequently used during the target protein's translation but not used as often by the background human proteome.
- **Translationlight** generates a light pulse whenever the selected tRNA codon pair sits in a ribosome, enabling visualization of protein translation inside living cells.
- **Brightny** validates the selectivity of Translationlight's identified compounds by eliminating global translation modulators, analyzing the compound's activity along the mRNA life cycle, checking the effect on similar proteins and critical pathways, and comparing the compounds to RNAi.
- **Compass** elucidates compounds' mechanisms of action and molecular targets in mRNA translation regulation, through the use of assays and algorithms focused on the biology of mRNA maturation, transport, localization and translation.

Anima's platform is designed to enable visualization of the translation, including where, when, and how much happens in real time in live cells.

Look at the Light

"In the screening system, we look at the light. If the compound changes the light–decreases or increases the light—it's because they decrease or increase translation," Slonim explained. "Then, our software automatically analyzes all those millions of images to identify the compounds that change and affect the light. These are the translation modulators eventually that we're after."

Translation modulators, according to Anima, can be tissue- or disease-specific.

"We've discovered those compounds that modulate translation, and we see that they work by inhibiting, let's say, the Huntingtin mutated protein," Slonim said. "The beauty of the approach of Anima is that we can very quickly tell how they work, the mechanism of action, and the molecular target. With that, we can find quickly not only something that works biologically, already quite advanced in comparison to an in vitro type of molecule, but we can see the microcosm of action and uncover the full biology of how this works. This is extremely valuable."

In addition to the Takeda-partnered candidates Anima's neuroscience pipeline includes "several" discovery programs against undisclosed target proteins subject to its collaboration with Lilly. The companies agreed to partner on discovery using Anima's platform, with Lilly agreeing to oversee clinical development and commercialization of products resulting from the collaboration.

Lilly agreed in return to pay Anima $30 million upfront, $14 million in research funding, and up to $1.05 billion tied to achieving development and commercial milestones. Lilly and Anima are saying little about their partnership: "The collaboration has been going extremely well, and essentially we are moving forward according to the plan," Slonim said.

He added that the Takeda collaboration will not include two candidates also in Anima's neuro pipeline—one is designed to fight Alzheimer's disease by targeting translation in tau protein; the other is aimed against repeat associated diseases.

Anima's pipeline also includes a preclinical program against respiratory syncytial virus advancing from discovery to optimization phases, and two oncology programs. The lead oncology program is designed to develop three translation inhibitors against the undruggable protein c-Myc, a transcription factor. Anima is also developing a discovery phase candidate against the KRAS gene.

12 Months Away

Furthest along in Anima's pipeline is a lung fibrosis program targeting a translation inhibitor of collagen type 1. That program is in IND-enabling studies, and is about 12 months away from the clinic, Slonim said.

"Collagen is the most abundant protein in the human body. It's everywhere — in the liver, the kidneys, bones, skin, tendons. Trying to go after the mRNA of collagen is a dilemma, obviously," Slonim said "But we found molecules that control the transla-

tion of collagen and the cells do it selectively in different tissues, so the molecules work only in the lungs. They are completely inactive in the liver, the bones, the skin, which means that these drugs are not like artillery, bombing the mRNA all over the place. They're like guided missiles. They go only in the lungs where there is disease."

Anima was founded in 2014 with technology developed starting in 2005 at, and licensed from, University of Pennsylvania, one of 17 academic institutions with which the company collaborates. In addition to the millions of dollars garnered through its collaborations with Takeda and Lilly, Anima has raised an undisclosed amount from private investors.

The company has grown to some 70 people, most of them R&D staffers based in Tel Aviv, additional staffers based in the Boston area and in Bernardsville, NJ, where Anima is headquartered.

Slonim is a serial entrepreneur with extensive experience in software development, having been a senior VP at Tecnomatix (acquired by UGS in 2005 for $230 million), co-founder and CTO of Mercury Interactive (acquired by HP in 2006 for $4.5 billion), and founder and CEO of Identify Software (acquired by BMC in 2006 for $230 million) as well as the startup acceleration program ffwd.me, which helped launch more than 25 diverse companies.

Speaking with GEN in 2019, Slonim recalled he was approached by Zeev Smilansky, PhD, who became Anima's co-founder and CSO. Smilansky "described an idea that sounded crazy," Slonim said, outlining the fluorescent labeling of tRNA to cause ribosomes to emit light pulses as they assemble protein. This allows researchers to visualize the production of individual proteins by ribosomes in real time. "Their production looks like clouds of light in the Milky Way," Slonim said.

The next logical step was to transfect the tRNA into diseased cells. "Once we started to 'see the light,' the idea for a drug discovery platform started," Slonim added. ■

Anima Biotech

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