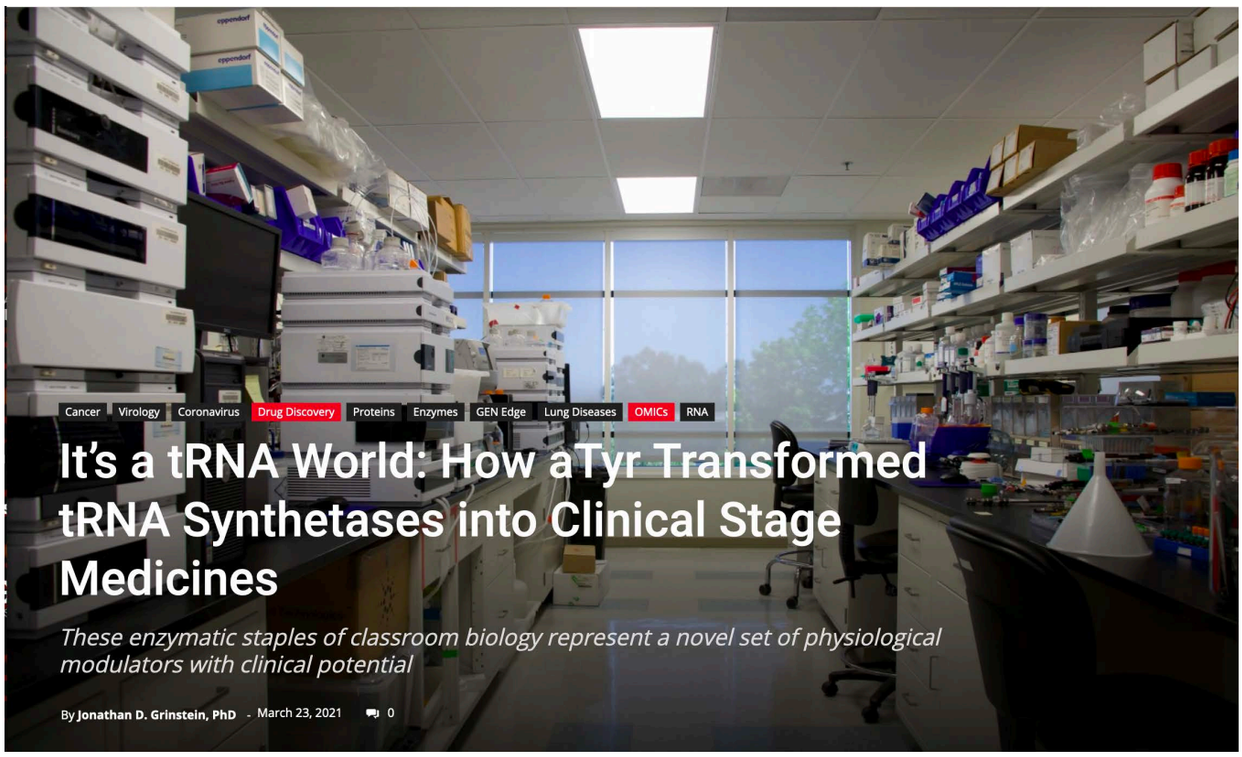
GENEDGE



[Source: aTyr Pharma]

RNA is having a moment. Several, actually. RNA vaccines —unproven in a clinical setting until last year—are leading the immunization charge against the COVID-19 pandemic. And the Nobel Prize-winning CRISPR technology relies on the precise programmability afforded by guide RNAs. Now, maybe, it’s time for another class of ribonucleic acid to grab the limelight—transfer RNA (tRNA), and the enzymes that make them.

Anyone who has studied molecular and cell biology is probably familiar with tRNA synthetases. These enzymes are part of the bread-and-butter mechanics of protein synthesis, catalyzing the attachment of tRNAs to their respective amino acids. Without tRNA synthetases, there wouldn’t be a proper translation from the genetic code of DNA to messenger RNA to the amino-acid building blocks of proteins. tRNA synthetase enzymes may be a a staple of biochemistry textbooks, but for many were just another term to memorize for exams and quickly forgotten.

As it turns out, tRNA synthetases aren't so easily dismissed. These enzymes may play important roles in cellular responses to certain disease states, in particular, cellular stress and tissue homeostasis. A protein derived from one tRNA synthetase gene can act as an extracellular modulator of angiogenesis.

aTyr Pharma (pronounced "a tire") was borne out of this discovery—the extracellular functionality and signaling pathways of tRNA synthetases. This publicly traded San Diego-based biotherapeutics company has built a global intellectual property estate directed to a potential pipeline of protein compositions derived from 20 tRNA synthetase genes and their extracellular targets. aTyr's primary focus is ATYR1923, a clinical-stage product candidate, which binds to the neuropilin-2 receptor and is designed to down-regulate immune engagement in inflammatory lung diseases.

GEN Edge spoke to Sanjay Shukla, MD, president and CEO of aTyr Pharma, to discuss how his company has evolved its approach to the discovery and development of innovative medicines based on novel tRNA synthetase activity. (This interview has been lightly edited for length and clarity.)

GEN Edge: **What was the company founded on? Has that been the same since launch?**

Sanjay Shukla: The company has gone through several evolutions. At each point, the biology on which the company was founded has continued to mature. We are starting to reap the dividends put into the understanding of tRNA synthetase biology.

We came out of the Scripps Research Institute, specifically Paul Schimmel's lab. His passion was tRNA synthetases, which are enzymes in all our bodies. When I was in school, all I understood about these enzymes was that they do a basic function, which helps us create proteins. They're intracellular enzymes that shepherd in amino acids to a tRNA and allow that catalytic

process when it reads in mRNA to create polypeptides. Paul discovered that these enzymes break apart into fragments and they leave your cells. Once they leave the cell, these fragments take on an additional role—a very non-enzymatic role.

The company aTyr was founded on trying to figure out what these protein fragments are doing outside the cell. They play a role at a very specific tissue level in controlling immune environments, sometimes activating an environment, sometimes down-regulating depending on the fragment. aTyr was founded to research and discover new therapies from this protein fragment library. For many years, the company spent a lot of time understanding how these fragments interact with the immune environment.

We've looked at specific fragments that have advanced into accelerated testing in discovery, understanding the target receptor, and seeing where these fragments might be enriched in which particular organ system. We've been able to mature a therapeutic that we now like for lung disease. There is a fragment that forms the backbone of our lead candidate, aTyr1923, that can play a significant role in modulating immune behavior in the lungs when there's an aberrant inflammatory response.

The mission is to develop medicines from this completely new area of biology and translate findings into where we can target the science, in which disease environment could we be most effective. From a vision standpoint, if we can create multiple therapies from this underground immune system, that would be a rather revolutionary new area of science. We do have a long view that many of these protein fragments can inform us about how they play a role in disease. There's the opportunity to create medicines.

GEN Edge: **How does being a publicly traded company affect what you choose to do?**

Shukla: If we're a private company, we could be a lot more like a research institution. We would be able to take our time, spend a few years on experimentation, and then put out a paper at that

point saying that we have 40% of this problem figured out. When you're a public company, you can't act as a research institute or tell your public investors that we're just in this to just continually learn about the science. You've got to get to a place where you are trying to create product opportunities, which is the reason why we've tried to collaborate more. [Ed note: aTyr trades under the symbol LIFE.]

For example, at the American Thoracic Society, we showed four animal models showing nice efficacy of anti-inflammatory effects of ATYR1923. That's where that marriage happened with a Japanese company getting involved early in the development of that drug. We took that opportunity. I thought this could be useful for us because I don't have an office in Asia right now and they could provide a lot of firepower for us, not only with capital upfront but also help us develop this in a region where we're going to have to go. After all, there's interstitial lung disease in Japan as well. We announced that deal early this year. That sets us up to have a really strong partner in an area of the world where they've already got the infrastructure and the teams are ready to build.

As a public company, we have to focus on generating value, having clinical programs with a goal [to develop] a product that eventually will be useful for this indication. Maybe private investors will give you that time, but nobody gives me that time. They want to know what's happening. We're even working on COVID now, so they want to know when that data is coming around. It's a different world.

GEN Edge: **What does aTyr's one-, five-, and ten-year plan look like?**

Shukla: I think in the next year, you're going to see us continue to advance several therapeutics, most notably our lead candidate. We would hope to move into almost a phase three. We do see a future with ATYR1923 as one of the leading drugs now for interstitial lung disease. We're the furthest along of maybe any company in the world with a potential therapy that could be useful in sarcoidosis patients or hypersensitivity pneumonitis

patients. These are all opportunities to treat hundreds of thousands of patients here in the US. We need better drugs because steroids are sometimes used and don't work that great. Steroids don't prevent fibrosis. We would expect that therapy to have a nice pathway to be that the first drug that we commercialize. That's closer to the three- to four-year time frame.

We're embarking on a new vertical of oncology. We will continue to mature that, and perhaps in the next year have ATYR2810 start to get ready to go into cancer patients, because right now we're doing all the IND-enabling work.

In the next five years, what I expect us to do is be able to replicate some of the findings with other tRNA synthetases. We just announced that we found two new receptors for two other tRNA synthetase targets. That will build out our portfolio. I would like to see us advance other fragments to a discovery and development stage.

Long-term, aTyr can be the type of anchor company that San Diego needs. We're the type of company with a protein platform library that is just different. aTyr has the ability to do that, but it might take another 10 years for us to get to that place. I think it'd be a cool core part of the story if we were there in 10 years.

Lately, we've been asked a lot of questions about COVID. We didn't have a goal there, but seeing the early literature around the overt, inflammatory response that some people had, especially if you're hospitalized, we started to look at the cytokines, and chemokine patterns. ATYR1923 downregulates many of those same inflammatory cytokines. At that point, we went to the regulatory authorities and said, do you think this makes sense from a rational point of view to maybe look at our drug and jump into this?

We're a very small company to do that, but it was based on real, rational biology that was maturing that then started to intersect with what we had. That's a trial that's going to roll out in the next month. We'll have some preliminary data, as we've enrolled 32 hospitalized COVID patients. A third of them got a placebo.

We ran a rigorous placebo-controlled trial. So we'll be able to learn mechanistic things and see some very early effects of our drug. Which cytokines, in particular, does it start to down-regulate? If people get better, faster, that will also be a great thing. You're starting to see now a toolkit developed with COVID pneumonia as well, but we see this more as another, it's interstitial pneumonia.

Our drug has applicability even beyond COVID and acute inflammatory distress. There's a lot of diseases viral pneumonitis is out there that caused an aberrant immune response. We think ATYR1923 could be a really interesting new kind of therapy that could be used perhaps in the acute setting. We're also testing it in the chronic setting with sarcoidosis patients. That's another example where we just learned about what was occurring. Then we said, well, now we have to jump in here because we're seeing a lot of connections to our therapy. A lot of companies just try and repurpose therapies.

GEN Edge: **How does such a small company get engaged in so many clinical trials?**

Shukla: We're a tight group and we're extremely efficient in how we do things. I've been in drug development for 25 years and I've had great experiences in a lot of big companies, but one thing I've learned is how not to do things. We are a very lean company. I joined as chief medical officer. I'm still doing that job as well as CEO. We have a lot of people that can wear a lot of different hats and do different things. We want people that can be functionally versatile. Some people just want to be experts.

Now, we're a 45-person company. We're running multiple phase II trials, and we've got a discovery candidate now and a couple of pipeline drugs. We act like a bigger company. We try to find folks that also are no-nonsense. As a small company, you've got to have people who are cool with that, who are not going to the big-time and say that I need to have eight people underneath me. Maybe we'll get there one day. I'm not saying that we have to always act like this. Right now, we're not the Yankees, but the Yankees don't win all the time either! We can still get things done as a small market club, right?