

# THE WALL STREET TRANSCRIPT

Connecting Market Leaders with Investors

## Arrowhead Research Corporation (ARWR)



**CHRISTOPHER ANZALONE, PH.D.** is the President and CEO of Arrowhead Research Corporation. He has a wealth of experience in nanotechnology, biotechnology, company building and venture capital. Prior to joining Arrowhead, Dr. Anzalone founded and built The Benet Group, a private equity firm focused on creating and building new nanobiotechnology companies from university-generated science. Included in The Benet Group's portfolio are investments in two nanotechnology companies: Nanotope Inc., a tissue-regeneration company, and Leonardo Biosystems, Inc., a cancer drug-delivery company. Prior to Benet, Dr. Anzalone was a Partner at Galway Partners, LLC, a private equity firm based in Washington, D.C., where he was in charge of sourcing, structuring and building new business ventures. He was also the Founding CEO of NanoInk, Inc., a leading nanolithography company. Dr. Anzalone holds a Ph.D. and M.A. in biology from the University of California, Los Angeles, and a B.A. in government from Lawrence University.

### SECTOR — HEALTH SERVICES

**TWST:** Would you begin with a brief historical sketch of the company?

**Dr. Anzalone:** We started as a diversified nanotechnology company. The idea was to build a holding company with multiple majority-owned subsidiaries underneath it to develop nanotechnology-based products in a number of industries. We have evolved from that model a bit over the last couple of years in order to focus on a single vertical to maximize operational and strategic efficiencies. The vertical we chose was nanomedicine because there are large unmet medical needs within health care that may be addressed by leveraging nanotechnologies. We have also increased the operational control of our subsidiaries.

Today, rather than a holding company with multiple subsidiaries, you can think of us as an operating company with multiple programs. Although we are still legally structured as a holding company with subsidiaries underneath, we actively operate our subsidiaries, which distinguishes our approach and still enables a cost-efficient business model. Our goal is to provide the investor with a balance between diversification and focus. We're solely focused on nanomedicine, and there are technical synergies among our subsidiaries. At the same time, we also provide a level of diversification that is, I think, unique for small biotech companies.

We currently have four subsidiaries, and each of those subsidiaries is based on platform technologies, so we have multiple shots on goal. Rather than being dependent upon one or two drug candidates, we have four subsidiaries. And each of those subsidiaries has the ability to create multiple drugs, or in fact, multiple classes of drugs or devices. We think that affords the company and our investors broader upside potential while also limiting downside risk.

**TWST:** Please take us through the subsidiaries and give us a sense of where they stand.

**Dr. Anzalone:** Our two leading majority owned companies are Calando Pharmaceuticals and Ablaris Therapeutics, and we are very excited about both. Calando, our most mature subsidiary, is a clinical-stage RNAi company. It is focused on the delivery of siRNA, or short interfering RNA, which are a class of molecules that trigger the RNAi process. In a nutshell, RNAi is a method of silencing target genes. We believe, along with many prominent science thought leaders, that RNAi can potentially revolutionize medicine. It's a whole new way of treating virtually any disease state by targeting those conditions at their genetic level. The basic premise is that, if you can target a certain gene or multiple genes that cause a disease and you can silence those genes, there should be no undruggable diseases anymore. This new class of therapeutics could also represent a better way of treating those conditions that are currently treated with small molecule drugs, and potentially increase specificity and decrease off-target effects, or side effects. I view RNAi as nothing less than a paradigm shift in medicine.

So we have this fantastic new science that many believe could transform medicine, but something has held the field back. Delivery has been that limiting factor. siRNA are very difficult molecules to deliver because they are easily degraded in the blood stream and difficult to shuttle into target cells. This unmet need represents a classic choke point. If a company is capable of overcoming the delivery question, it could enable the entire field — and therefore, create substantial value. We at Arrowhead look for choke points in large markets, and Calando sits squarely at this one.

Our initial focus is oncology, but we believe that we can eventually move beyond cancer. Last year, Calando published a paper in the scientific journal *Nature* showing that we were the first ones to successfully deliver siRNA systemically in humans. We believe we checked all the boxes. We showed a dose-dependent accumulation of our nanoparticle, our delivery vehicle, in tumor cells. We demonstrated a decrease in target RNA levels, and we showed a decrease in target protein levels. We also showed that those decreases in RNA and protein levels were mediated by the RNAi process. We have always believed that we are at the forefront of this field, and our progress last year further underscored that position by showing that we're the first ones to successfully deliver siRNA in people.

So where are we now? We have a system that is very well tolerated in humans, has the ability to shuttle siRNA into virtually any part of the body other than the brain, can be used to create a virtually limitless number of oncology RNAi drugs, may be customized to move into nononcology indications and we are nearing completion of our initial Phase I trial. We think that this will represent a significant event for the entire field of RNAi, and certainly for Calando. We are also focused on executing an initial corporate partnership this year and developing a second therapeutic candidate to bring to the clinic.

Ablaris Therapeutics, our antiobesity company, is also fairly mature in its development. We formed Ablaris in December 2010 through a technology licensing agreement with MD Anderson for an upfront payment of \$2 million. In order to defray these costs, we brought \$1.6 million of outside capital directly into Ablaris and retained 64% equity in the company. While it is our newest subsidiary, it's actually quite advanced technologically. And we expect to enter the clinic with Ablaris' first compound this year.

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The field of obesity is clearly a large and growing market. When I give presentations, I always show a slide on the market size. But I never really talk about it, because we all know this intuitively. However, we have approached this field very cautiously because there have been substantial regulatory hurdles to bringing an antiobesity therapeutic into the marketplace. Some of that the scrutiny, I think, is perfectly reasonable. The majority of obesity cases may be treated nonpharmacologically, and so the FDA has had a very closed stance on any safety signals with therapeutics as they go through the regulatory process. Because of that, we were interested in the market, but we were only willing to enter it if we could do so with a therapeutic that we thought, "A," had a favorable safety profile, of course. And "B," was not a CNS drug, or a drug active at the level of the brain. We believe that altering brain chemistry in order to decrease appetite would have a very large chance of off-target effects that could complicate the regulatory-approval process. With these parameters in mind, we identified technology out of MD Anderson that was very attractive.

What they developed and what we licensed is a therapeutic platform that targets vasculature feeding white fat tissue. The theory is to specifically eliminate some of the capillaries that feed white fat, thereby depriving the fat of nutrients and causing it to be removed by the body. If this works, it could represent a powerful new way of treating obesity that focuses on the fat itself rather than the brain.

The first paper on this platform was published in 2004 in the prestigious scientific journal *Nature Medicine*. And the results were stunning. They showed that in obese rodents they were able to decrease body weights by about 30% in 28 days after daily subcutaneous injections of the compound. Nobody had ever seen results like these, so there was a media frenzy in outlets such as *The Wall Street Journal*, *The New York Times*, National Public Radio and multiple television networks. Since that time, scientists at MD Anderson have done more work on the platform, and we have also seen third-party validation. A group of scientists at the University of Cincinnati led by Dr. Randy Seeley, who is a well-known and well-established obesity metabolism specialist, has been testing the platform over the past several years and has found very similar results. So we're excited about this set of compounds. We also believe that it can help to reverse symptoms associated with type two diabetes. We think it's a very powerful drug candidate. The group at MD Anderson has since moved into primates. They've now looked at dozens of primates both for safety and for efficacy and have found similar results. We believe that the data from those studies will be published this year in a high-profile journal. So we're excited about that validation as well.

Through our partnership with MD Anderson and the \$2 million investment, we have gained access to this suite of compounds and secured funding for initial clinical development. Importantly, all direct costs associated with the planned Phase I trial are covered by MD Anderson. These include costs associated with the preclinical toxicology studies to support an IND, preparation and filing of the IND, manufacture of the drug for the Phase I, and cost of operating the Phase I trial. And we believe we'll be in the clinic with Ablaris' first drug candidate by the end of this year.

**TWST: Please tell us about your minority-held divisions, Nanotope and Leonardo Biosystems.**

**Dr. Anzalone:** Nanotope is a regenerative medicine company with a powerful core platform technology that can be customized to regenerate multiple tissues. Simply by changing some of the parameters of the platform, we have shown in multiple animal models that we can reverse paralysis by regenerating spinal cord. We have also shown that we can regenerate bone, cartilage, accelerate wound healing and potentially treat many other underserved medical needs through regenerative medicine that does not involve the use of stem cells. It sounds like science fiction, but it's just good science. As with all of our platforms, Nanotope's work uses nanotechnology to accomplish things that would otherwise not be possible.

The platform is made up of fairly simple molecules that have a peptide sequence and a lipid tail. In solution, those molecules are monomers; however, once they are injected into the body, they self assemble into nanofibers, whereby the core of the fibers are made up of lipid tails and the whole surface of the fibers are the peptide sequences. So what this creates on a nanoscale, or microscale, are very small fibers on the order of maybe 10 nanometers in diameter. Those fibers are all quite similar on a fiber-by-fiber basis, but on a more macro scale, they form a mesh of fibers. This creates a scaffold that, on a macro scale, feels or looks like a gel. What we've found is that the scaffolding is quite

powerful as it can be made to be intrinsically bioactive. And that's where it's really different from other scaffolding plays. To the extent that you know how a certain peptide sequence will signal a cell type, you can encode that into this system.

The way I think of this is that other scaffolding materials are like trellises on which vines can grow. Our scaffolding is a smart trellis that can communicate with the vines and instruct them to grow in a certain way or to bloom in a certain way. So if you can translate that into a biological system, it gives you a scaffolding that can signal your target cells and cause them to regenerate when they would not otherwise do so. After the scaffold does its job, we believe it is safely broken down by the body. Importantly, by changing that peptide sequence, we are able to customize it to various tissues, making this a very broad platform. We are also able to engineer this scaffold to bind macromolecules, such as growth factors. So that gives us the ability to sequester growth factors or other macromolecules, and then present those molecules to target cells at very high levels.

As I mentioned, we have used this platform to regenerate spinal cord in animal models to reverse paralysis. We have incredible video of animals walking after only about nine weeks. It is really stunning.

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We've also shown that we can regenerate cartilage and bone in animal models, as well as demonstrated accelerated wound healing. We also believe we can treat peripheral artery disease. There are virtually limitless uses for this base platform. So our model with Nanotope is to develop this platform quite broadly, and to bring in partners fairly early in the development of specific therapeutics. We signed a partnership with Smith & Nephew at the end of 2010, and that's a good example of the types of partnerships that we are looking to secure with Nanotope. The Smith & Nephew agreement provides us with milestone payments and royalties based on a very narrow focus on cartilage regeneration. Smith & Nephew will cover the future costs of developing that compound in order to bring it to the clinic. We will receive milestone payments and royalties as that compound, or class of compounds, is developed and introduced into the marketplace.

Because Nanotope's technology offers a very broad platform, we believe we can enter into additional similar partnerships not once or twice, but potentially 10 to 15 or more times on a tissue-by-tissue or an indication-by-indication basis. Our strategy with Nanotope is to enter into partnerships early in the development stage, keeping our burn rate low by offloading substantial capital risk to our partners. We're also bringing in very specialized partners that have the ability and resources to not only develop compounds, but also bring them to market.

We also have an interest in Leonardo Biosystems, a next-generation drug-delivery company. This technology addresses the very complicated drug delivery process that is possibly too complicated for a single delivery vehicle. Mauro Ferrari, President and CEO of the Methodist Hospital Research Institute and member of Arrowhead's board, developed a multistage approach, if you will, whereby there will be two delivery vehicles. One delivery vehicle will be optimized to get through certain biological barriers and then release a smaller delivery vehicle inside that is optimized to get through other biological barriers. The primary system, or the primary vehicle, is porous silicon, optimized via

size and shape to get to tumor vasculature. It's focused right now solely on cancer. It will get to tumor vasculatures and then release its secondary carriers, or smaller particles, to get into the tumor cells. We believe that this approach can substantially increase the targeting efficiency of drugs across the entire drug spectrum. Whether this includes RNAi or small molecule drugs, we believe this system allows us to get to tumor cells much more specifically rather than globally. This technology is currently in preclinical development, but we think its potential is powerful and the broad platform will enable us to work with a number of partners in order to develop and market a diverse set of drugs. Although we are currently focused solely on cancer, it's possible that we can expand beyond this indication at some point.

**TWST: What's the competitive landscape like and what are some of your competitive advantages?**

**Dr. Anzalone:** We believe that we have several operating advantages and here is why: Because of our model and the multiple subsidiaries that we treat as operating units, we are able to consolidate management. That allows us to do two things. First, it allows us to bring in high-quality management that would be difficult for individual small biotech companies to attract. Second, it allows us to

keep those people busy, because they can work on multiple programs. We believe this structure gives us clear cost advantages over competitors. We also believe that we have advantages with respect to attracting shareholders since our model allows us to offer more limited downside exposure and broader upside potential by working on so many different areas within nanomedicine. Many small biotech companies are focused on one or maybe two drug compounds, and that smells more like a bet than a business to us.

By having multiple platforms — and within those multiple platforms, multiple chances to create various drugs — we believe that we can limit that downside risk. If you are a small biotech company with a single drug that you're bringing to the marketplace or into the clinic, your outcome is often binary. That company can be worth a lot of money if the drug works and gets through the FDA, or it can be worth zero if it fails. Our goal is to make our outcomes less binary than that. Finally, and this dovetails into the first point, by design each of our subsidiaries hold technical synergies with each other, which creates additional operational efficiencies where we believe our subsidiaries can work faster and more intelligently, because they have access to other scientists rather than just one very focused team.

**TWST: What are some milestones or indicators investors should be watching for? You mentioned Phase I on the Calando product.**

**Dr. Anzalone:** We have a number of catalysts that we hope to accomplish this year. Breaking these down by subsidiary, with Calando, we expect to finish the Phase I trial and execute on a commercial partnership this year. Those are two substantial milestones for Arrowhead. Additionally, we are looking to form a new scientific advisory board around Calando to assist in future development with these assets and ultimately establish new clinical candidates and clinical protocols.

With Ablaris, we have two major catalysts. We believe one is the publication of a paper that we will report on the primate results. The

second will be the completion of an IND filing and initiation of a Phase I trial. For Nanotope, we believe that we can execute another commercial partnership, akin to the one that we did with Smith & Nephew, in another tissue type. With Leonardo Biosystems, we believe that we are approaching a major milestone in optimizing our manufacturing of our silicon particles. By end of the year, we believe can have that process optimized and begin to scale that operation.

**TWST: Do you feel investors have a clear understanding of what you have to offer?**

**Dr. Anzalone:** That's something that we need to continue to work on. We've had a very difficult time in that area since our inception. At the beginning we were a diversified nanotechnology company, so we were in multiple industries. It was very difficult for both the buy side and sell side to understand us, because companies are generally focused in a single vertical. We have made that proposition much simpler this year, as we now hold a concerted focus in nanomedicine. So our story is a much easier to digest today than it was a year ago. Having said that, we are a small company. And we think we have a great story, but we need to get that story out and get in front a lot of people in order to be heard. For the most part, I think we are under the radar. But when investors hear about our model, the various platform technologies in development, the substantial markets we are addressing and how far this company has progressed, I believe our story resonates as an attractive investment opportunity.

**TWST: What would be the two or three best reasons for a long-term investor to look closely at Arrowhead?**

**Dr. Anzalone:** We believe that nanomedicine is going to transform the pharmaceutical and biotech industries, and we believe that we are at the forefront of that movement. We have a cluster of programs that are all in high-value markets and are based on world-class technology. Additionally, our broad technology platforms have the potential to bring multiple products into the clinic within these various large markets. We are focused on cancer. We are focused on obesity. And we are focused on regenerative medicine. Within each of these fields, we have platforms that will enable us to treat a number of large unmet market needs. As with all biotech, this does not happen overnight. That said, we believe that we are in the right markets, with the right technology platforms to create long-term value for our shareholders as we continue to execute on our operational objectives to advance and partner our programs.

**TWST: Thank you. (MJW)**

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