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## Garo Armen And Audacity At Agenus

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*Garo Armen*

What motivates a biopharma executive — a company founder, chair, CEO, or any other leader in the organization? In many industries and lines of business, where the sale of goods paves the simplest path to wealth, the prospect of great riches may be the only incentive needed. But how many entrepreneurs go into biopharma merely to get rich? I can tell you, from decades of interviewing biopharma execs, almost every one of them has a more personal, even idealistic, motive for doing business in this sector. I say that, though in my view, some have disappointingly failed to live up to their ideals. Garo Armen, veteran of Elan and founding CEO of Agenus, has shown the instincts for simple moneymaking on one hand and the humanitarian side of biopharma on the other. That is why I began our recent conversation by asking him how, in his career, he had managed to work well on both sides.

“Pursuing the mission with Agenus actually has been detrimental to my earning money,” Armen says. “Over the years, I ran my own investment firm, and I made a reasonable amount of money there. But the reason I’m running Agenus is not financial; it has been a mission. In fact, I have injected far in excess of \$12 million in the company out of pocket, which means I have zero financial incentive for doing what I’m doing right now.”

But his twin interests, finance and biopharma, are still plainly evident today in the Agenus pipeline and in the company’s new option for financing drug development, the Biotech Electronic Security Token (BEST). The strategies behind both examples are audacious. The Agenus pipeline contains candidates in almost every class of cancer immunotherapy, with the aim of ultimately offering one-stop shopping for combinations at a lower cost than combining separate brands from multiple companies. In parallel, the BEST option could lower the cost and risk of investment because it is product-specific and not tied up in the overall fortunes of the company and its other projects. Both of the initiatives are potentially big innovations that challenge traditional drug-development and finance models.

## **DOLLARS & SENSE**

Armen began his career as a scientist, earning a Ph.D. in physical chemistry at the City University of New York. While working on his postdoc, despite having no exposure to business, economics, or finance, he “made an observation” one day that piqued his interest in the way the financial markets worked. As earlier publications tell it, Armen noticed gas-pump indicators had too few digits to accommodate more than a 99-cent-per-gallon price, and at the time, prices were nearing a dollar per gallon and rising fast. He then found and invested in the main company supplying the indicators to gas pump makers, and when the company received the giant surge of new orders he expected, its stock rose and paid him handsomely.

He was hooked and soon made the “fascinating” transition from research to Wall Street finance. “At the time, my research was not in biologicals, it was in chemicals, so I didn’t have the same emotional attachment to it I may have had in immunology or cancer.” In 1973, his mother died in his arms, of cancer, when she was only 47 years old. But it took years for his awakened interest in medical progress to transform his career. “I didn’t get into biological science immediately after that experience because biology in medicine was still a black box to me. After a while, I got interested in pursuing companies in the biotechnology area. I spent a number of years on Wall Street tracking biopharma companies, seeing the science progress.”

Agenus was born in 1994, then under the name Antigenics, to apply the emerging science of IO. “By the early 1990s, we had scientific proof that cancers would react to the immune system,” Armen says. “But what we lacked were methods of activating the immune system properly, efficiently, and pointedly to combat cancer.” The company started with development of an individualized cancer vaccine to deal with the differences in disease, person to person. But the program soon ran into some major challenges.

“At that time, for a vaccine approach to tackle cancer, you needed to identify earlier-stage patients, typically Stage 2 or early Stage 3, and getting a readout of efficacy in those patients was a seven- to nine-year undertaking because early stage cancers progress very slowly.”

To produce statistically significant results, a Phase 3 trial would require many years, and in 2000, the company embarked on that journey with a renal cell carcinoma trial planned to take seven years. “Unfortunately, that trial didn’t work out the way we wanted,” says Armen. “Not because the product didn’t work, but because the study parameters changed midtrial, including the definition of qualified patients. We decided against doing another seven-year trial. So, we had gone from 1994 with the founding, to 2006, with the failure of the trial from the regulatory perspective, and from 2006 to 2014, in search of additional helpers that would make cancer vaccines more effective.”

In 2014, the company started a complete transformation with a series of acquisitions. “We obtained technology and product candidates that cover all of the key areas needed to effectively treat cancer: vaccines, checkpoint inhibitors and modulators, antibodies, including bispecifics and multispecifics, cell therapy, and adjuvants. We also have created an engine for innovating on a continuous basis.”

Armen says that “engine” helped Agenus land a partnering deal with Gilead in December 2018. “The engine has allowed us to take a slice of our portfolio and give that exposure to Gilead while keeping a very substantial slice for additional transactions. Also, our portfolio is continually replenished thanks to our innovation engine.”

## **BEST INTEREST**

Engines need fuel, of course, and the fuel for drug development is money. But money in what form? These days, many people are entering a new frontier of financing: crypto-currency. To this point, the blockchain-based monetary form has mainly served the single purpose of theft-proof money storage. It has not seen wider use as a business-funding tool. But Agenus could make history in that regard, with its new BEST offering, a “fincoin” established specifically to finance the company’s product development. Initially set to fund a Phase 3 trial of a single product, a successful BEST program would expand to cover development of other pipeline products.

“Creating this financing vehicle allows accredited investors to invest for the first time in specific development programs, rather than the entire company portfolio,” Armen explains. “It provides existing investors full exposure to the rest of a company’s portfolio without the dilution typical of equity offerings.” Armen makes it clear that the company sees BEST as a way to revolutionize the financing of drug development and “democratize” financing.

The emphasis on individual products in the BEST program actually squares well with the company’s “one-stop shopping” IO-portfolio strategy. Eventually, Agenus plans to offer a separate “fincoin” for each pipeline candidate. Investors will not be taking on the risk of an entire pipeline, but can choose to support a specific product or products out of the company’s broad portfolio.

“The BEST offering is aligned with our overall mission of speeding the development of IO therapies, advancing more combination trials, and expanding our reach to additional indications,” says Armen. “For eligible investors, BEST gives the option to pick products of their

interest for direct investment. For example, with our first BEST offering, investors will have the opportunity to invest in our latest-stage candidate, AGEN2034, our anti-PD-1 antibody.”

Under the program, according to Armen, existing equity shareholders will own the additional value of the select individual product above the BEST shareholders’ implied returns. Equity shareholders will continue to own the remainder of the full product line without the dilution typical of an equity offering. Agenus investors will have more options.

## **FULL-STOP SHOP**

As with the BEST initiative, Agenus has made bold plans for its portfolio of products. Its pipeline, packed with a wide range of cancer immunotherapies, may someday offer one-stop shopping for IO combinations, expressly as an alternative to assembling combinations of separate components from various suppliers. Consider the alternative: The annualized cost of leading IO products such as Keytruda and Opdivo is around \$171,000 each. Multiply that figure several times over with future new drugs expected to join the select group from which physicians compose therapeutic combinations.

The Agenus pipeline has its own PD-1 and CTLA-4 blockers that would compete with the current market leaders, Keytruda, Opdivo, and Yervoy. If that were all, however, it would be logical to ask, “Why bother?” Why duplicate what the clear leaders have done? The answer goes back to the company’s original mission of addressing the individual patient dimension in cancer.

“Our idea contradicts the current rationale of IO,” says Armen.

“Off-the-shelf compounds such as Keytruda or Opdivo work because the individualized component of the immune response is not resident in every single patient, but it is present in some of the patients responding to PD-1 inhibitors. With an anti-PD-1 drug, you are adding a compound to the individualized component that helps immune cells get to the cancer. The PD-1 inhibitor overcomes that blockage in the patient whose immune cells are already trying to target the cancer. That small population now represents nearly \$20 billion in product revenue for 2019.”

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Armen believes checkpoint inhibitors are now effectively treating and curing some patients who were not treatable before the drugs became available. “But how do we take that select group of responders and expand it so that cancer becomes either a chronic disease or a permanently cured disease for most patients? Keytruda or Opdivo alone will not do that. We need a lot more progress beyond PD-1 blockers. That is what our company is aiming to do.”

In other words, Agenus intends to become no less than the hub for IO-drug cocktails, offering off-the-shelf and personalized combination treatments together in various configurations — and at a lower total cost. “Because everything is under one roof, I can ensure responsible pricing in a proprietary cocktail,” says Armen. Some observers may look at the company’s strategy as a house of cards, where the success of all programs hangs on the fortunes of every one. Others could view

it as a well-balanced approach, with solid candidates giving buoyancy to the portfolio across the board. The innovative part is not in developing a unique new technology or product type, but in assembling the right tools from the emergent field.

Look at this from the other direction: If every new IO drug follows the pricing pattern of the current anti- PD-1 or anti-CTLA-4 products, it may come to a point where only people who can afford the shared cost or subsequently raised insurance premiums will get the treatments. “Insurance premiums will go through the roof, and government healthcare budgets also will go through the roof, and neither one of those is a desirable solution,” Armen says.

## **COMMERCIAL CROSSING**

Being a one-stop shop has no exit strategy. If you want to offer definitive combinations of IO therapies, you are in for the long haul, all the way to regulatory review and, if fate allows, from commercial approval onto the market. Agenus envisions moving its products as fast as possible through those steps and marketing them on its own in North America. Global commercialization of AGEN1423, a bispecific antibody targeting immune-resistance pathways, will be in Gilead’s hands, according to the agreement. The deal also grants Gilead options for commercializing one other global product and the right to opt into shared development and commercialization of another product in the U.S.

Agenus is determined to commercialize its anti- PD-1 and anti-CTLA-4 drugs in North America independently, then perhaps license the products to others elsewhere. “We are going through a systematic process of becoming a globally positioned company, but doing it in steps.”

Agenus now employs close to 300 people: 180 at its Lexington, MA, headquarters; 50 in Cambridge, UK; and 60 at its antibody manufacturing facility in Berkeley, CA. Perceptions of its progress depend on when you start counting. From its origins, the company has existed for 24 years, yet remains in the midstages of clinical development. From its “reinvention” in 2014, however, the pace of progress has been impressive in its sheer gathering of new assets for realizing its strategic goals. In its wide array of IO approaches, the current Agenus pipeline is the physical expression of company goals.

In a recent two-day strategy session with his senior management team, Armen reviewed Agenus’ goals from its strategy meeting in 2014. “I went through the list item by item. There were about nine or 10 bullets, and we have fulfilled every item except one. The one was exploring the biosimilars business, and we decided not to do that strategically. That was obviously a very important data point. There are two components of strategy — formulation and implementation. We spent most of the two days not on the formulation, but specifically on the implementation of our already-formulated strategy.”

Now, that phase of company growth has passed, and Agenus has imposed its own steep challenges in shaping its future. What will the company look like in five to 10 years? The one-stop portfolio strategy and the BEST initiative both make it clear Armen and his team want to challenge the industry’s status quo.

“Our industry has accomplished great things — but it hasn’t accomplished exceptionally great things,” he declares. “It’s not just about the industry reaching the trillion dollars in value threshold, it’s what the industry does to earn that. It’s not the dollar value as much as the value created for the people of the world. Healthcare companies — their importance is indisputable. They change quality of life in a very meaningful way. Yet as a group they have not gone through that threshold of value creation. I hope Agenus will be one of the companies that makes it through that threshold.”

The pipeline Armen describes is a dynamic one, where the idea is to anticipate and stay ahead of the swift-rolling tide of obsolescence. “We need speed of innovation because we are reaching a point where obsolescence rates will go up in our industry — all new medicines will become obsolete at a much faster rate than before. We need to keep ahead of this curve.”

The idea of obsolescence, as applied to biopharma products, is interesting. People wonder why Big Pharmas, despite their enormous efforts and funding behind R&D, never seem innovative enough. “If you can hide behind price increases to show profit growth or if you can hide behind making acquisitions and cutting costs and consolidating things in order to show earnings growth, then there’s very little incentive to do the difficult thing, which is to innovate,” Armen says. Agenus has certainly chosen the more difficult path — to stay within the small-company model as it attempts to develop a large-scale innovative portfolio.