THE BILLIONAIRE CHAIRMAN OF VACCINE MAKER MODERNA WANTS TO REINVENT SCIENTIFIC ENTREPRENEURSHIP

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Amy Feldman, Forbes.com, 15 November 2021

Noubar Afeyan launched 70 companies by pushing researchers to ask what if their craziest ideas were true. With $17 billion and a model of "parallel entrepreneurship," he can fund a lot of wild notions.

"Iconstantly say things that are unreasonable and seemingly crazy," says Noubar Afeyan, founder of venture firm Flagship Pioneering and chairman of Moderna. What if, he asked his researchers, microorganisms living in our guts–the "microbiome"–could help cure cancer? What if red blood cells could transport drugs along with oxygen? What if not all viruses were bad? And what if, he asked a decade ago, messenger RNA (mRNA) could be the basis of therapeutics?

"I said, 'You're crazy, it's never going to work,'" recalls Moderna CEO Stéphane Bancel of his first conversations with Afeyan about the subject in 2011. But as Afeyan, an Armenian immigrant by way of Lebanon and Canada, turned on the charm Bancel, who was then CEO of French diagnostics maker BioMérieux, relented and agreed to come to Moderna. "Noubar's genius was not trying to force the issue in my brain, but to make me think that it could change the world and that it was worth the risk," he says.


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Vaccine Billionaire
NOUBAR AFEYAN
"EVERY ONE OF OUR COMPANIES IS BORN TO ASPIRE TO WHAT MODERNA HAS DONE."
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Thanks to its mRNA Covid vaccine, Moderna now is a household name, with 12-month revenues north of $11 billion and a market cap approaching $100 billion. Afeyan, 59, is one of five billionaires associated with it, with an estimated $2.9 billion fortune (Bancel is another, worth some $7.5 billion). For Afeyan, though, the hope is that Moderna isn't a one-off stratospheric success, but just one of dozens of companies that could break out from the work he's been doing at Cambridge, Mass.-based Flagship for the past two decades.

Flagship is a venture capital firm with a total of $17 billion in assets that operates more like an incubator. Through it Afeyan is churning out scientific ideas in biotech, the life sciences and agriculture with the goal of creating and nurturing a half dozen or more companies each year. Most of those companies grow out of those what-if questions that Afeyan loves. "Every one of our companies is born to aspire to what Moderna has done," he told *Forbes* during an interview at Flagship's offices overlooking the Charles River. "Why wouldn't you think you can actually change the world in the particular area you are working on?"

Since Flagship's launch, Afeyan has helped start some 70 companies. Each began life as little more than an idea in a lab. If the idea proves promising enough, Flagship invests, and it operates for a time as a wholly owned subsidiary. The best of these subsidiaries will eventually take on outside investors before (hopefully) going public. So far, 30 of Afeyan's companies have completed the entire process. While Moderna is by far its largest, other publicly traded graduates include Denali Therapeutics (market cap $6.3 billion), which is working on treatments for neurodegenerative diseases; Quanterix (market cap $2.1 billion), which makes tools to measure proteins for disease detection and treatment; and Rubius (market cap $1.3 billion), which uses red blood cells as treatments for cancer and autoimmune diseases.

He calls his model "parallel entrepreneurship," meaning he wants to found multiple companies at a time, not just one or two, but six or eight. As its assets have grown the pace at which Flagship has founded startups has accelerated. Between 2000 and 2005 the firm produced an average of two companies a year. By 2020, Flagship had more than doubled the pace to average of five startups a year. "He's very provocative and very challenging and very demanding," says Simba Gill, CEO of Evelo Biosciences, a Flagship company focused on the microbiome, who first met Afeyan more than two decades ago. "He is very contrarian in all things."

Since 2007, when Flagship adopted its current model, through the first half of 2021, its net internal rate of return, or IRR, was nearly 40%, according to a source close to Flagship. Moderna has clearly super-powered those returns. Even after its recent pullback, Moderna stock is up eight-fold since March 2020. Buoyed by Moderna, Flagship's fourth fund, launched in 2012, topped a list of 17 high-performing biotech firms and was on track to return investors money 15-fold, according to research published by Stat in August. "Both Moderna and Flagship have been among the highest returning investments in history," according to minutes from the pension fund's May 2021 investment committee meeting.

Afeyan is leveraging that success to raise boatloads of new cash. In June, Flagship raised $3.4 billion for a new fund, a giant pool of money even at a time when investment has been flowing to biotechnology and therapeutics. With the new capital, Flagship is ramping up its investments in therapeutics, agriculture and nutrition. It is also building out a new division focused on preemptive medicine, a more personalized, predictive type of preventive health care, as well as health security to better prepare for future threats from infectious diseases. Without the pandemic, Afeyan says, putting his hand on his head, "we probably would not be as hellbent on doing it as we are now."

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The influx of cash will also test the ability of his model for parallel entrepreneurship to scale up even bigger and faster than it has to date. Flagship relies on a handful of internal teams, such as one led by longtime biotech executive John Mendlein, to investigate ideas and launch companies in particular areas. As Flagship has expanded, Afeyan has recruited a bevvy of high-powered executives to help out, both as partners of the firm and as CEOs of the new startups. But he still likes to keep a hand in everything. Even today he remains chairman of Moderna and is on the board of six other companies in the Flagship circle. "Noubar has to find the way increasingly to figure out how to run a bigger organization and keep his finger on the pulse," says David Epstein, who joined Flagship as an executive partner in 2017 after having been CEO of Novartis Pharmaceuticals. "I think it's not natural for him, it's not comfortable….The man is doing many, many things simultaneously.

Like many Armenians, Noubar Afeyan's family moved from country to country, trying to find a safe haven. During the Armenian genocide of 1915-16, in which as many as 1.2 million Armenian Christians living in the Ottoman Empire were killed, Afeyan's paternal grandfather and great uncle were taken away twice, he says. The second time, the German officers who were carrying out the deportations realized his grandfather had blue eyes and spoke German–and helped them to survive. "The Germans took pity on them," he says. "Even though it was the government's policy of carrying this out, the actual officers were revolted by seeing train loads of people being taken to their deaths."

His grandfather escaped to Bulgaria, where his father was born. Years later, as the Communist regime took over Bulgaria, the Afeyans moved again, escaping to Greece before settling in Lebanon in the early-1950s. "He was living a similar life to what I live now. He was not from the country. He was always having to prove himself," says Afeyan. He spent his childhood in Beirut until August 1975, when he fled the civil war with his parents and two older brothers at age 13, this time arriving in Canada.

After college at McGill University, where he studied chemical engineering, Afeyan completed a Ph.D. in biochemical engineering at MIT in 1987. A chance meeting with Hewlett-Packard cofounder David Packard at a National Science Foundation event in Washington, D.C., in 1985 left its mark. Packard, who died in 1996, described himself as a new breed of engineer, a blend of entrepreneur and

innovator. “I was literally mesmerized.” Afeyan says, “I started to learn everything I could about how to start companies.”

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In 1989, Afeyan founded PerSeptive Biosystems, a Framingham, Mass.-based maker of instrumentation used by biotech companies. He was an outlier then, he says, as both a young founder and an immigrant, at a time when neither was an advantage. “If I had thought about it a lot, I am very sure I would not have started a company. It was a very irrational thing to do,” he says. But he recalled Packard’s advice that when a field is brand new, just about any innovation in it will be valuable. “I thought I didn’t have much of a downside,” he says. “The prospect that I would’ve been throwing away a brand-new Ph.D. going into an area that would’ve failed—that thought never occurred to me.”

PerSeptive developed leading-edge technology in protein analysis, and grew to $100 million in revenue before Afeyan, sold it to scientific instruments conglomerate Perkin-Elmer for $360 million in 1998. He became chief business officer of Applera, the successor company to Perkin-Elmer’s life sciences business, but was soon thinking about his next move. Many founders become serial entrepreneurs, starting companies and moving on, sometimes in rapid succession. But Afeyan wondered if he could create a structure to start multiple companies at one time, always having multiple early-stage ideas and potential startups percolating in the labs.

“If you do something in parallel, you are forced to get to the essence of it,” he says. “I think of it as chess. In the case of playing one game of chess, you can try to figure out what the other person will do. If you play parallel chess, you have got to get to the essence. You cannot procrastinate over the particular move. That mindset of parallel entrepreneurship to me was a provocation.”

In 1999, Afeyan founded the predecessor company to Flagship Pioneering and set up shop in an office park in suburban Cambridge. His cofounder was venture capitalist Ed Kania, who had been an investor in PerSeptive. “It was one thing for me to . It was another to make it a process,” Afeyan says.

Afeyan, who became a U.S. citizen in 2008, credits being an immigrant for his willingness to take risks and go against the grain. “The seeming courage it would take to do these things is rooted in being unrooted,” he says. “Part of it is an innate comfort with discomfort and with not thinking that everything has to be just so.

At the time of Flagship’s founding two decades ago, biotech was out of favor and so-called “platform companies”–that worked on a concept like mRNA rather than a specific drug–were the most unpopular. “It was a very difficult time for biology. The dotcoms were infatuating the markets.

In biotech and VC, people were saying, 'the era of biotech is over, the era of the platform is over. We have learned that none of that has worked,'" recalls Doug Cole, a medical doctor and Flagship's managing partner who joined Afeyan as one of the first employees in 2001.

But Afeyan didn't care what anyone else thought. "Noubar has always fundamentally believed that you can change the world with platform science," says Evelo's Gill. "Everybody loves Moderna, but tend to be something that is in fashion or out of fashion. But that's the way Noubar thinks, and he has stuck with it the whole time."

Over time, Afeyan set up a structure for brainstorming new companies. He starts with those what-if questions. Draw a circle around what currently exists, Afeyan says, and then draw a bigger circle around what's adjacent to that. "What's outside that is where people think it is reckless to work," he says.

And that reckless zone is Afeyan's sweet spot because that's where the big breakthroughs will happen. There's also a structure to how Flagship's researchers consider dozens of ideas, accepting some and rejecting others. Afeyan describes the process as Darwinian. As the firm's researchers explore ideas, they'll change their approach–or even what they're working on–with little regard for how the outside world might view such seeming flip-flops. "All we are doing is running an evolutionary process," he says.

Ideas that survive–as a total of 89 have–get numbers rather than names to keep founders from falling in love with a pet project that may need to be killed. The firm files intellectual property claims (most ideas generate multiple patent applications) to stake out its turf and invests $1 million or $2 million max. Flagship filed 341 patent applications in 2020, more than double the number it had filed two years earlier; in the first half of this year, it cranked out 379 patent applications. If the idea proves out in the lab, Flagship gives the new company a name and commits $20 million or more to it as a wholly owned subsidiary. To date, 70 companies have been formed from those 89 ideas.

As the companies grow, Flagship brings in outside investors, typically raising $100 million or more, with a view toward ultimately going public. By incubating its own ideas and doing all the seed and early stage venture funding itself, Flagship typically still owns 50% or so at the time of its startups' IPOs, according to Afeyan. "It's a very different model," says Avak Kahvejian, a general partner at Flagship (and distant cousin of Afeyan's). "Noubar invented the model, if you will, and essentially trained us in doing this."

Consider Flagship's work in the microbiome, the flourishing microorganisms that live within us, especially in our guts. While scientists had talked about the microbiome for years, when Afeyan first broached the idea in 2008 of exploring its role in disease, including autoimmune diseases and cancer, it was pretty far out on the fringe. After an early exploration went nowhere, Flagship launched its first microbiome startup with Seres Therapeutics, which is creating therapeutics to restore health by repairing the function of an imbalance of microflora, in 2012. Today, Flagship has

created a half-dozen microbiome companies, including Evelo (founded 2014), Kaleido Biosciences (2015) and Senda Biosciences (2016). This remains a long game, however, as researchers work out the science and go through clinical trials. Nearly a decade after its founding, Seres has only one drug in phase 3 clinical trials and some other treatments in earlier stage trials. The publicly traded company has a market cap of $710 million.

The work in the microbiome, in part, led to more recent work on viruses as Afeyan and his team questioned whether there are viruses in our bodies that aren't pathological. "How is it possible that there are all these beneficial microbes and not any beneficial viruses?" Afeyan asks.

The answer matters because in gene therapy, treatments are delivered by viruses and those viruses have downsides. Afeyan wondered if a safe virus could replace the existing viruses in that role. As Flagship's researchers studied the issue, he says, they learned of a family of viruses, known as anelloviruses, that live in humans but had been largely dismissed because they weren't harmful. The research became idea number "FL46" within the firm's labs, and launched as Ring Therapeutics in 2017. In July, Ring raised $117 million, bringing in T. Rowe Price among other investors.

Not everything goes smoothly, of course. Flagship has shut down four companies in which it invested $10 million or more, as well as 13 early-stage startups in which it had invested less than that amount. This past April, for example, Ohana Biosciences, a fertility company that focused on sperm-based treatments, shut its doors and laid off most of its staff a little over a year after emerging from stealth.

Some bigger bets have gone sideways too. Indigo Agriculture was founded in 2013 to use microbes to make seeds more productive. It raised $1.1 billion, a huge sum for an agricultural startup, but has struggled to get its operations on track. In September 2020, Ron Hovsepian, the former CEO of software firm Novell who joined Flagship as an executive partner two years earlier, took over as CEO. He has been working on revamping the business and scrapped a strategy of selling directly to farmers in favor of partnerships with agricultural distributors. "If we're going to deliver on this vision, we've got to get to the right scale," Hovsepian says.

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Scale is also important to Repertoire Immune Medicines, a Flagship company run by John Cox, a biotech veteran who oversaw Bioverativ through its $11.6 billion sale to Sanofi. Repertoire is working to understand the inner workings of the immune system. Its focus: T cells, a type of white blood cells that helps protect the body from infection. "The underlying cause of most autoimmune diseases is related to T-cell misbehavior," Cox explains. "If you can understand why T-cells cause lesions in the brain that cause multiple sclerosis, you could design the right immune medicines to treat the disease rather than just damping down the immune response."

That's a classically big idea for Afeyan, and Repertoire has now raised more than $350 million from investors that include SoftBank and the Alaska Permanent Fund to pursue it. Like other Flagship companies, it's also a so-called "platform" company, something that Afeyan argues reduces the risk of the startups in its portfolio and allows any of them to shift from one area to another as the need arises, as Moderna did with Covid-19 vaccines.

"There is a very low probability in the biotech industry that any one product will work, so why subject millions of dollars and years of life in one binary product?," he says. "Moderna raised $1 billion and it engendered skepticism, putting it mildly. They said, 'How can anyone give you money?' The vaccine was developed two days after sequence. Where's the value? The vaccine or the platform? An investor today will believe the vaccine. I will go to my grave believing it is the platform."

Comments

Bo – 2022-02-15 21:35:16
In yesterday's Forbes... Moderna stock crash: Losses top $140B as insiders sell millions of dollars in shares
https://www.forbes.com/sites/jonathanponciano/2022/02/14/moderna-stock-crash-losses-top-140-billion-as-insiders-sell-millions-of-dollars-in-shares/?sh=78eae3c4106b

Pat – 2022-01-23 18:45:37
Also from FORBES -- In today's news (1/23/22) Moderna stock crash intensifies: Losses top $130 billion after scientists find Covid boosters aren't halting omicron infections
https://www.forbes.com/sites/jonathanponciano/2022/01/21/moderna-stock-crash-intensifies-losses-top-130-billion-after-scientists-find-covid-boosters-arent-halting-omicron-infections/?sh=496c024def5c

Masis – 2021-12-15 14:32:48
Dear Gerard, I believe, long before Charles de Gaulle, in 1906 the Armenian General Benevolent Union (AGBU) adopted the following motto: "In unity is strength".

Gerard Paraghamian – 2021-12-15 01:40:50
The great statesman of France Charles de Gaulle once said, "L'UNION FAIT LA FORCE", Unity (togetherness) is strength. Where is togetherness, unity, where is strength?

Hagop – 2021-12-01 22:49:48
"Comments containing inappropriate remarks, personal attacks and derogatory expressions are discarded."

Pat – 2021-11-28 01:20:49
If we live through the next few years, the truth will emerge for us to see the Great Reset and Noubar Afeyan for what they are. What would make us proud would be to discover that Noubar Afeyan has contributed some of his vast fortune to the military defense of Armenia (and that the Aurora Humanitarian Initiative champions Armenian humanitarians)!

Hagop – 2021-11-27 16:37:05
"Comments containing inappropriate remarks, personal attacks and derogatory expressions are discarded."

David – 2021-11-26 19:35:02
I would like to see prominent, active Armenian Americans such as Mr. Afeyan speak out against US policies which kowtow to Turkey and Azerbaijan. For example, Turkey and Azerbaijan have both deployed the worst kinds of terrorists, including ISIS, against Armenians. And even the US officially admits that Turkey supports ISIS and al-Qaeda. Where are our Armenian American activists? Where are our "friends" in Congress? Turkey and Azerbaijan are getting away with murder. And Israel is an all-out backer of Azerbaijani aggression against Armenians. And it has the backing of the top Jewish American organizations in this regard. Where's the outrage?

Roupen Dekmezian – 2021-11-25 22:11:10
Telo & Co and Hagop are making derogatory remarks which should not have appeared in this platform. But these remarks are amusing since their authors seem to be clearly uninformed of the latest advances in molecular biology. Both commentators are likely Armenians, and I sense jealousy and partisanship as motives behind their stance. Shame on them. Afeyan will prove to be one of the great scientist/entrepreneurs like Elon Musk. We should be so proud of him. Roupen Dekmezian, M.D. Houston, Texas

Hagop – 2021-11-25 16:46:46
He is destined to future Nuremberg trials with his paisanos Dr. Faucet and Bill Hates.

Telo & Co – 2021-11-25 01:43:43
Mr Afeyan should be happy to know that there are contrarians other than himself who are extremely skeptical about the efficacy of experimental genetic modification injections he has helped to invent with the help of the pharmaceutical mafia. He is no hero in our view.