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Alnylam (ALNY)'s John Maraganore Provides Leadership for RNAi Development and Biotech Industry
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CAMBRIDGE, Mass. – **Alnylam Pharmaceuticals** (**ALNY**) is led by a chief executive with a bold vision to use RNA interference (RNAi) to develop therapies that will lead to the end of rare diseases, such as Transthyretin-related hereditary (TTR) amyloidosis and various disorders of the blood.

John Maraganore, a former research scientist who headed molecular biology development at Boston-based **Biogen** (**BIIB**), has served as chief executive officer of Alnylam since 2002. Maraganore has overseen the growth of Alnylam since its days as a startup to now the largest RNAi biotech company in the world.

In an exclusive interview with **BioSpace** (**DHX**), Maraganore said he came to the company based on the innovative science the company was founded upon and wanted the opportunity to blaze a trail in an area that hadn't been heavily explored. While new paths and technologies take time, Maraganore said there's a sense of urgency around what Alnylam does because patients are counting on them.

"We feel strongly we have to get these drugs to patients. We're stewards of this science and have to be excellent. I'm the lucky guy who gets to lead this effort," Maraganore said.

Maraganore is now guiding the company's first RNAi therapy through regulatory approval. Alnylam is currently developing its Phase III lead candidate Patisiran for TTR amyloidosis at a small lab in Cambridge. The company anticipates Patisiran to clear regulatory hurdles by next year. In fact, by 2020, Maraganore anticipates Alnylam will be a multi-product company. He said the company has a "real engine" to develop new medications to treat various diseases.

"This is an exciting time for Alnylam, but more importantly for the patients facing the disease. We're committed to making a difference in their lives," Maraganore told BioSpace.

While at Biogen, Maraganore invented and led the discovery and development of Angiomax (bivalirudin for injection, formerly Hirulog) currently marketed by **The Medicines Company** (**MDCO**). However, following the failure of an initial Phase III trial for bivalirudin, Biogen shifted Maraganore's focus to a more business-oriented path as director of market and business development at Biogen. It was that shift in responsibility that would ultimately lead him to Alnylam and to become one of the leading voices for RNAi therapies.

RNAi is a natural mechanism of gene silencing. Much of the interest in RNAi is based on the fact that the RNAi mechanism operates upstream of protein production by silencing the mRNA that codes for such proteins, thereby preventing the disease-causing proteins from being made in the first place. By way of analogy, the RNAi approach is akin to "stopping a flood by turning off the faucet" as compared with today's medicines that simply "mop up the floor," Maraganore said.

Developing RNAi therapeutics to this promising point has taken more than 10 years and $1 billion "to figure out the biological mechanism."

"Now we can harness the technology to make medicines," Maraganore said.

Maraganore said the company has weathered much in its 16 year history, including a tough period around 2010 when a number of companies like **Merck** (**MRK**) and **Roche** (**RHHBY**) abandoned RNAi research. Because Alnylam is a much smaller company, it was able to take the risk and continue developing RNAi therapies.

"That risk is part of an important element for a company like ours. Those other companies got into RNAi and it failed, but we're succeeding because we took the risk. We have a realization that if we don't succeed, we die. That really clear … sharp… poignant fear and mortality is something that drives us to be successful. We can't just give up. It's a critical element of our success story to persevere," Maraganore said.

That innovative spirit earned Maraganore the **2016 Henri A. Termeer Innovative Leadership Award** from the **Massachusetts Biotechnology Council**. The award is given to an industry leader "who has a strong presence and commitment to growth in Massachusetts, actively supports community-based organizations, contributes to science education to prepare the future workforce, and creates a positive work environment that fosters motivation and collaboration," according to a **MassBio** statement.

When those pharmaceutical companies abandoned RNAi in 2010, Maraganore said that a number of potential investors who thought the technology would never pay off also walked away. But now that Alnylam is showing success with their RNAi therapies, investors and larger pharma companies are taking a closer look at Alnylam's research.

But that interest doesn't mean Alnylam is looking to be snapped up by a larger pharma company. Maraganore said the company remains committed to being an independent company, however, it has struck deals to support its research. In 2014, **Sanofi** (**SNY**) staked $700 million on Alnylam's technology in exchange for a 12 percent of the company. That funding is helping Alnylam's scientists push their research to potential commercialization.

"At the end of the day you can't fulfill your commitment to bring these medicines to market if you give someone else the keys to the car," Maraganore said.

It's that spirit of wanting to lead the development of RNAi therapies that keeps Alnylam focused on its mission of developing new drugs. Although he knows late stage trials can fail, Maraganore recognizes that any setback is a stumbling block on the pathway to developing a treatment for patients who have few treatments. Alnylam's mission, he said, is as a pioneer to innovate and discover necessary treatments for diseases from "the rare to the common." Maraganore also recognizes the need to ensure these often expensive medications are not financially out of reach of those who need them.

In September 2015 Maraganore **blasted** **Martin Shkreli** and **Turing Pharmaceuticals** for the 5,000 percent price hike on its 65-year-old toxoplasmosis drug, Daraprim. In an interview with CNBC, Maraganore said the pharmaceutical industry focuses on innovation for profit, rather than price hikes of decades-old drugs. Alnylam is taking a stance on innovative pricing during a coming MassBio panel. He said the company believes medicines that are "transformative and effective" should be valued correctly by payers. If those medications are not working though, patients should not be penalized financially for them.

Alnylam's innovative techniques include using its RNAi therapeutics to develop treatments for multiple illnesses, including TTR, hemophilia and other bleeding disorders, as well as hepatic porphyrias, beta thalassemia, hypertension, liver infections and more. Alnylam is **developing** an RNAi therapeutic targeting PCSK9, a protein regulator of LDL receptor metabolism, in collaboration with The Medicines Company. On Nov. 11, Alnylam announced that collaboration showed positive results in its Phase I clinical trial of ALN-PCSsc. If the drug candidate moves forward, and all indications are that it will, the drug could take on Amgen's anti-cholesterol drug Repatha and Praluent, which are both PCSK9 inhibitors. Alnylam's pipeline drug blocks the creation of PCSK9 in the liver using RNAi.

Many of the company's programs are still listed as being in the development stage, according to information on its website. However, in addition to the Phase III trials for patisiran, the company also shows a Phase III trial for its hemophilia candidate Revusiran. Alnylam also has ALN-HBV in the **pipeline** for hepatitis B virus (HBV) and ALN-HDV for the treatment of hepatitis D.

Last week, Alnylam announced a **Phase I/II trial for ALN-GO1**, a subcutaneously administered investigational RNAi therapeutic for the treatment of Primary Hyperoxaluria Type 1. ALN-GO1 has been granted Orphan Drug Designation for ALN-GO1 from the **European Medicines Agency** and the **U.S. Food and Drug Administration**. PH1 is an inborn error of metabolism that results in excessive oxalate production, kidney failure and further organ damage for some patients in infancy and in most patients by their mid-twenties. It effects about 5,000 people worldwide.

Maraganore said Alnylam's RNAi therapy has given the company tremendous momentum and is the reason the company is undergoing a rapid expansion. By the end of 2016 Maraganore said the company should have more than 500 employees and they anticipate that number to swell to more than 2000 by 2020.

"We're experiencing some dramatic and rapid growth of the company in a manner which is exciting and exhilarating. We want to make sure we're growing with a focus on hiring the best people," Maraganore said.

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