BUILDING A BUSINESS

Reflections on Alnylam

Recollections from an extraordinary 19-year journey guiding a tiny startup with an unproven therapeutic modality into a mature drug company with marketed products and >1,600 employees in nearly 20 countries provide lessons for those seeking to create the culture and values that are core to biotech success.

"The reasonable man adapts himself to the world; the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man."
—George Bernard Shaw

On 31 December 2021, I left Alnylam Pharmaceuticals after a 19-year journey as its founding CEO. In this personal reflection, and as Alnylam embarks on its 20th year as a company leading the RNA interference (RNAi) revolution, I want to highlight the highs and lows of building a company pioneering a new therapeutic modality from early startup to a fully fledged, independent global biopharma, something rarely achieved in biotech history. The core technology of RNAi, first described by Andrew Fire and Craig Mello[1] in the worm *Caenorhabditis elegans*, held much promise, but the field faced substantial hurdles, including intellectual property (IP) battles, learning how to deliver our drugs to relevant organs and cell types, showing animal and then human proof of concept (POC) and building a robust pipeline. And we would need to do that while maintaining access to capital throughout.

Today, with four RNAi therapeutics drugs launched around the world, a fifth drug program in registration and over a dozen programs in clinical development, it is gratifying to think that the Alnylam team was able to overcome these hurdles as we learned how to build a pure innovation-based company (Fig. 1). Some of the lessons may have been our own, but many more are common to building any enterprise: the need for clear vision and mission, strong founding IP, a robust scientific platform to exploit and a resilient culture to withstand the challenges that inevitably arise in taking novel therapeutics to market.

New beginnings

In early 2001, while at Millennium Pharmaceuticals, I received a phone call from Phil Sharp, a well-known Massachusetts Institute of Technology (MIT) professor and Nobel laureate. Phil and I had a longstanding relationship from my decade-long tenure at Biogen, where he was a founder, board director and chair of the scientific advisory board. In our call, Phil wanted to know if Millennium was interested in learning more about the work he and collaborators had conducted on RNAi and mammalian cells. I didn't know much about RNAi at the time and had the general impression that it was a biological process limited to invertebrates and plants.

Within a matter of weeks, a group of Millennium scientists met with Phil, Dave Bartel (Whitehead Institute), Phil Zamore (University of Massachusetts) and Tom Tuschl (then at the Max Planck Institute, now at Rockefeller University). Tuschl presented the findings from his laboratory (later published in *Nature* in May 2001[2]) showing that synthetic small interfering RNAs (siRNAs) could mediate targeted gene silencing through a sequence-based mechanism in mammalian cells. The significance of the findings was immediately clear. For a company toiling in post-genomics research, as Millennium was, a tool to interrogate gene function by specifically silencing any single mRNA would be immensely powerful.

Days after the meeting, I called Phil to inform him that Millennium would be interested in an exclusive license to the RNAi IP for research use and would be open to investing in a new company to explore the therapeutic potential of siRNA. But after conferring with his collaborators and MIT's technology license office guru, Lita Nelsen, Phil proposed a nonexclusive research license and indicated reluctance about starting a therapeutics company. Millennium thus became one of the first licensees for the 'Tuschl I' and 'Tuschl II' patents for research use.

Within a year, I began to hear of Alnylam's beginnings. Christoph Westphal, then at Polaris Ventures, and John Clarke of Cardinal Partners had seeded the new company with a $2.5 million Series A round of financing. Christoph brought intensity and passion to this effort, while John brought some needed gray hair and wrinkles. Phil and his four collaborators were joined by the Scripps Research scientist and bioentrepreneur Paul Schimmel as company founders. Paul (at Phil's request) was there to help navigate the world of startups, and he has the distinction of having changed the company's blasé original name of 'Precision Therapeutics' to 'Alnylam Pharmaceutics'. Paul's favorite aunt was an Arabic scholar, and "al nilam" means "string of pearls" (a nod to the strands of nucleotides in RNA) as well as being the name of the central star of Orion's belt.

In a call with Jean-Francois Formela and Peter Barrett at Atlas Ventures in the early summer of 2002, I learned that they had joined Bob Nelson at Arch Ventures as Series B investors to round out the Alnylam syndicate. They wondered if I might be interested in joining Alnylam as CEO, and suggested a follow-up meeting with Phil to hear his thoughts on the science. It's hard to decline a meeting with Phil, and I spoke to him later that summer. Although content at Millennium, I began to dig into RNAi further, clearly recognizing its potential to create a new class of innovative medicines. At the same time, it was clear that achieving delivery of siRNA would be the technology's key hurdle.

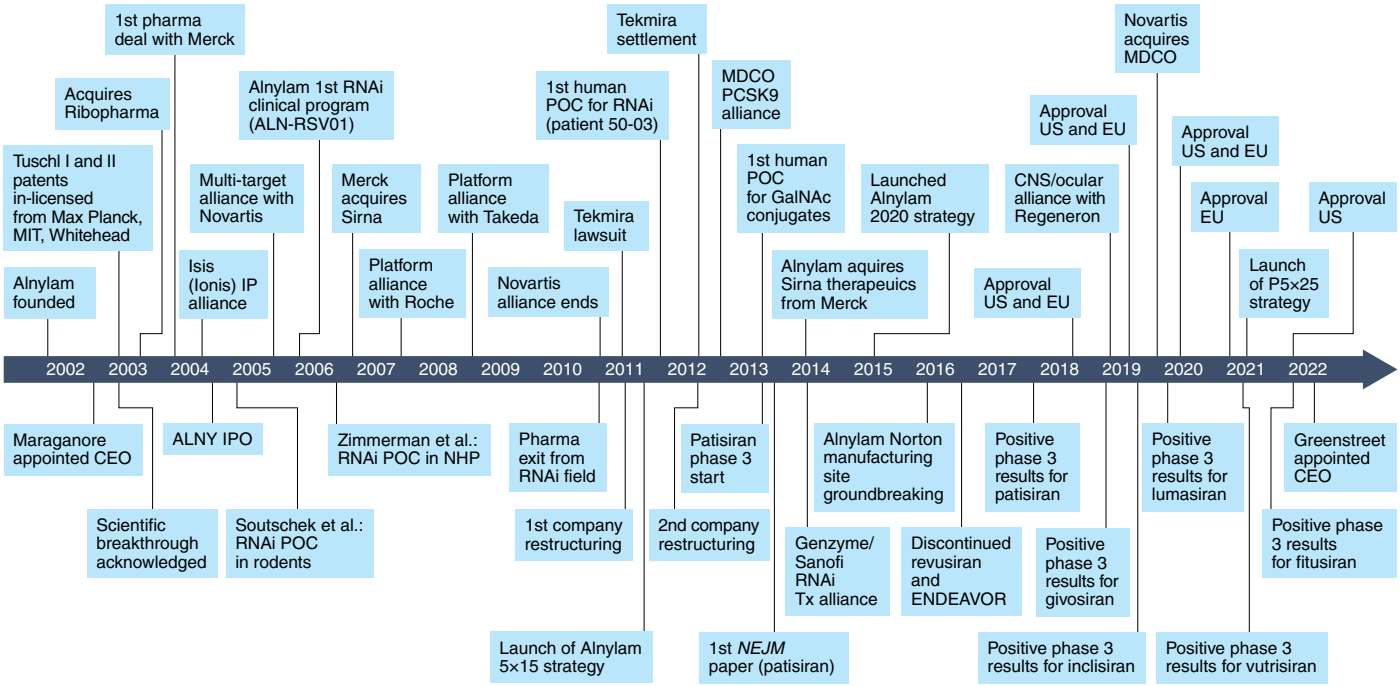

Fig. 1 | Alnylam timeline. Marking the high points in Alnylam's 20-year journey. ALNY, Alnylam; GalNAc, *N*-acetylgalactosamine; MDCO, The Medicines Company; NHP, nonhuman primates; *NEJM*, *New England Journal of Medicine*; POC, proof of concept; Tx, therapeutics.

Driving into work each morning, I couldn't stop thinking about the potential of RNAi as a new approach. It was like being asked to start a monoclonal antibody therapeutics company in the late seventies or early eighties with founding technology (and IP) from Georges Kohler and César Milstein. Yet many friends and colleagues (including my two older children) thought I was making a mistake and cautioned against the move. After the 'genomics bubble' burst, the biotech sector was in a dark winter, and investment in novel science was highly disfavored. Could the challenge of achieving siRNA delivery be overcome and done in a reasonable amount of time? Would the new venture succeed in raising the billions of dollars needed to create a successful biotech? Would it be possible to escape the vagaries of conventional drug discovery and build a reliable, reproducible and modular R&D platform that could deliver sustainable innovation? These questions swirled in my brain.

My decision was also complicated by the exciting period Millennium then found itself in. The first-in-class proteasome inhibitor Velcade (bortezomib) was in line for an accelerated approval as a therapeutic for multiple myeloma, and Millennium CEO Mark Levin wanted me to stay and help the company enter its new commercial stage. Yet Mark was also a friend and a mentor, and he encouraged me to pursue what excited me most. What I kept coming back to was that if the technology hurdles could be conquered, RNAi therapeutics were too great of an opportunity to walk away from.

On a personal level, I had recently gotten remarried. My Alnylam CEO offer letter was sent to my honeymoon suite in Mauritius. I felt I was in a period of new beginnings. I decided to take the plunge.

Maneuvering the IP thicket

At my first board meeting as Alnylam CEO in December 2002, I presented my vision and mission to crystallize the company's aspirations and direction. This was something Levin had taught me at Millennium. Our vision: Harness a revolution in biology for human health. Our mission: Build an independent, top-tier biopharmaceutical company founded on RNAi. Remarkably, those official words have not changed since.

I knew from the beginning that Alnylam would need to raise substantial capital from both investors and pharmaceutical partners to bring RNAi therapeutics to patients. We planned on needing $1 billion to $2 billion in capital and a period of 10–20 years to achieve this goal. I also knew that having a strong IP position on this emerging science would be critical.

Perhaps it wasn't surprising, then, that I spent my first day on the job in Munich, meeting with the Max Planck technology licensing office (then known as Garching Innovation). Our objective was to finalize license agreements for the fundamental Tuschl I and II patent families, where Max Planck had taken the lead on licensing rights for therapeutic applications on behalf of the four academic institutions (the others being MIT, the Whitehead Institute and the University of Massachusetts). It was appropriate for Max Planck to take the lead because the critical Tuschl II patent family was its sole invention, whereas Tuschl I was jointly owned by the four institutions.

Max Planck had a strong interest in seeing the invention generate economic growth in the EU. Accordingly, Max Planck asked us to establish EU operations for Alnylam within a few years to secure a license. This was hardly an easy pill for us to swallow, especially in a difficult funding environment, but we had no choice. To finalize the agreement, Max Planck needed the consent of the other three co-owners. UMass didn't agree to the terms and, after a competitive bidding process, ended up licensing its Tuschl I rights to Sirna Therapeutics—another RNAi upstart that repurposed itself from Ribozyme Therapeutics—for >$6 million in cash. Our license thus became co-exclusive with UMass on Tuschl I, but exclusive on Tuschl II.

Next, we needed access to another early IP family in the field: the Kreutzer–Limmer patent held by the German startup Ribopharma. The Kreutzer–Limmer patent had a remarkably early priority date in 1999,

well before Tuschl I and Tuschl II and just after the Fire and Mello patents that were made broadly available in non-exclusive licenses from the Carnegie Institute. In early 2003, we met with Roland Kreutzer and Stefan Limmer to discuss a potential merger with Ribopharma. We then visited their facilities in Kulmbach and were impressed by the scientific team they had assembled, led by biochemist Hans-Peter Vornlocher. Merging with Ribopharma would extend our patent leadership, enhance our research capabilities and fulfill our Max Planck obligations in Europe in one fell swoop. We announced the Ribopharma merger in July 2003.

Within a year, we were preparing for our initial public offering (IPO), and we also added my former Millennium colleague Barry Greene as chief operating officer (he later became president). Shortly after our S-1 filing with the Securities and Exchange Commission (SEC) in early 2004, we were surprised and puzzled by a claim from Isis Pharmaceuticals (now Ionis) stating that our activities related to an siRNA therapeutic infringed certain Ionis chemistry patents. We were in the early stages of R&D and years away from commercializing an siRNA therapeutic and thus covered under the 'safe harbor' from infringement claims afforded drug developers. Also, we had done extensive diligence on the IP landscape for RNAi at founding and believed we could operate outside of any existing IP. Yet we did recognize that the Ionis claim could affect our IPO, so we began negotiations and entered a broad cross-licensing agreement creating 'pax oligo' for years thereafter. We then moved forward with our IPO plans.

One would have thought that the IP story was over at this point, but things suddenly changed when pharma giant Merck bought Sirna for $1.1 billion in late 2006. A license to Tuschl II would still be needed by Merck for them to commercialize an siRNA therapeutic. Efforts to import and prosecute Tuschl II patent claims in the Tuschl I applications resulted in Tuschl II claims unable to be granted. The only way forward was through the courts, and led to the 2009 lawsuit *Max Planck and Alnylam v. UMass, Whitehead, and MIT*. It was settled two years later, and multiple Tuschl II patents were granted thereafter.

But it wasn't until 2014 that the saga of the Tuschl IP estate was finally put to rest, when Alnylam bought Sirna from Merck for $175 million, bringing exclusive rights to both Tuschl I and Tuschl II firmly inside Alnylam. Merck was convinced that Sirna's technology was best served in the hands of a committed, entrepreneurial company like Alnylam. They were right! In hindsight, perhaps we should simply have paid more in upfront cash to UMass and outbid Sirna back in 2003, but on the other hand the acquisition of Sirna, which had been nestled within Merck and coddled with >$1 billion in additional investment, brought in valuable technology and talent. Of course, the stories of Alnylam and Sirna also provided a rare lesson on the importance of culture in biotech (Box 1).

Box 1 | A 'randomized, controlled study of culture' in biotech

Sirna Therapeutics (né Ribozyme Pharmaceuticals) was born in early 2003 following a recapitalization of the business by a number of blue-chip investors, including Venrock, Oxford Biosciences and TVM. Sirna became Alnylam's archrival, often competing for IP and business deals. Behind the scenes, I was able to maintain a cordial and friendly relationship with Sirna CEO Howard Robin (now CEO of Nektar Therapeutics), including an annual lunch at the Clift Hotel during the J.P. Morgan Healthcare Conference in San Francisco. By 2006, Alnylam and Sirna had similar characteristics: each with about 100 employees and market caps around $500 million, and each with two or three validating pharmaceutical partnerships.

In October of that year, Merck acquired Sirna for $1.1 billion, representing a lavish 102% premium. The Sirna acquisition was a defining event for the RNAi field, but it also created what I refer to as a 'randomized, controlled study of culture' in biotech. Indeed, over a roughly seven-year period from 2006 through early 2014, Alnylam remained independent, invested ~$500 million in its science, created $4 billion in market value and filed eight INDs (two of them for what are now marketed products). In contrast, the 'Sirna arm' of the study invested ~$1.5 billion into the science but yielded no filed INDs and was purchased by Alnylam in 2014 for $175 million—a fraction of Merck's acquisition and investment costs.

These remarkably different outcomes underscore the power of culture in biotech. At Alnylam, we were willing to take appropriate risks, advancing even 'imperfect' molecules into development to safely learn from early human studies. Furthermore, as a focused pure play, Alnylam had a 'fear of mortality' that made it essential for us to succeed in bringing RNAi therapeutics to market. But Sirna was part of a larger company, needing to fulfill certain criteria around drug candidates, and RNAi was very far from a 'life or death' proposition. The acclaimed management consultant Peter Drucker once claimed that "culture eats strategy for breakfast." In the case of Alnylam's story—and perhaps many biotechs—that was an understatement!

Rational exuberance

The early years of Alnylam were marked by a 'rational exuberance' about RNAi as a potential disruptive technology for new medicines. In early 2003, *Science* magazine awarded siRNA the title of 'Molecule of the Year' and *Forbes* published an article on RNAi calling it "Biotech's Billion Dollar Breakthrough." The sentiment at the time is reminiscent of today's enthusiasm for gene-editing technologies. For Alnylam, the strong interest from investors and pharmaceutical companies allowed us to raise capital and form solid partnerships well before we had clinical data. We were also able to attract a strong team of founding scientists, including Muthiah 'Mano' Manoharan, our lead chemist, from Ionis; Victor Kotelianski, from Biogen; and Rachel Meyers, from Millennium.

We were short lived as a private company. We had raised a combined $17.5 million in our Series A and B rounds (both in 2002) and $24.6 million in a Series C associated with the Ribopharma merger in 2003, when we added Abingworth as a new investor. We then turned to the public markets. Notwithstanding enthusiasm for RNAi, most companies going public at that time had assets in phase 2 or 3, if not already on the market. We completed our IPO in May 2004 in a shaky market for biotechs (we had debated whether to delay the flotation), raising $30 million at a $98 million pre-money valuation (a ~50% discount to our offer price) and a share price of $6. This made us the first preclinical company to reach the public markets since the genomics bubble had burst. IPOs are often romanticized by company management and boards as a special 'Kitty Hawk' moment, but in reality they are simply financing events. To us, it was key that we would have sufficient news flow with science and pipeline progress, and partnerships to garner continued interest by public investors. We were confident that we would.

Alnylam also benefited from partnerships with major pharmaceutical companies. Having watched Millennium's remarkable deal-making over the prior decade, I recognized that pharma alliances were mostly about funding and external

validation and, if structured correctly, could be associated with a minimal 'tax' on the company's abilities to advance its own science and pipeline. Although there are notable exceptions, rarely do partnerships provide the 'big brother' benefits (such as drug discovery and development expertise) often advertised.

Our first deal was with Merck in late 2003. Stephen Friend, then Merck's head of molecular profiling and cancer research, was keen to access RNAi technology for in vivo target validation. We were reluctant to do a deal limited to the use of RNAi as a 'tool', so we expanded the partnership to include work on therapeutic targets contributed by Merck. It brought us only $7.5 million up front, but it still represented key validation for Alnylam's science. RNAi also caught the eye of Mark Fishman, then head of the Novartis Institute for Biological Research (NIBR). Mark had a much larger appetite for RNAi therapeutics and tasked his business development chief, Jeremy Levin, to evaluate potential deals with either Alnylam or Sirna Therapeutics. Alnylam won the bid in a $56.8 million upfront deal, including a purchase of 19.9% of the company's shares. Compared with Sirna, we presented as a stronger scientific partner, and we were also a neighbor, right there in Kendall Square in Cambridge. In the alliance, Novartis obtained rights to develop RNAi therapeutics toward 30 targets. At the time, we struggled with the scope of rights granted to Novartis, but ultimately decided that the range of opportunities for RNAi would be well above that number.

Perhaps in response to our Novartis deal, Merck soon acquired Sirna through a competitive process. After reviewing the associated SEC filings linked to the Sirna acquisition, we surmised that Roche was also a bidder and reached out to them to explore interest in a transformative deal for nonexclusive access to our platform (an unprecedented design in many ways). We entered a deal in which Roche won nonexclusive access to Alnylam IP for a limited number of therapeutic areas and also acquired our Kulmbach facility (formerly Ribopharma) for an upfront payment of $331 million. Importantly, Alnylam retained ownership and control of the Ribopharma IP. Barry helped drive the deal to completion after I managed to get alignment with Roche and our board. A year later, we forged a similar nonexclusive platform deal with Takeda, in one of the largest technology deals with a major Japanese pharma company. Again, Barry was key to success here, but he was also able to partner with Jason Rhodes, who had joined as our head of business development.

For a while, it seemed like nothing could stop the RNAi train. RNAi therapeutics had enormous luster as a potential new class of medicines, and many pharma R&D chiefs just couldn't miss out on the opportunity. Alnylam's balance sheet was bolstered with hundreds of millions of dollars in cash, but things began to turn for the worse at the start of the new decade. Our pharma partners were finding delivery to be more challenging than originally hoped, in part due to their desire to fit RNAi into their established therapeutic areas (for example, oncology) as opposed to simply following where the science and technology might lead them. Potentially easier programs targeting disease genes in the eye or lung with 'direct delivery' and disease genes in the liver where 'systemic delivery' was showing early promise were not enough. When confronted with an opportunity for a broad RNAi alliance on liver gene targets, one pharma R&D chief lamented that there were just too few targets of interest!

The RNAi therapeutics downturn began in September 2010, when Novartis declined to exercise its $100 million option to acquire broad nonexclusive rights to Alnylam's technology. After this, a combination of leadership changes and recession-driven profit-and-loss pressures at Roche led it to jettison its RNAi investment after just a three-year, toe-dipping sojourn. To say the least, the external sentiment about RNAi turned sharply sour. In early 2011, *New York Times* science reporter Andrew Pollack described it best in an article titled "Drugmakers' Fever for the Power of RNA Interference Has Cooled." I keep a paper copy of this article by my desk to this day.

With pharma exiting the space, so did many investors. ALNY began trading below cash, and an important source of capital dried up for us. On the one hand, we had accumulated a strong cash balance sheet from the business alliances and equity-based financings. On the other, we still had a long way to go, with the company rapidly approaching its tenth anniversary with no human POC in sight. We had no choice but to reduce our workforce so that we could 'live another day'. In one of the most painful decisions of my career as CEO, we let ~25% of our workforce go in September 2010 and then another ~33% at the start of 2012. I learned the importance of dealing with a tough moment like this with empathy and compassion. Barry and I actively worked to find new roles for all our departing employees. We kept a list of affected employees and their new potential job prospects, and reviewed it weekly at our management board meeting. I personally reached out to many contacts across the industry to find homes for our departing people. Our former Kulmbach colleagues, shed by Roche, managed to rally and form a successful RNA service business, Axolabs, in a nod to the regenerative properties of the axolotl salamander.

Conquering delivery

One thing we knew from the beginning was that turning siRNA from an experimental tool into a drug wasn't going to be easy! Double-stranded siRNA molecules are large, highly charged, susceptible to biodegradation, prone to stimulate immunity and cleared rapidly after in vivo administration. Achieving delivery of siRNA to the cytoplasm of target cells and tissues to effect RNA-induced silencing complex (RISC)-mediated gene silencing became our major 'Manhattan Project-style' focus. Our strategy was to launch a multi-pronged effort, including conjugates, lipid nanoparticles (a term we coined) and biomaterials. In the early years, our delivery efforts represented >80% of Alnylam's R&D investment and included multiple external collaborations with academic groups and companies. In Alnylam's first decade, several dozen externally sourced delivery systems for a range of tissues were evaluated, and the results were almost uniformly disappointing.

An early win was achieved using cholesterol conjugates. In a 2004 seminal paper by Soutschek et al[3], we demonstrated the first evidence of therapeutic gene silencing in a mouse, targeting liver-expressed apolipoprotein B (apoB). We were able to show robust knockdown of apoB and reduced levels of low-density lipoprotein (LDL) cholesterol. Unfortunately, these cholesterol–siRNA conjugates required very high doses of 50–100 mg/kg, and all our efforts to improve their potency failed. At the time, we wrongly avoided making extensive backbone modifications of the siRNA, fearing toxicities often seen with antisense oligonucleotides (ASOs); as a result, conjugates appeared to be a dead end. In hindsight, we were remarkably close to achieving a delivery solution that could have accelerated our timeline to marketed products by years, but we suffered from incomplete knowledge and ascertainment bias—all-too-common factors that derail scientific endeavors.

We turned our attention to lipid nanoparticles (LNPs), where a collaboration with Bob Langer and Dan Anderson at MIT, and a separate collaboration with Protiva, a Vancouver-based company (later merged with Tekmira and now named Arbutus), were showing promising early results. Our collaboration yielded early success with a lipid nanoparticle containing an ionizable

lipid, 1,2-dilinoleyloxy-*N*,*N*-dimethyl-3-aminopropane (DLinDMA), and an siRNA targeting apoB in nonhuman primate studies. The work was published in a seminal 2006 paper by Zimmerman et al[4]. that fueled much of the aforementioned pharma interest in the field, including the $1.1 billion Sirna acquisition by Merck.

The problem with LNPs was a narrow therapeutic index, with a steep dose response toward a sharp onset of morbid toxicity. In his leadership of our overall development efforts, Akshay Vaishnaw (then chief medical officer, now Alnylam president) and his team couldn't find an acceptable therapeutic index to support development. One of our first LNP efforts was aimed at hepatocellular carcinoma and used an ionizable lipid discovered from the Langer–Anderson collaboration, but we halted development after rodent and primate toxicology studies, where we found no acceptable therapeutic index to support clinical development, even in a cancer indication. We were sobered by these findings, and turned to the Protiva collaboration with DLinDMA-based LNPs to advance the ALN-VSP liver cancer program (a cocktail of two siRNAs targeting vascular endothelial growth factor (VEGF) and kinesin family member 11 (KSP)). But here, too, the therapeutic index was limiting and development was deemed tricky.

It became clear that novel lipids would be required to improve the potency and safety profile of LNPs. To that end, we formed a collaboration with Inex in 2006. Inex was founded by Pieter Cullis from the University of British Columbia and was the parent company of Protiva. As the result of a legal settlement (brokered in part by Alnylam) between Inex and Protiva, the two companies announced their merger in May 2008. The combined company was renamed Tekmira and shifted its focus away from discovering novel lipids, using DLinDMA as its 'go-to' ionizable lipid for delivery.

We continued to believe that we needed more potent ionizable lipids, and with the consent of Tekmira, we formed a collaboration with Cullis and two former Inex employees, Tom Madden and Mick Hope. They formed a company called AlCana (a fusion of Alnylam and Canada), and the Alnylam–AlCana relationship began its quest for novel ionizable lipids, ultimately leading to the MC3 lipids (for example, 1,2-dilinoleylmethyl-4-dimethylaminobutanoate; DLin-MC3-DMA).

One of Alnylam's key champions in this collaborative effort was Akin Akinc, a protégé of the Langer laboratory and an early Alnylam scientist. The MC3-containing LNPs showed a ~100-fold improved potency compared with DLinDMA LNPs, and a similar widening of the therapeutic index[5]. The ultimate proof of the impact was manifest in our first two clinical programs in transthyretin (TTR)-mediated amyloidosis (ATTR), with ALN-TTR01 and ALN-TTR02 (patisiran). ALN-TTR01 and ALN-TTR02 contained identical TTR-targeting siRNA payloads but employed either DLinDMA LNP or MC3 LNP, respectively. The results were stunning: the novel MC3 LNP (DLin-MC3-DMA) enabled potent TTR silencing and an acceptable tolerability profile, leading ultimately to the first RNAi therapeutic, Onpattro (patisiran), to reach the market.

With the development of MC3, delivery of RNAi therapeutics seemed largely in hand. A series of events in 2011 and 2012, including a legal dispute between Alnylam and Tekmira, highlighted to me that we needed to control our own destiny, with proprietary delivery technology and full control of manufacturing. To that end, Alnylam expanded research efforts in non-LNP delivery methods and settled our lawsuit with Tekmira to unambiguously establish Alnylam's rights and ability to manufacture LNP-based drugs and clear ownership of Alnylam's proprietary lipid molecules. Perhaps, in retrospect, it should have been clearer to me that Alnylam would need greater control over the core technologies for RNAi delivery. After all, it had been about 'delivery, delivery, delivery' from day 1.

An essential part of the Alnylam story has been our R&D strategy, which balances clear direction from leadership with continued efforts at the team level to innovate (see Box 2). The latter often occurred outside our formal efforts. As 2010 turned to 2011, a '20% time' project became increasingly important to us. Mano was championing conjugate-based delivery efforts in parallel with our advancing LNP-based programs. Specifically, he and his team had turned their interests from lipid-based conjugates to *N*-acetylgalactosamine (GalNAc)-based approaches, with the aim of targeting siRNA to hepatocytes via the asialoglycoprotein receptor[6].

This showed some early promise, but we were again hampered by a lack of potency, and the longstanding investment in conjugates was wearing thin. In a memorable meeting in my office, Mano appealed for "one last experiment" to evaluate greater stabilization of the siRNA backbone as a way to achieve enhanced potency. Akshay was equally vocal about recognizing the potential for conjugates and having a healthy respect for the challenges of developing an intravenous LNP-based delivery platform. I had learned over the years to listen to my colleagues; after all, we were on the frontiers of science together, and no one had all the answers. I consented to continue the GalNAc effort

Box 2 | Alnylam *kainotomia*

Aristophanes first used *kainotomia*, the Greek word for innovation, in 420 BCE in *The Wasps*. As a satirist, he mocked innovators as being unusual members of society. This resonated with Alnylam, especially in the early days, as many people questioned the likelihood of our succeeding with RNAi therapeutics. The spirit of *kainotomia* was our rallying cry to encourage creativity by our scientists and clinicians, but we also applied it across disciplines. We created a '20% time rule' (something I had learned from my days at Biogen in the 1980s), encouraging our scientists to devote as much as one-fifth of their time to pursuing their own ideas. We explicitly discussed *kainotomia* as one of the key principles in our core value of 'Innovation and Discovery'. There were many meaningful discoveries that emerged from this approach. In 2005, some of our scientists discovered 'antagomirs' as a way of targeting miRNAs[19]. In 2013, we published our work on 'rapidly eliminated' lipids, an advancement that was used by mRNA vaccine manufacturers during the COVID-19 pandemic[20]. Of course, this same spirit led to the discovery of GalNAc–siRNA conjugates, paving the way for a broad pipeline of RNAi therapeutic medicines[6].

Even as Alnylam grew, we kept this spirit alive while focusing on development and commercial milestones. To help with this, we annually dedicated capital to our platform effort and consistently elevated goals from this investment as corporate level objectives. Furthermore, we shined a light on our core science with our scientific advisory board meetings that started in December 2002 and continue to this day. These meetings are open to all Alnylam employees; every year, hundreds of employees participate. Though I have left Alnylam, I still join these meetings.

Box 3 | The conundrum of improving platform while advancing pipeline

As Alnylam matured its clinical pipeline, we maintained a steady, growing investment in our platform activities. There was a constant feedback loop of learning from advanced preclinical and even early clinical trial results, bringing them back into our platform team for improvement. These platform investments allowed us to discover alternatives to intravenously administered LNP formulations, such as GalNAc-conjugate siRNAs. They also enabled the expansion of delivery solutions beyond the liver with extrahepatic delivery. Perhaps the most poignant example of how we married platform advancement with pipeline development comes from the story of our GalNAc-conjugate platform and optimization of potency, tolerability and pharmacologic properties such as durability over time.

We started development of GalNAc–siRNA conjugates with a 'standard template chemistry' (STC) design. In the STC format, alternating 2′-*O*-methyl and 2′-fluoro modifications are placed throughout both strands of the double-stranded siRNA molecule, except at the center of the duplex, in which three consecutive 2′-fluoro moieties and three consecutive 2′-*O*-methyl moieties are placed in the 21-nucleotide sense strand at 9, 10 and 11 nucleotides from the 5′ terminus and in the antisense strand at positions 11, 12 and 13 from the 5′ terminus, respectively. Examples of STC-GalNAc–conjugate siRNAs included revusiran (which targets TTR) for hereditary TTR-mediated amyloidosis. Revusiran was the prototype GalNAc–siRNA conjugate, but it was poorly tolerated in a phase 3 trial and was therefore discontinued.

After learning that the STC–siRNA conjugates are metabolically labile, requiring very high doses that were poorly tolerated, we focused on more stabilized GalNAc–siRNA conjugate designs, such as 'enhanced stabilization chemistry' (ESC) siRNA. In the ESC design, the double-stranded RNA backbone contains two additional phosphorothioate linkages at the 5′ ends of both strands, with a total of six phosphorothioate linkages. In addition, the siRNA contains fewer 2′-fluoro substitutions, which further improves the molecule's metabolic stability. Examples of such conjugates include Givlaari (givosiran, targeting aminolevulinate synthase 1 mRNA) for acute hepatic porphyria, Leqvio (inclisiran, targeting proprotein convertase subtilisin kexin type 9 (*PCSK9*) mRNA) for adults with heterozygous familial hypercholesterolemia or clinical atherosclerosis requiring additional lowering of LDL cholesterol, and fitusiran (targeting antithrombin mRNA) for hemophilia A or B. The ESC-GalNAc–siRNA conjugates showed a markedly higher potency that STC, with as much as a 200-fold lower exposure. They also demonstrated an unexpected improvement in durability, facilitating dosing as infrequently as once every 6 months.

Although the ESC siRNA platform enabled a highly potent and durable knockdown of target mRNA, some of these molecules showed evidence of off-target effects in early human studies. These off-target effects became manifest through evidence of liver enzyme elevations that occurred within 30 days of an injection in a subset of patients. Even though there was evidence for adaptation of the liver effects, even with continued dosing, it was in our interest to make our RNAi therapeutic as well tolerated as possible: after all, if we were going to succeed in advancing siRNA to large population diseases, we would need an exquisitely well-tolerated profile. Accordingly, we designed the 'ESC+' format, with molecules that differ from the ESC format in the inclusion of a single thermally destabilizing nucleotide glycol nucleic acid (GNA) in the seed region of the siRNA, which has been demonstrated to reduce seed-mediated off-target effects. This chemistry retains the six phosphorothioate linkages in the ESC design in combination with a further reduction in the number of 2′-fluoro modifications and corresponding increase in 2′-*O*-methyl modifications. Examples include ALN-AAT02 (which targets α1-antitrypsin mRNA) for α1 liver disease, ALN-HBV02 (which targets all hepatitis B virus (HBV) protein mRNAs) for hepatitis B infection and ALN-HSD (which targets 17β-hydroxysteroid dehydrogenase 13 (*HSD17B13*) mRNA) for non-alcoholic steatohepatitis. Using both ALN-HBV02 and ALN-AAT02, we were able to show that ESC+ siRNAs achieve improved tolerability profiles in humans.

Our efforts didn't stop with ESC+, as we became interested in identifying RNAi therapeutics that could be administered once a year, just like a vaccine. This lofty goal was ultimately achieved with the 'Ikaria' design approach by using a newly optimized chemical modification pattern that combines exceptional metabolic stability and potency with high specificity (unpublished data). An example is ALN-TTRsc04 (which targets TTR) to treat ATTR amyloidosis, with a potential annual-dosing siRNA that achieves >90% TTR knockdown as indicated by preclinical studies.

and realize this last experiment's conclusion. The bet paid off! At an offsite meeting in Newport, Rhode Island, in the spring of 2012, Mano shared the initial GalNAc data with stabilized siRNA showing single-digit milligram per kilogram potency in primates. On that day, I knew more than ever that we'd succeed in bringing RNAi therapeutics to market. Renta Hutabarat, then our head of bioanalytics and drug metabolism and pharmacokinetics (DMPK), memorialized the achievement with an 'I love conjugate' T-shirt that I cherish to this day.

GalNAc conjugation subsequently emerged as the leading technology for the delivery of oligonucleotides, used for liver delivery by virtually every company in the RNA therapeutics space, including ASO giant Ionis and LNP champion Tekmira/Arbutus.

With a proprietary delivery technology amenable to subcutaneous administration in hand, we began to advance our first GalNAc conjugate into development, using our novel 'standard template chemistry' (STC) approach (see Box 3). The first molecule was revusiran, a subcutaneously delivered GalNAc-conjugate siRNA targeting TTR (I'll come back to revusiran below). While we were developing revusiran, we learned that further stabilization of the siRNA backbone conferred even greater potency improvements (Fig. 2 and Box 3), leading to the development of our 'enhanced stabilization chemistry' (ESC) design and the first clinical program for fitusiran, targeting antithrombin for the treatment of hemophilia. Our early clinical studies revealed a 10–20% incidence of troubling liver enzyme elevations, but in a remarkable series of investigational toxicology studies[7] led by then senior scientist Maja Janas, we were able to identify off-target hybridization of GalNAc–siRNA as the cause. Our chemistry team, led by Martin Maier, found a solution by introducing a destabilizing glycol nucleic acid (GNA) nucleotide into the seed region of the siRNA antisense

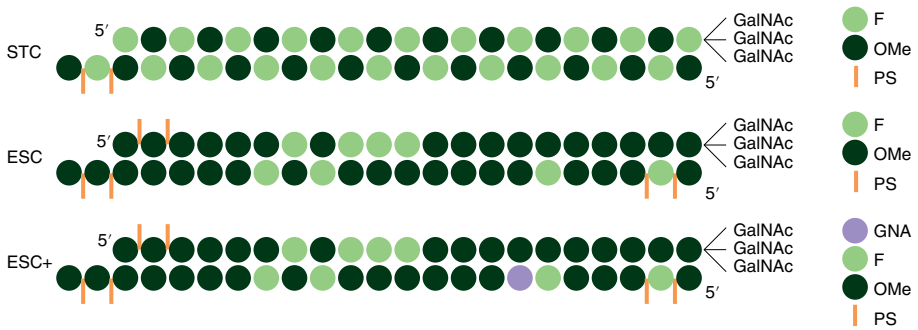

Fig. 2 | Evolution of conjugate siRNA designs. Representative examples of conjugate siRNA designs. The top strand depicted is sense (same sequence as that of target RNA), and the bottom is antisense strand. Keys for modifications: F, 2′-deoxy-2′-fluoro; OMe, 2′-*O*-methyl ribosugar; PS, phosphorothioate linkage; GNA, glycol nucleic acid; GalNAc, *N*-acetylgalactosamine. STC, standard template chemistry; ESC, extended stabilization chemistry; ESC+, extended stabilization chemistry plus.

strand in what became our 'ESC+' chemistry design (unpublished data). Finally, and most recently, our platform guru Vasant Jadhav identified even further advances in siRNA chemistry and design with an approach called 'Ikaria', enabling an annual dosing regimen for siRNA (unpublished results). This taught us that we always had to allow some freedom for research teams to keep developing the platform in the face of gradually increasing costs in other areas across pipeline-focused R&D and the company.

Our delivery efforts didn't stop with the liver. Thanks to a culture of '20% time' for scientists and our spirit of '*kainotomia*' (Box 3), some of our scientists began to probe central nervous system (CNS) and ocular delivery of siRNA with novel C16 conjugates. Thankfully, this was advanced as yet another 'skunk project', as I had, since the clinical success of hepatic delivery systems (LNP, GalNAc), decided that further extrahepatic efforts were a distraction. But the early data in rodents were encouraging, and the translation of results in nonhuman primates emboldened our efforts. With these preclinical data in hand, we forged an $800 million upfront deal with Regeneron in 2018 to advance a pipeline of RNAi therapeutics for CNS and ocular diseases. Just this past December, the first RNAi therapeutic targeting amyloid precursor protein, a crucial target in Alzheimer's disease, entered clinical development. We should soon see how this new frontier plays out!

Without a doubt, conquering delivery was foundational to building Alnylam. It was the key technology hurdle to turning Nobel-prize-winning science into medicine. There was never a 'straight line' to a solution—there rarely is in either science or business. Ultimately, the key was to persevere, follow the science and foster an environment of innovation. The ultimate solutions relied on fundamental advances in both novel delivery methods *and* novel chemistry applied to the siRNA itself. It was also critical to be bold and take risks, bringing prototypes into early clinical studies and learning (safely, of course) how to optimize based on findings in man. Finally, Delivery (capital 'D') has never been 'over' for us. We have continued (and continue) to optimize the technology to bring our best innovations to patients.

Alnylam 5×15

In late 2010, Alnylam had been hit on the head by a proverbial 'two by four'. Pharma had exited the siRNA field, investors had fled our stock and most people in the industry thought we were dead, only we hadn't lain down yet! I knew that this was the time to shed our somewhat romantic vision of RNAi therapeutics as broadly applicable and instead focus on building a clinical pipeline where we might best achieve delivery, namely in the liver.

I convened members of my core team, including Barry, Akshay and Sara Nochur, our head of regulatory affairs, to discuss a shift of focus from platform to pipeline. I was convinced that the only way to restore confidence in RNAi was to demonstrate unassailable human POC results. Using the analogy of hearing jingle bells and believing in Santa Claus (from the children's story *The Polar Express*), I reasoned that our external stakeholders needed to hear the 'bells' of human data.

We discussed communicating a set of five-year goals at the upcoming January 2011 J.P. Morgan conference. I wanted to propose a new strategy called 'Alnylam 5×15', with a commitment to advance five RNAi therapeutic programs into clinical development by the end of 2015. These programs would all be focused on liver-expressed, genetically validated disease targets (where we had achieved reliable delivery results in primates). In addition, we would focus on targets for which human POC could be realized as early as phase 1, based on biomarkers, and we'd create pivotal studies with endpoints meant to support regulatory approval and demonstrate value for payers. The team pushed back on this. With only one liver-targeting program in development at that time (ALN-TTR01), and no human POC data in hand, the team suggested that '2×15' or '3×15' might be a more manageable goal to promote publicly. I disagreed, saying that a reduced number of targets would not excite our stakeholders nor motivate our team.

And, so, Alnylam 5×15 it was! Our research organization rallied behind the new strategy. Teams of biologists, chemists and physicians were formed to triage the multitude of liver-expressed target genes. Research director Dinah Sah championed TTR amyloidosis, already a program entering the clinic. Her colleague Kevin Fitzgerald, now Alnylam's chief scientific officer, advanced several programs, including RNAi therapeutics targeting PCSK9 for hypercholesterolemia. We planned to bring these programs into development as rapidly as possible. Other programs, including ones in ALN-VSP liver cancer and respiratory syncytial virus, were sidelined or slated for senescence as we aligned around the new strategy.

In the fall of 2011, our first 'bell' was rung. Patient 50-03 in our ALN-TTR01 phase 1 study showed clear TTR knockdown, demonstrating for the first time the ability to harness RNAi in man. The first data were shared with a small group in advance of an offsite meeting at the University Park Hotel in Cambridge. It's interesting to speculate what would have happened if we hadn't seen the clear RNAi signal in that single patient. We had improved LNP technology in preclinical studies, so I suspect we would just have gone back and tried the optimized lipids. That said, our confidence in our ability to achieve our aspirational Alnylam 5×15 goals would almost certainly have been shaken. As of this writing, patient 50-03 continues to receive patisiran for hereditary ATTR with polyneuropathy 11 years later.

Patient 50-03 was the start of a remarkable series of clinical translational results with RNAi therapeutics. First, we were able to demonstrate improved TTR silencing with the ALN-TTR01 successor molecule, ALN-TTR02 (patisiran), and then

the use of a GalNAc conjugate, revusiran, with subcutaneous administration. Next, we were able to show potent silencing of PCSK9 and robust lowering of LDL-C in patients with hypercholesterolemia. In the case of fitusiran, our hemophilia treatment, we were able to show increases in thrombin generation and early signs of improved hemostasis. In our givosiran program, targeting the enzyme aminolevulic acid synthase-1 in patients with acute hepatic porphyria, we demonstrated lowering of the toxic disease metabolites. The 'bells' were now ringing loud and clear, and the outside world began to notice. As 2015 came to a close, we had managed to advance eight programs into clinical development, well above our target of five.

We were also well on our way to building a reproducible and modular platform. By the end of the 5×15 plan, we could reliably go from target concept to filing an Investigation New Drug application (IND) within a 1.5–2-year time frame, and, with human validation of liver delivery, have confidence that any program entering phase 1 would generally lead to target knockdown.

With this newfound success, we realized that we needed to prioritize our efforts and find a way to fund our burgeoning pipeline. First, in early 2013, we decided to partner for our PCSK9 program. At the time, ALN-PCS02 was being advanced in phase 1 as an intravenously administered LNP product; its GalNAc-conjugate follow-on compound (inclisiran) was still in discovery. Moreover, with four monoclonal antibodies from other companies targeting PCSK9 in advanced clinical stages, the competitive landscape wasn't attractive. We turned to The Medicines Company as a partner, knowing that CEO Clive Meanwell and his team had been brilliant in developing and commercializing the anticoagulant Angiomax (bivalirudin), a molecule I licensed to him in 1997 and that I invented while at Biogen.

Second, we sought a global partner for our core 5×15 portfolio, whereby we would retain rights in North America and Western Europe and the partner would lead development and commercialization in the rest of world. Over the summer of 2013, our then chief business officer Laurence Reid and I began courting a range of pharma partners. Still fresh from its acquisition of Genzyme, Sanofi was keen to rebuild its rare disease pipeline and became interested in a broad Alnylam partnership. A September meeting at the 'Genzyme Center' with Genzyme head David Meeker and Sanofi CEO Chris Viehbacher clinched the deal. Chris saw the power of the platform we were building, and also valued the opportunities for growth in global markets. The $700 million upfront partnership was announced in early 2014, and our share price surged to >$100 for the first time. This allowed us to close a number of secondary financings to support growth.

A new class of innovative medicines

Alnylam 5×15 laid the foundations for RNAi as a new class of medicines, but much work was still needed to bring these medicines to patients and to transform Alnylam into a fully integrated biopharmaceutical company. At the beginning of 2015, we introduced a new set of objectives called 'Alnylam 2020', with the aim of bringing three or more RNAi therapeutics to market by the end of 2020. This was yet another lofty goal, as we had only just started enrolling patients in our first phase 3 trial in 2014. The beauty of the five-year plans, which served to reduce strategic doubt and second guessing, was the way our employees adopted them as a rallying cry. It gave our team harmonization, and an understanding of why these goals were important to the company and to our ultimate mission of bringing medicines to patients.

Transitioning from early to late clinical development is not an easy feat. The design of our first phase 3 APOLLO study with TTR-lowering patisiran required substantial deliberation and alignment with global regulatory authorities. We knew we had to get this right because the biotech landscape is littered with now defunct companies that failed to succeed in phase 3 after early glimpses of promising data. Akshay led his team in a series of intense discussions and debates to rigorously consider trial design parameters and study endpoints. These efforts included input from external experts and access to natural history data. Alignment with regulators required multiple road trips. In a meeting with the Portuguese authorities, for example, we needed to communicate an unexplained death of a monkey in a toxicology study. We also needed to get payer input. Barry's nascent commercial team of Oved Amitay and Rena Denoncourt began discussions with the UK National Institute of Clinical Excellence (NICE) and commercial payers in the United States. In late 2013, we enrolled our first patient in APOLLO, our first randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of patisiran in hereditary ATTR (hATTR) patients with polyneuropathy. The die was cast.

We also had competition, as Ionis had catapulted ahead of us with their TTR-targeted ASO, inotersen, going right from phase 1 into a phase 3 trial. As inotersen is a subcutaneously administered ASO, we feared that intravenously administered patisiran would be less attractive for physicians and patients. Thankfully, our GalNAc-conjugate progress was bearing fruit, and we were able to advance TTR-lowering revusiran toward a phase 3 study called ENDEAVOR in 2015. ENDEAVOR was designed to evaluate the efficacy and safety of revusiran in hATTR patients with cardiomyopathy, a potentially larger opportunity than the polyneuropathy patient segment.

There was one cloud on the horizon. While ENDEAVOR was enrolling, we heard reports of worsening neuropathy in the ongoing revusiran phase 2 open-label study—an odd finding, as we'd expect the opposite result from a TTR-lowering drug. Out of the abundance of caution, we asked the independent Data and Safety Monitoring Board (DSMB) of the ENDEAVOR study to conduct an unblinded assessment of revusiran tolerability in the ongoing randomized study. In early October 2016, while driving to Vermont for a fall weekend, I received an urgent call from Akshay. The DSMB had recommended that we stop ENDEAVOR, not due to a neuropathy finding, but due to an imbalance of mortality against the drug arm. We immediately moved to discontinue the study. Having just hired Yvonne Greenstreet out of big pharma as our chief operating officer, I asked her to coordinate our efforts in ensuring effective communication with our many stakeholders. For Yvonne, it was a stark introduction to biotech!

The October 5 revusiran announcement was a shock to many around the world. Patients were gravely disappointed, as many had hoped that revusiran would offer a new treatment for their generally fatal disease. Alnylam investors fled the stock, with ALNY losing considerable—over $7 billion—market value in just one day. Investors feared a broader platform safety issue that applied to the entirety of the Alnylam pipeline and the RNAi therapeutics field. They were seeking answers that we just couldn't give, as we had few explanations for the mortality imbalance at the time. We launched an internal investigation to learn more and charged Laura Sepp-Lorenzino, one of our top scientists, with leading the effort.

Six years later, we still don't fully know the cause. But it does appear that the metabolically labile revusiran siRNA molecule was poorly tolerated in a frail population with advanced heart failure, with all the deaths occurring in the most advanced patients. Thankfully, our partners at The Medicines Company had garnered significant human safety experience with

inclisiran in hundreds of patients by that time, and they assured us that there was no fundamental platform issue per se. Regardless, many external stakeholders entered yet a new period of skepticism about Alnylam's prospects. Although we published the revusiran investigation findings[8], some criticized us for taking too long to do so. I beg to differ, as we achieved a remarkable level of transparency—including multiple presentations—throughout this trying and uncertain period.

To quote Friedrich Nietzsche, "That which does not kill us makes us stronger." Although ENDEAVOR was a horrible result for patients and an extremely difficult event for Alnylam, our team carried on and persevered.

Less than a year later, in late September, I received a phone call from then chief medical officer Pushkal Garg on a Sunday afternoon. The 225-patient APOLLO phase 3 study was a massive success, with the primary endpoint, a neuropathy impairment score called 'mNIS+7', achieving significance with a P value of 9.26×10^{-24}. All secondary endpoints and a number of exploratory endpoints also achieved statistical significance. When the full data were presented at the EU-ATTR meeting in November 2017, there were gasps from the audience as lead investigator David Adams presented the results. Barry, Akshay and I were seated together near the front of the auditorium and took it all in. It was a watershed moment for RNAi therapeutics and for Alnylam. Most importantly, it brought new hope for patients with hATTR polyneuropathy!

During the following few years, I received a number of excellent calls from Pushkal on Sunday afternoons. In 2019, we reported positive results for givosiran in the ENVISION phase 3 study in patients with acute hepatic porphyria, and in 2020 we reported positive results for lumasiran in the ILLUMINATE-A phase 3 study in patients with primary hyperoxaluria type 1. Most recently, vutrisiran showed positive results in the HELIOS-A phase 3 study in patients with hATTR polyneuropathy; vutrisiran has the identical sequence to the ill-fated revusiran, but employs a more advanced version of our GalNAc-conjugate ESC chemistry, achieving metabolic stability. Each of these programs has their own rich stories to tell in the future.

Elsewhere, our colleagues at The Medicines Company were also achieving strong results. Clive called me in August 2019 to share the ORION study data in thousands of patients, where biannual inclisiran demonstrated a >50% lowering of LDL-C, with a safety profile comparable to placebo. That summer night, eating dinner with the family in Nantucket, I knew that RNAi therapeutics would become a whole new class of medicines helping patients with both rare and prevalent disease.

Alnylam 2020 also saw a further maturation of the company. We had shown our powers of innovation, resilience and strength in research, but we could now also claim to have the same prowess in development. With each novel phase 1 POC, and then positive phase 3, a string of publications followed (a total of ten *New England Journal of Medicine* papers[9–18] from 2013 to 2021). These papers illustrated the potential of RNAi therapeutics in addressing previously 'undruggable' targets, but also showed the transformative nature of the benefit/risk profile in the diseases we were addressing. The papers were part of a decision we had made back in 2003—over the dining room table at my home—to consistently publish our research findings, choosing to prioritize the benefits of peer review over the downsides of enabling competitors. Behind these scientific papers lay substantial ingenuity across the disciplines of drug development: toxicology, DMPK, regulatory approval, pharmacology, pharmacometrics and clinical research. Each group established a roadmap for RNAi therapeutics where previously there was none. We had crossed into new territories in a series of diseases—ATTR amyloidosis, acute hepatic porphyria and primary hyperoxaluria—for which there had never been a notable Food and Drug Administration drug approval and where there was little to no landscape of natural history, clinical trial methodology or endpoints. The discipline of the strategy proved key, however, as we could reliably show that genetically validated targets acting proximally in each of the respective disease states could be addressed with RNAi therapeutics.

Bringing medicines to patients also requires excellence in commercialization. After all, it's only when medicines reach the market that a company can fulfill its obligations to patients. We were committed to bringing our innovation to markets on our own. We started by advancing a set of 'Patient Access Principles' in 2017, where we committed to put patients first, forego drug price increases above the rate of inflation and proactively seek out value-based agreements with payers. In early 2018, we obtained global rights to our core pipeline programs in a swap with Sanofi, giving them global rights to the hemophilia drug fitusiran in return. Barry took the lead on our commercial transformation, building capabilities for direct marketing in 20 countries and establishing distribution agreements for additional markets. We began to build commercializing capabilities across finance, legal, ethics and compliance, information technology, communications and other functions.

With the launch of patisiran under the trade name Onpattro in August 2018, we demonstrated that Alnylam could excel as a commercial organization just as it had as an R&D company. Two additional launches in the following two years (Givlaari (givosiran) and Oxlumo (lumasiran)) and Novartis's launch of Leqvio (inclisiran), now just approved in the United States, have heralded the emergence of RNAi therapeutics "with a bang, not a whimper" (a purposeful twist on the famous line from the T.S. Eliot poem "The Hollow Men").

Conclusion

To tell the full story of Alnylam would require a book rather than a reflection of this type. I have not covered how we learned to manufacture our drugs and committed to good manufacturing practice (GMP) production; how we built a global organization with >1,600 employees; how we commercialized medicines across multiple indications; how we raised $7.7 billion over the years to fund our efforts; and so much more! Because I am a scientist, my heart lies in R&D, but I would be remiss not to recognize the manufacturing, legal, compliance, finance, program management, human resources, medical affairs, commercial, corporate communications and many other groups across Alnylam that have contributed to the company's success. I have chosen to mention certain colleagues by name in this limited space for their contributions, but of course there are hundreds of others who were also critical to our story.

In October of 2021, I decided to transition Alnylam's leadership to Yvonne Greenstreet, a remarkable leader. After 19 years of being a 'man in the arena' for Alnylam and RNAi therapeutics, it is now time for me to explore a new chapter and help others build future Alnylams. I was proud of what I was able to accomplish with the help of a great team and their passion and commitment. I'm also excited about the company's future aspirations with its new P5×25 five-year strategy launched in early 2021. The common theme in my 19-year journey was the deep appreciation all of us had for our culture and core values: innovation and discovery, passion for excellence, sense of urgency, openness and transparency and commitment to people. Although *my* Alnylam story has ended, I have no doubt that *the* Alnylam

story and RNAi therapeutics are only at the beginnings of their impact for science, medicine and patients. ❐

John Maraganore ✉
Former founding CEO, Alnylam Pharmaceuticals, Cambridge, MA, USA.
Twitter: @jmaraganore
✉*e-mail: john@maraganore.com*

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Competing interests

J.M. is founding CEO of Alnylam Pharmaceuticals, where he is also on the scientific advisory board and a significant stockholder. He is an advisor for Arch Ventures, Atlas Ventures and RTW Investments. He is chair emeritus and a member of the Biotechnology Innovation Organization board. He is also a board member and/or strategic advisor for a number of public and private biotechnology companies.