Ionis: the invention and evolution of RNA-targeted therapeutics

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It is a well-known fact that the productivity of the drug discovery and development industry has been declining over decades[1]. There have been many factors cited as causal: some are merely the product of the success of the industry in treating acute and semi-chronic diseases; while others, to a large extent imposed on the industry, such as substantially increased regulatory demands, clearly have also contributed. Ionis was founded to address three major factors that are, in principle, within the control of leaders in the industry and might account for much of the declining productivity: first, the need for disruptive, more efficient drug-discovery technologies that can better exploit the advances in understanding the molecular pathology of diseases; second, the impact of the fully integrated pharmaceutical industry business model on innovation; and third, the need for strong scientific leadership, coupled with excellent management practices integrated into a culture of 'yes', instead of a culture in which 'no' is a far too frequent response.

In my view, quantum increases in productivity in any industry happen only when new, disruptive, more efficient product-development technologies are introduced. Since the foundation of Ionis in 1989, most companies have remained dependent on the inefficient small-molecule drug-discovery platform that has not changed in fundamental ways for many decades — arguably, even a century. Experience suggests that the size and multiple agendas of large, fully integrated pharmaceutical companies (FIPCOs), when coupled with the inefficient product-development platform, the high new-product failure rate, and the very long and costly product-development cycle, has impeded innovation and diminished the effectiveness of innovators over time. Additionally, in this business model, potential products are forced into single development and commercial channels. This leads to many excellent product candidates being terminated and, in fact, subordinates the products to the infrastructure. Moreover, these factors can lead to a risk-averse culture of 'no', which limits innovation, rather than what is needed: strong scientific leadership coupled with solid management practices in a culture where there is a bias to say 'yes' to novel ideas, galvanic scientific leaders, novel product opportunities and the commitment to take prudent risk.

In the aggregate, the notion of creating an entirely new platform for drug discovery, a new business model and a different corporate environment is a large and challenging agenda. It certainly is fair to ask for evidence that the proposed solutions might work. Fortunately, there is very clear evidence that they can do so in the biotechnology industry. At inception, the biotechnology industry was a response to the frustration that investors felt about the perceived lack of innovation of the major FIPCOs. In effect, investors said they believed that a distributed set of investments in small, creative organizations led by energetic entrepreneurs would be more innovative and a better investment, and they were right. Over the last several decades, every new drug-discovery platform, including monoclonal antibodies, gene therapy and RNA-targeted therapy, has been invented, advanced and validated by small biotechnology companies. Most of the major first-in-class breakthrough medicines have also been discovered by biotechnology companies, while FIPCOs have become primarily innovation buyers, depending on networks of investments in biotechnology companies for the new products they need. Successful biotechnology companies have routinely chosen to become FIPCOs, resulting in a decline in innovation and a reversion to buying novel therapeutics and ideas.

Today, in addition to the biotechnology industry, Ionis is proving that these factors can be addressed by drawing upon 30 years of scientific progress. A critical component that must be established is a vastly more efficient platform for drug discovery and development.

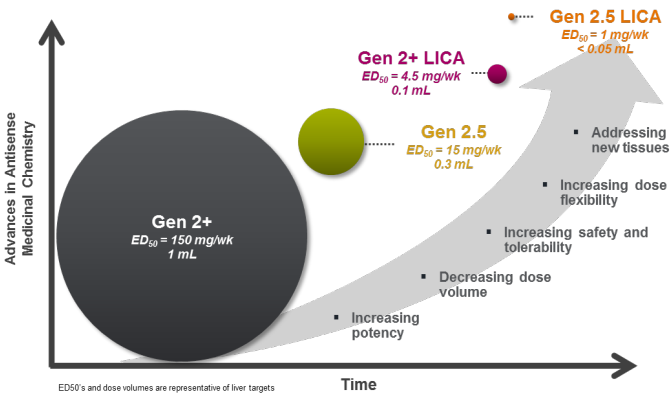

Figure 1. Advances in Technology Substantially Improve the Utility of ASOs. A graphical depiction of the impact of advances in medicinal antisense medicinal chemistry on the potency and other performance metrics of ASOs.

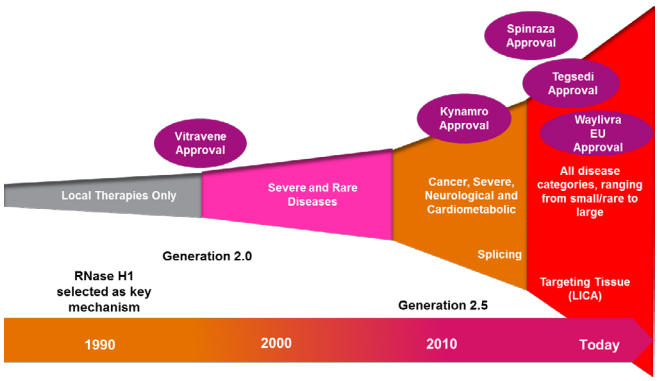

Figure 2. Impact of Advances in Antisense Medicinal Chemistry on the Breadth of utility of Ionis Technology. The impact of advances in antisense medicinal chemistry and the breadth utility of ASOs in the Clinic.

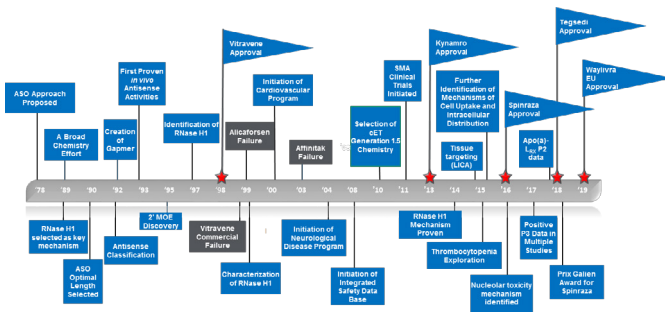

Figure 3. A Summary of Key Milestones in the Development of Ionis Technology. Key milestones in RNA targeted therapeutics at Ionis are the past 30 years. Flags and stars represent commercial approvals of ASO medicines.

RNA-targeted therapeutics is a medicinal chemically based discipline, albeit with new types of chemicals: chemically modified antisense oligonucleotides (ASOs). At Ionis, we created a medicinal chemical programme that remains the broadest and most productive in the RNA therapeutics sector. For more than 20 years, we have focused almost exclusively on enhancing the affinity and fidelity of ASO interactions with their cognate receptor sites in target RNAs, and that programme has been very successful. To that end, we examined modifications at essentially all sites in an oligonucleotide except those that would disrupt Watson–Crick hybridization.

However, we believed that the second position of the ribose moiety was the site most likely to yield dividends, because the shape of the ribose moiety plays a critical role in hybridization and it is the site that most nucleases use to catalyse cleavage of an oligonucleotide. So, in principle, in a single appropriate modification, we might enhance binding affinity for the cognate binding site in a target RNA and stabilize the oligonucleotide, which would support less-frequent dosing. That hypothesis proved to be correct and, as a bonus, we found that the proper second modification could substantially reduce the pro-inflammatory effects of ASOs. As expected, the increases in affinity translated into a substantial increase in potency (**Fig. 1**). The modifications also resulted in an increase in tissue half-life sufficient to support monthly or less-frequent dosing[2], and substantial improvements in safety and tolerability[3]. The enhanced properties of the modified ASOs thus supported their administration by essentially all routes of administration and laid the foundation for commercially acceptable oral administration[2].

More recently, our medicinal chemistry programme has focused on enhancing potency by targeting delivery to tissues and cells of interest, enhanced cellular uptake and optimized intracellular distribution, because we know that the vast majority of a dose of an ASO is not effective because it does not concentrate at the sites in which optimal effectiveness is achieved. Successes in these efforts have already been published[2,4,5] and we will be reporting additional advances based on this approach of equal or greater importance. We have refined the major pathways of productive cellular uptake ASOs, the sites to which ASOs distribute intracellularly and the key proteins responsible. Armed with that information, we are now studying new modifications that enhance our ability to concentrate more ASOs in the desired sites within the cell[5]. Furthermore, we have identified the major molecular mechanism of ASO-induced toxicities, and shown that straightforward medicinal chemical modifications can ablate or reduce the toxicity with little to no reduction in potency[6]. When these discoveries are combined with the new mechanisms of action that we have reported, the opportunities to use drugs based on the technology have broadened enormously (**Fig. 2**); we expect this trend to continue as we incorporate new advances into our pipeline.

The creation of RNA-targeted therapeutics has, indeed, been a remarkable journey. Today, seven RNA-targeted medicines have been approved for commercial use (five by Ionis) and perhaps as many as 100 or more RNA-targeted medicines are in development. At Ionis, we have more than 40 RNA-targeted drugs in development, with as many as 10 or more likely to be in pivotal trials by the end of next year. The set of milestones achieved to date in the technology is summarized in Fig. 3. We are proud of those accomplishments, but what is truly exciting is that the progress to date is simply a prologue to an even more exciting future.

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