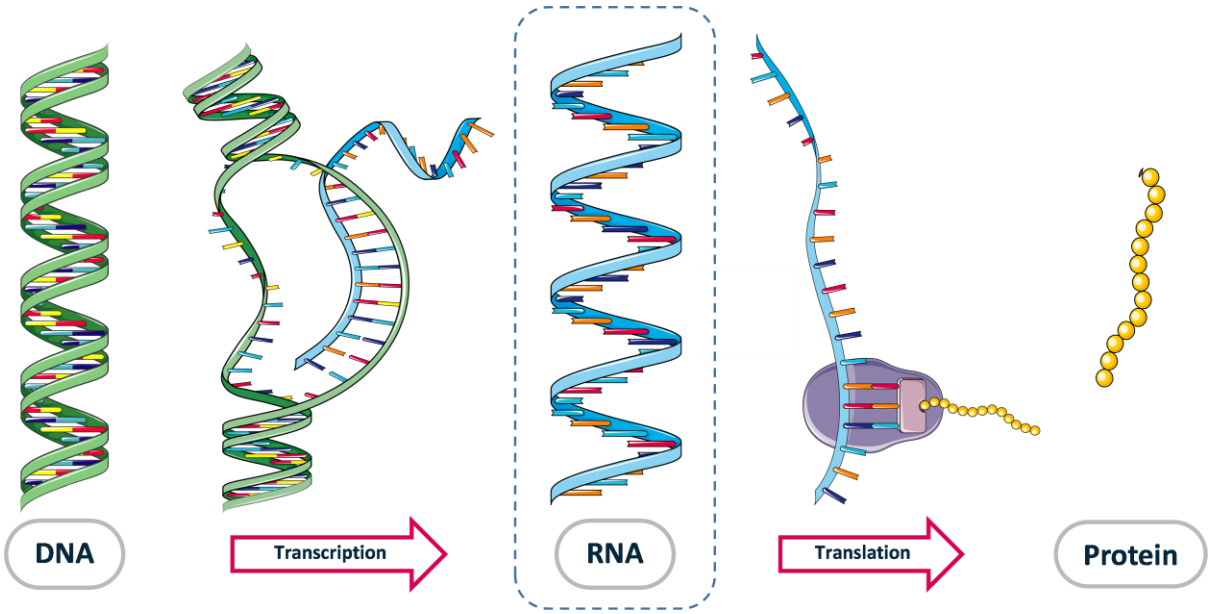
RNA Therapeutics:

The Future of Medicine is Here

Innovation in the medical field has strongly accelerated in the last century and we see it continuing at an even higher pace going forward. Just over 50 years ago doctors were pioneering heart transplantation in patients, today they are looking to impact the genetic material that dictates every detail of human biology in order to treat or cure diseases. In this technology showcase we will highlight one of the most advanced of such technologies, RNA therapeutics. We will describe the rationale behind this technology, as well as its strength and weaknesses compared to traditional medicines and other novel approaches.

What is RNA?

The central role of DNA in our biology is a well-known fact. However, the just as important function of RNA is somewhat underappreciated. While DNA stores the "instructions" for the production of every protein in our body, RNA is the tool without which such production could not take place. DNA is stored in the nucleus of our cells and is used to produce, via a process known as "transcription", a copy of RNA that after certain modifications is transported out of the nucleus. RNA is then used by other cellular machinery to form proteins in a process that is known as "translation". These proteins direct the functions/activities of our cells.



This sequence of events is at the base of life. However, if this genetic information contains 'errors' from birth or because of one or more mutations in our DNA during our life, the processes described above may produce non-functional or harmful proteins, causing disease. For decades, medical science has only been able to manage symptoms of many genetic disorders. With the new wave of innovation of genetic technology, today's RNA medicines have already proven they can successfully treat diseases for which only symptomatic treatment was available so far.

Trial & Error in RNA Therapeutics

Much like in the development of any technological advancement, the history of development of RNA medicines is rich in landmark discoveries as well as notable setbacks. The idea that manipulating and interacting with RNA could bring clinical benefit was well established, however translating that into practice presented numerous challenges. Examples of these are the stability of RNA strands as well as the difficulty to enter cells. The human immune system is well calibrated to make sure to attack and remove any genetic material that is not its own, and this very characteristic made it hard for therapeutic and synthetic RNA strands to reach the intended cells without being destroyed by our immune system first. Even when the administered RNA molecules managed to reach the intended tissues, due to their structure and electric charge it is also challenging for them to enter cells.

Many strategies have been attempted to overcome these obstacles, and after 30 years of trial and error medicine developers have come up with several effective methods to successfully deliver RNA therapeutics to the intended cells. For example, concealing the RNA strand in synthetic 'vehicles' that shielded the RNA from the action of the immune system and concurrently allowed for cell entry has been a successful approach.

An even more effective one has been to apply chemical modifications to the RNA molecule to better withstand the immune system action as well as attaching a "ligand" that is specifically targeted to enter specific tissues, for example liver cells.

From Symptomatic Treatment to a Cure?

RNA therapeutics present several advantages compared to the traditional technologies used in medicine discovery. Throughout the history of medicine, starting with the use of natural products like herbs and food followed by the so called "small molecules" like paracetamol and antibiotics, scientists have attempted to interact with receptors and other pathways in our biology to treat diseases. Decades of research have refined the methods with which molecules are selected, making them stronger and more selective. However, there are still evident limiting factors when it comes to treatment of a disease with small molecules, including low selectivity, lower influence in intracellular processes, and limited disease-modifying activity.

The need for better medicines led to the development of biologic medicines, including peptides, synthetic proteins and eventually engineered antibodies. Despite unlocking a whole new class of medicines that drastically changed the way many diseases are treated, antibody-based medicines still present several limitations, for example their large size, cumbersome manufacturing, and risk of triggering harmful immune reactions for patients.

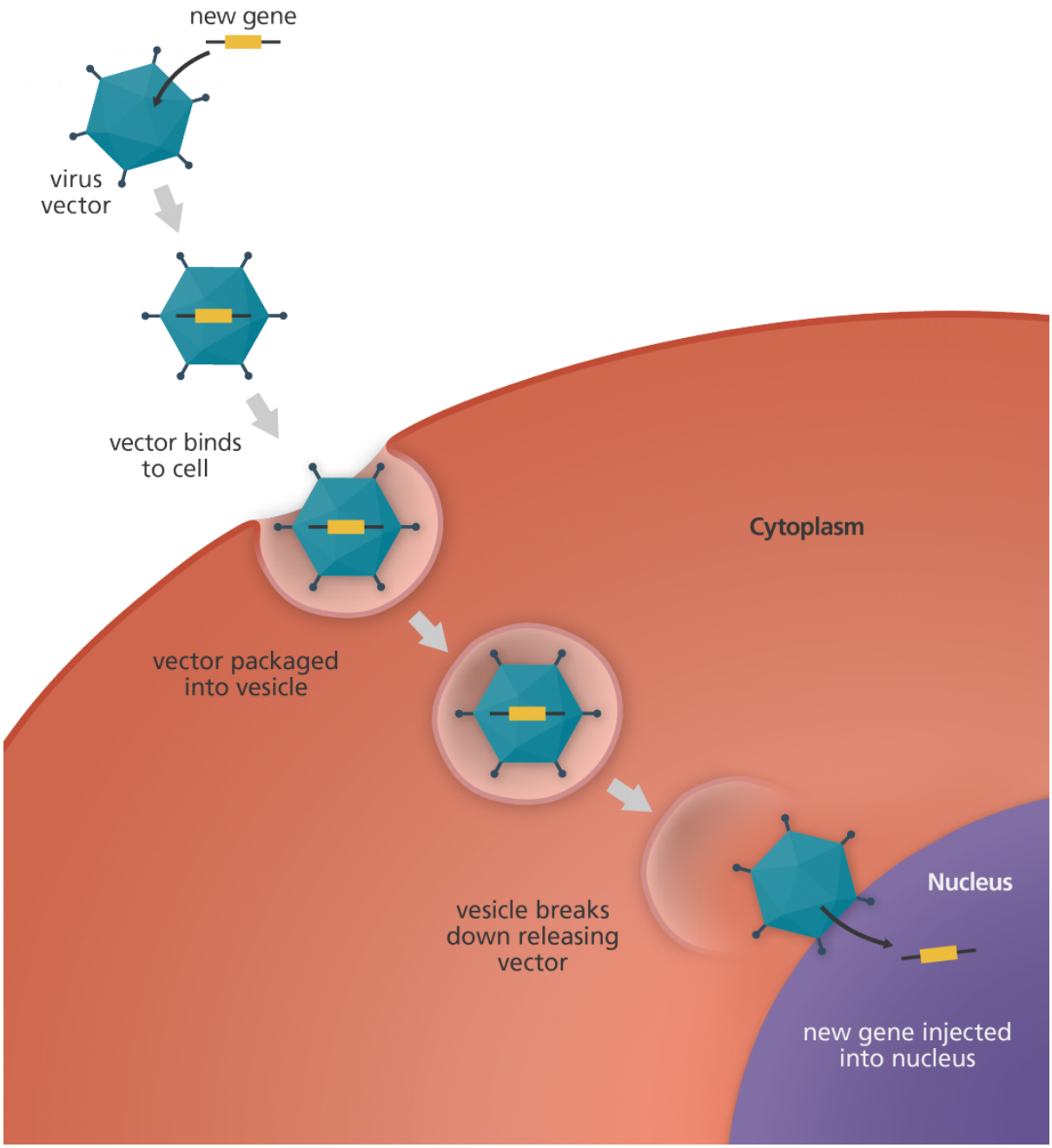
RNA therapeutics leverage positive characteristics of both small molecules and antibodies, while leaving many limiting factors behind. Like small molecules, RNA molecules are synthetic in nature and simple in structure, but with the right modifications can also effectively enter the cells and influence the genetic machinery as described above. Like antibodies, RNA medicines have high selectivity for their target, with minimum likelihood of off-target effects. However, unlike antibodies, RNA medicines can enter cells and precisely dictate the changes needed to address the root cause of the disease.

As already mentioned, many cellular processes, including the ones that originate disease, occur via protein-protein interactions. What if there was a way to stop the production of a harmful protein or to promote the production of a functional one? These are just two of the many modes of actions that are enabled by RNA medicines. In this way, the goal of therapy will no longer be to limit the disease mechanisms and its negative effects, but it will be to stop the disease at its source. To go from symptomatic treatment to a cure, this is how high the promise of RNA medicines is. By entering and manipulating the cellular machinery that originates every protein produced in our body, RNA medicines act on the

root of the disease, potentially providing profound disease-modifying effects or even a cure.

RNA Therapeutics and Gene therapy: Same Precision, Different Concept

Between the oligonucleotides strands employed in RNA therapeutics and the DNA delivered with gene therapy, it is not hard to confuse the two therapeutic approaches. However, there are some radical differences that are important to highlight. The core concept of gene therapy is to deliver a copy of the healthy gene that is mutated or missing in the patient. This genetic information is delivered via a vehicle, often an engineered virus. Once delivered the gene cannot be taken out of the cell, the process is irreversible.



There are some similarities between RNA and Gene Therapy: both leverage genetic precision in target engagement and therapeutic effect and both aim at modifying and possibly solve the root cause of the disease. However, there are some crucial differences between the two. A particularly important differentiating factor is that RNA medicines need repeat dosing, for example once a quarter, to have sustained therapeutic effects, while gene therapies are designed to be delivered as a one-time infusion, without need for further dosing. A one-and-done model for gene therapy clearly has the benefit of only needing to treat the patient once and, if all goes well, the patient's disease is cured or permanently improved. At the same time, this one-time dosing presents some challenges.

For example, given many gene therapy medicines do not integrate with the patient's genetic material and it is not currently possible to administer additional doses, the applicability of these medicine is limited to tissues whose cells never or very slowly renew, such as nerve cells, adult liver cells, and eye cells. Furthermore, given the treatment is irreversible, there is a possibility of causing permanent undesired toxicities or side effects, therefore extremely careful consideration in the development and risk/benefit profile to patients is needed. In the case of RNA medicines, while repeat dosing means that the patient will require continuous treatment to get the disease under control, it also means that the risk for unwanted side effects would not be permanent. Furthermore, RNA medicines can be delivered to different tissues regardless of cell renewal rate.

Lastly, single-dose gene therapies are challenging in every aspect of traditional medicine development, from clinical trial design, to regulatory requirement, as well as health insurance reimbursement plans. Though it is clear that gene therapies will have an increasingly important role in the treatment of diseases, we believe that RNA medicines carry considerably lower risks while retaining important advantages compared to more traditional small molecule and antibody medicine.

Different RNA therapy Technologies: RNA interference, antisense, mRNA and ADAR

As the RNA therapy field advances, diverse approaches have already yielded blockbuster medicines, while the next generation is in development. Prime examples are RNA Interference (RNAi) medicines and Antisense Oligonucleotides (AONs) medicines. RNAi is a naturally occurring phenomenon whose discovery earned the scientists involved the Nobel Prize in Medicine in 2006. Learning how to harness this process has the potential to unlock new ways of treating diseases with high unmet medical need. In RNAi, a double stranded RNA fragment is delivered to the cells, and after cellular processing, it stops the translation of messenger RNA that codes for the faulty, disease-originating protein. The base-pairing precision already mentioned in the paragraphs above ensures that off-target effects are minimized and that only the intended effect is obtained.

AONs are mostly single stranded and, with the due chemical modifications, do not require a vehicle to be transported to the cells after administration. Unlike the double-stranded molecules used for RNAi, AONs can be of variable lengths and do not need cellular processing to exert their therapeutic effect. This allows for broader range of chemical modifications possible to modify and improve the medicines using this technology.

Each with its advantages and disadvantages, RNAi and AONs both have delivered unprecedent efficacy for the diseases that so far had little to no treatment options. In fact, after decades of improvement and research in this field, the first RNAi and AONs medicines have been approved in the last few years, completely disrupting the treatment paradigm. Examples for RNAi and AONs approved medicines are Onpattro and Spinraza, respectively. Onpattro was approved in 2018 for the treatment of polyneuropathy caused by a disease called transthyretin amyloidosis, and Spinraza in 2016 for the treatment of spinal muscular atrophy, a rare neuromuscular disease that often affects newborns. Both medicines showed in clinical studies to be highly effective over a placebo treatment.

Another type of RNA medicines that has recently come to the public attention is mRNA technology, the concept used in the first two Covid-19 vaccines approved in the western world developed by BioNTech/Pfizer and Moderna. By using a delivery system based on nanoparticles, mRNA medicines deliver the instructions to cells to produce proteins that would otherwise not be produced in our body.

RNAi and AONs are two of the most advanced RNA technologies, but the field is in constant evolution. For example, some companies are developing technologies that would allow selectively editing the RNA in the cells, with the precision of changing one single nucleotide, leaving the rest untouched. This approach exploits adenosine deaminases acting on RNA (ADAR) to deliver precise and targeted changes to mRNA responsible for the production of harmful proteins. Despite it being in early stage of development, this technology and many others hold great promise for the future of the already disruptive RNA medicines.

From Rare to Common Diseases

As already mentioned, the first RNA medicines are now in the market mostly treating rare diseases. Though it made sense to start testing these new technologies in rare, genetically well-characterized diseases, it is now clear that the RNA medicines' potential is not limited to them. For example, an RNAi medicine that strongly lowers LDL-cholesterol, commercialized under the name Leqvio, was recently approved in Europe and can be used to treat millions of people. This highlights how broad the spectrum of application for RNA medicines is. Furthermore, RNA companies are closing in on expanding the amount of organs targetable with their medicines . new technologies are now in, greatly expanding the number of diseases that can be treated with RNA medicines.

Outlook

Through decades of investments and research, RNA medicines are now an established treatment technology and there is a wave of them coming to the markets driven by tens of companies. The benefit they can bring to patients is clearly exemplified by the already approved RNA medicines, and the continued efforts to improve the technology and expand its applicability herald the important role that RNA therapeutics will have in getting to a better treatment or even cure for millions of people.

Best regards on behalf of the Aescap team,

Patrick J. H. Krol
Portfolio Manager Aescap Life Sciences

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The selection of companies in our portfolio is based on 'high conviction' - extensive fundamental analyses combined with intense interaction with management and relevant experts. The fund's performance is fueled by stock picking and an active buy and sell discipline. Biotech stocks are known for their very low correlation and high volatility, caused by media, macro-events and short-term speculative investors. This creates an ideal setting for a high conviction fund manager to invest in undervalued companies with a great mid- and long-term earning power. The fund has an average annual net performance target of 20% over the mid-term (4-5 years)

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Aescap • Barbara Strozzilaan 101, 1083 HN, Amsterdam, The Netherlands
Tel. +31 20 570 29 40 • E-mail: service@aescap.com