RNA Modulation: Gabriele Campi

Why we should take a second look at RNA technology

As a scientist first, but also as an investor, I have always believed in the potential of RNA molecules as therapeutics. While most current drugs aim to stop disease by modulating existing proteins, RNA molecules operate one step earlier. In the case of RNA interference (RNAi), they modulate the genes involved in different pathological processes. The RNA molecules, small interfering RNA and microRNA, both degrade messenger RNA (mRNA) and prevent it from being translated into proteins.

I am the co-founder of the investment company AurorA Science, which recently led a Series B financing round for the Dutch company InteRNA Technologies, which is developing RNA therapeutics for the treatment of advanced solid tumours. This is an ambitious project, but with a potential for success. This is because the RNA therapy sector, which started with great momentum and slipped into disfavour, is now back with new technology and confident leadership.

Most observers credit the US scientists Craig Mello and Andrew Fire for inspiring the wave of RNA therapeutics research that started at the turn of the last millennium. Messrs Mellow and Fire received the Nobel Prize in Physiology or Medicine in 2006 for describing the role played by double-stranded RNA in silencing genes that code for the production of disease-causing proteins. At the time of the award, a number of small companies were already starting to exploit the RNAi technology, including Sirna Therapeutics.

In 2007, Merck & Co bought Sirna for $1.1 billion in cash. At the time, Merck had an ongoing partnership with Alnylam Pharmaceuticals, a university spin-out with a patent position in RNAi. That same year, Roche reached a deal with Alnylam, paying $331 million upfront for access to its RNAi technology.

But what looked like a new wave of therapeutics ran into difficulties after a number of early clinical programmes were halted by the Food and Drug Administration following adverse events. Developers were seeing off-target effects from the therapies including unexpected innate immune responses and most importantly, problems with delivery of the drugs into the cytoplasm of target cells.

With doubts raised about the drugs' safety and delivery, Roche and Merck started to cut their exposure. Roche was first, with a decision to discontinue RNAi research and early development in 2010. A year later, it sold its RNAi assets to Arrowhead Research Corp. In 2014, Merck sold Sirna to Alnylam for $175 million in cash and equity, plus milestone commitments of up to $105 million per product – roughly 25% of the price it had paid for Sirna in 2007.

Alnylam may have looked like a winner at the time, but it too encountered a setback. In 2016 it discontinued development of revusiran, a siRNA therapeutic for hereditary ATTR amyloidosis with cardiomyopathy, for safety reasons. A review of a Phase 3 study found that more patients died in the treatment arm of the study than those who were on placebo. However, the decision to discontinue revusiran didn't affect another late-stage molecule – patisiran.

Patisiran is also a siRNA but for a different disease: hereditary ATTR amyloidosis with polyneuropathy, an autosomal dominant neurodegenerative disease. In 2018 patisiran (Onpattro) was approved by the FDA. It is delivered to cells by lipid nanoparticles rather than GalNAc (N-Acetylgalactoseamine-siRNA conjugates).

Since the end of 2018, investors have made a cautious return to the RNA therapy space with a targeted funding of existing RNA companies. In parallel, new companies are entering the arena. An unexpected boost to the industry has come from the development and approval of the first mRNA vaccines to treat Covid-19 from Pfizer/BioNTech and Moderna.

I have always believed in the potency of RNA interference and modulation techniques that allow a researcher to target specific messenger RNAs through the use of siRNAs, or multiple targets, with microRNAs. Like every powerful technology however, it needs to be fine-tuned and well controlled. Transcriptomic experiments are crucial, not only to certify the direct effect of the molecule on the target(s), but also to detail what downstream modulation the intervention can exert, in addition to shedding light on potential safety issues and off-target delivery. InteRNA Technologies' lead compound, INT-1B3, which is in clinical development, exploits potential anti-tumoural activity in a miRNA-based fashion. The company intends to revert the reduction of miRNA-193a-3p observed in tumour cells using a miRNA-193a-3p mimic integrated into lipid nanoparticles.

The convincing feature of INT-1B3 stands in its dual mechanism of action that addresses multiple hallmarks of cancer simultaneously. First, it directly targets tumour cells and the tumour microenvironment by modulating multiple signaling pathway components across the PTEN tumour suppressor pathway and the oncogenic PI3K/Akt and Ras/MAPK pathways, resulting in the inhibition of proliferation and migration and induction of cell cycle arrest and apoptosis.

Second, it triggers the immunogenic tumour cell death process as well as the down-regulation of the adenosine-A2A receptor pathway through inhibition of CD39/CD73, leading to a decrease in immunosuppressive FoxP3/Lag3 regulatory T cells and monocytic myeloid-derived suppressor cells. As a result, the immune system is activated, and long-term immunity is triggered by the recruitment of CD8+ effector T cells, leading to decreased metastasis development and improved animal survival.

At AurorA Science we tend to focus on science, working to build a portfolio solidly based on innovative therapies. Our technical committee of scientists from Italfarmaco and Rottapharm Biotech enables us to conduct in-depth scientific due diligence, while our board of directors with Guido Guidi as chairman, and the entrepreneurs Lucio Rovati and Francesco De Santis as members, gives us a structured direction.

This article was written by Gabriele Campi, PhD, co-founder and managing partner of AurorA Science of Milan, Italy.