NUCLEIC ACID INSIGHTS

OLIGONUCLEOTIDES: TARGETING & DELIVERY

SPOTLIGHT

INTERVIEW

Pushing the boundaries of siRNA targeting and delivery

Although siRNA therapeutics have made significant progress in terms of their stability and safety, key challenges relating to the specificity and efficiency of delivery remain. **David McCall**, Senior Editor, BioInsights, talks to **Merle Fuchs**, Co-Founder and CEO of PRAMOMOLECULAR GmbH, about promising approaches to address this issue and continue expanding the range of applications available to oligonucleotide therapeutics.

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Q Tell us about your background in the nucleic acids space.

MF: I am a molecular biologist by training. I did my PhD at the lab of Nobel Prize winner Manfred Eigen, at the Max Planck Institute for Multidisciplinary Sciences in Göttingen. It was a great place to learn interdisciplinary work, which is something I really love. After my PhD, I worked for nearly 25 years as a consultant for high-tech startups as well as mature companies. I had my own company, and I am co-founder of an additional seven high-tech startups. One of those is BianoGMP, which was recently acquired by EUROAPI. BianoGMP produces

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GMP-compliant therapeutic oligonucleotides. It was through this work that we became aware of the problem of delivery of therapeutic oligonucleotides to locations other than the liver. Around the same time, we also became aware of the research of a particular academic group whose leader spent nearly his whole academic life developing covalent, lipid-based delivery molecules for mononucleotides. Our idea was that if these molecules work for mononucleotides, they may also work for oligonucleotides. We took our own money and started our first animal experiment. We only looked at three organs: the liver, lung, and kidneys. With the first delivery molecule we observed a high silencing efficiency in the lung, but not in the kidneys and not in the liver, which was quite interesting.

With these results, we managed to acquire funding from the German Ministry of Economics. The grant is called EXIST-Forschungstransfer and it's the most important and prestigious funding for pre-seed high-tech projects in Germany. With this money, we were able to generate additional data and start PRAMOMOLECULAR in 2021.

Q Can you frame for us the key challenges in targeting and delivery of siRNA therapeutics, both historically and currently?

MF: Historically, the challenges were stability and safety, but these issues have now been resolved. Today, the important topics are endosomal escape, cell entry, transfection rate outside of the liver, and specificity/organ preference.

Q Can you tell us more about PRAMOMOLECULAR and its focus?

MF: 'Pramo' means 'ferry' in Esperanto, and our name was chosen because we utilize covalent lipid-based 'ferry' molecules. We couple defined lipids via defined chemical bonds directly to the siRNA, which helps to stabilize the siRNA and to ferry it through the cell membrane. Interestingly, we see different organ preferences in the combination of siRNA and lipid-based delivery molecules, with higher organ preference for the lung, heart, and pancreas, but a comparatively much lower preference for the liver, kidneys and skeletal muscle.

Currently, we are focusing on KRAS mutations in non-small cell lung cancer and in colon cancer for local applications. We have also started to search for siRNAs against heart proteins for use in heart failure, but this work is at a very early phase. We have concentrated initially on

the organs where we see the highest transfection rates. PRAMOMOLECULAR doesn't know precisely why we have this organ preference, but we see it and we use it. Biology still involves an element of alchemy!

Q What differentiates PRAMOMOLECULAR's approach?

MF: I believe we have the most straightforward covalent lipid-based delivery system out there for our target organs, particularly if you compare our approach to our most important technological competitor, DTx Pharma. There is not a lot of data about them available, but what we have seen is that they use several delivery molecules per each siRNA, and we only need one. They are able to target neuromuscular disorders via neuroproteins, and we address these proteins in our three target organs. DTx was bought by Novartis last year for US$500 million fixed with a potential further US$500 million in milestone-dependent payments. We think we also have a very interesting approach and could build a similar story.

Q Looking across the wider oligonucleotide field today, where do you currently see exciting innovations that can expand the application and the success of these technologies in the therapeutic setting?

MF: I think covalent delivery is the cutting edge at the moment. There had been lots of siRNA approaches using nanoparticulate systems, but if we look at the technologies that are in the clinical phases, most of them are either naked siRNA, or a combination of covalent delivery molecule and siRNA. I believe we will also see more and more innovation in the local delivery applications because we see that even here, delivery is a problem. It is not enough to directly introduce your drug into the organ. For example, at the beginning of this year, the US FDA didn't accept the data from Sylentis' Phase 3 clinical trial of a naked siRNA against dry eye disease due to inefficiency. We think that even for these local applications, you should use a delivery molecule. Our technology's particular advantage is that it makes it easy to do this. Our delivery molecules can be coupled as an additional phosphoamidite during the last step of oligonucleotide synthesis, and it is very easy to test whether you can increase the transfection rate, even for local applications.

There are lots of efforts underway utilizing lipid-based delivery molecules. For example, at the end of 2022, Alnylam Pharmaceuticals published a *Nature Biotech* paper where they showed data from their own lipid-based delivery molecule. Most of the data addressed the central nervous system, but they also had a dataset where they addressed the lung. We compared their data with our own. For the biodistribution data, we used non-optimized siRNAs, and Alnylam used highly optimized siRNAs. They were able to show, after systemic application, a silencing rate of 40% whereas we, with our non-optimized *in vivo* systemic application,

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showed 50%, which would suggest that our molecule may be the more efficient of the two. We believe that our proprietary linker sterically aligns the siRNA and lipids in a particularly favorable way for membrane transition.

Q And looking to the future, what for you will be some key directions for innovation in the oligos field, both in terms of technology platform/modality development and specific indications?

MF: In the beginning, nearly everybody in the field concentrated on orphan diseases but today, we see lots of other diseases being approached. Cancer is a hot topic, but poses a lot of problems. We have seen clinical data from cancer trials—for example, from Silexion Therapeutics (formerly Silenseed). They had a local approach and were not able to show high efficiency, but I believe they are working to improve their delivery technology. Cancer will be an increasingly key focus moving forward.

Very recently, the University of Nashville, TN, published another delivery approach based on lipid-based, non-particulate delivery systems in *Nature Communications*. Like us, they covalently couple long-chain lipids to siRNA via a chemical linker. But they also use several hydrophilic 'spacers'. In three xenograft mouse models of human triple-negative breast cancer, they achieved an impressive reduction in tumor growth by silencing the MCL-1 mRNA. I also wonder how many innovations in the field of *N*-acetylgalactosamine (GalNAc) are possible. Lots of molecules have entered clinical trials using the GalNAc system and this will remain a hot topic. And there are a number of associated approaches to optimize endosomal escape, but I don't think any of those have entered first-in-human trials as yet.

Q Finally, can you sum up one or two key goals that you have for your own work/role over the foreseeable future?

MF: We are still in a quite early preclinical phase, but we are now concentrating on strategic preclinical development, with an aim of entering the clinic in 2026.

My most important job at this stage is to communicate. We are very interested in partnerships with both small and medium-sized enterprises but also with big pharma. My core responsibility is to find enough money to finance our approach.

AFFILIATION

Merle Fuchs
Co-Founder and CEO,
PRAMOMOLECULAR GmbH

AUTHORSHIP & CONFLICT OF INTEREST

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