

Interview with Roland Kreutzer, Managing Director of Alnylam Europe

# Really better than Antisense?

RNAi has been widely hyped. Will siRNA drugs be better than antisense, small molecules and antibody-based drugs? An interview with Roland Kreutzer, Managing Director of Alnylam Europe, about the opportunities and characteristics of siRNA drugs – and about Alnylam itself.

**D**r. Kreutzer, why is RNA interference better than antisense therapeutics?  
**Roland Kreutzer:** Well, it starts with the molecule itself. Antisense molecules are single-stranded and very unstable. Before using the RNA, you have to find ways to stabilise it. Mostly, people solve this problem by synthesising DNA instead of RNA. They further stabilise this DNA with certain chemical modifications, which tend to be toxic. So you can't go very high in concentration. On the other hand, the antisense mechanism isn't very effective. So you need high, almost stoichiometric concentrations for the RNase H mechanism to work. RNA interference is very different. It needs only minute doses of siRNA to gear the catalytic mechanism. And siRNA is much more stable because of its double-stranded nature.

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*RNAi was first described in 1998 in C. elegans by the two Nobel Prize winners Fire and Mello. Not even ten years later the technology has made it well into clinical testing. Alnylam has its first candidate nearly in phase II. Other companies are about to start phase III.*

**Kreutzer:** Yes, it's one advantage of RNAi to shorten the developmental period. In comparison to drug development for small molecules we can skip the tedious high-throughput lead molecule screening. We just choose the target and produce tailor-made siRNAs.

*Provided that you know what goes wrong in a disease...*

**Kreutzer:** Yes, sure. This is a rational approach. We need to know something about the mechanisms behind a disease. How the targets affect the disease. So we

depend on basic research and the advance of molecular understanding.

*Do the siRNA drugs address the same targets as other drugs? Just using a different mechanism for manipulation?*

**Kreutzer:** Some may use the same targets. However, the other big advantage of siRNA is that we are able to aim at



non-druggable targets, too. Targets, that haven't been susceptible to small molecules or antibodies. With small molecules you can do things like blocking the active centre of an enzyme. But if interactions between proteins are the cause of a disease, small molecules are of little help. Antibodies can block interactions, but are best for targets on the cell's surface. With siRNA drugs we don't have these constraints and are able to go for completely new targets. Especially intracellular targets.

*Though there always have to be targets to silence, you can't enhance a gene using siRNA.*

**Kreutzer:** Not directly, but knowing the pathway you can always find a way for upregulation, too. In hypercholesterolemia for example, we get more LDL receptors by silencing its inhibitor PCSK9 in the liver. And more LDL receptors mean less LDL cholesterol in the blood. So the trick is to enhance one gene by silencing an other.

*"The problem is to overcome the cell membrane. That's a big obstacle, because siRNA is a highly charged molecule."*

*In the beginning, most siRNA companies focussed on the local application of siRNA drugs. Your siRNA therapeutic against RSV infection is administered as nasal spray. It seems that everyone else is focussed on the macula degeneration therapy...*

**Kreutzer:** Well, it's a local delivery, too. Although I imagine it to be unpleasant, the injection of drugs into the eye seems to be quite straightforward. At least this is what ophthalmologists say. And there are some good targets for stopping the neovascularisation responsible for the loss of vision. Therefore, many companies are into it.

*Then there is systemic delivery, for which there is no ultimate solution yet. Along with other companies, is Alnylam trying several different systems?*

**Kreutzer:** Yes. For the approach published in *Nature*, we used SNALPs licensed from Protiva – stable nucleic acid lipid particles. With their help we could efficiently and in low dosage silence apo B in liver cells. In parallel, we started a cooperation with the Canadian firm Tekmira, using their liposomal system of delivery, for which we already have good data in animal model. Furthermore, we are testing all kinds of delivery systems including our own developments. Just last week, we

filed a new patent for a delivery method developed as part of a PhD-thesis in our labs. I expect that these systems will allow us to aim at other diseases, too. There are some very good ones among them.

*Each one is a bit different? One works better in the liver, one in the kidney?*

**Kreutzer:** Yes, exactly. They are organ and tissue specific. However, this specificity is only one part of the problem. The other is to overcome the cell membrane. That's an even bigger obstacle, because siRNA is a highly charged molecule.

*And when you have found a way to enter the affected cells, for how long does the siRNA effect last?*

**Kreutzer:** We know from cell culture and *in vivo*, that a single dose of siRNA has a continued effect over several weeks.



*This means that for patients with chronic diseases they will have to be injected every few weeks. Or will there be a way to take it orally some day?*

**Kreutzer:** Although it's an aim for the future, an oral application is not in sight yet. That's why we focus on non-chronical diseases first, where the cure can be reached within half a year with only a few injections. Applications, where you get siRNA for the rest of your life are not in Alnylam's focus for now.

*Are you thinking about genterapeutic approaches for chronic diseases?*

**Kreutzer:** There are some siRNA companies, that work on gene therapy but we are committed to siRNA therapeutics on a chemical-synthetic basis. Gene therapy is always problematic for public acceptance. Besides, there are publications in siRNA gene therapy showing problems with overdosing. With bringing the drug in from outside, we can control the dosage easier.

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*How expensive will siRNA be? Isn't RNA synthesis quite expensive?*

**Kreutzer:** Yes, at the moment it's still expensive. But I assume that it will become considerably cheaper as we have seen for DNA, too. Then the cost of goods will not play a big role anymore.

*So if siRNA therapy in the future becomes cheap and rapid to develop, would it provide a chance for otherwise neglected and rare diseases?*

**Kreutzer:** I think so. If siRNA technology advances the way we hope and expect, it will become a technology for neglected diseases and for individualised medicine, too. But first things first. In the next years we have to build the base and see if siRNA therapeutics lives up to its promises.

*Still, siRNA drugs have already come somewhere. When you started with Ribopharma, did you imagine that the field would be where it is now, only eight years later?*

**Kreutzer:** We hoped so, but the idea was so new that in the beginning we had difficulties finding investors. We started off with half a million euros from the state, managed to raise four million in venture capital and then another four million.

*Ribopharma merged with the US company Alnylam Pharmaceuticals, three years after you and Stefan Limmer started the business in the very north of Bavaria. Alnylam was newly founded then, wasn't it?*

**Kreutzer:** Yes, Alnylam was founded the year before by Tom Tuschl, Phil Sharp and others, who are the inventors of the so called Tuschl patents. And they started off very differently. From the beginning they had a professional management and seed capital of 17 million dollars. The Ameri-

can way. Think big! And great names on the board, important people from the science and biotech scene in the US.

*Is this the reason why Alnylam's name and principal office was chosen for the corporate group after the fusion?*

**Kreutzer:** Yes, absolutely. Alnylam dominated because of their greater potentials. That's obvious.

*I imagine this to be difficult for the founders of a company like you.*

**Kreutzer:** We were perfectly aware about giving up our autonomy. However, the benefits overwhelmed. First of all the combination of fundamental patents, secondly the gain in financial potential and thirdly the professional management. And as you can see, it paid off. I think we couldn't have made a better decision.



*What's for you the best sign that it worked out?*

**Kreutzer:** Alnylam's success is phenomenal. In the short time of less than four years since the fusion, the company has built a substantial product pipeline and reached a considerable market capitalisation. That's gigantic. I think, there aren't many other examples like this.

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