

siRNA at Novartis

Innovation in Novartis R&D



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“Silencing” disease for patients

Scientists at Novartis are ushering in a new era in medicine as they explore the potential of siRNA therapeutics. Instead of counteracting a harmful protein, as most drugs do, siRNA prevents its production in the first place.

“The promise of siRNA is the versatility of the approach and the idea that this approach can hit any target in the genome,” says Mark Keegan, a member of the global siRNA formulation screening team (Pharma Development). More targets translate into more applications. “There is literally no disease area where you couldn’t use this approach,” says Michael Keller, also on the formulation screening team. Keegan, Keller and other members of the team are working together to develop innovative approaches for developing siRNA-based therapies.

The Promise of siRNA

Most diseases are caused by the inappropriate activity of specific proteins because too much (or too little) or an abnormal protein is produced. The ability to stop the production of abundant or abnormal proteins would result in new treatments for a wide range of diseases. Once proven, that is the promise of siRNA, a sophisticated technology that holds great hope for patients.

Here is how it works. RNA is typically a long, single-stranded molecule which carries instructions from the DNA in the nucleus, which then sends instructions to the ribosomes in the form of messenger RNA (mRNA). siRNA stands for “Short Interfering Ribonucleic Acid” because siRNAs interfere with mRNA and thus the production of proteins. siRNAs activate a complex biochemical process by which specific mRNA molecules are sliced and degraded. When these molecules disappear, the corresponding gene is silenced, and no protein is made.

siRNA: A new therapeutic class

siRNA therapeutics are part of a newer class of medicine called “biologics” along with antibodies and therapeutic proteins. Biologics are large and complex molecules produced by biological processes [See Biologics at Novartis in the R&D Innovation series]. Low molecular weight (LMW) drugs are the most widely-used class of medicinal compounds. Both LMWs and biologics work to reduce the activity of malfunctioning or abundant proteins, but in some cases none of the more established classes of medicine are able to interfere with the disease-causing proteins. This represents the opportunity for siRNA therapeutics.

“We’re left with a large number of important disease targets which are not druggable,” says David Morrissey, Head of RNAi Therapeutics at Novartis Institutes for BioMedical Research (NIBR). “So siRNA is expanding the druggable universe.” Theoretically, siRNAs can silence or slow the production of any protein a cell can make, so this technology offers medicine an exciting option: a completely new therapeutic class.

Benefits and challenges

As in any drug discovery process, there are benefits and challenges, and siRNA is no different. Once a gene target is selected, dozens of siRNAs which are complementary to various parts of the gene are synthetically constructed. This is the easy part, and a benefit of, the process; the challenge is getting them into the cell because siRNAs are repelled by the cell wall. However, several companies are working on this and various delivery methods do exist, including the use of nanoparticles and liposomes, among others.

Once inside the cell, the siRNA works to silence the target gene. About 10% of the time, the wrong gene is silenced because of sequence

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similarity. Another concern is that siRNAs, like viruses, are double-stranded, so they also can set off an immune response. The immune response either can be harnessed as a secondary attack against the disease—another positive—or it can be suppressed by siRNA design modification.

Although an siRNA therapeutic must be administered frequently—monthly or even weekly—once in the cell they are systematically transferred from one cell to another through an amplification effect. This is a key component to the success of siRNAs, since to be effective they must get into all cells that are affected by the disease. For example, if you add an siRNA therapeutic to the root of a plant you will see an effect in its leaves. Similarly, although it is best to inject an siRNA therapeutic directly into the disease site (such as the eye in age-related macular degeneration [AMD]), less direct and more patient-friendly delivery methods also can be used, such as an eyewash.

Within three or four months, the best siRNA candidate can be determined for a particular target gene, and after that, theoretically, a drug can be ready for market within two years. When siRNA therapy matures, it will radically shorten the time a drug needs to work its way through the pipeline—a major benefit of this therapeutic.

Novartis and siRNA

Novartis scientists are working on RNAi therapeutics to address a broad spectrum of human diseases: Age-related Macular Degeneration (AMD), cancer, cystic fibrosis, Alzheimer’s and Huntington’s Disease. “The reason we’re really excited about siRNA is it gives us a generic platform for taking out a protein,” says John Hastewell, Global Head, NIBR Biologics Center. “This is a mechanism in the body that we can use for therapeutic purposes which is applicable to all proteins. It is very powerful and very specific.”

Many companies have entered the siRNA field. However, Novartis was among the first major pharmaceutical companies to enter and significantly invest in RNAi therapeutics. In early 2010, the entire NIBR RNAi group in Basel, Switzerland, now split between two buildings, will move into one facility (over 1000 sq ft) and be co-located with expertise in imaging technology and biomarker development. Through its various research teams and ongoing collaborations, Novartis is well-positioned to harness the latest scientific advances and expand its ability to meet patient needs.

