

Making Sense OF ANTISENSE TECHNOLOGY

► *Brett Monia, Ph.D., Chief Operating Officer and Senior VP, Antisense Drug Discovery and Translational Medicine at Ionis Pharmaceuticals, talks about the company's pipeline of antisense technology products.*

Antisense technology presents an opportunity to manipulate gene expression within cells to prevent or increase the production of proteins involved in disease processes. Because proteins are fundamental components of all living cells and include many types of molecules, such as enzymes, hormones, and antibodies, that are necessary for carrying out the body's functions, the overproduction or abnormal production of proteins leads to a variety of disease states.

Ionis Pharmaceuticals' antisense technology led to the development of its breakthrough therapy Spinraza. Spinraza is approved in the United States, the European Union, Brazil, Japan, and Canada for the treatment of spinal muscular atrophy (SMA). (Biogen is responsible for commercializing the therapy.) SMA is characterized by loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscular atrophy and weakness.

"Spinraza has changed the lives of SMA patients by extending and improving their quality of life," says Brett Monia, Ph.D., chief operating officer and senior VP, antisense drug discovery and translational medicine, Ionis Pharmaceuticals.

In the Phase III program, Spinraza treatment was shown to significantly reduce the risk of death or permanent ventilation in infants with SMA. New analysis from the company's Phase III study showed infants with SMA, who initiated treatment with Spinraza earlier in the disease, demonstrated greater benefit and improvement in motor function outcomes. SMA infants treated before symptom onset are able to achieve motor milestones generally consistent with normal development.

"Our platform is a third way to discover drug targets, using RNA, which is different from approaches using monoclonal antibodies and small molecule target proteins," Dr. Monia says. "We are targeting RNA molecules, which make proteins."

Therapies created using antisense technology offer advantages over small molecules and monoclonal antibodies, including specificity, ability to pursue a much broader range of targets, all with improvements in efficiency. As a consequence, better drugs can be discovered much more rapidly than small molecules or antibodies, and there is a broader array of targets implicated in human disease that can be exploited.

"By targeting RNA, we prevent the bad protein — the protein that causes the disease — from ever being made," Dr. Monia says.

"Our drugs look like DNA molecules, but

they're chemically modified and they use the same natural process that RNA and DNA use to bind to each other," Dr. Monia explains. "Our drugs, which bind selectively to RNA, can prevent that RNA from being translated into protein."

Antisense drugs can work through other mechanisms to change the way a protein is made (e.g., via altering splicing of the RNA as Spinraza does in SMA) and can also increase protein production via enhancing translation of the mRNA into protein.

Dr. Monia points out that antisense technology products are about 10 times larger than traditional small molecules but far smaller than antibodies. Additionally, antisense therapies are created through chemical reactions instead of being made through fermentation.

Ionis has a pipeline of more than 40 drugs. The company's late-stage research includes therapies for both rare and common diseases. One such product is inotersen, an antisense drug being developed to treat patients with hereditary TTR amyloidosis (hATTR). This is a fatal disease that causes peripheral nerves to stop working and damages the heart, kidneys, and other organs. In patients with ATTR, the TTR protein builds up in tissues including peripheral nerves, the heart, gastrointestinal system, eyes, kidneys, central nervous system, thyroid and bone marrow, interfering with normal function.

"We've shown that our drug targets the disease-causing protein and blocks its production," Dr. Monia says.

Ionis submitted marketing authorization applications for inotersen in November 2017 in the United States and the European Union. The FDA has granted orphan drug designation, fast track status, and priority review to inotersen. The European Medicines Agency has granted orphan drug designation and accelerated assessment to inotersen.

Another Phase III program is volanesorsen, an antisense drug discovered by Ionis and co-developed by Ionis and Akcea Therapeutics, an affiliate of Ionis, which is being evaluated to treat patients with either familial chylomicronemia syndrome (FCS) or familial partial lipodystrophy (FPL).

Volanesorsen is designed to reduce apoC-III protein production and reduce triglycerides. ApoC-III is a protein produced in the liver that regulates triglyceride metabolism in the blood. Volanesorsen is currently under regulatory review in the United States, European Union, and Canada for the treatment of patients with FCS, and has been granted



Dr. Brett Monia

priority review in Canada. The U.S. and European regulatory agencies have granted orphan drug designation to volanesorsen for the treatment of patients with FCS. The European regulatory agency has also granted orphan drug designation to volanesorsen for the treatment of patients with familial partial lipodystrophy (FPL), another rare metabolic disease.

"We've shown that in patients with severely elevated triglyceride levels, that volanesorsen lowers triglycerides down to normal levels, and as a consequence, patients feel a lot better," Dr. Monia says.

Another promising therapy is IONIS-HTT to treat patients with Huntington's disease. IONIS-HTT is an antisense drug designed to reduce the production of the huntingtin (HTT) protein. A genetic mutation in the HTT protein is the known cause of Huntington's disease. Mutant huntingtin is a toxic protein that progressively destroys neurons in the brain. As a result, patients experience loss of mental faculties and physical control as their disease progresses, inevitably resulting in death.

The results of a completed Phase I/II study in early stage HD patients found dose-dependent reductions of mHTT levels, the first time any drug has lowered the level of this toxic protein. Ionis has partnered with Roche for further development and commercial activities.

In cancer, the company is working with AstraZeneca to develop a therapy that targets STAT3, a protein involved in the production of key factors critical for tumor cell growth and survival. STAT3 is found to be over-active in a variety of cancers, including brain, lung, breast, bone, liver, and multiple myeloma.

"IONIS-STAT3 (AZD9150) has produced impressive activity in combination with the AstraZeneca drug Imfinzi, an immuno-oncology drug," Dr. Monia says. "Our STAT3 drug works through an immuno-oncology mechanism." ^{PV}

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