Emerging Company Profile

ProNAi: The other interference

By Michael Flanagan
Senior Writer

While some RNAi technologies have achieved proof of principle in the clinic and brought in big deals over the last couple of years, ProNAi Therapeutics Inc. thinks its DNA interference technology could provide dosing advantages by directly shutting off the target gene rather than seeking to stem the flow of mRNA transcripts. The company's lead DNAi agent, PNT2258, will enter Phase I testing for cancer early next year.

"The value proposition from ProNAi is that, unlike the RNAi agents, which require repeated dosing in order to keep inhibiting the RNA cascade, we should only need two copies of the DNAi construct to shut down the target gene in each cell. That means we'd be able to use lower doses for a shorter time period, so DNAi should result in an improved toxicity profile," President and CEO Richard Gill told BioCentury.

Based on technology licensed from Wayne State University, ProNAi (Kalamazoo, Mich.) has shown in animal models that a single-stranded oligonucleotide with a single base pair mismatch is capable of targeting the 5' promoter region of a specific oncogene in the cell, thus blocking transcription.

RNAi approaches, such as double-stranded small interfering RNA (siRNA) agents, work by binding mRNA transcripts, which are continually expressed by a disease gene. According to Gill, this means RNAi-based treatments will tend to be given in higher doses to block the translation of multiple mRNA transcripts into protein products, and the need for higher dosing will be less cost effective.

In preclinical testing, ProNAi determined that 10-20 mg/kg/day is the ideal IV dosing regimen for PNT2258. He added that it has a wide therapeutic window, "as you don't see any toxicology issues until 75 mg/kg in monkeys and 30-35 mg/kg in rats."

As has been the case with RNAi, COO Robert Forgey said one of the major stumbling blocks for DNAi has been finding a method for effectively delivering an agent systemically to the target cells. He believes ProNAi has overcome this problem by licensing access to a liposomal encapsulation technology from Novosom AG (Halle, Germany), which allows for transport of the oligonucleotide through the bloodstream by encapsulating it in a liposome with a neutral surface charge.

"Many RNAi technologies have gone to chemically modifying their compounds in order to improve their half-life, which increases production costs," noted Gill.

"This is not something we have to do because the liposomal encapsulation provides the half-life."

Gill believes ProNAi will be the first company to begin human testing with a DNAi agent when it begins the Phase I trial of PNT2258 to treat cancer early next year. The compound targets the Bcl-2 oncogene, which plays an important role in dysregulation of apoptosis in tumor cells and has been linked to chemotherapy resistance in cancers such as non-Hodgkin's lymphoma (NHL).

PNT2258 has shown activity when combined with Rituxan rituximab in preclinical models of lymphoma, as well as in combination with Taxotere docetaxel for melanoma or prostate cancer. Based on discussions with FDA, however, the company's plan is to first conduct an all-comers Phase I trial to get a better look at how it works in an array of cancers and in combination with a variety of background treatment regimens, said Gill.

In parallel with the Phase I start, ProNAi is seeking investors to top off a B round in the $25 million range, which Gill expects will include $12-$13 million in new money, with the rest converted from an earlier bridge financing. This money will see the company through to late 2009, when he hopes to have proof-of-concept results from the Phase I trial to attract a potential partner.

Gill said the proceeds from the B round also will be used to take a lead candidate from a second DNAi program into preclinical development next year. The program targets the c-myc oncogene, which increases cell proliferation and is overexpressed in a number of cancers.

Genentech Inc. (DNA, South San Francisco, Calif.) and Biogen Idec Inc. (BIIB, Cambridge, Mass.) market Rituxan. sanofi-aventis Group (Euronext:SAN; SNY, Paris, France) markets Taxotere.

ProNAi Therapeutics Inc.

Kalamazoo, Mich.

Technology: Single-stranded DNA interfering therapeutic agents

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2004 by Robert Forgey, Neal Goodwin, Don Parfet, Mina Sooch and Eli Thomssen

University collaborators: Wayne State University

Corporate partners: None

Number of employees: 9

Funds raised: $13 million

Investors: Grand Angels, Biosciences Research Commercialization Center, Apjohn Ventures, Michigan Technology Tri-Corridor, Michigan Economic Development Corp., Amherst Fund and Sigvion Capital

CEO: Richard Gill

Patents: 1 issued covering single-stranded oligonucleotides that target specific DNA sequences