Strategy

A handful would be fine

By Michael Flanagan
Senior Writer

Regulus Therapeutics Inc. has not yet put anything in the clinic from its microRNA discovery platform, but it has translated the technology’s potential into a pair of lucrative deals with pharma partners before reaching its third birthday.

Two years after signing a discovery deal with a potential value of more than $500 million with GlaxoSmithKline plc, Regulus last week entered a partnership with sanofi-aventis Group that could turn out to be even bigger. The biotech thinks it has the bandwidth to do another deal or two over the next couple of years, but recognizes the importance of ring-fencing a few programs to build its own business.

MicroRNAs are endogenous, single-stranded RNAs that regulate gene expression by binding to mRNA to inhibit translation or promote mRNA degradation. An individual miRNA can simultaneously target multiple mRNAs, meaning it potentially can repress the expression of a large number of proteins.

“The reason that pharma is so interested is because microRNA therapeutics represent a new approach, and one that has the potential to control entire pathways rather than just hitting on single targets,” said President and CEO Kleanthis Xanthopoulos.

“Multi-factorial diseases have multiple components, and that’s why drugs often prove ineffective. But if you can modulate an entire pathway rather than just one target, then you will have a much bigger therapeutic effect,” he added.

The potential has not been lost on big pharma.

Less than a year after being established as a JV between Alnylam Pharmaceuticals Inc. and Isis Pharmaceuticals Inc., Regulus partnered with GSK to discover and develop antagonists of four miRNA targets to treat immuno-inflammatory diseases.

Regulus received $20 million up front and is eligible for $144.5 million in milestones for each of the four programs, plus tiered royalties up to double digits.

GSK and Regulus entered a separate deal in March to develop therapeutics targeting microRNA-122 for all indications, with HCV as the lead indication. The biotech is eligible for more than $150 million in upfront and milestone payments, plus tiered royalties up to double digits.

Xanthopoulos noted that Regulus was in a position to bring on partners almost as soon as the company was formed because Alnylam and Isis had laid the groundwork for the technology. Indeed, he said, Regulus was endowed with over 900 patents and patent applications, more than 600 of which were issued, covering methods of use, chemical modification and administration of oligonucleotides, and their use in addressing specific targets.

Regulus reorganized as an independent company in January 2009.

“We have had talks with a number of pharma and big biotechs, and the majority of them have indicated an interest in complementing their pipeline with microRNA therapeutics,” Xanthopoulos noted. “But this poses the strategic challenge of trying to decide how many deals we can realistically take on.”

Moreover, he said, “we have said from the beginning that we don’t want to be a just a transaction shop that develops programs for other people. So I don’t think that making a dozen deals is going to benefit Regulus in the long term.”
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Under the second large partnership with sanofi-aventis, the partners will collaborate on
discovery and preclinical development, after which the pharma will be responsible for all
development and commercialization costs. The deal is focused on fibrosis.

Regulus could receive over $750 million from the deal, including $25 million up front,
a $10 million equity investment subject to mutual agreement on company valuation, plus
research support, milestones and royalties.

Unlike a lot of recent deals that are back-loaded with regulatory and commercial
milestones, “there is the potential for some significant monies to be coming our way while
still at the preclinical stage,” Xanthopoulos said. “If you split them up into preclinical,
clinical and commercial milestones, they are evenly distributed among the three pots.”

He noted the numbers included in the new partnership are slightly richer for Regulus.

“The technology has had another two years to mature and we’ve made progress in
understanding the biology of microRNA therapeutics,” Xanthopoulos said. “The deal with
sanofi also includes a compound that is in lead development in the microRNA-21 program,
which is not something that was included in the Glaxo deal.”

Another distinguishing feature, he said, was the inclusion of a three-year, $50 million
option for sanofi-aventis to incorporate Regulus’ microRNA discovery technology into its
research labs for use with an undisclosed number of additional programs. If the pharma
exercises this option, Regulus would have opt-in rights.

In the microRNA-21 (miR-21) program, Regulus has a lead program in preclinical
testing for fibrotic diseases.

In 2008, the company published a study in Nature showing that an antagomir-21 against
miR-21 reversed fibrosis and significantly improved cardiac function in mice with failing
hearts.

Regulus is optimizing antagomir-21 compounds, but has not provided a timeline for
entering the clinic.

The biotech hopes to nominate its first clinical candidate this year and enter Phase I testing
in 2H11, though the company is not disclosing whether it will be from one of its collaborations
or an in-house program.

“Programs headed for niche indications and areas of unique unmet medical need, such
as certain oncology indications,” are more likely to be assets that Regulus would be more
interested in hanging onto, Xanthopoulos said.

In the meantime, he said, “our sweet spot would be to have three or four of these large
partnerships, so I could see us doing maybe one or two more over the next two to three
years.”

COMPANIES AND INSTITUTIONS MENTIONED

Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY), Cambridge, Mass.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Isis Pharmaceuticals Inc. (NASDAQ:ISIS), Carlsbad, Calif.
Regulus Therapeutics Inc., Carlsbad, Calif.
sanofi-aventis Group (Euronext:SAN; NYSE:SNY), Paris, France