

BioCentury

Technology Briefing

The pulmonary route for Rebif

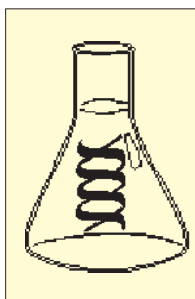
Serono SA and U.S. marketing partner Pfizer Inc. reported \$1.1 billion in sales last year for Rebif interferon-beta-1a for multiple sclerosis. But three subcutaneous injections each week are less than ideal. To solve that problem, Serono has exclusively licensed fusion protein technology from Syntonix Pharmaceuticals Inc. that it will use to develop a multiple sclerosis candidate that can be delivered less frequently via pulmonary inhalation.

"If successfully developed, interferon beta:Fc could be an alternative not only to Rebif, but to all interferon-beta treatments for MS, as it would provide an easier way to administer therapy," said Andrew Galazka, senior vice president of scientific affairs at Serono (SWX:SEO; SRA, Geneva, Switzerland).

All marketed interferon beta products are given via injection: Avonex interferon beta-1a from Biogen Idec Inc. (Cambridge, Mass., BILB) is given once per week intramuscularly, and Betaseron interferon beta-1b from Schering AG (FSE:SCH; SHR; Berlin, Germany) is given every other day subcutaneously.

Syntonix President and CEO Garen Bohlin said the company's Transceptor technology is based on the intracellular neonatal Fc receptor (FcRn), which is responsible for transporting antibodies across epithelial cells. By linking a product to the Fc region of an antibody, he said, Syntonix designs fusion proteins that can cross the epithelial cell barrier and make pulmonary delivery possible.

Syntonix's Fc fusion proteins have an increased half-life in preclinical testing in comparison to other fusion proteins, according to Alan Bitonti, vice president of R&D. "Our monomeric



fusion proteins are able to cross epithelial barriers much better than dimers," he said, "and they have a longer half-life because they bind better to the FcRn," which protects them from the body's natural catabolic process.

In this case, the Fc fusion proteins are monomers that consist of a single interferon beta attached to each Fc construct. Using Transceptor, Syntonix has designed Fc fusion proteins that allow for pulmonary delivery of large molecules such as erythropoietin (EPO), Factor VIII and Factor IX, as well as interferons

alpha and beta.

Pharmacokinetic results from a 2002 human study of an EPO:Fc "corroborated the animal data" that showed the delivery method is viable, said Bohlin.

The company has done feasibility testing with an interferon beta:Fc in non-human primates, which the company said displayed good pharmacokinetics and induced an increase in serum neopterin levels comparable to subcutaneous Rebif. Neopterin is a biomarker associated with interferon-beta activity.

"Typically, we achieve bioavailability of about 30-55% with our pulmonary products versus intravenous dosing in the animal models, which is extraordinary for proteins and compares well with pulmonary insulins that are somewhere in the 5-10% range," said Bohlin.

Galazka expects interferon beta:Fc to enter clinical development within two to three years. He said it is likely to require full clinical development.

Syntonix (Waltham, Mass.) will receive an upfront fee and is eligible for milestones and royalties. —Michael Flanagan

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