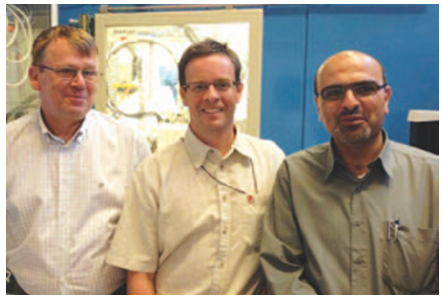
EDITORS' pick

Galecto Biotech

By targeting a sugar-binding protein, a Swedish startup hopes to provide new lung fibrosis treatments.



Galecto founders Hakon Leffler, Ulf Nilsson, and Bader Salameh. (Tariq Sethi and Hans Schambye, also co-founders, are not pictured.)

Idiopathic pulmonary fibrosis (IPF) is frequently fatal and lacks good treatment options, yet historically, the disease has generated tepid interest from biotech and big pharma. That is now changing. Since Brisbane, California–based Intermune's p38 MAP kinase Esbriet (pirfenidone) gained approval in Europe in 2011, Gilead Sciences, Bristol-Myers Squibb and Biogen Idec have all acquired fibrosis companies, and at least six others have compounds for IPF in clinical development. Many of these programs pursue proteins in traditional inflammatory pathways—cytokines like transforming growth factor beta (TGFβ) or interleukin 13—but one little Swedish startup, Galecto Biotech, is chasing a more unusual lectin target, galectin-3.

Galectin-3 (unlike other galectins) not only binds to β-galactoside sugars like lactose but also acts through noncarbohydrate mechanisms, including binding to itself. Tariq Sethi, a pulmonologist and researcher at King's College, London, first reported in 2006 that galectin-3 knockout mice are largely protected from liver fibrosis (*Proc. Natl. Acad. Sci. USA* **103**, 5060–5065, 2006), and two years later showed similar protection from kidney fibrosis (*Am. J. Pathol.* **172**, 288–298, 2008). By then Sethi had been working for several years with medicinal chemist Ulf Nilsson and immunologist Hakon Leffler, both at Lund University, Sweden, who were synthesizing and characterizing novel galectin-3 inhibitors. The three men subsequently reported that blocking galectin-3 with a small molecule (TD139) reduced lung fibrosis in a mouse model of the disease (*Am. J. Respir. Crit. Care Med.* **185**, 538–546, 2012). Two years ago, together with receptor biologist and biotech industry veteran Hans Schambye, they founded a virtual company, Galecto Biotech, to develop TD139 and other compounds.

How does inhibiting a sugar-binding protein reduce fibrosis? According to Galecto's founders, it interferes with signaling from receptors for the cytokine TGFβ, a potent inducer of lung fibrosis, helping fibroblasts that accumulate in areas of lung damage to differentiate into myofibroblasts that secrete collagen and other extracellular matrix proteins, generating the scar tissue that can often lead to respiratory failure and death. Sethi and his colleagues propose that galectin-3 binds to itself and to TGFβ receptors, forming lattices that hold the receptors at the cell surface. They have shown that interfering with galectin-3 reduces expression of TGFβ receptor at the cell surface of lung epithelial cells by almost 80%.

Despite this dramatic effect on receptor numbers, classic TGFβ signaling through receptor phosphorylation of Smad transcription factors surprisingly remains unaffected. Sethi says he couldn't believe this result at first and directed his students and postdocs to reproduce the findings many times. Other signal transduction was altered, however, because inhibition of galectin-3 blocks activation of β-catenin, a protein in the Wnt signaling pathway that has been linked to collagen production and fibrosis.

This partial and selective effect on TGFβ signaling, Sethi speculates, may be why TD139 has proven safe in preclinical testing. Care is warranted, because TGFβ is a problematic drug target. TGFβ knockout mice, for example, self-destruct from massive inflammation. And in cancer, TGFβ can be a facilitator of invasion and metastasis as well as, paradoxically, a tumor suppressor, depending on the cellular context. Sethi says Galecto is mindful of the risk of acute inflammation and cancer from inhibiting TGFβ, but the fact that galectin-3 inhibitors still allow much TGFβ signaling should provide a margin of safety. Reassuringly, galectin-3 knockout mice are phenotypically completely normal, and Schambye says Galecto has treated mice for two weeks chronically with TD139 with no toxicity. Sethi adds that galectin-3 inhibition, in his hands, seems to inhibit cancer growth rather than promote it.

Pulmonologist Dean Sheppard, director of the lung biology center at the University of California, San Francisco (who worked on an anti-αvβ6 integrin antibody that Biogen Idec has now taken into phase 2 for IPF), says that the fact that galectin-3 inhibitors reduce fibrosis in three different organs is encouraging because it suggests a general pathway for galectin-3 antifibrosis activity. He considers galectin-3 one of many potentially attractive targets in fibrosis, noting that other agents now in development have also been very effective in mouse lung fibrosis models. One caveat Sheppard notes is the 10-mM dosage of TD139 delivered directly to mouse lungs, which suggests an insufficiently potent compound. Sheppard also hopes the company can show that galectin-3 does not interfere with the protein's well-established role in neutrophil recruitment to sites of infection.

Sethi says that TD139 has *in vitro* potency against galectin-3 in the nanomolar range, and his group only delivered high concentrations to mice to conclusively demonstrate efficacy in a model of established fibrosis. Although he agrees that interference with neutrophils could be a concern, he hasn't seen any worsening of infections in mice. He points out that galactin-3 in any case would not have the kind of global immunosuppressive effect that many current fibrosis drugs, including high-dose steroids, routinely produce in IPF patients. Galecto's scientific founders continue to work on the mechanism by which galectin-3 promotes fibrosis, including the possible role of macrophages, which secrete galectin-3 but also may be acted on by the protein, causing the macrophages to adopt a phenotype that promotes scarring and chronic inflammation. Although the role of macrophages in human IPF is controversial, Schambye says that the fact that galectin-3 inhibitors appear to target pro-fibrotic signaling in both fibroblasts and macrophages gives Galecto's compounds a theoretical edge over others in development. In any case, he adds, there is room for more than one effective compound because drug combinations will probably eventually become standard treatment. And, as IPF is a heterogeneous disease, Galecto is working towards identifying patients with high galectin-3 levels who may be more likely to respond to inhibitors of the lectin. Clinical researcher Raghu Kalluri, of MD Anderson Cancer Center in Houston, would have liked to see more proof-of-concept studies with TD139. "But one must keep patients' needs in mind," he adds. "Pulmonary fibrosis is a deadly disease with no available treatments. One can't wait five years for another knockout experiment. If there are enough safety data, one must not stop the development of a potentially important drug."

The company, which has raised a total of €10 ($15.8) million thus far, expects to debut TD139 in the clinic sometime next year.

Ken Garber *Ann Arbor, Michigan*

Corrected after print 30 August 2013.

Correction

In the version of the article entitled "Galecto Biotech" (*Nat. Biotechnol.* **31**, 481, 2013) originally published, in paragraph 2, "Galectin-3" was said to be "like," but is "unlike other lectins." The photo caption should have included Hans Schambye, also a co-founder; and Tariq Sethi's first name was misspelled as Tarik. At the end of the article, Raghu Kalluri's name was misspelled as Khalluri. The errors have been corrected in the HTML and PDF versions of the article.