

# BioCentury

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## Emerging Company Profile

### Stromedix: Untangling fibrosis

By Karen Bernstein  
Editor-in-Chief

The biology of fibrosis and fibroblasts are well understood, and there are multiple pathways and targets known to regulate fibroblast activity. Yet there are no marketed drugs for fibrosis and relatively few in development, despite the importance of fibrosis in diseases of the liver, kidney, lung and heart, and morbidity and mortality equivalent to cancer. Stromedix Inc. hopes to change that equation.

Fibrosis is a tissue-level phenomenon resulting from the excessive activity of a form of fibroblasts called myofibroblasts. It occurs when the body tries to repair chronic tissue injury. The biology of fibrosis is the same whether the cause is viral, chemical, physical or inflammatory. Ongoing cycles of injury and repair lead to an accumulation of scar tissue and disruption of normal tissue architecture and function, followed by organ failure.

Part of the problem in figuring out how to tackle fibrosis is that it is a pathology, not a disease, and thus it runs orthogonally to the conventional therapeutic paradigm, according to co-founder and CEO Michael Gilman. Nor are there validated clinical endpoints or trial designs.

For Gilman, who used to be EVP of research at Biogen Idec Inc. (BIIB, Cambridge, Mass.), the first question thus was

#### Stromedix Inc.

Cambridge, Mass.

Technology: Fibrosis biology

Disease focus: Fibrosis

Clinical status: Preclinical

Founded: 2006 by Michael Gilman, Michael Gallatin, Atlas Venture, Frazier Healthcare Ventures

University collaborators: University of California, San Francisco

Corporate partners: None

Number of employees: 6

Funds raised: \$4.4 million

Investors: Atlas Venture and Frazier Healthcare Ventures

CEO: Michael Gilman

Patents: 6 patent families licensed from University of California and/or Biogen Idec Inc. including composition of matter and use of alpha(v)beta(6) antibodies in fibrosis, cancer and other indications

choosing the right first indication and designing a compelling clinical experiment.

“The problem is that most fibrotic diseases unfold over a period of 15-20

years,” he said. “And it’s a tissue-level phenomenon, so unless you look at tissue, everything else is indirect. So you need a patient population that will get fibrosis fast and homogeneously, and from whom you can get tissue.”

As a result Gilman rejected idiopathic pulmonary fibrosis (IPF), the area where most companies are working, because it would be impossible to get tissue biopsies. He also didn’t want to bet on an indirect measure of fibrosis in this setting, lung function as measured by changes in forced vital capacity (FVC), which is what several companies are looking at.

Gilman also doesn’t think that endpoint would provide his quick proof-of-concept.

“First of all, it’s an indirect measurement of fibrosis; we don’t really know the relationship between the two,” he said. “Second, seeing a change in FVC requires a long trial.”

Another possible indication was radiation-induced fibrosis in the lung, but it wasn’t clear what the trial design should be: when to treat, what to measure — and biopsies also weren’t going to be possible, he said.

Gilman thinks the right population is transplant patients. Donor organs are subject to acute insults followed by long-

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PO Box 1246  
San Carlos CA 94070-1246  
Voice: 650-595-5333  
Fax: 650-595-5589  
[www.biocentury.com](http://www.biocentury.com)

**DAVID FLORES**  
President & CEO

**KAREN BERNSTEIN, Ph.D.**  
Chairman & Editor-in-Chief

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**Stromedix,**  
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term inflammation and toxicity from chronic administration of cyclosporine and tacrolimus.

Indeed, a 2003 study in the *New England Journal of Medicine* showed that donor kidneys are free of fibrosis at day zero, but that by one year 94% have histological fibrosis. The amount of fibrosis in biopsies at six months is a clear indicator of how long the graft will last.

Transplant recipients thus make up a group of patients who progress rapidly and relatively homogeneously, and where it is possible to obtain tissue.

As a result, for proof-of-concept studies, Stromedix plans to enroll transplant patients with biopsy-proven chronic allograft nephropathy (fibrosis).

Having thought about how to approach the problem, Gilman put together a shopping list of interesting targets and pathways. Stromedix in-licensed an IND-stage MAb against integrin alpha(v)beta(6) from BIIB in May. The big biotech had been developing it for IPF but dropped it in 2006.

Alpha(v)beta(6) is a critical activator of TGF beta, which is the key cytokine for induction and maintenance of activated myofibroblasts. TGF beta is synthesized and secreted in a latent form, in complex with latency-associated peptide (LAP). Alpha(v)beta(6) binds to LAP and converts the TGF beta complex into an active form, where it can act on neighboring fibroblasts and epithelial cells.

One of the attractions of alpha(v)beta(6) is that it is expressed almost entirely on injured epithelial cells. Thus, it provides a mechanism for attenuating TGF beta activity selectively at sites of tissue injury. Knockout mice lacking alpha(v)beta(6) are generally healthy, but resistant to fibrosis.

Stromedix plans to start a Phase I trial in January 2008 and hopes to have Phase II proof of concept in renal transplant in late 2009. The company plans to use gene expression and histology endpoints based on a second biopsy.

Alpha(v)beta(6) also is up-regulated in many epithelial tumors, making cancer another potential area of focus.

Stromedix, which is in the process of raising a series B round, plans to outsource as much work as possible to make its money last. It has no plans to partner prior to having Phase IIa data.