REPRINT FROM JANUARY 13, 2014

BioCentury

THE BERNSTEIN REPORT ON BIOBUSINESS™

Product Discovery & Development

Niche play on TGF beta

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Scholar Rock LLC's first disclosed deal provides a glimpse into how the company thinks it can exploit new structural biology insights about well-trodden growth factor targets to develop new therapies.

The biotech has partnered with **Johnson & Johnson**'s J&J Innovation and Janssen Biotech Inc. units to discover and develop biologics that can selectively modulate TGFB1 activity in local microenvironments without disrupting the growth factor's physiological activities elsewhere.

> ***"We think we can develop agents that selectively dial up or dial down the activity of the growth factor in local microenvironments."***
>
> **Nagesh Mahanthappa, Scholar Rock**

Launched in November 2012, Scholar Rock is using insights from structural biology to develop a suite of assays for identifying compounds it calls "niche activators." These selectively affect the activation of specific growth factors via co-factors in the extracellular and cell surface microenvironments.

The biotech says the approach could help avoid side effects that may stem from systemic targeting.

Under last week's deal, the partners will focus on discovering and developing biologics that modulate transforming growth factor (TGF) beta 1 (TGFB1) in autoimmune diseases and cancer.

Janssen has an exclusive worldwide option to license, develop and commercialize resulting biologics. Scholar Rock will receive an undisclosed amount of research support and is eligible for option payments, milestones and royalties.

TGFB1 controls multiple cellular processes including proliferation, differentiation and migration. The cytokine is important to multiple physiological processes including immune modulation and wound healing. TGFB1 drives the differentiation of undifferentiated T cells to the Treg cell phenotype. It also is associated with a range of pathological conditions including autoimmune disease, cancer and fibrosis.

TGFB1 is produced in an inactive form and the bulk of it is stored as a latent complex in the extracellular matrices of many tissues.

Data published by the lab of Scholar Rock co-founder Timothy Springer have described the structure of latent TGFB1 and multiple distinct activation mechanisms. Springer, who is on Scholar Rock's SAB, is a professor of biological chemistry and molecular pharmacology at **Harvard Medical School** and a professor of medicine at **Boston Children's Hospital**.

Scholar Rock CEO Nagesh Mahanthappa said these insights have given the company the know-how to identify molecules that could target specific epitopes on TGFB1 to affect its activation locally and in specific microenvironments. He said these epitopes are not being pursued by other companies working on the target.

"By focusing on the TGF beta latent complex and its associations with various co-factors, presenting antigens and other molecules, we think we can develop agents that selectively dial up or dial down the activity of the growth factor in local microenvironments," Mahanthappa told BioCentury.

According to Mahanthappa, systemically delivered therapies that target TGFB1 also could affect the growth factor's normal activity elsewhere in an undesirable manner.

At least 16 companies are developing compounds that directly target TGFB1. Most of these compounds are inhibitors to treat cancer and fibrotic diseases. Most would be expected to have systemic effects.

Eight companies have candidates in Phase II testing. **Eli Lilly and Co.** has two: LY2382770 and LY2157299. The former is a neutralizing mAb against TGFB1 in Phase II testing to treat diabetic kidney disease. LY2157299 is a small molecule inhibitor of TGF beta receptor 1 (TGFBR1, ALK5) in Phase II testing to treat glioma and hepatocellular carcinoma and in Phase I/II testing to treat pancreatic cancer.

Sanofi's **Genzyme Corp.** unit is developing a pan-specific human mAb against TGF beta to treat focal segmental glomerulosclerosis, which can lead to kidney failure. The mAb was originally discovered by Cambridge Antibody Technology, which **AstraZeneca plc** acquired in 2006.

Acceleron Pharma Inc. and partner **Celgene Corp.** are developing ACE-536 to treat beta-thalassemia and myelodysplastic syndromes (MDS). ACE-536 is a modified activin receptor type 2A (ACVR2A) fusion protein that acts as a ligand trap to inhibit members of the TGF beta superfamily such as TGFB1.

Digna Biotech S.L. has disitertide (P144), a topical formulation of peptide 144 TGFB1 inhibitor, for scleroderma.

Gradalis Inc. has its FANG vaccine for melanoma, colorectal cancer and ovarian cancer. FANG is an autologous tumor-based vaccine composed of a plasmid encoding GM-CSF and a bifunctional short hairpin RNA (shRNA) that down-regulates

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TGFB1 and TGF beta 2 (TGFB2).

TissueGene Inc. and partner Kolon Life Science Inc. have TissueGene-C in Phase II testing to treat osteoarthritis. The product is given via intra-articular injection and is a fixed-ratio mixture of non-transduced allogeneic human chondrocytes and allogeneic human chondrocytes expressing TGFB1.

Kolon Life Science is a subsidiary of **Kolon Group**.

Localizing tolerance

Michael Elliott, VP of immunology scientific innovation at the J&J Boston Innovation Center, said the immunology unit at Janssen had been aware of the work in the labs of Scholar Rock's co-founders before the company was formed.

"Our interest is in the development of compounds that could induce the local release of TGF beta 1 to drive the development of Tregs in disease-specific microenvironments to promote immune tolerance," he told BioCentury. "We started talking with the folks behind Scholar Rock at the very first stages of company formation."

Elliott noted systemic delivery of recombinant forms of TGFB1 is less attractive than Scholar Rock's local targeting approach given the cytokine's small size and short half-life, in addition to its potential to induce a multitude of unwanted effects in non-diseased tissues.

Elliott said the autoimmune diseases of prime interest to J&J's Janssen unit are rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and psoriasis.

"If we are successful, it would represent first-in-class compounds that have a mechanism of action distinct from other compounds that target TGF beta 1," said Robert Urban, head of the J&J Boston Innovation Center.

Most companies working on TGFB1 are developing candidates to inhibit the growth factor's activity. Such inhibitory therapies could suppress Treg development, and thus be of benefit in certain types and stages of cancer, or help block the growth factor's fibrosis-promoting effects.

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>
> **Robert Urban, J&J Innovation**

Mahanthappa said the first candidates to be developed under the collaboration are likely to be mAbs. But he added that Scholar Rock's platform does not restrict the company to a particular therapeutic modality.

"TGF beta 1 is a well-validated therapeutic target and mAbs represent a well-validated therapeutic modality," he said. "But it is not beyond the pale to think that other molecular classes, such as macrocycles, could also be used to modulate the structural features that we have identified in TGF beta to exert a localized effect against the growth factor."

Mahanthappa said Scholar Rock's major objective under the collaboration in 2014 is to get pharmacological POC.

"We want to show that you can get a mAb that targets TGF beta 1 through the mechanism of action that we have identified and show that it is indeed able to selectively and locally modulate the activity of the growth factor," he said.

In parallel, Mahanthappa said Scholar Rock will assess the potential of selectively targeting TGFB1 activity in therapeutic settings outside the scope of the J&J collaboration, such as in wound healing and fibrosis.

He added that the company has plans eventually to evaluate selective targeting of other growth factors.

"Our initial focus is on development of molecules to target TGF beta, but at least in the foreseeable future, we do plan to expand to other growth factors as well," Mahanthappa said.

Indeed, the latent property is not unique to TGFB1. Other growth factors in the TGF beta superfamily, such as myostatin and growth differentiation factor 11 (GDF11), also have latent forms that need to be activated before they can exert their physiological effects.

Springer's lab also has reported that key amino acids in a region of TGFB1 critical for keeping the growth factor in its latent state — called a fastener region — are conserved across myostatin and GDF11.

The Scholar Rock collaboration is one of eight deals announced by J&J Innovation last week. In the same announcement, J&J Innovation also said it partnered with the Israeli government, **Takeda Pharmaceutical Co. Ltd.** and OrbiMed Israel Partners to establish a new Israeli biotech incubator *(see BioCentury Extra, Wednesday, Jan. 8)*.

COMPANIES AND INSTITUTIONS MENTIONED

Acceleron Pharma Inc. (NASDAQ:XLRN), Cambridge, Mass.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Boston Children's Hospital, Boston, Mass.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Digna Biotech S.L., Madrid, Spain
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Genzyme Corp., Cambridge, Mass.
Gradalis Inc., Carrollton, Texas
Harvard Medical School, Boston, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Kolon Group, Kwachon City, South Korea
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Scholar Rock LLC, Cambridge, Mass.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
TissueGene Inc., Rockville, Md.

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