BIOTECHNOLOGY

Scholar Rock Inc.

Niche modulators target dysregulated growth factors

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Business: Biological development of niche modulators
Founded: January 2013
Founders: Timothy Springer, PhD, and Leonard Zon, MD (Harvard Medical School and Boston Children's Hospital); Amir Nashat, PhD (Polaris Partners); Nagesh Mahanthappa
Employees: 12
Financing To Date: $20 million
Investors: Polaris Partners; ARCH Venture Partners; Timothy Springer; EcoR1 Capital; The Kraft Group
Board Of Directors: Amir Nashat, Chairman; Katrine Bosley (Editas Medicine); Kristina Burow (ARCH Venture Partners); Michael Gilman, PhD (Padlock Therapeutics); Timothy Springer; Nagesh Mahanthappa
Scientific Advisory Board: Timothy Springer; Leonard Zon; Barry Coller, MD (Rockefeller University); Joan Massagué, PhD (Memorial Sloan-Kettering Cancer Center); Daniel Rifkin, PhD (New York University Langone Medical Center); Lynn Sakai, PhD (Oregon Health & Science University, Portland Shriners Research Center); Akshay Vaishnaw, MD, PhD (Alnylam Pharmaceuticals Inc.)

Growth factors play a wide-ranging role in a variety of cellular processes. As the name suggests, they often help regulate the growth and expansion of specific types of cells. That has obvious implications for cancer, which was an early target for drugs designed to inhibit the effects of growth factors. A famous example is the human epidermal growth factor receptor (HER-2) and **Genentech Inc./Roche**'s *Herceptin* (trastuzumab), which is effective against some forms of breast cancer.

But success stories like Herceptin aren't all that common. Growth factors are difficult to attack. They interact with receptors on cell surfaces that in turn transmit signals to the interior of the cell. These receptors frequently occur on many different cell types, and that both dilutes the effect of the drug and can lead to off-target effects.

Researchers at **Scholar Rock Inc.** have a different approach in mind. They hope to use antibodies to home in on latent forms of growth factors that get stored as complexes with other proteins in the spaces between cells. The approach could work because these complexes are unique to the individual types, so a therapy tailored to a specific complex could be very specific.

The company's focus is on the transforming growth factor-beta (TGF-beta) family of growth factors.

It was well known that some in the TGF-beta family are produced in inactive forms, and they are stored in the fibrous extracellular matrix (ECM) that fills the space between cells in tissues. When the need arises, enzymes transform some of these inactive forms into their active forms, which then interact with target cells. Timothy Springer, a professor of medicine at **Harvard Medical School** and **Boston Children's Hospital**, who is a scientific co-founder of Scholar Rock, demonstrated that proteins called integrins and other elements help to direct activation of those growth factors. And critically, he realized that the mix of factors is unique to different cell types.

All the investigators needed was a means to target these unique complexes. Fortunately, a new technology has emerged in the past few years that allows researchers to custom design monoclonal antibodies that can bind to several targets at once, and therefore specifically attach to the complex environment of latent growth factors.

Scholar Rock researchers have begun to generate such novel antibodies, which they call "niche modulators." "If we can combine those structural insights with contemporary recombinant antibody discovery methods, we should be able to make very powerful therapies that can modulate the latent forms of these growth factors," says Nagesh Mahanthappa, president and CEO of Scholar Rock.

The company doesn't want to just shut down activation of growth factors. It should also be possible to design antibodies that would do the reverse, promoting the release of active growth factors, and such therapies could find use in conditions like musculoskeletal diseases, which could be countered by encouraging growth of specific types of cells.

Earlier this year the firm entered a partnership with **Janssen Biotech Inc./Johnson & Johnson** that focuses on TGF-beta 1, which promotes growth of regulatory T cells that go on to dampen the immune response. The growth factor also plays a role in other aspects of the immune system, as well as wound healing and scarring. Blocking TGF-beta 1 could release the brakes on the immune system and allow it to begin hunting down cancer cells, while promoting TGF-beta 1 activation could help to quiet an overactive immune system in autoimmune diseases such as rheumatoid arthritis. But generally blocking TGF-beta 1 would affect both systems, causing potential side effects.

Scholar Rock thinks it can rely on the distinctive microenvironments of different cell types to tease apart those activities. A carefully designed antibody could lock on to the extracellular environment of T cells and have no effect on the cells that influence wound healing and fibrosis that are part of the scarring process. Another antibody could do the reverse, targeting wound healing and fibrosis – countering the scarring and fibrosis that contribute to end-stage kidney disease, for example – while sparing the immune system. The company is currently pursuing both strategies.

"It's a concept that we believe will be generalizable," says Mahanthappa. That could open up other processes and diseases that those growth factors contribute to, such as fracture repair, liver cirrhosis, and muscular dystrophies.

The company is working on two strategies with Janssen: developing antibodies to promote an increase in T regulatory cells, which in turn tamp down the immune response; and the opposite intent – inhibiting activation of TGF-beta 1 in hopes of reducing regulatory T cell activity and ramping up the immune response. That strategy could pay off with current attempts to recruit the immune system to attack cancer

cells. An antibody that supercharges the immune response could be combined with therapeutic agents designed to direct an immune response against cancer cells such as so-called checkpoint inhibitors like drugs that target programmed cell death protein 1 (PD1). "We're looking at both sides of that coin," says Mahanthappa.

Even as it pursues those compounds, Scholar Rock has an internal program chasing another angle: developing antibodies that affect scarring without altering the immune system. Such a therapy could find use in indications like pulmonary fibrosis (scarring), and liver and kidney fibrosis that can occur in diabetes and end-stage kidney disease.

The company's programs are in the preclinical stages. Its researchers have developed some initial antibody candidates that can both promote and inhibit various members of the TGF-beta family. Examples include bone morphogenetic proteins and growth and differential factors – the growth factors are implicated in physiology and disease of many different tissues, including bone, cartilage, skeletal and cardiac muscle, and the immune system, as well as key elements of metabolism. By the end of 2015, Scholar Rock aims to identify its first development candidate, which would require further tests before clinical trials could begin.

That's a lengthy road, but the company is in good shape, Mahanthappa says, having concluded a $20 million Series A financing in September. He hopes to land at least one more corporate partnership in 2015. "Partnerships are a very important aspect of our business model," he says.

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The company could also go it alone in some cases. "In some indications we will need a large partner, but in other areas we can focus on individual patient populations and advance those programs on our own. We intend to be a free-standing biotech with its own pipeline," explains Mahanthappa.

Scholar Rock hasn't performed any specific market analyses yet. "I'm quite confident there are a number of indications in the therapeutic areas we're looking at where the potential market sizes are in the billion-dollar range. This approach has the potential to generate multiple billion-dollar blockbusters," says Mahanthappa.

Other companies are working in the TGF-beta space. Most are focused on developing traditional antibodies against the active growth factor or blocking its cell surface receptor. **Genzyme Corp./Sanofi** has an anti-TGF-beta antibody in development for fibrosis, as does **Eli Lilly & Co. Regeneron Pharmaceuticals Inc.** has a program targeting growth differentiation factor-8, for musculoskeletal indications. **Acceleron Pharma Inc.** has developed decoy versions of receptors that attract and trap growth factors, which it is developing for various conditions.

Mahanthappa has decades of experience in the biotech field. He co-founded the RNA interference company Alnylam, where he established and helped manage alliances with pharma partners. Later, he co-founded Avila Therapeutics, and served as vice president of corporate development and operations.

The company's senior vice president of research, Katherine Turner, started out at The Genetics Institute and later became head of discovery immunology at Wyeth, and then moved on to Biogen. **SU**

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– Jim Kling