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TRANSLATION IN BRIEF

SCHOLAR ROCK'S NICHE

Scholar Rock LLC, which attracted $20 million in investments and a big pharma deal before releasing any data, is now providing evidence that its niche modulator compounds can in fact specifically target transforming growth factor β1 (TGFβ1) and other growth factors in disease tissues with a unique mechanism.

At the Federation of American Societies for Experimental Biology (FASEB) scientific research conference on TGFβ this summer, the company presented data on its first antibody, showing it specifically binds and activates latent TGFβ1 to modulate T cell activity.

TGFβ1 and other members of the TGFβ superfamily are involved in a broad range of diseases, but selectively targeting the individual growth factors — and hitting the targets only in diseased tissues — has been a challenge for drug developers. Activating the TGFβ pathway could help treat inflammatory diseases, while inhibiting it could help treat cancer and fibrosis.

At least eight companies have biologics or small molecules targeting TGFβ1 in clinical development for cancers, autoimmune diseases or fibrotic diseases, but none has reached the market. According to Scholar Rock CEO Nagesh Mahanthappa, "Traditional approaches involve antibodies binding the mature growth factor, which might be potent but will be systemic and will inhibit it everywhere, not only in the diseased tissues." That can be dangerous because widespread activation or inhibition can cause excessive inflammation or fibrosis.

Scholar Rock's solution is to target latent forms of the growth factors — precursor structures in which the growth factors are shielded from receptor interactions by a latency-associated peptide.

Mahanthappa told BioCentury that it is the variability of latency-associated peptides bound to the latent TGFβ family members that allows specific antibody binding to them in diseased tissues, because different peptides form complexes with the growth factors in different tissues or disease states. Scholar Rock is exploiting the structural variability of the latency complexes caused by the different binding proteins to design antibodies specifically active in diseased tissues, but is not disclosing details of how the molecules bind.

The antibody increased T cell differentiation into Tregs and suppressed proliferation of effector T cells — effects that should dampen the immune response in inflammatory diseases.

In the presentation, the company showed that the first modulator binds latent TGFβ1 with nanomolar affinity, in a way that releases the growth factor from the latency structure and results in increased TGFβ1 activity.

In addition, the company showed the antibody could modulate production of T regulatory cells (Tregs), a known immunological effect of activating TGFβ1. In mouse T cells, the antibody increased T cell differentiation into Tregs and suppressed proliferation of effector T cells — effects that should dampen the immune response in inflammatory diseases.

Last year, Scholar Rock partnered with the J&J Innovation and Janssen Biotech Inc. units of Johnson & Johnson (NYSE:JNJ) to develop niche modulators of TGFβ1 to treat autoimmune diseases and cancers. Although the company's first data cover a TGFβ1 modulator, Mahanthappa said that it is also developing modulators against other TGFβ family members not covered by the deal, as well as TGFβ1 inhibitors that work by stabilizing the latent complex.

He added that Scholar Rock recently began testing modulators of latent growth factor complexes including TGFβ1 in preclinical animal studies.

The company has not disclosed which target, compound or indication it plans to pursue first for clinical development, but hopes to nominate a development candidate this year and enter the clinic in 2016.

— Lauren Martz

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