Scholar Rock Announces Publication in Science Translational Medicine of Preclinical Data Detailing a Potent and Selective Inhibitor of TGFβ1 Overcoming Primary Resistance to Checkpoint Inhibition

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- Retrospective analyses of clinical tumor samples identify TGFβ1 as the most prevalent TGFβ isoform in most solid cancers

- Preclinical results demonstrate highly selective inhibition of TGFβ1 activation with SRK-181-mIgG1 overcomes key mechanism of primary resistance to checkpoint inhibition therapy

- Selective inhibition of latent TGFβ1 activation with SRK-181 has demonstrated an improved preclinical safety profile compared to conventional inhibitors of TGFβ signaling

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Mar. 26, 2020-- Scholar Rock (NASDAQ: SRRK), a clinical-stage biopharmaceutical company focused on the treatment of serious diseases in which protein growth factors play a fundamental role, today announced the publication in the peer-reviewed journal *Science Translational Medicine* of preclinical data that established the therapeutic rationale for evaluating a potent and highly selective inhibitor of transforming growth factor-beta 1 (TGFβ1) activation to overcome primary resistance to checkpoint inhibitor therapy.

“With this publication, we are sharing the strong body of preclinical evidence we have built supporting the clinically-derived rationale for evaluating TGFβ1’s key role in primary resistance to checkpoint inhibitor therapy and the potential of a highly specific inhibitor of TGFβ1 activation to overcome this challenge. In the second half of this year, we may gain early insights from our Phase 1 proof-of-concept trial in patients with solid tumors on SRK-181’s potential to overcome the immune exclusion that we believe leads to primary resistance to anti-PD-(L)1 therapy,” said Alan Buckler, Ph.D., Chief Scientific Officer of Scholar Rock. “Moreover, these published data provide further validation of Scholar Rock’s proprietary platform to develop antibodies that locally and selectively target the precursor form of growth factors with the aim of avoiding the dose-limiting toxicities that have hindered traditional approaches to targeting growth factors.”

The introduction of immunotherapy, including checkpoint inhibitor therapy, has revolutionized the treatment of a wide variety of cancers, delivering profound and durable responses for many patients. Unfortunately, this therapeutic approach is only effective in a small subset of patients; even at the outset of treatment, some tumors show primary resistance to anti-PD-(L)1. Human tumor profiling and several preclinical studies have implicated TGFβ signaling activity as a potential point of intervention to overcome primary resistance to checkpoint inhibition. However, the development of therapies targeting TGFβ signaling has been hindered by dose-limiting cardiotoxicities, potentially due to non-selective inhibition of multiple TGFβ isoforms.

As detailed in the *Science Translational Medicine* publication “Selective inhibition of TGFβ1 activation overcomes primary resistance to checkpoint blockade therapy by altering tumor immune landscape,” SRK-181 inhibits TGFβ1 activation with high selectivity and has demonstrated in preclinical studies the potential to overcome primary resistance and meaningfully expand the number of patients who could benefit from checkpoint inhibitor therapy. (Martin et al., Sci. Transl. Med. 12: 25 March 2020)

- Based on RNAseq data from the Cancer Genome Atlas (TCGA), TGFβ1 is the most prevalent isoform expressed in the majority of human cancer types, with the exception of breast cancer, mesothelioma, and prostate cancer, where TGFβ3 is also expressed. This finding was also observed in examination of individual samples.
- TGFβ1 is likely expressed by multiple cell types within the tumor microenvironment and each cell type produces TGFβ1 in different large latent complexes (LLCs). This is supported by TCGA data, which indicates essentially all tumor types express mRNA encoding all four LLC-presenting molecules, namely LTBP1, LTBP3, GARP, and LRRC33. By targeting the precursor form of TGFβ1, SRK-181 achieves exquisite isoform specificity, inhibiting latent TGFβ1 activation in all known molecular contexts without binding to latent TGFβ2, latent TGFβ3, or any of the three active TGFβ growth factors.
- Scholar Rock identified three syngeneic mouse tumor models that recapitulate key features of human primary resistance to checkpoint inhibitor therapy: MBT-2 (bladder cancer), Cloudman S91 (melanoma) and the EMT-6 (breast cancer) mouse models. Combination treatment with SRK-181-mIgG1 and an anti-PD-1 therapy resulted in tumor regression or control and survival benefit across these three identified cancer models. This tumor response was also shown to be durable, where mice with no measurable tumor at treatment cessation remained tumor free.

	MBT-2 bladder cancer model (Response: %, N)**	**Cloudman S91 melanoma model (Response***: %, N)**	**EMT-6 breast cancer model (Response*: %, N)**
Control	0% (0/12)	0% (0/11)	0% (0/9)
Anti-PD1 monotherapy	0% (0/13)	25% (3/12)	0% (0/9)

SRK-181-mIgG1 monotherapy	0% (0/12)	0% (0/12)	0% (0/10)
Anti-PD-1/SRK-181-mIgG1, 3 mg/kg	29% (4/14)	75% (9/12)	NT
Anti-PD-1/SRK-181-mIgG1, 10 mg/kg	57% (8/14)	44% (4/9)	50% (5/10)
Anti-PD-1/SRK-181-mIgG1, 30 mg/kg	NT	73% (8/11)	NT

* For EMT-6: Response is defined as animals that achieved a tumor volume at study end of less than 25% of the 2,000mm^3 survival threshold.
** For MBT-2: Response is defined as animals that achieved a tumor volume at study end of less than 25% of the 1,200mm^3 survival threshold.
*** For Cloudman S91: Response is defined as animals that achieved a tumor volume at study end of less than 25% of the 2,000mm^3 survival threshold.
NT: Not tested

- The tumor regression and control demonstrated in the EMT-6 breast cancer model, which expresses both TGFβ1 and TGFβ3, suggest TGFβ1 is the key isoform contributing to checkpoint resistance and highlights the possibility that selective TGFβ1 inhibition may have therapeutic potential in overcoming primary resistance across a broad spectrum of cancers, irrespective of the expression of other TGFβ isoforms.
- Dose-limiting cardiotoxicities have challenged the therapeutic development of TGFβ pathway inhibitors. Selective inhibition of latent TGFβ1 activation with SRK-181 has demonstrated an improved safety profile as compared to pan-TGFβ inhibitors. In a 4-week repeat-dose rat toxicology study, the no-observed-adverse-effect-level (NOAEL) was the highest dose tested of 100 mg/kg once weekly, which is well above the doses necessary to elicit robust anti-tumor responses when combined with anti-PD-1 antibody.
- Following combination treatment with SRK-181-mIgG1 and anti-PD-1, there were significant increases in intratumoral effector T cells and decreases in immunosuppressive myeloid cells, suggesting TGFβ1's multiple contributions to primary resistance to checkpoint inhibition.
    - Overall percentage of the CD45+ immune compartment did not change.
    - Ten-fold increase in CD8 T cell representation (average of 34% vs. control average of 3.5%). Single-agent treatment with anti-PD-1 or SRK-181-mIgG1 only resulted in modest increases that did not reach significance in the study.
    - Significant reduction in immunosuppressive M2-like macrophages (14% vs. control average of 47%) and myeloid-derived suppressor cells (MDSC; 1.4% vs. control average of 10.9%).

About SRK-181

SRK-181 is a potent and highly selective inhibitor of TGFβ1 activation and is an investigational product candidate being developed to overcome primary resistance to checkpoint inhibitor therapy, such as anti-PD-(L)1 antibodies. TGFβ1 is the predominant TGFβ isoform expressed in many human tumors, particularly for those tumors where checkpoint therapies are currently approved. Based on analyses of human tumors that are resistant to anti-PD-(L)1 therapy, TGFβ1 is implicated as a key contributor to exclude immune cell entry into the tumor microenvironment, thereby preventing normal immune function. By overcoming this immune cell exclusion, Scholar Rock believes SRK-181 has the potential to induce tumor regression when administered in combination with anti-PD-(L)1 therapy. A Phase 1 proof-of-concept clinical trial in patients with locally advanced or metastatic solid tumors is ongoing. The effectiveness and safety of SRK-181 have not been established and SRK-181 has not been approved for any use by the FDA or any other regulatory agency.

About Scholar Rock

Scholar Rock is a clinical-stage biopharmaceutical company focused on the discovery and development of innovative medicines for the treatment of serious diseases in which signaling by protein growth factors plays a fundamental role. Scholar Rock is creating a pipeline of novel product candidates with the potential to transform the lives of patients suffering from a wide range of serious diseases, including neuromuscular disorders, cancer, fibrosis and anemia. Scholar Rock's newly elucidated understanding of the molecular mechanisms of growth factor activation enabled it to develop a proprietary platform for the discovery and development of monoclonal antibodies that locally and selectively target these signaling proteins at the cellular level. By developing product candidates that act in the disease microenvironment, the Company intends to avoid the historical challenges associated with inhibiting growth factors for therapeutic effect. Scholar Rock believes its focus on biologically validated growth factors may facilitate a more efficient development path. For more information, please visit www.ScholarRock.com or follow Scholar Rock on Twitter (@ScholarRock) and LinkedIn.

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Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding Scholar Rock's future expectations, plans and prospects, including without limitation, Scholar Rock's expectations regarding the timing of its clinical trials for SRK-181; the potential of SRK-181 to address certain patient unmet needs; and the ability of any product candidate to perform in humans in a manner consistent with nonclinical or preclinical study data. The use of words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe,"

“estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify such forward-looking statements. All such forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include Scholar Rock’s ability to provide the financial support, resources and expertise necessary to identify and develop product candidates on the expected timeline; preclinical data and results may not be predictive of clinical results; Scholar Rock’s dependence on third parties for development and manufacture of product candidates including to supply any clinical trials; and those risks more fully discussed in the section entitled "Risk Factors" in Scholar Rock’s Annual Report on Form 10-K for the year ended December 31, 2019, as well as discussions of potential risks, uncertainties, and other important factors in Scholar Rock’s subsequent filings with the Securities and Exchange Commission. Any forward-looking statements represent Scholar Rock’s views only as of today and should not be relied upon as representing its views as of any subsequent date. All information in this press release is as of the date of the release, and Scholar Rock undertakes no duty to update this information unless required by law.

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