Scholar Rock Demonstrates that Highly Specific TGFβ1 Inhibition Combined with Anti-PD1 Drives Tumor Regression and Survival Benefit in Preclinical Models of Primary Resistance to Checkpoint Blockade Therapy

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- *Preclinical Data Presented at the Society for Immunotherapy of Cancer's (SITC) Annual Meeting Shows Highly Specific Inhibitor of TGFβ1, SRTβ1-Ab3, Renders Resistant Solid Tumors Vulnerable to PD1 Blockade*
- *Isoform-specific Inhibition of TGFβ1 by SRTβ1-Ab3 Resulted in an Improved Preclinical Toxicity Profile Versus Non-selective TGFβ Inhibition*
- *Company to Host Investor and Analyst Event and Live Webcast on Saturday, November 10, 2018*

CAMBRIDGE, Mass., Nov. 09, 2018 (GLOBE NEWSWIRE) -- Scholar Rock Holding Corporation (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 new preclinical data from its TGFβ1 cancer immunotherapy program. In syngeneic mouse models of primary resistance to checkpoint blockade therapy (CBT), combination treatment with a highly specific inhibitor of TGFβ1, SRTβ1-Ab3, and an anti-PD1 antibody resulted in tumor regression or tumor control as well as significant survival benefit. In addition, adult rats treated with SRTβ1-Ab3 with weekly doses up to 100mg/kg for 4 weeks showed an improved preclinical toxicity profile compared to pan-TGFβ inhibition. Detailed results are being presented at the Society for Immunotherapy of Cancer's (SITC) 33rd Annual Meeting in Washington DC.

"We are proud to be presenting these exciting results that demonstrate a highly specific TGFβ1 inhibitor overcomes primary resistance to checkpoint blockade therapy while minimizing the toxicities associated with pan-TGFβ inhibition," said Nagesh Mahanthappa, Ph.D., President and CEO of Scholar Rock. "Despite the clinical breakthroughs achieved by cancer immunotherapy, there remains significant unmet need with a majority of patients failing to respond to checkpoint inhibition. These preclinical results, using models that we believe better emulate human tumors resistant to CBT, could potentially provide a new avenue in the pursuit of novel therapies for patients with cancer."

TGFβ1 is the predominant TGFβ isoform expressed in many human tumors, particularly those for which CBT is an approved treatment. Based on analyses of human tumors that are resistant to CBT, TGFβ1 is implicated as a key contributor to immune exclusion that leads to primary resistance observed in patients. Scholar Rock evaluated SRTβ1-Ab3, a highly specific inhibitor of TGFβ1, in syngeneic mouse tumor models sharing key features that can be observed in resistant human tumors: high expression of TGFβ1 over TGFβ2 and TGFβ3, active TGFβ signaling, immune exclusion, and minimal to no response to anti-PD1/PDL1 therapy. In these preclinical studies, treatment with SRTβ1-Ab3 drove effector cell infiltration and expansion and rendered solid tumors vulnerable to PD1 blockade.

Highlights from the preclinical data being presented at SITC for the poster, titled "Defeating checkpoint resistance: Highly specific inhibition of latent TGFβ1 activation renders resistant solid tumors vulnerable to PD-1 blockade" (Poster #550), include:

- SRTβ1-Ab3 is a fully human antibody that binds latent TGFβ1 with high selectivity and high affinity, potently blocking the growth factor's activation, and with minimal or no binding to TGFβ2 and TGFβ3 isoforms.
- In syngeneic mouse tumor models that reflect human primary resistance to CBT, treatment with SRTβ1-Ab3 rendered the MBT-2 (bladder cancer) and Cloudman S91 (melanoma) tumors vulnerable to anti-PD1 therapy.
- Combination treatment with SRTβ1-Ab3 and an anti-PD1 antibody resulted in tumor regression or tumor control.

	MBT-2 tumor model (Response*: %, N)	**Cloudman S91 tumor model (Response**: %, N)**
Control	0% (0/13)	0% (0/11)
Anti-PD1 monotherapy	0% (0/13)	17% (2/12)
SRTβ1-Ab3 monotherapy	0% (0/12)	0% (0/12)
Anti-PD1/ SRTβ1-Ab3, 3 mg/kg	29% (4/14)	83% (10/12)
Anti-PD1/ SRTβ1-Ab3, 10 mg/kg	57% (8/14)	78% (7/9)
Anti-PD1/ SRTβ1-Ab3, 30 mg/kg	–	73% (8/11)

* For MBT-2: Response provides percentage of animals that achieved a tumor volume at study end of less than 25% of the 1,200mm^3 survival threshold.

** For Cloudman S91: Response provides percentage of animals that achieved a tumor volume at the interim study cutoff of less than 25% of the 2,000mm^3 survival threshold. This study is ongoing to continue assessment of response durability.

- Combination treatment with SRTβ1-Ab3 and an anti-PD1 antibody in the syngeneic mouse tumor models resulted in statistically significant survival benefit when compared to anti-PD1 monotherapy.
    - In the MBT-2 study, median survival was not reached at study end in the anti-PD1/ SRTβ1-Ab3 10mg/kg combination group.
    - In the ongoing Cloudman S91 study, median survival was not yet reached in any of the three combination groups.
- In contrast to age-matched naïve mice, complete responders from the anti-PD1/ SRTβ1-Ab3 combination groups rejected re-challenge with MBT-2 cells after a washout period of 7 weeks, demonstrating durable immunological memory.
- Adult rats treated with SRTβ1-Ab3 up to a weekly dose of 100mg/kg for 4 weeks showed an improved preclinical toxicity profile versus a pan-TGFβ antibody and an ALK5 inhibitor.

Scholar Rock will host an investor and analyst event beginning at 2:00 p.m. ET on Saturday, November 10, 2018. The live webcast may be accessed by visiting the Investors & Media section of the Scholar Rock website at http://investors.scholarrock.com. An archived replay of the webcast will be available on the Company's website for approximately 90 days following the presentation.

The poster can be accessed at: http://www.scholarrock.com/platform/publications/

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.

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 ability of its inhibitor of TGFβ1 to render tumors vulnerable to checkpoint blockade therapy, including the inhibitor's ability, as a monotherapy or in combination with other therapies, to affect tumor regression, tumor control or survival; the toxicity profile of its inhibitor of TGFβ1; and the ability of its inhibitor of TGFβ1 to be a monotherapy or combination therapy for patients with cancer. 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 the reproducibility of any preclinical data presented; the inability to produce similar data in patients compared to the data from preclinical studies; data generated from Scholar Rock's future nonclinical studies and clinical trials; and Scholar Rock's ability to obtain, maintain and protect its intellectual property as well as those risks more fully discussed in the section entitled "Risk Factors" in Scholar Rock's Quarterly Report on Form 10-Q for the quarter ended September 30, 2018, 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.

Scholar Rock Contact:
Investors/Media
Catherine Huchu@scholarrock.com
917-601-1649

Media Contact:
The Yates Network
Kathryn Morriskathryn@theyatesnetwork.com
914-204-6412

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