Scholar Rock Announces Publication of Preclinical Data on the Therapeutic Benefit of Inhibiting Myostatin Activation in Models of Spinal Muscular Atrophy

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Data Published in Human Molecular Genetics Demonstrate that a Highly Specific Inhibitor of Myostatin Activation Effectively Increases Muscle Mass and Function in Preclinical Models of SMA Therapeutic Intervention

CAMBRIDGE, Mass., Nov. 27, 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 the publication, "Specific Inhibition of Myostatin Activation is Beneficial in Mouse Models of SMA Therapy" in the peer-reviewed journal *Human Molecular Genetics*.(1) The publication details preclinical studies demonstrating that a highly specific inhibitor of myostatin activation effectively increased muscle mass and function in mouse models of Spinal Muscular Atrophy (SMA). In addition, despite baseline serum levels of inactive latent myostatin being lower in the SMA mice than in mice without disease, successful target engagement was observed as evidenced by increased levels of latent myostatin in serum following treatment. Together, the results support the potential for myostatin blockade as a therapeutic strategy to address motor functional deficits in SMA.

"Despite recent advances with the advent of SMN upregulator therapy, there remains significant unmet medical need to improve muscle function in patients with SMA," said Nagesh Mahanthappa, Ph.D, President and CEO of Scholar Rock. "These preclinical results highlight the therapeutic opportunity of inhibiting myostatin activation to address the muscle atrophy and weakness in SMA. We believe that SRK-015, currently in a Phase 1 trial of healthy volunteers, has the potential to be the first muscle-directed therapy for patients with SMA."

The preclinical results published today in *Human Molecular Genetics* demonstrated that specific blockade of myostatin activation, in conjunction with SMN upregulator treatment, improved muscle mass and function in SMNΔ7 mouse models of SMA. Highlights from the study include:

- In SMNΔ7 mouse models of SMA, dosage and timing of intervention with a small molecule SMN2 splice modulator were varied to modulate disease severity.
    - In the model with a relatively more severe SMA phenotype, mice received four weeks of treatment with muSRK-015P (the mouse analog of SRK-015) as well as optimal doses of the SMN upregulator that mimic the use of therapy to more fully restore SMN expression. This led to a significant increase in muscle strength, as demonstrated by a 44%-51% increase in maximal torque of the plantarflexor muscle group, compared to control animals treated only with optimal doses of the SMN upregulator over the same treatment period.
    - In the model with a relatively less severe SMA phenotype, mice received four weeks of treatment with muSRK-015P, together with background therapy with optimal dosing of the SMN upregulator that was started shortly after birth. This resulted in a 20%-30% increase in maximal torque of the plantarflexor muscle group, compared to control animals not treated with muSRK-015P.
- Treatment of SMNΔ7 mice with muSRK-015P resulted in a multi-fold increase in serum levels of latent myostatin, which confirms the presence of the target in these models and successful target engagement from systemic administration of the antibody.
- In addition, while the absolute level of serum latent myostatin was lower in the more severe SMA mouse group than in the normal control group, the levels were comparable when normalized to body weight or gastrocnemius muscle weight. This finding suggests that the lower serum latent myostatin levels in the SMA group do not reflect reduced production or concentration of myostatin target in diseased skeletal muscle but may instead be attributable to reduced overall muscle mass. This interpretation is supported by the observation that treatment with muSRK-015P resulted in an accumulation of latent myostatin to equivalent levels in both the earlier and later SMN intervention severity models. Importantly, the relevance of myostatin as a target in this SMA preclinical model is demonstrated by the effects of muSRK-015 upon muscle mass and function.

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

(1) Long, K., O'Shea, K., Khairallah, R., et al. Specific Inhibition of Myostatin Activation is Beneficial in Mouse Models of SMA Therapy. 2018. *Human Molecular Genetics*, ddy382

About SRK-015
SRK-015 is a selective inhibitor of the activation of myostatin and is an investigational product candidate for the treatment of patients with spinal muscular atrophy (SMA). Myostatin, a member of the TGF-beta superfamily of growth factors, is expressed primarily by skeletal muscle cells and the absence of its gene is associated with an increase in muscle mass and strength in multiple animal species. Scholar Rock believes the inhibition of the activation of myostatin with SRK-015 may promote a clinically meaningful increase in muscle mass and strength. A Phase 1 clinical trial in healthy volunteers is ongoing. The U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation (ODD) for SRK-015 for the treatment of SMA. The effectiveness and safety of SRK-015 have not been established and SRK-015 has not been approved 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.

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 potential for myostatin blockade as a therapy to address motor functional deficits in SMA, the ability of its inhibitor of myostatin activation to provide therapeutic benefit to patients with SMA, and the applicability of the preclinical data to humans, including patients with SMA. 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 Hu
chu@scholarrock.com
917-601-1649

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

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