Arvinas Publishes First Peer-Reviewed, In Vivo Data from its Proprietary PROTAC Technology

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PROTACs demonstrated to degrade oncology target BET proteins, causing cell death in prostate cancer cells and tumor growth inhibition or regression in mouse models of prostate cancer

NEW HAVEN, Conn., June 7, 2016 /PRNewswire/ -- Arvinas LLC, a private biotechnology company creating a new class of drugs based on protein degradation, today announced the publication of a peer-reviewed joint Arvinas-Yale Universitypaper focusing on the development of degraders of bromodomain and extraterminal domain (BET) proteins for the treatment of castration-resistant prostate cancer (CRPC). The paper, entitled "PROTAC-Induced BET Protein Degradation as a Therapy for Castration-Resistant Prostate Cancer" (DOI: 10.1073/pnas.1521738113) by Raina et al., was published online on June 6, 2016, in the *Proceeding of the National Academy of Sciences* (*PNAS*).

The paper demonstrates that following treatment with a BET-degrading PROTAC, castration resistant prostate cancer (CRPC) cell lines underwent apoptosis, or programmed cell death. The small molecule BET inhibitors JQ-1 and OTX015 were 10-500 fold less potent in terms of producing cell death than the PROTAC, indicating the superiority of the BET-degrading PROTAC in achieving tumor cell death *in vitro.*

In *in vivo* experiments with mouse models of CRPC, administration of the BET-degrading PROTAC resulted in a dose-dependent decrease in average tumor size, with significant reductions evident at the higher dose levels compared with control. At the highest dose level, the PROTAC induced tumor regressions with two of 10 mice showing no sign of tumor following treatment. Treatment in these models with the BET inhibitor OTX015 resulted in tumor growth inhibition, but at a level consistent with progressive disease.

"The publication of this paper is the first demonstration of PROTACs' ability to inhibit the growth of a solid tumor *in vivo*," commented Craig Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular and Developmental Biology and Professor of Chemistry and Pharmacology at Yale University. "It's an important milestone for the technology, which focuses on degrading proteins to treat disease as opposed to simply inhibiting them."

The paper demonstrates the utility of PROTACs in degrading BRD4 – a member of the BET family – as a potential treatment for CRPC. BRD4 is often required for expression of tumor-driving oncogenes such as cMyc and is implicated in many solid tumors and hematologic cancers.

"BRD4 is implicated in multiple cancers and I am thrilled to see this technology move closer to the clinic," said Dr. Patricia LoRusso, a pre-eminent leader in early phase drug development, currently a Professor of Medicine and Associate Director of Innovative Medicine at Yale Cancer Center.

A link to this publication can be found on the Arvinas website in the publication section (www.arvinas.com/publications).

"The research we executed demonstrates that BET protein degradation clearly provides a superior benefit to small molecule inhibitors in both *in vitro* and *in vivo* models," said Manuel Litchman, M.D., President and CEO of Arvinas. "This research confirms our approach to degrading disease-driving proteins and provides us validation as we continue to advance our BRD4 PROTAC toward clinical development in hematologic cancers and solid tumors."

About Arvinas

Arvinas is a pharmaceutical company focused on developing new small molecules aimed at degrading disease-causing cellular proteins. We are translating these innovative protein degradation approaches into novel drugs for the treatment of cancer and other diseases. Many diseases are a result of mutant or unregulated proteins, whose absence may confer clinical benefit to patients. To address these pathological intracellular proteins, Arvinas is developing a new therapeutic paradigm based on the elimination of pathological proteins. Our innovative protein degradation technology uses small molecule drugs to "tag" specific proteins to be degraded by the ubiquitin/proteasome system (UPS), a system that is responsible for the normal turnover of proteins within the cell.

Based on groundbreaking research conducted at Yale University by our Founder and Chief Scientific Advisor, Craig Crews, PhD, Arvinas has developed a platform technology to induce the degradation of intracellular proteins: Proteolysis-Targeting Chimera (PROTAC). The ability of PROTAC-based drugs to induce protein degradation offers advantages over inhibition of protein function and the opportunity of targeting previously "undruggable" proteins. This greatly expands our ability to create drugs for many new therapeutic targets. For more information, visit www.arvinas.com.

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