ARVINAS

INSPIRING A NEW PHARMACEUTICAL PARADIGM

Arvinas Publishes First Peer-Reviewed Paper on its Proprietary PROTAC Technology

PROTACs demonstrated to degrade oncology target BRD4, with superior results compared to traditional inhibitors

NEW HAVEN, Conn., June 4, 2015 – Arvinas LLC, a private biotechnology company creating a new class of drugs based on protein degradation, announces the publication of a joint Arvinas-Yale University paper focusing on the development of degraders of BRD4, a protein implicated in both solid tumors and hematologic cancers. The paper, entitled "Hijacking the E3 Ubiquitin Ligase Cereblon to Efficiently Target BRD4" by Lu et al., was published online June 4, 2015, by *Chemistry & Biology* (ISSN: 1074-5521). The major points of the paper are:

- It demonstrates that Arvinas' proprietary PROteolysis-TArgeting Chimera (PROTAC) technology degrades BRD4, a protein that plays a key role in regulating expression of MYC and other important oncogenes.
- In Burkitt's lymphoma cells, the PROTAC ARV-825 caused rapid (within ~ 6 hours), potent (pM), and long-lasting (greater than 24 hours) degradation of BRD4. In contrast, traditional inhibitors were found to upregulate the BRD4 protein.
- Degradation of BRD4 is superior to inhibition of the target, providing more profound and long-lasting inhibition of MYC and inducing more apoptosis of cancer cells. This is strong evidence that PROTACs could be a better and more efficacious strategy for targeting BRD4 than traditional small molecule inhibitors.

These studies are consistent with Arvinas' goal of applying its degradation technology platform to novel, high interest targets like BRD4 to produce pharmacologic effects superior to standard inhibition approaches. Additional BRD4 degradation data from both *in vitro* and *in vivo* studies were presented at the annual meeting of the American Society of Clinical Oncology on May 31, 2015, in poster format (www.arvinas.com/publications).

"Looking at all of this information together, it is clear that chimeric molecules can be created to degrade target proteins with high specificity and potency," commented Craig Crews, Ph.D.,

Lewis B. Cullman Professor of Molecular, Cellular and Developmental Biology and Professor of Chemistry and Pharmacology at Yale University.

“In light of the enormous potential of BRD4 degradation across a wide range of both hematologic malignancies and solid tumors, Arvinas is committed to advancing its program in order to further understand the benefit that BRD4 PROTACs could provide for patients,” said Manuel Litchman, M.D., President and CEO of Arvinas.

About PROTACs

PROTACs (PROteolysis-TArgeting Chimeras) are bifunctional small molecules that target proteins for degradation and removal from a cell. These molecules induce a cell’s own quality control machinery to bind to a particular protein and “label” it for degradation, thus removing a protein from the system entirely. This contrasts to a more traditional drug development approach that inhibits proteins. However, only 25 percent of the body’s 20,000 proteins can be inhibited. Proteins that cannot be inhibited can potentially be degraded using Arvinas’ approach, radically expanding the number of disease-causing proteins that can become the targets of new drugs.

About Arvinas

Arvinas is a pharmaceutical company focused on developing new small molecule strategies 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 “rogue,” uncontrolled proteins, whose absence could bring great clinical benefit to patients. To address these pathological intracellular proteins, Arvinas is developing a new drug paradigm based on the elimination of these proteins. Our innovative protein degradation technology uses small molecule drugs to ”tag” specific proteins to be degraded by the ubiquitin/proteasome system (UPS), which is responsible for the normal turnover of most proteins within the cell.

Based on groundbreaking research conducted at Yale University by our Founder and Chief Scientific Advisor, Craig Crews, Ph.D., Arvinas has developed a platform technology to induce the loss of intracellular proteins: Proteolysis-Targeting Chimera (PROTAC). The ability of PROTAC-based drugs to induce protein degradation (instead of protein inhibition) offers the advantage of potentially targeting “undruggable” as well as “druggable” elements of the

proteome. This greatly expands our ability to create drugs for many new, previously unapproachable targets. For more information, visit www.arvinas.com.

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