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Syros' Scientific Founders Publish on First Selective CDK12 and CDK13 Inhibitor as Promising Approach for Treatment of Cancer

Novel Small Molecule Approach to Targeting Transcriptional Kinases Validates CDK12 and CDK13 Biology in Cancer

Syros Holds Exclusive Rights to Research, Develop and Commercialize This and Related Selective Small Molecule Inhibitors

Research Findings Published in Nature Chemical Biology

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Syros Pharmaceuticals (NASDAQ: SYRS) announced today that research from its scientific founders validates CDK12 and CDK13, members of the transcriptional cyclin-dependent kinase family that play a critical role in regulating gene expression, as promising new drug targets for a range of aggressive and difficult-to-treat cancers. These findings were possible as a result of the discovery of a highly selective CDK12 and CDK13 inhibitor by Syros' scientific founders and underscore the potential of Syros' pioneering approach for understanding and drugging transcriptional targets to advance a new wave of medicines that control the expression of disease-driving genes.

The research from Nathanael Gray's lab at Dana-Farber Cancer Institute and Richard Young's lab at the Whitehead Institute for Biomedical Research, which was published online today in the peer-reviewed scientific journal *Nature Chemical Biology* (Zhang T., et al., "Covalent targeting of remote cysteine residues to develop CDK12 and CDK13 inhibitors"), shows that inhibiting CDK12 and CDK13 with a small molecule selectively decreases the expression of DNA damage response genes and super-enhancer associated transcription factors implicated in cancer, including acute leukemia and breast and ovarian cancers. The results suggest that a selective CDK12 and CDK13 inhibitor could be effective as a monotherapy in certain cancers and as a combination therapy in other cancers by increasing their susceptibility to targeted therapies involved in DNA damage repair such as PARP1 inhibitors.

Transcriptional kinases have been historically difficult to drug selectively, and the absence of selective CDK12 and CDK13 inhibitors has hindered the ability to study the consequences of inhibiting them in healthy and cancerous cells. Using a novel chemistry approach, Syros' scientific founders designed the first selective CDK12 and CDK13 inhibitors. This novel class of inhibitors achieves its selectivity in part by covalently, or irreversibly, binding to a cysteine residue near the kinase domain that is unique to some transcriptional kinases. This approach was first used to create SY-1365, Syros' first-in-class selective CDK7 inhibitor, which is on

track to begin a Phase 1/2 trial in the first half of 2017.

Syros holds all research, development and commercial rights to the research compound described in the paper, as well as related compounds, through both ownership of the intellectual property and a license from Dana-Farber. Syros is leveraging its unique expertise in drugging transcriptional kinases to create selective CDK12 and CDK13 inhibitors suitable for clinical development.

“A key focus of our proprietary gene control platform is understanding and drugging transcriptional targets, including transcriptional kinases. By modulating these targets with small molecules, we aim to control the expression of the critical set of genes driving the disease with a single drug,” said Eric Olson, Ph.D., Syros' Chief Scientific Officer. “These findings provide further evidence of the therapeutic potential of selectively inhibiting transcriptional kinases as a promising approach for treating a range of aggressive cancers. Building on the work of our founders, as well as our success in creating SY-1365, we believe we are uniquely positioned to create selective inhibitors of CDK12 and CDK13 that can achieve a therapeutic benefit without the toxicities associated with less selective CDK inhibitors.”

Selectivity has proven critical in targeting the CDK family. While pan-CDK inhibitors have shown anti-tumor activity, their clinical utility has been limited due to their toxic effect on blood cells. By contrast, Syros’ selective CDK7 inhibitor SY-1365 has been shown to induce tumor regression and prolong survival in preclinical models of acute leukemia, while having minimal effect on blood cells counts, demonstrating a more favorable profile than a non-selective CDK inhibitor.

About Syros Pharmaceuticals

Syros Pharmaceuticals is pioneering the understanding of the non-coding region of the genome to advance a new wave of medicines that control expression of disease-driving genes. Syros has built a proprietary platform to systematically and efficiently analyze this unexploited region of DNA in human disease tissue to identify and drug novel targets linked to genomically defined patient populations. Because gene expression is fundamental to the function of all cells, the Company’s gene control platform has broad potential to achieve profound and durable benefit across a range of diseases. Syros is focused on cancer and immune-mediated diseases and is advancing a growing pipeline, including its lead drug candidates SY-1425, a selective RARα agonist for genomically defined subsets of patients identified by its platform, for a range of cancers including acute myeloid leukemia and myelodysplastic syndrome, and SY-1365, a selective CDK7 inhibitor for a range of blood cancers and solid tumors. Led by a team with deep experience in drug discovery, development and commercialization, Syros is located in Cambridge, Mass.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995, including without limitation statements by the Company regarding: progress in its clinical development of SY-1365; its drug development strategies; its plans to develop CDK inhibitors and the potential safety and efficacy profile of such inhibitors; and the potential benefits of the Company’s gene control platform. The words ‘‘anticipate,’’ ‘‘believe,’’ ‘‘continue,’’ ‘‘could,’’ ‘‘estimate,’’ ‘‘expect,’’ ‘‘intend,’’ ‘‘may,’’ ‘‘plan,’’

‘‘potential,’’ ‘‘predict,’’ ‘‘project,’’ ‘‘target,’’ ‘‘should,’’ ‘‘would,’’ and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including: Syros’ ability to: advance the development of its programs, including SY-1425 and SY-1365, under the timelines it projects in current and future clinical trials; obtain and maintain patent protection for its drug candidates and the freedom to operate under third party intellectual property; demonstrate in any current and future clinical trials the requisite safety, efficacy and combinability of its drug candidates; obtain and maintain necessary regulatory approvals; identify, enter into and maintain collaboration agreements with third-parties; manage competition; manage expenses; raise the substantial additional capital needed to achieve its business objectives; and successfully execute on its business strategies; risks described under the caption “Risk Factors” in the Company’s Quarterly Report on Form 10-Q for the quarter ended June 30, 2016, which is on file with the Securities and Exchange Commission; and risks described in other filings that the Company makes with the Securities and Exchange Commission in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and the Company expressly disclaims any obligation to update any forward-looking statements, whether because of new information, future events or otherwise.

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