Kymera Therapeutics to Share Novel Preclinical Findings Reinforcing the Advantage of IRAK4 Degraders over Kinase Inhibitors as well as First STAT3 Degrader Results in a Preclinical Model of Th17 Inflammation

May 5, 2022

-Data to be shared at the American Association of Immunologists (AAI) Annual Meeting

-Results highlight potential for IRAK4 degraders to broadly impact TLR/IL-1R-driven inflammatory and autoimmune diseases in a manner superior to kinase inhibitors

-Findings support further exploration of STAT3 degraders in Th17-driven autoimmune indications

WATERTOWN, Mass., May 05, 2022 (GLOBE NEWSWIRE) -- Kymera Therapeutics, Inc. (NASDAQ: KYMR), a clinical-stage biopharmaceutical company advancing targeted protein degradation to deliver novel small molecule protein degrader medicines, today presented new preclinical results demonstrating that STAT3 degradation alleviates Th17 inflammation and is active in a preclinical animal model of CNS inflammation, and that IRAK4 degradation blocks multiple innate immune signaling pathways across different immune cell types in a manner superior to kinase inhibitors. Data will be shared in two separate posters at the American Association of Immunologists (AAI) Annual Meeting 2022, taking place from May 6 - 10, 2022 in Portland, Oregon.

“Collectively, the findings demonstrate the advantage of using degraders to effectively drug signaling nodes driving inflammation as well as the translation of *in vitro* activity to *in vivo* proof of concept in animal models of autoimmune disease,” said Anthony Slavin, Vice President, Immunology. “The impact of STAT3 degradation on immune and stromal cell activation and Th17 inflammation leading to potent effects in a mouse model of multiple sclerosis, as well as the broad effect of IRAK4 degradation on TLR-mediated signaling and cytokine induction and its superiority to kinase inhibition, underscore the clinical potential of these degraders in the treatment of inflammatory and autoimmune disorders.”

STAT3 is a transcriptional regulator that has been linked to numerous cancers as well as multiple autoimmune and fibrotic diseases. Heterobifunctional degraders have emerged as a novel therapeutic modality with great potential to drug historically “undruggable” protein targets like STAT3. Kymera has previously shown its selective STAT3 degraders can suppress the growth of tumors in preclinical models of lymphoma and solid tumors. Findings presented at AAI reveal for the first time the activity of Kymera’s STAT3 degraders against Th17 inflammation, including *in vivo* proof of concept in a clinically relevant mouse experimental autoimmune encephalitis (EAE) model of multiple sclerosis. Degradation of STAT3 inhibited Th17 development and cytokine release, which in turn blocked disease induction and also mitigated ongoing disease in the EAE model.

IRAK4 is known to play a significant role in inflammation mediated by the activation of toll-like receptors (TLRs) and IL-1 receptors (IL-1Rs). While TLR and IL-1R signaling via IRAK4 is involved in immune surveillance, abnormal activation of these pathways is the underlying cause of multiple inflammatory and autoimmune diseases, including atopic dermatitis (AD), hidradenitis suppurativa (HS) and rheumatoid arthritis (RA). The function of IRAK4 is dependent both on its kinase and scaffolding activity; therefore, targeting both functions with a degrader has the greatest potential to inhibit IL-1R/TLR pathway activation. Data to be shared in a second poster showed that potent and selective IRAK4 degraders effectively block TLR-mediated NF-kB and MAP kinase signaling and cytokine induction across multiple different immune cell subsets, including monocytes and B cells, with activity that was superior to IRAK4 kinase inhibitors.

“We are excited to expand the study of our STAT3 degraders from oncology into inflammation and autoimmune indications, where our findings with respect to impact on Th17 development and activation and Th17-mediated diseases open up multiple development opportunities for this novel approach to drugging the JAK-STAT pathway” said Nello Mainolfi, PhD, Co-Founder, President and CEO, Kymera Therapeutics. “The data showing both the mechanistic as well as functional differentiation of IRAK4 degraders compared to small molecule kinase inhibitors further demonstrate the degrader advantage not only for undruggable targets like STAT3, but also for targets like IRAK4 where the full impact of targeting can only be realized by addressing both the scaffolding and catalytic functions of the protein.”

Posters at AAI Annual Meeting:

- Title: STAT3 degraders inhibit cellular activation, cytokine production, and Th17 development, resulting in profound inhibition of autoimmunity in the MOG-EAE model of CNS inflammation
  - Abstract Number: 2297
  - Session Day/Time: Saturday, May 7; 2:30-3:45 p.m. PT
  - Location: Oregon Convention Center, Portland, OR
  - Presenter: Jeffrey Sullivan, Research Associate I, Immunology, Kymera Therapeutics
- Additional Research Highlights:
  - STAT3 degradation showed broad and potent activity in-vitro against TLR receptor and cytokine-induced activation of immune and stromal cells.
  - STAT3 degradation in CD4+ helper T cells potently inhibited Th17 development, decreasing IL-17, IL-22, IL-8/CXCL8, and TNFa production, with concomitant increase in Treg numbers, that was superior to JAK1/2 kinase

inhibition.

  - STAT3 degradation was subsequently evaluated in-vivo in a murine EAE model of multiple sclerosis, with dose-dependent decrease of incidence, disease onset and histopathology observed in comparison to a S1P1 inverse agonist or steroid treatment.

- Title: Selective IRAK4 degradation, not kinase inhibition, blocks TLR-activated NF-Kβ and p38 signaling leading to broad cytokine inhibition

  - Abstract Number: 2188
  - Session Day/Time: Sunday, May 8; 2:30-3:45 p.m. PT
  - Location: Oregon Convention Center, Portland, OR
  - Presenter: Virginia Massa, Research Associate II, Immunology, Kymera Therapeutics

- Additional Research Highlights:
  - IRAK4 degradation, but not kinase inhibition, inhibited NF-Kβ p65 activation and phosphorylation of p38 pathway members by TLR agonists in monocytes and B cells.
  - Peripheral blood mononuclear cells (PBMCs) pretreated with an IRAK4 degrader and then stimulated with the TLR7/8 agonist, R848, exhibited significantly broader inhibition of cytokines (IL-6, TNFα, IL-8 and IL-1β) compared to those pretreated with a selective IRAK4 kinase inhibitor.
  - An IRAK4 degrader inhibited B cell IL-6 production induced by the TLR9 agonist CpG, whereas an IRAK4 kinase inhibitor did not.
  - A sustained effect of the IRAK4 degrader on both target pharmacodynamics and cytokine inhibition was observed, unlike IRAK4 kinase inhibition.

Kymera is collaborating with Sanofi on the development of degrader candidates targeting IRAK4, including KT-474 (SAR444656), outside of the oncology and immuno-oncology fields.

About Kymera Therapeutics
Kymera Therapeutics (Nasdaq: KYMR) is a biopharmaceutical company pioneering the field of targeted protein degradation, a transformative approach to address disease targets and pathways inaccessible with conventional therapeutics. Kymera's Pegasus platform is a powerful drug discovery engine, advancing novel small molecule therapies that harness the body's innate protein recycling machinery to degrade dysregulated, disease-causing proteins. With a focus on undrugged nodes in validated pathways, Kymera is advancing a pipeline of novel therapeutics designed to address the most intractable pathways and provide new treatments for patients. Kymera's initial programs target IRAK4, IRAKIMiD, and STAT3 within the IL-1R/TLR or JAK/STAT pathways, providing the opportunity to treat patients with a broad range of immune-inflammatory diseases, hematologic malignancies, and solid tumors. For more information, visit www.kymeratx.com.

Founded in 2016, Kymera is headquartered in Watertown, Mass. Kymera has been named a "Fierce 15" biotechnology company by Fierce Biotech and has been recognized by the Boston Business Journal as one of Boston's "Best Places to Work." For more information about our people, science, and pipeline, please visit www.kymeratx.com or follow us on Twitter or LinkedIn.

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, as amended, including, without limitation, implied and express statements regarding its: strategy, business plans and objectives for the IRAK4 and STAT3 degrader programs; and plans and timelines for the clinical development of Kymera Therapeutics' product candidates, including the therapeutic potential and clinical benefits thereof. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: the impact of COVID-19 on countries or regions in which we have operations or do business, as well as on the timing and anticipated results of our current preclinical studies and future clinical trials, strategy and future operations; the delay of any current preclinical studies or future clinical trials or the development of Kymera Therapeutics' drug candidates; the risk that the results of current preclinical studies may not be predictive of future results in connection with future clinical trials; Kymera Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of the Company's planned interactions with regulatory authorities; and obtaining, maintaining and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Quarterly Report on Form 10-Q for the period ended March 31, 2022, filed on May 3, 2022, as well as discussions of potential risks, uncertainties, and other important factors in Kymera Therapeutics' subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Kymera Therapeutics' views only as of today and should not be relied upon as representing its views as of any subsequent date. Kymera Therapeutics explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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