

Small Molecule Inhibitors of the Lineage Plasticity Driver ONECUT2

Jagpreet Singh Nanda¹, Yanpeng Xing², Lillian M. Torres¹, Madhusudhanarao Katiki³, Brad Gallent¹, Chen Qian¹, Sungyong You⁴, Beatrice S. Knudsen⁵, James Turkson⁶, Ramachandran Murali³, Michael E. Jung², and Michael R. Freeman¹

¹Departments of Urology and Biomedical Sciences, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Health Sciences University, Los Angeles, California 90048, USA

²Department of Chemistry and Biochemistry, University of California Los Angeles, Los Angeles, California 90095, USA

³Department of Biomedical Sciences, Cedars-Sinai Health Sciences University, Los Angeles, California 90048, USA

⁴Departments of Urology and Computational Biomedicine, Cedars-Sinai Health Sciences University, Los Angeles, California 90048, USA

⁵Department of Pathology, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah 84112, USA

⁶Department of Medicine, Division of Hematology-Oncology, and Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Health Sciences University, Los Angeles, California, 90048, USA

Background: Androgen receptor (AR)-directed therapies are highly effective in prostate cancer, but treatment ultimately selects for resistant tumor populations, including lineage-plastic and AR-indifferent states. ONECUT2 (OC2) is a transcriptional regulator of prostate cancer lineage plasticity and treatment resistance and represents a potentially druggable mechanism underlying adaptation to AR suppression. We developed first-in-class small-molecule inhibitors that directly target the OC2 DNA-binding domain and have shown in vivo efficacy as monotherapy in multiple published studies

Methods: Structure Activity Relationship (SAR) studies, medicinal chemistry, surface plasmon resonance, microscale thermophoresis, pharmacokinetics, stability and safety studies, drug sensitivity and xenograft studies.

Results: Our next-generation inhibitor, JYX-72cis, engages OC2 through a defined covalent mechanism and exhibits improved potency, solubility, stability, and pharmacokinetic properties relative to the first-generation compound CSRM-617. JYX-72cis demonstrates single-agent antitumor activity in preclinical prostate cancer models, including hormone-sensitive disease. Notably, in 22Rv1 castration-resistant prostate cancer cells, JYX-72cis profoundly sensitizes cells to enzalutamide, a widely used AR antagonist, with combined treatment nearly eliminating clonogenic survival. Ongoing medicinal chemistry is generating additional mechanism-directed analogs. JYX-72cis is presently undergoing IND-enabling studies.

Conclusions: Our findings provide pharmacologic proof-of-concept that OC2 is a therapeutically actionable regulator of prostate cancer lineage plasticity and support a strategy in which OC2 inhibition is combined with AR-directed therapy to suppress adaptive resistance and potentially delay or prevent emergence of treatment-resistant disease.

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