



# Seminar Series



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Subject Matter Expert

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583952

## Pharmacodynamic assay for evaluation of first-in-class pyruvate kinase-M2 activators in cancer tissues

September 2 • 12:05 – 1:20 p.m.

### ABSTRACT

**Background:** A new class of compounds target conversion of enzymatically inactive dimeric pyruvate kinase-M2 (PKM2), to an active tetramer PKM2 to tilt the balance between glycolysis and oxidative phosphorylation as a mechanism to suppress metabolic advantage of tumor cells. The dimer PKM2, which is also a transcription factor regulating reprogramming of metabolism, diverts glucose to macromolecule biosynthetic pathways to support proliferation. The researchers developed pharmacodynamic (PD) assay of PKM2 modulation and evaluated in vivo target engagement using a known allosteric PKM2 activator.

**Methods:** The PKM2 modulator [N-(4-(4-(2-methoxyphenyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide] (C. Kung et. Al., Chem & Biol 2012) was synthesized at DCTD, National Cancer Institute (NCI). The PD response was determined in H1299 xenografts (n=3/group) dosed daily at 6, 20, and 60 mg/kg for 10 days and tissue samples were collected 2, 6, 24, and 48 hrs post dose 1, 3, and 10. Tumor volumes were recorded biweekly until 20 days after treatment was stopped. Sandwich immunoassay reactive to monomer/dimer but not tetramer PKM2 was developed on the Luminex® platform. The assay showed >80% lower PKM2 levels in multiple tumor cell lines treated in vitro with PKM2 activator.

**Results:** PD analysis showed PKM2 was largely (>80%) accumulated in nuclear fraction of tumor lysates. Compared to controls, the nuclear accumulation was decreased by 30-60% at 24-48 hrs post dose 10 in 60 mg/kg dose group. No significant changes were observed in PD response at lower doses and at earlier time points. Marginal decrease in tumor volume (-18%, p=0.082) was observed in 60 mg/kg dose group on day 8. Growth rate of xenografts between vehicle and drug treated groups were similar.

**Conclusions:** Our results validate utility of PD assay for monitoring novel PKM2 activators and nuclear accumulation suggest mechanism of PKM2 modulation may involve transcription. PKM2 modulation was only effective after multiple dosing (10 days) at highest dose tested. However, PD response was consistent with marginal efficacy and suggests prolonged treatment with higher doses may be required to reverse the metabolic fate of cancer cells. Importantly, our PD assay provides a critical tool to confirm PKM2 modulation and help guide optimal dosing in translational studies. Funded by NCI Contract No HHSN261200800001E.

### BIO

Dr. Payal Weiss graduated with a doctorate in bioengineering from The Pennsylvania State University in 2012. She is a highly accomplished scientist with more than twelve years of experience in multidisciplinary fields including immunology, biochemistry, pharmacology, and engineering. Her experience includes developing, qualifying, and validating immunoassays for the detection of metabolic biomarkers and vaccine contaminants. She participated in the cross-validation of the developed assays with biorad and Rules Based Medicine (RBM). In addition, she has managed PK/ADA validation of PK studies for pre-clinical – phase III clinical trials, resulting in three successful IND submissions, leading to the success of drug therapies for the treatment of Hodgkin's lymphoma, lymphoma, and atypical hemolytic uremic syndrome (aHUS).

Currently, she is supporting the Defense Threat Reduction Agency's RD Chemical and Biological Technologies Division (CB) as a scientific adviser. Of note, Dr. Weiss worked with GSK to complete the preclinical testing of a new vaccine for respiratory syncytial virus (RSV), a respiratory illness that impacts the elderly and young children. The work was published in the International Journal of Toxicology in February 2021. Since then, the RSV candidate vaccine has moved to phase I clinical trials.