Pharmacodynamic Model of Vorinostat Effects in Multiple Myeloma Cells and Xenografts

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Objectives: To develop a mechanistic pharmacodynamic model to characterize vorinostat effects in multiple myeloma cells and apply the model as a translational platform to link exposure-response relationships in murine tumor xenografts.

Methods: Relative expressions of p21, pNFκB, Bcl-xL and cleaved PARP were measured using immunoblotting in U266 myeloma cells exposed to vorinostat (2 and 5 μM) for up to 48 hours. Cellular proliferation was measured using WST-1 reagent up to 96 hours. Vorinostat concentrations were measured in cell culture media by LC/MS/MS up to 120 hours. Turnover models were applied to describe protein dynamics that linked to cellular proliferation. Pharmacokinetic and tumor growth data in murine xenografts were extracted from literature [1,2]. The cellular model structure and parameters were fixed for scaling the cellular system to describe tumor dynamics. All modeling was conducted using a naïve pooled approach with maximum likelihood estimation in ADAPT 5.

Results: In vitro and in vivo vorinostat pharmacokinetics were described using a biexponential function and a standard two-compartment model. The final cellular model (Fig.1) consisted of indirect effects on Bcl-xL, indirect effects with a transit compartment on p21, pNFκB and cleaved PARP, an exponential growth rate constant for cellular proliferation, and a first-order rate constant for cell death. pNFκB and cleaved PARP stimulated production and degradation of Bcl-xL. Cell growth was inhibited by p21, and cell death was regulated by the relative ratio of cleaved PARP (pro-apoptotic) and Bcl-xL (anti-apoptotic). All parameters were estimated with reasonable precision. Tumor dynamics were well described by fixing biomarker signaling components from the cellular model and estimating the tumor growth rate and cell death parameters only.

Figure 1: Pharmacodynamic Model of Vorinostat in U266 cells

Conclusions: Vorinostat exposure-response relationships were successfully described by a mechanism-based pharmacodynamic model in U266 cells. The model was scaled to xenografts and can potentially serve as a translational platform for designing vorinostat combination treatments.

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