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**Objectives:** Urea cycle disorders (UCD) are rare genetic diseases which can result in hyperammonemia causing irreversible brain damage and death. The objective of this research was to facilitate early-stage drug development for UCD by developing a Quantitative Systems Pharmacology (QSP) model that can be used to develop and test drug targets in silico, and to elucidate the effects of novel drug therapeutics on blood and urine metabolite concentrations.

**Methods:** A Urea Cycle Disorder (UCD) PhysioPD\textsuperscript{TM} Platform was developed to test potential drug treatments on the metabolism of amino acids, ammonia, and urea. The UCD Platform included protein and amino acid metabolism in the muscle, liver, and kidney. A Virtual Patient (VP) was created to simulate the relevant physiology of an adult male with late onset ornithine transcarbamylase (OTC) deficiency, a representation of the UCD disease state. Changes in plasma ammonia and glutamine were tested with four weeks of simulated treatment with different hypothetical drug treatments including restricted protein diets and select amino acid transporter inhibitors (SAATi). Based on the findings from the original simulations, an additional nine hypotheses were developed to explore the perceived discrepancies between simulations and preclinical data and seven of these were tested. This hypothesis testing enabled the prioritization of experimental work to evaluate sensitive uncertainties.

**Results:** Simulations with either restricted protein diets and/or SAATi treatment resulted in decreased ammonia production which may contribute to declines in plasma ammonia concentration. Simulated treatment with SAATi decreased plasma ammonia and glutamine concentrations. Research indicated that some SAATi would have improved efficacy if co-administered with citrulline or arginine. Additional hypotheses for SAATi mechanisms of action and combinations of hypotheses were identified for testing in the Platform.

**Conclusions:** Research conducted in the UCD Platform provided guidance to support more definitive preclinical experimental design and compound evaluation. In addition, the research identified two therapeutic approaches that would combine well with a SAATi target. Quantitative modeling facilitated the development and testing of hypothetical drug targets in early-stage drug development.