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Tumor activated prodrugs of the glutamine antagonist 6-diazo-5-oxo-L-norleucine (DON) with improved therapeutic index

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6-diazo-5-oxo-L-norleucine (DON) is a glutamine antagonist with robust anticancer efficacy, yet its therapeutic potential has been hampered by its biodistribution and toxicity to normal tissues, specifically gastrointestinal tissues which are known to be highly glutamine-dependent. Given DON's promising efficacy, we identified a strategy to deliver it selectively to the tumor while minimizing its peripheral toxicity. Our tumor cell-targeted glutamine antagonist prodrugs are designed to circulate intact as inert prodrugs in plasma and be preferentially biotransformed to DON in tumor cells, permitting significant dose reduction and improved therapeutic index. Our prodrug design is based on the elevated activities of specific tumor-associated proteases (e.g. HDAC, Cathepsins) to serve as "triggers" for prodrug activation. By using specific promoieties, we identified several prodrugs stable in plasma, gut and liver, yet were readily cleaved to DON in tumor cells. When directly compared to DON, our best prodrug exhibited a 27-fold enhanced tumor cell-to-plasma ratio and actively inhibited tumor cell proliferation. Based on the encouraging *in vitro* results, our future studies are planned for evaluation of these compounds pharmacokinetics and efficacy in dog and swine tumor animal models.

Biography

Rana Rais is an Assistant Professor of Neurology at the Johns Hopkins School of Medicine and Director of the Drug Metabolism and Pharmacokinetics group of Johns Hopkins Drug Discovery (JHDD). Prior to joining Johns Hopkins, she was granted a Research Science Regulatory (RSR) fellowship at US FDA to evaluate the biopharmaceutic properties of new molecular entities from new drug applications. She received her PhD in Pharmaceutical Sciences with substantial experience in biopharmaceutics, drug transport, drug metabolism, pharmacokinetics, preclinical formulation and prodrug synthesis and characterization. As a part of JHDD, she has taken primary responsibility for leading the DMPK group, conducting drug discovery research and writing of over 50 peer-reviewed articles in high impact journals. She has served as a consultant and provided research support to several pharmaceutical biotech companies including Transcept, Braeburn, Helsinn, Bayer and Dracen Pharmaceuticals. Most recently she co-founded a new spin-out biotechnology company to commercialize JHU drug discovery inventions, that received a $41 Million Series A funding. She is a co-inventor on nine patents, several of which have been out-licensed to pharmaceutical companies and have led to two Johns Hopkins based spin-outs.

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