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Mechanistic investigations of α-glucosidase activity

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Emergent BioSolutions is currently developing antivirals with an iminosugar structural motif that targets the endoplasmic reticulum (ER) alpha-glucosidase enzymes. The mechanism of action is based on the inhibition of host glycosylation pathway that leads to misfolded viral glycoproteins, resulting in reduced viral infectivity. Data generated by Emergent and others indicate that iminosugars have the potential to be developed as a treatment for diseases such as Dengue Fever, influenza, Ebola, and Zika. To support our drug discovery efforts, preliminary mechanistic investigations into the protein synthesis and folding pathway have been initiated. We have verified the impact of inhibition on α-glucosidase activity by showing inhibition of viral proliferation in human cell lines knocked out for each of the ER glucosidases using CRISPR-Cas9. With collaborators at the Oxford Glycobiology Institute and a commercial MALDI-MS vendor, we evaluated in vitro glycan profiling in the CRISPR cells by both a chemical derivatization/HPLC method and by MALDI-MS of permethylated glycans. These orthogonal techniques confirm that knock-out of alpha-glucosidase 1 and alpha-glucosidase 2 enzymes prevents the cleavage of the terminal glucose units involved in glycoprotein maturation. Examining the changes in glycan product distribution after treatment of cell extracts with alpha-glucosidase 1 reveals the loss of a single glucose, while treatment with alpha-glucosidase 1 and alpha-glucosidase 2 results in the loss of two and three glucose units. These techniques can be used to confirm the mechanism of action of new chemical entities from our iminosugar med-chem program. Work described here was performed in collaboration with Anthony Treston and Kelly Warfield of Emergent, Dom Alonzi and Nicole Zitzmann of Oxford University and Craig Day of Utah State University.

Biography

Daniel C Hill is a PhD chemist with 20 years' experience in the pharmaceutical industry solving complex problems in results-driven departments working on programs in early discovery supporting candidate selection, drug development and on through to marketed commercial products. Dan has diverse experience in a variety of therapy areas along the critical path of drug discovery and development including Neurokinin Receptor Antagonists, gamma-Secretase, 5HT-1b Receptor Antagonists, Gap Junction Modulators, Topoisomerase Inhibitors, and Iminosugar alpha-Glucosidase Inhibitors.

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