Introduction:

Genetic and gastrointestinal disorders are among the most devastating side effects of cancer therapy. In many cases, mucositis, colitis, diarrhea, and other drug-induced conditions limit tolerability of chemotherapy. Some targeted therapies, such as PI3K inhibitors, are also known to cause gastrointestinal (GI) side effects. Thus, understanding the molecular mechanisms of GI toxicity caused by chemotherapeutic and targeted agents may provide insights into key genes and pathways, highlighting potential targets suitable for co-therapies that can mitigate them. To this end, we have used computational methods to explore the connections between GI diseases such as Crohn’s disease (CD), inflammatory bowel disease (IBD), GI effects caused by bacteria and viruses, and GI toxicity caused by drugs or compounds. In total, we have investigated over 60 publicly available datasets that included conditions such as intestinal, neonatal, colorectal, and multiple PI3K inhibitors. We also performed whole transcriptome profiling of the human EpiIntestinal™ in vitro model treated acutely with diverse PI3K inhibitors at their respective plasma steady-state concentrations. The data and conclusions presented here outline a novel approach to identify non-obvious connections and pathways that could potentially inform on both mechanisms of toxicity as well as potential strategies for mitigation.

Materials and Methods:

Core Genes of PI3K Inhibitors

Inhibitors Segregate by Isoform Selectivity

Autoptogenes Regulation Acroix PI3K Inhibitors and C. diff

Gene Expression Profiling and Machine Learning to Characterize the Molecular Mechanisms of PI3K Inhibitor-Induced Gastrointestinal Side Effects

Fullerton2, J. Grahnen1, W. Proctor2, L. Pham1, M. Tseng2, J. Fine2, B. Goldberg1, P. Lum1 and S. Chandler2

1 Auransa Therapeutics, Palo Alto, CA; and 2 Genentech, South San Francisco, CA.

The closest preclinical model for PI3K inhibitors is the treatment of T of C. difficile in human ileocecal epithelial cells (GSE28005).

CONCLUSIONS

1. We assessed transcriptional changes of a diverse panel of clinically relevant PI3K inhibitors in a reconstituted small intestinal epithelial model, proposing to map similarities of these gene changes to diverse and extensive publicly available data sets.

2. The closest match for PI3K inhibitor gene response was that of Tox A of C. difficile, thus supporting a non-obvious connection between an infectious disease etiology and PI3K inhibition related GI adverse events.

3. As part of these findings a common autophagy signature was observed across PI3K inhibitor molecules and Tox A’s response of C. difficile.

4. These findings present new hypothesis to test in regards to pathways resulting in PI3K inhibition mediated GI toxicities and potential mitigation strategies.