Pathway-based Analysis of the Liver Response to Intravenous Methylprednisolone (MPL) Administration in Rats: Acute versus Chronic Dosing

Alison Acevedo[1], Ana Berthel[4], Debra DuBois[5,6], Richard R Almon[5,6], William J Jusko[5,6], Ioannis P Androulakis[1, 2, 3]

[1]Biomedical Engineering Dept.;[2]Chemical and Biochemical Engineering Dept.;[3]Dept. of Surgery, Rutgers-Robert Wood Johnson Medical School;[4] Dept. of Biochemistry, Mount Holyoke College; [5] Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, SUNY Buffalo, [6] Department of Biological Sciences, State University of New York at Buffalo, SUNY Buffalo,

Corticosteroids are drugs designed to copy the structure of cortisol (a hormone produced by the adrenal glands) which regulates metabolic and immune molecular pathways. These drugs are used to treat injuries and diseases that cause the body to suffer from a chronic inflammatory response. For example, a rheumatoid arthritis patient must take corticosteroids to treat their chronic condition indefinitely in order to reduce their pain and swelling, among other symptoms. A patient who has just had an organ transplant must also take these drugs indefinitely in order to prevent their body's immune system from rejecting their new, and foreign, organ.

These drugs are essential to a basic healthcare system and are used globally. Unfortunately, taking corticosteroids for long periods of time can harm the body as well. This is because corticosteroids are processed in the same biochemical pathways that cortisol, the body's natural hormone, is processed in. Patients must endure these problems because corticosteroids are the best option for any chronic inflammatory disease.

Our research works to characterize, or map, the effects of corticosteroids within different organs of the body. In this particular study, we focus on one specific drug: Methylprednisolone – a corticosteroid that is commonly used by patients. We also focus on liver tissue because it is one of the most significant targets of corticosteroid effects. We conduct animal studies measuring the influence of corticosteroids over time and in different doses and dose schedules within the liver in order to understand how different dosing schedules influence the liver. This is important to understand completely because it is not clear how a patient's dosing schedule influences their symptoms.

Using tools from the field of quantitative systems pharmacology (computational tools for drug development in the pharmaceutical industry) we perform meta-analysis of the gene expression data collected from these tissues. By identifying the behavior of genes, we can predict how the drug will affect the liver at the molecular level. This research, and other similar studies conducted in our lab, allow scientists to understand how a drug affects a tissue and helps them to improve the design of corticosteroid therapy. In this way, we hope to improve the lives of patients who depend on this drug to live healthy and comfortable lives.