

James & Esther King Biomedical Research Program

Kojetin, Douglas

*Molecular Therapeutics
The Scripps Research Institute*

*2010 Program
New Investigator Research
(3-year project)*

Project Title: Dynamic Regulation of Allosteric Communication Networks in PPARgamma Pharmacology

Project Summary: Our long-term goal is to understand how nuclear receptor (NR) transcription factors (proteins that bind DNA at specific sites to regulate copying) function and contribute to disease development and progression for purposes of preventative and therapeutic control. Tobacco smoke contributes to numerous health issues; in heart disease patients, tobacco smoke significantly affects the expression of a particular NR protein, PPARg. As an obligate heterodimer (protein partner) with the NR protein RXRa, PPARg regulates the expression of genes involved in cellular metabolism, growth, differentiation, and inflammation. Recent emphasis has been placed on a new class of selective PPARg drugs that preserve beneficial properties and decrease side effects of current PPARg drugs. Understanding how existing PPARg drugs work will aid the development of next-generation PPARg drugs. To accomplish this, we will test the hypothesis that pharmacologically distinct PPARg ligands (drugs) modulate (1) the surface used for interacting with other proteins and the ability to preferentially recognize one protein over another of RXRa/PPARg; (2) the function of RXRa/PPARg via unique allosteric (change in shape and activity) changes in dynamics. We predict these studies will provide new insight into how ligands control PPARg function and may provide the basis for the development of novel therapeutics for disease treatment.