Title:	**PPAR-sparing insulin sensitizers; path for development and clinical evaluation**
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Background and aims: We have proposed that development of insulin sensitizer therapies has been delayed because of focus on nuclear receptor activation. Further, superior pharmacological profiles, [e.g., less plasma volume expansion (and edema) as well as greater reductions in blood pressure and corrections of dyslipidemia] might be obtained by minimizing direct activation of nuclear receptors. These studies seek to establish whether a series of insulin sensitizers could be established that limit or avoid interaction with nuclear receptors. We also aim to directly benchmark a prototype ñPPAR-sparingò compound against pioglitazone in the clinic.

Materials and methods: Sixty novel analogs were generated and evaluated for PPARɔ binding activity with a florescence polarization assay (Invitrogen) using rosiglitazone as a positive control. Selected compounds were tested for anti-diabetic activity in KKAy mice. Compounds (10-100 mg/kg/day) were given by oral gavage for 4 days and fasting plasma glucose, insulin, and triglycerides were measured. To determine whether these compounds might interact with other PPAR transcription factors, AlphaScreen assays were set up with twelve nuclear receptor cofactor peptides for PPARɔ, PPARŬ, and PPARŭ using positive controls rosiglitazone, GW7647, and GW0742, respectively. A preclinical package was developed for testing a prototype PPAR-sparing analog in human clinical trials. Phase IA (single dose) and Phase IB (seven doses) were completed in comparison to 45 mg pioglitazone in normal human volunteers.

Results: The novel analogs demonstrated a range in binding to PPARɔ as compared to rosiglitazone. Five analogs demonstrated little to no binding to PPARɔ even at 100 uM compound. Forty percent of the novel analogs have demonstrated anti-diabetic pharmacology in vivo. The ability of the analogs in this series to lower circulating levels of glucose, insulin, and triglycerides in KKAy mice demonstrates no correlation with PPARɔ binding. The PPAR-sparing analogs with anti-diabetic activity were also tested in the AlphaScreen assays for all three PPAR subtypes. The PPARɔ sparing nature of the compounds established from initial direct binding studies was confirmed. None of the compounds interacted with PPARŭ. The interaction with PPARŬ was either similar to or less than pioglitazone. A preclinical support package was created for the prototype PPAR-sparing analog that supports clinical testing at up to 50% higher exposure relative to pioglitazone (and its active metabolites) for 28 days. Phase IA and Phase IB clinical studies were completed demonstrating no safety concerns, a twelve hour half-life, steady state circulating levels of active drug after two days of dosing, and the expected increase in circulating biomarker, adiponectin.

Conclusion: We conclude that it is possible to create PPAR sparing compounds with anti-diabetic pharmacology. We are now exploring the clinical pharmacology of the prototype PPAR-sparing compound vs pioglitazone in non-diabetic and diabetic patients. We are also evaluating whether selective mitochondrial interactions might predict more optimal insulin sensitizing pharmacology.