Characterisation of a novel selective PPARγ modulator (SPPARγM) with insulin sensitizing and glucose lowering properties

T Allen¹, SA Moodie²†, F Zhang²†, A Smith¹, F Gregoire², E Clemens², J Luo²,
GEO Muscat¹*, TA Gustafson²*

* Corresponding authors  † joint first authors

¹Institute for Molecular Bioscience, University of Queensland, St. Lucia QLD 4072, AUSTRALIA.
²Metabolex, Inc. 3876 Bay Center Place, Hayward, CA 94545

Background - PPARγ is a member of the Nuclear Hormone Receptor (NR) superfamily, and the NR1C subgroup that includes PPARα and PPARδ. Inherited mutations in the PPARγ gene lead to dysfunctional lipid and glucose homeostasis. The NR1C subgroup functions as fatty acid (FA) sensors, and couples fluxes in low affinity dietary lipids/FAs to the transcriptional regulation of genes in lipid and glucose homeostasis. For example, the mono and polynsaturated (but not saturated) FAs modulate PPARγ in the µM range. The total concentration of nonesterified FAs in human serum can exceed 1mM, and the more prevalent FAs can account for up to 20-40% of this total. The pathophysiological significance is underscored by many reports that diets rich in unsaturated FAs lower cholesterol and triglycerides levels, and elevate HDL cholesterol levels in animals and humans. Furthermore, the dietary polyunsaturated to saturated fat ratio differentially affects the body mass index in populations with common variants of the PPARγ gene, highlighting the importance of PPARγ (gene)-nutrient interactions.

Halofenate, a phenoxyacetic acid [(2-acetoamidoethyl (p-chloro-phenyl) (m-trifluoromethylphenoxy) acetate)] was tested clinically in the 1970’s as a hypouricemic, and hypolipidemic drug. Halofenate was shown to be very effective in lowering plasma triglycerides, cholesterol, uric acid and bilirubin levels in patients with a variety of hyperlipoproteinemias. Interestingly, hypoglycemic and hypoinsulinemic effects were serendipitously observed in dyslipidemic type II diabetic (NIDDM) patients after halofenate monotherapy, and in combination with oral hypoglycemic drugs. The therapeutic (and time course of the hypoglycemic) effects of halofenate mirrored some aspects of the TZD class of insulin sensitizers that are potent synthetic activators of PPARγ.

Objectives - We hypothesized that halofenate might act as an insulin sensitizer and we present data to show that halofenate is a selective PPARγ modulator (SPPARγM) with therapeutic utility.

Outcomes - We show that halofenic acid: (i) selectively activates PPARγ in a dose dependent manner (~EC₅₀ 30 µM); (ii) binds directly to human PPARγ (Ki of ~18-30 µM); and (iii) is a partial PPARγ agonist with ~ 20% the activity of the full agonist rosiglitazone. The partial agonism of halofenic acid reflects a unique footprint in the context of interactions with transcriptional cofactors. For example, the differential displacement of corepressors (N-CoR and SMRT) and the defective recruitment of the coactivators (p300, CBP and TRAP220). Specifically, halofenic acid displaced the co-repressors N-CoR and SMRT from PPARγ in a dose dependent manner yet did not induce recruitment of the co-activators p300, CBP or TRAP 220, relative to the potent PPARγ agonist, rosiglitazone. In addition, halofenic acid selectively modulated specific PPARγ responsive genes in differentiated 3T3-L1 adipocytes. In contrast to the potent agonist, rosiglitazone, halofenic acid did not induce genes involved in fatty acid storage and transport. Moreover, halofenic acid did not induce differentiation of primary human pre-adipocytes, and neutralized rosiglitazone-mediated adipogenesis. In vivo studies demonstrated that halofenate displays vigorous insulin sensitizing and glucose lowering properties in ob/ob mice.

Conclusions - These results demonstrate that halofenate is a novel selective PPARγ modulator that induces differential cofactor displacement and recruitment. Moreover, it demonstrates therapeutic anti-diabetic properties in the absence of adipogenic properties that lead to deleterious weight gain with TZD treatment in type II diabetic patients.