# Covalent modulators of PPARγ: towards a new targeted cancer therapy

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**Abstract**

Peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-activated transcription factor of the nuclear receptor superfamily, which plays integral roles in adipocyte differentiation, insulin sensitivity, metabolism, immunity and inflammation. In addition, upregulation of PPARγ has been linked to certain cancers, including a subset of bladder and prostate cancers, and negative modulation of PPARγ with small molecule ligands has been shown to exert an anticancer effect. Furthermore, overactive PPARγ signalling in luminal bladder tumours has been found to modulate the tumour microenvironment to enable escape from immuno-surveillance. Thus, PPARγ is a promising therapeutic target for the treatment of PPARγ-upregulated cancers.

Although PPARγ agonists are well known in the context of metabolic disease, relatively few PPARγ antagonists and inverse agonists have been reported. We have generated a library of over 500 small-molecule covalent modulators that undergo nucleophilic aromatic substitution with Cys285 of PPARγ, and discovered ligands with a range of functionalities that selectively target the receptor with low to sub-nanomolar biochemical affinities and cellular potencies. This presentation will detail the design, synthesis, and biochemical evaluation of our lead covalent PPARγ ligands, as well as insights from initial in vivo pharmacokinetic experiments.

**Biography**

Jasmine is nearing completion of her PhD studies at the University of Western Australia (UWA) under the supervision of A/Prof. Matthew Piggott. She completed a Bachelor of Science in 2021, majoring in Chemistry and Pharmacology, and graduated with First Class Honours in Chemistry. Her doctoral research, conducted in collaboration with UWA and The Kids Research Institute spin-out company Setonix Pharmaceuticals, focuses on the design, synthesis and biological evaluation of covalent modulators of PPARγ for cancer. With a strong passion for drug discovery, Jasmine has also completed internships working on new antibiotic discovery (University of Illinois), MDMA-inspired medicinal chemistry (UWA–Emyria), and GPCR pharmacology (Perkins Inst.).