Coregulator peptide binding profiling of PPARγ treated with agonist rosiglitazone and antagonist GW9662.

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Study Design
Ligand effects on PPARγ were studied using PamChip® array containing 53 coregulator peptide binding motifs. Rosiglitazone specifically induced binding to the LXXLL motifs derived from the coactivators CBP, p300, SRC1, TIF2, SRC3, PRIP, IKBB, DAX1, SHP, RIP140, and TRAP220, whereas interactions with the corepressor motifs NCORLXXXLXXL2263 and SMRTLXXXLXXL2342 were reduced compared to vehicle treatment (figure 1, 2). In contrast to rosiglitazone treatment, the antagonist GW9662 failed to induce binding to any of the coactivator peptides (figure 2). The compounds rosiglitazone and GW9662 were further characterized by preparing full dose-response curves. Example curves on two coregulator peptides are shown in figure 3.

Key Findings
Using the peroxisome proliferator-activated receptor γ (PPARγ) as a model Nuclear Receptor, we were able to generate ligand-specific interaction profiles (agonist rosiglitazone versus antagonist GW9662. Using the PamChip® arrays the authors were able to identify TRIP3 as a novel regulator of PPAR γ-mediated adipocyte differentiation (Koppen et al. 2009)

“Author Quote”
An obvious application of high throughput Nuclear Receptor - Coregulator interaction profiling is the initial screening of novel Nuclear Receptor agonists and antagonists that may have clinical applications.

Background
Nuclear receptors (NRs) are major targets for drug discovery. Upon ligand binding, NRs undergo a conformational change, which alters their binding preference for coregulators. Short a-helical sequences in the coregulator proteins, LXXLL (in coactivators) or LXXXLXXL (in corepressors), are essential for the NR-coregulator interactions. However, little is known on how specificity is dictated.

To obtain a comprehensive overview of NR-coregulator interactions, a PamChip® microarray containing 53 coregulator peptides was used to study the interaction of PPAR (peroxisome proliferator-activated receptor γ) and peptides on the array. Note, in 2010 a PamChip containing 155 coregulator proteins has been developed.

Conclusion
The PamChip® nuclear receptor coregulator profiling array provides a drug development and biological discovery platform for nuclear receptor ligands. These analyses can help to select more effective compounds in the early stages of drug development.