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Structural mechanism of partial agonists and antagonists of PPARgamma for use as antidiabetics

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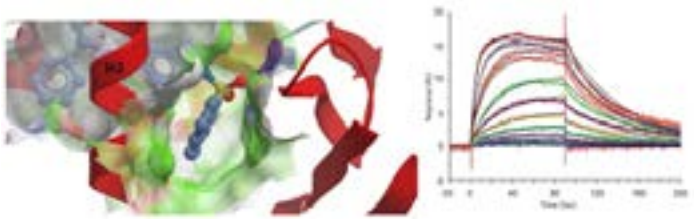
Synthetic full agonists of Peroxisome proliferator-activated receptor gamma (PPARγ) have been prescribed for the treatment of diabetes due to their ability to regulate glucose homeostasis and insulin sensitization. While the use of full agonists of PPARγ has been hampered due to severe side effects, partial agonists and antagonists have shown promise due to their decreased incidence of such side effects in preclinical models. No kinetic information has been forthcoming in regard to the mechanism of full versus partial agonism of PPARγ to date and little structural and dynamic information is available which can shed light on the mechanistic difference between full and partial agonists as well as antagonists. We have used X-ray crystallography, cellular assays, Hydrogen Deuterium Exchange (HDX), and Surface Plasmon Resonance (SPR) to probe the mechanism of several PPARγ partial agonists and antagonists. Our findings demonstrate that not only do partial agonists and antagonists act through distinct transcriptional mechanisms, they also demonstrate differences in structure, dynamics, and kinetics as compared to full agonists.



Biography

John B Bruning completed BSc from Texas A&M University in 1997. He began crystallography in the Laboratory of Yousif Shamoo at Rice University. He worked on the structural mechanism of the human sliding clamp and its interactions with DNA replication proteins. He received PhD in 2005 and completed 2 successful Post-docs. The first was at the Scripps Research Institute from 2005-2007 working on structural studies of nuclear receptors including PPAR, RXR, ER, and TR; second Post-Doc was with Jim Sacchettini in the Houston Medical centre. He was a part of the TB structural genomics consortium. He received his first faculty position at the University of Adelaide in 2012 as a Lecturer. He was tenured in 2015 and promoted to Senior Lecturer in 2016. He was also appointed Adjunct Professor of the Scripps Research Institute in 2016.

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