Project 1: The Effect of Tributyl Tin on the Pathways Controlled by the Retinoid-X-Receptor (RXR) Gamma

Dr. Carl Wagner

Tributyl tin (Bu_3SnCl) was used from the 1960s until it was recently banned (2008) as a paint additive for ocean-going ships to keep barnacles and other marine life from attaching to the ships (reducing fuel-efficiency). Tributyl tin binds to the retinoid-X-receptor (RXR), and structures for tributyl tin bound to the RXR alpha isoform's ligand binding domain demonstrate the binding pattern—see Fig 3 below from work by le Maire (EMBO reports Vol 10, 2009, 367-373).

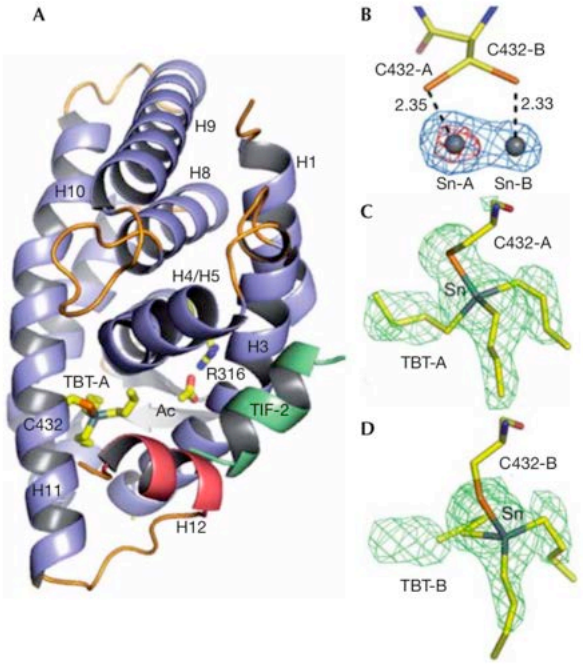

Fig 3 | Structure of the RXR-α ligand-binding domain in complex with TBT and TIF2. (**A**) Overall structure of the complex in cartoon representation. The TBT is shown bound to Cys 432 through a covalent interaction, and an acetate molecule (Ac) involved in a salt bridge with Arg 316 are depicted. This acetate, not essential for RXR activity, derives from the crystallization condition. (**B**) Anomalous difference electron density map contoured at 15.0σ (red) and 5.0σ (blue) showing two tin sites facing the two alternative positions of Cys 432 (A,B). (**C,D**) The two positions of TBT (TBT-A and TBT-B) bound to Cys 432-A and Cys 432-B are shown in the F_O–F_C omit map contoured at 3.0 σ. LBD, ligand-binding domain; RXR-α, retinoid X receptor-α; TBT, tributyltin; TIF2, transcriptional intermediary factor 2.

There are three RXR isoforms, RXR alpha, RXR beta and RXR gamma—with RXR gamma impacting several neurological disorders. Tributyl tin is known to possess detrimental neurological effects in a number of organisms—mice, fish, etc. A potential project for research in my lab could be to investigate how TBT binds to RXR gamma.

Project 2: Retinoid-X-Receptor Binding: A comparison of therapeutic and adverse effects due to subtype

A natural product called valerenic acid has been shown to bind to RXR alpha and RXR beta—see Fig. 4 from Merk and co-workers (J. Med. Chem. 2018, 61, 5442-5447). Extracts of *Valeriana officinalis* appear to possess neuroprotective characteristics. Again, there's no report of valerenic acid binding to RXR gamma. Perhaps a comparison of the way a natural product (found in the environment) binds to RXR gamma and exerts therapeutic effects versus an environmental contaminant like TBT that exerts detrimental effects would be an exciting project for undergraduates.

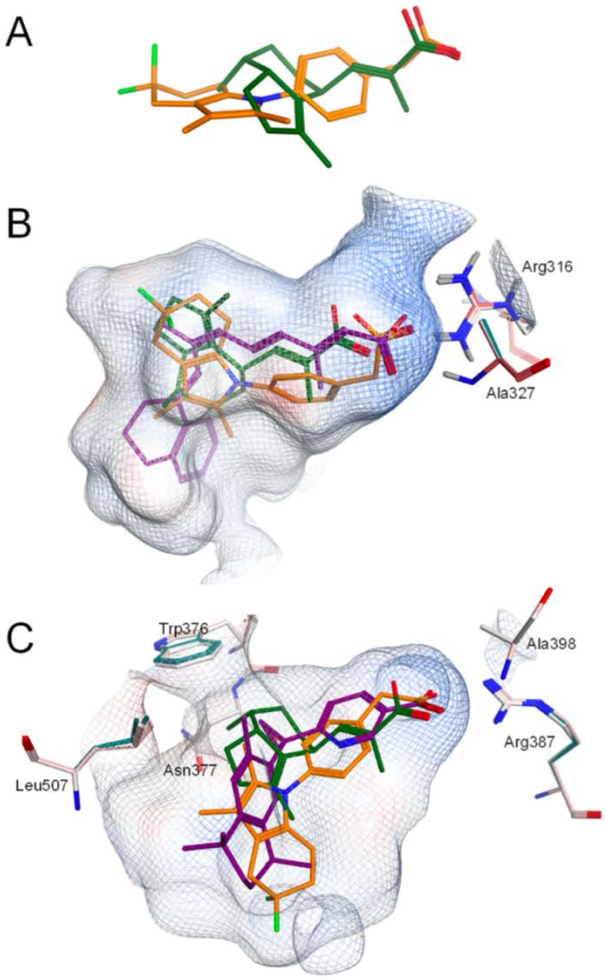

Figure 4. Superimposed crystal structures (A) of valerenic acid (dark green) and its de novo-designed mimetic **3** (orange): proposed binding modes in the RXRα (panel B, PDB code 4K4J) and RXRβ (panel C, PDB code 1H9U[26]) ligand binding sites. Compounds were docked using GOLD[24] software.