Use of X-ray crystallographic data for computational modelling of receptor-ligand interactions: design of steroidal inhibitors of breast and prostate cancer cell growth

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Hormone-sensitive tumours, such as breast or prostate cancers, are leading causes of death, and manipulation of steroid signaling is an effective treatment. X-ray structures of steroid receptors have been solved in complex with anti-cancer drugs (e.g. tamoxifen); and steroid modifying enzymes have been solved in complex with steroidal anti-tumour drugs (e.g. exemestane, Abiraterone). Although X-ray crystallography is essential for structure-based drug design, the vast chemical space prevents experimental analysis of all interacting compounds. To design novel anti-tumour steroidal compounds, we use X-ray crystallographic data from protein-ligand complexes as templates for molecular dynamics, Monte Carlo and molecular docking simulations using freely available resources. X-ray structures of proteins in complex with steroidal drugs used to treat hormone-dependent cancers were chosen: estrogen receptor, androgen receptor , aromatase (CYP19), 17α-hydroxylase (CYP17), 17β-HSD family enzymes and aldo-keto reductases (AKR1Cs) [1]. We use *in silico* methods to ask: Is it possible to reliably model new receptor-ligand complexes using X-ray structural data from known receptor-ligand structures. Simulation results are correlated with *in vitro* and anti-proliferation tests using human cancer cells. In general, *in silico* computational methods appear to predict the molecular targets of steroidal compounds, and can refine protein X-ray crystallographic data to model new ligand binding geometries (Fig 1) [2-4]. However, modelling ligand binding starting from *apo* structures is likely to fail. Moreover, for flexible ligand sites, X-ray structures of chemically similar ligand complexes appear necessary, combined with refinement by molecular dynamics or Monte Carlo. Thus, additional X-ray structures of proteins bound to diverse steroidal ligands are necessary for design of improved anti-cancer steroidal compounds.

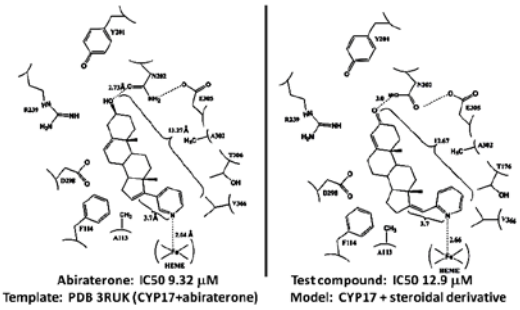

Figure 1. Example: modelling binding by new steroidal derivatives using X-ray structural data (CYP17 + anti-cancer drug Abiraterone). Predicted binding energies correlate with anti-proliferative activity.

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