

What do we Really Know About the Drugs we Take?

The Bourne Laboratory <http://www.sdsc.edu/pb>

The above question is one our laboratory has been addressing for several years now. What is clear is that for small molecule drugs the notion of one drug effecting one receptor to treat one disease is unlikely to be true for new chemical entities (NCEs) and pharmaceuticals (those rare NCEs that make it to the marketplace). The questions then become ones of:

- *Polypharmacology* - what are *all* the targets that bind a given drug?
- *Network pharmacology* - what are the *cumulative effects* on a variety of biochemical and protein-protein interaction networks?
- *Systems Pharmacology* – what are the *cumulative effects* on the phenotype and can those effects be modeled for improved outcomes?

We have made some inroads in each of these three areas. Our focus is on determining the side effects of existing compounds and identifying repurposing opportunities with an emphasis on neglected tropical diseases. We are particularly interested in the clinical follow-on to our basic research findings.

Over time we have developed a software pipeline combining techniques from structural bioinformatics and chemical informatics to identify targets and the implications of pharmaceutical action on those targets. Example components of our pipeline are:

- Start with a 3-dimensional structure (either experimental or modeled) of the lead-receptor complex – the primary binding site.
- Start with a ligand and go target fishing based on what that ligand and chemical modifications might bind to.
- Search the drugable proteome for similar (secondary) binding sites using a Sequence Order Independent Profile-profile Alignment (SOIPPA) algorithm [1] which locates sites and sub-sites considering both chemical and evolutionary constraints and, as the name suggests, does not rely on a conserved linear relationship to the primary sequence.
- The search space defined by the drugable proteome is kept manageable through the use of a geometric potential [2] that discriminates potential binding from non-binding sites in the individual proteins comprising the drugable proteome.
- Extract known ligands from primary and secondary sites.
- Perform cross-docking studies to validate the secondary sites. That is that the drug or lead bound to the primary site binds to the secondary site and any small molecule bound to the secondary site also binds to the primary site where the drug or lead is binding.
- Use molecular dynamics simulations to further analyze the promising cross-docking results.

- Analyze the docking scores and chemical features to establish whether the secondary sites are significant.
- Review all available clinical and literature information to attempt to confirm the secondary sites.
- Review the secondary sites in the context of biological pathways in an attempt to define (or confirm) the physiological outcomes.
- Where possible use existing metabolic or other reconstructions e.g. based on flux balance analysis, to model off-target action dynamically.

We have been successfully applied this pipeline to explain side effects of existing drugs through single and multiple off-targets, proposed alternative uses (repositioning) for existing drugs and helped select among lead compounds for clinical trial. Here is a summary of some findings to date:

- Propose a secondary binding site for the class of drugs known as Select Estrogen Receptor Modulators (SERMs), which includes the popular anti-cancer treatment **tamoxifen** and offers an explanation for the side effects observed in these drugs [3].
- Reposition the existing drugs **encapalone** and **tolcapone** used in the treatment of Parkinson's disease. We suggest, and have some experimental in vivo and in vitro experimental support, that these inhibitors may be effective against extreme drug resistant tuberculosis [4].
- We have proposed a mechanism for why **torcetrapib**, a Pfizer cholesterol-controlling drug taken out of stage III clinical trials after 15 years and \$800M of development failed [5]. In this case the drug is suggested to bind to up to 12 off-targets which have been mapped to biological pathways and subsequently used to explain the observed outcome. The related drugs **anacetrapib** and **JTT705** have different binding profiles and biological outcomes that map to those differences by pathway and literature analysis. This study highlights the role that systems biology plays in the future of drug discovery.
- We have identified several secondary targets of 4,5-dihydroxy-3-(1-naphthylidiazonyl)-2,7-naphthalenedisulfonic acid, a known micromolar inhibitor of *Trypanosoma brucei* RNA editing ligase 1 for treatment of sleeping sickness. On-going work is attempting to improve the efficacy of this drug and reduce side effects [6].
- In collaboration with Bernhard Palsson's group we have used a metabolic network model to explore the off-target effects of the failed phase III clinical trial drug **torcetrapib** [7]. We have extended this approach to identify antibacterial mechanisms (under review).
- We have computed the complete drug-target network for *Mycobacterium tuberculosis* revealing new targets and potential drug repositioning options [8]. This has been repeated for human and *Plasmodium falciparum* (unpublished)
- **Raloxifene** is an estrogen receptor modulator that has been shown in animal models to positively impact *Pseudomonas aeruginosa* infection. In collaboration with Fiona Brinkman's group we have suggested reasons that have been experimentally tested [9].

- **Nelfinivir** is a protease inhibitor that also has a positive effect on a number of solid tumor types and a clinical trial is underway. We have found low-affinity binding of **nelfinivir** to a number of human protein kinases and provided a hypothesis for the observed phenotype [10].

Beyond collaborative academic search we have collaborated with the following pharmaceutical companies:

- Limerick BioPharma
- Optima Pharmaceuticals
- Johnson and Johnson

Summaries of our work in relation to others can be found in three reviews:

- L. Xie, S.L. Kinnings, L. Xie and P.E. Bourne 2011 Predicting the Polypharmacology of Drugs: Identifying New Uses Through Bioinformatics and Cheminformatics Approaches in *Drug Repurposing* M. Barrett and D. Frail (Eds.) Wiley and Sons.
- L. Xie, L. Xie, S.L. Kinnings and P.E. Bourne 2012 Novel Computational Approaches to Polypharmacology as a Means to Define Responses to Individual Drugs, *Annual Review of Pharmacology and Toxicology* 52: [\[PDF\]](#)
- L. Xie, L. Xie, Y. Zhang & P.E. Bourne 2013 Structural Systems Pharmacology for Complex Diseases and Personalized Medicine (Review) *PLoS Comp. Biol.*, submitted.

[1] L. Xie & P.E. Bourne 2008 *Proc. Nat. Acad. Sci. (USA)* 105(14) 5441-5446. [\[PDF\]](#)

[2] L. Xie & P.E. Bourne 2007 *BMC Bioinformatics* 8(Suppl 4):S9. [\[PDF\]](#)

[3] L. Xie, J. Wang & P.E. Bourne 2007 *PLoS Comp. Biol.* 3(11) e217. [\[PDF\]](#)

[4] S.L Kinnings, N. Liu ,N. Buchmeier, P.J. Tonge L. Xie and P.E. Bourne 2009 *PLoS Comp. Biol.* 5(7) e1000423. [\[PDF\]](#)

[5] L. Xie, J. Li, L. Xie, & P.E. Bourne 2009 *PLoS Comp. Biol.* 5(5) e1000387. [\[PDF\]](#)

[6] J.D. Durant, R.E. Amaro, L. Xie, M.D. Urbaniak, M.A.J. Ferguson, A. Haapalainen, Z-J. Chen, A.M. Di Guilmi, F. Wunder, A. Tersteegen. P.E. Bourne & J.A. McCammon 2009 A Multidimensional Strategy to Detect Secondary Pharmacological Targets in the Absence of Global Structure and Sequence Homology *PLoS Comp Biol.* 6(1): e1000648. [\[PDF\]](#)

[7] R.L Chang, L. Xie, L. Xie, P.E. Bourne B.O. Palsson 2010 Drug Off-Target Effects Predicted Using Structural Analysis in the Context of a Metabolic Network Model. *Plos Comp. Biol.* 6(9): e1000938. [\[PDF\]](#)

[8] S.L. Kinnings, L. Xie, K.H.Fung, R.M. Jackson, L. Xie and P.E. Bourne 2010 The *Mycobacterium tuberculosis* drug gome and its Pharmaceutical Implications. *PLoS Comp. Biol.* 6(11): e1000976. [\[PDF\]](#)

[9] S.J. Ho Sui, R. Lo, A. R. Fernandes, M. D.G. Caulfield, J. A. Lerman, L. Xie, P. E. Bourne, D.L. Baillie and F. S.L. Brinkman Identifying potential drug repurposing opportunities: The estrogen receptor modulator Raloxifene attenuates *Pseudomonas aeruginosa* pyocyanin production and virulence. Submitted.

[10] L. Xie, T. Evangelidis, L. Xie and P.E. Bourne 2011 Drug Discovery Using Chemical Systems Biology: Weak inhibition of multiple kinases may contribute to the anti-cancer effect of Nelfinavir *PLoS Comp. Biol.* 7(4) e1002037. [\[PDF\]](#)

Examples of press generated by the above papers can be found at:

- Science Now <http://news.sciencemag.org/sciencenow/2011/04/computer-algorithm-may-speed-dru.html?ref=hp>
- Science Daily (<http://www.sciencedaily.com/releases/2010/11/101108151344.htm>)
- Reuters
(<http://www.reuters.com/article/healthNews/idUSTRE56202020090703?feedType=nl&feedName=ushealth1100>)
- MIT Technology Review (<http://www.technologyreview.com/Biotech/19911/>)
- Science Daily (<http://www.sciencedaily.com/releases/2007/11/071128092115.htm>)