An Investigation of Allostery in Epidermal Growth Factor Receptor Using Sextant with Dynamics Simulations to Expand an Apo Site

PolarisQB

Introduction

Computational drug design typically requires a well-defined protein-ligand complex. Frequently, only *apo* structures, which do not have bound ligands, are available. This limits exploration of druggable targets to sites that are open and relatively rigid in their *apo* states.
Here we explore a scenario where sequence-activity information has identified an allosteric site in the hinge region of EGFR (Fig. A). We use molecular dynamics to expand a pocket to grow small molecule binders in the *apo* site.

Method

- Interacting side chains are trimmed (key interactions with Lys52, Met73, Thr97, Phe163, Leu169)
- Sextant generates a small molecular probe in the site (Fig. B)
- Side chains returned, followed by 6 ns of dynamics simulation
- Process is repeated with larger molecular probe (Fig. B)
- QuADD generates candidates using final molecular probe as template

Conclusions

- 15 of 346 ***QuADD***-generated structures exactly reproduced the protein-ligand interactions (PLIFs) observed in the allosteric inhibitor and each exhibited greater ligand efficiencies (Figs. C & F)
- The ***QuADD*** molecules have low structural similarity to the allosteric inhibitor (*m.w.* 544, Fig. E)
- Using ***Sextant*** and ***QuADD*** in combination with dynamics simulations can enlarge an *apo* binding site so that lead-like candidates can be generated in the site