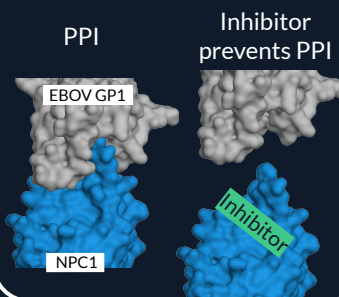


Sextant: A new tool for designing custom molecular templates for Protein-Protein Interaction Inhibitor Drug Design



A Objective: PPI Inhibition



Introduction

Inhibiting Protein-Protein Interactions (PPIs) with small molecules is considered by many to be the most difficult area of drug discovery. Here we developed a method for designing custom templates into empty binding pockets and designed a library of small molecules to inhibit interaction human NPC1 and Zaire Ebolavirus (EBOV) GP1 protein (Panel A).

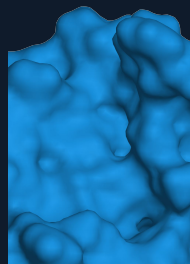
Method

- The NPC1 pocket of interest (without template molecule B) is the input for the Sextant process for building small molecule templates (C).
- QuADD returned a library of candidates, including 470 with dGs more favorable than the Sextant template (D, examples).

Conclusions

- The Sextant method designs templates into binding pockets.
- QuADD returns a strong candidate library
- This method can be applied to other protein pockets.
- This work is a part of a [DARPA IMPAQI contract](#). [More details here](#),
- To learn about our PPI wet lab results, [contact us](#).

B Input: NPC1 pocket of interest



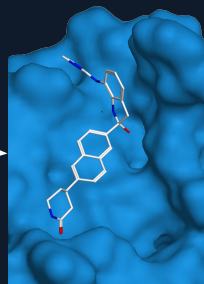
C Sextant method

Dock fragments of small molecules into pocket

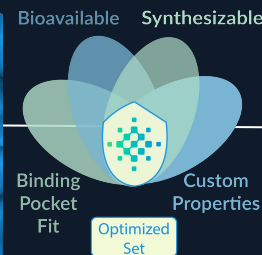
Create diverse small molecules from combinations of top-scoring fragments

Redock to identify top small molecules templates

Custom template



D



Output: QuADD candidates

