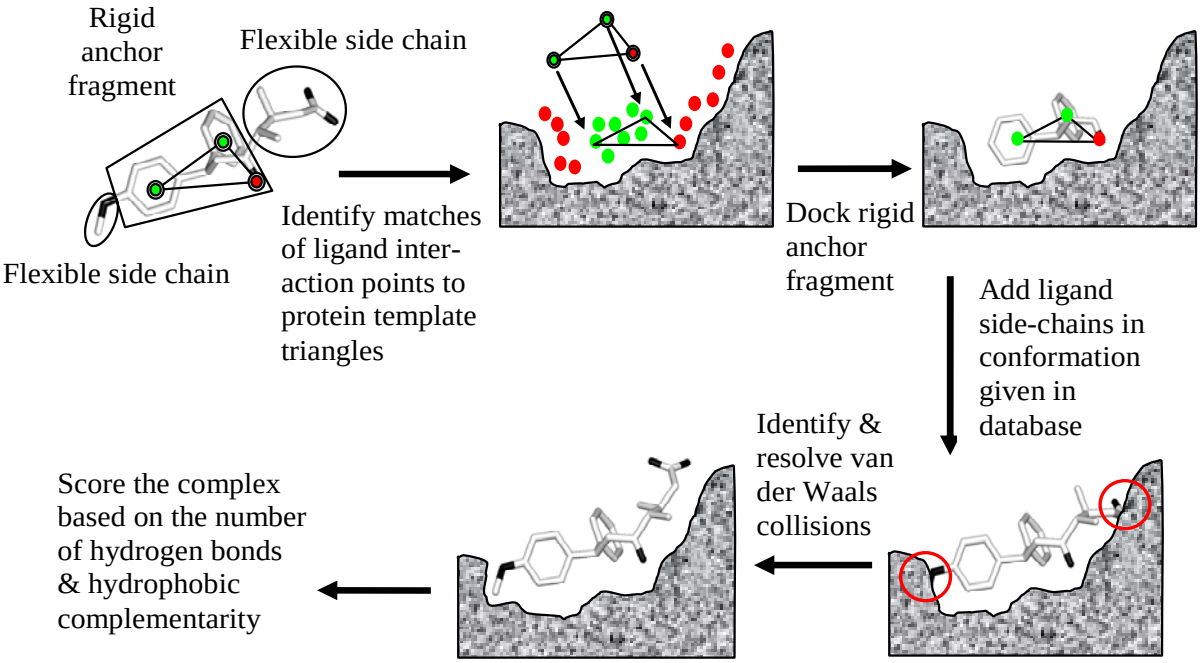
Structure-based computational screening with SLIDE

Increase in efficiency and reliability of computational tools has enabled VS to become a valuable method in drug discovery, complementing experimental high-throughput screening (HTS).

SLIDE (Screening for Ligands by Induced-fit Docking, Efficiently) is a computational screening tool developed by the Kuhn group [1-3]. The work-flow of SLIDE is illustrated below:



The protein binding site is initially represented by a template consisting of points identified as the most favorable positions for ligand atoms to form hydrogen bonds or make hydrophobic interactions with the neighboring protein atoms. An exhaustive search is performed comparing triplets of template points to every combination of three interaction points in the ligand in a search for complementary shape and chemistry. Upon finding good matches, a full atom representation is used to model induced complementarity by making adjustments in the protein side chains and ligand to ensure steric fit. This approach has been shown to successfully model the majority of protein side-chain motions upon ligand binding[3]. Each collision-free ligand orientation is scored based on the number of hydrogen bonds and the hydrophobic complementarity with the protein.

Using the apo structures of the enzymes is important because it presents a conformation that is not biased toward binding known inhibitors. This is especially crucial when the goal is discovering new classes of inhibitors. SLIDE's ability to model side-chain flexibility when docking ligands, starting from the apo conformation of the protein, coupled with its high screening speed and docking and scoring accuracy, are strong advantages of this virtual screening approach. SLIDE also explicitly predicts the structural complex between the protein and ligand, which allows further optimization of the new ligands for higher affinity and protein

selectivity (e.g., binding to thrombin over other coagulation and digestive serine proteases). SLIDE has been successfully used to identify low to mid-micromolar inhibitors for asparaginyl tRNA synthetase from the human parasite *Brugia malayi* [4,5].

In collaboration with several experimental groups, computational screening is performed in the Zavodszky lab to identify compounds that inhibit various target enzymes followed by biochemical, biological, structural characterizations for hit validation and optimization.

Targets of interest:

1. ***Mycobacterium tuberculosis*** **shikimate kinase** (SK) is an enzyme in the shikimate pathway, essential for bacterial survival and with no human homolog – an excellent target for antimicrobial drug development. This is a collaboration with Honggao Yan, Department of Biochemistry and Molecular Biology at MSU (http://www.bch.msu.edu/faculty/yan.htm).
2. **Urokinase-type plasminogen activator** (uPA) plays a key role in tumor invasion and metastasis. High levels of uPA in primary tumor tissues are associated with unfavorable prognosis with high risk of disease recurrence.
3. **Arachidonic acid metabolizing lipoxygenase** (P-12-LOX) is involved in prostate cancer progression: the level of P-12-LOX expression increases at advanced stages of the disease; overexpression of P-12-LOX in human prostate cancer cells stimulates angiogenesis and tumor growth; an inhibitor of P-12-LOX was found to slow down metastasis. In collaboration with Jerzy Jankun (http://golemxiv.dh.meduohio.edu/~jerzy/) and Ewa Skrzypczak-Jankun (http://golemxiv.dh.meduohio.edu/~ewa/) from the Medical University of Ohio, we are searching for nutraceuticals (compounds found in food) to inhibit uPA and P-12-LOX in an attempt to slow down cancer progression.
4. **RbgA** is an essential GTPase in the assembly of ribosomal subunit 50S in the bacterium Bacillus subtilis. Small molecules or peptides that bind to this protein can disrupt ribosome biogenesis. This is a project in collaboration with Rob Britton from the Department of Microbiology at MSU (http://www.msu.edu/~rbritton/).

References

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