

AGEP-T Project Descriptions

Project Title: In Situ combinatorial crystallography at NSLS II

Where: Brookhaven National Laboratory

Department: Photon Science

Main facility: NSLS-II Crystallography beamlines AMX/FMX

Auxiliary facility: BNL / LSBR Acoustic Laboratory

- NSLS-II at Brookhaven National Laboratory is a state-of-the-art facility for delivering x-ray beams with world-leading brightness.
- The Acoustic Laboratory is a unique facility for assembling biological experiments using sound pulses

Project Overview:

This project will center on developing novel methods for drug discovery that combine computational chemistry, organic synthesis, crystallography, and drug discovery. All stages of the drug discovery pipeline will be automated using in situ addition of each successive experimental building block onto the crystallography "mesh" where the data collection will ultimately occur. We will use AutoDock VINA for simulation, acoustic droplet ejection (ADE) for experimental assembly, and x-ray crystallography for visualizing the result. Roughly speaking, we are attempting to combine reliable click-chemistry with a diffraction-based bio-assay.

Project Description:

We are calling the technology in situ combinatorial crystallography, and we are calling our combinatorial libraries SPOT libraries (sample preparation on target). We will generate a library of fragments as part of a completely integrated drug discovery pipeline that has no human involvement at any stage between target selection and hit identification. The project has many features similar to click chemistry, but not all. Click chemistry is closely tied to a deliverable concept that we will not need to consider. By tying organic synthesis to specimen to a bio-assay, we can greatly streamline the process, including all considerations related to synthesis deliverables. Consequently, some of the click chemistry requirements as described by Scripps would be relaxed or not relevant (for example, purification, stereo specificity, toxicity, and all environmental concerns).

The successful postdoctoral candidate will handle all the specimen preparation, assay, and drug discovery aspects. Our principle objective is proof of concept for a novel technology for drug discovery at throughput that is several orders of magnitude faster than any existing technology. Initially, will attempt to find therapeutic compounds for commercially available test proteins (for example SOD, with possible significance to ALS). When proof of concept is established, we will seek expressed protein targets.

Regarding computation, I have sufficient computation skills for proof of principle. I hope to generate chemical libraries with a very high diversity; too high even for fourth generation synchrotrons such as NSLS II. This means that some computer simulation will be needed for a pre-screen step in drug discovery. Since we will focus principally on allosteric (eg ALS) and/or large protein classes with high similarity in the active site (eg asthma), it will be possible to tightly target the simulation step so that it is computationally efficient (in one case we will pre-screen for binding, in the other case for NON binding). The SPOT library consisting of "likely" compounds (10,000 or

so) will be automatically fed to the synthesis instrumentation for generating the fragment library directly at the point of use. The remaining components of the assay (including protein) will be added once the chemical synthesis is complete. Each assay will contain a cocktail of chemicals that result from 2 or 3 building blocks plus catalyst. We hope that, on average, the most common product will be present at no more than 1000 times the concentration of the least common product (we are looking for micro-molar binding, so a very small amount of the desired chemical is OK). Dynamic character is OK, but not a plus; I hope to avoid it by neutralizing the catalyst or by driving the reaction to completion (for example removing a gaseous by-product).

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