Structure-guided Drug Discovery for Protein Kinases Using Fragment-based Lead Identification/Lead Optimization

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Structural GenomiX, Inc. (SGX) has developed an integrated target-to-lead platform that combines high-throughput X-ray crystallography with a fragment-based approach to lead identification/optimization. The proprietary *FAST*™ (Fragments of Active Structures) process exploits crystallographic screening to detect, visualize, and identify small ligands (MW 150-200) that are bound to the target protein. Each member of the *FAST*™ fragment/scaffold library was designed to be amenable to rapid chemical elaboration at two or three points of chemical diversity using high-throughput organic synthesis. Initial lead optimization involves using our knowledge of the co-crystal structure of the target-fragment complex and advanced computational chemistry tools to guide synthesis of small focused linear (one-dimensional) libraries. These linearly elaborated fragments/scaffolds are then evaluated with *in vitro* biochemical and cellular assays and co-crystallography. Thereafter, optimal variations at each point of chemical diversity are combined to synthesize focused combinatorial (two- or three-dimensional) libraries that are again examined with assays and co-crystallography. (The potential chemical diversity of the fully elaborated *FAST*™ fragment/scaffold library far exceeds 160 million compounds.) These focused combinatorial libraries typically contain multiple novel compounds of low molecular weight (<350) that bind the target protein at low nM IC_{50} and already display considerable selectivity. Thereafter, compound series are prioritized for further medicinal chemistry and compound development efforts using the results of *in vitro* and *in vivo* ADME and *in vitro* toxicology studies in concert with structural information. Successful applications of the *FAST*™ fragment-based lead discovery/optimization process will be presented for both protein kinases (Syk and Gleevec-resistant BCR-ABL) and proteases (Factor VIIa).

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