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Fragment Based Drug Discovery for Oncology Targets. Stephen K. Burley, Chief Scientific Officer and Senior Vice-President Research, SGX Pharmaceuticals, Inc., San Diego, CA.

SGX Pharmaceuticals, Inc. (SGX) has developed a fragment based drug discovery platform that utilizes high-throughput X-ray crystallography for lead identification/optimization. The proprietary *FAST*TM (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*TM fragment/scaffold library was selected to be amenable to rapid chemical elaboration at two or three points of chemical diversity using parallel 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-crystal structure determinations. 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 crystallography. (The potential chemical diversity of the fully elaborated *FAST*TM fragment/scaffold library far exceeds 160 million compounds.) Active 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. Successful applications of the *FAST*TM fragment-based lead discovery/optimization process will be presented for a portfolio of well validated oncology targets, including wild-type and Gleevec-resistant BCR-ABL.