The Discovery of Potent Novel Compounds using a Fragment Based Structural Approach Coupled with Automated High Throughput Chemistry.

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Abstract 2(several pages for the abstracts brochure of the meeting):

High throughput screening (HTS) has serious limitations in the generation of good quality novel chemical matter for drug discovery programmes. As an alternative to HTS, Sareum uses a powerful set of technologies which allow the discovery of novel chemical matter against any structurally tractable protein target followed by the rapid optimisation of multiple chemotypes to provide several high quality chemical series for lead optimisation. This process provides a rapid method for generating novel intellectual property with a long patent life against both new and well-established pharmaceutical targets.

The first part of the Sareum process involves the use of high throughput protein expression and crystallographic methods to establish structural methods amenable to robust ligand-protein x-ray structure determination. These methods include both multi-construct 96-well insect cell and bacterial expression followed by multi-column protein purification and subsequent extensive crystallographic screening to identify appropriate protein crystal forms. In parallel to the generation of a robust structural method Sareum scientists also develop an assay method suitable for identifying template or fragment-like compounds. Extensive computational selection is used to select a compound screening set of 1000-2000 structurally diverse template molecules. These molecules are soluble, lead-like molecules with a mean molecular weight of 280 Da, which fall at the high end of fragment-like compound and low end of HTS compound space (Figure 1).

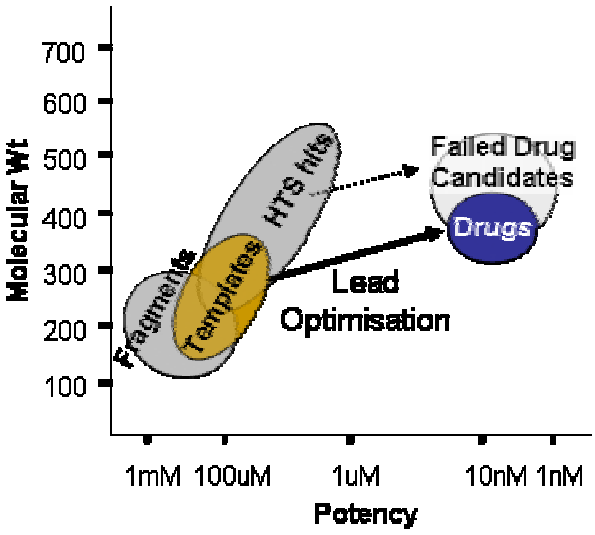

Figure 1. Graph showing the mean molecular weight and potency of Template compounds used in Sareum's screening process compared to smaller Fragments and larger HTS compounds. The low Mw and lead-like properties of Sareum's Templates allows successful rapid lead optimisation.

At Sareum, this approach has led to a successful screening hit rate of between 5 and 10% across different enzyme protein families with a large number of novel templates identified. Different modes of Template binding have been successfully identified by this process including both enzyme active site and allosteric inhibitors. The generation of structural data is then an essential part of the template optimisation process which allows both Template verification and the initiation of the medicinal chemistry process. The protein-ligand structures are used in the design of virtual Template libraries, which after several rounds of *in silico* docking are used to design focused libraries of up to 96 members for synthesis. To accelerate this part of the process, Sareum has developed a powerful automated solution phase medicinal chemistry platform, which allows full exploitation of this structure-based rational/library-based approach. This platform uses robust robotic methods to replicate many conventional *by-hand* medicinal chemistry methods on a high-throughput platform. Initial lead-like compounds are produced after a single round of chemistry optimisation (Figure 2) and further rounds of chemistry with extensive structural support allow focused lead optimisation to produce quality candidate molecules free of any intellectual property issues.

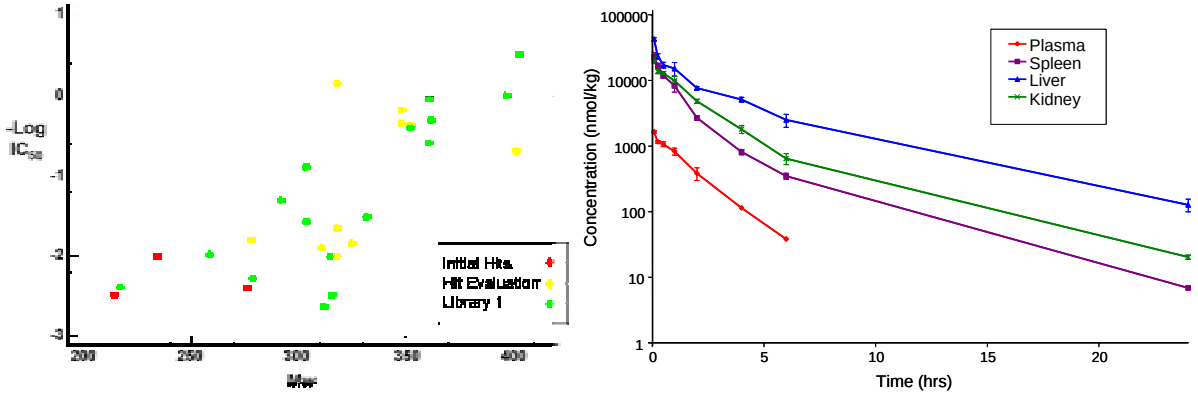

Figure 2. A; Plot showing how initial Sareum Template hits are expanded and improved in just one phase of Template library generation. B; Template compound pharmacokinetic qualities in mouse after just one round of library expansion (initial 5mg/ml dose of compound iv).

Overall, the structure-based drug discovery methods used at Sareum allow the discovery and rapid exploitation of novel chemical matter against any structurally tractable target, including those targets traditionally seen as difficult drug targets in the Pharmaceutical industry.