chemistry is executed to improve the druglike properties of the evolving lead series, including selectivity, cell permeability, cellular activity, and liver microsome and hepatocyte clearance. Again, the time required to complete this stage of the process is a function of the particular target.

End game

The final stages of any drug discovery process are focused on identifying one or more compounds suitable for development candidate nomination, thereby committing significant resources to preparation of an investigational new drug (IND) application. At SGX, there is no "bright line" between SAR optimization and development candidate seeking. Structure-guided optimization of lead series continues with added feedback from the results of in vivo intravenous and oral pharmacokinetic studies in both mouse and rat, demonstrations of in vivo efficacy using various mouse xenograft tumor models, and preliminary fourteen-day toxicology studies in rat. The duration of the end game, simply put, is as long as it takes to achieve the desired balance among in vitro cellular potency, selectivity, oral bioavailability, half-life, in vivo efficacy, and absorption/distribution/metabolism/excretion (ADME)/safety properties [cytochrome P450 inhibition and induction, receptor inhibition profile, genotoxicity, and human ether-à-go-go related gene (hERG) channel binding].

Postscript

In closing this section, it is remarkable that the SGX fragment-based structure-guided drug process is entirely pragmatic in terms of when and where fragment information is exploited. Insights from cocrystal structures of fragments bound to the target of interest (and for some protein kinases, critical off targets) influence not only fragment elaboration but also lead series SAR optimization. Cocrystal structures coming from the initial x-ray screen of our core fragment library and fragments from other sources provide valuable information regarding possible interactions between small-molecule ligands and many of the functional groups comprising the enzyme active or allosteric site. In some cases, fragment hits that were not subject to elaboration later serve as the inspiration for choice of R groups during fragment/lead optimization. We have also developed proprietary computational chemistry software to overlay and merge experimentally identified fragments to create entirely new fragments (also commonly referred to as scaffolds) using a tool designated SMERGE (Scaffold MErging via Recursive Graph Exploration). The products of SMERGE have provided new starting points for structure-guided optimization that build rapidly on a wealth of information regarding the SAR implications of adding a particular R group to a particular site of a previously elaborated scaffold. For certain lead series, such merged fragments have helped us overcome unattractive druglike properties or navigate intellectual property constraints.

Lessons from FAST

Key experiences coming from application of the SGX fragment-based structure-guided drug discovery process to twenty-four protein targets, twenty of which are protein kinases, are presented below. Three "lessons" central to fragment-based approaches are reviewed, including (1) the importance of fragment library design, (2) the selectivity of fragment hits identified in x-ray screens of protein kinases, and (3) that the optimization potential of a fragment hit is not correlated with initial binding affinity.

Lesson 1: Fragment library design

Figure 3.4 illustrates three histograms that compare various properties of the SGX core fragment library and the hits obtained from twenty-four targets drawn from four protein families. It is remarkable that the properties of the fragment hits closely mirror those of the entire fragment library. This finding reflects the target agnostic nature of the composition of our core fragment library. We consciously sought to create a fragment screening library with maximum potential for chemical diversity that was not biased toward any one particular target class. As we continue to add fragments to our screening library, we will seek to further increase the potential for chemical diversity with ongoing attention to tractability in terms of synthetic elaboration.

Lesson 2: Fragment selectivity revealed by x-ray screens of protein kinases

Figure 3.5 summarizes our x-ray screening experience across twenty protein kinase targets. When we embarked on this odyssey, we naively assumed that fragment hits would be intrinsically nonselective and that selectivity would come only during the course of elaboration of such hits. Our experience with the protein kinases argues otherwise. Nearly 75% of the fragment hits detected by x-ray screening of protein kinases bound to only one of the twenty targets. Under the conditions of this very stringent screening process, we appear to be identifying "privileged" ligands (or scaffolds). This unanticipated benefit of our strong reliance on x-ray screening may well explain our success in elaborating fragment hits under structural guidance to produce highly selective kinase inhibitors. During the iterative design/chemical elaboration/biochemical assay/cocrystal structure determination process of optimizing attractive fragment hits, we strive to preserve the original anchoring interactions between the growing fragment and its target. With timely access to structural information we can monitor the impact of synthetic changes to the growing fragment to ensure that we do so. In rare cases (~5%), we have detected alterations in the mode of fragment binding, some of which have been exploited as opportunities with which to pursue alternative SAR regimes.