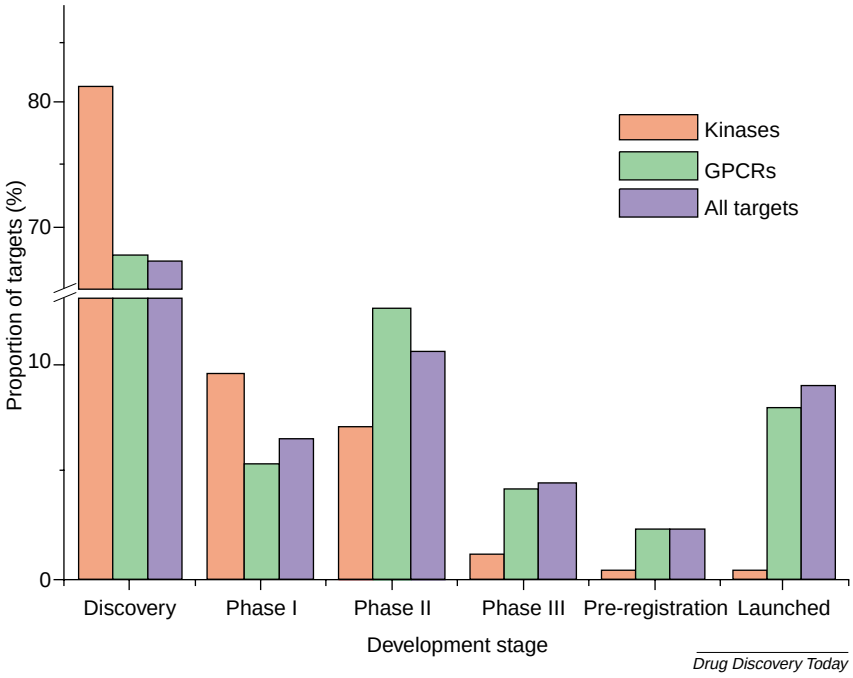

Figure 1. The proportion of drugs in various stages of development [4].

The size of the protein kinase family also presents challenges in terms of selectivity and functional redundancy. The neat clusters of subfamilies that are seen when comparing sequences of kinase catalytic domains are poorly correlated with the selectivity observed for inhibitors. This forces one to assay compounds widely or to make careful structure-assisted analyses of the amino acids that form the binding sites. True selectivity can be a most elusive goal, further compounded when inhibition of a subset of kinases is necessary to achieve the desired response. Indeed the 'selective' inhibitor Gleevec is likely to achieve its efficacy in part from its activity against several kinases. Selectivity hurdles could of course be even higher when one considers the use of kinases inhibitors to treat chronic diseases.

As the industry continues to identify protein kinase inhibitors and turn these into drugs, the answers to these questions and concerns will become clearer, but for now much consideration is needed as to whether protein kinases represent an under-exploited family of drug targets or whether the few drugs we are beginning to see are the result of a disproportionate effort by the pharmaceutical industry that will need to be maintained to gain further successes.

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De novo chemical ligand design ▼

Chemical genomics is an emerging field that embraces target-specific chemical ligands and the genomic study of biological systems [1]. It is especially advantageous in a situation where a traditional genetic approach is inapplicable. In addition to its ability to provide a better understanding of the function of a protein, chemical genomics can also significantly improve therapeutic developmental strategies. Because its power relies mainly on the availability of a specific ligand(s) that binds to the protein of interest, many diverse approaches have been developed for the discovery of small molecule ligands, such as screening of natural products, development of combinatorial chemical libraries and *de novo* ligand design (Fig. 1).

The first computational ligand design methods were developed about two decades ago. Since then, tremendous improvements have been made as a result of the increase in computational power, the availability of high-resolution protein structures, the development of combinatorial chemistry and the advent of the genome era [2]. Zanders *et al.* recently provided an overview of the *de novo* approach in designing target-specific probes for chemical genomics [3]. There are two general areas for *de novo* ligand design: a structure-based approach when the three-dimensional structure of the target protein is known;

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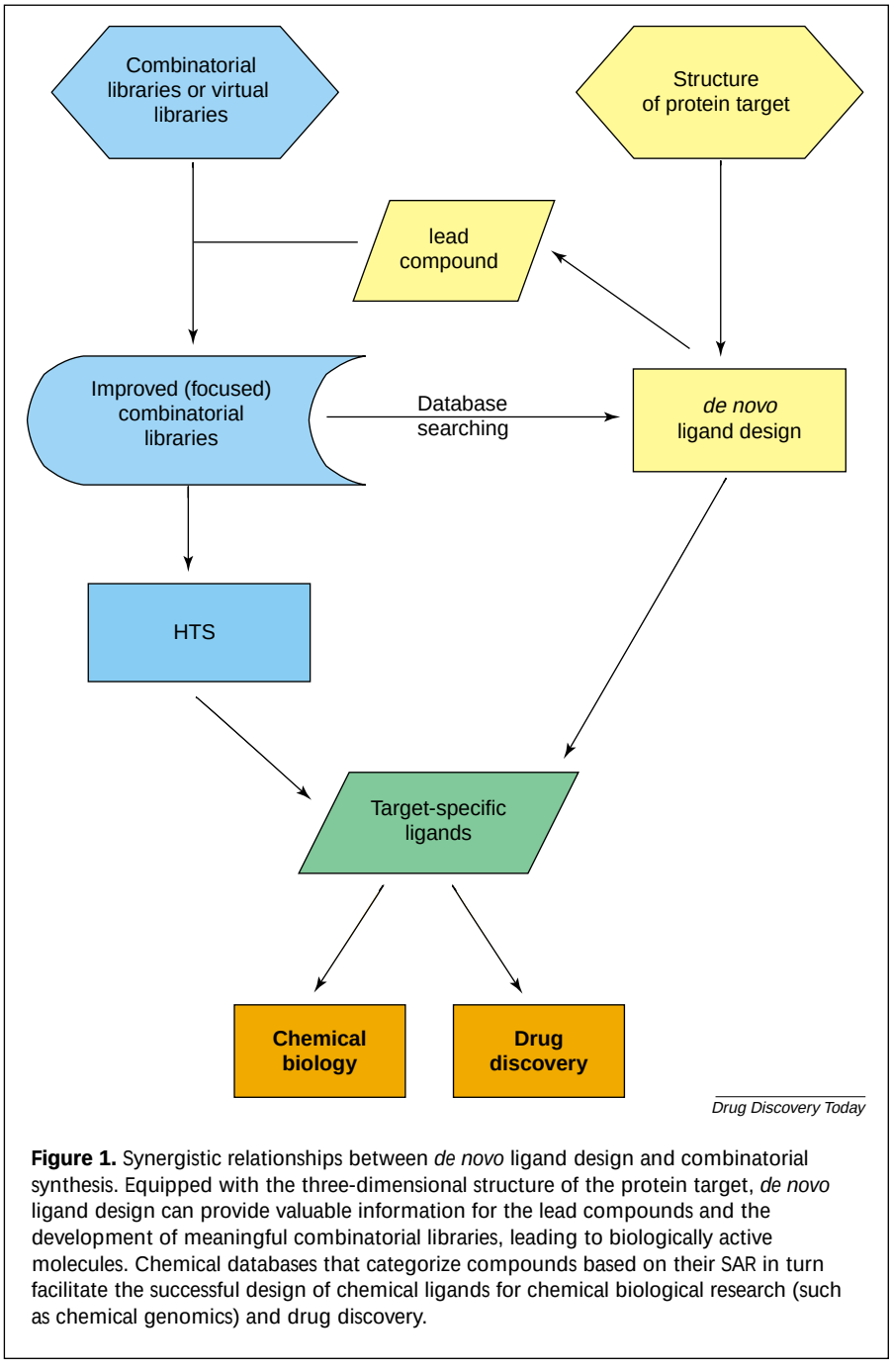

Figure 1. Synergistic relationships between *de novo* ligand design and combinatorial synthesis. Equipped with the three-dimensional structure of the protein target, *de novo* ligand design can provide valuable information for the lead compounds and the development of meaningful combinatorial libraries, leading to biologically active molecules. Chemical databases that categorize compounds based on their SAR in turn facilitate the successful design of chemical ligands for chemical biological research (such as chemical genomics) and drug discovery.

and a ligand-based approach when the structure of the target protein is not known, but several compounds or natural ligands for the protein are available. Zanders *et al.* described the general steps for generating a hydrogen-bond map (site points) for the active site of the target protein on which *de novo* ligand design would be based. A typical site can contain as many as 30 site points. The goal is to choose a subset of site points for ligand design that provides the most specific interaction between the ligand and the protein. In the ligand-based approach, compounds known to bind to the target protein are superimposed and used to generate the 'virtual' site points of the target site of the protein. Novel ligands are designed in a similar way to the structure-based approach.

In addition to the aforementioned approach, there are also other popular and practical methods for *de novo* ligand design. Two well-known methods are GRID [4] and multiple copy simultaneous search (MCSS) [5]. Both algorithms use energetics approach to determine the most favorable binding position for a specific fragment or functional group in the target site. In addition, algorithms such as HOOK and computational combinatorial ligand design (CCLD) have been developed to combine these approaches with database searching and virtual chemical library construction (for a review see [2]). Together with functional studies of the target protein, these approaches can lead to a better understanding of the structure–function relationship of the protein and lead compounds for combinatorial chemical libraries synthesis [6,7].

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