have a good impact on drug discovery as would the direct accumulation of knowledge coming out of proteomics initiatives.

What do you think have been the major advance in proteomics in the past six months?
Well I think the emergence of protein microarrays as a tool to scan the proteome is a big advance There are now effective surfaces to bind proteins and effective means to detect signals resulting from probes binding to specific protein targets. This is an area I think will undergo exponential growth in the next couple of years and could well reach the point where it could become, for protein analysis, the equivalent of the DNA microarray for genomic analysis.

What would you like to have achieved by the end of your career at HUPO?
I would like to ensure that HUPO has a broad membership base, that it has already developed its own scientific, education and training agenda, and that there are some funds in the HUPO account to enable it to sustain itself.

What would you like to have achieved by the end of your career?
I would like to think I have succeeded in what I originally set out to do, which was to be a cancer physician on the one hand, and a cancer investigator on the other. If I were able to impact in any way on an aspect of cancer medicine, be it earlier diagnosis or better therapy, I would be elated.

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The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*, e-mail: Rebecca.Lawrence@elsevier.com

Protein kinase drugs – optimism doesn't wait on facts ▼

Current reviews of research directed towards protein kinases present an optimistic view of the field. In a recent issue of *Drug Discovery Today* [1], Scapin discusses how structure-based drug design has been applied to great effect against several protein kinases. Other encouragement is drawn from the approval of Gleevec™ (Novartis; http://www.novartis.com) for the treatment of chronic myeloid leukemia [2] and the potential to assay lead compounds for selectivity against an ever-growing panel of protein kinases [3].

Although it would be churlish to detract from some great achievements in this field, one cannot escape the observation that drugs targeting protein kinases are still rare, as seen in Figure 1. This leads one to question whether the current optimism is well founded, given that protein kinase programs account for approximately a fifth of the current research programs in many large pharmaceutical companies [3,4] and that protein kinases comprise the largest gene family coded for by the human genome that has proven tractable to inhibition by small-molecule therapeutics.

One could argue that the industry has only recently begun to focus on protein kinases as drug targets; indeed Figure 1 shows that the vast majority of kinase drugs are still in the discovery research phase. However, the targets of most launched drugs have been identified following functional assays. This traditional approach revealed few protein kinases; the Rho-dependent protein kinase ROCK, one possible target of the drug fasudil (used to treat cerebral vasospasm) is a rare example of this. Perhaps the timelines of such assays are poorly suited to identifying compounds operating in the signal transduction cascade, where longer term gene expression effects are the endpoint. One could also reason that these processes might be less relevant to the diseases that the pharmaceutical industry is focused on.

The vast majority of kinase inhibitors target, at least in part, the ATP binding site, which has been proven to bind a wide selection of chemical types [5]. There is no evidence to suggest that these compounds have physicochemical properties that are at odds with those required by orally bioavailable drugs [6]. It is also hard to imagine that the necessary chemical tools, fundamentally adenosine mimics, have only recently been a focus of synthetic chemists. Inhibition of protein kinases by ATP competitive compounds is, however, made more difficult by the high cellular level of ATP, a problem that is circumvented by compounds that prevent activation of the kinases, rather than competing with endogenous cofactor [7].

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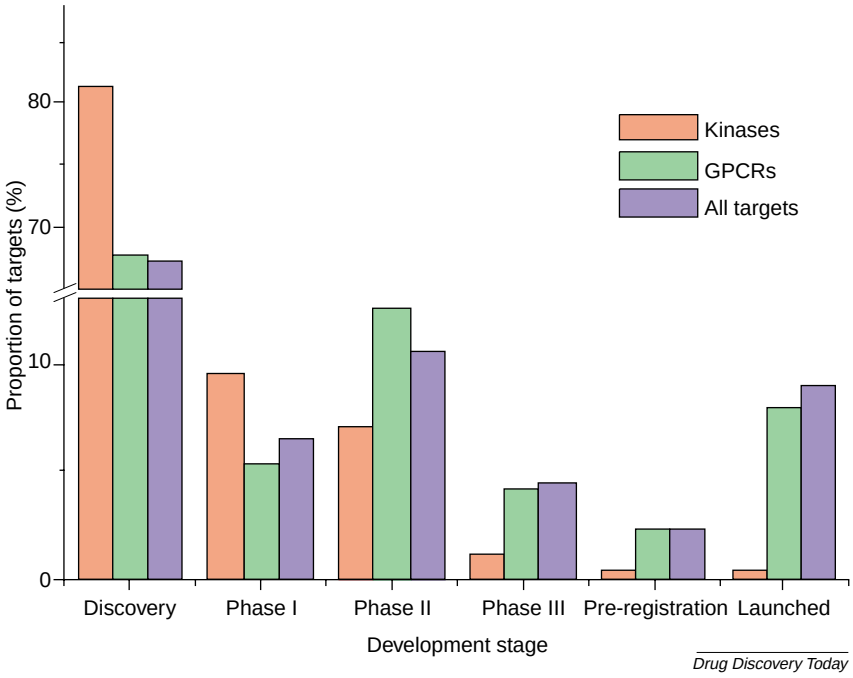

Figure 1. The proportion of drugs in various stages of development [4].

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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