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Drug discoverers – you need us! – Reply ▲

Initial letter: Federsel, H-J. (2001) *Drug Discov. Today* 6, 397–398

Response from Nicholas Meanwell

In contemporary drug discovery campaigns, multi-disciplinary teams routinely focus attention on simultaneously optimizing several parameters associated with lead molecules including biological activity, physical properties, toxicological potential, metabolic stability and a broader range of pharmacokinetic attributes. The anticipation is that, by selecting compounds that meet stringent criteria, the overall objective of enhancing candidate success (measured by entering crucial proof-of-principle efficacy studies in Phase II human trials) will more probably be achieved. However, often of lesser concern during the discovery phase, but ultimately of paramount importance to the overall success of a drug candidate, is the facility with which significant quantities of bulk drug substance can be produced.

With all of the major pharmaceutical houses focussed on delivering new chemical entities in a predictable fashion against timelines that seem to be perpetually shrinking, the expedient production of significant quantities of drug candidates in a practical fashion while adhering to regulatory and safety guidelines represents a significant challenge. Against this backdrop, the appeal by Hans-Jürgen Federsel, in a recent letter to the *Discussion Forum*, that process R&D should be fully participating partners in the later stages of drug candidate identification seems to be not only reasonable but necessary and essential to orchestrate a seamless and flawless transition. Indeed, successful anticipation and implementation provides obvious benefit when timelines for first-in-man studies that were once considered ambitious objectives, but which are now routine expectations, are achieved.

The strategic model described by Federsel has merit, either as practiced by AstraZeneca or in a form modified to more effectively complement individual organizational structures and business cultures. The system relies on maintaining an awareness of developments early in the drug discovery process, largely through communication between chemists who together constitute a broader community of practice, with subsequent and timely practical involvement as the project enters the final phases of candidate identification. Such an interface offers the potential for mutual benefit with discovery chemists developing a heightened awareness for, and a deeper appreciation of, the issues associated with the large-scale production of compounds while providing process R&D scientists with the opportunity to observe the decisions required to successfully identify a drug candidate. An optimal arrangement, practiced where feasible at Bristol-Myers Squibb (BMS), has process R&D and drug discovery chemists working in close geographical proximity and collaborating to solve synthetic problems in a fashion that produces advances ultimately synergistic in nature.

The key issue implicit in Federsel's discussion is the need to educate those immediately outside of the process R&D environment about the challenges faced in producing bulk drug substance. To some extent, process R&D chemists could be falling victim to their own past successes where elegant and practical synthetic approaches to targets that presented a significant degree of difficulty have been developed. Two compounds that come to mind as specific examples from BMS' process R&D group are the thromboxane-receptor antagonist Ifetroban®[1–3] and the dual metalloprotease inhibitor Vanlev®[4], striking accomplishments that heighten expectations.

However, several factors are emerging that have the potential to contribute to enhancements of the discovery chemistry–process R&D interface. The effect of increased productivity realized over recent years as drug discovery has evolved into a more industrialized process has afforded a larger number of discovery scientists the opportunity to participate in project teams assembled to usher candidates through the early stages of the development process. These teams are providing important forums for discovery chemists to glean unique insights into a broader range of process R&D issues, an awareness that has the potential to influence their strategic thinking as they devise synthetic approaches to drug candidates. As perhaps an ultimate extrapolation, discovery chemists at BMS have accompanied candidate compounds into early development, being seconded for several months as part of an exercise designed to be mutually educational and beneficial. Second, with additional preliminary *in vivo* toxicology studies planned before candidate nomination, demands for substantial quantities of drug substance at earlier stages of the discovery continuum are increasing. This provides drug discovery chemists with the

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challenge of developing synthetic routes of perhaps greater practicality than has been typical in the past.

As a medicinal chemist, I have had several opportunities to observe first-hand the benefits of an early and close collaboration between discovery and process chemists and I fully concur with Federsel's point of view. However, I believe that the message needs to be communicated more effectively to those outside of the community of organic chemists to cultivate a more sympathetic audience, a task of far greater difficulty.

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Too many targets, not enough target validation – Reply ▲

Initial letter: Szymkowski, D.E. (2001) *Drug Discov. Today* 6, 398–399

Response from Leodevico L. Ilag

In a recent letter, David E. Szymkowski rightfully argued for the dire need to link the causal role of a gene or gene product to a particular disease or functional context. It is essential to directly identify the function of each protein because proteins often represent the functional representative of a gene and over 90% of the targets for marketed drugs are proteins and not the DNA or RNA[1]. Furthermore, it is becoming clear that proteins can perform multiple functions depending on the cellular location of the protein, cell type where the protein is expressed, multimeric state of the protein, and substrate bound to the protein[2]. Moreover, human genes are composed of multiple protein domains providing additional functional versatility compared with the worm and fly[3].

Inactivating protein function

Since the protein is the more appropriate target for a drug, it is imperative that the methods that directly inactivate protein function are used. Szymkowski provided a table listing several approaches (i.e. knockout/transgenic mice and antisense oligonucleotides/ribozymes) that act at the DNA or RNA levels and not directly at the protein level. Although inactivation strategies based on these nucleotide-based knockout or knockdown strategies are popular, interpretation of the results from these methods are complicated by genetic compensation and polar mutation effects. Since the expression of several gene products or proteins that can be translated from the disrupted DNA or RNA is affected, it will be difficult to assign their respective function(s).

Among the other approaches listed, neutralizing antibodies and small-molecule agonists/antagonists represent methods that directly inactivate protein function. Although antibodies provide an efficient way of obtaining specific binders to proteins, the success rate of obtaining neutralizing antibodies is unsatisfactorily low[4]. However, small-molecule agonists/antagonists are available only for a few classes of molecules that are related to existing drug targets. It will be difficult to obtain small-molecule agonists/antagonists for totally novel proteins with undefined functions.

Alternative approach

An alternative approach to assess the causative role(s) of novel protein targets, not mentioned by Szymkowski, is a method called chromophore-assisted laser inactivation (CALI). CALI was developed as a method to determine the *in situ* function of proteins in cellular processes[5]. CALI converts a non-function-blocking antibody into a blocking reagent with a high probability.

To perform CALI, a ligand (e.g. antibody) is labeled with the dye malachite green (MG) and binds to the protein of interest, and the complex irradiated with 620 nm laser light[5,6]. At this wavelength, cellular components are not damaged, but the light is absorbed by the dye, which in turn generates hydroxyl radicals that selectively inactivate the protein bound by the MG-labeled ligand[7]. Unbound MG-labeled reagents do not cause significant damage because the effects of CALI are spatially restricted[8] to within 15 Å of the dye moiety due to the short lifetime of the hydroxyl radical[7]. Furthermore, CALI does not lead to obvious nonspecific damage to cells or tissues and CALI has been tested against a diverse array of both intracellular and extracellular proteins in primary cells, cell lines and model organisms[9]. Moreover, the high spatial and temporal resolution of the method offers several advantages over the other approaches.

Thus, CALI represents one of the tools that can provide causal relationships between correlative data and function leading to the selection of the few targets that are worthy of a full drug development effort.

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