The role of the medicinal chemist in the drug discovery process: current status and future prospects

The need for the pharmaceutical industry to produce a constant stream of new NCEs has never been more paramount but with constantly changing R&D paradigms what is the role of the modern medicinal chemist? This article argues that with more versatility and the ability to work across various scientific disciplines the medicinal chemist will become a vital and, indeed, indispensable key to the future success of the industry.

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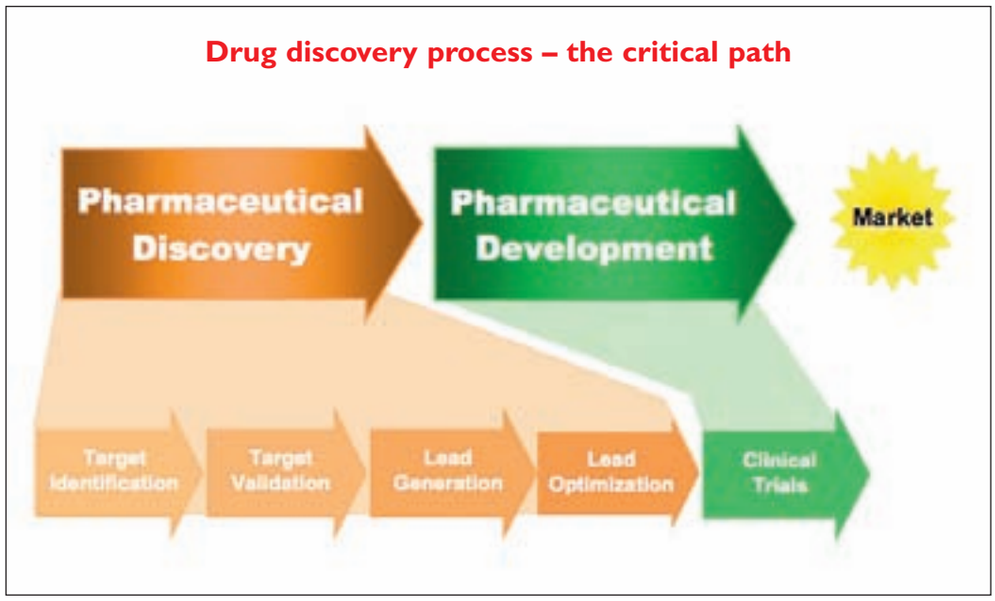
At the present time and perhaps more so than at any time in its history, the pharmaceutical industry in the US and, indeed, worldwide faces numerous major challenges that threaten its future ability to thrive. Despite the much heralded advances in currently and once fashionable areas such as 'genome derived' target identification[1] and combinatorial chemistry[2] and major investments in new technologies the industry has not been able, in general, to produce a steady supply of new NCEs (or finance clinical development of the number of compounds required to ensure continued growth and financial success) that are necessary to provide the funds to sustain overall organisational viability and research funding[3]. As a result, over the past few years major pharmaceutical companies have been consistently tinkering with their R&D paradigms in an attempt to improve their drug discovery process. Reductions of candidate attrition rate or identifying 'losers' earlier in the discovery process have been key themes[4]. What is the role of today's medicinal chemist in all this? Several excellent reviews and/or opinions have appeared in the literature on this topic[5] over the past few years. A number of these comment on older, traditional roles of chemists and will not be touched upon here.

In today's discovery environment there is no question that the medicinal chemist needs to be more versatile than ever before and be able to work across scientific boundaries. They need to be able to think innovatively and outside the box. They need to be both willing to maintain and hone their given skill set while being open to embrace new techniques and innovations. The days are long gone when a chemist can expect to start and finish a career by finely handcrafting the elaborate synthesis of multi-step targets and feel that they have done a good job by producing 10-20 compounds a year. Gone are the days of 'mindlessly' making huge libraries of compounds for High Throughput Screening (HTS) that just add numbers to a collection. Quality of compounds, whether based on novelty, physicochemical properties or purity is now of paramount importance[6]. Today's medicinal chemist is part of a team that handles essentially all the components of the drug discovery process. They need excellent communication and interpersonal skills in order to be

Figure 1



able to function effectively as a part of a multi-functional and multi-dimensional project team that consists of biologists, computational chemists, structural biologists including x-ray crystallographers, high throughput screeners, chemoinformatics scientists, information management technologists, pharmacokineticists, toxicologists, etc. In order to work effectively with scientists from these other disciplines, they need to be able to acquire at least a rudimentary knowledge of these disciplines.

At this point, having set the stage for an evaluation of current and future roles of the chemist, let us take a tour through each part of the drug discovery process in order to see where the medicinal chemist plays a significant part.

From a synoptic perspective the current paradigm can be depicted in modular form as shown in **Figure 1**.

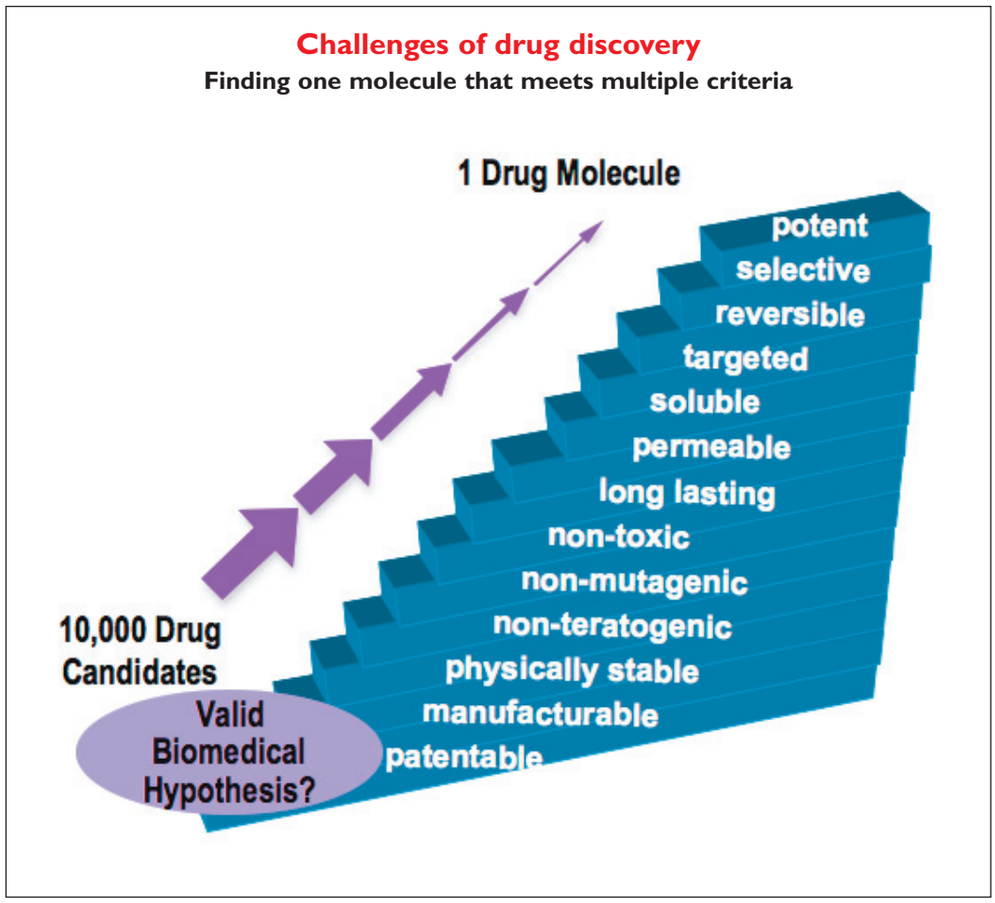
An initial part of the process involves one of the most critical components, namely target identification and validation[7]. The medicinal chemist is playing a larger role in this process of late. This is due, in part, to the current popularity of chemical genetics[8], both forward and reverse, for the identification of pharmacologically active compounds from phenotypic screens. There are numerous successful examples of this approach. The role of the chemist in this module has been to provide novel compounds as pharmacologic probes. Diversity Oriented Synthesis (DOS), as propounded by Schreiber[9], has been utilised as a tool to direct synthetic chemistry efforts towards a set of small molecules with properties unseen before. The role of the chemist in providing compounds for screening whether it be it high throughput, high content, fragment-based or phenotypic, is best covered under the Lead Identification/generation banner and has been under the spotlight over the past few years as companies have focused significant effort on improving the quality, diversity and size of their corporate screening collections. Numerous articles have been written on the ideal size and composition of a collection. Given that it has been postulated by Bohacek and colleagues[10] that more than 1,060 molecules are synthesisable and that the Beilstein database from 1779 to the present contains only ~107 molecules, it is a tremendous challenge for the chemist to decide what molecules to make. To this end, the chemist should be familiar with contemporary structure-based design techniques[11], protein structure[12], and their associated privileged structures[13]. Virtual ligand screening techniques should also come into play wherever possible[14]. Knowledge of protein structure has facilitated the construction of numerous focused libraries of compounds targeted at kinases, GPCRs and nuclear hormone receptors[15]. Aside from DOS techniques, numerous approaches have been undertaken for the construction of libraries of diverse structures. Current thinking is that libraries of smaller size (100-250 members) based on a greater selection of chemotypes are more diverse and cover greater chemical space than libraries of large number of compounds constructed around a few chemotypes[16].

Numerous innovative approaches have been

adopted by medicinal chemists for the construction of such focused or diverse collections. Of particular note has been the utilisation of multiple component coupling reactions such as the Ugi and Passerini for the rapid and efficient construction of diverse screening sets centred on pharmaceutically relevant chemotypes. These reactions are particularly useful as they have the capability of delivering compounds of diverse structure in a single reaction step. This area has been reviewed extensively[17]. The work of Hulme and co-workers on the development of a Ugi/Deprotection/Cyclisation (UDC) protocol that secured libraries of key heterocyclic pharmacophores such as dihydroquinoxazolinones, benzodiazepines, diketopiperazines is noteworthy. At Abbott, one of our approaches towards the production of novel, drug or lead-like compounds has been to incorporate latent reactivity into the inputs of Ugi-derived libraries. To this end we have used post-Ugi modification reactions such as the Heck reaction, the Huisgen triazole synthesis and the intramolecular nitrile oxide cyclisation reaction to produce novel heterocyclic scaffolds for inclusion in our corporate screening set[18]. These types of approaches highlight the considerable potential for synthetic creativity and innovation on the part of the synthetic/medicinal chemist in the early stages of the drug discovery process. In addition, it would be remiss of the author not to mention the utility of natural products as potential sources of hits/leads. Many natural product aficionados are still bemoaning the de-emphasis of this avenue of research at the expense of combinatorial chemistry a number of years ago. This situation may change with a recent renaissance of this line of investigation[19]. The chemist must also be fully cognizant with other approaches to add useful compounds to the screening set and the interplay with related drug discovery disciplines such as fragnomics, or fragment-based drug discovery[20] and concepts of both drug-like[21] and lead-like[22] structures which are critical to an understanding of what building blocks have the highest likelihood of being translated from hits to leads and subsequently, drug candidates. Chemists may well be involved in the process of synthesising libraries of compounds for corporate file enhancement that are to be used for HTS campaigns. Although many companies have contracted a substantial portion of this work out (India and China have been the beneficiaries of recent trends in how this process is managed[23]), a significant amount of work is still carried out by high throughput synthesis groups like the Glaxo SmithKline (GSK) compound factory initiative. Chemists in these groups need to be expert in automated chemistry techniques including parallel synthesis, which may be done in a variety of more or less sophisticated equipment including shaker blocks/liquid handlers, and automated platforms such as the ChemSpeed™, which has found utility in our laboratories. Much high throughput chemistry has been enabled by the use of polymer-supported reagents[24]. Ley's group at Cambridge have been major players in advancing our knowledgebase in the area; however industrial groups such as that at GSK and our own High Throughput Organic Synthesis group at Abbott have also made significant contributions in developing effective and reliable standardised reaction protocols for a plethora of synthetic transformations ranging from simple amide bond forming reactions to palladium catalysed coupling reactions to the development of robust new routes to heterocyclic rings of pharmacological relevance. Chemists also need to be able to fully utilise microwave chemistry, which has come much into vogue over the past few years. The ability of microwave chemistry to improve productivity in the pharmaceutical laboratory is now a given. In addition, the optimisation and utilisation of parallel synthesis in the microwave[25] will also provide a significant boost to the chemist's ability to deliver large numbers of compounds in a timely manner.

Once hits are identified from high throughput screening (or other sources) the chemists may become involved in Hit to Lead (H2L) studies when hits from screens are effectively triaged and closely scrutinised for ability to serve as full blown lead compounds. Several companies, including AstraZeneca, have established separate H2L groups which, having been given relevant criteria for qualifications of a lead compound by the Therapeutic Area teams, thoroughly evaluate the potential of hits from HTS to fulfill these characteristics. These processes involve the assessment of a compound's reactivity (false positive hit-target poison), patentability/freedom to operate issues around the structure and its congeners (known chemotype – numerous patents on chemotype for same or different biological targets?), biological or chemotype history (had it been optimised for another target previously internally or externally, are there possible off-target effects to be considered, was it purchased from commercial vendors), optimisability including physicochemical properties such as clogP, solubility, ligand efficiency[26], chemical tractability and initial SAR studies. This process requires a

Figure 2



significant investment in information management technology particularly if a screen identifies numerous hit series, including collection of all available data on hits and all SAR related to initial studies carried out on multiple chemical series. The goal of this process is to identify several chemical series for Lead Optimisation efforts. Current dogma suggests that working on multiple lead series can reduce risk of attrition due to off-target effects[27]. Chemists working in these areas must be able to handle and analyse significant amounts of data and enjoy the challenges of discovering robust leads for the 'more traditional' lead optimisation chemist to work on. The H2L chemist should enjoy the challenge of working on many early stage projects and assimilating at least a basic knowledge of the biology, pharmacology and medicinal chemistry of projects spanning many therapeutic areas.

The contemporary medicinal chemist should also, ideally, have a good understanding of the different formats available for HTS and the different types of assays that can be run. This can be particularly important if they are involved in a miniaturisation initiative such as the one reported at GSK where considerable effort and investment has gone into developing microflow reactor technology that provides a basis for carrying out ultra-high throughput chemical synthesis on a scale that is compatible with highly miniaturised modern screening techniques. GSK believes that the use of such systems could bring about reductions in cycle times, and reagent costs necessary to increase laboratory output to many thousand of compounds per day[28]. Other initiatives in industry and academia in the medicinal chemistry technology area include the development of Passflow reactors as promoted by Kirschning[29] and others and 'Synthesis Machines' as proposed by a number of groups including Lectka[30] and Ley. These initiatives build on advances in solid phase chemistry and polymer supported reagent chemistry made over the past few years.

Once compounds or chemical series have been slated for chemical optimisation studies chemists will work as part of project teams in order to

advance members of these series to candidate status. As can be seen from **Figure 2** this is a formidable challenge. The enormity of the problem does not exclusively reside in identifying compounds that effectively target 'validated target' proteins. Aside from the fact that these candidates should exhibit, ideally, pharmacokinetic properties commensurate with once a day dosing they must exhibit a superior safety profile. This means that it should avoid, as much as possible, hitting the multitude of other targets out there, particularly those that would give rise to undesired off-target related side-effects which could limit or preclude development.

Databases of 'biological fingerprints' of compounds and, indeed, chemotypes are now commercially available, eg CEREP's Bioprint database, and these are being used to proactively predict potential off-target effects of compounds related to specific structural and/or mechanistic classes and potential development compounds[31]. Today's chemist needs to be aware of these enabling tools. Also, on the topic of the assessment of off-target effects of compounds, the majority of practising medicinal chemists are now thoroughly acquainted with the need to avoid compounds that interact with hERG channels[32], compounds that exhibit the potential for clastogenic or mutagenic activity in man and compounds that may act as inhibitors or inducers of any of the key cytochrome P450 class of enzymes, such as 3A4 or 2D6 that direct the hepatic metabolism of drugs and the potential drug-drug interactions[33]. The chemist should be familiar with possible metabolic 'hotspots' on molecules and with ways to modify them in order to alleviate or eliminate the problem. Many good reviews of this topic have appeared in the literature[34] and computer programs for the prediction of potential sites of metabolism of small molecule drug candidates are currently being developed and commercialised. In a similar vein, interaction of drugs with drug transporters such as PgP is currently the topic of much interest and once again knowledge of this problem and potential solutions from a compound structure modification/manipulation standpoint is critical to the success of today's chemist[35]. The above examples highlight the significant number of tools that the current practitioner must have in their arsenal of medicinal chemistry weapons. In this context it must be noted that considerable effort is currently being expended by 'major pharma' on approaches towards the identification of potential reactive metabolites of drug development candidates. As toxicity is now the major leading cause of attrition of compounds in the clinic, and indeed, on the market this issue is of paramount importance. As idiosyncratic toxicity is quite often identified late in the game and, in many cases, after a drug has been on the market a significant period of time it is absolutely critical to the success of the industry that these debacles, which can be financially paralysing are avoided. As mentioned above, the medicinal chemist can play a significant role in the solution to this problem by producing compounds that, if metabolised, are converted to relatively benign progeny of the parent. This area of research has been recently and excellently reviewed by, among others, Evans et al at Merck[36].

Also, on the drug safety front, databases, of which many are currently commercially available, are being developed in order to allow the chemist access to data regarding the potential toxicity, including genotoxicity of classes of small molecules. Although needing much further work and input such collections may, in the future, provide a treasure trove of information for the chemist on structures and, more significantly, substructures to be avoided. The contemporary medicinal chemist must be technologically savvy and comfortable with all aspects of data integration and management. For example, he or she has to be able to manipulate, analyse and, hopefully, make sense of huge amounts of data, whether it be HTS, H2L, Structure Activity Relationship (SAR), Pharmacokinetic (PK), *in vivo* pharmacologic activity, or Structure Toxicity Relationships (STR). They need to be fully conversant with technology that allows them to do this, eg Spotfire™.

On a final note related to drug safety and the prediction of off-target effects the chemist has begun to play a significant role in the emerging area of chemical proteomics and metabolomics. Several proteomic strategies utilise synthetic chemistry to create tools and assays for the characterisation of protein samples of high complexity. These approaches include the development of chemical affinity tags to measure the relative expression level and post-translational modification of proteins in cell and tissue proteomes. In addition, recently, Cravatt and co-workers have reviewed the emerging field of activity-based protein profiling, which aims to synthesise and apply small molecule probes that monitor dynamics in protein function in complex proteomes[37]. Specific examples of efforts in the pharmaceutical industry include approaches to scan the proteome for targets of small molecule kinase inhibitors[38].

In summary, let me assert that chemistry remains a truly discriminating and invaluable science that plays a critical role in the drug development

process currently ongoing in the pharmaceutical industry. It is the scaffold on which all key components of the drug discovery paradigm are assembled and it is the engine that drives the other components of the machine. To illustrate this point, if we simply focus on one aspect of the chemist's function one might argue that a company's success at delivering clinical candidates will be hugely dependent upon the leads that it obtains. Most often these compounds are identified from corporate compound collections. These leads are produced by the chemists. They have to be produced and optimised creatively in order to provide all important intellectual property rights for the organisation. An organisation, it may be argued, is as good as its compound collection.

Looking into the crystal ball, as outlined above, one can only see medicinal chemoevolution proceeding in such a manner that it becomes more and more vital and indispensable to the future success of the industry. As for the chemists themselves, those that display flexibility, a willingness to work across boundaries and an ability to think outside of the box will thrive.

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