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Medicinal chemistry for 2020

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Abstract

Rapid advances in our collective understanding of biomolecular structure and, in concert, of biochemical systems, coupled with developments in computational methods, have massively impacted the field of medicinal chemistry over the past two decades, with even greater changes appearing on the horizon. In this perspective, we endeavor to profile some of the most prominent determinants of change and speculate as to further evolution that may consequently occur during the next decade. The five main angles to be addressed are: protein–protein interactions; peptides and peptidomimetics; molecular diversity and pharmacological space; molecular pharmacodynamics (significance, potential and challenges); and early-stage clinical efficacy and safety. We then consider, in light of these, the future of medicinal chemistry and the educational preparation that will be required for future medicinal chemists.

At one time, the term ‘drug discovery’ aptly described the most common path by which a molecular entity that could become a clinically useful drug was obtained. Medicinal chemistry has taken quantum leaps in the past three decades, notably with developments in 3D-structure analysis and understanding, high-throughput screening (HTS) and virtual screening. With the advent of rational drug design in all of its many manifestations, the current process is much more accurately referred to as ‘drug creation’ or ‘drug design and creation’ [1].

Very often, the starting point for drug creation is HTS (Figure 1), which, at first, take seems anything but rational in approach and does not constitute a medicinal chemistry effort *per se*. Even so, the design (by medicinal chemists) has already begun at this stage, because it is now almost universally recognized that **druglikeness** or, at least, **leadlikeness** [2,3], needs to be an attribute of the compounds comprising a fruitful screening collection for a particular class of targets, with medicinal cheminformatics playing a central role. The reasons for this should be obvious with respect to *in vivo*- or cell-based phenotypic screening, but the need remains even when the screening is conducted *in vitro* (perhaps on a microchip). Regardless, validated hits gleaned from screening efforts constitute only the earliest starting points on the path towards creating a drug. Moving forward, biopharmaceutical properties and some pharmacological attributes are now explored (via analog synthesis and evaluation) very early during the creation process – during hit-to-lead if screening was the starting point, otherwise beginning with the earliest phases of lead optimization. If target-structure-based drug design

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is to be pursued, either *de novo* or, more commonly, beginning with hit-to-lead or lead optimization, extensive understanding of macromolecular structure and molecular recognition is requisite. Lead optimization often now involves iterative rounds of *in vivo* preclinical pharmacology studies aimed at generating analogs that will attain the best possible efficacy in subsequent clinical trials, as well as the widest possible margin of safety (via mechanistic feedback from toxicology studies). Forward progress cannot be optimally achieved, however, unless drug-design teams can fully understand and logically act on the results. Thus, although medicinal chemistry has always been a multidisciplinary science, during the past two decades it has arguably become much more so. The question we then ask at this stage is, are medicinal chemists losing their identity? The answer is no! A medicinal chemist becomes a multidimensional puzzle solver, incorporating all of the necessary information to rationally create molecular entities, iteratively, such that one or more can ultimately become a clinically valuable drug. The body of science brought to bear on this endeavor has vastly expanded over the past couple of decades, however, and will continue to grow and evolve, a fact that has manifold implications.

In the next decade, structures of many more protein–protein complexes will become available [4–6]. Targeting each and every protein in the complex network of protein interactions that may have a possible human disease-pertinent function, though, in practicality, represents an impossible task. A source of hope is that the experimental and theoretical tools of systems biology should increasingly enable the identification of optimal, robust choices for molecular intervention. Even so, multiple possibilities will emerge for a given disease state in most cases, especially when the genetic and phenotypic characteristics of individual patients, and their particular circumstances, are taken into full account. Still, these possibilities will be finite in number, and one would expect basic pharmacology research to focus here over the next few decades. Extensive medicinal chemistry or chemical biology support for the creation of molecular ‘tools’ intrinsic to these efforts will be needed to achieve the greatest possible impact. Going forward into preclinical studies, further constraints are imposed by limited available development resources, in turn driven by clinical economics. Bringing a new molecular entity to the market is now estimated to cost within the order of a billion dollars or more [7,8] and even with efficiency gains resulting from scientific advances and intensive systemic optimization of the development process, costs will likely continue to rise. Thus, achieving continued molecular therapeutics-based clinical gains (addressing unmet medical needs) will happen at a rate contingent less on advances in basic biomedical sciences than on the availability of resources for translating these to practice. Restated, the numbers of potential drug targets and screening hits identified matter much less than the level of continued investments in development. As an exception, top-flight medicinal chemists can potentially play central roles in improving clinical success rates, thereby increasing the overall cost effectiveness of the enterprise.

At present, most stages of the development of drugs are carried out in industrial settings, with the public sector (including academia) focusing mainly on biochemical mechanism, macromolecular target identification, and early-stage compound identification or generation. Much basic research occurs within the pharmaceutical industry as well. Recently however, big pharmaceutical companies have reported plans to reduce their R&D expenditures (Pfizer, for example) [9], mostly due to expirations of numerous lucrative patents. A large backlog currently exists of viable **lead compounds** awaiting optimization (by medicinal chemists) and even of promising clinical candidates awaiting resources for regulatory filings and clinical studies. Phase IIB and III pipelines (Figure 1) appear lean, however, due to the combination of increased Phase I and IIa failure rates with escalating costs-per-entity of clinical trials and declining overall investment. Given this scenario, what happens over the next decade to the medicinal chemistry enterprise and to the industry that has supported the vast majority of it, is critically important. It is not our place to comment further on the merits

of sustaining total global investment in drug and biologics development, but we note the cruel irony represented by the fact that the resource outlook looks particularly grim just when the knowledge-based opportunities have never been richer, and when the scientific power of medicinal chemistry to capitalize on these opportunities to improve the human condition has reached such unprecedented heights. Presumably, though, there will continue to be a need to educate and train new medicinal chemists so that the enterprise can persist in the long term. Although these trainees should emerge as chemists first and foremost, and, furthermore, chemists with considerably increased computational and cheminformatics acumen, they must also gain a broad knowledge and working understanding of key areas of biochemistry and structural biology, as well as pharmacology, pharmaceuticals, toxicology and the clinical sciences. In support of these assertions, and to sort through some of their implications, this article focuses on status overviews and perceived trends in the key medicinal chemistry scientific areas of protein–protein interactions (PPIs), **peptidomimetics**, molecular similarity and diversity, molecular pharmacodynamics, and early-stage consideration of clinical efficacy and safety in drug design. In addition, we discuss some potential implications of the changing landscape of the pharmaceutical industry and ongoing evolution of the public-sector enterprise, for medicinal chemistry going forward. We then conclude with some thoughts concerning the education and training of medicinal chemists for the near-term future.

Protein–protein interactions for drug design

Cellular functions such as growth, transcription, translation and biochemical pathways that control these functions are regulated by multiprotein complexes. It is estimated that more than 650,000 PPIs occur in humans [6]. It is well established that numerous diseases are caused by aberrant PPIs, and modulation of these PPIs is attractive for the emerging class of drug-like molecules [4,5,10]. In the past 10 years, techniques such as pull-down assays [11] and yeast two-hybrid systems [12] have made it possible to investigate the network of PPIs in cellular systems. Furthermore, using computational methods, databases have been developed as a resource for prediction of PPIs [13,14]. However, in terms of drug creation, targeting PPIs is still in its infancy. Proteins often form a large complex network, in which they regulate biochemical functions. The PPI surfaces are quite large, and some complexes have multiple interacting sites. We ask, is it possible to selectively inhibit or modulate PPIs? Are the surfaces of PPIs completely flat without any cavities where a small molecule can ‘snuggle in’? Are cavities formed transiently during the dynamics of the interactions? Several of these questions must be answered in greater detail in order to design a small molecule for PPI modulation. Furthermore, in a structure-based drug-design approach the structural details of the protein complexes and the interactive surfaces of two proteins involved in the complexation are needed. Examples of structures of protein–protein complexes are shown in Figures 2 & 3. These proteins have continuous or discontinuous interacting surface areas of nearly 1500 Å². The next question that has to be considered is the size that a small molecule can be to target such large interacting surfaces of proteins. Traditionally, drug-like molecules at least reasonably adhere to characteristics encapsulated by Lipinski’s rule of five [15]. PPI inhibitors may likely follow an altered set of rules in most cases, a few such examples are available in the literature [16,17]. Wells and McClendon discuss the myths about disrupting PPIs and provide insights into myths about PPI modulators [17]. An example of modulation of PPI of proteins that interact via flat surfaces is seen in the case of IL–2 and its receptor IL–2R α . Another example of PPI modulation that is successful in terms of design of inhibitors is between P53 and human double minute 2 protein (HDM2) [16,17]. However, in the case of the P53 and HDM2 interaction, the P53 binding site on HDM2 is a cleft rather than a flat surface. The drug-discovery process in these two examples illustrates how mutation studies combined with x-

ray crystallography and a fragment-based approach using medicinal chemistry are used to successfully to modulate PPI.

Although PPI modulation for drug design appears promising, there are challenges in the future [16–19]. One of these is the limited number of crystal structures of complexes of proteins available in the database. The structure elucidation of protein–protein complexes depends heavily on x-ray crystallography since the NMR method of structure determination has been limited to a molecular weight of <20 kD. Recently, the segmental isotopic labeling method has made it possible to study proteins of molecular weight >20 kD [20]. Even if the structure is elucidated by NMR or x-ray crystallography, finding hot spots for drug design requires further analysis. The dynamic nature of PPIs poses another challenge. Crystal structures may not reveal the tractable hot spots in PPIs that exist in proteins in their native/cellular environment under dynamic conditions. Molecular dynamics (MD) simulations can, in principle, be used to generate a dynamic picture of the complex, but available computing power, theory and algorithms will continue to impose severe constraints for the foreseeable future. Advances with respect to the ability to accurately find and characterize transient hot spots in PPIs will play a major role. MD simulations of such large systems in a nanosecond–microsecond time scale requires supercomputers and algorithms that can handle tens of thousands of atoms. Recently, new coarse-grained (CG) algorithms [21] have attracted the attention of computational chemists, and an example of a report in the literature describing CG-MD simulations of ion channels in a lipid bilayer is illustrated in the report by Spijker *et al.* [22] At present, though, there are no reports of modeling protein–protein complexes using the CG method. One of the limitations of this method is resolution of the structures that will result from using the CG algorithm in MD simulations of protein complexes. The CG model treats groups of atoms in a functional group as a particle, thus reducing the number of particles for MD simulation [21]. The resulting 3D model of protein complexes may, thus, provide only a low-resolution picture, failing to provide sufficient detail at the site of an interaction hot spot for target structure-based drug-design efforts. Appropriate modification of the CG model should prove to be useful in the future for the study of PPIs. An algorithm developed by the D.E. Shaw Research Foundation, in conjunction with extremely high performance computing power, uses an all-atom approach to perform the MD simulation of biomolecules such as ion channel proteins in lipid bilayer [23]. This algorithm could be used for modeling protein–protein complexes and their dynamic nature, providing the desired simulations of PPIs over a nanosecond time scale. Whatever computational methods are used, in almost all cases of the modeling of protein complexes reported so far, the starting protein structure was drawn directly or indirectly from a crystallographic structure template. In proteins with multiple domains, such as epidermal growth factor receptors (EGFRs), crystal structures of extracellular domains (ECDs) are available in multiple (e.g., open and closed) conformations [24–26]. In some cases, transmembrane domains and cytoplasmic kinase domains are available [27,28]; however, these protein structures are available in pieces as separate domains. To model the dimers of such systems, the entire protein, including the ECD, and transmembrane and cytoplasmic domains, must first be assembled in proper orientations. Once this is accomplished, based on data such as cryo-electron microscopy, hetero- or homodimers of the protein complexes are built. For EGFRs, complexes have several contact points (Figure 4), including two contact points in the ECD domain, transmembrane domain and a contact point for transphosphorylation in the kinase domain. For such protein complexes, inhibition of any one contact point may prove important in the design. Molecular modeling methods [19,27] supported by experimental data will play a major role in constructing valid PPI models of such multidomain proteins, and, more importantly, determining the hot-spot regions [29,30]. Over the next 10 years, structural details of at least a modest number of protein–protein complexes will become available from mutational studies in combination with x-ray crystallography, NMR, and other sources of structural and biophysical information.

Increasingly, it should be possible to predict structures and key attributes of protein complexes using docking methods [31]. Using the individual 3D structures of proteins available in the protein data bank, possible structures of the complex of two proteins can be explored. Such docked models of proteins could potentially provide a structural basis for design of drug molecules. At present, though, few protein–protein docking methods are available [31–33] and these are only in the early stages of development. In addition, each of these methods has limitations in predicting the proper orientation of two proteins involved in a complex. Protein–protein docking methods predict various possible poses that may or may not actually be mechanistically relevant. The methods depend heavily on shape and electrostatic complementarity [31,32]. The user must set constraints for docking positions based on mutation data available in the literature and then choose the apparent most appropriate model from a set of resultant poses. Future structural biologists will engage heavily in accurate prediction methods of protein complexes and docking methods based on training sets of data available in the literature. Furthermore, a database that provides kinetic constants of PPI will help in validating the models of protein complexes derived from protein-docking studies [34]. Creation of a database of parameters of amino acid mutation in the PPI along with binding energies and kinetic constants will play a major role in advancing medicinal chemistry research. Even with all these data available, when a potential binding site is identified in PPIs, the atomic features of molecular surfaces may not be detailed enough to design highly specific/selective small molecular ligands. The binding pocket may be so general that there is no specificity between different PPIs involved in different biochemical pathways, or the pocket may be too shallow or the hot spots may be discontinuous in nature and spread around a large area [5,10]. In such cases, a medicinal chemist's knowledge of how to outfit a hypothetical PPI modulator molecule with functional groups will be very important. This type of design often depends on the experience and the intuition of a chemist. The situation is not bleak though in this case, since hot-spot regions in protein complexes are made from amino acids. As more 3D structures become available, the structural features of hot spots become more obvious. Given that there are only 20 amino acids in proteins, the interaction of different amino acids in different possible ways is finite, and even if we consider different orientations of amino acids in space, these are limited by side chain rotation restrictions and allowed regions of the Ramachandran map. The key point for the future of PPIs and their modulation is elucidation of high-resolution 3D structures of protein complexes.

Proteins, peptides & peptidomimetics

At present, PPI modulators may be grouped into three classes: antibodies, peptides/peptidomimetics and small molecules. Antibodies have been used to identify protein surfaces that are important for interaction. Monoclonal antibodies (mAbs) are the most successful class of PPI inhibitors at present [35]. Because of their high specificity for their target protein and their stability in human serum, they currently dominate the PPI modulators that have high therapeutic value. Most of the antibodies have common general methods of production and purification since their properties are similar. The cost of developing antibodies may be less compared with new small-molecule drugs, because once the production and purification processes are established with one type of antibody, very similar methods can be used to produce and purify other types. Furthermore, it may be possible to reduce the cost of antibody production using different expression systems. Protein production and purification systems in mammalian or *Escherichia coli* or insect cells are well-established techniques. The use of plant cells may enable further cost reductions [36]. Among biotechnology products, antibodies constitute a large number of therapeutic agents [37]. At present, 24 mAb therapeutics have been approved by the US FDA for marketing, and nearly 80 antibodies are in clinical development [38]. In terms of antibody therapeutics, what is the role of the medicinal chemist? There are at least two major areas in

the future where a medicinal chemist can contribute to the creation of mAb therapeutics. mAbs are being used in conjunction with small molecules as a combination therapy [39,40]. Another developing trend is conjugation of small molecules to antibodies [41,42]. At present, very few such examples exist; however, this trend seems likely to grow in the next 10 years. Recent data from clinical trials (Phase II) of brentuximab vedotin, a mAb targeting CD30 linked to an anti-microtubule agent, monomethyl auristatin E, showed the positive effects of the antibody–drug conjugate in anaplastic large-cell lymphoma and Hodgkin’s lymphoma [41–43]. Trastuzumab–DM1, an mAb to human epidermal growth factor receptor-2 (HER2) conjugated to a maytansine derivative, is currently in clinical trials for HER2-positive breast cancer [44]. In the preparation of conjugates of mAb, a medicinal chemist needs to understand the protein chemistry and conjugation chemistry so that the conjugation process does not denature the protein or block the binding region of the antibody or the small molecule of interest.

Although protein therapeutics have gained momentum in the past 20 years [45], there are problems associated with them. Despite the success of mAb therapeutics, the major disadvantages of mAbs are routes of administration as well as immunogenicity. Even humanized versions of mAbs can produce immunogenic responses [46,47]. In terms of pharmaceutical interests, the major disadvantages are the routes of administration. Antibodies cannot be administered orally because of their large molecular weight, and therefore, they are administered via a parenteral route. Another major drawback of antibody therapeutics is the inability of these molecules to cross cell membranes, which largely restricts their application to extracellular target interventions. One way to circumvent this problem is to design small peptides or peptidomimetics to mimic the binding region of larger proteins to the macromolecular target of interest [48]. For example, PPIs are concentrated in a few key residues placed in a particular 3D arrangement; these regions can be continuous or discontinuous in terms of protein sequence. If only a few amino acids mediate the contact between two proteins, then a compound mimicking properties of one of the interfaces of a protein should act as a competitive inhibitor and prevent the interaction between the binding partners. At present, more than 40 peptide therapeutics are on the market, and several are in clinical trials [37]. Peptides, however, also suffer from disadvantages as drug candidates. Compared to antibodies, peptides are more susceptible to serum and tissue protease degradation and, partly on that basis, are often rapidly cleared from the circulation in a matter of minutes [49,50]. Various strategies have been attempted to circumvent this general problem [50,51], most of which might be described as the design of modified peptides, either peptidal or non-peptidal peptidomimetics. x-ray crystallography- and NMR-derived 3D structures of complexes of proteins, with or without small-molecule ligands bound, have revealed structural motifs that are particularly important in PPIs. In the majority of cases, interacting domains exhibit secondary structure, such as α -helix, β -sheet/ β -strand, or β -turn (for some examples, see Figure 5). Extensive research into peptide chemistry, the design of peptide therapeutics and peptidomimetics in recent decades has provided enough information to give a strong boost to further efforts over the next decade [51,52]. Peptidomimetics designed based on key protein recognition motifs can be made stable against most of the enzymes that degrade proteins and peptides [49,52]. Physicochemical and biopharmaceutical properties can be altered to achieve desired characteristics with peptidomimetics versus peptides and peptidomimetics can be more readily designed to traverse biological membranes. Peptidomimetics can be readily tagged with fluorescent or lanthanide (e.g., europium) chelating tags for ligand–receptor interaction studies or for imaging purposes. Such tagging tends to have greater limitations with small organic molecule ligands, where it may be more difficult to identify ways to attach tags so that they do not block essential pharmacophoric moieties. A wide variety of backbone and side chain modification strategies exist, along with the ready commercial availability of β -amino acids that can be easily incorporated [51,52]. Examples of advanced development in

this area include design of a stapled peptide reported recently, in which α -helix-mimicking secondary structure was introduced using an organic linker, a strategy termed 'hydrocarbon stapling' [53]. The stapled peptide targeting myeloid leukemia cell differentiation protein 1 (MCL-1) was protease-resistant and exhibited enhanced cellular uptake. It was highly selective for the MCL-1 receptor, and binding studies suggested that it did not show any binding to the related and similar B-cell lymphoma 2 (BCL-2) family of receptors [54]. Other examples include reports from Sun *et al.*, [55] and Yin *et al.*, [56], which illustrate how design, synthesis and suitable binding assays (fluorescence, NMR) as well as docking studies can be used in the design of cell-permeating peptidomimetics. Clinically relevant examples of peptidomimetics that modulate PPIs include p53:MDM2 [35], smMLCK:calmodulin [56], Smac:BIR [55] and Bak BH3:Bcl-2/bcl-Xl [57]. There have been a number of projects aimed at modulating p53:MDM2 interactions. In one of the most recent reports, Lee *et al.* exploited pyrrolopyrimidine-based α -helix mimetics instead of stapled peptides to create a cell-permeable dual modulator, which modulates MDMX/MDM2 interactions [58]. These types of examples refute the misconception that peptide-based drug design is not a fruitful means of drug creation. As more and more suitable peptidomimetics are designed, along with synthetic strategies designed to enable arrays of compounds to be produced for investigating SAR and subsequent modifications as needed for **multidimensional optimization** (e.g., deliverability, pharmacokinetics, clinical efficacy and safety), an increasing number of peptidomimetic-based drugs should appear in clinical trials and, eventually, the market.

Finally, it is worth noting that for biological characterization and iterative optimization of PPI modulators, which may have relatively lower affinities for their targets, rapid, sensitive assays must be devised. Those that directly measure inhibition or modulation of dimerization or multimerization will be most informative. Methods such as surface plasmon resonance (SPR) [59], SAR by NMR [60], isothermal microcalorimetric assay [61], and fluorescence assay [62], provide information on binding of PPI inhibitors. SPR and microcalorimetric assays are still not widely used because they have been developed relatively recently compared with NMR for target screening purposes, although the basic principles have been known for a long time. In recent years, advances in SPR allowed its use for fragment screening, including elimination of non-specific (false-positive) binders [63,64]. Implementation of SPR imaging along with chemical microarrays and advanced microfluidic liquid handling has enabled the use of SPR for screening large number of compounds. SPR has advantages in terms of screening and binding studies during drug-discovery stages compared with other techniques like NMR. Notably, SPR analysis for binding and kinetic studies requires very small quantities of protein compared with other biophysical techniques of screening (ten- to 100- fold less). Furthermore, SPR can also be used to study membrane-imbedded proteins, using standard SPR technology as well as nanoplasmonic sensing with cell-membrane mimics [59,65].

Molecular diversity & pharmacological space

Even when we restrict our analyses to molecules that meet the description of 'small molecules' (in the pharmaceutical sense), and include only those atom types normally found in drugs, the resulting number of potential structures is of the order of approximately 10^{60} [66]. Of this vast universe of molecules, however, it has become quite clear that likely only a small fraction (still constituting a very large number) fall in the small bubbles of **chemical space** that constitute **pharmacological space**, and only a fraction of these entities satisfy even the most relaxed sets of criteria for 'drug-likeness' [5,66]. Grappling with this scenario has prompted much focus on the closely related aspects of molecular similarity and molecular diversity. Cheminformatics, a discipline that has long been formalized and applied in the realm of analytical chemistry but that has only more recently come to the fore

and become part and parcel to medicinal chemistry, continues to evolve in its applications to the design or selection of molecules for inclusion in compound libraries (virtual as well as physical) for screening [67–70] and **diversity-oriented synthesis** (DOS) programs [71–73], and for similarity searching for lead identification and scaffold-hopping [74–77]. One interesting aspect of DOS, also applicable to certain combinatorial or highly parallel-synthesis efforts, is that virtual libraries can be created based on structures that have yet to be made, but that could, in all likelihood, be synthesized (i.e., virtual collections of structures that should be rapidly synthesizable on-demand, with high probability of success, if identified in a virtual screening program). In this regard, DOS efforts have focused on obtaining high degrees of structural novelty and three dimensionality, via short, elegant and readily executable synthetic pathways that take advantage of such strategies as the build/couple/pair approach described by Schrieber [72]. Inspiration for these endeavors was provided, in part, by the incredible structural diversity and non-intuitive structures (e.g., artemisinin and dynemicin) occurring among secondary metabolite natural products [78–80], and hopes of artificially exploring completely new areas of chemical space given the plethora of possibilities associated with state-of-the-art organic chemistry. So far, these efforts seem to have helped confirm that the bubbles constituting pharmacological space include only a very small fraction of small-molecule space (as noted earlier) and that these bubbles will rarely, if ever, be stumbled upon by chance. Unprecedented opportunities seem to exist, however, if ways can be found to identify such islands, averting the need for interesting but unfruitful stumbling. (after all, the science of medicinal chemistry aims to eliminate as much trial and error as conceivably and practically possible). As just one piece of evidence for the untapped potential, a biological network interaction analysis of known macromolecular targets for natural products indicates a substantial discrepancy in the nature of these targets as compared with known disease-associated genes [81]. For medicinal chemistry, this suggests the exciting likelihood that exploration of pharmacological molecular space has barely begun, especially within the realm of molecules having considerable three-dimensionality from the get-go– to wit, ones that are not likely to be dreamed up by putting pencil to paper. Various physical and *in silico* approaches to the fragment-based design of lead compounds [82–86] in conjunction with highly 3D scaffolds for similarity searching seem to represent a particularly promising general strategy for identifying high-novelty lead compounds, particularly in arenas – such as PPI modulators, where the ligand efficiency demands are high, and the hit-to-drug optimization funnels are particularly narrow [5,17,87]. A hypothetical lead-creation process based on this central approach is presented at the end of the section entitled ‘Early-stage consideration of clinical efficacy & safety’.

Molecular pharmacodynamics significance, potential & challenges

Not only do the currently exploited macromolecular targets for drugs and biologics include only a modest fraction of the estimated theoretical number (*vide supra*), but many of the potential ways by which these targets might serve therapeutic purposes, in terms of molecular mechanism of action (MMOA), have been underexploited to date; to wit, enzymes have most often been targeted with competitive inhibitors, and receptors most often with competitive antagonists or, less commonly, with full agonists. This situation has been changing with increasing rapidity [88–97], but Swinney and Anthony [98] build a compelling case that, “the importance of [testing the three hypotheses implicit to target-based approaches] may be an underappreciated challenge that, if neglected, could contribute to increased attrition rates for such approaches. In other words, it is clearly difficult to rationally identify the specific molecular interactions from all of the potential dynamic molecular interactions that will contribute to an optimal MMOA, [and] the key biochemical nuances [for achieving] an optimal pharmacological response could be missed [by adhering solely to] target-based approaches” [98]. Gleeson and colleagues also recently explained

why overemphasizing drug-to-target binding affinity during lead optimization can actually increase the odds of producing candidate drugs having substandard biopharmaceutical character (unacceptable ADME profile) [99]. Imming *et al.* compellingly argue the importance of considering the dynamics of drug–target interactions, which we term molecular pharmacodynamics, towards attaining optimal, or even acceptable, clinical profiles [100]. Swinney and Anthony further contend that, “greater development and use of translational phenotypic assays”, is key to optimizing leads in ways that improve the chances for clinical success, from both efficacy and safety standpoints. Although, they rightly suggest that molecular descriptors for the dynamics of processes linking drug-target engagement to biological response generation will typically be more elusive than those associated with equilibrium binding. Ligand-based approaches, that is, SAR generation in traditional fashion, can address this information gap, but with the caveat that absent target-structure-based understanding of way-station experimental results, many more compounds will likely need to be synthesized and tested to ultimately produce a few having the most desirable response characteristics. Furthermore, with a lack of structure-based mechanistic understandings, translation to humans may be much less predictable. This should be unsurprising, in light of observations by Imming and colleagues that in situations where dynamics play an extensive role in drug response, “It is necessary to move away from the descriptions of single proteins, receptors, and so on and to [instead] view the entire signal chain as a target” [100]. Even in animal models humanized with respect to the intended macromolecular target(s), disparities will always exist for signal transduction pathways, with pharmacodynamic consequences that may range from modest to profound.

When molecular pharmacodynamics largely govern response characteristics, we may yet be some years away from being able to predict, *a priori*, exactly what changes to make in a ligand structure to cause defined effects on complete signaling pathways and, in turn, on cellular function. Fully rational, structure-based design under such circumstances requires understandings generated by MD simulations; sufficient computing power to conduct reasonably valid simulations for systems having the complexity of many macromolecular drug targets has only quite recently become available [101,102] and, even so, with interpretability constraints such that solid experimental corroboration is invariably demanded. Continued computational advances, though, should increasingly enable structural dynamics-based design – which is, changing ligand structures to alter the kinetics of macromolecular motion in multimeric protein assemblies in predictable ways. At least a few modest inroads towards this goal seem likely to be made within the next decade.

Even when the dynamics of macromolecular motion play a much lesser role in achieving particular response characteristics, though, the abilities of medicinal chemists to exploit MMOAs beyond those based solely on equilibrium binding have only recently begun to benefit greatly from structural biology-based understandings. For example, pharmacologists and medicinal chemists have known about partial agonism, and the significance of intrinsic activity, for many decades, but only much more recently have the molecular bases for these phenomena been coming to light in ways that lend to target-structure-based, rather than ligand-based, design applications. As yet, only a very few marketed drugs were purposefully designed as allosteric effectors or partial agonists (e.g., varenicline [93] and aripiprazole [103]).

Aside from the slow conceptual uptake by drug-creation teams, perhaps a key reason that ligands with out-of-the-ordinary molecular pharmacodynamic characteristics have been underexploited is that molecular pharmacodynamics, and even intrinsic activity (for receptors) and allosteric modulatory actions (for enzymes), are much more sensitive to small differences in protein structure, and to sequence differences external to the ligand-binding domains. This means that even when a particular nonhuman receptor or enzyme behaves

quite analogously to a human one with respect to competitive orthosteric ligands, it may exhibit quite disparate pharmacological responses to, for example, partial agonists or allosteric modulators, even if associated signal transduction cascades or biochemical pathways are nearly identical. For nonhuman targets (e.g., bacterial, viral and parasitic) the effects of genetic variation may be pronounced, perhaps prohibitively so, in terms of the advent of resistant strains, though this will not be true universally, given the success of linezolid [104] and retapamulin [105]. In conclusion, prospects are steadily improving for drug-design teams to exploit the complete array of molecular pharmacodynamic possibilities associated with potential drug targets in rational fashion, rather than by trial-and-error 'probing of the black box'; however, design teams can only capitalize to the degree that they are able to assimilate and apply pertinent structural biology findings.

Early-stage consideration of clinical efficacy & safety

Many of the implications of the rapidly advancing sciences aimed at considerably improving the percentage of compounds beginning Phase I clinical trials that ultimately reach market do not fall within the direct purview of medicinal chemists as drug designers. Yet, there are at least two general areas where they can play key roles.

First, first-in-class drugs rarely remain as best-in-class drugs for an extended period of time, especially in areas of high market demand [106]. On that basis, second- and third-generation drugs are created based on observed clinical deficiencies, the needs of specific patient populations, or desired changes in clinical characteristics prompted by new areas of application [107]. Medicinal chemists have been engineering such incremental improvements, in iterative fashion, since the advent of modern pharmaceuticals (consider, for example, evolutions beginning from antipyrene, morphine and cocaine). Two huge changes in recent years, though, are that:

- Rapid scientific advancements may outmode a particular mechanism of action before a second-generation drug can be brought through, or even to, clinical trials;
- New ways of predicting clinical efficacy early in the drug-creation process have been rapidly coming online.

Though the first point simply constitutes an unavoidable challenge, the second means that 'second- or later-generation' compounds can, at least in principle, be created prior even to initiation of the first human clinical trial. Enabling that prospect, though, requires drug designers who understand pharmacological nuances and the validity and scope-of-applicability of preclinical predictions well enough to effectively design next-generation molecules in an iterative fashion. In this context, 'pharmacological' would include all pertinent areas of biopharmaceutics, such as biotransformation, transporter-mediated impacts, and serum and tissue protein binding. It may even prove sometimes possible to engineer in robustness [108] via careful attention to molecular pharmacodynamics of ligands for an otherwise prohibitive target.

Second, an ever-increasing proportion of toxicological phenomena are becoming sufficiently understood at the molecular level to allow for actionable drug-design feedback to be obtained [109]. In many instances, then, this means that it may be possible to 'design out' the structural source of a problem from a drug molecule at the point when it is identified [110] or, ideally, even earlier in the drug-creation process, to screen for structural liabilities prior to synthesis or initial testing. In the latter case, heuristic computer programs [111] have largely supplanted medicinal chemists' rules of thumb (such as, for example, do not put an aromatic nitro moiety within a drug structure). Heuristic analysis, as well as recent QSAR-based approaches [112,113], will, unquestionably, cause some perfectly good and useful

drug molecules not to ever be synthesized or tested; as any good chemical toxicologist or medicinal chemist knows, subtle structural changes can make a compound that is toxicologically unacceptable into one that is safe, and vice-versa (note that several marketed drugs include aromatic nitro moieties and can be used safely in many patients). Moreover, potency, as it impacts required dose ranges, may unsurprisingly play a deciding role in the acceptability of a drug, due to limited-capacity ('threshold') detoxification mechanisms. As an example, troglitazone and pioglitazone undergo the same toxicoactivating pathway for biotransformation of their structurally identical thiazolidinedione ring moieties, but efficacious troglitazone doses were approximately tenfold those of pioglitazone, and troglitazone had to be demarketed (see Kalgutkar and Didiuk for other examples [109]). Toxicological feedback into the drug-design process can arise, when applicable, as early as in a virtual library-design process, become prominent in hit-to-lead and lead optimization steps [67], or result from clinical experience, during clinical trials certainly, but also during post-marketing surveillance (we would, of course, ideally like to eventually preclude post-marketing adverse events as a source of feedback, but achieving that ideal surely lies many years into the future). Quoting from Kramer *et al.*, "The earlier identification of dose-limiting toxicities will provide chemists and toxicologists with the opportunity to characterize the dose-limiting toxicities, determine structure–toxicity relationships, and minimize or circumvent adverse safety liabilities" (i.e., via additional rounds of drug redesign–synthesis–testing) [110]. Given the rapidly increasing extent of molecular-level mechanistic toxicological understanding now occurring, medicinal chemists with the right biological education should, in principle, be the most equipped among individuals involved in the increasingly intertwined drug-creation and preclinical evaluation processes to appreciate the significance of toxicological information in such ways that it can be brought to bear on iterative drug-design improvements.

A hypothetical lead-creation process, serving to bring together some of the ideas from the preceding sections, might go as follows:

- Biochemical pathway analysis indicates that a particular multi-protein complex occupies a node constituting a switching point between a pathological versus normal state. The analysis further shows that molecular intervention cannot be made in 'full-on' fashion, but requires something more akin to maintaining audio volume within a comfortable range: an allosteric activator is needed, but the molecular-level efficacy (intrinsic activity) must be limited (a Goldilocks scenario);
- Reliable information concerning not only the 3D structure, but also the dynamics of a key region of the multi-protein complex becomes available through a combination of experimental and advanced protein-modeling approaches, including artful advanced MD simulations. This information suggests that a molecule that could increase the propensity of a small loop of one protein to assume a particular conformation, but that would not interfere with the binding of this protein to another protein in the complex, and would, also, not significantly increase the associated enthalpy of PPI, should have the desired allosteric activator properties;
- From the available information, the 3D shape demands for such a molecule are largely apparent; this knowledge is necessary, but not nearly sufficient [114]. An *in silico* pseudoreceptor model [115] is, therefore, created, and fragment screening [67,116] is executed (also *in silico*) using a scoring algorithm known to be particularly suited to the nature of the targeted PPI 'pocket';
- Fragments are identified that should bind with suitably high affinity within all adjoining regions of the binding pocket. Some of these are overlapping. A

pharmacophore model is created based on a composite of these fragments, and compared with other pharmacophores proposed by automated routines in a certain proprietary software package based on the same pseudoreceptor construct. Three alternative pharmacophore models are adopted based on the consensus of a small group of medicinal chemists;

- The three alternative pharmacophores are used in 3D similarity searches [117] of a virtual library of 10 billion structures arising from a DOS scheme, where only approximately 300 have actually been synthesized towards validating the robustness of the imbedded general synthetic routes. Approximately 150 hit structures are identified in aggregate from all three searches. Only 18 of these are identified by more than one of the three pharmacophores, and only two by all three. None of the 150 hit structures have ever actually been synthesized;
- A similarity cluster analysis [118] is carried out on the 150 hit structures, from which 70 relatively disparate structures are selected;
- The 70 structures are subjected to rigorous docking analysis, again based on the pseudoreceptor model, involving consensus-scoring methodology, and provisions for limited target (pseudo-receptor) flexibility [119,120] as deemed appropriate based on the PPI model. Approximately 30 of the structures cannot be docked under these constraints. Of the remaining 40 molecules, another 25 are rejected because detailed visual scrutiny reveals that they would, based on the PPI model, interfere unacceptably with protein movement proposed to be critical for the desired allosteric activation;
- The 15 remaining hits are synthesized via the DOS schemes, none of which involve more than five synthetic steps. These syntheses require approximately 1 month for three chemists to complete, including structure and purity verifications;
- In total, seven of the compounds are shown experimentally to exert the biochemical effects on certain human cells in culture consistent with the proposed allosteric interaction mechanism. The possibilities for definitively proving the proposed mechanisms (experimentally) are discussed, but the conclusion is reached that this is an issue of scientific, rather than practical, importance, at least at this stage;
- Of the seven compounds exhibiting the desired effect, the hit-to-lead chemists deem that four are sufficiently tractable synthetically for further exploration (preliminary SAR towards further pseudo-receptor model validation and refinement, molecular pharmacodynamics 'range-finding' with respect to the required allosteric characteristics stated earlier, and other early optimization goals). The remaining three structures are temporarily 'kept in the hopper' for possible scaffold-hopping analysis, pending the results of the hit-to-lead effort (estimated to take about 6 months) and the results of early preclinical screens (both experimental and *in silico*) on resultant leads, seeking to identify possible off-target sources of prohibitive side effects or toxicities, and initial proof-of-concept pharmacology in humanized animal models.

Current trends in medicinal chemistry & future perspectives

With abundant data from genomics and proteomics, there is no doubt that there will be many more drug targets in the coming decades. It has been estimated that if all marketed drugs were considered with known molecular targets, these targets would number only 482 [100,121]. Based on genomics/proteomics and ligand-binding studies, it is now estimated

that nearly 5000 targets could be hit by traditional drug substances, 2400 by antibodies and another 800 by protein pharmaceuticals. These targets include enzymes, receptors, ion-channels, transport proteins and DNA or RNA. These numbers seem to suggest a bright future for medicinal chemists; however, for target-based drug-design approaches [122], bottlenecks are the availability of 3D structures of biomolecular targets and, at an earlier and more basic level, bioassays based on identified targets that provide feedback suitable for iterative design efforts. Considering the present situation in the pharmaceutical industry, the global economy, and the funding situation for public-sector research, the future viability of drug discovery and medicinal chemistry is debatable. Here, we review the recent literature that encompasses the debate concerning different models for drug-design and development research. The advantages and disadvantages of each model are discussed.

In the past two decades, the advent of combinatorial chemistry, and high-throughput synthetic and natural product screening, has overloaded the start of the pipeline with hit compounds [123]. Screening millions of compounds at super speed, however, does not mean that we find compounds that will make it to preclinical and clinical development. This is one place where medicinal chemistry should continue to play a major role in the future. Medicinal chemists must create lead compounds from validated hits, via hit-to-lead chemistry/biology, and subsequently incorporate the full array of 'drug-like' properties via lead optimization, before extensive and costly late-stage preclinical development occurs. Once medicinal chemists create or identify lead compounds, further work on preclinical pharmacology and toxicology will be carried out, with critical evaluation of the data. The overarching goal is to achieve 'fail early, fail cheap', because the more often that candidate drugs enter clinical trials [124,125] and fail, the less profit is delivered by the enterprise in aggregate, and the less interest there is in continued investment. The past decade has produced lead compounds in large numbers; however, the later-stage clinical pipelines are lean, and major pharmaceutical companies have been losing their patent protection for blockbuster drugs at a frightening rate [124,125]. In the past two decades, the cost of developing a drug has sky-rocketed, with an estimated cost of at least a billion dollars for bringing a drug to the market [7,8]. The vast majority of the drug-development funding is provided by the private sector, and at present, the majority of drug creation is still implemented in industry, with a mandate for commercial success (i.e., profits). Some are predicting that in the next few years pharmaceutical companies will widely adopt a different model, much more of a risk-minimized approach. It is even possible that, in the Western world at least, soon the majority of science (i.e., medicinal chemistry) will be conducted in public-sector settings [126,127] and, moreover, with companies outsourcing most of the preclinical development and even Phase I clinical trials. Companies will choose only the most promising compounds and will focus their strengths on conducting clinical trials and gaining approval for marketing. This type of public-sector– industrial partnership could potentially create a win–win situation for both sides. Such a scheme was proposed by Chas Bountra, head of the Structural Genomics Consortium at the University of Oxford (UK) [124,125]. In his proposal, intellectual property (IP) restrictions would be lifted, and academics would publish preliminary data on prospective drug candidates, which would mostly comprise medicinal chemistry and pharmacological findings. Preclinically validated compounds would then be selected by industry, financial negotiations would take place, and the development process to bring the drug to the market would be continued in the private sector. This would save initial costs of research for industry, and also support academic research, wherein medicinal chemistry would play an increased role. The model of collaboration through academic–industrial partnerships has already gained momentum in the UK [128]. For example, the Wellcome Trust has initiated a seeding drug discovery initiative program, which has committed awards to 19 academic institutions and 11 companies for research projects. A recent report lists at least six pharmaceutical companies partnering with academics in four countries, including nine US academic institutions [129]. However, do

such models deny the medicinal chemist his/her creativity and force him to give away or cheaply sell out IP? This remains to be seen in the success of this partnership between academics and industry over time.

With the slowed pace of clinical drug development in the next decade, more focus will be placed on a stronger role for science in drug creation [127]. In the current situation, pharmaceutical companies simply cannot take big failures [124,125]. If the number of compounds sent for full-blown preclinical development is limited based on improved mechanistic studies and early preclinical filtering done in academic/public-sector settings, companies will be better positioned to handle the remaining unavoidable development risks. If this scenario were to become increasingly prevalent during the coming decades, one might argue that, historically, nearly all major drug discoveries were made in industry, and thus, that the proposed model of academic-industrial partnerships would greatly set back the already slower pace of availability of new drugs in the market. In addition, some would say that academic researchers, who are not driven by commercial success, might devote excessive time to endless questions related to the science behind molecular mechanisms. However, recent reports document that, in contrast with widespread assertions that almost all new drugs are created in the private sector, the public sector in fact contributed directly or indirectly to the discovery of 153 products in the past 40 years (9.3% of the approved drugs by FDA) [130–132]. Of these 153 marketed products, 93 small molecules, 36 biological agents, 15 vaccines, eight *in vivo* diagnostic materials, and one over-the-counter drug originated either wholly or partly from public-sector research institutions. These figures should tend to allay fears concerning negative impacts on the pace and cost-effectiveness of discovery and innovation but, perhaps, instead raise questions concerning the industrialization of academic institutions and diversion from the supposed primacy of education missions.

These proposed changes in industry to concentrate more on drug development and leave the initial-stage ‘science’ to the academic domain are in concert with recent trends in NIH focus, where there have been shifts toward translational research [133]. Although translational research may, in principle, refer even to basic research that ultimately leads to clinical outcomes, the starting point with respect to medicinals tends to be a molecular entity that modulates a biochemical pathway and leads to an understanding of a disease, and possible therapeutic application. Some intend that translational research will focus more on therapeutic pipeline research, so that it will fill the gap left by industry in the R&D sector in the next few years. According to the Director of the NIH, Francis Collins, the NIH wants to create a non-traditional way of fostering drug development [134]. The investment of the NIH in translational academic research would, in part, be intended to ‘de-risk’ projects that might otherwise be economically unattractive to the private sector. Such efforts will elucidate molecular mechanisms of human diseases, and will also bring out the risks associated with the interactions of drug targets, and off-target effects. Some of these pipeline research efforts must, necessarily, be supported by medicinal chemists, from the initial creation of molecular entities to their modification as needed during risk assessments, which will be based on molecular-level understanding of deleterious interactions of the chemical entity with human physiology. Although public-sector research may slow the drug-creation and development processes in their earlier stages, increasingly detailed studies related to the pharmacological, pharmaceutical, and toxicological effects of a molecular entity should provide feedback in the final stages of drug development to the clinicians who make the decisions to proceed with or kill a project, and thereby increase efficiency by reducing the failure rate. This scenario would, at least, limit the number of candidates proceeding to full-blown preclinical development, and thence, to even more expensive clinical trials.

The partnership of academia with industry will also benefit from increased sharing of information. The aforementioned Wellcome group is pushing for open-access chemistry, where genomic and proteomic data, as well as the results of cheminformatics analyses, are made widely available to academicians [135]. In the last two decades, big pharmaceutical companies and research institutes have generated a tremendous amount of data that were heretofore available only internally, or provided only to partner organizations in heavily guarded fashion; now, large bodies of these data have been made available to the public domain, and some institutions are investing heavily to capitalize. In the USA, for example, University of California at San Francisco has established a large center for research into drug design and development. Pfizer is reportedly drawing up a grand plan to invest in drug development-ready research in academia through a series of collaborations with leading medical centers. One of the first of these projects, which was announced in November of 2010, is also with University of California at San Francisco; the aim is to expand this model to collaboration with medical centers worldwide [136]. A few other translational research centers are focusing on basic research related to medicinal chemistry [137,138]. While major pharmaceutical companies like Pfizer and the Wellcome Trust have publicized plans for partnership with academic institutions, what is the role of small pharmaceutical companies in future drug discovery and medicinal chemistry? Biotechnology companies, and small and medium entities (SMEs), have been involved in partnership with academic institutions or state-funded research institutions for more than a decade. In fact, many small pharmaceutical companies and startup biotechnology companies are spin-offs of academic research innovations, and this will likely continue over the next 10 years. There are examples of mixed ventures that resulted in drug-discovery centers in the USA, UK and Canada [139]. Certainly, not all SMEs are closely connected to academic or other public-sector institutions. The roles that such organizations play are very actively evolving, and will undoubtedly complement efforts of other players, fill key gaps and simply compete for partnership.

With many state-assisted universities facing the challenge of severe budget crises, one of the possible ways to retain the vitality of research and training is to partner with the private sector, despite the associated compromises. Professors and their students would have to orient themselves for some form of translational output, apart from basic research. A collateral benefit of such academic-industry partnerships is that they will help keep a domestic pharmaceutical R&D job market. Companies are aggressively cutting costs, in unprecedented ways, at present. If academics are not willing to participate in collaborations, companies may, ultimately, outsource most of the early discovery-stage work, likely to SMEs, but also to other countries, which would further diminish job opportunities for domestic graduates. With proper academic-private partnerships, it should be possible to keep a component of basic research and academic independence yet participate in the challenging applied research aimed at unmet medical needs while simultaneously compensating for the changing funding environment.

However, there are significant concerns about the way the public-private model works. Project milestones will be set, and will be periodically evaluated for successful attainment by a steering committee. Even when the milestones are achieved by a project investigator, if the results suggest that the risks are too great to take the project to industry for the later stages of drug development, funding will be terminated. In such situations, academics are left in the middle of nowhere. The IP distribution issue was already mentioned earlier. Another drawback to this model stems from the greatly increased rate of acquisitions, mergers, and reorganizations of pharmaceutical companies over the past two decades. Following such events, if new leadership is not interested in a project in that an academic institution is participating, funding would likely be terminated in the middle of a project. Another major drawback for academics is the constraints that are placed on the publication

of data. What can be published invariably depends on approval by the industrial partner. If important data are only partially publishable, a manuscript may not be accepted, particularly by journals with high impact factors. Without publication, students working on projects may be challenged to convince their review committees of acceptance of their not-peer-reviewed/unpublished work. At the same time, supervisors or project leaders will face the challenge of submitting research-funding applications to federal agencies with fewer publications in a particular field in which they are seeking funds. In the USA, this will represent an even greater obstacle than in the past, as new NIH guidelines require recent publications in the field in that the principle investigator is looking for funding in, rather than depending more on total numbers of past publications by the principle investigator. Above all, a major question to be addressed in this model is, do academicians lose too much of their academic freedom by engaging in such research? Thus, for a medicinal chemist, there are real compromises. The discipline of medicinal chemistry is largely an applied science, and, apart from issues of academic freedom, medicinal chemists always experience the intrinsic risks. Compensatory incentives are associated with the great potential for end results that are beneficial to society. If society maintains an interest in the creation of new medicinals towards addressing unmet medical needs, then the centrality of medicinal chemistry as well as its scientific power and potential in these endeavors must be fully appreciated, and recognized with altered economic policies and adjustment of funding structures in ways that reflect the unique attributes of the enterprise.

The model of the NIH creating translational research centers, which emphasizes that it will help take the scientific discoveries to practical applications by turning the research output into actual drugs or treatments, has also caused debate. If the NIH gets heavily involved in creating drugs, and especially during their development, is NIH partially converting itself into a public-sector pharmaceutical company? There will be polarization among academics between those that have support or are funded by industry, and those that never partner with industry. According to Roy Vagelos, former Chairman of Merck, the NIH should stick to basic research. There is also concern that if the focus of the NIH funding shifts excessively to the drug-development process rather than remaining on basic science, this will pull resources away from producing new knowledge and discoveries [201].

The making of a future medicinal chemist

With these ongoing and potential changes in the industrial landscape, and large amounts of genomic, proteomic and other data becoming available to the public domain, there may be a need to change the ways that we educate and train medicinal chemists. The facts and expectations presented in this perspective argue that future medicinal chemists should not just be 'suppliers' of compounds to HTS teams or biologists/pharmacologists for *in vivo* study; rather, they should be fully engaged in R&D projects related to drug creation. To make such contributions, medicinal chemists must come to thoroughly understand, for example, areas as diverse as 3D structure and function of proteins, cheminformatics, biochemical pharmacology over a broad range of mechanisms, and the biochemistry and physiology of absorption, distribution, biotransformation (drug metabolism) and toxicity. Attaining a deep grasp of the complexities of these areas, in terms of their connections to medicinal chemistry, requires sufficient time and exposure. Two questions we can ask, then, are:

- What educational model(s) would be optimal for the enterprise?
- How can aspiring medicinal chemists best gain a high-value set of attributes and, given competing demands, not have their knowledge and skills so diluted in all areas that they are of no immediate – or even eventual – practical use to

anyone (anecdotally, the justification for the “train as an organic chemist, learn the biology later” approach)?

Within industry, the majority of medicinal chemists have historically been bred by hiring synthetic organic chemists and educating them over many years to become medicinal chemists, a path that has been self-propagating. Accordingly, most students aiming for senior industrial medicinal chemistry positions have gained PhD-level education and training in synthetic organic chemistry, followed by one or more postdoctoral fellowships, which might or might not have a medicinal chemistry or chemical biology focus [140]. And, although there are many nominal medicinal chemists in academic research, many were educated and trained solely or mostly as synthetic chemists. An alternative, somewhat less-common path has been to obtain a PhD in medicinal chemistry (typically in a program associated partly or fully with a pharmacy school) followed by one or more postdoctoral fellowships, held within a synthetic organic chemistry group if employment in a traditional industrial medicinal chemistry environment was the end goal. Something more akin to this latter pathway potentially offers some key advantages (provided the chemistry robustness is maintained), notably greater opportunities during graduate study for direct research collaborations with pharmacologists, pharmacuticists and toxicologists, for more programmatic emphasis on drug design, and for more education and exposure in the pharmaceutical sciences. Moreover, with the continuing evolution of the discipline and its associated body of science, an increasing fraction of medicinal chemists may not need to have synthetic chemistry as the main focus of their education and training. Thus, we propose a core educational model for future medicinal chemists (Figure 6), wherein graduate students will be educated and receive some training in three basic core areas: organic chemistry, theoretical and practical foundations of computational chemistry, and structural biology, with further emphases governed, in part, by a student's aptitudes, inclinations and future aspirations. These thoughts are consistent with the characterization of medicinal chemistry by Krogsgaard-Larsen and colleagues as a trans-disciplinary pursuit [141]. Students who enter medicinal chemistry should thus have a strong background in chemistry and mathematics from their undergraduate educations. Thence, in a Master's degree program or in the first two years of a PhD program, they will learn selected aspects of synthesis, computational chemistry and structural biology, but with a research project and a majority of didactic course work focused mainly in one of these areas. Thereafter, training and accompanying education will heavily emphasize one particular area, such as synthetic medicinal chemistry, or natural products chemistry, or applied computational chemistry. Students will also begin learning essential affiliated subjects (cheminformatics, pharmacology, biopharmaceutics and chemical toxicology), so that they can read more broadly in pertinent areas, and gain more from their early interactions with scientists from interfacing disciplines. This structure would likely necessitate extending didactic course work considerably longer than has most often been typical of graduate programs, but would afford trainees the benefit of time to assimilate complex concepts gradually. The advent of increased academia–industry partnerships, and a relaxing of IP restrictions, may enable more medicinal-chemists-in-training to have opportunities for industrial internships (ideally, of at least 6 months' duration). Worldwide, some academic programs have already been demanding this for many years. There are reports suggesting that industrial medicinal chemistry sometimes now manifests as chemical biology [142], and an internship would allow a student to experience such an environment at first hand, aiding them in better assessing and refining their aspirations, and more knowledgeably choosing subsequent paths and opportunities to pursue.

With the addition of postdoctoral training to reach the level of expertise in a chosen area of emphasis typically sought by industrial or academic employers alike, this model represents no shortening of paths that have long been lengthy (arguably too lengthy, if subsequent

reward, tangible or intangible cannot justify the investment). In that light, there are other possible models for medicinal chemistry education and training. According to Doyle, in the future, chemical education will be more individually programmable [143]. With rising educational costs and decreasing state and federal funding, the education system will, in response, be maximized for problem-solving with specific talent. Doyle's thoughts would seem to suggest commencing earlier, with tailored undergraduate programs, potentially offering opportunities for shortened time frames and, thereby, greater efficiency. However, if students do not obtain a sufficiently general education at the undergraduate level, their future choices may be inordinately constrained. With rapid changes happening in almost every field, such training might become obsolete in only a few years. A possible variation, mitigating this last concern, would be to include more medicinal chemistry while teaching organic chemistry and biochemistry at the undergraduate level, also including computational chemistry and cheminformatics as areas of considerable emphasis, perhaps even a specific minor. In this model, students would have sufficient background in general organic chemistry and biochemistry to make larger deviations in their subsequent careers, while still having a jump-start in developing medicinal chemistry acumen. Such models were discussed in 2003 [144], and a few accelerated BSc/MSc programs in medicinal chemistry have been in existence for many years. We expect, though, that medicinal chemistry education, as in the past, will continue to occur mostly at higher levels. We have argued above for increased discipline-specific preparation during graduate education, namely during Master's degree and PhD programs, as opposed to waiting to begin during postdoctoral training or regular employment [140]. We suggest that such proposed shifts to earlier incorporation of educational breadth will increase the effectiveness in highly collaborative environments of medicinal chemists at all levels, as well as reduce the front-loaded educational investment burden on industry. The key proviso is that didactic education and research experiences must be robust in a student's particular area of emphasis.

Regardless of the pathways designed to achieve it, the overall final goal should be to produce/develop medicinal chemists who will be key participants in all stages of drug creation, starting from design and continuing to producing more effective and safer molecular entities that are useful to treat human diseases.

Executive Summary

- With rapid advances in rational-design approaches in recent decades, the 'drug-discovery' process has become a 'drug-creation' process, at the center of which are medicinal chemists. They have become multidimensional puzzle solvers, bringing to bear a body of science that has vastly expanded over the past couple of decades, and will continue to rapidly grow and evolve.
- Partly based on advances in systems biology, protein-protein interactions (PPIs) have become an attractive focus. Although therapeutic PPI modulation with small molecules shows promise, stiff challenges include the limited availability of detailed 3D structural information for complexes of proteins. Molecular dynamics simulations will increasingly provide actionable information, and we anticipate a surge in the creation of peptidomimetics as PPI modulators.
- Cheminformatics continues to evolve in its applications to the design or selection of molecules for inclusion in compound libraries (including virtual ones) for screening, for designing diversity-oriented synthesis programs, and for similarity searching for lead identification and scaffold-hopping. The exploration of pharmacological space has likely barely begun.

- Many of the potential ways by which macromolecular targets might serve therapeutic purposes, in terms of molecular pharmacodynamics, have been underexploited. Continued theoretical and computational advances should increasingly enable drug-design teams to exploit the complete array of possibilities, while better predicting and addressing problems associated with translation to humans and pharmacogenomic-based response variations.
- Lead optimization increasingly entails iterative rounds of *in vivo* preclinical pharmacology and toxicology studies aimed at generating analogs that will attain the best-possible clinical efficacy and widest possible margin of safety. Actionable mechanistic feedback may shorten this process, and increase success rates, but only when medicinal chemists know how to capitalize.
- Given current economic constraints, industry may increasingly shrink or outsource the early stages of drug creation and development. The next decade will see increased medicinal chemistry collaboration between industry and public-sector institutions; productivity will depend on recognizing and addressing various caveats.
- Given current trends, medicinal chemistry trainees should continue to emerge as chemists first and foremost, furthermore having computational and cheminformatics acumen considerably greater than in years past. To be maximally effective, however, they will also need to gain strong working understandings in key areas of biochemistry and structural biology, as well as pharmacology, pharmaceuticals, toxicology, and the clinical sciences; early introduction and persistent exposure as part of well-structured graduate programs could effectively enable this aim to be met.
- Top-flight medicinal chemists can play greater roles in improving drug-creation efficiencies and clinical success rates, thereby increasing the overall cost-effectiveness of the enterprise and, in turn, more quickly satisfying unmet medical needs.

Key Terms

Druglikeness	The concept of druglikeness is generally taken to pertain to small-molecule pharmacotherapeutic agents rather than biologics of any type, and reflects the extent that the structure of a molecule is similar in character and attributes to what is typical of marketed drugs and those in late-stage clinical trials.
Leadlikeness	Similar in nature to the term druglikeness, but includes wider tolerances to allow for the types of structural changes typically made during lead optimization, and may also refer to the extent that a lead compound is synthetically tractable for lead optimization.
Lead compound	Molecule that is identified from the literature (including patents) or, coincidentally, for example, from the observation of a potentially useful side effect, or from a screening program followed by hit-to-lead chemistry that exhibits desired pharmacological activity, and which is amenable to lead optimization.

Peptidomimetics	Describes molecules that are designed to emulate pharmacophoric portions of a peptide, but are either composed of stereochemically altered or unnatural side chain containing or backbone <i>N</i> -substituted amino acids, or of nonpeptide bioisosteric substitutes for portions of the peptide structure, or of a mixture of these two general types of moieties.
Multidimensional optimization	Equivalent to multi-objective optimization; refers to lead-compound optimization in a manner such that two or more characteristics essential for clinical success are assessed with each round of iterative compound design and synthesis, aiming to simultaneously improve all these characteristics, or make acceptable trade-offs when structure–attribute paths towards different goals diverge.
Chemical space	Refers in informatics fashion (rather than in a literal sense) to the set of all theoretically possible molecules, which, in practicality, is infinite in number, but even so is constrained to molecules comprised of physically possible (stable) atom-to-atom bonds, connectivities and configurations.
Pharmacological space	Subset of chemical space composed of all molecules that can bring about defined, specific physiological changes in organisms, in dose-dependent fashion.
Diversity-oriented synthesis	Endeavor of designing and executing schemes of organic reactions, typically comprised of a relatively small number of steps, aimed at predictably producing arrays of structurally dissimilar products, each ideally having substantial topological novelty.

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Figure 1. Stages in the drug creation and development process
IND: Investigational new drug; NDA: New drug application.

Figure 2. Protein-protein interactions of multi-domain protein EGFR

(A) Only extracellular domains I-IV of the crystal structure of EGFR are shown (PDB ID: 3NJP). Notice that domains II and IV make contacts. (B) The crystal structure of the monomer of human epidermal growth factor receptor 2 (HER2) is shown (PDB ID: 3N85). Antibodies directed at domains II and IV of HER2 have clinical significance. Antibodies directed against domain II disrupt the protein-protein interactions of EGFR and HER2.

Figure 3. Protein–protein interactions of cell-adhesion molecules CD2 and CD58 (PDB ID: 1QA9) that have important implications in immune response and autoimmune diseases

The interaction surface is nearly 1500 Å². In the crystal structure, ten salt bridges, five hydrogen bonds and one hydrophobic interaction were observed between the two proteins. Mutational analysis and binding studies suggested that mutation of Y86 by Ala disrupts the PPI 1000-fold. The antibody drug alefacept, directed against the PPI modulation, is therapeutically used for severe chronic plaque psoriasis. Small peptides/peptidomimetic molecules are targeted to the CD58 adhesion domain to modulate PPI [145,146]. PPI: Protein–protein interaction.

Figure 4. Multidomain heterodimer of EGFRs

Several contact points in the protein have protein–protein interactions, which is useful for drug design.

Figure 5. Examples of peptide epitopes/secondary structures that are exhibited by protein–protein interaction contact areas

Although large proteins form heterodimers, protein–protein interaction contact areas could be small where a small peptide/peptidomimetic could fit in. (A) MCL-1 complexed with helical peptide (PDB ID: 3KZ0), (B) Crystal structure of extracellular segment of integrin $\alpha 5 \beta 3$ in complex with Arg–Gly–Asp peptide. The β -turn epitope is bound (PDB ID: 1L5G). (C) PDZ domain with C-terminal model peptide of receptors from membrane proteins. The β -sheet/ β -strand epitope structure is bound (PDB ID: 3KZE). (D) Integrin $\alpha 2$ I domain/ collagen complex (PDB ID: 1DZI).

Figure 6. Educational activities of a future medicinal chemist

Venn diagrams represent the overlapped training and education in three areas of medicinal chemistry that form the foundations of medicinal chemistry (left) and knowledge required (right) to converse with other related disciplines of science required for drug creation. Training and knowledge in these areas associated with an internship in industry will prepare a medicinal chemist for the future.
Med. chem.: Medicinal chemist.