CHAPTER FOUR

The Evolving Role of the Medicinal Chemist

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1. INTRODUCTION

Pharmaceutical Research has undergone a dramatic evolution in the past decade including substantial changes in medicinal chemistry. Driven partly by scientific and technological advances, and partly by seismic structural changes in the biopharmaceutical industry, the medicinal chemist's role has expanded but, paradoxically, seems to have shrunk in importance in the eyes of many business leaders. We aim to counter the view that medicinal chemistry can be treated as a 'service' to drug discovery and rather is a central component. We would like to encourage and motivate medicinal chemists to be more proactive in advertising the scope and importance of the discipline and in shaping its future.

This chapter builds on a recent publication from one of us [1] and will discuss the impact of some of the recent changes in science, process and business structures. We present an outline of the present-day drug discovery process and the business structures in which it is operated. This is followed by our view of the changing role of the medicinal chemist and the characteristics that will be required for its further evolution. Many medicinal chemists will have experienced the perception voiced from inside big pharma [2]: 'medicinal chemistry is often referred to as a "mature science" evoking images of the grandfather of drug discovery – geriatric, slow and even grumpy.' This description in no way reflects the present-day profession.

The majority of medicines that reach pharmacies and patients are synthetic chemicals and are invented by medicinal chemists [3]. Even with 'biologics' assuming a greater importance in the balance sheets of pharmaceutical companies, there is increasing emphasis on the molecular characterisation of these medicines, and medicinal chemists are now becoming involved in designing chemical modifications to optimise the effectiveness of protein drugs. The combination in a single molecule of small-molecule drug and protein, for example, in antibody–drug conjugates, is of growing significance [4]. Our belief is that medicinal chemistry is critical to the creation of new medicines, and for its contribution to be maximised, perceptions, including those of the medicinal chemists themselves, need

to change. We, the practitioners, are the only people who can change them! As educators and employers, medicinal chemists have a crucial role in developing the medicinal chemistry skills portfolio as it adapts to the changing biopharma landscape.

2. DEFINITION

Medicinal chemistry is the study, understanding, design and experimental manipulation of the structure of molecules that modify biological function in a physiological and/or pathological system [5]. It is both science and art [6] and requires complex puzzle-solving skills [7].

Medicinal chemistry underpins the understanding of how chemical structure dictates physicochemical properties, and how these properties induce physiological function and control the fate of the molecule in whole organisms. The core competencies of the medicinal chemist include design and sourcing of compounds (often by synthesis), structural analysis and interpretation of mode-of-action studies of potential new medicines.

At the heart is the development of structure–activity and structure–property relationship hypotheses that lead to the prediction of improvement in biological properties in the next series of compounds to be sourced.

A European Federation for Medicinal Chemistry position paper on medicinal chemistry captures the increased range of medicinal chemistry: 'Over the last decade, the scope of medicinal chemistry has broadened considerably, and the molecules it deals with now show an increasingly larger structural diversity, blurring the border to biochemistry. Beyond small synthetic ligands and natural products, medicinal chemists have now developed numerous examples of modified peptides and proteins, antibody drug conjugates, multifunctional molecular constructs or synthetic vaccines. Medicinal chemistry has also expanded beyond drug optimization: at the earliest stages of drug discovery, it now provides molecular tools for therapeutic target identification and validation, to explore biological pathways, as well as to study toxicological mechanisms. In the latest phase of drug discovery and development, medicinal chemistry provides imaging ligands and diagnostic tools, to better understand diseases and facilitate the clinical evaluation of novel drugs' [5].

3. THE DRUG DISCOVERY PROCESS

Although it was once considered a linear process, the progression through target identification and validation, Lead finding and optimisation towards a candidate drug is now much more chaotic, and boundaries between these once clear stages have become blurred. Targets are not considered validated until there is clinical proof of efficacy. Leads usually have to have drug-like characteristics that were once typically introduced in the optimisation phase. Companies and funders still like to define boundaries (milestones) between the phases, but these vary very much between organisations and from project to project. In the following subsections, we highlight the most important phases and milestones of the drug discovery process and the key involvement of medicinal chemists.

3.1 Target Identification and Validation

A drug target is a molecular mechanism in a biological system which, if modulated (stimulated or inhibited), may lead to therapy for a disease state. Commonly, drug targets are proteins and nucleic acids that are disregulated in a disease. Druggable targets are those whose function can actually be modified by direct binding of a potential drug. Therefore, assessment of druggability is an important criterion in the target identification and selection process and, particularly, in the decision to start a target-based drug discovery programme.

Target-based drug discovery became popular in the industry about 30 years ago due to advances in molecular biology, genomics and high-throughput technologies (e.g. screening, combinatorial chemistry). It was believed that drug discovery based on single targets might become a routine process. However, success has proved elusive and this initial enthusiasm has evaporated. It is now well recognised that biological pathways involved in disease states are complex and frequently degenerate and so identifying a physiologically relevant single target is more difficult than at first thought. Many drugs (for example imatinib) initially discovered and developed using the single target-based approach were later found to exhibit multi-pharmacology, and this proved to be the basis of their therapeutic and commercial success. Besides the elaborate efforts to identify appropriate targets, a major bottleneck in the target-based approach is the rigorous 'validation' (see below) of a novel target. Consequently, phenotypic screening, particularly when applied to defined signalling pathways, has seen a

revival over the past decade. For bioactive molecules identified initially by phenotypic screening, considerable effort will be applied to identification of the target(s). Although not essential, having this knowledge eases the optimisation towards drug candidates and their development and regulatory pathway to the market.

For target-based projects, a solid basis for the decision to start work on a particular target is crucial. If this decision is wrong, then all of the work carried out in the project will be wasted. In earlier times, this decision was taken before involvement of medicinal chemists. Now their role in assessing druggability is vital.

The work leading to, and supporting, a solid target hypothesis for the deliberate decision to start a drug discovery project is often misleadingly referred to as target validation. True validation is achieved only when a new medicine is effective in the clinic and generally available to patients. In our opinion, a more appropriate descriptor is target characterisation, i.e., providing sufficient evidence that the potential target actually plays a role in a disease, and that its modulation may ameliorate or reverse a disease phenotype. Support for the hypothesis that *modulation of the target will produce a useful medicine* can be generated in many ways. These include observing genetic evidence in patients, such as familial susceptibility to disease, and identification of disease-specific mutations, using biomarkers of target activity in assessing progress of the disease, and knockout/knock-in studies in cellular systems, artificial organs and in laboratory animals. Some companies spend many months, or even years, on such biological validation or characterisation studies prior to the decision to start Lead finding. Validation by genetic and biological means has its pitfalls and may not predict the true action of target-modulating drugs. Thus, the huge spending on biological target validation before starting to search for chemical matter is at risk of being wasted. An alternative approach is to start (in parallel) with chemical target characterisation, and the recently created discipline of chemical biology is very much focussed in this area.

Bunnage *et al.* [8] assert that: 'Applying a rigorous chemical biology approach to the selection and validation of clinical targets will increase the success of drug discovery initiatives'. The emphasis should definitely be on 'rigorous' [9,10].

Some researchers attempt to use what they call 'chemical tools' to achieve this proof of concept (PoC). This is dangerous ground. A 'tool' is perceived not to be a drug candidate because it has some known liability which would prevent its development as a drug. This would be OK if all

criteria for the conduction of reliable and interpretable animal studies are met and the liabilities would just be prohibitive for clinical development, e.g., hERG or CyP inhibition. However, common liabilities include insufficient on-target selectivity or an inadequate pharmacokinetic profile. In the case of compromised pharmacokinetic profile, the tool could indeed assist the validation process if it is biochemically selective and can be administered so as to achieve effective concentrations at the proposed site of action; if the fault is lack of selectivity however, the off-target activity will frequently compromise the confirmation of the hypothesis. Most worryingly in terms of the finances of drug discovery, a failure to prove the concept with a 'tool' compound is rarely taken to show invalidation of the target. A well-designed experiment could indeed invalidate the approach and would dramatically reduce the costs of drug discovery by allowing projects to be stopped at an early stage. However, advocates of the particular project will usually find some excuse to continue the project; such as 'the tool was not good enough'. In order to be a useful tool, it must be accepted to be *good enough* to invalidate the target before such 'PoC' studies are initiated.

Bunnage *et al.* [8] outlined a four-pillared framework for validating a target for clinical purposes, highlighting the benefits of building each pillar through a rigorous chemical biology approach. These pillars refer to establishing that the compound penetrates to the site of action, engages the target and affects the activity of the target as well as showing that the altered activity has desirable phenotypic consequences. They emphasise the importance of chemical probes in complementing the molecular biological approaches to validation. 'Chemical probes have proven to be very impactful not only because they are complementary to genetic approaches …, but also because they have unique advantages. They can rapidly and reversibly inhibit a protein or a protein domain in cells or animals, be used in almost any cell type and reveal temporal features of target inhibition. When coupled with biological methods such as RNA silencing RNAi, they can distinguish between effects due to scaffolding and effects due to inhibition of catalytic or protein-interaction activity. In this way, chemical probes can be quite effective at invalidating drug targets. Multiple chemical probes can also be used in synthetic lethal screens to investigate the connectivity between distinct pathways. Finally, and importantly, the results obtained with chemical probes are more relevant for translational studies as they are more likely to mimic the pharmacology realized when a therapeutic small-molecule drug is used'.

Particularly when target characterisation has been performed by biological means only, it is crucial to challenge and verify the target hypothesis

throughout the whole project lifetime with appropriate probes, Leads and drug candidates as soon as they are fit for decisive cellular and animal testing. This programme of target characterisation/validation continuously reduces the risk of hypothesis failure and guides investment decisions.

3.2 Lead Finding (Includes Assay Development, Hit Finding and Hit-to-Lead)

The term 'Lead' has a floating definition in the community and ranges from (non-optimised) confirmed screening hits to compounds with *in vivo* proof of efficacy in animals. Early-stage pharmaceutical research has two milestones of utmost importance: demonstration of efficacy in a PoC study in a relevant animal model and delivery of the clinical development candidate. This is reflected in a two-stage optimisation in medicinal chemistry, i.e. firstly, establishing structure–activity relationships (SARs) and making the initial chemical matter fit for interpretable *in vivo* studies (frequently referred to as 'Hit-to-Lead', H2L) and, secondly, further refining selected series to qualify for studies in man ('Lead Optimisation', LO). We prefer to use the term 'Lead' for a partially optimised series with *in vivo* efficacy and with the clear potential for further optimisation, which is in line with the output from the H2L phase.

It is not our aim here to engage in semantics, but rather to emphasise the two important milestones. Therefore, we have amalgamated assay development, hit finding and H2L in this section, with *in vivo* proof of efficacy as the end point.

There are several widely used approaches to begin this process. These include random screening (HTS); biased screening (±virtual screening); and rational design, including structure-based, mechanism-based and target class-based design.

After choosing a disease to target, the research team's first task will be to develop target product profiles (TPP), one for the Lead with criteria enabling reliable animal studies to transition into LO and one for the candidate with criteria for candidate nomination to transition into development. These profiles constitute a list of compound characteristics and anticipated ranges required for transitioning into the next phase and depend on the primary indication and its available gold standard therapy, preferred route of administration, safety requirements for the primary indication and any knowledge on the competition. Thus, they are project specific and have to be adapted according to new information and results.

The next task is to select a series of biological assays that will form a screening process in which active compounds (hits) will be identified and filtered to remove those that do not meet the required criteria. Assay development is a highly important step in Lead finding and involves creating robust and reproducible assays with orthogonal read-outs to avoid assay-specific artefacts. The primary assay has to be miniaturised for the appropriate throughput and adapted as far as possible for automated procedures. It will ideally be complemented with a cascade of on-target biochemical and cellular assays, functional cellular assay, counter-assays for specific read-outs and unwanted or off-targets specificity/selectivity. *In vitro* ADMET assays will also be carried out.

The choice of primary assay type is the subject of much debate. Until the 1980s, the only available way of identifying active compounds was in assays of biological function, often even in pharmacological animal models. This approach is now usually carried out in cell function systems and is termed phenotypic screening. As understanding of genetics and molecular pathology developed, diseases were described in terms of the biological pathways and proteins (targets) whose function was disrupted. For the next 30 years, the dogma was that the target-based approach to drug discovery was the only way to go. When the target-based approach is adopted, it may involve a high-throughput binding assay followed by a lower throughput functional assay to confirm the actives. More recently, a body of opinion has formed that believes that our lack of complete understanding of disease processes has led to the relatively poor productivity of target-based pharmaceutical research [11] (see also Section 3.1). There are many cases in which we have learned that it is inadequate to study a target in isolation of the remaining biological context. In one set of examples, nature has developed redundant mechanisms to overcome modulation of a single biological target. In another, agonistic activity on an isolated receptor can lead to functional antagonistic activity in whole cells as receptor engagement results in internalisation and functional inactivation. This is exemplified by the action of fingolimod at the sphingosine-1-phosphate receptor [12]. Consequently, screening of whole pathways and in cells has received more attention and a return to phenotypic screening (sometimes called 'high content screening', or 'systems biology') is now prevalent. Even when the target-based approach is adopted, it is increasingly recognised that confirmation of functional effect is an urgent requirement following identification of the screening hit.

The choice of assay type has a big impact on the medicinal chemistry approach. Understanding the relationship between structure and biological

activity is complex even when a single protein is targeted. It becomes much more complicated when the assay read-out is the endpoint of multiple biological steps, any of which could be modified by the test compound. The medicinal chemist will need to contribute to the decision between target-based and phenotypic approaches. If the target-based route is selected, then choice of target assumes critical importance (see later). The next important task of the medicinal chemist is to decide which compounds will be subjected to the primary screen. The two broad approaches are screening a large compound set (often more than 1 million) or using a smaller set chosen to satisfy a particular feature of the assay. In the target-based approach, the second option will often use the structure of the target protein (or information from related targets) as a guide to compound selection. Structure-based virtual screening, as a prelude to the laboratory screen, has had some successes and continues to develop. Virtual screening cannot replace the physical experiments but may reduce the numbers of compounds to be screened and hopefully increase the hit rate. There is not a clear boundary between the high-throughput and focused approaches. The large compound set may be selected based on ideas of maximising diversity in coverage of chemical space or may be chosen based on drug-likeness or lead-likeness principles.

Other approaches to finding Leads are based on the structures of known active compounds including in some cases the natural mediator of a biological process. Historically, these have perhaps been the most productive. Fragment-based approaches [13], in which hits with very low molecular weight provide the starting point, and physicochemical properties in relation to potency are tightly monitored through the optimisation phase, have been receiving more and more attention due to several success stories. A prerequisite for an efficient fragment-based approach is the availability of structural information. The main challenge for the medicinal chemist is to start from very small molecules and grow them adequately in the multi-parameter optimisation process. This is often considered to be more straightforward than starting from already large, lipophilic molecules. In one ideal scenario, structural information on two discrete fragments binding to two different sites on the target protein allows the design of molecules with the two fragments linked to each other, usually resulting in a substantial gain in activity.

3.2.1 Hit Triaging and Hit/Lead Quality

The triage of a hit list (the set of actives from the screening approach) is a very important step in pharmaceutical research and represents a challenge for

medicinal chemists. At this stage, it is decided which chemical matter is further processed and optimised, and which is discarded. The hit list is 'cleansed' of undesirable compounds and prioritised for follow-up in a chemistry programme. Compounds may still be undesirable even if their initial biological data look promising. Medicinal chemists can contribute to hit list triage by careful application of filters based on structural, physicochemical and patent-related information. Decisions to eliminate compounds are generally made in a team environment in order to collect as much input as possible.

Triage is necessary since many well-curated screening libraries still may contain compounds that interfere with the assay read-out or have structural features or properties not compatible with the specific project goals. Such collections have often grown over a long period of time and do not represent state-of-the-art quality. Besides elimination or de-prioritisation of compounds with structural no-gos (generally toxic or unstable fragments, promiscuous compound classes, those causing interference with assay read-out), filtering and selection criteria may include physicochemical and biopharmaceutical parameters, ligand efficiency, 'rule-of-five' (see later), metabolic stability, chemical tractability and intellectual property (IP) aspects. Several useful computational methods are available to support hit triage and clustering of the hits into classes with a common or similar scaffold [14]. The final selection resides with the expertise and judgement of the medicinal chemist.

The quality of the chemical starting points and the Lead(s) are vital elements in determining eventual success. Poor selection here wastes a great deal of resource. Different aspects of quality require consideration.

The compounds to be tested must be of sufficient purity and stability (that is chemically stable as well as stable under the assay conditions) and be sufficiently well characterised for the test result to be reliably attributed to the drawn structure. This may seem obvious, but in the early days of high-throughput screening, this was often overlooked in the search for ever greater numbers, particularly at the apex of interest in combinatorial chemistry, more than a decade ago. Compounds may degrade over time in solution (companies usually keep their screening collections in DMSO solution over years) as well as in bulk. Therefore, it is essential to retest interesting primary hits either from freshly prepared solutions or even from re-synthesised material. Moreover, commercially available compound collections advertised for screening purposes often contain undesired structural elements since these compounds are easily and cheaply synthesised.

In organisations carrying out significant numbers of different screens, it became apparent that some compounds showed as actives in multiple screens and that particular structural elements caused this promiscuity. These were designated as PAINS (pan assay interference compounds) [15]. New substructure filters have been developed [16] for removal of PAINS from screening libraries and for their exclusion in bioassays and the concept has received wide acceptance. Even inexperienced drug hunters now have little excuse for falling into the trap of following such hits. Many compounds form colloidal aggregates in solution resulting in false positive read-outs. This feature has been extensively studied by Shoichet [17] and 'aggregators' are now routinely expelled from hit lists. A particular example of false positive hits occurs with compounds that polymerise on storage and form polyanionic surfaces that unspecifically interact with many proteins. The authors of a recent survey concluded: 'Remarkably around 500 related derivatives of N-phenyl-2,5-dimethylpyrrole are reported in numerous patents and publications as biologically active compounds' [18].

Higher quality implies a greater probability of successful progression through later stages of the project. Lipinski observed that successful orally administered drugs generally conform to a limited range of lipophilicity, molecular weight and hydrogen-bonding capacity and published guidelines to direct LO. Put simply, Lipinski's guidelines (rule-of-five) state that 90% of all orally bioavailable drugs have molecular weight less than 500, log *P* less than 5, fewer than 5H-bond donors and fewer than 10H-bond acceptors. Lipinski stated that 'poor absorption is more likely if these physicochemical limits are surpassed' [19,20]. Attempts to increase target affinity have typically resulted in increased molecular weight and lipophilicity. This has led medicinal chemists to consider 'Lead-like' physicochemical properties which leave room for the addition of mass and lipophilic grease to improve potency and still remain within the range of properties required for good pharmacokinetic outcomes. Essentially, these are more stringent criteria than Lipinski's rule of five and include restricting molecular weight (<350) and *c* log *P* (<3) [21]. A further extension of this thinking led to the concept of ligand efficiency, a parameter representing a combination of physicochemical properties with target affinity [22–24] and this is an important feature of the fragment-based approach described above.

When considering the makeup of compound sets (libraries) for screening, in addition to the physicochemical constraints described above,

the diversity of the set has to be decided. Two approaches are common: (i) maximise diversity in chemical space to increase the chance of a random hit, or (ii) focus on known areas where hits are likely to be more abundant. In the latter case, this will often be guided by knowledge of the structure of the protein target or by knowledge of other known hits.

Modern cheminformatics tools have significantly improved and expedited the process of hit list triage. Structural alerts, and even lack of novelty, do not automatically lead to the series being stopped, but do help with prioritisation.

3.3 Lead Optimisation

After Leads have been identified, they must be optimised to make the molecules fit for *in vivo* testing; first for testing in animals, followed by another optimisation for application in humans.

In this phase, the medicinal chemist plans modifications to the structure of the lead to deliver all of the required properties of the candidate drug.

These properties will have been defined at the start of the project in the TPP (see Section 3.2) and will include the required criteria for: efficacy, safety, exposure and developability (including formulation for the targeted route of administration, initial scale-up and optimisation of synthetic route, feasibility study for production). Many criteria must be satisfied simultaneously and it will often be the case that maximising utility in one of the objectives will compromise quality in another (the challenge of multiparameter optimisation).

Developments in recent years have placed more emphasis on prediction of outcomes rather than experimental observation in animals. This has led to an enhanced role for the medicinal chemist in designing aspects of developability into the drug candidate. For example, it is usual in today's projects for the medicinal chemist to be involved in designing positive outcomes for safety and pharmacokinetic studies. *In silico* predictors are valuable in the initial designs, and *in vitro* experimental results produce a training set for the next design cycle.

3.3.1 Efficacy

The true demonstration of efficacy will be achieved only in clinical studies in diseased patients, but increasing confidence that this will be a likely outcome must be generated during the LO phase. Usually, the prediction of efficacy in human will be driven by sequential determination of the binding affinity

and potency against the isolated protein target, then in the cell and eventually in a whole organism.

To achieve a pharmacodynamic effect, the drug must occupy its target in the patient at a sufficient concentration and for a sufficient time to modify function. We will discuss pharmacokinetics in Section 3.3.2, but more recently, it has emerged that residence time at the receptor is an important parameter for efficacy and not wholly dependent on pharmacokinetics (usually measured as concentration in plasma over time). Binding affinity is generally measured at equilibrium as K_i. It is now recognised that the on rate (k_{on}) and off rate (k_{off}), whose ratio determines the K_i, are important too [25]. The ligand residence time (LRT), defined as the reciprocal of k_{off}, often determines the efficacy of a drug in the whole organism.

If pharmacokinetic residence time is shorter than LRT, then a kinetic model is necessary to drive the decision-making on dose and therapeutic margin for *in vivo* studies. For anti-infectives, longer residence times may give less opportunity for development of resistance and more generally there will be consequences for safety assessment.

For the medicinal chemist, designs to modulate off-rates now come into the equation [25–31]. In this context, irreversibly and/or covalently binding molecules have experienced a renaissance [32,33] after decades of suspicion in drug discovery due to safety concerns. Moreover, consideration of the thermodynamic aspects of ligand–receptor interactions may help in designing efficient ligands [34,35]. Demonstration of target engagement will be an important contributor to decision-making in clinical development and the medicinal chemist will frequently be involved. In some cases, this will require access to radio-labelled analogues to allow imaging studies [36].

3.3.2 Pharmacokinetics

Lack of efficacy continues to be the most common reason for failure in the clinic, especially for molecules which are first in a mechanistic class, and even more for CNS diseases where there are no good animal efficacy models. To generate efficacy in the clinic, the drug must achieve a sufficient concentration for a sufficient time at its target in the right tissue. Tissue exposure is dependent on several physicochemical and biopharmaceutical properties of the drug; each property has to be in the right range and together they have to be appropriately balanced. Frequently, there is the perception and hope that property issues such as poor solubility can be overcome by formulation expertise in the drug development phase. Formulation techniques may help

to increase drug concentrations and to balance exposure over time, but it is clear that formulation can rarely work wonders and solve very poor compound properties.

Plasma exposure is relatively easy to measure, but relatively complex to interpret. It is derived from the combined effects of absorption, distribution, metabolism and elimination (ADME) and does not necessarily correlate with target tissue exposure. The real target is in the human, so in the LO (pre-clinical) phase, we are concerned with predicting human exposure. There are several layers to the prediction. Measurement of plasma levels following administration of the drug to animals allows calculation of plasma exposure, clearance and volume of distribution. If the requirement is for the drug to reach the central nervous system, this can be determined in animals. Analysis of these parameters in multiple animal species enables a reasonably reliable prediction of the human exposure—allometric scaling. It is not ethical to perform unnecessary experiments in animals and so, in order to evaluate a large number of compounds in the LO phase, a second level of prediction involves carrying out *in vitro* cellular studies to evaluate, for example, gut permeability, liver metabolism and plasma protein binding. A third level of prediction involves predicting *in vitro* biological results from measured physicochemical properties of the compound. Measured values for partition coefficient between octanol and water (log *P*/log *D*), pK_a and solubility typically contribute to pharmacokinetc prediction. Yet a fourth level of prediction involves only the computer. The physical properties are predicted solely from computational analysis of the drawn chemical structure. Substantial progress has been achieved in this area [37], but is not yet ready to substitute for wet experiments, particularly when entering new substance classes.

Early ADME evaluation, which is routinely used in the industrial setting, not only represents a technical challenge to find evaluation techniques which will be predictive, but also provides a huge knowledge management challenge. Building databases to collect the data is not too demanding, but using massively multi-dimensional data to inform decision-making is very much so. Today, and we believe that it will remain so for the next 20 years, the judgement capacity of the human brain is superior to any computational method for effective decision-making in LO. It requires broad interdisciplinary knowledge, experience and analytical skills to successfully make judgements in ways which are defensible in the face of scrutiny by the project team.

Many types of experiments assist ADME profiling and there are some good software systems for modelling whole animal/human PK. Key

properties influencing many other measured parameters are lipophilicity and (aqueous) solubility. Kinetic solubility is routinely measured in a high-throughput mode, but slower thermodynamic solubility is utilised only for selected compounds in more advanced projects. Lipophilicity can be measured by traditional solvent partition but is more routinely determined now by chromatographic methods. However, calculated values can be generated very quickly and are particularly valuable for ranking analogues within a compound class. Metabolic stability and clearance, respectively, are measured using liver microsomes or hepatocytes: the use of human systems and comparison with data from animal equivalents greatly improve the prediction of human pharmacokinetics from the whole animal data. Permeability is assessed using colon (CaCo2) or kidney (MDCK) cells. Plasma protein binding studies allow an estimation of the fraction of drug in the plasma that will be available to achieve the desired concentration at the receptor.

3.3.3 Safety

In principle, toxicity can be target related (modulation of the target protein causes toxicity) or compound related. In the latter case, this may be caused either by the off-target activities of the compound itself or those induced by metabolites. So-called 'idiosyncratic' toxicity has gained in notoriety in recent years and has been associated with the formation of reactive metabolites such as epoxides. Demonstration that there are no reactive metabolites is an additional study typically undertaken in the LO phase [38].

Project or compound failures due to safety concerns are significant: about 30% of projects/compounds, from LO to New Drug Application (NDA) filing, will fail for this reason. Many compounds generate some preclinical safety concerns, especially at high doses, so we need to carefully discriminate between those that are manageable, or not even relevant to humans, and those that do pose a real risk.

If a compound is going to fail, then we wish to fail early so as to avoid high downstream costs. No one relishes the prospect of failure due to lack of safety in the clinic. In the toxicology field, this is more problematic since there is little evidence that early studies are fully predictive of real human toxicology. Indeed, it is unlikely to be possible ever to demonstrate true predictability, since for ethical and regulatory reasons we are unlikely to want to test candidates that are predicted to show a safety risk. False positive prediction of safety problems will ensure that many potential candidates are unnecessarily discarded. Clearly useful data will be generated from study of

compounds which have caused toxic effects in human (true positives), but finding the true rate of false positive prediction is not achievable.

There are many ways of predicting toxicity with differing levels of complexity. Software programs are available to assess a chemical structure for so-called 'Structure Alerts' [39] but reflect only collected empirical knowledge and do not allow *de novo* identification of a risk of a new structural feature. In general, compounds with structural alerts will now be excluded in the Lead identification phase.

In vitro predictors include evaluation of the Lead against a wide range of potential off targets [40]. Prediction of mutagenicity based on *in vitro* studies was one of the first areas in which predictive toxicology was consistently applied [41]. A positive result in the Ames mutagenicity test almost always stops the progression of a candidate drug, before any animal toxicology studies are carried out.

With increasing knowledge of safety risks and their pharmacological basis, more and more safety considerations and experimental investigations have been shifted from later-stage development to the early drug discovery phase; for example, formerly, hERG inhibition was not assessed during early drug discovery but this is standard practice today. This adds further dimensions to the multi-parameter optimisation and increases the challenge of identifying preclinical candidates.

3.3.4 Multi-Dimensional Optimisation

The key parameters in moving towards identification of the final candidate drug depend on the TPP for the particular therapeutic option under consideration. As discussed, improvement in one parameter frequently negatively influences another. Therefore, a drug is always a compromise solution to a multi-parametric problem. It is rarely the most potent member of a series.

It is often easy to increase potency by adding 'grease' (for example alkyl chains, halides and alicycles) to a structure and thereby increasing its lipophilicity. The most challenging parameters to optimise are usually solubility, metabolic stability, bioavailability and the selectivity for a specific target. There are no universal best practices for simultaneously solving all of these issues in all projects.

The iterative cycle of design, synthesise, test, evaluate and redesign is usually steered by the medicinal chemist and has now become tremendously more complex. Computational methods help, but multi-dimensional optimisation cannot be computed in its entirety.

The screening cascade is no longer a case of simple gates. The concept of decision trees must now be replaced by landscape mapping where structure–activity contours are recognised in multiple dimensions simultaneously. So for a typical project, solubility, permeability, clearance and a range of safety indicators will all be evaluated to some extent in parallel with efficacy determinants. Then, compounds will be selected for individual more detailed pharmacokinetics/pharmacodynamics/toxicology evaluation before selection as development candidates.

The medicinal chemist is a key driver of this part of the process and must develop the skill and judgement to achieve the right balance of properties in a potential drug candidate. This will almost always require extensive exposure to a variety of project situations.

Medicinal chemists have the role of explorers in virgin territory, attempting to create a contour map of structure–activity correlations in multiple dimensions. The purpose is to have a sufficiently good picture that a route can be predicted to the promised land of a candidate that has the potential to meet all of the properties of the target product profile; i.e., it has to be fit for application in patients.

3.3.5 The Candidate Selection Decision

The process of creation of a new medicine has many phases. However, everything changes at the point when a candidate drug is selected. Up to this point, the emphasis is on finding an active compound and making new compounds that improve on the properties of the best compound presently available. Afterwards, all work is focussed on demonstrating that one compound can achieve a dose in humans that is sufficiently efficacious and safe to solve a medical need, and that an appropriate business model can be developed to make it economically feasible to bring the new medicine to patients.

Thus for the whole of the drug discovery process up to the point at which a Candidate is selected, the medicinal chemist is the focal point. A Lead structure has to be identified. Changes are made to the structure of the Lead molecule to modify the physicochemical properties that in turn modify the affinity and functional effect of the drug at its target and modify the ability of the drug to access its target in the biological system. The changes in structure also direct activity on other targets (which could lead to adverse effects) and also the way in which the organism handles the drug (ADME).

4. BUSINESS STRUCTURES FOR DRUG DISCOVERY

Towards the end of the twentieth century, a group of 20 or so large pharmaceutical companies exerted complete domination of the drug discovery landscape. It was not uncommon to see chief executives predicting more than 10% compound annual growth rate for the foreseeable future, despite the fact that within a short time period this would overtake total world GDP and could not possibly be achieved without an exponential increase in the number of new medicines launched. When it became clear that this strategy is not viable, merger and acquisition was the initial response. Companies no longer grew by internal innovation but by buying the pipeline of a competitor. However, this concept was also of limited success.

The bubble burst R&D output reached a peak in 1996, and in the following years the annual number of launches of new medicines declined. An increasing emphasis has been placed on improving research productivity and return on R&D investment, which are generally perceived to be low [42].

Significant changes were needed in the business model and many different approaches have been adopted.

4.1 FIPCo

Historically, a single company provided vertically integrated operations from research through development to marketing and sales. These fully integrated pharmaceutical companies (FIPCos) were very effective for 50 years. Indeed, they were so profitable in the 1990s that more consolidation was promoted by the consultants. Size is good for incremental advances and for managing the life cycle to extract maximum bang for the buck. Large organisations are generally less good in achieving innovation. Individual and technological 'disrupters' are shunned by the bureaucracies necessary to operate a very large operation. Thus, the big companies produced less and less internal innovation and 'external' innovation became a buzzword.

FIPCos are today encouraged by the management consultancies to 'exit research to create shareholder value' and to change research and development to 'search and development' (Morgan Stanley Research Report, 2010).

4.2 FIPNet

It is now very rare for a company to carry out all operations internally. Many pieces of work are outsourced. This might be to access external skill sets not

available within the company, to manage peaks and troughs in demand on resources or to achieve cost savings. This mode of operation has been described as a Fully Integrated Pharmaceutical Network (FIPNet).

4.3 Biotech

Venture capital funds have achieved some significant biotech successes in the past two decades. They have funded start-up drug discovery enterprises operating in a lean way with minimal internal staff complemented by some outsourced operations. Small companies should be more flexible and cheaper to operate but, in general, the biotech route has not delivered on the high expectations of 20 years ago. The companies suffer from a very high attrition rate when focusing on single assets and, particularly outside the USA, from chronic underfunding. Value generation in drug discovery cannot be easily accelerated when budget is a rate-limiting factor. The necessity to go for fund-raising over and over again, and the associated time pressure, frequently leads to poor decision-making in the critical phases. Immature products are frequently over-promoted and critical flaws overlooked, leading to increased attrition. This statement holds true mostly for asset-focused biotech companies and not so much for platform technology or service providing companies. Despite the many disappointments, there have been some successes, but in general, the successful companies are then swallowed up in acquisitions by the large pharmaceutical companies.

4.4 CRO

The growth of external providers of the technical skill sets for drug discovery Contract Research Organisations (CROs) has provided an opportunity for investors to adopt a different, virtual business model in which the owner of a portfolio of assets (projects) holds the funds and the operations are carried out at a service provider.

The CROs have several different modes of operation. A pure fee-for-service company generates experimental data and the rights to this IP are wholly owned by the client. The range of providers includes those that only carry out experiments to the client's design through to those that provide all of the design, the client simply providing the funding and cost control. All of the many facets of drug discovery from target discovery through candidate identification and clinical development can be sourced from this type of business structure. Some providers can offer the 'one-stop shop' preferred

by some clients, while others provide only single skill sets and the client puts together a supply chain of providers.

4.5 Hybrid

Many of today's most interesting companies fall into the hybrid category with a sliding scale between the two extremes of low risk/low reward to high risk/high reward for investors.

At the low end, we have CROs who adopt 'shared risk' with clients. They accept a lower fee and receive a bonus for success. They have no rights to the products.

Next, we have the 'Alliance' model. This company has different types of collaboration but broadly they agree a disease area with a client and generate project ideas for a relatively small access fee. If the client selects a project, that triggers a payment which is used to progress the project through a series of milestones, each of which triggers a payment that more than covers the cost of advancing to the next milestone. If at any time the client declines to take the project on to the next stage, rights to the IP revert to 'Alliance'.

Many of the hybrid companies are built on a particular technical or platform approach (e.g. Addex, Heptares, Astex) where their ability to create alliances derives from their particular technical skill.

A different hybrid version (at various times operated by Evotec among many others) is to operate largely as a fee-for-service company and to use some of the revenues to fund the generation of fully owned IP.

Some companies mainly do their own drug discovery and occasionally, to reduce the cash burn, accept an alliance fee for particular projects often with milestone payments (with or without some retained IP rights).

4.6 Social Enterprise

All of the operator types described above are regular companies limited by shares aiming to deliver financial returns to their shareholders.

More recently, a different type of operator has emerged. Here, the main aim is more altruistic. Scientists frustrated by lack of take up of their ideas, and governments unhappy with the economic output from their investments in academic research, encourage the early-stage translation of ideas through the first stages of de-risking in order to make them more attractive to investors.

As the large pharmaceutical companies wind down their discovery operations, there is a burst of growth in academic drug discovery operations.

A recent survey [43] identified 78 such organisations in the USA working in small-molecule drug discovery. Many of these have joined a newly established Academic Drug Discovery Consortium (ADDC) which has more than 80 members worldwide [44].

This situation is rapidly being replicated around the world. The UK academic drug discovery operations were recently reviewed [45,46].

What exactly constitutes an academic drug discovery centre is loosely defined [47] and essential elements of professional drug discovery (for example project management, assessment of ADME parameters, professional medicinal chemistry) are frequently missing in academic organisations. An efficient paradigm for early drug research with important enhancements to the pure academic setup is the concept of professional translational research centres [48]. These build on scientific excellence in academia and professionally translate basic research results into industry-standard drug research projects.

The primary education and knowledge generation missions of an academic institute are not easily aligned with those of a drug discovery enterprise. The disadvantages of the academic system can be avoided by establishment of autonomous institutes. This avoids the potential financial risk to the education system and removes the problem of conflict of purpose. Six such autonomous drug discovery institutes from around the world have formed a global alliance and no doubt more will join [49]. Some of these are configured as charitable foundations where profits are used to grant fund more projects, and others are set up as social enterprises in which all profits are reinvested. It is very common for governments and academic institutions to be important stakeholders in such institutes. Various legal structures are possible, but the overall aim is to achieve focussed high-quality drug discovery in an enterprise that reinvests profits into sustaining and growing the institute rather than for the financial benefit of shareholders.

5. MEDICINAL CHEMISTRY EMPLOYERS

The conclusion from all this turmoil in the business of producing new medicines is that the employers of medicinal chemists are now very much more diverse than was the case a decade ago and require differing talents and skill profiles (all-rounder versus specialist). This creates great challenges to the medicinal chemist in choosing a career path and in ensuring appropriate education and training.

The operator manages the laboratories in which the experimental processes of drug discovery are carried out. This is where the experimental

data underpinning the IP residing in the drug itself are created. The funder of the operations may still itself be the operator (as in the FIPCos), but frequently the operator is providing medicinal chemistry as a service to the funder.

The medicinal chemists themselves can find employment in the laboratories of the operator or (less frequently) in the offices of the portfolio manager, e.g., to manage CRO activities. In large organisations (FIPCos), this difference is captured in the debate on organisational structure. Should the organisation units be project- or therapeutic area-centred? Or should they organise around scientific discipline? Should the medicinal chemists be distributed to the projects or provided from a central function as a service to the project? Usually, a matrix system with several reporting lines is a practical solution, but requires employees who can do creative work in such an environment.

We have seen in the above discussion of the drug discovery process that understanding the critical relationship between chemical structure and biological properties lies at the heart of successful creation of new medicines. This is the core competence of the medicinal chemist. Whatever business structure employs the medicinal chemist, whether as a service provider or as a driver, it must find ways to recruit and nurture the best practitioners who can develop specific additional skills required for the type of organisation and position, such as communication, organisation, mentoring, leadership and negotiation competence.

For those organisations that are unable to host an internal critical mass of medicinal chemistry competence, including funders of a virtual portfolio of projects and small (possibly single project) start-ups, the decision on how to access expertise will greatly influence success and sustainability. Should the work be done in house or outsourced? Outsource the design of compounds or only the synthesis/sourcing? Employ an in-house fully competent medicinal chemist or use a consultant? All of these can succeed, but in the long term, those organisations that do not have the critical mass will rely on others to educate and train the next generation of competent people.

6. EDUCATION AND PROFESSIONAL DEVELOPMENT FOR MEDICINAL CHEMISTS

The development of a medicinal chemist will cover the key skill sets for drug discovery: clear understanding of the team goals (TPP) shared with all the other disciplines, the ability to select the most appropriate technical tools, competence in experimental design and the vision to map

SAR landscapes. In addition to these skills that have been discussed in Section 3, IP management is another core competence. Protection of the IP surrounding a new therapeutic is critical to its commercial success. For new molecular entities, the medicinal chemist will always be a crucial part of the IP management. This will often be as an inventor, but even when this is not the case, it is the documented work of the medicinal chemist that will form the description of the 'reduction to practice'. It is the medicinal chemists who will know what is possible (from both the SAR and the synthetic accessibility point of view) to extend the claims and how likely it is that competitors will follow similar tracks, so they will be influential in determining both the scope and the timing of the filed patent. Very broad scope in an initial filing that cannot be reasonably exemplified within the priority years do not help and may even be obstructive for the company's own later filings, and the timing of the first filing impacts the competitiveness but also the patent life span and, consequently, commercial success of marketed drugs. IP management is almost always a skill that is learnt on the job, through interaction with professional patent attorneys and experience in drafting cases.

The great breadth of skills required in a fully functional medicinal chemistry operation creates a conflict for educators and careers advisers. Should their teaching be aimed at breadth or depth?

In earlier times, the route was straightforward; a deep training in one of the required skills was followed by immersion in a drug discovery organisation where the primary skill was fully utilised and over a period of many years the broad range of skills was added on the job, driven by participation in a range of projects.

For many years, most medicinal chemists began their career with a deep training in organic synthesis, often to post-doctoral level. This reflected the importance of sourcing the compounds to be tested as a pressure point in earlier versions of the drug discovery process. This process is now very different. The importance of superior molecular design is recognised as a critical success factor in drug discovery and development. Understanding the structural properties that impact protein binding and function, permeability across membranes, metabolic liabilities, safety profile and many others are now just as critical as sourcing the compounds. Synthesis is still an important component, but this is increasingly carried out in organisations other than the one employing the medicinal chemist (e.g. CROs). Knowledge of what it is possible to synthesise with reasonable resources will of course remain an important component of the design process.

This evolution implies that the deep initial training of a future medicinal chemist could be in one of several relevant disciplines, ranging from organic synthesis through structural biology, computational chemistry to analytical chemistry, biochemistry, molecular biology or cell biology.

Any of these and more can be the starting point for addition of the wider range of skills of the medicinal chemist.

The organic growth of the complete, rounded medicinal chemist is now possible only in a few organisations. Organisational change occurs frequently and widely across the industry. Careers with most of the operators have a shorter timeframe than before, and this provides opportunities for different routes of career development.

An alternative approach is to learn medicinal chemistry in an academic setting. At the undergraduate level, the aim would be to expose the student to the wide skill set. At the Ph.D. level, this would usually involve in-depth immersion in a single project, often covering a wider range of skills than the corresponding medicinal chemist over the same time period in a traditional pharmaceutical company. The drawback of this path is that many academic organisations do not have the infrastructure and know-how to assess all of the critical parameters required for professional drug discovery. Thus, the focus often is on potency, neglecting other important drug properties. This shortcoming is being addressed by several dedicated academic drug discovery groups and the educational path should benefit. Our view is that education of medicinal chemists in academia with the necessary infrastructure should be fostered and strengthened. Intensified exchange between academia and industry to gain from experience and know-how from both sides, including exchange of personnel, will help.

After a broad foundation, depth in one or more of the individual skill sets can be added later in response to specific requirements of the job/project. Sometimes, this in-depth learning will come from colleagues and often from external suppliers of skills. Size of the operation is critical for efficient know-how building and transfer. Most employers (even large pharmaceutical companies) will now use external providers of specific skill sets, and the present-day medicinal chemist may learn this skill in depth by managing a contract with an external provider.

Employers are diverse. It is now unusual for any one organisation to have the critical mass in medicinal chemistry (including the synthesis aspect) that encourages an in-house nurturing of the knowledge base. Project-based medicinal chemistry groups whether in small companies, 'performance units' in large companies or CROs have little 'spare' capacity to promote

training or to develop and publish principles of medicinal chemistry. Developing principles of medicinal chemistry used to be a key role for the medicinal chemistry functions of large pharmaceutical companies. It is now more often left to academic groups.

The role of CROs as reservoirs of drug discovery skills has not yet been widely recognised.

Exposure to many successful and unsuccessful projects is a key component of learning. Those CROs providing 'integrated' drug discovery services have a great opportunity to effectively develop high-level skills and to be knowledge leaders. Impediments, including a heavy focus on cost containment and the need for firewalls between projects, will need to be overcome. The dilemma between 'apparent productivity' (many reactions by rather cheap means to please the customer by numbers and low costs) and 'efficient service' (careful design and going for the high-hanging fruits, too, to professionally move the project forward) has many facets in medicinal chemistry and is amplified by interfaces, distance and cultural differences.

Many specialist technologies are already incorporated in CROs. Indeed, frequently CROs are attractive to their clients because of their technical expertise, for example, in crystallography or catalysis. The ability to focus on a single skill and provide to multiple clients allows them to develop critical mass and to become world leaders in their skill set.

Another facet of pharmaceutical business fragmentation is an increased willingness to form partnerships to address shared problems in a precompetitive environment. Organisations such as the European Lead Factory, the Structural Genomics Consortium and several others employ many medicinal chemists. There is inevitably much discussion of the boundary between competitive and precompetitive research.

Crowdsourcing medicinal chemistry provides a further opportunity for driving forward the science. Several initiatives encourage input from medicinal chemists wherever they operate. Medicines for Malaria Venture (MMV; www.mmv.org) has led the way. GlaxoSmithKline, the Genomics Institute of the Novartis Research Foundation and St. Jude Children's Research Hospital released the details of 20,200 compounds active against malaria (malaria hits) into the public domain. They also made available physical samples of 400 diverse active compounds. All that is asked in return is that the recipient continues the virtuous cycle of sharing and collaboration by releasing their data into the public domain.

The Drugs for Neglected Diseases initiative (www.dndi.org) has adopted a similar approach.

MMV also launched an open source drug discovery programme using a 'crowdsourcing' model, initially working with scientists in Australia. Dr. Mat Todd at the University of Sydney posts all the details of his research online in an electronic lab book (http://opensourcemalaria.org/). As posts are made, alerts go out via social media to source expertise from the global scientific community. The team also holds regular open web conferences, which anyone can join, to discuss and contribute to the project.

In the antibacterials field, an Australian lab (www.co-add.org/) now invites all chemists to send compounds for testing against drug-resistant bacteria. This initiative is funded by the Wellcome Trust.

7. THE MEDICINAL CHEMISTRY 'PHENOTYPE'

Looking around at our medicinal chemistry colleagues, they seem to form two general types. In one form, the reductionist approach prevails. Biological effects are driven by molecular interactions which can be described as the sum of the quantum mechanical components of the system. Another equally excellent group sees patterns and in recognising the patterns can predict the effect of the next structural modification. Some of the very best medicinal chemists appear to have split personalities and can operate in both of these modes simultaneously.

7.1 Sporting Analogies

As we have seen, the components of medicinal chemistry are many and diverse. The vast number of techniques now available to the medicinal chemist might imply that it is necessary to be proficient in them all, the decathlete approach. But drug discovery is a team sport and the individual needs to know the range of valuable approaches available, but not necessarily be expert in all. Medicinal chemists need to be able to choose the appropriate technology for each individual project situation and then find an expert provider if it's not themselves. Still, to be able to fulfil this task efficiently they must have a broad basic skill set and to know which technologies exist and where. Medicinal chemists are often integrators of these skills. So rather than a decathlete, a better sporting analogy could be the scrum half in a rugby team who sees a lot of the ball and distributes it appropriately to their teammates, who each have their own expertise. A shortcoming is that the ball in rugby has to be passed backwards, so maybe an even better fit is to the playmaker in a soccer team who receives the ball frequently, can pass it in any direction and, of course, scores the occasional goal if possible! Most

importantly, the spirit in the team has to be right with all players sharing the same overall goal.

It is clear that not all medicinal chemists can usefully become broad super decathletes or even excellent playmakers. There is ample room in medicinal chemistry for many different individuals with individual skills. There is opportunity for the expert javelin thrower as well as the broad-skilled all-rounder. Different cultural appreciation may exist for expert versus all-rounder, and we have to work jointly to overcome this potential issue. In our experience, there are large cultural differences, for example, between different geographical regions or between companies. Some organisations value teamwork, some place more emphasis on individual contribution.

7.2 Language

To be fully effective, the medicinal chemist must be able to adapt to, or translate, the technical languages of other team colleagues, and understand the cultural differences between the many disciplines, ranging from non-reductionist systems biologists to rules-driven development folk.

The translation requires simplification without loss of scientific rigour and allows the chemist to participate in other discussion forums, including development, commerce and public understanding. This important skill facilitates collaboration across disciplines.

7.3 Mother

The new molecular entity that becomes a therapeutic is conceived and first sees the light of day in the medicinal chemistry laboratory. Medicinal chemists therefore often see themselves as the mother of the drug. Like most mothers, they will want to nurture the baby through the whole process and even when it fledges, leaves research and emerges in development, progress is followed with proprietorial interest. Indeed, some medicinal chemists are motivated to change career direction and take on roles in development to follow their emerging adult progeny.

7.4 Continuous Professional Development

There is no slow down in technical advance. It is important that medicinal chemists add to their already large range of knowledge areas and influence more widely. When medicinal chemists are involved in target selection and when they are involved in business direction, better results are likely.

Constructing a team with all of the important components is the key to success. Since each project will require different skills, flexibility is a key parameter in selecting employees. Fragmentation in the industry has led to big changes. In small organisations, it is likely that there will be more broad-skilled people and the super experts will probably be more happily employed in CROs where they can provide their skills to many 'customers'.

8. CHANGING PARADIGMS

Each decade has its own 'new paradigm' for drug discovery. In each case, the advance has been significant, but has had the unfortunate effect of developing hubris and encouraging herd behaviour as adherents believed that this really was the ultimate solution, and provided a recipe for successfully creating new medicines. In addition, the environment and conditions for the pharmaceutical industry have seen considerable changes. While research and development were more or less separate organisations and money was not a real issue in the golden ages, this is very different today. A very positive change in industry was the fostering of interdisciplinary teamwork which has become an accepted success factor particularly in today's drug research.

8.1 1970s: Target-Based Drug Discovery

Histamine antagonists and ACE inhibitors were among the first 'blockbuster' drugs, and the focus on biochemical targets and target families rapidly took over from phenotypical modification *in vivo* as the only way to do drug research. The rapid control of the newly discovered human immunodeficiency virus was greatly facilitated by its small genome (only nine genes) and the discovery of a relatively few host proteins important to the virus life cycle. It took several decades for a substantial body of opinion to realise that undue emphasis on this one approach could be responsible for poor productivity.

A retrospective analysis of the target-based discovery approach to antibacterials provokes a more realistic appraisal [50]. GSK evaluated 300 targets in 7 years with no new medicines. Even the relatively simple lifestyles of bacteria do not seem to be amenable to this approach. At the same time, phenotypical assay development has undergone great advances, and medicinal chemists are learning to live with the more complex SAR analysis that is needed.

For some human diseases particularly those with well-defined genetic causes (such as some cancers), the target-based approach may still be the most appropriate.

8.2 1980s: Structure-Based Drug Design

There is no doubt that those of us who saw the first pictures of our compounds co-crystallised with their protein target were inspired to believe that this was indeed *the* solution. The few occasions when a designed structural modification resulted in improved activity mirrored by the predicted new bound structure caused us to downplay the many more examples where the structure gave a post hoc explanation for an unpredicted result. Cognition bias was recognised only belatedly, after the herd had formed.

The legacy of 'Beautiful Targets' [51] is still a useful contributor to target selection.

8.3 1990s: Large Numbers; HTS and Combinatorial Chemistry

Industrial drug discovery became a numbers game with measurable (countable) goals also affecting medicinal chemistry. Amplified by the introduction of new technologies like combinatorial chemistry and high-throughput testing, the preferred strategy in many industrial medicinal chemistry groups shifted more towards producing a large number of analogues driven by the attitude: 'we synthesize what we can rather than what we believe is the best molecule' [52].

Who could disagree with the notion that more experiments would certainly give more positive results and a clearer direction? It turned out that too often more in quantity terms led to very much less in quality. Not only did we not produce more drugs, we consumed vastly more resources getting there. It took too long to realise that buying more lottery tickets when the number pool is very large is a poor investment strategy.

8.4 2000s: Metrics

This period was characterised by increased awareness of the importance of the right compound properties and more integration of development aspects into research (developability, formulatability, toxicity assays). Fragment-based approaches and the concepts of ligand efficiency [22,53], lipophilic ligand efficiency [54] and many other similar descriptors came to dominate medicinal chemistry thinking. More recently, the numbers-based

approach has in turn come under criticism [55] and the debate as to its value continues [56,57].

8.5 2010s: Kinetics and Thermodynamics of Binding

Better detailed understanding of the ligand–receptor interaction [58], target engagement and length of occupancy has led to better design and more effective translation into clinical efficacy [59].

9. FUTURE DIRECTIONS

We are of course not able to predict the future. However, it is already clear that some of today's advances will find increasing roles in the search for new therapeutics and will probably be added to the general inventory of key knowledge strands for the medicinal chemist.

Peptides have seen a revival recently in pharmaceutical research with main efforts directed towards solving problems of their delivery and stability. Based on cyclic peptides and natural products, substantial interest in macrocycles as potential therapeutic agents has emerged [60] as these compounds may offer advantages with regard to drug-like properties. RNA-based therapeutics may also play an important role in the future [61].

Large molecules, mostly proteins, have a greatly increased role in therapy. Chemical modification of proteins to address their 'drug-likeness' deficits in terms of stability and distribution or to use their properties through conjugation to deliver small molecules more effectively to their targets will continue to expand.

One rapidly growing field involves harnessing natural systems. Most of the historical advances in pharmaceutical intervention have come from administering drugs that bind directly to a human target and directly modulate its function to reduce disease symptoms. As chemical biology advances, we are learning how to harness the natural regulatory processes.

9.1 Regenerative Medicine

Regenerative medicine is an emerging, multidisciplinary science that aims to replace or regenerate human cells, tissues or organs, to restore or establish normal function. Research on the potential of small molecules and small-molecule drugs in regenerative medicine is currently increasing [62]. This includes enabling novel cell therapy approaches and augmentation of endogenous cells for tissue regeneration, facilitating the generation of target cells

for cell therapy, improving the interactions between cells and biomatrices for tissue engineering, and enhancing endogenous stem cell function for tissue regeneration. All of these approaches may need small molecules designed, for example, to support cell expansion, stem cell differentiation or *ex vivo* cell treatment. In regenerative medicine, the focus is on activating adult stem cells with small-molecule drugs and generating target cells by small molecule-induced cell fate conversion.

9.2 Proteolysis-Targeting Chimaera (Protacs)

The natural process for removing proteins that are damaged or are no longer required involves modifying them by ubiquitinylation which targets them for the protein degrading systems in the cell. Attempts to use this system for knocking down proteins involved in disease processes are now gaining momentum [63]. This approach has great potential value in validating targets as well as a new approach to therapeutics.

10. CONCLUSIONS

The technical processes of creating new medicines and the business environments in which they are carried out have undergone, and continue to undergo, dramatic change. Disease biology is complex and multifactorial, and patients have individual characteristics. There is and will be no 'new paradigm' applicable to all therapeutic challenges. There is no one-size-fits-all answer. As new technologies and approaches emerge, they each add to the armoury of the drug hunter and need to be included in the repertoire. Each new medicinal objective requires its own tailored solution. The real skill of the medicinal chemist practitioner is the ability to choose the most appropriate approach for each individual project situation and then to be able to operate the approach with technical expertise.

Present business trends under-emphasise the production and development of new medicinal chemistry talent. Educators and those involved in creating and driving sustainable drug discovery businesses must combine to provide the environment in which the next generation of successful medicinal chemists can evolve and thrive.

Careers that provide the opportunity to continuously develop intellectual skills and use them for the direct benefit of humankind at the same time as creating valuable economic output are rare. Attracting the next generation into our profession should therefore not be difficult. The education and professional development of the next generations of drug hunters is critical.

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