Foreword to the First Edition

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

I am delighted to have been invited to write an introduction for The Handbook of Medicinal Chemistry: Principles and Practice. The editors and authors have played an outstanding role in covering all of the major components of modern medicinal chemistry in an expert and timely manner, within a comprehensive handbook relevant to newcomers and experienced scientists alike. This volume will be a pleasure to read through, and then to pick out relevant sections for in depth consultation. I am sure Principles and Practice will be in constant use, as different problems arise in drug discovery projects almost on a daily basis, and will become essential reading for medicinal chemists of whatever background and experience.

An overview of the dramatic progress we have made with healthcare quality shows that life expectancy has consistently risen over the past century with an increase from 60 to over 85 years for women in most industrialised nations. Similar trends are evident for men and equally importantly, the developing world is now moving in the same direction. While improved standards of hygiene, nutrition, housing and other factors are obviously important, it is estimated that 40% of the recent increase in life expectancy in the US is due to modern medicines largely discovered by the pharmaceutical industry:[1] powerful antibiotics are available to treat life-threatening bacterial infections; hypertension (the silent killer) can be controlled by any number of once-daily therapies; elevated cholesterol which is a major cardiovascular risk factor, is well managed with statins, while H2 antagonists and even proton pump blockers are available over the counter to treat gastric ulcers. When HIV/AIDS appeared on the scene in the early 1980s, it was considered a death sentence and control was thought to be beyond our reach due to facile transmission and potential for resistance. Today, over thirty drugs from six mechanistic classes are available, and those in the West who contract the virus have enjoyed much improved quality of life and longevity. Importantly, similar benefits are now emerging in the developing world where for example, life expectancy in Kwa Zulu-Natal has risen from 49 in 2003 to 60 years in 2011 as affordable anti-retroviral combinations became available in the public healthcare system. Hopefully, recent headlines from The Economist such as: “The end of AIDS? How 5 million lives have

The Handbook of Medicinal Chemistry: Principles and Practice, 2nd Edition
Edited by Simon E. Ward and Andrew M. Davis
© The Royal Society of Chemistry 2023
Published by the Royal Society of Chemistry, www.rsc.org

been saved and a plague could be defeated" are now within sight, and a fair balance between drug pricing and health benefits will become commonplace.

Despite such outstanding success, there are still tremendous healthcare challenges facing medicinal chemists and the whole drug discovery community. We all know that cardiovascular disease (CVD) is a major risk factor responsible for over four million deaths in Europe each year, but few realise that 80% of global CVD mortality actually occurs in low- to middle-income countries which are disproportionately affected. The prevalence of obesity in US adults will grow to 50% by 2030, and it is also estimated that 92 million Chinese already suffer from Type 2 diabetes. While malaria, TB and HIV are still scourges in many parts of Africa, non-communicable diseases killed 36 million people in 2008 which represents 63% of total deaths, with the majority occurring in emerging nations. In any one year, 40% of Europeans will be affected by some type of brain disorder with total annual costs of care around Euro 800 billion, more than CVD, cancer and diabetes combined. Mental depression is responsible for 38% of all morbidity and 23% of Quality-Adjusted Life Years (QALYs) lost, whereas the corresponding figures for cancer are 3 and 16%, respectively. The WHO has forecast an impending disaster due to unchallenged increases in antimicrobial resistance, but only four new classes of antibiotics have been introduced over the past 40 years. In response to these major threats to health and well being, the demand for new medicines will continue unabated, albeit with different emphasis on quality of life or longevity depending on regional differences in economic and social development. However, new paradigms for research focus, organisation, cooperation and funding will be required, as we adjust to an ever changing scenario of contracting Pharma and withdrawal from major therapeutic areas. This introduction offers a personal perspective on some factors that may influence success and failure in drug discovery, and suggests how the sector might learn from the past and evolve in the future.

Size and organisation are key factors for innovative drug discovery which have been overlooked in endless rounds of mergers and acquisitions over the past decade, and the relentless drive to international research conglomerates. During the period when we were most productive at the Pfizer research laboratories in Sandwich, our total staffing was probably around two to three hundred, but that period witnessed outstanding discoveries such as amlodipine, diflucan, doxazosin and sildenafil. Our research was driven by dedicated scientists working together in multidisciplinary teams towards common objectives within a supportive, but focussed environment. Unusually, drug metabolism experts were also integral members of discovery projects which provided a significant competitive edge, as we did not have to beg, borrow or steal from development which was the norm throughout Pharma at that time. While we fully understood the need to compete internationally, we operated largely on a local and personal scale where a trip to the US was an annual treat, not a weekly routine. We all knew each other, managers and directors walked the job, and we were not distracted by administration. Scientists were constantly in and out of each other's laboratories as we had a hunger to generate, share and exploit new data that would drive our projects forward. Face to face discussions were the norm, and stimulated a level of intellectual challenge far beyond impersonal e-mails and text messages. The current journals section of the library was a focal point for discussions where we swapped ideas as we jostled for the latest articles,

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

but paper copy has largely disappeared and individual online access may not generate the same thought- provoking synergies unless alternative communication networks are established. In addition, we valued our "Tribal Elders" who had "been there, done that" and freely shared their experience, but successful role models have largely disappeared in today's cost cutting climate. However, the added value generated through a mentoring and supportive culture coupled with institutionalised learning cannot be over estimated.

As we grew we had to adapt, and I became drawn to the concept of the Roman Centurion who traditionally leads and cares for 100 soldiers which seemed a sensibly sized unit, particularly in a research environment. When there were 100 chemists in my discovery group, I knew them all and what they were doing, and I was also able to engage at a personal level. However, as the group expanded it became more difficult to maintain that level of interaction, and informal discussions were diluted. Dunbar's number of 150 is an estimate of the social contacts humans can cope with, obviously at differing levels of engagement, which is roughly in line with the Centurion concept. The average size of a village in the Domesday Book of 1086 was also around 150, and any further increase stimulated migration to form new settlements. These numbers intuitively feel right as they reflect the importance of personal contact, and also address the critical mass necessary for survival. Similar considerations should underpin drug discovery organisations where large groups should be broken down into nimble, multidisciplinary units that can be managed and led on a personal scale. Teams should be largely autonomous but accountable, with innovation and a data-driven culture recognised and rewarded, rather than the consensus management and upward decision making that has ossified Pharma in recent years.

Critical mass is probably more important than size *per se* as the ability to respond rapidly to breaking science can make the difference between success and failure. For example, we quickly realised that half a dozen chemists on a lead optimisation project would not be competitive, whereas 12 to 15 could hold their own. However, we could never manage the teams of 20 to 40 that others mobilised as duplication, poor communication and a loss of personal responsibility inherent in such large groups compromised productivity and motivation. Innovative scientists often want to be different, but some can drift into peripheral activities with a lack of focus and commitment to team objectives. Crucially, the concept of critical mass and nimble research units became confused with absolute size in the fruitless drive to build the largest R&D organisations. Even before the merger with Wyeth, Pfizer had an annual R&D budget of nearly $8 billion with thousands of staff spread over eight centres on three continents, which may not be conducive to a personal or nimble approach. The negative impact of mergers and acquisitions on productivity is well documented[2] as research simply cannot be effectively managed in such massive units, nor can innovation survive, particularly with multiple locations, cultures and ever changing leadership. Technology can be expanded in a modular manner and centralised facilities for HTS, gene sequencing and other service operations are efficient and cost effective, but innovation simply does not scale. If readers were to take one key message from this introduction, it would be my strong conviction that drug discovery is a personal and shared experience, not a metrics-focused, mechanical event. So many times, successful projects are driven by a small

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

core of dedicated champions with a burning desire to address particular medical needs, working together in a research-friendly environment not dominated by numbers.

Hype and premature over-investment in new technologies are other examples of how Pharma lost its way with the drive towards "faster, cheaper, better," but quality was lost in the pursuit of numerical goals. Most companies thought that industrialisation of drug discovery was the way of the future and that attrition need not be improved if the number of candidates entering development was significantly increased. Numbers and metrics became key drivers and innovation and personal accountability were lost in the process. Gone were the days of research proposals that laid out a biological rationale and thoughtful chemistry plans that were subject to rigorous challenge, and HTS assumed the default mode for new projects. HTS became a macho competition across Pharma with migration from 96 to 384 to 1536 well plates, and the drive to generate millions of data points over the shortest time frame. However, assays were often not robust, and quality control was poor. Compound collections contained everything chemists had registered, and it took some time to weed out frequent hitters, reactive intermediates and undesirable structural flags that were never intended to included in screening files in the first place. Unfortunately, re-building these collections also became numbers driven as it was easy to impress senior managers with the claim to synthesise millions of peptides overnight, but without adding that these compounds had little utility for drug discovery. Combinatorial libraries constructed from simple, non-peptide building blocks suffered a similar fate as focus on "what we can make" rather than "what we should make" led to large collections of closely related compounds with low value for screening, particularly as mixtures. Some Pharma companies responded by investing up to $100 million in building diverse, multi-million compound collections, but such large files are rarely screened routinely as representative sub-sets usually provide an idea of the relevance of the overall library to a particular target. However, it is encouraging that HTS has matured considerably over the past decade, where greater attention to assay reproducibility and compound quality has been rewarded with viable hit matter identified much of the time. More recently, advances in computational chemistry and structural biology have led to the integration of virtual screening with smart HTS which has further increased success rates. Such improvements are a tremendous advance, but the time-scales and resources required for new technologies to reach maturity are quite sobering.

Of course, the allure of HT-everything drove massive investments in numerous other technologies including every "omics" under the sun, often through fear of losing out to competitors rather than an appreciation of real value or time scales involved. The Gartner Hype Cycle neatly summarises new initiatives passing through a technology trigger, peak of inflated expectation, trough of disillusion, slope of enlightenment and plateau of productivity that we have all experienced. Multiple external collaborations often proved a distraction from drug discovery, and some major investments from the 1990s are still way off delivery. For example, billions have been invested in DNA- and RNA-based therapies as interest shifted from antisense to ribozymes to RNA interference, although it was obvious that delivery would be a common problem that still has not been solved generically. However, the first systemic antisense drug was approved in 2013, some 23 years from "a blank sheet of paper to market" which again brings

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

home the timescales required for new technologies to bed-in and mature. Gene therapy involves the simple concept of introducing a gene into a cell to express a particular protein involved in disease, but the few regulatory approvals to date are limited to niche indications with return on investment still a long way off. Perhaps the highest hopes were raised over the sequencing of the human genome which was announced in draft form in 2001, with ambitious claims that this would revolutionise healthcare diagnosis and treatment. This may turn out to be the case, but more than a decade later, millions of gene sequences are in hand with "the dream" still far from reality. Maybe the fundamental thought processes outlined by James Watson in The Double Helix put such numbers-driven approaches into context. However, some genes and SNPs have shown a weak association with disease but there has been little impact on target validation or patient selection, except for particular cancers. In the latter case, identification of genetic markers of drug sensitivity has proved to be extremely powerful in patient stratification for clinical trials and targeted therapies, but there has been little progress with other diseases.

Improved candidate survival is another key issue, as the enormous cost of bringing a new medicine to market is unacceptable since it also includes wasted investment in the numerous failures that occur throughout the drug discovery and development process. Alarmingly, recent surveys suggest that less than 10% of preclinical candidates that enter development reach the market, and it is difficult to imagine that any other business sector would accept such an appalling failure rate. Reducing attrition must be a major priority for Pharma in general and medicinal chemists in particular, since even modest improvements would have a significant impact on the cost-effective output of new medicines.

The individual reasons for candidate failure have been well documented, but the dual themes of mechanism- and compound-related attrition are particularly relevant during the discovery phase. Validating a new target in the laboratory is a daunting task even with today's sophisticated technologies and realistically, only a certain level of confidence can be established that a particular pathway or mechanism will be relevant in man. To mitigate risk, mining gene families has received particular attention on the assumption that experience with one clinically-relevant member could be extended to close relatives. While this may apply to druggability, there seems to be a high level of biological redundancy such that seemingly attractive targets may not be involved in physiological or pathophysiological processes. For example, despite convincing rationale for disease relevance and the discovery of potent ligands for numerous members of the adenosine and PDE families, only a handful of drugs have actually resulted. Clearly, animal experiments are still poorly predictive of the clinical situation, particularly for CNS and cancer where above average attrition is par for the course. Mechanism-related failures may also be a consequence of evaluating new drugs in heterogeneous patient groups such that efficacy signals from responsive subsets are lost in the noise.

Reducing mechanism-related failures calls for greater innovation and investment in target validation, but animal models always have limitations and rapid progression of quality candidates to the clinic may be more informative. This will require developing robust biomarkers that confirm drug activity in relevant tissues, identifying patient subgroups that respond to a particular mechanism of action and establishing definitive

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

clinical end points. Overall, a much better understanding and interpretation of PK/PD relationships will be required, and early enough to influence discovery projects. Some consider that these initiatives will fragment markets, but the cost of clinical trials and attrition will be significantly reduced, and surely targeting patients with a high chance of response must be a key objective? Pre-competitive collaborations for both target validation and patient selection will become more common, and there are encouraging signs that Pharma is moving in this direction.

Given such significant investment in biological and clinical sciences, medicinal chemists have a key role to play in designing high quality candidates capable of completing definitive Phase 2 proof of concept studies where full dose–response relationships can be explored. Their challenge is to optimise the physicochemical and molecular properties they so well understand to eliminate compound-related failures such that decisions on candidate progression can be made on efficacy and safety data alone. 30% of all candidate failures are due to inadequate clinical efficacy, but probing new mechanisms with sub-optimal compounds provides minimal learning at significant cost. Indeed, analysis of 44 Phase 2 programmes at Pfizer[3] confirmed that the majority of failures was due to lack of efficacy, but in 43% of those cases it was not possible to conclude that the mechanism had been properly tested due to limited exposure and target engagement.

The Lipinski Rule of Five is now part of the fabric of drug design since these data-driven guidelines summarise the physicochemical parameters that influence permeability and oral absorption. While there are exceptions, medicinal chemists who push the guidelines to the limit usually bequeath compound-related deficiencies to their colleagues at some stage in the discovery and development process, and which often come home to roost in the clinic. Various analyses have shown that molecular weights of drug candidates decrease along the development pathway which must raise at least an amber flag to those pursuing lead series with molecular weights above 400. Increasing molecular weight and lipophilicity is seductive as this allows introduction of structural diversity and novel substituents that improve potency and allow differentiation from prior art. However, while low oral doses are obviously preferred for clinical candidates, the median target affinity for current small molecule drugs is around 20 nM, so the goal of continually driving down absolute potency may be less important than focussing on ligand efficiency which reflects the average binding energy per heavy atom. Ligand lipophilicity efficiency may be even more relevant for lead optimisation as this provides a constant reminder that SARs should be developed without compromising physicochemical properties.

For compounds with high molecular weight and lipophilicity, solubility is almost invariably compromised and is often not improved during lead optimisation such that bioavailablity may be low and variable. Such compound-related limitations are significant barriers to exploring dose–response relationships in the clinic and may also have a negative impact on eventual commercialisation. Compounds at the fringes of the guidelines tend to be more susceptible to CYP oxidation/induction, which can reduce bioavailability through first pass metabolism, generate biologically active and/or toxic metabolites and lead to significant drug–drug interaction liabilities. Encouragingly, medicinal chemists now have a greater understanding of the scientific principles that control absorption, distribution and metabolism, and failure during development for pharmacokinetic factors has been reduced from 40 to below 10%.[4]

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

Entropy driven, non-specific interactions are important for binding between small molecules and proteins so compounds with high molecular weight and lipophilicity tend to be promiscuous with significant off–target activities. Given that safety issues in animals and man are responsible for some 30% of candidate losses, medicinal chemists should work within physi–cochemical parameters associated with success, not failure. Of course, there are exceptions such as natural products and some anti-virals for example, and larger, more complex molecules may be required to block protein–protein interactions, but passive drift outside the guidelines should be avoided.

The challenges to medicinal chemists are clear: physicochemical property inflation should be reduced; compound-related failures eliminated; and attrition significantly improved. We have a unique responsibility for discovering new drugs that will meet future medical needs and to ensure the viability of industry-based research in years to come, but personal accountability can be eroded as the drug discovery processes is broken down into compartments with "experts" assigned to artificial stages from design to candidate selection. Such fragmentation may simplify metrics, but may be personally unrewarding and less productive than a holistic approach where chemists have target laboratory and clinical profiles in mind even as they consider early hit structures.

Phenotypic screens were common in the 1970s when I joined Pfizer, and the rigorous mechanistic approach pioneered by Sir James Black was only just starting to make an impact. I became a member of the antihypertensive project where we were trying to improve on pra- zosin, a diaminoquinazoline derivative discovered by our colleagues in Groton. It had been suggested that prazosin acted as a PDE inhibitor, but the biological target was unknown so our screening sequence was alarmingly simple: synthesis then oral administration to spontaneously hypertensive rats, which actually was common practice at that time. Of course, a fall in blood pressure confirmed oral availability and perhaps our compounds were hitting a single target, but negative results were difficult to interpret and we abandoned the project. Some time later, Sandwich pharmacologists showed that prazosin was the prototype for a new mechanistic class of post-synaptic α_1-adrenoceptor antagonists and we immediately understood why these compounds lowered blood pressure. Screening switched to functional blockade of noradrenaline-induced vascular contraction through α_1-receptors which enabled us to rapidly identify the basic pharmacophore responsible for affinity and selectivity, while interrogation of the prior art suggested how SARs could be developed in an innovative fashion. Almost immediately, we synthesised UK33,274 (doxazosin), a potent and highly selective α_1-adrenoceptor antagonist that was later marketed as Cardura®, a once-daily antihypertensive agent that attained annual sales of over $1 billion.

When we started our calcium antagonist project to seek a once-daily follow on to nifedipine for the treatment of angina and hypertension, we screened compounds in guinea pig hearts as we thought we should target the cardiac rigour that occurs during an ischeamic attack. We did indeed discover a novel series of anti-rigour agents, but without a trace of calcium antagonist activity. Again, when we moved to specific binding and functional screens, we made rapid progress with the discovery of UK48,340 (amlodipine), a potent and selective calcium antagonist with complete bioavailability and a 30 hour half-life in dogs. This compound is marketed as Norvasc® (Istin® in the UK) for the once-daily treatment of angina and hypertension and became the World's

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

fourth most popular drug with annual peak sales of $5.5 billion. I am convinced that neither amlodipine nor doxazosin would be bringing benefit to patients today if we had not moved from such crude and inappropriate phenotypic screens to defined mechanistic targets, but of course one size does not fit all.

Our attempts at phenotypic screening at the animal or organ level were poorly considered and were not productive, and like most of the industry we became attracted to mechanism-based approaches. This was driven not only by difficulties in rational prosecution of lead matter, but also from our experience that "no mechanism" candidates had higher failure rates in development. In addition, there was always a lingering fear that unexpected side effects might appear in the clinic when biological targets were not defined. Accordingly, one might assume that rational, target-based approaches would dominate today's landscape but surprisingly, in my view at least, 37% of first in class NMEs approved by the FDA over the decade up to 2008 originated from phenotypic screening. A defined mechanism of action may be preferable, but it is not essential for regulatory approval where agencies focus more on efficacy and safety. Some consider that phenotypic assays are more relevant for a complex disease condition than screening against a single molecular target, but follow-up can be challenging as activity reflects multiple parameters such as access, distribution and promiscuity. In addition, Structure-Based Drug Design is not relevant and "ligand efficiency" has limited value, and the richness of prior art is often lost when targets are unknown. Despite these caveats, innovative medicinal chemists have a fine record in overcoming such challenges and translating phenotypic hits into successful clinical drugs. Traditionally, there has been a poor and well-documented return from HTS against single antimicrobial targets, and phenotypic screening has proved more appropriate. For example, the Medicines for Malaria Venture has recently coordinated screening of Pharma libraries in a phenotypic, blood-stage malaria assay where numerous, attractive leads were identified, some of which have been transformed into high-quality clinical candidates. Wider use of carefully defined phenotypic screening should be expected in future as newer technologies such as chemical proteomics have significantly facilitated target identification, and some claim up to a 70% success rate within months or even weeks.

The relative merits of small molecules and biologicals are regularly debated as if it were one class or the other, whereas both will play important roles in meeting future medical needs. It is expected that up to eight of the top ten drugs in 2014 will be biologicals which is taken by some to mark the end of small molecules, but this may be an artefact of timing in that Biotech was initially some way behind Pharma, and these products have taken time to mature. Indeed, several leading biologicals have passed or are near the end of their patent life and "The Cliff" does not respect particular molecules. Generic biosimilars will make an increasing impact, although there are still hurdles particularly in the US, but revenues may not be eroded as rapidly as for small molecules. While biologicals have been outstandingly successful for the treatment of arthritis, cancer and diabetes, for example, these molecules are expensive to make and can cost thousands of dollars each month, without offering the convenience of oral administration for chronic diseases. Dose simplification has been an important driver for the widespread acceptance of statins and for the success of anti-retroviral therapies in the developing world for example, which would be impractical with biologicals.

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

Regenerative medicine and stem cell therapies will also find a place for some diseases, but such approaches are likely to focus on specific patient populations, given potential high cost and specialist administration. Pressures on healthcare budgets will increase as the population ages, but there should be a continuing role for novel, small molecules that provide cost effective therapies that can be conveniently taken by mouth. Indeed, 26 of the 39 NCEs approved by the FDA in 2012 are small molecules with only two monoclonal antibodies which may be a pointer to the future, or simply a reflection of a "one off" mix of research projects initiated some ten or more years ago. Whatever the future holds, medicinal chemists will be key players addressing clinical needs not only through small molecules but also with the design and production of hybrid biological therapies, and full participation in new chemical and synthetic biology initiatives.

Pre-competitive collaborations will become more important in the future in order to reduce cost, risk and duplication. Most pharma portfolios probably share 70–80% similarity with multiple and parallel investments in the same targets, and often molecular scaffolds. For example, several companies took neurokinin and endothelin antagonists to the clinic over similar periods but with little reward, while the cumulative time and effort committed to renin inhibitors was absolutely staggering. Such duplicative failures might be avoided through pre-competitive collaborations between industry and academia for target validation, particularly given the alarming claim that far less than 50% of biological publications can be repeated by third parties. Surely, we are past the point where individual Pharma/Biotech companies can continue to make parallel investments to reach the same negative conclusions given the tremendous pressures the industry is facing? Identifying patient populations that respond to new mechanisms of action is also essential, but this will require cooperative investment from industry, academia, health services and regulators. If validated targets and patient subsets do enter the public domain earlier than at present, then responsibility for establishing a competitive edge and robust IP will depend largely on innovative medicinal chemistry which will simply become too valuable to contract out. There are signs that the community may be moving towards precompetitive collaborations with the Structural Genomics Consortium championing more open interactions and providing wide access to chemical tools to probe new targets. Medicinal chemists play a central role in such initiatives by designing prototype molecules and developing analytical capability to build our understanding of biological pathways and mechanisms, and for target validation. Strict criteria for compound potency and selectivity should be demanded for proof of concept studies, and a further frame shift in chemical innovation will be required to exploit receptors and enzymes currently considered undruggable, and for those yet to be discovered.

On a broader precompetitive front, the EU Innovative Medicines Initiative has launched a new Euro 224 million programme jointly funded with industry to channel academic and industry partners towards new classes of antibiotics that address antimicrobial resistance. A further EU Public Private Partnership will invest nearly Euro 200 million to bring together multiple partners to create a Lead Factory comprising a European Screening Centre and compound collection. Access to HTS and 0.5 million diverse structures could enhance the rate of lead generation across the community, particularly for academic researchers who have previously had difficulty in identifying

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

tractable chemical matter. In the US, a National Centre for Advancing Translational Sciences has been established with focus on facilitating translation from the laboratory to clinic which could have significant pre-competitive impact, although there are vociferous critics of both mission and budget. Ten pharmaceutical companies have formed a non-profit organisation called TransCelerate BioPharma to accelerate the development of new medicines, while DataShare aims to create a repository of information from cancer trials carried out by Pharma, academia and public institutions that can be shared across the community. More broadly, an international AllTrials initiative is campaigning for industry and regulators to make full Clinical Study Reports available, and GSK has taken the lead amongst large Pharma by agreeing to participate. Such precompetitive collaborations in drug discovery and development not only have the potential to reduce costs and risks, but also to bring significant patient benefit.

Economic conditions will become harsher than in the past with unflinching pressures on budgets at national, regional and local levels. Healthcare costs overall and drug prices in particular will be under the closest scrutiny as we move more towards an ageing society. Continued rises in health investment as a percentage of GDP will simply not be sustainable worldwide. New medicines will have to demonstrate positive outcomes over existing treatments, with hard evidence of reduced mortality and morbidity, improved quality of life and savings in overall healthcare budgets. There will be high expectations, or more likely demands, for innovative and cost- effective medicines that will transform treatment paradigms and justify reimbursement. Although NICE in the UK has led the way in relating treatment benefits and costs to QALYs and Disability-Adjusted Life Years, such agencies are now commonplace throughout the world and criteria for reimbursement are becoming more stringent. Indeed, 2012 may prove to be a watershed with respect to pricing and reimbursement as five orphan drugs approved by the FDA have annual prices between $100 000–300 000 while several new anti-cancers will cost from $7000–10 000 per month, and there is already significant pushback from oncology experts. Healthcare systems may not be able to offer such expensive new therapies unless significant clinical benefit can be demonstrated, but earlier industry-agency agreement on target efficacy/safety criteria could minimise negative reimbursement decisions currently taken after years of costly investment. Encouragingly, the FDA has introduced a "breakthrough" status for fast tracking innovative new medicines based on Phase 2 data which resulted in the approval of ivacaftor for cystic fibrosis in 2012.

There have been high expectations that the developing world would provide a more welcoming environment as living standards rise, but leading countries such as China and India are driving down drug costs even more aggressively than in the West, and are tending to favour local manufacturers. Bringing cost-effective healthcare to the general population is their first priority, although expanding middle classes may be willing to pay higher prices for some new medicines. However, these markets are currently not robust enough to support investment in R&D at historical levels and few new drugs have emerged from generic companies. Given the mantra that "innovative R&D follows premium priced markets" it is unlikely that high-investment pharmaceutical research will make a major shift eastwards in the near future, particularly given worrying threats to IP that had previously been secured elsewhere. However, China has announced a

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

five-year plan to invest $7 billion in academic projects that might lead to new drugs and eventually spawn an innovative pharmaceutical industry, although the need to build expertise and depth is openly accepted.

So what of the future? Some ten years ago, I suggested to a sceptical audience that the future pharmaceutical industry would be largely located in the US with outposts in Europe and Japan, which may well come to pass. However, even the US is in flux as budget deficits and pressure to reduce healthcare expenditure continue to force down drug costs and R&D investment. Consequently, traditional organisations are consigned to the past as the number of leading pharmaceutical companies in the US has declined from 42 in 1988 to 11 today, and all have undergone significant downsizing with major site closures. In the UK, international players such as AstraZeneca, GSK, Pfizer, Merck, Novartis, Organon (Merck/Schering) and Roche have abandoned modern research facilities, there have been thousands of job losses and the overall situation is probably still meta-stable. Indeed, decentralisation of R&D organisations is in full flow, as Pharma continues to minimise fixed costs by externalising routine research activities to CROs, and by working more closely with the academic community. For example, AstraZeneca has significantly reduced resource on neuroscience research and has moved to a virtual model where a small internal team collaborates with leading academic centres to share reward and risk. Pfizer has established Centres for Therapeutic Innovation in Boston, New York, San Diego and San Francisco to facilitate interactions with academic institutions, and has placed their own staff in collaborator laboratories. While these initiatives should provide early access to new biology, translation to successful drug discovery projects still has to be realised, and there will be the inevitable trade off between publications and IP. In addition, core expertise within Pharma, particularly medicinal chemistry, cannot be eroded too far, as successful collaborations require complementary intellectual contributions from both partners, and coherence on objectives.

Simple arithmetic suggests that given the significant scale of Pharma contraction and reduction in R&D investment, the number of new drugs reaching deserving patients will decrease, and there are also concerns that whole therapeutic areas are being abandoned. Historically, around five First in Class new medicines have been approved each year and any decline would leave major clinical needs unsatisfied. This shortfall will probably not be compensated for by Biotech where investment in early stage companies has been severely scaled back, nor is it clear that continued Pharma investment will be sustainable even at today's levels. Alternative models for R&D funding will be required involving academia, charities, governments, industry and private investors. However, given the time-scales and uncertainties traditionally inherent in drug discovery programmes, there may be pressure from funding bodies to reduce costs and risks through increased emphasis on target validation, attrition, predictive toxicology, and patient selection, and to develop more open collaborations. Funders may also need to be convinced that lessons from the past have been learned, and that cost effective and sustainable models for drug discovery can evolve to provide acceptable returns on investment.

Now would be an opportune time to strengthen drug discovery capabilities in the public sector by co-localising industry-experienced medicinal chemists alongside world class biologists and clinicians with a real commitment to the discovery of new medicines. In many cases, a fundamental change in mind set will be required for medicinal

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

chemists to be accepted as equal partners, rather than as a service function. It will be important to build up chemistry to a critical mass as simply adding a few experienced scientists to established academic groups would not be effective. Of course, there are already research institutes and academic centres focused on drug discovery but not on the scale now required, and integration of Pharma veterans within the wider community will take time as there is little appreciation of the skills base required for medicinal chemistry. However at steady state, barriers between "academic" and "industry" researchers may soften and there would be increased permeability across previously defined disciplines and sectors. Of course, broadening individual skill sets should not be allowed to compromise quality control. Drug discovery centres would be more output-focussed than traditional academia with set objectives and goals, but rigid metrics would not be appropriate; the traditional industry dichotomy of "scientists" and "managers" would disappear, and a culture of innovation and scientific excellence would flourish. Long-term investment in the most challenging disease areas such as antibacterials and neurosciences would be encouraged and supported. There will also be important roles for Public Private Partnerships some of which have attracted significant funding for drug discovery, and have appointed scientists with industry experience who are building real and virtual R&D portfolios with multiple projects ranging from early hits to regulatory approval. These organisations and charities have traditionally focused on diseases of the developing world and cancer, but similar commitments to a wider range of therapeutic areas will be required in the future. Overall, there is a strategic and pressing need to strengthen competitive drug discovery initiatives outside Pharma and Biotech, and concerted efforts from interested parties will be required to ensure research capabilities are commensurate with future medical needs.

Drug discovery organisations will be more heterogeneous in the future, but research units could be roughly scaled in multiples of 50–100, with say a total of 200–300 multidisciplinary scientists providing an optimal balance of critical mass, personal interactions, individual accountability and potential for commercial success. Multidisciplinary teams would have disease and project focus, and would be closely integrated with clinical and academic colleagues. Medical need and scientific excellence would be fundamental drivers for project selection, which would be owned by teams through target validation, hit discovery, lead optimisation, candidate selection, biomarker PK/PD to clinical proof of concept. All team members would be actively involved in science right up to the limit of their abilities, including project leaders and directors. Skilled laboratory scientists would be recognised and rewarded with proper career progression. There would be ready access to the most relevant technologies such as HTS, protein crystallography, computational chemistry, fragment screening *etc.*, which would be expertly exploited as enablers rather than constraints or solutions *per se*. Of course, goals would be defined at group and personal levels and decisions taken with respect to portfolio priorities rather than individual preference, but the driving force would be quality not quantity. This would engender a culture of innovation and realism in which knowledge transfer and training of future generations were also highly valued. "Think global, act local" would recognise a fiercely competitive external environment, but focus on personal interactions and knowledge-based decisions would be much more effective than continual multi-site meetings, transatlantic travel and late night video conferences.

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023

Medicinal chemists have never been in such a strong position to meet the challenges that now face drug discovery given the major scientific advances we have experienced over the past decades. We have unprecedented knowledge to design and synthesise new molecules, understand protein structure and function, and to appreciate the physicochemical factors that control delivery, efficacy and safety. We have the tools we need to exploit the massive worldwide investment in biomedical sciences, and to be more innovative and effective in execution and decision making from idea to proof of concept. Our challenge is to work with biology and clinical colleagues within a research-driven, but sustainable environment to integrate and apply our skills to discover innovative molecules that will meet the medical needs of the twenty-first century.

S. F. Campbell, Kent, UK

Acknowledgements

I am most grateful for the interest, encouragement and insightful comments from Julian Blagg, Duncan Campbell, Manoj Desai, David Fox and Graeme Stevenson.

References

1. F. Lichtenberg, *NBER Working Paper*, 2003, 9754.
2. J. L. LaMattina, *Nat. Rev. Drug Discovery*, 2011, **10**, 559.
3. P. Morgan, P. H. Van Der Graaf, J. Arrowsmith, D. E. Feltner, K. S. Drummond, C. D. Wegner and S. D. A. Street, *Drug Discovery Today*, 2012, **17**, 419.
4. I. Kola and J. Landis, *Nat. Rev. Drug Discovery*, 2004, **3**, 711.

Downloaded from http://books.rsc.org/books/edited-volume/chapter-pdf/1495157/bk9781788018982-fp019.pdf by guest on 24 September 2023