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## Drug Discovery into the 21<sup>st</sup> Century

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### 1. Introduction

Medicines discovery has come a long way since our ancient ancestors from the Neanderthals to the people of Mesopotamia, Egypt, Greece and China used herbal remedies to treat the sick people. In mediaeval times the quest for the *elixir of life* was pursued by alchemists, but it is the scientists of the past 100-150 years who have had success by translating laboratory-based discoveries into drugs that have literally saved countless millions of lives (Sneader, 2005). The German stock market collapsed in 1873 and it was during the recovery period that the upsurge in the economy led to an expansion of chemical and electrical industries. The significant investment in the manufacture of synthetic dyes soon put Germany well ahead of all its competitors. As a consequence, German chemists did not only become very influential in the field of organic chemistry, but also led to the rise of the German pharmaceutical industry. Central to this industry were leading manufacturers including F. Bayer & Company and Farbenfabriken Hoechst who realised that their chemists researching and developing dyes also had the potential to produce new medicines (Sneader, 2005). One such scientist was Paul Ehrlich. Ehrlich was fascinated by colourful dyes and their capacity to interact with histological and cellular structures. Over several decades, he benefitted from chemical companies who provided hundreds to thousands of new dyes for his research. Given these dyes were biologically evaluated individually, the number of compounds probably exceeded the thousands or even millions of compounds being evaluated as a part of high-throughput screening (HTS) employed in academia and industry today. Ehrlich taught us that, in the broadest sense, the biological effect of a chemical compound such as a dye depends on its chemical composition and the cell on which it acts. He was able to establish a connection between chemistry, biology and medicine in an ingenious fashion; chemical dyes were the catalyst for this *revolutionary association* (Strebhardt & Ullrich, 2008). Simultaneous to his fascination of dyes, he also was inspired by his contemporaries carrying out research in immunology including Louis Pasteur, Robert Koch, Emil von Behring and Shibasaburo Kitasato. At the turn of the 20<sup>th</sup> century Ehrlich developed the receptor theory, which became instrumental to the understanding of how the binding of drugs to various types of receptors could occur due to structural differences in chemical compositions. He notably stated “Wir müssen chemisch zielen lernen” which translated to English equates “we have to learn how to aim chemically”. Ehrlich’s experiences with the treatment of infectious diseases with drugs derived from the German dye industry impelled him to look for ways of using organic chemistry to modify certain starting dyes in various ways to create new chemical structures with potential improved biological activity (Strebhardt & Ullrich, 2008). Ehrlich is often

described as the founder of chemotherapy and his 'magic bullet concept' is still what today's scientists strive to aim for: to develop small molecules that attack pathogens yet remain harmless to healthy tissues.

During the two World Wars essential medicines normally supplied by Germany dried up and a gradual change in favour of synthetic drugs came about. Synthetic organic chemistry became an exceptionally important discipline and is still one of the cornerstones of drug discovery. Synthetic organic chemistry has continually adapted to embrace innovative techniques and methodologies central to drug development. Much synthetic drug discovery emerged from cancer drug development and began with an observation that mustard gas, employed in chemical warfare during World Wars I and II, destroyed lymphatic tissue and bone marrow formation. The observations made by Drs. Gilman, Goodman and co-workers laid the foundation for conducting the first clinical trials with nitrogen mustards ( $\beta$ -chloroethylamines) in 1942 at Yale-New Haven Hospital, but a report of the clinical results was only made public four years later, due to the cloak of secrecy during World War II (Goodman *et al*, 1946; Hirsch, 2006). An array of DNA alkylating agents ensued, which paralleled an increased understanding of DNA in the 1950s. A number of other agents subsequently emerged, such as the vinca alkaloids and purine/pyrimidine synthesis inhibitors (Denny, 2002). These advances were, to a large extent, driven by the National Cancer Institute (NCI), enabling the assessment of primarily cytotoxic agents. By the 1970s, the importance of natural product-based early drug discovery had been realised (Denny, 2002). Unfortunately, the synthesis of many of these frequently promising, novel agents was often too complex and too expensive to allow progression into early stage clinical trials. This situation facilitated a paradigm shift whereby natural product screening was implemented into stage discovery initiatives, providing an opportunity to identify natural products as *bona fide* lead compounds. These leads were then subsequently developed into truncated molecules, which were more amenable to synthesis. More recently, advances in organic chemistry have successfully enabled the complete synthesis of many complex natural products, a milestone that has dramatically improved the ease with which chemists can now deal with the complexity of many of these naturally-derived architectural structures. Synthetic chemistry has also been instrumental in the development of drug delivery and prodrug strategies, which have focused on the development of selective therapeutics with reduced side-effect profiles (Brown & Wilson, 2004; Rooseboom *et al*, 2004). Although research in cancer medicines was the driver of much synthetic drug discovery it did run parallel with research against other diseases as illustrated in Figure 1.

Today, the emergence of the genomics era and the focus of events at the molecular level is changing the landscape of drug discovery. A wealth of convergent data that has caused many to not only speculate on an expanding druggable genome, but also given an optimism for grasping new opportunities to take drug discovery to the next level has become available (Billingsley, 2008). The number of gene products that are targets for existing drugs has been a topic for much debate and depends on the analysis performed, however, a valid estimate is in the region of 300-500 gene products (Overington *et al*, 2006). As the human genome is estimated to encode 20,000-25,000 human gene products, the number of drug targets is likely to increase. However, it will take some time to validate targets at the protein level, which has an added level of complexity. Both gene and protein expression profiling methodologies have been emerging over the last decade or so to monitor and catalogue changes in the expression of genes and their respective protein products. As such there are serious challenges ahead. Our understanding of human disease at the molecular level to

elucidate changes in biochemical processes associated with disease phenotypes is of high significance. From a drug discovery point of view, the ultimate goal is to generate identifiable therapeutic targets while reducing drug development attrition.

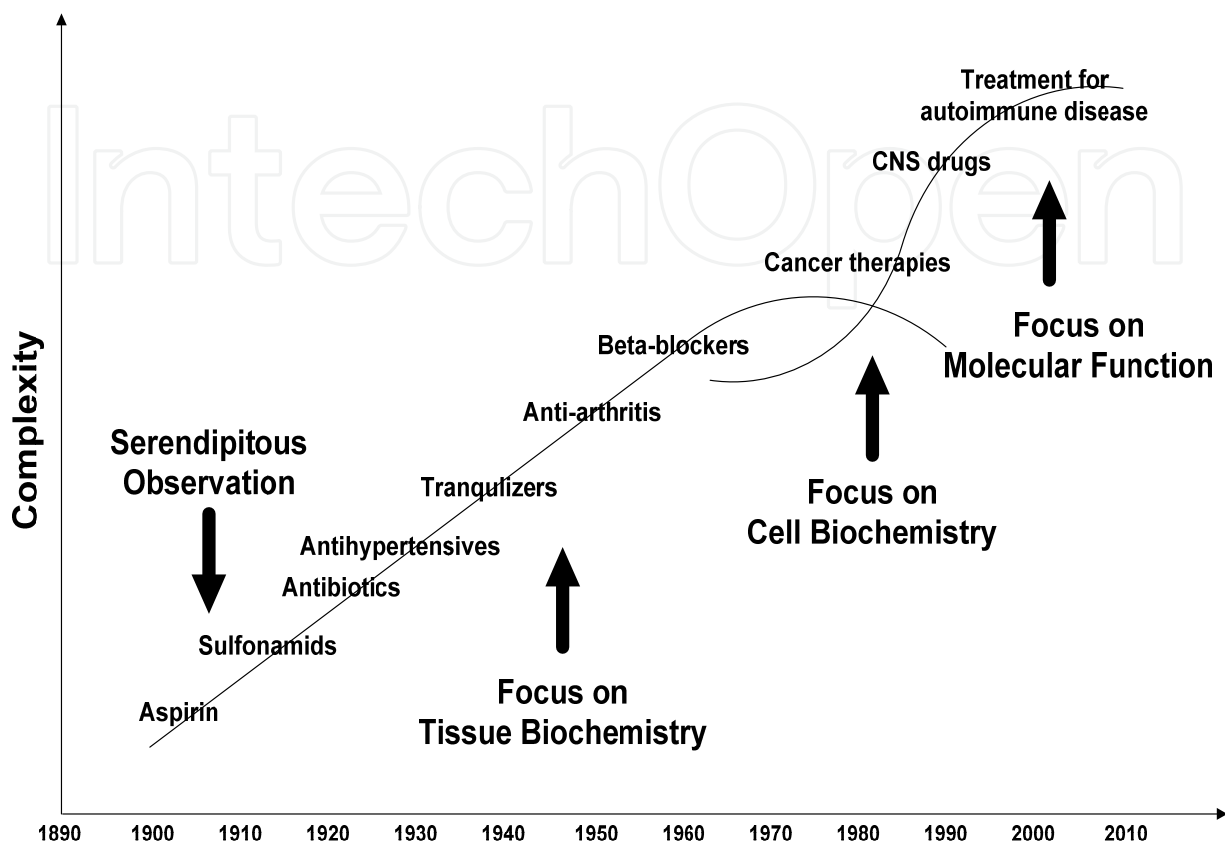


Fig. 1. Chronology of drug innovation. (Reprinted with permission from the Biopharmaceutical Industry Contributions to State and US Economics, available at [www.milkeninstitute.org/pdf/biopharma\\_report.pdf](http://www.milkeninstitute.org/pdf/biopharma_report.pdf), Milken Institute).

The mapping of the human genome was a gigantic landmark. Can scientists working at the interface of chemistry and biology in drug discovery utilise the data available to them to discover new ground-breaking drugs? Will the ever increasing cost of drug discovery halt the progression, especially in times of recession? Will research and development (R&D) in the emerging markets be an opportunity to climb to the next level of understanding in how to develop successful drugs? These are some of the questions that will be discussed in the following sections.

## 2. The evolution of modern drug discovery

At the beginning of the 20<sup>th</sup> century drug discovery was largely carried out by individuals such as Paul Ehrlich and his associates. This is now impossible, and requires teamwork encompassing members from various disciplines including chemistry, computational modelling, structural biology and pharmacology. This section outlines a general approach to drug discovery which has been dominant over the past couple of decades. The approach to drug design depends on the objectives of the design and investigational team, but will also depend to some extent on the disease that is targeted. The information available from the

literature about a specific disease or target is used by the research team to decide what intervention would be most likely to bring about the desired result. The exact nature of the project progression depends on the resources available: for example, an academic group may not be as expansive as a large pharmaceutical company in terms of how to tackle the problems of validating a novel target or developing 'hit' and 'lead' compounds that will be able to modulate that target. The drug discovery process outlined in Figure 2 is, therefore, an approximate model which is employed by pharmaceutical companies, but one which a small biotech company or a university also can engage in through multiple collaborations. This discovery process can be instigated at several points and adapted to bring about the results needed to take a project to the next level. For a recent in-depth review of the early drug discovery process, see (Philpott *et al*, 2011).

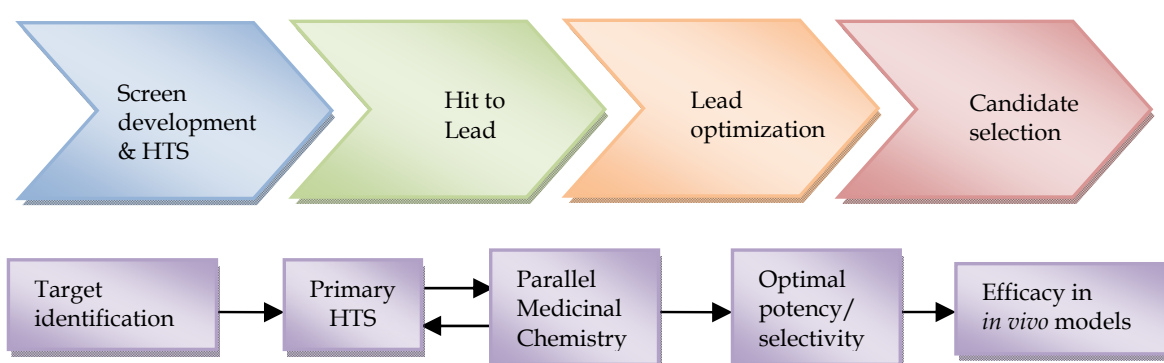


Fig. 2. The multi-faceted drug discovery process in the 21<sup>st</sup> Century.

Up until the mid 80s, drug discovery was focussed on isolation of natural products and medicinal chemistry was central for a research team to find more potent and selective compounds than the natural product or synthetic compound themselves. After isolation and characterisation of the natural products, structure-activity relationship (SAR) studies were and still are a vital tool in optimising a pharmacophore. Initially, a drug design process was an iterative course of action between the synthesis of new compounds by a synthetic/medicinal chemist and the screening of these for biological activity by a pharmacologist. The drug discovery process was chemistry-focussed rather than target-driven. As outlined in Figure 2, the discovery process of a drug now involves a multidisciplinary effort that is synergistic, which often encompasses HTS procedures. It is also one that often follows rules that are based on empirical findings from clinical investigations such as Lipinski's rule of 5 (Lipinski *et al*, 1997). 'Hit' compounds are progressed into a 'lead' compound, which undergoes thorough pharmacological and toxicological testing. The results of these tests enable a research team to decide whether it is profitable to continue with the progression of a specific project. The scenario is often to screen virtual or commercial libraries of compounds to identify hit molecules. The second stage is to prepare libraries of small molecules based around the hit molecule, measure their activity and correlate the results to determine the chemical structure with optimum activity. This analysis may make use of SARs, computational chemistry, combinatorial chemistry and enzymatic and cellular assays to help unravel biological activity derived from unique mechanism of action of a small molecule. The selection of a lead compound and the development of a synthetic pathway for its preparation on a large scale for preclinical and clinical investigations must also be considered at an early stage in the discovery process. If



the lead molecule cannot be synthesised on a large scale progression to clinical evaluation will not be possible. Similarly, researchers must also devise suitable *in vitro* and *in vivo* tests to assess the activity and toxicity of the compounds produced. If there is no suitable way of testing a hit or lead molecule *in vivo* the project may come to a halt unless it is decided to spend resources on developing appropriate models.

Nowadays, hit and lead molecules with proven activity are assessed for susceptibility for phase I and II metabolism in the very early stages of the discovery process. For example, many HTS technologies are now available to detect cytochrome P450 (CYP) substrates or inhibitors, which should decrease the number of withdrawals of novel drugs from the market due to affinity for major CYP metabolising isozymes. HTS CYP data can be used to guide medicinal chemistry away from these interactions at an early stage and in certain cases might entirely solve the issue by targeted modification of the CYP interacting functionality (Zlokarnik *et al*, 2005).

HTS methodologies have been developed and have enabled research teams to generate vast numbers of compound variations of a desired pharmacophore. Combinatorial chemistry (combichem) was first applied to the generation of peptide arrays in 1984 and evolved rapidly into a new discipline that was hailed to revolutionise drug discovery (Lam & Renil, 2002). The early generations of combichem scientists captured the fascination of the industry, and coined or modified the common use of a number of buzzwords, phrases, and abbreviations that became widespread in the literature including deconvolution, diversomer, split-and-mix, multipin, SPOC or SPOS (solid-phase organic chemistry or synthesis), submonomer synthesis, T-bag (Teflon bag) to name a few (Moos *et al*, 2009). Interestingly, from the discovery point of view, the scientists working in the combichem environment require different management solutions to classical synthetic chemists. For example, chemists planning a traditional synthesis to obtain a target compound or a natural product typically conduct a retrosynthetic analysis to determine the best, and perhaps cheapest, way to obtain the target. In contrast, combinatorial chemists will primarily consider forward synthesis strategies that are founded in which building blocks are commercially available or indeed worth synthesising. Accordingly, chemical information systems that can be quickly accessed via updated databases of inventory and commercially available reagents are invaluable tools in reagent acquisition by the combinatorial chemists. While combichem matured from solid-phase synthesis to solid-supported synthesis, new synthetic strategies and techniques evolved. Some of these are now well integrated into the drug design process including microwave synthesis (Gedye *et al*, 1986), fluororous synthesis (Studer *et al*, 1997), click chemistry (Sharpless *et al*, 2001) and flow reactors (SalimiMoosavi *et al*, 1997). As with traditional drug design, combichem relies on organic synthesis methodologies and exploits automation and miniaturization to synthesize large libraries of compounds, which can accelerate the drug discovery process. The combinatorial approach is often systematic and repetitive, using sets of commercially available chemical reagents to form a diverse set of molecular entities. It is very powerful in early stage discovery and allows HTS to take place, combining rapid synthesis of chemical compounds to be screened using both enzymatic and cellular assays for evaluation. The quick turnaround of data allows a flow of information, which enables second and third generation of compounds to be generated in rapid fashion. Combichem mostly concerns “parallel” synthesis and “split-and-mix” synthesis (Figure 3).

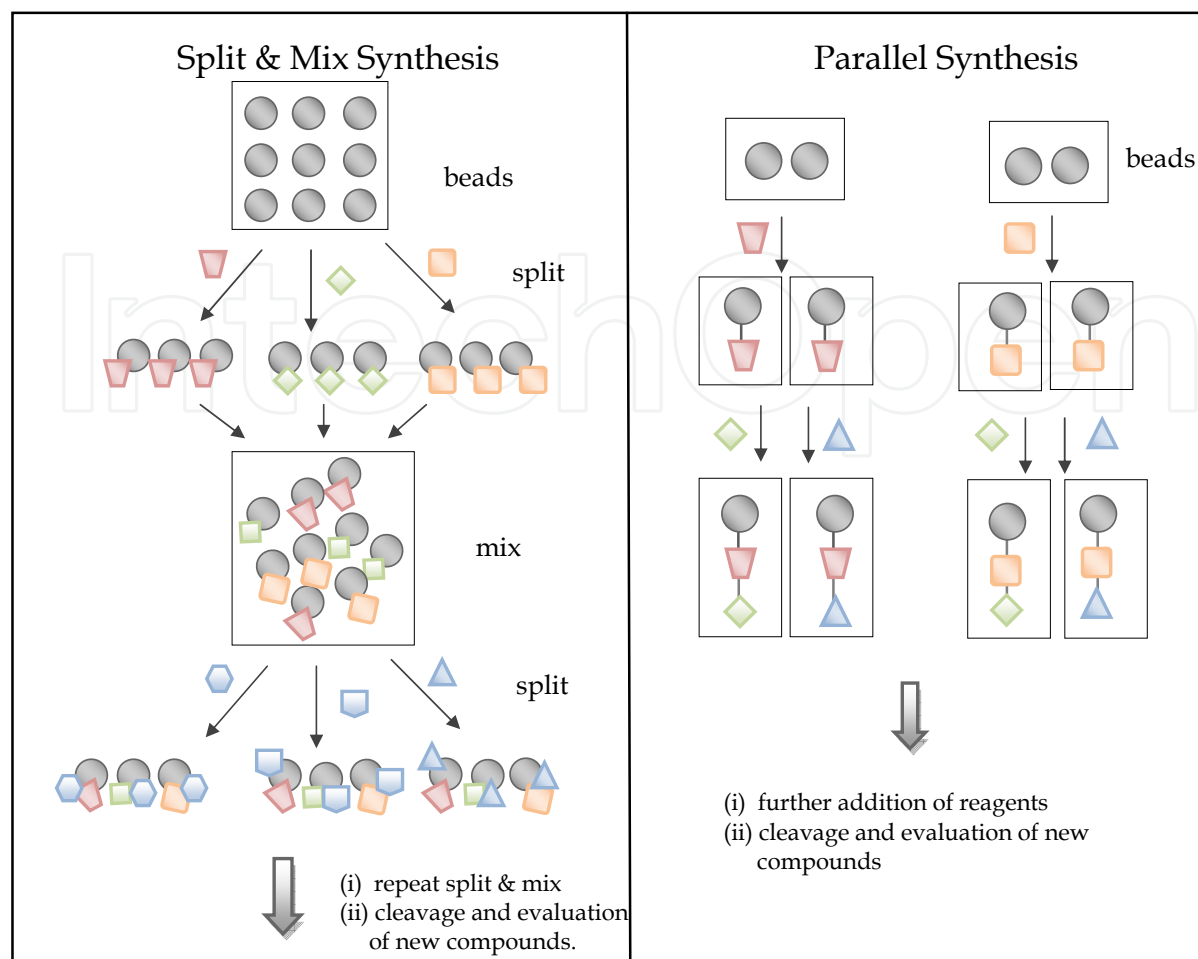


Fig. 3. Combinatorial chemistry approaches. The parallel synthesis is generally used to generate larger quantities of a small number of compounds and split and mix to generate smaller quantities of a larger number of molecules.

There is no doubt that combichem has become a mainstay tool of the drug discovery process. The strength of combinatorial techniques is based on the creation of large populations of molecules, or libraries that can be screened efficiently *en masse* in a short period of time. The vast amounts of money spent on development of combinatorial techniques have not yet resulted in many drug successes. The only real success story at present is the development of the multikinase inhibitor sorafenib, which now has been approved for clinical use by the *Food and Drug Administration (FDA)* for the treatment of advanced renal cancer (Wilhelm *et al*, 2006). However, combichem has spun out many exciting technologies that now occupy a central place in the biotech industry. The mapping of the human genome may have provided a new area of application of combichem in combination with other HTS methodologies including techniques and instruments developed for DNA microarrays. Indeed, high-density chemical microarrays can now be synthesized *in situ* on glass slides or be printed through covalent linkage or non-specific adsorption to the surface of the solid-support with fully automatic arrays. In conjunction with the one-bead one-compound combinatorial library method, chemical microarrays have proven to be very valuable in 'hit' identification and 'lead' optimization. HTS protein expression systems, robust high-density protein, peptide and small-molecule microarray systems, and automatic mass spectrometers are essential tools for the field of functional proteomics (Lam & Renil, 2002). In despite of this more focussed approach

to drug discovery, combichem has been disappointing in delivering drugs to the market (Rydzewski, 2008). One of the main reasons is that combichem has been built on peptide chemistry that now has use in protein and nucleotide research, but which is not best suited to producing orally active drugs (Moos *et al.*, 2009). Another limitation of combichem is that small molecules developed via this technique do not cover broad *chemical space*. When comparing the properties of compounds in combichem libraries to those of approved drugs and natural products, it has been observed that combichem libraries suffer particularly from the lack of chirality, as well as structure rigidity, both of which are widely regarded as drug-like properties (Feher & Schmidt, 2003). Since the enormous success with natural products as drugs or use for drug development in the 70-80s, it has not been fashionable by the pharmaceutical industry to use these as leads for drug development. Often because of the complex structural architecture of natural products, which make them difficult to synthesise in the laboratory on a large scale basis. However, what cannot be disputed is that natural products cover much chemical diversity. As chirality and rigidity are the two most important features distinguishing approved drugs and natural products from compounds in combichem libraries, these are the two issues that are essential components of diversity-oriented synthesis (DOS) that aim at coverage of the chemical space, instead of libraries consisting of colossal numbers of compounds.

## 2.1 Discovery of small molecules to explore biological pathways and uncover new targets

The mapping of the human genome, the improved understanding of both pathological causes and function of biological targets and the development of HTS technologies ought to have resulted in a higher number of new chemical entities (NMEs) for medicinal use. So why has this not been the case? There may be several reasons, which will now be considered. Computational molecular modelling has provided scientists with an insight into biochemical events at the molecular level. An understanding of the binding process of small molecules to many macromolecules such as DNA is well understood, however the same cannot be said about other targets. Many stones are still left unturned, perhaps due to the lack of interest or belief that so-called “undruggable” proteins can be successfully targeted. It has been estimated that only 10–14% of the proteins encoded in the human genome are ‘druggable’ using existing ‘drug-like’ molecules (Hopkins & Groom, 2002). However, given that the *chemical space*, the complete set of all possible small molecules, has been calculated to comprise  $10^{30}$ – $10^{200}$  structures depending on the parameters used (Bauer *et al.*, 2010) there are an incredible number of yet uncovered chemical structures. Considering the limitations of chemical libraries in addressing challenging targets, it is important to recognize that the vast majority of accessible libraries of small molecules are based on existing drugs (Moura-Letts *et al.*, 2011). Drugging targets that are within our capacity to accept as targets and exercising principles such as Lipinski’s “rule of five” that have yielded success in the past is safe territory, so it is perfectly understandable that we want to continue such lines of research. “Me too” compounds are likely to give pharmaceutical companies a financial return and academic scientists may obtain grant funding if the proposed research makes sense. Grant reviewers can appreciate the hypotheses and the scientific methodologies and may be inclined to fund projects that will give an outcome of sorts. However, it also appears that industry, research councils and other funding bodies want to keep an element of blue-sky research – they just don’t want to fund it. Historically we know that serendipity has played a major part of most success stories. So to cut out funding that is not to support blue-



sky but mainstream research is likely to have profound consequences. Although Lipinski's "rule of five" has merit and a place in drug discovery it may also be an Achilles heel in progressing new drug discovery projects (Abad-Zapatero, 2007). Why? A drawback is that the shape and size of drugs become limited. Unless carefully used, HTS technologies such as combichem will continue to only generate low hit rates, particularly when screening against challenging targets (Boehringer *et al*, 2000; Edwards *et al*, 2007). Additionally, optimisation of lead compounds can be problematic owing to the often large and relatively lipophilic nature of the screening hits (Chessari & Woodhead, 2009a). Wise men will always use experiences from the past and present, but discovery of NMEs must also entail trespassing new horizons or in the drug discovery world, new chemical space.

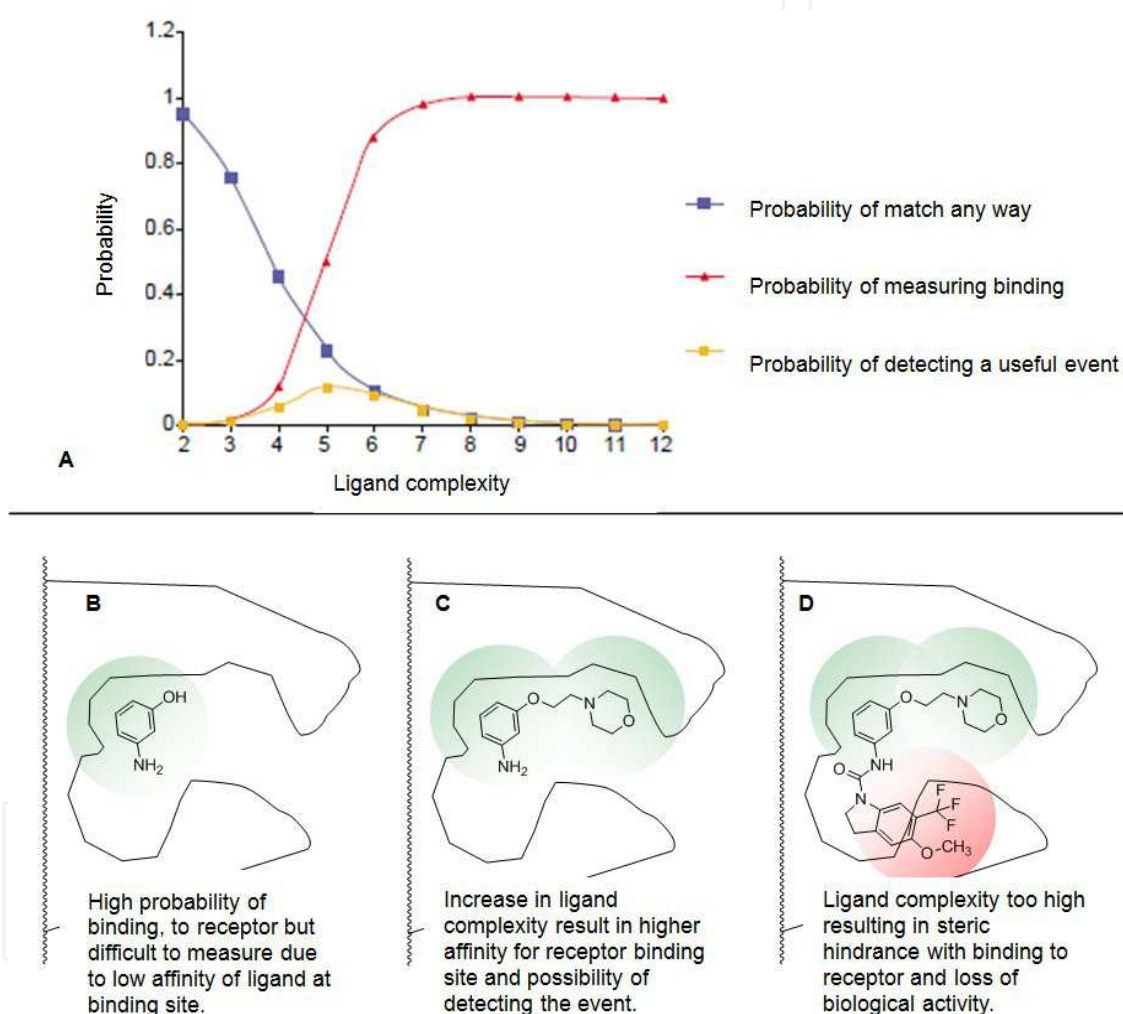


Fig. 4. (A) Success landscape for a binding site of ligands with increasing molecular complexity. (Reprinted with permission from Zartler & Shapiro, *Curr. Opin. Chem. Biol.* 2005, 9(4), 366-370, copyright (2005) Elsevier and *J.Chem. Inf. Comput. Sci.* 2001, 41, 856-864, copyright (2001), American Chemical Society). (B-D) An example of increase in ligand complexity using 3-aminophenol as starting material.

An insight into the difficulties in successful drug development is provided by Hann and co-workers who in their study suggest that if a drug discovery process starts with very simple chemical structures, then there is a better chance of finding both detectable binding and a

unique binding mode. Similarly, lead molecules that are simpler also give more available chemical space for optimization, especially in light of the properties that are needed for oral bioavailability (Zartler & Shapiro, 2005). Figure 4A shows the trade off between detecting binding and a unique match. Essentially, the chance of finding a detectable and unique binding mode is dependent on the chance of determining binding and the chance of having a distinctive binding mode or match. For example, if 3-aminophenol was a ligand in a screening collection, there would be a high probability of it binding, but due to low affinity and time of occupancy at the binding site, it would be difficult to detect any such binding (Figure 4B). If 3-aminophenol was further reacted to afford 3-(2-morpholinoethoxy)aniline, the complexity of this ligand would increase and the probability of the binding would increase as a result. However, if the aniline amine moiety was derivatised with a fluorinated indoline to generate a ligand of high complexity, steric hindrance would hamper any binding in this specific receptor model (Figure 4D). By increasing the molecular complexity of a ligand the chance of measuring the binding is enhanced, but at the same time such modifications may also augment the likelihood of negative interactions (Zartler & Shapiro, 2005).

One approach toward broadening our understanding of the relationship between structure and function of a target protein is to generate many new small molecules, simple in shape and size, which are in accordance with Hann's study, that modulate the proteins' functions. This enables the study of the interactions of ligand and protein. The past 10 years have seen the screening of specific components of small molecules evolve from a niche area of research to become an important tool known as fragment-based drug discovery (FBDD). Fragments are defined as low molecular weight (MW <300), moderately lipophilic (clogP < 3) and highly soluble organic molecules (Chessari & Woodhead, 2009a). As a consequence, medicinal chemists use hit compounds to probe new chemical space in a number of ways as illustrated in Figure 5.

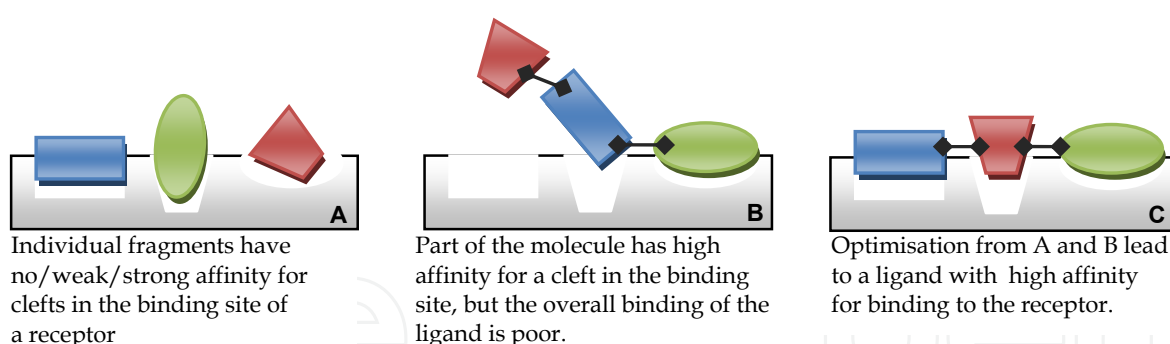


Fig. 5. Fragment-based drug discovery.

The first medicinal chemistry approaches employing FBDD as a key component of the discovery process can be traced back 15-20 years. In contrast to combichem, FBDD strategies have had a more rapid impact in terms of developing drugs with clinical potential. The wide variety of contexts in which FBDD is now being used (SAR-by-NMR, HTX, scaffold-hopping, selectivity mapping) illustrates its practical utility in mainstream medicinal chemistry. The promise of more resourceful technology has fuelled enthusiasm for FBDD, which is design intensive and enabled by structural biology. Indeed, screening fragments, particularly when using sensitive biophysical techniques may also allow scientists to tackle some of the more challenging drug discovery targets. Fragment libraries statistically cover

chemical space better than drug-like or lead-like libraries and as a consequence fewer compounds need to be screened. Also fragment-based screening tends to deliver high hit rates with the additional benefit of providing multiple start points for optimisation programmes (Chessari & Woodhead, 2009a).  
FBDD’s recent successes outlined in Table 1 (Chessari & Woodhead, 2009b) indicate that use of this design intensive drug discovery approach is delivering results that have paved the way to clinical evaluation and it may not be long before the first drug reaches the marketplace (de Kloe *et al*, 2009).

Compound	Company	Target	Progress	Detection method
ABT-263	Abbott	Bcl-X <sub>L</sub>	Phase 2	NMR
AT9283	Astex	Aurora	Phase 2	X-ray
LY-517717	Lilly/Protherics	FXa	Phase 2	Computation/X-ray
NVP-AUY-922	Novartis/Vernalis	Hsp90	Phase 2	NMR
Indeglitazar	Plexxikon	PPAR antagonist	Phase 2	HCS/X-ray
ABT-518	Abbott	MMP-2 & 9	Phase 1	NMR
AT7519	Astex	CDK2	Phase 1	X-ray
AT13387	Astex	Hsp90	Phase 1	NMR/X-ray
IC-776	Lilly/ICOS	LFA-1	Phase 1	NMR
PLX-4032	Plexxikon	B-RafV <sup>600E</sup>	Phase 1	HCS/X-ray
PLX-5568	Plexxikon	Kinase Inhibitor	Phase 1	HCS/X-ray
SGX-523	SGX Pharmaceuticals	Met	Phase 1	X-ray/HCS
SNS-314	Sunesis	Aurora	Phase 1	MS

Table 1. Fragment derived compounds and furthest stage of clinical development.  
(Adapted with permission from Chessari & Woodhead, From fragment to clinical candidate-a historical perspective. *Drug Discov Today*, 2009, 14(13-14), 668-675, copyright (2009) Elsevier).

2.2 Exploring chemical space

Drug discovery today critically depends on HTS of compound libraries *in silico* and *in vitro*. Novel chemical structures (also known as chemotypes) are of particular interest since these might display different properties to drug-like small molecules and may be used to interrogate biological pathways. Unfortunately, most approaches to create new compounds rely on using commercially-available known starting materials or building blocks and utilise existing reactions to generate small molecules, which are not well-suited to uncover novel chemotypes (Reymond & Fink, 2007). A change to the discovery of small molecules that possess biological activity, but are under-represented in commercial screening collections may provide suitable fragments for further development. An analysis by Stoichet and co-workers (Shoichet *et al*, 2009) revealed amongst other things that currently commercially-available compounds and libraries have more in common with compounds derived from natural products and metabolites than with a virtual library of 26.4 million molecules (chemotypes containing of up to 11 atoms of C, N, O, and F comprising 110.9 million stereoisomers). Is this a surprise? Stoichet argued that the reason current libraries are effective at all in identifying new chemotypes is that they are based, albeit largely unintentionally, on structures in naturally occurring molecules, which have coevolved with proteins that bind them.

In a recent study, Tan and co-workers analysed 40 top-selling small molecule drugs (39 of which are orally bioavailable), a collection of 60 diverse natural products (including the 24 identified by Ganesan as having led to an approved drug from 1970 to 2006) and 20 drug-like compounds from ChemBridge and ChemDiv. Each compound was analyzed for 20 calculated structural and physicochemical parameters, and then principal component analysis was used to replot the data in a 2-dimensional format representing 73% of the information in the full 20-dimensional dataset (for full details, see (Bauer *et al*, 2010).

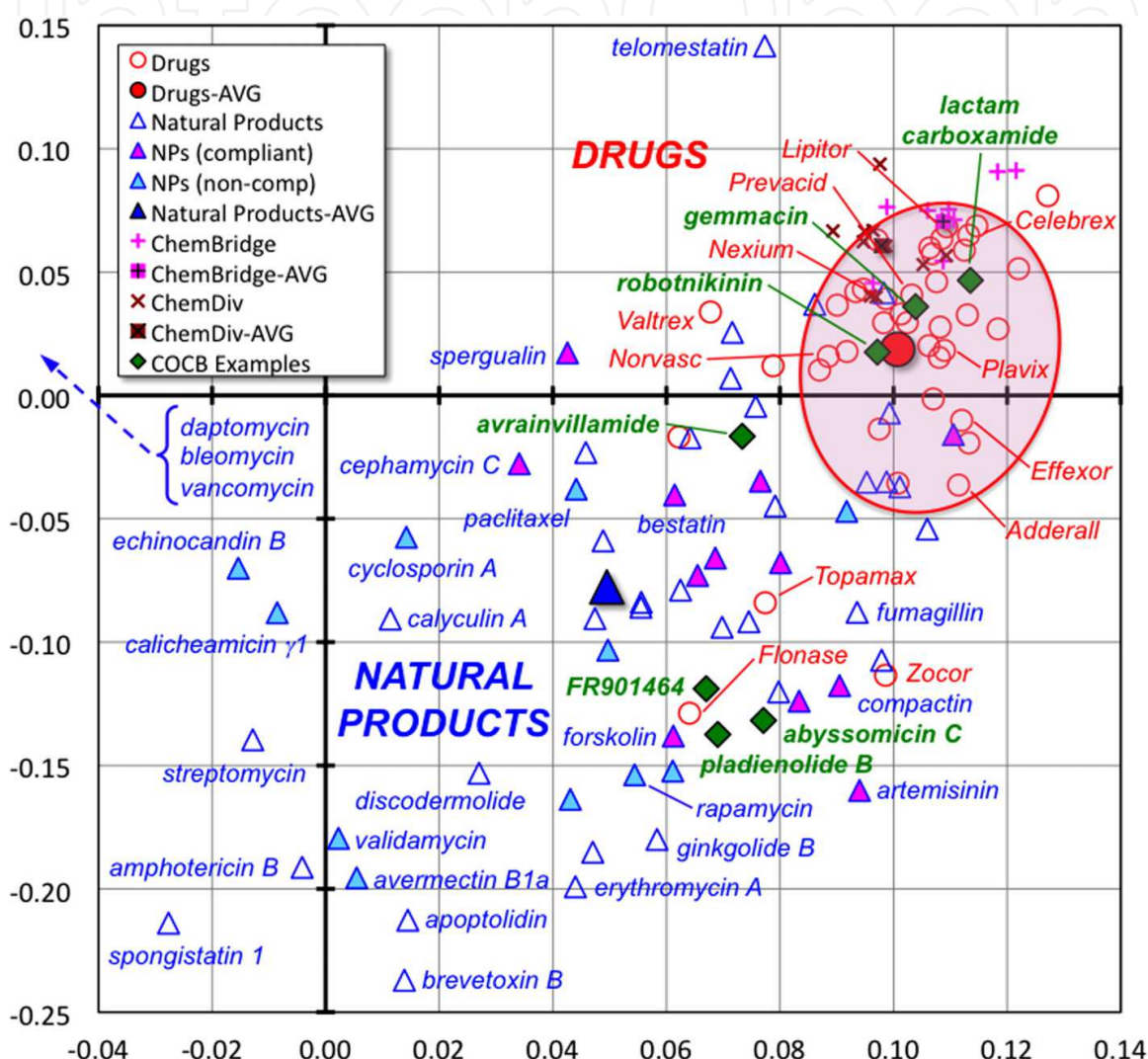


Fig. 6. Principal component analysis of 20 structural and physicochemical characteristics of 40 top-selling drugs (red circles), 60 natural products (blue triangles), including Ganesan's rule-of-five compliant (pink filled) and non-compliant (blue filled) subsets, and 20 compounds from commercial drug-like libraries (ChemBridge, pink pluses; Chem Div, maroon crosses). The two unitless, orthogonal axes represent 73% of the information in the full 20-dimensional dataset. Recent examples of natural products and library-derived probes that address challenging targets discussed herein are also shown (green diamonds). (Reprinted with permission from Bauer *et al.*, Expanding the range of 'druggable' targets with natural product-based libraries: an academic perspective. *Curr. Opin. Chem. Biol.*, 2010, 14(3), 308-314, copyright (2009) Elsevier).



Putting the details aside, the key message from this data representation (Figure 6) is that the top-selling drugs are located as a cluster in a specific area of the plot with the drug-like libraries overlapping the same regional zone. Moreover, the few outlier drugs are natural products or derivatives, and these molecules, along with the 60 natural products, span a much broader range of chemical space. In part, this study points to natural products as chemical architectures that not only cover chemical space best but also are likely to be suitable for developing probe and drug-like molecules that can modulate macromolecular proteins in various ways.

Small molecules have great potential to aid the process of understanding and improving human health. Accordingly, there is much incentive for using small molecules to explore new chemical space by employing methodologies that are aimed at exploring uncharted waters and leaving well-researched areas behind, but by no means forgotten. As we have seen, FBDD is beginning to prove that developing technologies outside mainstream medicinal chemistry can be fruitful. Aware of the fact that bioactivity is not randomly dispersed in the vast chemical space, chemists have been cultivating hypotheses that can bring them closer to the islands of bioactivities. Natural products have always been a source of inspiration and their structural motifs provide biologically relevant starting points for library synthesis to generate new molecules integrating pharmacophores known to produce biological activity. In addition to FBDD, emerging tools to guide compound discovery include diversity-oriented synthesis and chemical genetics.

### 2.2.1 Diversity-oriented synthesis

Diversity-oriented synthesis (DOS) aims to synthesize small molecules that cover incongruent targets in a multidimensional descriptor space (Burke & Schreiber, 2004). Essentially what this means is that multiple regions in a confined chemical space are targeted with small molecules often comprising a fragment of a pharmacophore with proven biological activity. Such collections are also essential to chemical genetics, which is discussed further below (section 2.1.2.). DOS is built on a solid platform comprising traditional medicinal chemistry but can also incorporate HTS technologies such as combichem. Essentially, drug discovery of small molecules can be categorized into three approaches that cover chemical space differently: The first approach uses target-oriented synthesis (TOS) and resembles a well-trodden path that relies primarily on nature to discover molecules with useful, macromolecule-perturbing properties. After isolation and characterisation, natural products possessing biological activity become a target for chemical synthesis. Using conventional synthetic chemistry based on retrosynthetic planning, the aim of TOS is to populate a discrete point in chemical space that is known to yield biological activity (Figure 7A). The second approach uses either medicinal chemistry or combichem and aims to explore chemistry space that is in close vicinity to a precise region known to have useful properties (Figure 7B). The source of the starting or lead compounds can vary and may include a natural product, a known drug or pharmacophore, or a rationally designed structure derived from i.e. a crystal structure of a macromolecule of interest. The aim in this approach is to access diversity to some degree using diverse building blocks and usually involves synthesising analogues of a given target structure using retrosynthetic planning. The synthesis effort in DOS aims to create a broad distribution of compounds in chemistry space (Figure 7C), including currently poorly populated (or even vacuous) space, and in the future, space found empirically to correlate best with desired properties. Synthesis pathways employed in DOS are branched and divergent, and they are planned in



the forward-synthetic direction (Bender *et al*, 2006; Burke & Schreiber, 2004; Spring *et al*, 2008).

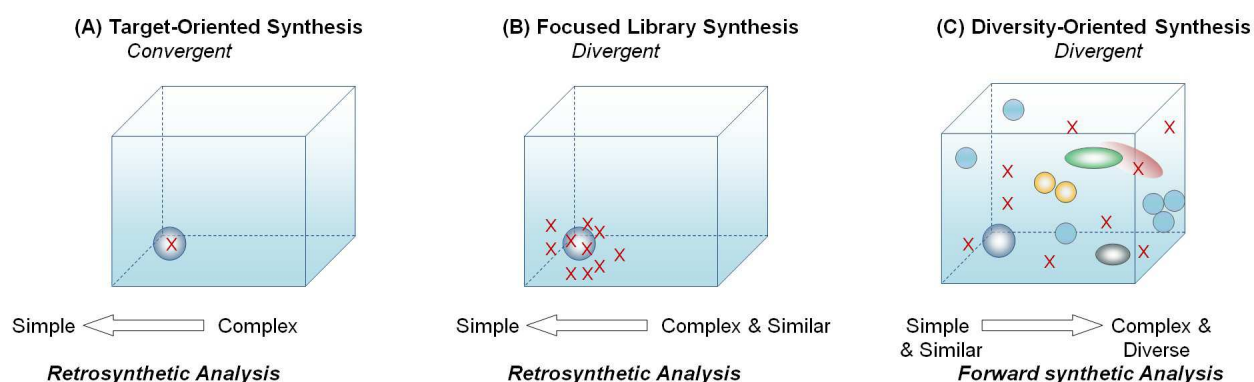


Fig. 7. TOS, focused library synthesis and DOS; a comparison of the planning strategies used (i.e. retrosynthetic or forward synthetic analysis and convergent or divergent synthesis) and the chemical space interrogated (i.e. focused point/area or diverse coverage). (Adapted with permission from Spring *et al*. (2008) Diversity-oriented synthesis; a spectrum of approaches and results. *Organic & Biomolecular Chemistry*, 2008, 6(7), 1149-1158. Available at <http://dx.doi.org/10.1039/B719372F>, Copyright, The Royal Society of Chemistry (2008).

As described in two prominent reviews (Burke & Schreiber, 2004; Spring *et al*, 2008), skeletal diversity can be achieved principally in two ways. The first method involves the use of different reagents and a common building block as starting point. This 'reagent-based approach' is also known as a branching pathway. The second method or the 'substrate-based approach' uses different building blocks that contain pre-encoded information of desired architectural geometry which are subjected to a common set of conditions leading to a diverse set of small molecules (Figure 8). Although there are not many successes at this point in time, DOS is used increasingly as an attempt to probe biological pathways or develop NMEs. Conceptually, it is important to appreciate that it is the functional diversity and not the structural diversity of small molecules that is a key measure of success in the application of DOS. For specific chemical strategies of DOS application, see for example (Burke & Schreiber, 2004; Hanson *et al*, 2010; Nielsen & Schreiber, 2008b; Spandl *et al*, 2008).

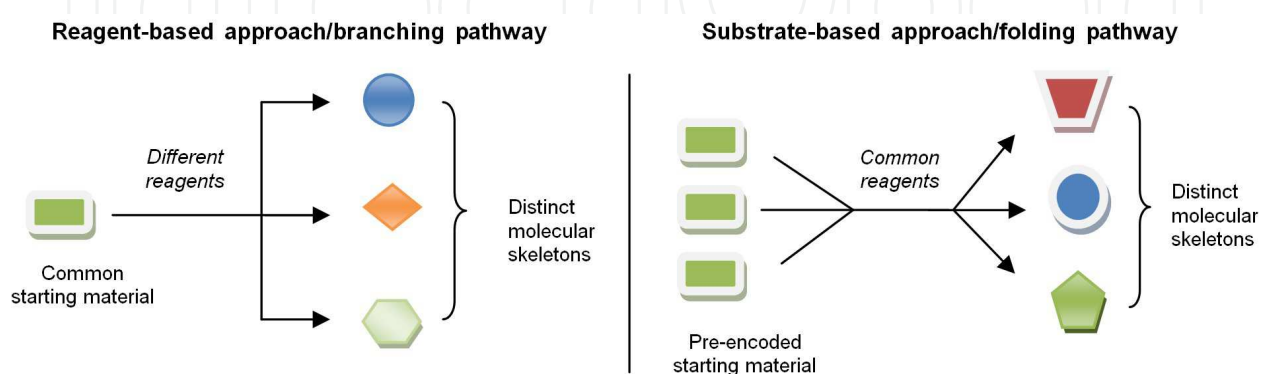


Fig. 8. Two common approaches for achieving skeletal diversity in DOS is "reagent-based approach/branching pathway" and "substrate-based approach/folding pathway".

### 2.2.2 Chemical genetics

In many ways, modern genetics began with the applied and theoretical work of the nature of inheritance in plants by German-Czech scientist Gregor Mendel in the mid-19th century. In comparison, the science in chemical genetics is only a couple of decades old, but has been gaining momentum in recent years. Chemical genetics has very much its origin in classical genetics and uses most of the methods and terminology already established. Genetic knockouts have been key to illustrating biological pathways and causations of pathological diseases and now the fields of chemical biology and related modern fields are enabling small molecules to be discovered and developed and used as chemical 'knockdowns'. To understand a system, you need to perturb it. This principle underlies most of the experimental sciences and explains why our depth of understanding of biological systems has been largely determined by the availability of tools that can be used to disrupt them (Stockwell, 2004). In order to close the genotype-phenotype gap, biological research has to reach beyond genomics, proteomics, and dissection of biological systems into their prime constituents (Bon & Waldmann, 2010). Protein function is regulated in complex networks with other biomacromolecules, small molecules and supramolecular structures like membranes (Zamir & Bastiaens, 2008). Whereas genetic manipulation results in a permanent alteration of the native structure of the network, chemical perturbations with small molecule modulators of protein function provides temporal control using dose-response explorations without fundamentally transforming the biological network (Stockwell, 2004). It is very attractive to use small molecules to perturb a biological system because of their dynamic nature, which offers many advantages: (i) ability to target a single domain of a multidomain protein, (ii) allows precise temporal control that is critical for rapidly acting processes, (iii) can target orthologous or paralogous proteins, enabling comparisons between species or redundant functions, and (iv) do not directly alter the concentrations of a targeted protein, thus avoiding indirect effects on multiprotein complexes (Lehar *et al*, 2008a).

The small molecules used to probe biological networks are ideally developed by mainstream medicinal chemistry and increasingly supported by modern methodologies such as DOS in order to encompass regions of chemical space that are not defined by existing screening collections as discussed previously. Essentially, chemical genetic studies can be designed to be either *forward* or *reverse* depending on the direction of learning that underlies their motivation (Nghiem & Kawasumi, 2007; Stockwell, 2004). *Forward* studies involve evaluating many chemical probes against one or a few phenotypes in order to identify active compounds, and reverse studies execute multiple phenotype measurements on a few related chemical probes to characterize their function. In both cases, the chemical probes can be analyzed across a panel of phenotypic assays to identify either broad activity or selectivity between the phenotypes (Lehar *et al*, 2008a). To elevate the complexity of the test system to reflect for example upon a diseased state of a cell combination chemical genetics (CCG) can be employed. CCG can be defined as the systematic testing of multiple perturbations involving chemical probes and can include either chemical combinations or mixed chemical and genetic perturbations. Classical and chemical genetics (Figure 9) are generally divided into *forward* screens, in which uncharacterized perturbations are tested against a selected phenotype to detect genes associated with that phenotype, and *reverse* studies, in which a specific gene or protein is modulated and multiple phenotypes are monitored to determine the effects of that specific target (Nghiem & Kawasumi, 2007; Stockwell, 2004). Studies involving combined perturbations can be similarly classified with the mechanistic focus shifted from individual targets to interactions between them (Lehar *et al*, 2008b).

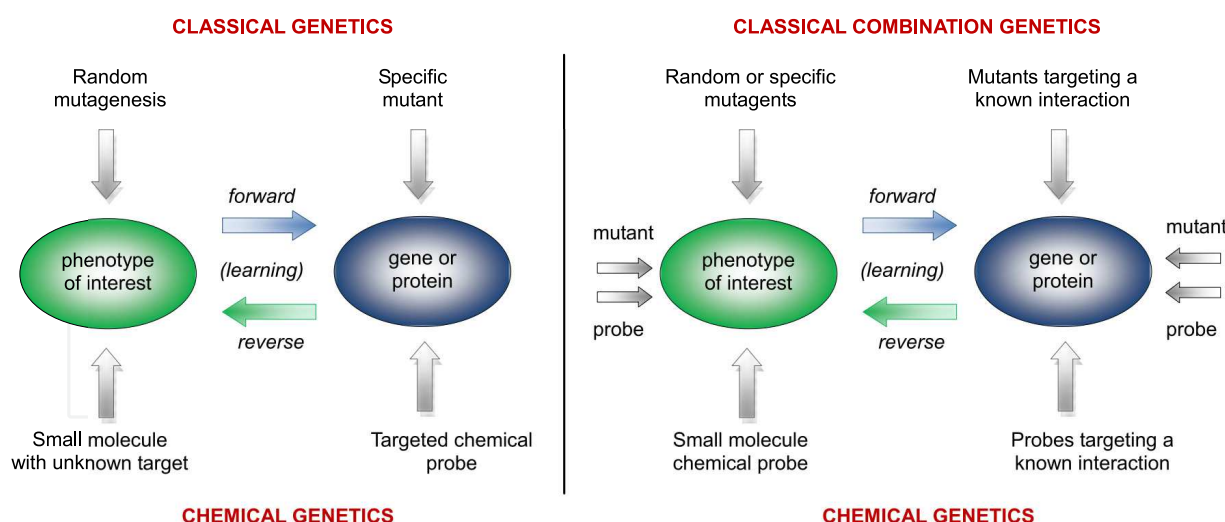


Fig. 9. Combined perturber studies in the context of forward and reverse genetics. The essence of classical and chemical genetics is to explore the function of individual genes or proteins. In combination chemical genetics, the focus of investigations shifts from individual targets to interactions between them or conditional target dependencies, and the perturbations are applied as combinations. (Adapted with permission from Lehar *et al.* Combination chemical genetics. *Nat. Chem. Biol.* 2008, 4 (11), 674-681, copyright 2008, Macmillan Publishers Ltd).

Chemical biology has clearly made an impact in drug discovery and great strides towards offering new technologies that can progress our understanding of human health has been made. Given the temporal control offered by small molecules and the ability to use combinations of small molecule modulators, chemical genetics promises to complement the use of pure genetic analysis to study a wide range of biological systems. Chemical genetics aims to answer questions in complex test systems and may provide the field with commercial chemical probes that can be used to probe pathways and elucidate more about biological targets. The discovery of the potent and selective deacetylase inhibitors tubacin and histacin are examples of how powerful DOS and chemical genetics can be in combination with computational methods such as principal component analysis (Haggarty *et al.*, 2003). However, good chemical probes for *in vitro* and especially *in vivo* perturbation are not easy to come by as small molecules are generally pleiotropic and they have multiple dose-dependent molecular targets that are often not fully characterized, which leads to unexpected activities. Obstacles and challenges are similar to those in drug development: small molecules often have inherent problems such as *in vitro* aggregation, poor solubility, difficulty in crossing biological membranes and reactive or toxic functionalities. At present, development of chemical probes for *in vivo* testing may be too ambitious a goal. As a result, evaluation of the effect of chemical 'knockdowns' in clinically relevant tissue should in the near future be in more complex assays that mimic for example malignant tissue. 3D cell culture technologies are increasingly becoming essential to *in vitro* screening. High content screening (HCS) has improved cell-based assays by combining high-resolution digital imaging with powerful software algorithms to increase the amount of data produced per well. 3D cell culture will not only empower HCS by supporting *in vivo* morphologies with current cell types, but also enable the use of primary and stem cells in drug discovery. Regardless of the challenges, primary and stem cells will become the focal point of 3D cell culture in the coming years (Justice *et al.*, 2009), which could take chemical genetics to the

next level. In summary the success of chemical genetics heavily relies on the availability of chemical libraries that offer structural diversity of small molecules that possess biological activity and complement libraries of compounds based on drugs and natural products (Lehar *et al*, 2008a). However, there is still a gap between developing commercial probes and inventing innovative drugs to treat illnesses.

### 3. R&D is moving global but will innovation increase?

*“Trying to invent new drugs is no picnic.”* Sir James Black (1924-2010).

Only a small percentage of design and construction of scientific hypotheses that form the basis for a project actually yield exciting lead agents, let alone NMEs. Although the level of investment in pharmaceutical research and development (R&D) has increased dramatically since 1950 to US\$50 billion per year at present, the number of new drugs that are approved annually is no greater now than it was in those days (Munos, 2009). From 1950 to 2008, the FDA approved 1,222 new drugs comprising of NMEs or new biologics (Figure 10). Historically, only approximately 1 out of 15–25 drug candidates survives the detailed safety and efficacy testing (in animals and humans) required for a drug to become a marketed product. As if these numbers were not disconcerting enough, from the industry’s point of view, of the few drug candidates that successfully become marketed products, only one in three will become a major commercial product (Zhao & Guo, 2009). The discovery and development of a drug has often been quoted to take 10-15 years and cost in the region of \$800 million to bring to market although the exact figure is probably much lower; i.e. the cost of NMEs is no doubt very high and close to \$800 million but in contrast “me-too” drugs where most research has already been established the costs are nowhere near this figure (Angell, 2004). Regardless of the exact cost of developing a drug, the process of its development is a high-stakes, long-term and risky activity that has few peers in the commercial world, but the potential benefits to the millions of patients with serious diseases provide a constant motivating force for everybody involved in drug discovery.

A closer analysis reveals that 28 small-molecule first-in-class NMEs that entered the market between 1999 and 2008 were first discovered using phenotypic evaluation methods such as the employment of cell-based or whole-organism assays (Figure 11). Moreover, 17 NMEs were from target-based approaches and 5 NMEs were derived from natural substances. In contrast, 83 (51%) of the 164 follower drugs were discovered via target-based approaches. A possible contributing factor to this trend could have been a lag time between the introduction of new technologies and strategies, and their impact in terms of the number of approved first-in-class NMEs derived from such approaches. However, such a lag is not strongly apparent in a comparison of the cumulative number of NMEs from the two approaches during the period analysed (Swinney & Anthony, 2011).

#### 3.1 Investment in education is vital to innovation

The investment in R&D has increased substantially in recent decades in efforts to obtain favourable market position and exclusivity in terms of IP position. The annual number of truly innovative new medicines approved by the FDA is not on the rise as highlighted in the previous section. Given the embracement of HTS technologies including combichem and FBDD combined with the improved understanding of disease pathogenesis, it is disappointing that there is no apparent evidence of an increase in the number of NMEs



approved. An immediate answer is related to the accelerating costs of R&D which hampers progression of many research projects. Another deep-rooted answer may be related to education policies: how pupils in schools as well as both under- and postgraduate students in universities are being taught in the chemical, physical & biological sciences. Firstly, the development of HTS is costly and therefore largely inaccessible to academia that often carries out drug discovery on a shoe-string budget. One consequence is that academia, who historically has been the driver of much innovation, will feel not only compelled to lower

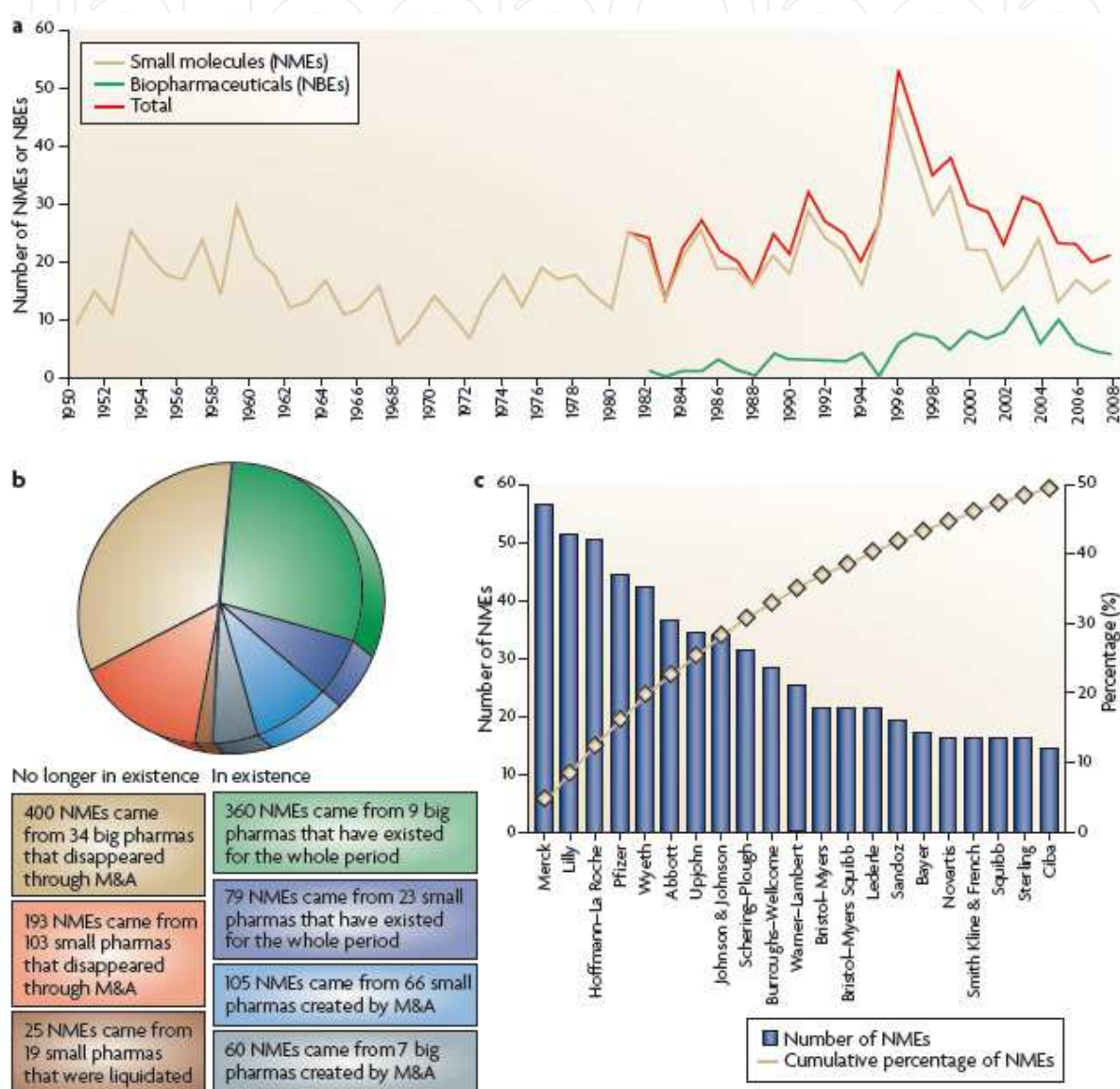


Fig. 10. Origins of new drugs. (a) Timeline of approvals of NMEs and new biological entities (NBEs) by the FDA between 1950 and 2008. (b) Characteristics of the 261 organizations that have produced the 1,222 NMEs approved since 1950. (c) 21 companies have produced half of all the NMEs that have been approved since 1950, although half of these companies no longer exist. In (b) and (c), both new small molecules and new biologics are grouped as NMEs for simplicity. M&A, mergers and acquisitions. (Reprinted with permission from Munos, B. Lessons from 60 years of pharmaceutical innovation. *Nature reviews*. 2009, 8 (12), 959-968, copyright 2009, Macmillan Publishers Ltd).



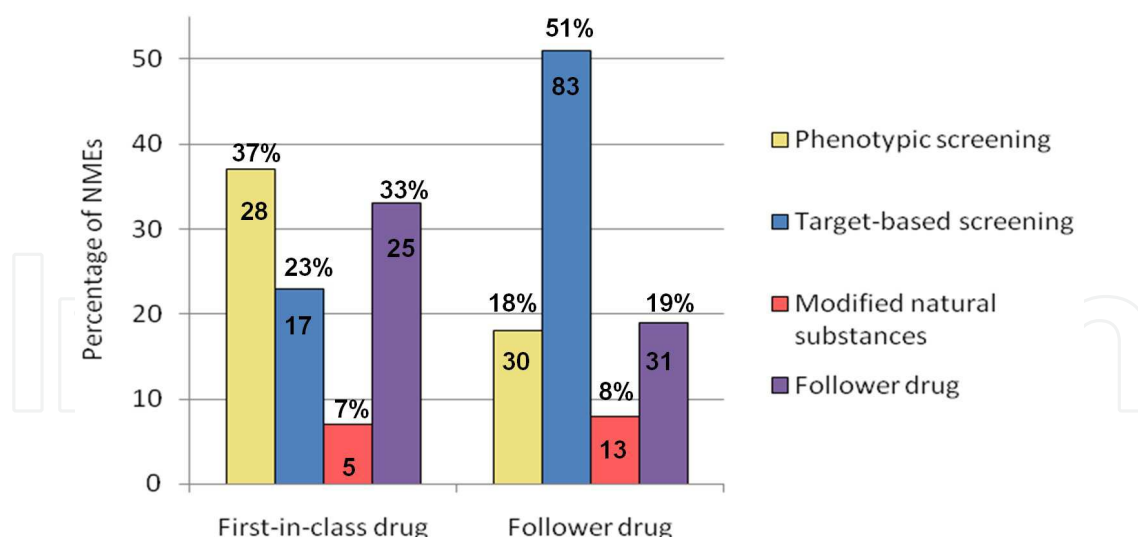


Fig. 11. The distribution of new drugs discovered between 1999 and 2008, according to the discovery strategy. The graph illustrates the number of NMEs in each category. (Adapted with permission from Swinney & Anthony. How were new medicines discovered? *Nature reviews*. 2011, 10(7), 507-519, copyright 2011, Macmillan Publishers Ltd).

their ambitions, but also hand over the baton to pharma- and biotech companies when it comes to innovative initiatives; that would be disastrous for many reasons. In particular, students would not be educated in using cutting-edge equipment and HTS technologies. Secondly, the approval of NMEs is also affected by the demonstration of adequate clinical safety and efficacy in humans which has become more complex, and ever-increasing amounts of data are now required by regulatory agencies (Lombardino & Lowe, 2004). Thirdly, it could also be argued that the dwindling supply of new drugs is related to a decrease in output by stifling the creativity of the scientists involved in drug discovery? This statement requires a more comprehensive discussion. In the western world the funding climate of academic institutions has changed and the pharmaceutical industry, in spite of scaling back on research operations and sizeable job cuts in 2010 (Mullin, 2010), is slowly returning to the funding levels available pre-recession and the international banking collapse in September 2008. For example, the UK funding landscape is having an impact on attracting and training students in synthetic organic chemistry. Many medicinal chemists working in the biotech and pharmaceutical industries received their PhDs in organic synthesis, a consequence of the view that excellence in organic synthesis is a prerequisite for a successful medicinal chemistry career (Frantz, 2003). However, the rise in small biotech companies has resulted in a demand for scientists that have research experience in multidisciplinary disciplines, and a broader education than in a single area such as synthetic organic chemistry (Pittman, 2010). Obtaining funding for chemical sciences may become more challenging in the future, due to a shift away from “responsive mode” applications; the success rate of EPSRC (the main British funding body for chemical sciences) applications has dropped from approx. 25% to 10% (Crow, 2008), and this coincided with a recent policy to limit applications from persistently unsuccessful academics (Lewcock, 2009). The EPSRC plans to cut research grant expenditure by £61 million to £372 million between 2010-2011 and 2014-2015. It will also stop accepting grant proposals regarding funding for PhD students by 2012, which instead will be supported exclusively through Centres for Doctoral Training Accounts (DTAs). Although, this shift provides a small £13 million rise in funding

for studentships through to 2015 to offset the research grant decline it is potential very damaging for British universities that do not hold DTAs (Extance, 2011).

Restricting support is likely to result in a reduction of the pool of potential answers/solutions to critical problems, which arise from current and future challenges. This has led to concerns within industry that a reduced emphasis on organic synthesis would negatively impact the quality of future generations of scientists working at the interface of chemistry and biology (Pors *et al*, 2009). To balance these changes the EPSRC has initiated “grand challenges”, where money is available to address key priorities for future collaborative research, such as in human health. These funding policy changes present opportunities for academics that can adapt, and a likely consequence is an increased degree of collaboration between organic synthesis and other disciplines. Ultimately this may result in the establishment of highly collaborative centres focused on chemical biology, drug discovery and other disciplines that support this important thematic initiative. One concern that industry has with such collaborative centres is that the students may find it more difficult to acquire highly specialised physical and synthetic organic chemistry skills and/or tools that would allow them to compete in a highly competitive job market. If, however, these centres do provide a thorough educational opportunity these PhD students may prove to be highly qualified for a career in medicinal chemistry and chemical biology, where success in projects frequently relies upon the successful collaboration and integration of multiple disciplines that are necessary for not only combating the major diseases, but also for becoming leaders in innovation (Pors *et al*, 2009).

Martin Schuurmann, the chairman of the European Institute of Innovation and Technology (EIT), has recently (Burke, 2011) opinionated that although Europe is a leader in research, it is not often in innovation. He believes that there are several reasons for this: a lack of education in entrepreneurship; too great a focus on research alone, rather than on the triangle of education, research and business; a lack of focus on entrepreneurship as the key driver for innovation; and a weak leadership, typically embodied by committees. Although Schuurmann was talking broadly about innovation, there is no doubt that education and experience in entrepreneurship is vital to innovation in drug discovery too. Europe currently offers insufficient opportunities for young investigators to progress independent careers and to make the transition from assisting supervisors/projects leader to being independent researchers in their own right. As a consequence, highly talented research scientists are being hold back in their career progression and there is also a danger that these promising young scientists are encouraged to seek advancement outside the continent. In an attempt to maintain the best scientists of the future generations in Europe, the European Union has established *Starting Independent Researcher Grants* (ERC Starting Grants), which aim to support up-and-coming research leaders who are about to establish or consolidate a proper research team and to start conducting independent research in Europe. The budgets for the 2009 and 2010 calls were €325 and €580 million with a successful funding rate around 15% and 10% respectively for the two calls (European Research Council, 2011). The low success rate suggests high competition across Europe to obtain such prestigious grants, but is actually favourable to scientists working in *Life Sciences* where around 35% of the total funding was allocated in both 2009 and 2010. As such the European Union recognises the importance of research at the chemistry/biological interface, which in part underpins drug discovery.

While the system for funding students is slightly different in the USA, similar challenges and obstacles remain for principal investigators and the students in their laboratories. Take

the example of cancer drug discovery, the National Cancer Institute, which is part of the National Institutes of Health (NIH) and the U.S. Department of Health and Human Services (DHHS), remains the principal agency for cancer research with other research grant support available from the Center for Disease Control (CDC) and Prevention and the Department of Defence (DOD) (National Cancer Institute, 2011a). The NCI is one of 27 Institutes and Centres that make up the NIH annual operating budget, which is allocated by the US Congress has remained flat at approximately \$4.8 billion since 2004 (National Cancer Institute, 2011b); a number that has drastically lowered the funding payline with success rates for new Research Project Grants (better known as a RO1 grant) currently at or below 10% in year 2008 and 2009 (U.S. Department of Health & Human Services, 2010). While scientists earlier in their career are often supported for a period of 3-5 years through several financial mechanisms including foundations and academic departments, the current funding situation remains dichotomised given these significant federal budget constraints. While there is an appreciated need to support those in the earliest stage of their career the risk-reward equation from the viewpoint of many of these funding agencies is one that does not currently support innovative or highly translational research programs. Unfortunately, these programs are often the foundation of budding young scientists in drug discovery. With no or very little funding available to fund young academics there is a widespread concern in both the UK and US that innovative initiatives are stagnant or even on the decline. Indirectly, the tough financial times in Europe and the US may benefit the emerging countries such as China. Because of its traditional education philosophy and the “one-child” policy of the past 30 years, Chinese parents are eager to educate their child in the best possible institutions and invest between RMB 10,000-15,000 (USD 1,200-1,800) per year of study in higher education (Lian, 2005). This is a substantial amount of money that a lot of families have to borrow, but ensures a hard-working mentality and ability to survive that benefit project leaders in governmental and industrial research environments. These qualities coupled with a desire to learn from the West are central to education of the newer generations of students in China and ultimately to the establishment of the Pharma industry and rapid increase in the numbers of smaller biotech companies.

Whether in Europe, the US or in the emerging countries, new strategies are emerging as a result of re-focusing and restructuring of the drug discovery field, leading to a new ‘front end’ between pharma and academia which aims at more successfully taking new therapeutic entities through pre-clinical and clinical development to the market (Tralau-Stewart *et al*, 2009). By addressing “grand challenges” such as in healthcare and in setting up collaborative centres with a focus on drug discovery it may be that academia can benefit from advice and support from the pharmaceutical and biotech industries given their longstanding success in this field. During difficult economic times, however, many private sector companies are forced to reduce their R&D budgets. This is an opportunity for academics to fill an important innovation gap. In the business sector we are witnessing this change through the significant licensing as well as merger and acquisition activity that has been documented through numerous partnership deals between academic institutions and pharmaceutical companies. The goals of academia and industry may become more closely aligned if, as suggested by the research councils of the UK, there is a shift in academia from fundamental/basic research towards knowledge transfer and innovation. The EPSRC, for instance, encourages the formation of partnerships between academia and industry through

its postgraduate CASE awards, which already serve to strengthen the ties between the two. Industry also contributes in a positive manner to undergraduate teaching of medicinal chemistry in many universities through educational tools, including industrial case histories as well as more traditional academic lecturers. However, some people in industry have the opinion that many of the key skills and novel techniques that are a part of modern drug discovery in industry are lacking at undergraduate level (Frantz, 2003). The challenge for universities is to ensure that the medicinal chemistry content of their chemistry courses is relevant to modern drug discovery and to address the opportunity for greater collaboration between industry and academia. Given the importance of the early stage knowledge transfer and the development of these core competencies, many institutions both in the UK and USA have developed or are developing both undergraduate and graduate curricula with a focus on bioinformatics, biotechnology and the interplay between the two. Whilst concerns over course content are, however, important for attracting and educating skilful chemists (Price & Hill, 2004), arguably the greater threat to medicinal and synthetic organic chemistry is funding. It is vital that both industry and academia work with public funding bodies to ensure that the core disciplines that will provide the next generation of innovative and skilled medicinal chemists are appropriately supported at the public, corporate and government level (Pors *et al*, 2009).

### **3.2 R&D in the emerging markets: An opportunity for collaboration and innovation?**

The uncertainty of the funding climate and the lack of innovation (as measured by number of NMEs being approved for market) have naturally given cause for concern. In contrast to what has happened in the western countries after the recession, it appears that emerging markets are on the rise, partly because of heavy investment by the largest pharmaceutical companies in countries such as China over the past decade. Principally, the significantly lower cost of research in emerging economies has led to a substantial increase in the outsourcing of the more routine activities such as compound synthesis and preclinical toxicity tests, but also outsourcing of R&D to augment internal capabilities of pharmaceutical companies are on the rise (Tremblay, 2010). Besides China, the pharmaceutical companies have used considerable efforts in establishing themselves in the emerging markets including China, India, Brazil, Russia, South Korea and Mexico. Given that 85% of the world's population lives in these countries combined with more open policies has meant that R&D has accelerated enormously in these countries. In 2004, China was the fastest-growing pharmaceutical market with growth rates of 28%. In 2015 Asia is expected to overtake Europe in pharmaceutical sales and become the second largest pharmaceutical market after the United States (Hughes, 2010). By 2050, Asia is projected to be the largest pharmaceutical market (Ward, 2008), which will have significant impact on drug discovery as a whole. The growth of the Chinese health-care market is largely being driven by the changing age profile of the population, its rapid economic development, and urbanization (Ward, 2008). As a consequence, the disease profile in China is changing. For example, type 2 diabetes was a rare disease in China 20 years ago, but its commonness has doubled in the past decade, with more than 55 million people affected today. A recent study conducted from June 2007 to May 2008 reported that 9.7% of the general adult population in China has diabetes and 15.5% have pre-diabetes, compared with 2.4% and 3.2%, respectively, in a similar study in 1994 (Yang *et al*, 2010). This increase in disease incidence has been ascribed to longer life expectancy and lifestyle changes that have occurred through



rapid economic growth in especially Asia. As the emerging markets grow, an appreciation of population factors and changes associated with modernization is vital to dealing with and predicting how the Chinese health-care market will evolve (Ward, 2008). This is already starting to impact early-stage research aimed at specific medical needs of patients in these regions but also clinical trials are initiated with focus on enrolling enough patients from central as well as remote regions of China. Both early-stage research and clinical trials are of huge interest to the pharmaceutical industry that is investing heavily in Asia. Current discussion also concerns whether the focus of medical research is directly applicable for patient populations in Asia (Hughes, 2010). China has an estimated 100 million people suffering from hypertension and, with 62% of males being smokers, the country's lung cancer rates are among the highest in the world (Hughes, 2010). India, the second largest populated country in the world with over a billion citizens, has also seen an increase in lifestyle-associated diseases. By 2025, there will be more than 185 million people over the age of 60 years in India. As is often the case with an elderly population there is an increased risk of developing diabetes, cardiovascular disease and maybe also region specific diseases. As a result it is important to think of the medicines that will be available for these countries with regard to the types of disease, as well as their cost and accessibility (Hughes, 2010). Despite of the investment in the emerging markets, recent data show that the US remains the single-largest location of pharmaceutical invention (Friedman, 2010). They also show that while the established pharmaceutical countries remain strong, there is little measurable innovative activity in terms of NMEs from India or China between 2001 and 2009. However, the factual situation is probably somewhat different due to a substantial time lag of 10 years or more between the initial discovery of a potential drug and its market approval. Indeed, China became the world leader in 2009 in terms of the number of chemistry patents published on an annual basis, according to Chemical Abstracts Service (CAS), a division of the American Chemical Society (Rovner, 2010). Accordingly, the recent nature of the increase in investment in innovative research in China and other emerging countries (Friedman, 2010) could facilitate an opportunity to innovate in a number of areas and as a result lead to a higher number of NMEs for market approval in the future. As such, the outlook for the patient is clearly very exciting. The next 50 years could see joint efforts between established and emerging markets in advancing many industries and technologies including drug discovery. The strategic planning and the vision by the pharmaceutical industry and American and European governments would facilitate a continuous input from established markets with R&D expertise that would maintain a high level of leadership in innovation, but also enable the emerging markets to be key players in future innovation.

#### 4. Future directions

*"Prediction is very difficult, especially about the future."* Niels Bohr (1885 – 1962)

Drug discovery has come a long way since Paul Ehrlich's research into dyes for medicinal properties. Drug discovery now requires a multidisciplinary effort and the continuing need for the education of excellent scientists working at the interface of chemistry and biology is imperative, not only to successful drug development, but also to the exploration of new targets using small molecules to probe cellular and molecular mechanisms. Indeed, small molecules designed and synthesised in chemistry laboratories have been shown to be valuable for treating diseases and constitute many of the medicines marketed today (Nielsen & Schreiber, 2008a). Consequently, their effect on biomedical research during the past decade has been dramatic, providing both new tools for understanding living systems as



well as enabling a didactic transition from biology to medicine (Dobson, 2004; Nielsen & Schreiber, 2008a; Stockwell, 2004). The foundation of HTS technologies, the availability of chem- and bioinformatic databases coupled with emerging tools such as FBDD, DOS and chemical genetics has led drug discovery into the 21<sup>st</sup> century with optimism for further advancement and understanding of what is required for successful drug development. We know that there is no “magic bullet” around the corner, but through hard work and innovative thinking we are likely improve our knowledge and slowly but incrementally develop better drugs. There must also be an element of braveness and entrepreneurship if we are to solve challenging targets and there is a need for industry and governmental organisations to finance such ventures. For example, ventures into underexploited regions of chemical space is to expand the range of ‘druggable’ targets, such that the identification of new ligands for currently challenging targets such as protein-protein interaction (Fuller *et al*, 2009) ultimately becomes routine. Success in this endeavour is likely to have major positive impacts in medicinal chemistry, chemical biology and drug discovery (Moura-Letts *et al*, 2011). It is worth noting, however, that the commercial success of a drug is not related to the novelty of the mechanism upon which it is based, but the differentiation that it provides (Booth & Zimmel, 2003; Ma *et al*, 2008). Finding a new therapeutically relevant target is extremely difficult and pioneering drug discovery has become prohibitively expensive. Many validated targets should also be further exploited alongside innovative initiatives to provide better products with lower risk and cost (Zhao & Guo, 2009).

However, there is cause for concern. Declining government funding and reformed educational policies in the western world are likely to have serious implications for drug discovery educators and practitioners, which could widen the already significant gap between research scientists at the highest level and the education of students at undergraduate and postgraduate level. There is a real concern that the scientists of tomorrow will not possess the ‘right’ tools in the toolkit to be able to effectively interrogate and address the questions being asked by research scientists in academia and industry today. The challenges can only be met if the government agencies worldwide are willing to invest in the education of academics and students alike. The onus is also on academics to be able to adapt to the rapidly changing funding priorities (Pors *et al*, 2009). In addition, drug discovery is entering a period of uncertainty where it is vital that opportunities in the emerging markets are grasped by the horn. A close collaboration between the pharmaceutical industry, governments in US and Europe and the emerging markets is essential for adapting to ever-increasing costs of drug discovery. Accordingly, the recent nature of the increase in investment in innovative research in China and other emerging countries could facilitate an opportunity to innovate in a number of areas and as a result lead to a higher number of NMEs for market approval. The next 50 years could see joint efforts between established and emerging markets in advancing drug discovery. The strategic planning and the vision by the pharmaceutical industry and American and European governments would facilitate a continuous input from established markets with R&D expertise that would maintain a high level of leadership in innovation, but also enable the emerging markets to be key players in future innovation.

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Drug discovery and development process aims to make available medications that are safe and effective in improving the length and quality of life and relieving pain and suffering. However, the process is very complex, time consuming, resource intensive, requiring multi-disciplinary expertise and innovative approaches. There is a growing urgency to identify and develop more effective, efficient, and expedient ways to bring safe and effective products to the market. The drug discovery and development process relies on the utilization of relevant and robust tools, methods, models, and validated biomarkers that are predictive of clinical effects in terms of diagnosis, prevention, therapy, and prognosis. There is a growing emphasis on translational research, a bidirectional bench to the bedside approach, in an effort to improve the process efficiency and the need for further innovations. The authors in the book discuss the current and evolving state of drug discovery and development.

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