Beyond the genome

Future perspectives of drug-discovery chemistry

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Dedicated to Professor Alain Krief, at the occasion of his 60th Birthday.

Summary **Au-delà du génome : de nouvelles perspectives en chimie thérapeutique**

Small molecules drug discovery in the post-genome era can be defined as the intersection of the genome and the chemical space. The fraction of the genome of interest is the one which is coding for proteins which play a critical role in diseases or pathological states and which are also considered as druggable (amenable to proteins function modulation by small molecules). The chemical space, per se, has almost no limit, and has to be reduced to practice, on the basis of chemical feasability, compounds drug-like properties and compounds ability to modulate proteins function. The aim of chemical genetics is to provide tools to discover new drugs at the intersection between these two worlds. One way is to extend the diversity of existing collection of compounds with respect to pharmacologically relevant diversity. The other approach consists of identifying new targets (kinases or phosphatases for example) within known « druggable » families, by exploring intra-cellular signal transduction pathways. Moving from chemical genomics (one ligand for every gene product) to chemical genetics (one drug like molecule modulating the function of one druggable target) will be a critical success factor in post-genomic drug discovery.

Mots-clés **Médicaments, chimie thérapeutique, chimie génétique, kinases, phosphatases.**

Key-words **Drugs, medicinal chemistry, chemical genetics, kinases, phosphatases.**

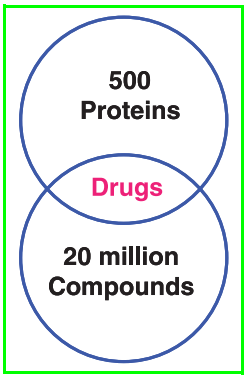

Figure 1 - XXth Century drug discovery.

Most of known drugs (around 10'000) discovered to date achieve their activity through interactions with 500 different proteins. Chemists, so far, have identified and characterised around 20 millions of discrete molecules (either synthetic molecules or natural products) which cover a large panel of very distinct properties, including the ones which make useful therapeutic agents (*figure 1*).

Functional genomics and proteomics efforts aimed to characterise the 30/35K genes of the human genome will probably and rapidly identify 5 to 10K new proteins of therapeutic relevance (defined as the ones which play a critical role in diseases or pathological states and which are also considered as druggable, in other words, amenable to protein function modulation by small molecules). It means that the number of targets for small molecule drug discovery may suddenly increase by a factor of at least 10 to 20.

How are chemists going to face this challenge?

The portion of the chemical space which has been explored so far is indeed very small: it has been estimated that the theoretical number of small molecules (MW < 650) obtainable by combining the most frequent atoms found in drugs or nature, while respecting valence rules is between 10^{40} to 10^{60} (*figure 2*).Of course, these numbers are totally unrealistic but simply (?) tell us that the chemical space is essentially unexplored and has almost no limit. This is in sharp contrast with the human genome, which is fully decrypted and well defined. The good news here is that chemistry has a bright future in the post-genome era since we are mastering a field of investigations which has never been as open and promising as it is today (in particular in terms of generating competitive advantages in the drug discovery race of the next decades). The bad news is the syndrome of « the needle in a haystack ». It is nice to have a boundaryless chemical space, but how to focus and reduce it to practice without spending time and resources in useless and endless directions?

How will combichem offer the diversity we need to hit forthcoming unknown new targets?

So the challenge of small molecules drug discovery in the post genomic era is to find new drugs at the intersection

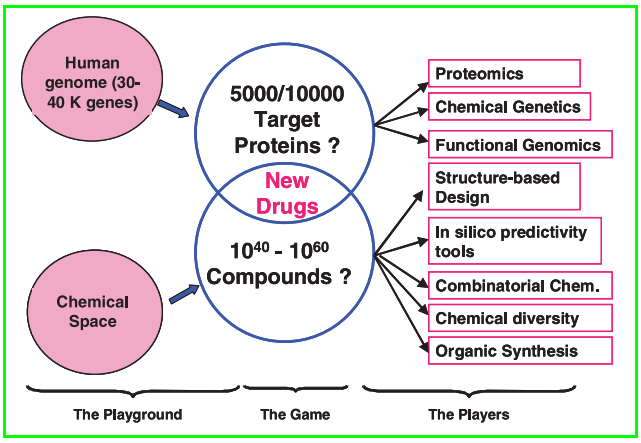

Figure 2 - The challenge of the XXIst Century.

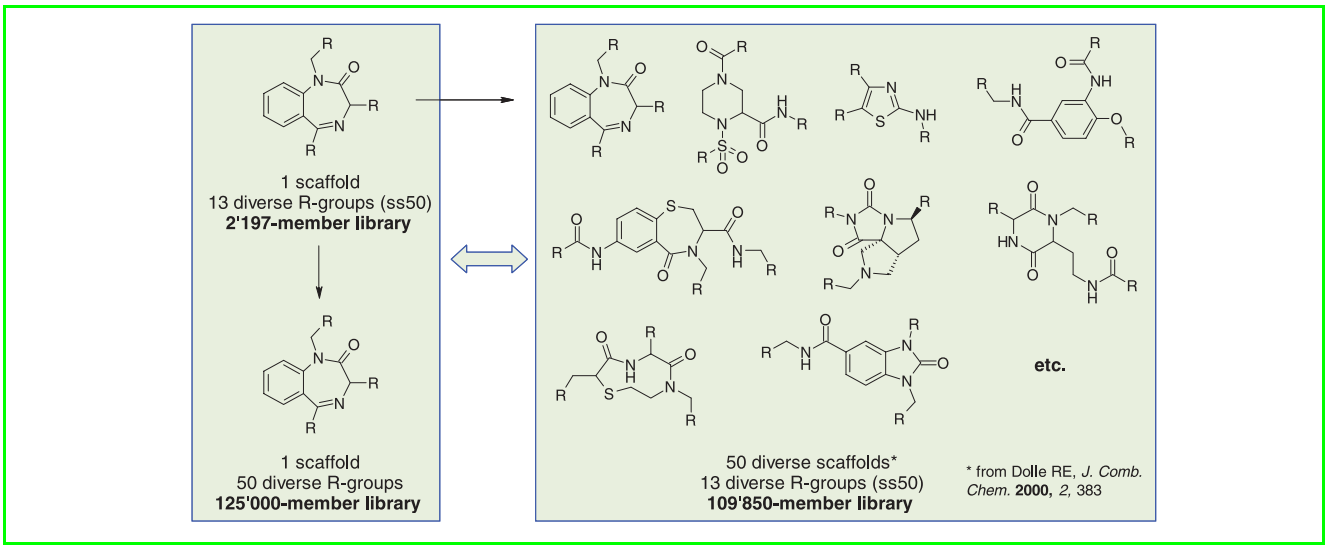

Figure 3 - Primary library of benzodiazepine derivatives.

between the genome (proteome) and the chemical space. One way to face this challenge is to extend the chemical diversity of compounds to be initially screened for their ability to bind to newly discovered proteins and evaluated further for their ability to modulate the function of these new proteins.
Synthesis of compounds libraries through combinatorial chemistry techniques is generally recognised as the method of choice towards that goal. But… how can we optimise combinatorial chemistry to increase diversity for efficient drug discovery? And one frequently asked relevant question is the following: is it better to synthesise a huge library around a single scaffold or is it better to prepare small libraries around various scaffolds? Let's take the example (*figure 3*) of a primary library of benzodiazepine derivatives with 3 points of diversity, each with 13 different groups (leading to a total of 2'197 member library). In order to increase the diversity (and ultimately increase the chance to hit novel unknown proteins), is it better to prepare a single benzodiazepine library of 125'000 cpds (by combining 50 different R groups instead of 13 (in each position) or is it better to prepare a 50 scaffolds library of 2'197 cpds each (keeping 13 different substituents in all 3 positions)?
In order to address that question, chemists at Serono have developed a new computational method to assess and visualise diversity in terms of 3D molecular shape. Normalised ratios of principal moments of inertia (calculated from Corina 3D structures of individual molecules) are plotted into 2-dimensional triangular graphs defined by three corners, corresponding to archetype « envelope » shapes of spheres, discs and rods. Some examples of molecules exhibiting these extremes as well as intermediate geometries are shown *figure 4*.

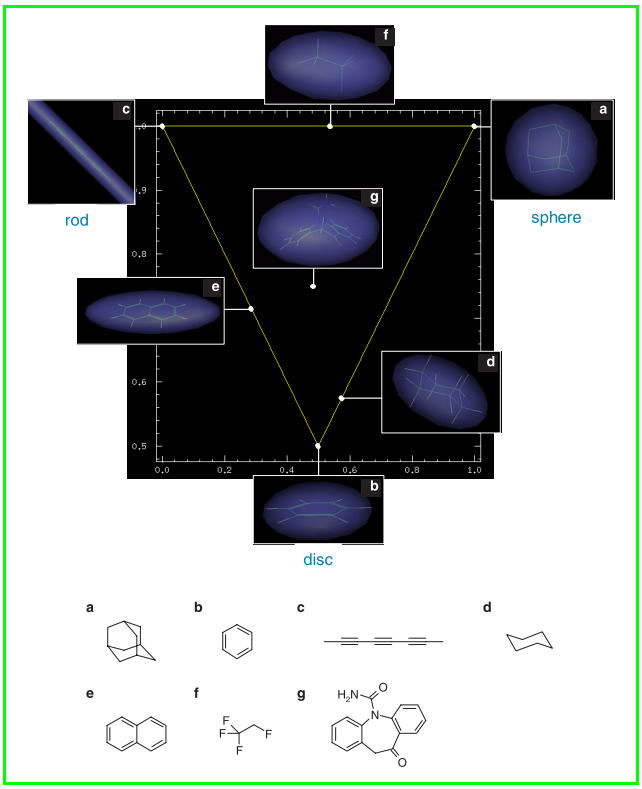

Figure 4.

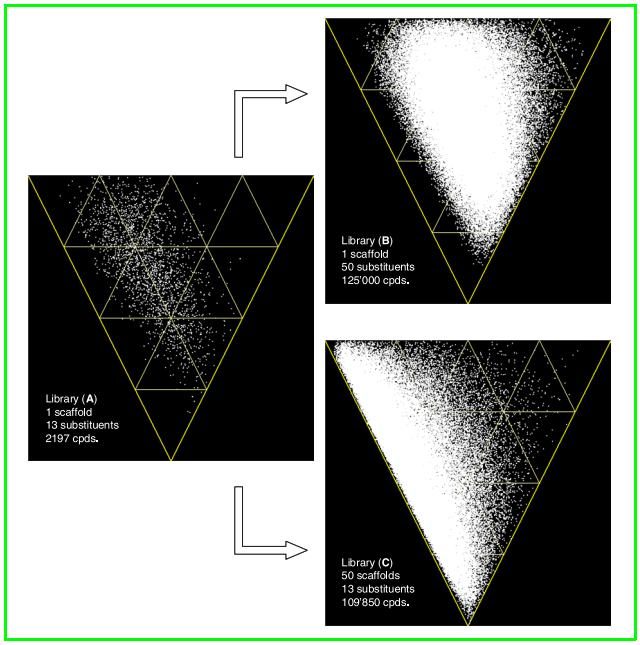

Figure 5 - Comparative visualisation of the 3 libraries described in *figure 3*.

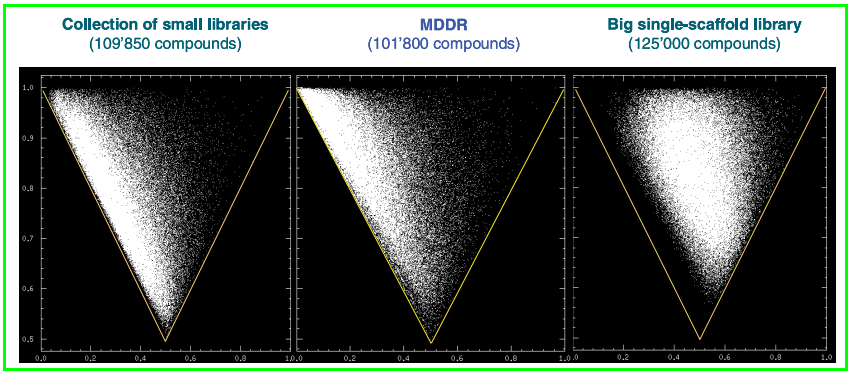

Figure 6 - Comparison with MDDR (101'800 compounds).

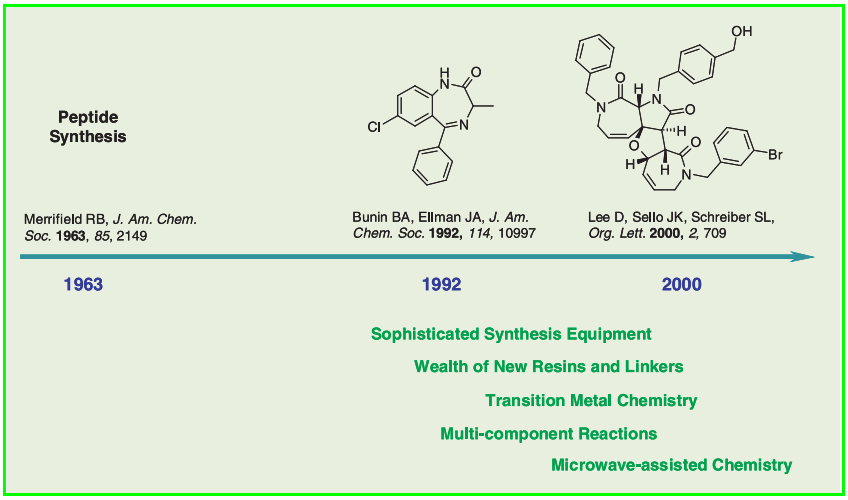

Figure 7 - Future evolution of combichem.

The *figure 5* displays a comparative visualisation of the 3 test libraries described in *figure 3*, according to the shape diversity analysis described above.
It appears clearly that the multi-scaffold library (C) is more diverse than the single-scaffold library (B) in terms of molecular shape, in that it contains more compounds with discoïd and elongated shape. But… is this pharmacologically meaningful? To address this question, the shape diversity analysis has been applied to a collection of compound known to interact with biological targets, namely the MDL Drug Data Report (MDDR) collection, comprising 101800 compounds, currently under investigation as potential drugs.
Results analysis (*figure 6*) show that there is a high similarity between the « multiple scaffolds » collection and MDDR, while the empty regions of the « big library » appear pharmacologically relevant. The other observation is that none of the displayed library is populated by « sphere » shaped or « globular » molecules. Instead, libraries built from a broad selection of currently available scaffolds (as the multiple scaffolds library described here) tend to be quite redundant among each other. On the other hand, we know that many natural products have got unique 3D-architectures found to interact with a broad range of biological targets. The lesson is that combichem in the future should not only focus on the generation of new and diverse scaffolds, but particularly also on new more « natural product-like » chemotypes. This is where the new generation of combichem should go (*figure 7*) and where the chemical diversity will come from.

In practice, this means that synthetic chemists will need access to large amounts of natural-product derived building blocks, will require sophisticated synthetic and purification equipments for library production, will look for new resins and linkers to increase the scope of application of solid-phase chemistry, and will rely tightly on the invention or validation of new reactions (as for example transition metal chemistry) or new technologies (as for example micro-wave assisted synthesis) to push limit of chemical feasibility. Combichem will move its focus from quantity to **quality**, in terms of numbers (less molecules but better chosen, more scaffolds), in terms of purity (no mixture, each individual compound will be properly analysed) and amount of material produced (at least a few mgs each, in order to evaluate and confirm activity of library compounds in sophisticated, diverse, functional assays, and not only in a single-shot binding assay).

Do we have new targets to fit our diversity?

Most of protein functions associated with pathological conditions are mediated by protein conformational changes and protein-protein interactions. In terms of drug discovery, what counts is to find ways to modulate a target protein function, not to hit the protein itself. This means that, partner proteins (upstream or downstream), which are able to control the function of a target protein, become themselves exciting targets for drug discovery. Understanding the complex processes of protein crosstalk becomes therefore essential, in particular to discover new individual target proteins belonging to well-known classes of therapeutic targets (enzymes for example). This is the world of « signal transduction » (*figure 8*), which for chemists has the tremendous advantage to propose new targets for drug discovery within the scope of current knowledge and know-how.

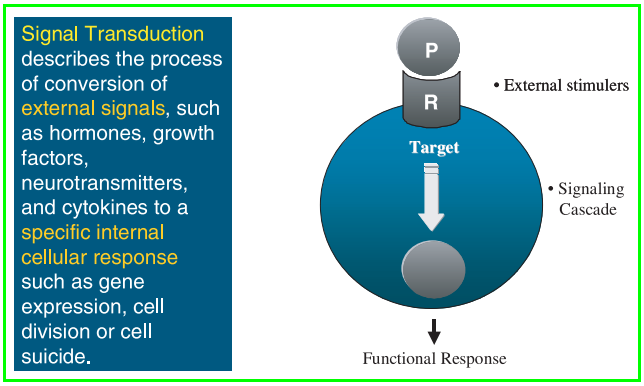

Figure 8 - Signal transduction.

Indeed, plenty of signal transduction molecular mechanisms involve proteins conformational changes, which are under the control of kinases and phosphatases, two enzyme

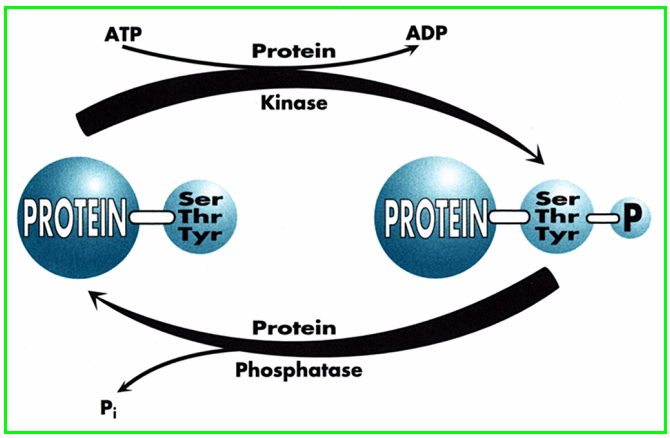

Figure 9.

classes that are tractable targets for drug design. Protein kinases catalyse the phosphorylation of Ser, Thr or Tyr residues (*figure 9*) of proteins, leading to phospho-proteins which generally adopt a different conformation, allowing them to interact with different partner proteins compared to the native, un-phosphorylated ones. Phosphatases, on the contrary, catalyse the de-phosphorylation of these phospho-proteins.

It is important to note that both enzyme types function through very distinct mechanism since kinases are all characterised by a well-preserved ATP-binding site, close to the catalytic site (since kinases transfer one phosphate residue to proteins, generating ADP as a by-product) while phosphatases work in a way totally independent of ATP, generating inorganic phosphate upon the cleavage of the phospho-protein bond.

Since the pioneering work of Ed Fisher and Ed Krebs (who were awarded the Nobel prize in 1992), the reversible phosphorylation of proteins has been widely recognised as central to the regulation of most aspects of cell function and cell physiology. Increasing numbers of human diseases are known to involve mutations, over-expression, genetic association or malfunctioning of protein kinases and phosphatases, and their regulators and effectors. Signal transduction, mediated by protein phosphorylation is extremely complex and our understanding of signalling mechanisms and their implication in diseases is still in its infancy. However, it represents a fantastic field of investigation to explore where small molecules will play a critical role, both in helping understand cell biology mechanisms to gain knowledge and progress, but also,

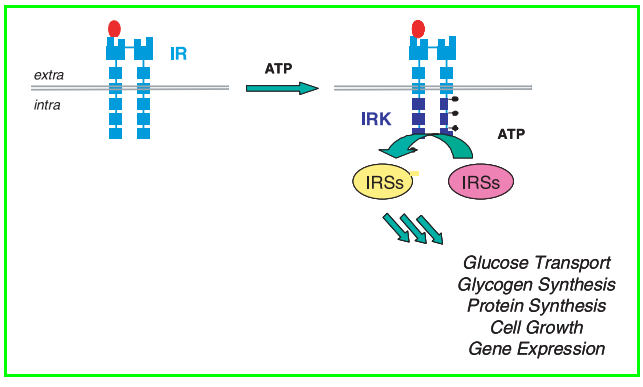

Figure 10 - The insulin receptor mediated signal transduction.

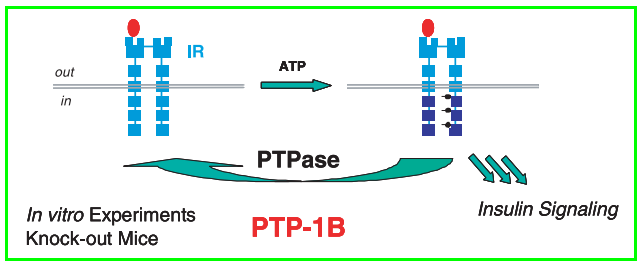

Figure 11 - PTP1b and insulin receptor desensitisation.

hopefully, in proposing therapeutic solutions to unmet medical needs.

Let's take the example of insulin which implication and therapeutic usefulness is well-known in diabetes type 1, while diabetes type 2 is characterised by insulin-resistance and impaired glucose tolerance with dramatic consequences for patients (blindness, kidney failure, amputations and heart diseases). Insulin resistance appears to involve an early process in insulin signal transduction which is initiated through the binding of insulin to the membrane insulin tyrosine kinase receptor (IR), which causes auto-phosphorylation of the receptor kinase and activates phosphorylation of other protein substrates, including IR substrate proteins (IRS-1, IRS-2, etc.) leading to a cascade of intracellular events which mediate the biological effect of insulin (*figure 10*).

Activation (phosphorylation) of the IR by insulin is reversed by the action of protein tyrosine phosphatases (PTP's) among which PTP1B has been clearly identified as a major player, based on in vitro experiments and knock-out mice models (*figure 11*).

Interestingly enough, it has also been found that PTP1B is involved in regulating the leptin-signalling pathway as well, and resistance to the leptin hormone is a hallmark of obesity. Thus, PTP1B is thought to function as a negative regulator of insulin and leptin signal transduction; PTP1B inhibitors have therefore the potential to restore insulin/leptin sensitivity and should be effective in treating type 2 diabetes and obesity, which are linked diseases.

The search for PTP1B inhibitors is currently extensively pursued by several pharma and biotech companies. Our efforts in Serono, based on rationale design (screening of focused libraries around proprietary scaffolds design with the help of PTP1B X-ray structures and in-house SAR studies), followed by drug-like properties optimisation led us to identify PTP1B inhibitors which increase glucose uptake in C2C12 muscle cells and decrease plasma glucose and insulin levels in genetically modified obese mice (db/db) upon oral administration in a dose dependant manner, with no sign of toxicity. Efforts are currently pursued to move the most promising PTP1B inhibitors to the clinic and evaluate their therapeutic potential in diabetic or obese patients.

The insulin/PTP1B example illustrates in a powerful way that blocking phosphatases can stimulate a signal transduction cascade and therefore mimick or replace a secreted protein which action is beneficial in pathological conditions. Inhibition of kinases (which, most of the time positively relay signalling events) is, on the opposite, a powerful way to inhibit or control signal transduction cascades, which become particularly relevant in drug discovery when pathological conditions are associated with stimulation of

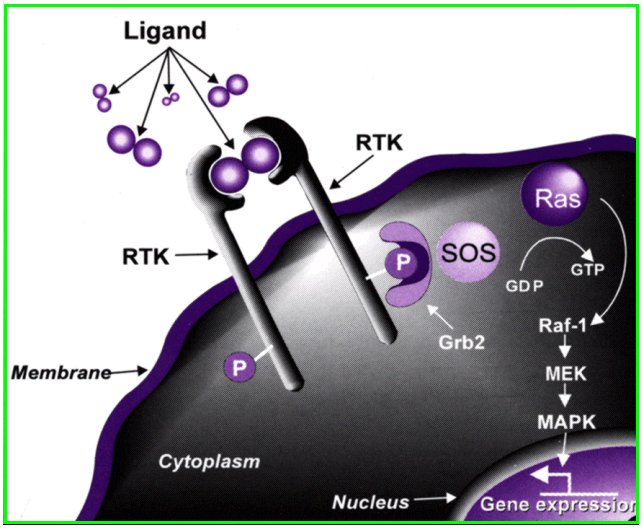

Figure 12 - The MAP kinase cascade in drug discovery.

intra-cellular signalling (see the example of MAP kinase cascade in *figure 12*). This is the case in important therapeutic areas like cancer, inflammation and apoptosis-related disorders where efforts to find selective kinase inhibitors have literally exploded in the last five years. A landmark event occurred in May 2001 when Gleevec, the first important drug targeting specifically a protein kinase (ABL) was approved for clinical use to treat chronic myeloid leukaemia.

The human genome encodes for around 500 different kinases, which control most of cellular events, directly or indirectly. This is what makes kinases attractive as a drug target class. However this also raises immediately two important questions: what kinase for what disease? And how to design selective inhibitors for specific kinases of therapeutic interest?

What kinase for what disease?

Validation of individual kinases for drug discovery (which means to get enough convincing evidence that inhibitors of such kinases will demonstrate a therapeutic effect in patients during phase II clinical trials) is not trivial and remains one of the most challenging aspect of post-genomic drug discovery. Dissection of signal transduction mechanisms is certainly a good starting point, generally followed by knock-out animal experiments and/or pharmacological studies with known inhibitors. However, none of these approaches is fully satisfactory and new ones are currently under investigation based on chemical genetics, as for example the Analog-Sensitive Kinase Allele (ASKA) technology where chemists have engineered modified kinases and inhibitors (by generating functionally active kinase mutants which are specifically inhibited by chemically modified inhibitors), thus allowing to study specific responses in vivo in knock-in animals (and therefore validate the kinase for a given disease) prior to start « Med Chem ». Such mouse disease models with functionally intact, specifically and pharmacologically inhibitable kinase targets will also provide invaluable information with respect to therapeutic index linked to the target kinase inhibition, new substrates identification and biomakers discovery. This is a beautiful example where a multidisciplinary approach (chemistry, together with structural biology, molecular biology, genomics and pharmacology) is providing new breakthough tools which will allow drug discovery to progress very rapidly.

Designing selective kinase inhibitors

Beyond the choice of the kinase, the next challenge will be to design selective inhibitors. So far, the vast majority of kinase inhibitors reported to date are ATP competitive, which means that they bind to the ATP binding site, which is common for all kinases and which is highly conserved in terms of amino acid sequence. It is therefore not surprising that plenty of ATP-competitive inhibitors are poorly selective (as for example staurosporine). But… is it possible to design selective ATP-competitive inhibitors? As part of our programme directed toward the discovery of JNK inhibitors in inflammation/apoptosis related disorders, we have discovered a new chemical class of ATP-competitive inhibitors derived from the benzothiazole scaffold. First compounds from this series which were identified as potent JNK inhibitors also displayed strong activity against a few other kinases, as shown by the selectivity profile depicted in chart A below (*figure 13*).

Chemical modifications based on JNK 3D-structure, docking experiments and in-house SAR data provided second generation JNK inhibitors, which were found highly selective

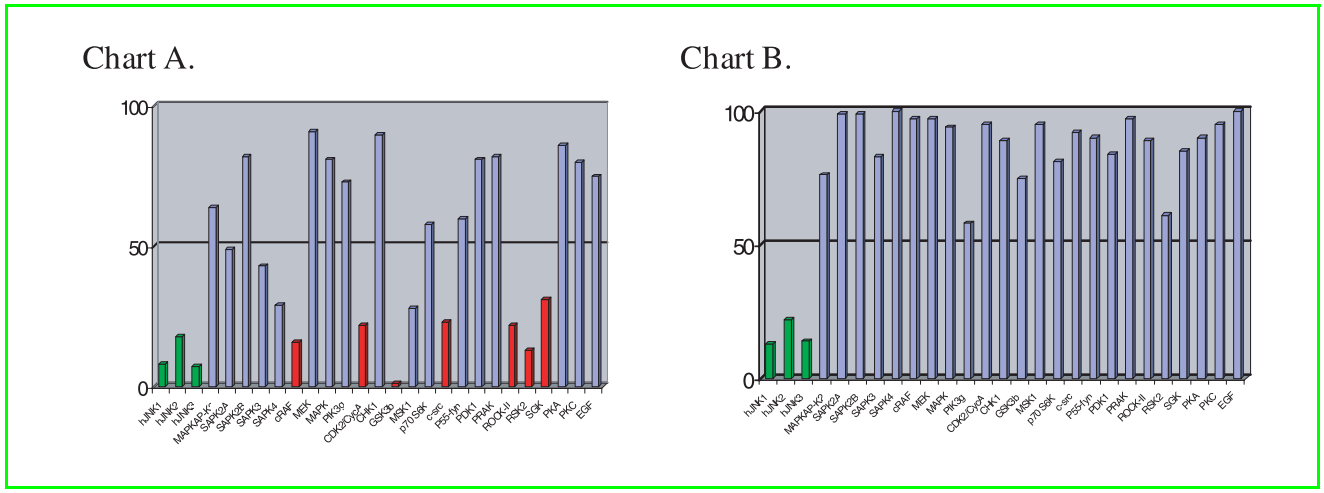

Figure 13 - Kinase selectivity profile.

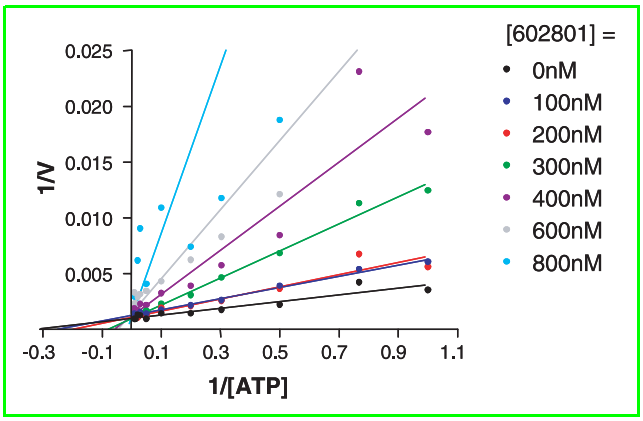

Figure 14.

versus other kinases, as shown by the selectivity profile depicted in chart B (*figure 13*). Kinetic experiments at various ATP and inhibitor concentrations demonstrate that this compound is purely ATP competitive as shown by Lineweaver-Burk representation of *figure 14*.

The best JNK inhibitors identified so far from this project are currently evaluated in pre-clinical studies, based on preliminary promising results in animal models of auto-immune diseases and neuronal apoptosis.

This example shows that it is possible to design new potent selective inhibitors of kinases, which are ATP competitive. The starting point is a generic kinase scaffold (hopefully proprietary) from which selectivity can be achieved through proper substitution driven by rationale design based on the kinase specific sequence and its 3D structure. This is a powerful tool, because it can be applied to different kinases, from the same central scaffold, providing proper information is available to direct chemists efforts in the right direction. Forthcoming kinases of therapeutic interest (among the 500 ones encoded by the human genome) will benefit from recent progresses in bioinformatics (in particular prediction of 3D structure based or primary sequence) and high-throughput production of protein constructs associated with new crystallisation technologies, which will provide new kinase 3D models or real structures for in silico design of selective inhibitors.

What about non-ATP competitive inhibitors?

An alternative way to avoid promiscuity in the design of kinase inhibitors is to look for non-competitive inhibitors with respect to ATP, with the aim to hit interactions at kinase sites, which are not commonly found within the enzyme class. Very little is known to really define a strategy based on rationale design for such type of inhibitors and therefore high-throughput screening of highly diverse collection of compounds remains as one of the most promising approach. This is the one we have followed as part of our efforts to find new MEK inhibitors as potential anti-cancer agents (see *figure 12*). Screening of 50K compounds led to the identification of a few positives among which AS701173 was characterised as a potent (IC_{50} = 30nM) non ATP-competitive inhibitor since inhibition of MEK by that particular inhibitor was independent of ATP concentrations used in the assay conditions (*figure 15*).

Evaluation of AS701173 against a panel of 40 available kinases show that this compound is highly selective for MEK since none of the other kinase was inhibited by more than 20% at 10µM (*figure 16*).

Lead optimisation based on this new selective MEK inhibitor is in progress and promising preliminary results have recently been obtained with newly found analogs demonstrating potent activity in tumour cell proliferation assays and in *in vivo* models of cancer.

From a chemist perspective, these two examples show that combinatorial chemistry and chemical diversity (cfr MEK selective inhibitors) on one side, as well as « surgical » modifications of molecules in a precise way driven by rationale design (cfr JNK selective inhibitors design) on the other side are complementary tools in drug discovery; both of them can only lead to success if chemists master the art of organic chemistry, and if the art of organic chemistry is continuously offering new methods, reactions, reagents, strategies to solve new emerging challenges.

Kinases and phosphatases inhibitors described above illustrate the potential of signal transduction in drug discovery where understanding of cell biology events has allowed to identify druggable targets which play a critical role in diseases and for which chemists are able to design potent and selective inhibitors with promising therapeutic

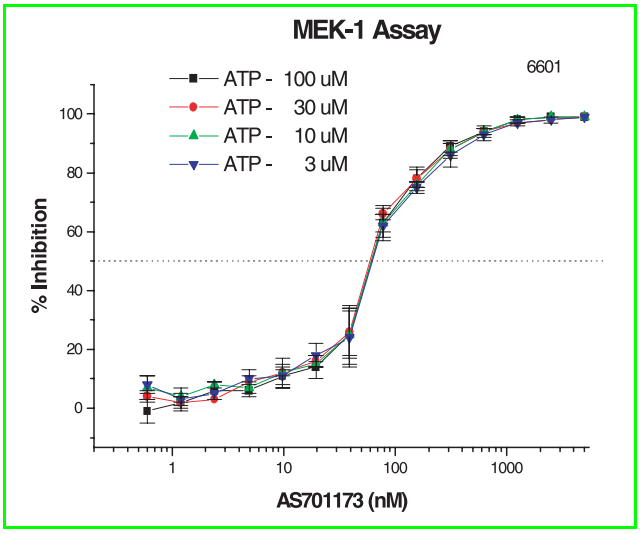

Figure 15 - AS701173 does not compete with ATP.

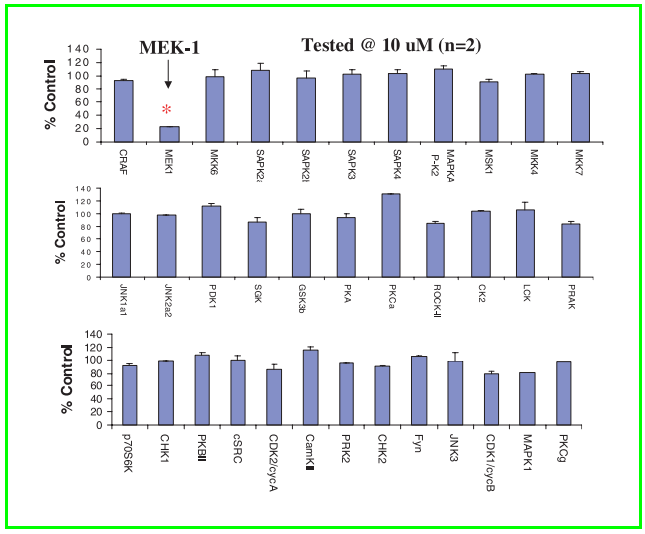

Figure 16 - AS701173 selectivity between 40 kinases.

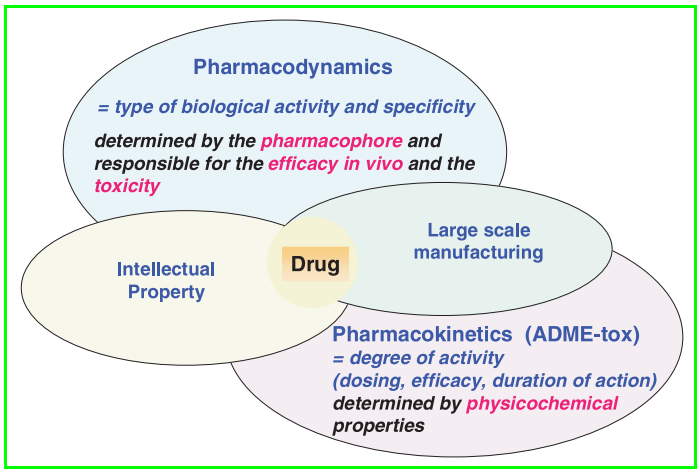

Figure 17 - A successful drug has a good balance of potency, safety and appropriate pharmacokinetics.

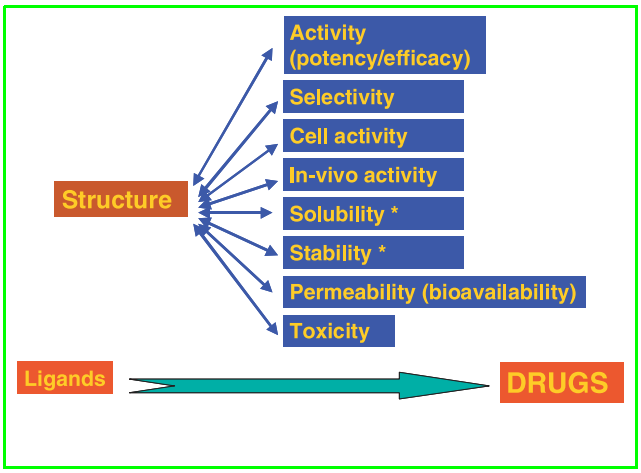

Figure 18 - A multidimensional challenge.

applications. This drug discovery strategy has enormous potential since, on one hand many proteins that will be identified as key players in pathological conditions will be up- or down-regulated, directly or indirectly by kinases or phosphatases. On the other hand, the design and synthesis of selective, potent, cell permeable drug-like inhibitors of kinases and phosphatases is within the scope of chemists current expertise. Synergy between synthetic chemistry, computational chemistry, enzymology, bioinformatics, cheminformatics, cell biology, structural biology and molecular pharmacology will provide the necessary technology platform to speed-up the discovery of inhibitors and improve the quality of drug candidates.

The goal is to find drugs, not ligands or inhibitors

A lot of emphasis has been given in the last few years to the first steps of drug discovery, which consist in finding the best possible molecules to interact with target proteins. This is important, since it is the basis of molecular drug discovery, but certainly not enough to have a drug which will cure patients. To become a drug (*figure 17*), a molecular must not only hit the molecular target, but has also to get access to it *in vivo*, hopefully upon oral administration, without being metabolised or excreted too fast or too slowly, and without significant unwanted side-effects (toxicity).

For economic reasons, new drug candidates must also demonstrate sufficient novelty to insure strong intellectual property, and last but not least, the synthesis of the molecule must be scalable to allow manufacturing production for clinical trials and the market.

All these important properties are determined by the chemical structure of the drug candidate and therefore are additional challenges for drug discovery chemists. This is not new; what's changing is the simultaneous integration of all these drug-like properties as early as possible in the drug discovery programs. In the past, chemists used to optimise molecule properties in a sequential manner, taking care of drug-like properties improvement at the very last stage of the process. In the future, chemists will have to consider all these parameters in parallel (*figure 18*) and progress molecules by improving various requested properties at the same time.

Drug design is becoming a multi-dimensional challenge where mastering experimental data (with the help of sophisticated cheminformatics tools) and in silico predictive tools (in collaboration with computational chemists) will become key success factors. Understanding structure-activity is not sufficient anymore, but being able to anticipate and modulate structure-permeability, structure-metabolism, structure-toxicity relationships will become a serious competitive advantage. This is not easy, because the molecular basis of these complex processes is not yet well understood and tools available today are far from being satisfactory. This is a challenge for the future and we should keep in mind that « old » areas like pharmacology, pharmacokinetics and toxicology remain essential pillars for successful drug discovery. Of course, these areas are also progressing very fast, thanks to genomics/proteomics efforts which won't only help understanding role of proteins in diseases but also roles of proteins and protein networks in metabolism, toxicology or drug transport and biodistribution. In addition, pharmacogenomics and pharmacogenetics will also dramatically change the face of drug discovery. It will be the job of the chemists to understand progresses made there to rapidly apply new findings to the design of better, safer molecules to be developed as medicines (the right drug at the right dose for the right patient, at the right time).

Conclusions

We are now in the post-genomic era. The way to conduct drug discovery is changing a lot as illustrated by the emergence of new terms like proteomics, kinome, signalsome, metabonomics, etc. which, in science, are symptomatic of deep transition periods. Doors open by the human genome initiative easily lead scientists to the XXIst Century version of the Middle-Age alchemist dream: find one small molecule ligand for every gene product (sometimes referred as the new chemical genomics paradigm). Successful drug discovery needs more focus, and the focus will be at the intersection (*figure 19*) of the druggable genome and the drug-like chemical space.

This is the challenge for the future and it will be a multidisciplinary adventure since the only way to success will be through interactions between disciplines on both sides (as illustrated here by signal transduction as a way to explore the druggable genome and kinases/phosphatases as targets

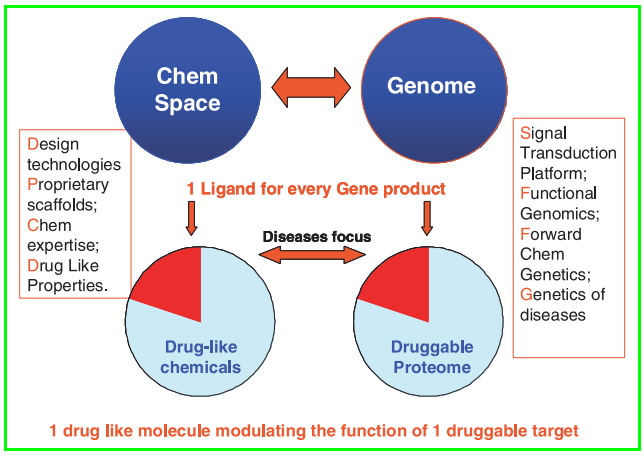

Figure 19.

to design drug-like molecules). If we move from the alchemist dream to the real life, our goal will be to find for each therapeutic project, one drug-like molecule modulating the function of one druggable target (*figure 19*). But this is only one step ahead, not the end of the story. Because biology is much more complex than a simple collection of individual proteins characterised by their structure and function, because proteins work as multifunctional pieces of very complex networks; and this is what makes the future so exciting!

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