Bioorganic & Medicinal Chemistry xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Perspective

# Change or be changed

## Reflections of the workshop 'Future in Medicinal Chemistry'

Ruth Brenk [a,*], Daniel Rauh [b,*]

[a] Biological Chemistry and Drug Discovery, College of Life Sciences University of Dundee, Dow St., Dundee DD1 5EH, UK
[b] Technische Universität Dortmund, Chemische Biologie, Otto-Hahn-Strasse 6, D-44227 Dortmund, Germany

Like almost no other scientific discipline, drug discovery and drug development improved both the quality of life as well as the life expectancy over the last hundred years. This was mainly driven by medicinal chemistry which is a traditional discipline rooted in organic synthesis and concerns the discovery, development, identification and interpretation of the mode of action of biologically active compounds at the molecular and cellular level. In its modern form, medicinal chemistry finds itself sandwiched between target discovery and clinical application and also focuses on target identification and target validation. However, the complexity of drug development and successfully bringing a drug to the market, is still facing major roads blocks and plagued by high attrition rates and rising R&D costs. As a consequence, a whole industry finds itself at a crossroad.

Medicinal chemistry, *quo vadis?* was the central question that brought together about sixty participants to a three-day workshop in January 2012 organized by the Medicinal Chemistry division of the German Chemical Society (GDCh), the German Pharmaceutical Society (DPhG) and the Swiss Chemical Society (SCS). The participants were chosen from the disciplines of medicinal chemistry, computational chemistry, organic chemistry, chemical biology, biology and clinical medicine to cover a diverse range of disciplines which are of immediate relevance to modern drug discovery and development. In addition, there was an exiting mix between upcoming and established scientists from both academia and industry. The remote setting of Seeon Abbey in Upper Bavaria, a former Benedictine monastery which already served as a refuge for Haydn and Mozart, provided an inspirational environment for stimulating discussions, as this workshop truly held up to its name: five impulse lectures outlined the future challenges of medicinal chemistry in different areas and set basis and stimulus for group discussions that were then summarized in the plenum and further discussed. The goals of the workshop were not only to debate on future perspectives and hot areas of Medicinal Chemistry, but also to bring together scientists from different disciplines which normally would not meet in their day-to-day research routine and to facilitate setting up a network between experienced and younger scientists from academia and industry.

### MedChem essentials and future needs

Lack of clinical efficacy and unexpected toxicity are still the major causes for frustratingly high attrition rates. Dr. Tobias Gabriel from Novartis Pharma AG, Switzerland started off by highlighting that best-in-class selectivity is an ever more important prerequisite for success in drug development. The tendency to increase the lipophilicity of a biologically active molecule in hit- and lead-optimization counter acts in achieving this goal as nonpolar protein–ligand interactions are often less specific and more lipophilic compounds are therefore often less selective. Further, he stressed that the residence time at the receptor is an important property of drug molecules with ideal molecules having high $k_{on}$ rates (fast binding) but low $k_{off}$ rates (slow dissociation) to maximize the time the receptor is occupied. Increasing drug selectivity and thereby shifting the equilibrium between wanted and side-effects as well as increasing drug-target residence times provides relevant inspirations for more successful future compound optimization strategies. Additionally, during the subsequent discussion it became evident that although it is generally accepted that modulating more than one target is necessary to obtain a clinically relevant effect, the challenge is to define which ones to hit and for which ones selectivity is key to success. Deciphering signaling network architectures and to quantify the flux of information passing these networks is one of the great challenges in fundamental basic research to foster drug discovery. This problem lies at the heart of systems biology. This rising discipline is in need of the development and detailed validation of highly selective tool compounds to chemically perturb complex network architectures in order to discover vulnerable nodes, which can be targeted with innovative new drugs. The shift in basic and applied research to more complex systems also raised the controversial questions whether phenotypic screens can play a role in prioritizing compounds without having to fully understand the underlying pathways and mode of action. Further, it was questioned if it is always possible to achieve the desired selectivity profile with a single compound. Combination dosing of selective drugs, which is already clinical practice for most kinase inhibitors in oncology should therefore be considered as alternative strategy. It was also pointed out that the concepts and ideas on how to design inhibitors and antagonists are rather evident, but the molecular mechanisms for activators and agonists are much less clear and therefore rich for discovery opportunities. With respect to target occupancy and drug-target

* Corresponding authors. Tel.: +44 1382 386230; fax: +44 1382 386373 (R.B.); tel.: +49 231 755 7056; fax: +49 231 755 5159 (D.R.).
*E-mail addresses:* r.brenk@dundee.ac.uk (R. Brenk), daniel.rauh@tu-dortmund.de (D. Rauh).

0968-0896/$ - see front matter 
http://dx.doi.org/10.1016/j.bmc.2012.04.038

residence times, it was stated that we have only a very limited understanding on how to optimize on- and off rates in a rational way. A better understanding of the detailed energetic and kinetic aspects of protein–ligand interactions could therefore make a big impact in this area. Further, it was stressed that long residence times are usually reached with covalent inhibitors. It might therefore be a good idea to start looking at this type of compounds again. However, this will require considering the turnover rates of protein re-synthesis, as fast rates will counteract the effect of covalent inhibitors.

## Extension of chemical space

The following impulse lecture was given by Professor Herbert Waldmann, Max-Planck-Institut für molekulare Physiologie, Dortmund (Germany). Waldmann reminded the audience that not all top selling drugs are rule-of-five compliant. Often forgotten compound classes are peptides with over 70 therapeutic peptides on the market, some of which reached blockbuster status already. This type of compounds should therefore not be ignored when exploring novel targets and chemical space. Another promising compound class are macrocyclic natural products and their analogues. Such complex molecules are pre-validated by nature for biological activity and therefore represent promising starting points for compound development. They are often rich in sp3-configured centers, which distinguishes them structurally from regular drug molecules, derived from classic medicinal chemistry endeavors. Genome mining combined with metagenomics and synthetic biology has the potential to become rich sources to isolate these otherwise often difficult to synthesise complex materials. Finally, it should not be forgotten that also RNA molecules and their regulation constitute promising drug targets. Exploiting these might lead to completely new therapeutic approaches.

Inspired by this lecture, lively group discussions took place. A hot topic was the question what peptides can deliver what small molecules or biologicals cannot. Their particular place was seen as agonists and activators for extracellular targets that otherwise cannot be modulated. Further, peptides might also have a role to play as tool compounds for timely target validation in vitro and in vivo and for assay development. Especially, since due to advances in the field, mainly driven by academia, synthesising a diverse set of peptides, including such containing non-natural amino acids, was considered relatively straight forward. However, it was pointed out that finding the right formulation for these molecules remains a challenging task, which might limit their therapeutic applications and restrict them to diseases for which non-oral drug administration is acceptable.

There was a general consensus in the discussion that macrocyclic natural products constitute a valuable compound class for drug discovery. The difficulty in obtaining pure compounds and making analogues was identified as main reason for natural products being less in the focus for drug discovery. Synthetic biology might offer some solutions to these problems and it will be very exciting to see which advances are made in the near future. In similar vein, disappointment about RNAi not holding up to its promises as potential therapeutics prevailed but great openness about RNA molecules, and in particular riboswitches, as potential drug targets persisted.

Finally, it was questioned if molecular space up to 500 Da is already thoroughly explored. While peptides and macrocyclic compounds cover chemical space beyond 500 Da, many opportunities were still seen for smaller molecules. In particular, chemical elements such as S, P, B, and Si could be used much more frequently and also synthetic routes to new, more sp3-center rich carbon atom containing heterocycles remain to be developed.

## Drug targeting and delivery

Prof. Rainer Haag, Freie Universität Berlin (Germany), introduced new concepts for drug targeting and drug delivery. Numerous polymer-protein conjugates such as anchoring enzymes or therapeutically relevant proteins to polyethylene glycol derivatives have been developed over the years and several of them received approval by the FDA. Coupling small molecule anticancer drugs to high molecular weight polymers through cleavable linker systems is an effective method for improving the therapeutic index of clinically established cytostatics. Another class of polymer therapeutics currently receiving great attention are drug-delivery systems based on well-defined multivalent and dendritic polymers. However, it also became clear that targeting approaches in the clinic i.e. by antibody conjugates would only be successful if the mass balance between the drug and its carries is improved.

In the subsequent group discussions, the general need for new drug formulations was also pointed out as chemistry is likely to continue to deliver lipophilic molecules. The formulation toolbox should contain a mix of low and high tech approaches such as for example new solubilizers, pH sensitive formulations, dendrimers, and targeted antibodies. The later will require investment in linker chemistry to improve loading and to develop cleavable linkers. To use the potential of multivalent polymer therapeutics the fate of the carrier in the human body also has to be better understood. Further, since these compounds are heterogeneous, clear guidelines are needed on which methods for characterization are sufficient for subsequent approval. To drive the field forward, a consortium instead of a single company might best tackle these issues. From a strategic point of view, it was also suggested to better link formulation scientists with medicinal chemists. In pharmaceutical companies, the former are often located in the development departments whereas the later belong to the discovery units. As a consequence, cross talk only starts in the late stages of a project while it might actually benefit best from a much earlier input. Further, it was pointed out that rational tissue design to facilitate the detailed study of transport mechanisms as well as cell or even cellular compartment specific drug delivery would constitute a major break-through. Consequently, there is the great opportunity to funnel the understanding of transport mechanisms for the exploitation of specific drug delivery. Finally, while prodrugs come with inherent challenges such as the need to fully characterize both prodrug and the effective compound, this concept was proven successful in the past and a case was made for not ruling out this approach too quickly when facing delivery issues in drug development.

## Genome analysis—finding pathways for personalized medicine

Two impulse lectures given by Professor Paul Workman, Institute of Cancer Research, London (UK) and Professor Christof von Kalle, National Center for Tumor Diseases, Heidelberg (Germany) centered around genome analysis and personalized medicine. Cancer is a disease of the genome and characterized by the accumulation of somatic, tumor-specific alterations. The current explosion in sequencing throughput and the dramatic drop in sequencing costs have enabled researchers to fully characterize in detail genetic alterations in the genomes of all major human cancer types. Such projects allowed for the identification of genetically activated oncogenes as prime cancer drug targets. Clinical success stories, exemplified by HER2-amplified breast cancers that are susceptible to treatment with HER2-targeted antibodies, chronic myeloid leukemia bearing the BCR-ABL translocation that can be treated with ABL kinase inhibitors and EGFR-mutant lung adenocarcinomas that are shrunk by EGFR inhibitors immediately, fuel the expectations

Please cite this article in press as: Brenk, R.; Rauh, D. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.04.038

that additional drug targets will be discovered to role out targeted cancer therapies on a wider range. However, the development of novel agents often fails because of lack of efficacy. This inherent problem of targeted therapies highlights the importance of properly validated drug targets and stresses the need for basic disease biology. The case of targeted therapies in cancer not only offers opportunities for basic research, clinical development and patient treatment, but it also highlights that the genome of a cancer patient has to be take in account when designing clinical trials. Most likely, the classic regime of clinical trials with efficacy studies placed in phase-II has to be rethought.

The demonstrated progress in personalized medicine in the treatment of cancer was welcome in the group discussions. It was also pointed out that genomics must not stay isolated but be combined with other 'omics' techniques such as proteomics, metabolomics, transcriptomics, and epigenomics to reach its full potential. However, it remained unclear if using genome-based personalized medicine approaches will have a similar impact in therapeutic areas other than cancer which might have less clear links to genome information such as diabetes, Alzheimer's, cardiovascular diseases and osteoporosis. Applying information rich technologies to non-life threatening diseases is likely to reinforce a debate around the ethical issues connected to generating detailed genomic information about potentially healthy individuals. The hope is, however, that these strategies will deliver well-validated drug targets, which will then lead to better treatment options.

## Conclusions

The workshop 'Future in Medicinal Chemistry' and its general topic *quo vadis*? gave a unique opportunity to discuss the future of medicinal chemistry with participants from a broad range of disciplines. It reinforced the distinguished role that medicinal chemistry plays in drug discovery but also highlighted hot topics such as reducing toxicity by increasing compound selectivity, optimizing the residence time of drug molecules with their receptors, exploration of chemical space, both below and above 500 Da, the need for new drug delivery systems to solubilize drug molecules and to deliver them to the site of action, the opportunities of genome analysis for target identification, drug discovery and the design of clinical trials as well as systems chemical biology to better understand disease biology and to direct target selection. However, the question remains on how to effectively and in which form to tackle these challenges. For medicinal chemistry to stay at the forefront of drug discovery the community has not only to take more risk in frontier research to achieve major breakthroughs, it also has to invest into excellent education of the upcoming generation. Organic synthesis and the art of making molecules belong to the core tools every medicinal chemist has to master. However, due to the multidisciplinary nature of drug discovery young scientists also need a profound understanding of biological mechanisms, enzyme and receptor functions and disease biology. Only such knowledge will enable them to play an integral part in the development of innovative new medicine. The discussions made clear, that platforms are needed and funding models are to be invented to support interactions between academia and industry to foster innovative Medicinal Chemistry and drug development by considering the needs of both academia and industry. Interdisciplinary, academia driven basic research initiatives with strong ties to the pharmaceutical industry such as the Chemical Genomics Centre of the Max Planck Society and the BMBF (Federal Ministry of Education and Research) funded initiative 'Medicinal Chemistry in Dortmund' might serve as role models in this respect. The latter initiative for example, does not only focus on basic research in modern, innovative drug discovery, it also aims at strengthening graduate training in Medicinal Chemistry at the Technische Universität Dortmund in cooperation with local and global industry partners.

Overall, the three-day workshop proved to be a fantastic forum with the right mix of excellent impulse lectures and ample time for discussions. It not only fostered exchange of experience between academia and industry and upcoming and established scientists from a broad range of disciplines but it also set the foundation for more regular meetings of this kind to shape a network which will be crucial to take advantage of the transitions currently under way.

« T*he* old is crumbling down—the times are changing » Wilhelm Tell IV/2.

Medicinal chemistry, take your chances!

Please cite this article in press as: Brenk, R.; Rauh, D. *Bioorg. Med. Chem.* (2012), http://dx.doi.org/10.1016/j.bmc.2012.04.038