MedChemINterACTION and the future of Medicinal Chemistry

On May 24th and 25th scientists from academia and industry met in Berlin at the Brandenburgische Akademie der Wissenschaften for MedChemINterACTION. The meeting was initiated by the Medicinal Chemistry Division of the German Chemical Society GDCh with the intent to provide a forum for lively interaction among practitioners who shared their experiences and discussed challenges and future fields of action for Medicinal Chemistry in the drug discovery process. This diverse group of experts agreed that substantial technological, societal and economic changes will impact on the pharmaceutical industry, but there was little doubt that small molecules will continue for the years to come to substantially contribute to new drugs addressing unmet medical needs. However they will not be the only modality of importance as they have been in the past, and technical set-up for their generation might be considerably different from current practises. Further digitalization was expected being a key driver of change in this field.

Source: Franz von Nussbaum

Initiated by Stefan Laufer (University of Tübingen) and Franz von Nussbaum (Bayer AG) and organized together with Karl-Heinz Baringhaus, Anna K. H. Hirsch, Oliver Koch, Joachim Mittendorf, and Dennis Schade on behalf of the Medicinal Chemistry Division of the German Chemical Society GDCh, MedChemINterACTION brought together forty eight invited experts from academia and industry, some of them just starting out their career and many having already quite a history in the field. The heading of the introductory session led by Franz von Nussbaum, "Academia & Industry: *Quo vadis* MedChem? Let's work together!" set the scene and provided the Leitmotiv for the two-days meeting. It captured very well the two main topics to be discussed: medicinal chemistry's impact on drug discovery's challenging (in many cases declining) success rates and its future role in light of actual developments. In times where the funding of medicinal chemistry is challenged as a result of seemingly declining innovation and productivity in the entire industry, there is a clear need for collaboration between industry (to meet its demand for innovation with the aid of external sources) and academia (especially when progressing a project towards clinical development, but also

in all other phases of drug discovery and development). The event proofed that medicinal chemists are well aware of the challenges posed by digitalization, by new technologies such as PROTACs (proteolysis targeting chimeras) and DNA encodes libraries and new chemical modalities as well as an ever increasing level of data complexity. Still there was a discussion whether digitalization and such new technologies and modalities will really be disruptive or just add to the armamentarium of drug discovery. Four sessions assigned to selected "hot" topics of early drug discovery provided a presentation from academia and industry each highlighting the speakers' and their respective groups' active contributions to the field. Extensive and vivid discussions gave an insight into the participant's vision and expectations with regard to future needs and developments.

Target finding, the first of the four topics, is at first sight not primarily the task of medicinal chemists but has a decisive influence on the success of a discovery program. Even though Chemical Biology and Biochemistry excel in this area there are increasing opportunities for medicinal chemistry to support target finding and validation, for example with chemical probes. Especially the quality and robustness of target validation, i.e. demonstrating the target's relevance for a particular disease, is expected to filter out approaches with a low likelihood to demonstrate efficacy in clinical trials later on. Stefan Laufer (deputizing for Lars Zender) illustrated how the application of RNAi screening for new druggable lethalities and vulnerabilities of cancer cells led to the identification of new treatment response modifiers. These examples for functional target discovery and validation from bench to bedside were taken from the Tübingen Center for Academic Drug Development,[1] a member of the international academic drug discovery consortium[2] thus also providing an example for academia's contributions to drug development and for a new level of academic collaboration and international networking.

The power of proteomics was demonstrated with a number of examples presented by Marcus Bantscheff (Cellzome). The platform set up at Cellzome allows an impressive range of insights into a compound's activities. Target and off-target identification, physical evidence of target interactions on protein level, characterization of protein interactions in cells, thermal shift assays on proteome-wide scale, proteome dynamics and regulation in mature and nascent systems are but some of the options the technology offers.[3-6] Robust data, as can be generated with the approaches presented, are cornerstones for successful target identification. Smart computational links between integrated omics-databases and systems biology would be on the wish-list for the future and add even more power to the technology.

Lead finding, or **lead generation** as is the preferred term of the speakers of this session, is the next challenge after having a new target validated. Since quite some years this quest is not only followed by industry but also by academic groups and consortia. The diversity of the situations that may be encountered in terms of target types, different modes of actions and drug modalities are obstacles to routines and standardization. Access to a sufficient range of chemical space and diversity is a prerequisite that has nurtured the idea of collaborations. Phil Jones (University of Dundee) presented the European Lead Factory[7] which is one of the most prominent examples of private public partnerships. Since its launch 2013 the initiative has built up a joint compound collection of more than 500.000 compounds that is continuously enlarged by complementary libraries and run 72 high throughput screens for target programs yielding more than 5000 qualified hits. Currently the majority of project proposals come from the Netherlands and the UK and a wider spread of participation would be hoped for as well as an expansion to include also phenotypic screens.

Approaches to generate leads in novel target spaces were presented by Karin Briner (Novartis). She emphasized that Medicinal Chemistry should bring structural thinking at molecular level with atomic resolution to drug discovery with the ultimate goal to provide molecular solutions for patients. In her first example a phenotypic hit evolution led to small molecules that have a correcting effect on SMN2 splicing[8] and thus could allow treatment of spinal muscular atrophy, a debilitating motor neuron disease. Another example given by her was the identification of allosteric SHP2 inhibitors which would have a considerable potential for the treatment of solid tumors.[9] Two starting points for compounds stabilizing the inactive form of the enzyme resulted from a high throughput screening and were used for a structure based hit to lead generation which yielded compounds for proof of concept experiments in mice. The examples demonstrated very well the potential of small molecules beyond addressing orthosteric binding sites in receptors and enzymes. Briner emphasized the importance of synthesis driven innovation and the systematic and knowledge based exploration of chemical space. She also advocated to be bold when assessing a new approach. An early toxicological de-risking can give a substantial boost for a project whilst prior optimization to near optimum might be wasted efforts.

The value of computational chemistry for drug discovery is undisputed in general but the devil is in the details. Tim Clark (University of Erlangen) summarized the strengths and shortcomings of current docking methods and molecular dynamics simulations especially with regard to scoring binding affinities. While the latter were demonstrated to reasonably work in a number of cases (provided that enough calculation power is applied to allow for sufficient sampling rates and duration of simulation), the analysis of docking methods he presented was not reassuring. Not surprisingly, this triggered a high level discussion of the experts. A recent review nicely summarizes methods, current challenges and future directions of computational methods for drug design for practitioners.[10]

Mireille Krier (Merck KGaA) strongly advocated “the power of in silico”. With a number of examples like an electronic lab journal as a flexible knowledge sharing platform, a virtual library of compounds accessible by the synthetic methodologies and chemicals available to Merck chemists, an integrated workflow for compound optimization utilizing predictive models based on machine learning methods (physicochemical properties, pharmacokinetics, certain toxicology parameters, selectivity) she underlined the value that in silico applications can provide to medicinal chemists to make compound optimization faster and more focussed. The last of Krier’s examples was Chematica, a retro-synthesis software combining expert chemical knowledge, network search functionality and artificial-intelligence algorithms. An acid test for the programs efficiency has recently been published[11] and the discussion it stirred among chemists[12] involved in organic synthesis was not surprisingly mirrored also at MedChemINterACTION.

Apt to the call “Let’s work together!” the session **Collaboration** provided respective views from academia and industry. Stefan Jaroch (Bayer) highlighted the necessity of external innovation and expertise for pharmaceutical industry. In his overview he introduced the various levels and types of interactions that Bayer, like other companies, and an academic group or independent research institute could develop to advance common research interests. The spectrum covers a broad range of models, from crowd sourcing for new ideas, provision of venture capital and research

collaborations to strategic alliances and consortia. Irrespective of the model, he emphasized the quintessential ingredients for success to be a collaborative spirit and a joint vision. An independent review of various models of collaboration, the opportunities they offer and actual examples has recently been published.[13] The collaboration between Bayer and the Lead-Discovery Center Dortmund (LDC) on specific kinase inhibitors was mentioned as a special success leading to more than one clinical candidate.

Peter Gmeiner (Universität Erlangen) explained the underlying structural research and extensive computational efforts applied to three projects targeting G-protein coupled receptors run in international collaborations. The most advanced project identified a novel opioid receptor activator with the potential for an analgesic treatment devoid of the issues of opioids (effects on respiration and addiction).[14] These efforts have led to the formation of a start-up company, Epiodyne Inc., which tries to bring the compound to the clinic and has ensured series A funding.

In a compelling talk Detlev Mennerich (Boehringer Ingelheim Venture Fund) explained on the basis of a real-world example the steps and timelines that it took to form a start-up and ensure the first round of funding. Mennerich provided valuable insights and details for potential future entrepreneurs. To stay authentic was his advice when going through the strenuous phase of repeatedly showcasing one's project to raise first funds. Unfortunate for Germany based innovators, he made no secret of the fact that tax incentives for research funding in other European countries – such as France - indeed constitute a competitive advantage for those.

The talks with their substantial technical and scientific quality supported very well the main objective of the program: To develop an idea of future roles of medicinal chemists and of the developments and resulting challenges in their field. One answer to the question where medicinal chemistry ought to go was provided by Karin Briner: "(Medicinal Chemistry)...should not go lower than cure of the disease!" That this goal can only be achieved by the joint efforts of a multitude of disciplines goes without saying, but medicinal chemistry is a central port in the drug discovery process to which all data flow back to contribute to the design of the next generation of compounds towards a potential clinical candidate. This may explain why in the context of the productivity crisis of the pharmaceutical industry the performance of medicinal chemistry has been the topic of quite critical discussions in recent years.[15-17] Since Christopher Lipinski's gentle therapy suggestions by the Rule of Five[18-19] the control of a molecules "body mass index" has become common practice, i. e. physicochemical properties that have an impact on adsorption, distribution and half-life of a potential drug are critically monitored and tuned early on. More sophisticated indices to score "drug likeness" have emerged and their relevance and proper application (and cases of justified violation) have been discussed.[20-23] Accordingly, main compound related reasons for attrition in clinical trials have shifted away from insufficient pharmacokinetic properties and have become insufficient efficacy or safety (therapeutic window) of compounds investigated.[24] This underlines the importance of identification of targets with relevance for the human disease and the intense quest for robust biomarkers that would inform early about effects relevant to the pathology in question.

MedChemINterACTION offered ample room for critical discussion but the question was not only how to make the "right" small molecules but if small molecules will still be the right approach for tomorrow. Only two small molecules show up in the list of the ten top selling drugs of 2017,[25] but noteworthy small molecules remain the mainstay of HIV infection and hepatitis C treatment in spite of the potential power of antibodies and vaccines. The notion was shared that small molecules will

continue to significantly contribute to new medicines due to (in addition to lower costs) greater versatility (oral drugs, compounds that reach intracellular targets) as has also been outlined by Campbell et al. in their analysis of medicinal chemistry's past, present and potential future.[26] As nicely exemplified by Briner's talk before, chemical space as well as target space are continuously expanded generating new opportunities for small molecules to address medical need.

Academicians were repeatedly encouraged to **become entrepreneurs** and to progress their discoveries to practical applications with start-up companies. Academia's scientific breakthroughs will spark innovation and the increasing importance of collaborations with industry is equally seen by both sides.[13, 27-28] The opportunity to exchange on the different mind-sets and expectations of the two "worlds" was intensely used and the paramount importance of trustworthy relations repeatedly emphasized. Some of the issues mentioned for German universities are the granularity of public funding and the occasional competition with other domestic research institutions.

In a morning session organized by Joachim Mittendorf (Bayer AG) quite some controversy could be observed in the discussion of the **skill set expected from tomorrow's medicinal chemist** and how curricula of Universities should be adapted to prepare for this (this topic has already resonated in the community for some time).[29,30-32] Industry representatives confirmed continuing demand for fresh talent but could not provide quantification. In general, a sound scientific training, skills to communicate science, and qualities as problem solvers are expected from potential candidates. While there was consensus that medicinal chemist's role will shift more towards a drug discoverer / hunter / designer there were different views as to what extent this will lend minor importance to the command of organic synthesis or even make it redundant. Though a principal and deep understanding of basic chemical principles and reactions will also be key in the future, an encyclopaedic knowledge of multiple reaction variants might be less important for the education of future medicinal chemists as this knowledge can be brought faster to the process by computers. Aficionados of in-silico driven processes see, with the advent of artificial intelligence systems for synthesis planning[11, 33] and lead optimization[34-35], the synthesis of molecules becoming a commodity which can easily be outsourced. They would rather recommend some algorithm-literacy for the future medicinal chemist. In contrast some representatives from industry expect medicinal chemists also in the future to have distinctive knowledge of organic synthesis as a pre-requisite for the (knowledge based) exploration of chemical space. Support by novel technology is highly appreciated, but the user should be able to scrutinize the output.

In 1957, the German poet and author Hans Magnus Enzensberger has mused in his poem "gespräch der substanzen" (conversation of the substances) about the communication of chemical matter. In our scientific context this communication is the key for biological activity in general and drug action in particular. Understanding the "language" of molecules would allow us to understand pathology and thus provide a rational approach to drug discovery. Knowledge of chemical reactivity and how molecules interact and react are the first humble syllables we have learned and apply mainly in a trial and error fashion. The advent of big data, tremendous and constantly increasing computing power and first successful applications of artificial intelligence might bring us much closer to this goal and even constitute the Stone of Rosetta for this task. Will they make medicinal chemists redundant? Those still waiting for the paperless office, drug design from scratch, the lead explosion by high throughput screening and the glut of targets from the human genome project take a relaxed stance. As change is generally occurring at an ever increasing speed we will not have to wait too long to see if Amara's law[36] applies again.

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