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A Perspective on Chemistry and Society

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Novartis

Perspectives and Opportunities in Medicinal Chemistry: A View from the Novartis Institute for BioMedical Research in Basel, Switzerland

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Abstract: An opinion on changes and opportunities for the pharmaceutical industry in Switzerland, as seen from the Global Discovery Chemistry platform of the Novartis Institutes for BioMedical Research in Basel.

Keywords: Digitalization · Drug discovery · Medicinal chemistry · Synthesis

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Martin Missbach is the NIBR Basel Site Head for Global Discovery Chemistry. He has a long experience in drug discovery in the area of autoimmunity, inflammation and transplantation. Both have a 30-year record of scientific leadership in drug discovery.

1. Introduction

Medicinal chemistry in Switzerland is a very dynamic area of research. Basel is the home of many leading international companies and hosts a growing number of innovative biotech companies, many in the Switzerland Innovation Park Basel Area. The latter serves as a catalyst for innovation, offering co-working spaces and shared research facilities across four locations, including the Novartis Campus.[1]

In this article, the authors discuss the recent evolution of drug discovery, and the opportunities they create for Novartis and the pharmaceutical industry in Switzerland.

2. A Strong Commitment

Novartis is a medicine-focused company, with research and development being at the heart of its activities. In early 2022, it will open a fully renovated building on the Basel campus (Fig. 1) hosting a large part of the Global Discovery Chemistry activities in Basel. This investment will facilitate cooperation and synergies, reinforcing the quality and effectiveness of drug discovery and optimization programs. Medicinal chemists, analytical chemists and several advanced technology groups will benefit from these state-of-the-art facilities.

Fig. 1. The new Global Discovery Chemistry building (left, with wall painting from Swiss artist Claudia Comte) on the Novartis campus in Basel.

Besides updated chemical and analytical laboratories, pilot-sized bioreactors in the lower floor of the new building will enable to access larger amounts of biologically produced natural products and custom-made enzymes. The latter will enable the exploration of chemical spaces that are difficult to reach synthetically, as well as the development of greener processes for building block synthesis, chemical production, or late-stage functionalization of complex molecules.

3. A New Research Environment

The Sars-Cov-2 pandemic has profoundly influenced scientific research, temporarily limiting lab-based operations and preventing face-to-face interactions. It had strong consequences on medicinal chemists and their working environment, forcing many scientists to work remotely. It fundamentally changed the perception of the workplace and the dynamics of professional interactions. Most scientific meetings became virtual, from informal coffee breaks to large scientific symposia. This led to permanent changes in the way people perceive their work, creating new ways to communicate independently of physical meetings, commuting and international travel. While it took time to get used to it, most people now agree that a combination of physical and virtual presence has become the most effective way to work and share information. This change was enabled by the deployment of more efficient group collaboration software, in a direct response to the situation caused by the pandemic.

Novartis has implemented a flexible working model to adapt to a diversity of work requirements. It allows any option, from working remotely to being exclusively on site for lab-based scientists. This added flexibility provides a powerful means to optimize the time usage of all associates, on both a personal and professional basis, improving quality of life and scientific productivity.

In parallel, efforts are ongoing to increase work force diversity, to enhance the quality of research by contrasting and syner-

gizing different approaches, experiences and thought processes. Diversity is a broad concept embracing education, gender and cultural diversity, and provides the basis to adapt to changing societal trends. Equal opportunity was discussed extensively over the last few years, and led to significant efforts to remove historical career obstacles, *e.g.* for women in leading scientific positions. These discussions had a clear impact on our society and brought about much-needed change. A challenge for the future will be to maintain the diversity of opinions and scientific approaches in the novel cultural environment of our community, which comes with its own norms and expectations.

4. Opportunities

The scientific continuum across chemical biology and medicinal chemistry evolves rapidly.[2] As borders between scientific specialities dissolve, drug discovery exploits synergies to take on a variety of therapeutic approaches. Most striking has been the progress achieved by the integration of new technologies into the practice of drug discovery, including activity-based synthesis of chemical probes[3] and novel screening technologies (*e.g.* cryo-electron microscopy[4] or DNA-encoded synthesis[5]), as well as protein degraders[6] and imaging agents.[7] Beyond these technological advances, some fundamental changes are taking place in the practice of medicinal chemistry, as illustrated by the increasing role of chemical biology, the upcoming wave of computer-driven applications and, interestingly, the re-emergence of enzymatic-driven chemical transformations.

4.1 *The Impact of Digitalization*

Artificial intelligence (AI) and machine learning become increasingly important technologies in drug discovery. Despite the scientific complexity of their application to medicinal chemistry, AI begins to show impact in some important aspects, including in predicting the three-dimensional structure of proteins.[8] Machine learning also proves very helpful in scrutinizing and analysing large sets of data, including from massive databases such as ChEMBL or PubChem, and in developing predictive models. Beyond classical compilation and analysis, the development of generative chemistry applications also provides suggestions for novel molecules, by combining partial structure-activity relationships, profiling data and predictive models.[9] To accelerate the development of such tools, Novartis announced in 2019 a multi-year research and development alliance with Microsoft, the AI Innovation Lab. It focuses on AI empowerment, bringing AI applications to the desktop of every medicinal chemist, as well as AI exploration. The lab will tackle some of the hardest computational challenges within life sciences, including several aspects of chemical optimization.

4.2 The Promise of Automation

At first sight automation sounds like a process that should only be applied to highly repetitive tasks, which do not need regular attention or human intervention. However, while the art of drug discovery is far from an engineering process that can be automated easily, some individual steps are amenable to automation. It starts with, but is not limited to, the handling of the many individual data points generated during the synthesis and analytical characterization of a molecule, even prior to tests in biological assay systems. Automating workflows, data capture and interpretation frees up a lot of time for more creative activities for medicinal chemists.

Furthermore, the combination of data digitalization and automation enables the delegation of repetitive tasks – not to service labs but to computers and robotic systems. For instance, integrated drug discovery platforms, which utilize micro-scale chemistry, real-time biological and physicochemical characterization as well as machine learning driven compound design, can take over the tedious task of chemical space exploration around specific scaffolds. By accelerating the optimization of specific properties through automated, iterative exploration, they also allow medicinal chemists to focus on the most innovative aspects of drug discovery.

4.3 The Potential of Biotransformations

The exquisite ability of enzymes to enable site- and stereospecific transformations makes enzymatic catalysis an attractive tool in synthesis. The use of such reagents was however historically limited by the biotransformations achieved by natural enzymes, and by their substrate specificity. Recently, the engineering of novel enzymes optimized for specific reactions[10] enabled the extension of their application range, including unconventional biotransformations such as stereo-controlled halogenations[11] (Fig. 2).

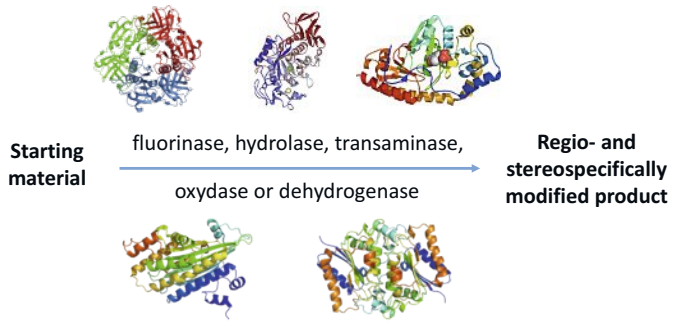

Fig. 2. Some enzyme classes useful for regio- and stereospecific chemical transformations.

With such tools in hand, biocatalysis can be used to prepare synthetically challenging molecules, and to explore chemical space regions that might otherwise be neglected during drug discovery programs. Custom enzymes evolved to enhance specificity and enable efficient transformations can be produced in large amounts, to support both chemical optimization and production,[12] making them particularly valuable. The increased availability of such reagents also opens the door to late-stage functionalization of drug candidates. This provides innovative molecules, with unique intrinsic properties and potential for further modification. Biotransformations are also an efficient method for metabolite synthesis. They allow the evaluation of potential drug liabilities resulting from metabolic products, arising from intrinsic activities, or from an interference with the pharmacological effect of the parent compound. Finally, the application of enzymatic transformations to specific steps of building block or drug candidate synthesis often leads to a reduced consumption of organic solvents and energy. Enzymatic reactions usually perform well in aqueous media at room temperature or slightly above. They hold the potential for more environmentally friendly chemistry, especially at large scale.

4.4 *The Value of Outsourcing*

A judicious use of outsourcing also helps scientists focus on complex issues and creative solutions, by providing additional, external resources for standard synthetic and profiling activities. Far from replacing experienced medicinal chemists, it allows them to focus on scientific challenges rather than operational needs. Typically, novel entities, unprecedented targets and technologies such as radioligand therapies or targeted protein degradation will be pursued internally, while library synthesis, building block production, and the standard activities of drug optimization programmes may be outsourced.

5. Opening the Framework

Opportunities related to collaborations with academic partners in Switzerland were discussed recently.[13] They are not the only source of external innovation for Novartis and other pharmaceutical companies, which look for innovative techniques, targets and drug candidates worldwide. Indeed, collaborations between academic centres, small and large pharmaceutical companies create a number of mutual benefits. These go from sharing biological tools with a larger community to study a disease at the cellular and atomic level, to developing new technologies or sharing risk for larger endeavours.

Interactions with the members of the chemical biology and medicinal chemistry community across the world are important, and no pharmaceutical company conducts research in complete isolation. In Switzerland, several learned societies regroup the medicinal chemistry, chemical biology and related scientific communities (Fig. 3). By organizing conferences and courses, as well as providing incentives for high quality research, they play an important role in fostering exchanges and the pursuit of new ideas within the scientific community. The participation in the activities of learned societies plays an important role in exploring new ideas and scientific challenges, and in revealing areas of innovation at the intersection of scientific disciplines.

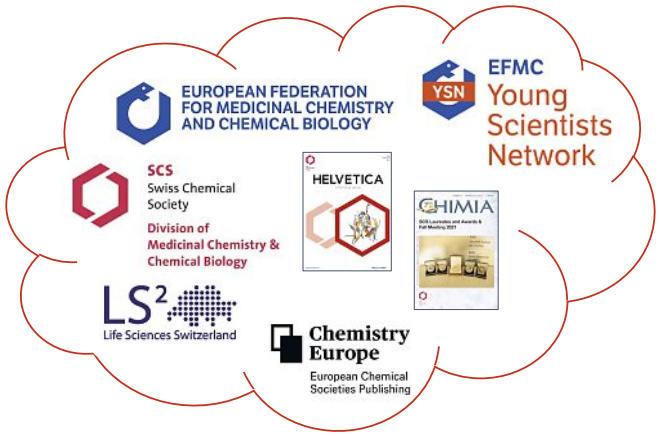

Fig. 3. The Swiss Chemical Society, the European Federation for Medicinal chemistry and Chemical biology, as well as Life Sciences Switzerland represent the medicinal chemistry and chemical biology community in Switzerland.

6. The Challenges that Remain

While drug discovery made impressive scientific progress over the last decades and identified drugs that changed the lives of millions of patients, many challenges remain. Despite improved success rates in late-stage phases, many drug candidates fail in the course of clinical development. Indeed, the rate of success in the pharmaceutical industry has hardly improved over time.[14] This is in part due to the difficulty of identifying therapeutically relevant targets, the complexity of some of the novel targets pursued, and a limited ability to predict dose, safety and efficacy in patients.

The identification of therapeutic targets heavily relies on high-throughput biology, including screens based on CRISPR/Cas9 gene editing, single cell RNA sequencing, or affinity proteomics. Medicinal chemists contribute to this effort by providing optimized, tailored tools to explore cellular biology. The principle of such tools, or chemical probes,[15] is to influence a specific cellular pathway and observe the effect of this perturbation on a disease-relevant parameter. Unfortunately, it is not easy to ensure that such molecules are perfectly selective, and even when they are, that their study in artificial or isolated systems is relevant. In addition, many disease models in animals are insufficiently validated or have intrinsic limitations,[16] leaving scientists with a limited ability to predict efficacy in human patients. The fundamental assumptions at target selection, that underlie otherwise successful medicinal chemistry programs, can end up being a major cause for failure in clinical settings.

Predicting the pharmacokinetic behaviour of drug candidates in patients has made significant progress, and drug candidates rarely fail in the clinic due to inadequate absorption or elimination.[17] In contrast, improper prediction of target engagement remains a frequent source of failure in the clinic,[18] especially for indications where preclinical models are poorly predictive of efficacy in humans.[19] A more systematic use of target engagement assays, both in animals and patients, *e.g.* imaging agents for positron emission tomography (PET), can however help address this issue. Similarly, the ability to tailor the route of administration, and to exploit diverse formulations to modulate the duration of action of drugs, has created novel opportunities. Extending the half-life of short acting drugs by different mechanisms (ligation to fatty acids to modulate duration of action, encapsulation in nanoparticles or embedding in slowly degrading matrices) proved successful in many different applications.[20] In addition, long-acting depot formulations, which by their nature prevent missing a dose, can help address the issue of poor patient compliance.

In contrast, predicting toxicology still remains difficult, and many drug candidates fail due to safety issues, or lack of efficacy related to doses limited by safety. Despite significant efforts, the investigative toxicology[21] of both oral and topically-administered drugs[22] remains a challenge. In the future, the use of integrated databases and computational tools to support the translational safety assessment of new drugs might facilitate their assessment, and the prediction of toxicological liabilities.[23]

Finally, the art of translating preclinically optimized candidates into clinically efficacious drugs remains a challenge in drug development. Further improvements are required for the prediction of human efficacious doses, and for refining the use of clinical biomarkers for patient selection and demonstration of efficacy. Likewise, the development of efficient clinical protocols to study chronic diseases or address new indications quickly and with good predictability remains difficult. A close collaboration between translational medicine and preclinical research experts fosters progress on this front, and this dialog should start at an early stage in a drug discovery project. Such challenges, often combined with pressure on costs, may lead to sluggish progress in the development of classical drugs as much as of innovative approaches, including cell-based or gene therapies.[24]

7. What Will Not Change

The quality and inter-disciplinarity of drug discovery science, across the chemical biology and medicinal chemistry continuum, are fundamental requirements for success. They result from the collaboration of highly educated and creative scientists, whose open-mindedness and curiosity is the basis of innovation. Novartis heavily invests in both technical and cultural aspects of drug discovery, striving for continuous improvement of its research activities.

The development of novel methods in organic chemistry enables many new technologies, and synthetic proficiency remains a critically important expertise. DNA-encoded libraries, miniaturized automatic synthesis systems, the exploration of new modalities, radioligand therapies as well as the optimization of ligands for classical drug targets rely on the synthesis of complex molecules. They often require the synthesis and functionalization of novel scaffolds, which frequently include a high level of structural complexity. During the drug discovery process, these

molecules are modified to optimize multiple parameters, and ultimately must be prepared in large amounts for *in vivo* testing and clinical development. While people far afield sometimes entertain the misperception that organic chemistry is a mature science, it remains an area where constant progress is critical. In parallel, the need for more sustainable and environmentally friendly processes adds another level of scientific complexity. Sophisticated organic chemistry is thus required to make such drug development projects possible, with optimal use of the latest technological developments.

8. Conclusions

Medicinal chemistry in drug discovery is a dynamic science. It strives to integrate the latest developments brought about by progress in digitalization, automation, and a better understanding of cellular pathways and human diseases. Over the last few years, medicinal chemists explored many innovative therapeutic opportunities such as new modalities or chemically modified biologics, as well as novel technologies to take advantage of advances in hit generation, synthetic methods, as well as data capture and processing. Medicinal chemists show remarkable flexibility and adaptability, and have the courage to explore concepts that require multi-disciplinary skills. Breaking down barriers to further enrich collaborations with drug discovery partners will be the key of their future success. Partnerships with cell biology, physics, medicine and related sciences are necessary to take on the current challenges of drug discovery. It is good to see medicinal chemists embracing and often leading this change, steadily improving science and communication, and taking up new therapeutic challenges.

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