DOI: 10.1002/anie.201201677

The Future of Medicinal Chemistry

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Medicinal Chemistry is often referred to as a mature science. We believe that this is a misperception. What is probably more accurate to state is that our efforts in pharmaceutical R&D have been remarkably successful. For example, protease inhibitors such as saquinavir (Invirase, Fortovase) and ritonavir (Norvir) have revolutionized the way medical doctors can treat HIV infections today. Oncology may serve as another example: Kinase inhibitors such as imatinib (Gleevec) and vemurafenib (Zelboraf) are effectively used to treat certain forms of cancer. So it is fair to state that medicinal chemists have been very successful in some disease areas by delivering molecules as medicines that have drastically improved both quality of life as well as progression-free survival of patients who in previous times would have died because of their devastating medical condition.

While citing these examples as successes, we must admit that we are far away from being able to treat or even cure many life-threatening diseases known today. And we are also far away from being able to address challenging targets with traditional medicinal chemistry methods, such as inhibiting protein–protein interactions, to name an often-debated example. Medicinal chemistry is a mature science—again, no. In sharp contrast, we believe that there is a much wider role for medicinal chemists to play than they are currently permitted by industry to have.

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Phenotypic Discovery

Despite the enormous progress that molecular biologists and pharmacologists have provided us with, phenotypic screening methods offer a large potential for drug discovery. A recently published analysis of drugs approved by the American Food and Drug Administration (FDA) between 1999 and 2008 showed that the contribution of phenotypic screening to the discovery of new classes of small-molecule medicines exceeded the number of those derived from purely target-based approaches. Consequently, the use of more holistic screening approaches, for example stem cells, disease-like cell types, or even directly in vivo applied pharmacology approaches such as the SmartCube technology, will enable the discovery of new targets as well as the description of novel disease-relevant pathways. An important prerequisite for the successful application of phenotypic screening formats is a high level of reproducibility and ability to predict the in vivo efficacy. Medicinal chemists must be able to successfully drive a structure–activity relationship by using such phenotypic assays in order to design and synthesize molecular probes with which pharmacologists will describe disease pathways and potential new targets using methods such as chemoproteomics, which in turn will enable chemists to further refine such molecules to ultimately deliver drug candidates for these newly described targets and pathways.

Regenerative Medicine

For many widespread chronic diseases with damage or partial loss of organ function, no cure exists today. Diabetes may be taken as a prominent example where the function of pancreatic β-cells has been damaged. On the other hand, if we had small molecules that were able to trigger cellular self-renewal mechanisms or cell-type-specific activation of somatic stem-cell differentiation, then such treatments would potentially cure diseases by "molecular organ repair" and restoration of organ function. In an alternative regenerative medicine approach, one may take a patient's skin cell that is reprogrammed in vitro into a pluripotent stem cell, which thereafter might be implanted into diseased tissue such as the pancreas of diabetes patients. If we now had a small molecule that was able to trigger differentiation of implanted stem cells into fully functional pancreatic β-cells, we would restore organ function and potentially cure diabetes. Today, more than 100 small molecules are described that can affect stem-cell survival, proliferation, differentiation, and most dramatically the entire reprogramming of somatic cells into pluripotent stem cells. There is

no doubt that the research field of regenerative medicine will significantly advance over the next few decades and thus may lead to regenerative treatment options for patients. We are convinced that small molecules will play a pivotal role in further advancing the research field of regenerative medicine—an enormous opportunity of untapped potential for medicinal chemists.

Epigenetic Targets

There is an ever-growing body of evidence that epigenetic changes of DNA—and to a certain extent also of RNA—play a profound role in normal development as well as in disease manifestation and progression, and it is known today that chromatin remodeling can lead to heritable changes in gene expression. The best-understood modifications currently originate from so-called "writers" and "erasers" that lead for example to DNA methylation and histone deacetylation, which both in turn suppress gene expression. On the other hand, such altered sequences are recognized by "readers" such as bromodomains, chromodomains, and other protein epitopes. As these DNA and chromatin alterations are caused by enzymes that are acting in the cell nucleus, the entire class of emerging epigenetic targets calls again for small molecules as therapeutics that are able to readily penetrate membranes of both the outer cell as well as the nucleus. Epigenetic targets are currently intensively investigated and there is no doubt that new drug targets will emerge from research in epigenetics. As described for phenotypic screening approaches, here again, medicinal chemists will design and synthesize molecular probes including tools for chemoproteomic approaches with which pharmacologists will describe disease pathways and potential new epigenetic targets—another rapidly emerging research area for medicinal chemists.

Peptide Therapeutics

More than 60 peptides are currently FDA-approved marketed drugs, the most prominent example being insulin. Furthermore, during the past 10 years, much experience has been gained by industry and regulatory authorities through the development of biologics. What has been learned here may be now applied and combined with our strong historical knowledge about peptides, peptoids, β-amino acid peptides, and in more general terms with the entire world of peptides containing nonnatural amino acids. Such complex molecules can nowadays be synthesized fairly rapidly by experienced peptide chemists. In addition, tailored polypharmacology approaches can be designed into a single peptide sequence that may exert multiple agonistic functions; an example is the combination of incretin hormones. Moreover, peptides may be further stabilized as bioconjugates, for example with covalently bound endogenous lipids that increase the stability and half-life of the peptides in plasma. And last but not least, the research field of cell-penetrating peptides offers enormous potential to also reach intracellular compartments with peptide therapeutics. Peptides are of particular interest for intracellular targets that cannot be easily addressed by small-molecule approaches, such as protein–protein interactions. We firmly believe that the field of peptide research in pharmaceutical R&D deserves an in-depth re-evaluation.

RNA as a Drug Target

While medicinal chemists traditionally concentrated on the target class of proteins for the treatment of human diseases, the biosynthesis of proteins has been largely neglected as a complimentary principle for therapeutic interventions. We believe that targeting RNA, in particular messenger RNA (mRNA), provides a huge potential for small molecules as therapeutics. Posttranslational control of gene expression may result in an entire world of new medicines. The approach is of particular interest for the treatment of genetic diseases, and such diseases in which the protein function or processing of the protein itself is causal for the disease. In other words, instead of inhibiting the aspartic protease BACE for the treatment of Alzheimer's disease, one may think of molecules that downregulate the biosynthesis of the amyloid precursor protein, which in turn would reduce the formation of disease that causes amyloid beta fragments. Or to mention another example, instead of inhibiting cholesterylester transfer protein (CETP), one might think of a small molecule that effectively downregulates CETP expression through posttranslational control of mRNA processing at the ribosome. And there is another beauty of the approach: the protein itself will serve as intrinsic clinical biomarker for dose selection and response prediction.

Innovation, Creativity, and Governance Structure

In more general terms, we are convinced that medicinal chemists must broaden their horizons and diversify at a pace that matches our increasing understanding of chemical biology and network pharmacology. As a consequence, the themes we briefly outlined in this Editorial go far beyond traditional borders of medicinal chemistry and might lead us to a new level of what future pharmaceutical R&D will be able to deliver to society.

Keeping in mind that innovation cannot be scheduled, a large challenge for pharmaceutical R&D leaders remains the creation of an entrepreneurial governance structure in medicinal chemistry that supports such innovative research themes in industry. How can we create the right working environment that fosters innovation and creativity to allow medicinal chemists to reach across boundaries of scientific disciplines, and supports the right balance and focus on efficiency and innovation, at the right point in time? We suggest the development and implementation of models that enable scientists to have non-bureaucratic access to the resources required for innovation, relieve them from pressure to reach challenging targets, and reward them for entrepreneurial behavior in a manner that recognizes their contribution to innovation.