Editorial

According to IUPAC's 'Glossary of Terms used in Medicinal Chemistry', medicinal chemistry is a "*chemistry-based discipline …. that is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships*." It is clear from this definition that medicinal chemistry is at the core of drug discovery and of vital importance to the development of new and life-saving therapies. As every scientific discipline, medicinal chemistry is constantly evolving, thereby embracing new technologies, new biological target classes, new modes of action and new chemotypes, including molecules well beyond the rule-of-five space and conjugates of small molecules with biological macromolecules. Thus, what once seemed to be prohibitive, undoable ('undruggable' targets), or not technically feasible, has now become possible or at least within reach. Think of covalent drugs, the inhibition of protein–protein interactions, or the introduction into clinical practice of oligonucleotide-based drugs. It is inevitable that the selection of topics for a special issue on medicinal chemistry is deliberate to some extent and not all important aspects of the field can be covered here. Nevertheless, I believe that this collection of articles features many facets of modern medicinal chemistry in its broadest sense, written by true experts in their field of research.

The issue starts out with a review by ***Jörg Scheuermann et al.*** on the state-of-the art in DNA-encoded library technology and its impact on the discovery of new hits and leads, which represent the critical entry points into every small molecule drug discovery program. This is followed by an insightful perspective by ***Gisbert Schneider et al.*** on the use of machine learning approaches and artificial intelligence in the generation of new simplified scaffolds from bioactive natural products, but also for target prediction. There can be no doubt that such approaches will deeply penetrate future drug discovery programs.

Cansu Kaya & Anna K. H. Hirsch present an innovative approach towards the discovery of new antibiotics, which is a highly topical area of research, given the global health threat posed by antimicrobial resistance. However, as we have painfully learned over the last 2.5 years, drug-resistant bacteria by no means are the only infectious entities that are threatening human health and well-being. In their contribution, ***Joy E. Thames & Kathie Seley-Radtke*** review what we have recently learned about the mode of action of nucleoside-based antivirals and the efforts that have been made to discover new nucleosides as inhibitors of the SARS-CoV-2 RNA polymerase to establish new treatment options for COVID-19.

As alluded to above, covalent inhibitors had not been considered viable drug candidates for a long time, but the tide has turned on this issue. This is vividly illustrated in the review by ***Laura Hillebrand & Matthias Gehringer***, which highlights the importance of covalent kinase inhibitors in cancer therapy and provides a comprehensive perspective on ongoing research in this area. While not quite as prominent as kinase-directed drugs, inhibitors of histone deacetylases (HDACs) over the last 15 years have emerged as important additions to our armamentarium in the battle against cancer and the current status of HDAC inhibitors as drugs and drug candidates is reviewed by ***Rossella Fioravanti et al.***

G-protein-coupled receptors comprise the largest family of drug targets and this issue includes two contributions that present recent developments in the field. ***Peter Gmeiner et al***. review the (rather surprising) potential of the bitter taste receptor TAS2R14 as a new target for drug discovery against pulmonary diseases, while ***Erick M. Carreira, Marc Nazaré, Uwe Grether et al***. discuss the design and application of superior chemical probes for the endocannabinoid system that includes the well known CB1 and CB2. Drug discovery directed at the endocannabinoid system has been of interest for some time and recently has gained significant traction for a number of disease indications.

Two classes of biological targets that are clearly under-addressed in drug discovery, albeit for very different reasons, are discussed by ***Johanna Huttunen & Kristiina M. Huttunen*** and ***Gerhard Müller & Joe Lewis***. Huttunen & Huttunen discuss how amino acid transporters could possibly be exploited as targets, but also as transport vehicles for new targeted anticancer drugs. Gerhard Müller reviews recent progress in the search for phosphatase inhibitors, which are a very important class of potential drug targets but until not too long ago had not yielded to potent inhibition by drug-like molecules; and Lewis and Müller discuss how this has changed.

Although the potential of oligonucleotides as drugs was first recognized several decades ago, this potential was reduced to practice only much later. By now, however, oligonucleotide drugs are here to stay and why that is and what it took to get there from a medicinal chemistry perspective is described in the review by ***Jonathan Hall et al***.

Enjoy reading!

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The Editorial Board of CHIMIA thanks guest editor Prof. Karl-Heinz Altmann for organizing this special issue on Medicinal Chemistry, providing an excellent overview of the many facets of modern medicinal chemistry.