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A new landscape of chemical modalities in Chemical Biology and Drug Discovery

Over the last decades, major scientific progress has enabled the discovery of drugs that significantly improve patients' lives through improved standard of care. In some cases, curing a disease has become a reality as illustrated by the field of Hepatitis C and in some rare cases, cancer. In other therapeutic areas such as respiratory, pain or diabetes, medicines are helping to control a disease or its associated symptoms. In this respect, the next, and more desirable, level of aspiration is to reverse and cure these diseases rather that continuing to look for marginal improvements in standard of care. This ambition calls for a focus on exciting but highly complex novel biology around regenerative medicines and requires to develop our understanding in cell regulation and proliferation. Interestingly, these processes are highly synergistic with many aspects of oncology. In fact, novel biology is today at the centre of all therapeutic areas. In parallel, and to further foster a patient- and disease-centric paradigm, genomics analyses carried out on patient samples are promising a long list of novel, often unprecedented targets, whose causality has however to be demonstrated.

To address these targets and develop our biology understanding, chemical probes are required for both target-centric and phenotypic approaches. With this prospect in mind, small molecules play a major role, considering the breadth of modulators available for a wide range of targets. However, many targets originating from genomics or from the study of biological pathways are orphan from ligands and are not the prime applicable space for small molecules, typically due to their large surface area. Protein-protein interactions, and in particular transcription factors, remain a major challenge, despite some isolated examples of success. In this respect, other chemical modalities are better suited. These so-called 'New Modalities' cover many chemical classes including a new generation of usually hyper-modified peptides, macrocycles, a renaissance of natural products, and nucleic acid-based molecules.* In addition, these modalities can be combined and linked to generate further New Modalities.

This range of molecules enable the interrogation of biological systems in complementary ways. Beyond the classical agonism/antagonism approach that can be achieved with small molecules, peptides and macrocycles, other mode-of-actions are being accessed with other modalities. Antisense oligonucleotides can in particular decrease or even deplete protein levels both for intracellular and secreted proteins. Excitingly, modified mRNA provides the opportunity to intracellularly express a protein, for example to upregulate protein levels. Another exciting avenue is to leverage classical modalities such as small molecules differently. The so-called proteolysis targeting chimeras (PROTAC) connect two small molecules to drug a protein target in a different way, through protein degradation. This example illustrates how classical and potentially New Modalities can be brought together, creating additional New Modalities to manipulate cell biology.

This emerging picture of chemical biology and drug discovery is this year again reflected in the program of the RICT conference. Alongside small molecules, New Modalities are being covered, including through the lens of drug delivery. Across therapeutic areas, chemical modalities are been approached with the necessary expansion of the chemical biology and drug discovery toolkit, including chemical and fluorescent probes, kinetics and synthesis. Novel biology is also being unveiled such as novel ways to regulate molecular targets such as GPCRs, and novel screening approaches towards these. The conference program further reflects how the boundaries between chemical biology and 'traditional' medicinal chemistry are increasingly blurring. It also aligned with the need to close the loop between drug discovery and clinical settings, moving closer to patients. Performing *in vivo* chemistry is one approach which may enable shorter feedback to preclinical research and further foster a paradigm of personalised medicines.

The RICT conference also provides drug discovery scientists with the possibility to prepare for the changing landscape of drug modalities. The breadth of knowledge and skills required today, and even more in the future, may appear daunting for medicinal chemists. It however represents an opportunity to tap into their vast creativity and answer biological questions in the most appropriate way, both for science and for the benefits of patients. Even for larger modalities, such as oligonucleotides where drug design is typically following sequence-base rules rather than the arguably innovative design seen in small molecules, chemists can further contribute to these modalities. Many areas including formulation, or for enabling the delivery and uptake of these modalities to the right cell types and tissues, benefit from a medicinal chemist's insights and mindset towards structure-property relationships. For example, antisense oligonucleotides tend to distribute to liver, spleen and kidney and chemists can design solutions to access other tissues and cells through targeted delivery with drug conjugates. These conjugates, which are another good example of mixed modalities, contain small molecules components such as a linker but also possibly small molecules as targeting ligands, providing evidence that applying a breadth of 'traditional' organic and medicinal chemistry expertise is possible.

Overall, medicinal chemists and chemical biologists have the opportunity to be the drivers of an integration of chemical spaces, bringing together modalities, and seeing the range of solutions to address biological questions and for therapeutics as a continuum of modalities. Scientists are equipped like never before to manipulate cell biology, and will undoubtedly further develop their knowledge during the RICT conference.

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Reference:

*New Modalities for challenging targets in Drug Discovery. Valeur, E.; Gueret, S.; Adihou, H.; Gopalakrishnan, R.; Lemurell, M.; Waldmann, H.; Grossmann, T.N.; Plowright, A.T. *Angew. Chem. Int. Ed.*, **2017**, *56*, 10294-10323.