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## Advances in Chemical Probing Concepts for Chemical Biology Applications [Editorial]

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## **“Advances in Chemical Probing Concepts for Chemical Biology applications”**

### ***Guest Editors***

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Chemistry at the interface of Biology is playing an increasingly important role in biomedical science, facilitating new cutting-edge technologies to understand the biology and discover new treatments for human diseases.<sup>[1]</sup> The concept of “chemical genetics” recognized the power of bioactive molecules as tools to study biological processes.<sup>[2]</sup> In analogy to genetic perturbations, forward and reverse chemical genetics approaches can be distinguished.

In forward chemical genetics, the phenotypic changes of cellular systems after exposure to small molecules are studied, with the aim of identifying the underlying target and pathway biology (target agnostic approach). In reverse chemical genetics, a compound with specific activity for a particular known target is used to study the phenotypic consequence of target modulation (approach focused on protein of interest).

The development of chemical reactions that proceed in living systems without compromising biochemical integrity of the system under study (bioorthogonal chemistry) has been a breakthrough for chemical genetics approaches.<sup>[3]</sup> (Nobel Prize in Chemistry 2022, <https://www.nobelprize.org/prizes/chemistry/2022/press-release/>) Bioorthogonal Chemistry has enabled probing a broad range of biomolecules (glycans, proteins, lipids, nucleic acids) in biological systems at various levels of complexity (cells, tissues and animals) with excellent biocompatibility.

The role of Chemical Biology has gained significant importance for the deconvolution of novel druggable targets from “omics” approaches and phenotypic screening technologies, opening the field of chemoproteomics.<sup>[4]</sup> Revealing and characterizing novel putative drug targets is the foundation of chemical probe-based drug discovery, which complements the “classical” phenotypic and target-based approaches. The power of combining “omics” approaches and chemical probing regarding expansion of the druggable space is exemplified by the breakthrough discovery of KRAS G12C inhibitors – a target considered to be undruggable for decades - such as Sotorasib and Adagrasib FDA-approved in 2021 and 2022, respectively.

Dedicated research on chemical probes as tool compounds in biomedical research has led to the definition of specific profiles for chemical probe vs. drug molecules.<sup>[5]</sup> High-quality and high-impact probes are designed for the respective biological hypotheses or question asked in a drug discovery context and may be inspired by known ligands of a given target. Functionalization of these probes with non-drug-like moieties, such as click moieties, reactive groups (e.g., warheads), photocages, photoswitches, protein-tags, degradation-tags or fluorescent dyes enables probes to be used in multiple contexts.

Thus, advances in chemical probe concepts gain more and more importance for detailed studies of physiological and molecular processes, helping to address challenges in Medicine, including emerging infectious diseases, antimicrobial resistance, cardiovascular diseases, neurosciences or cancer.

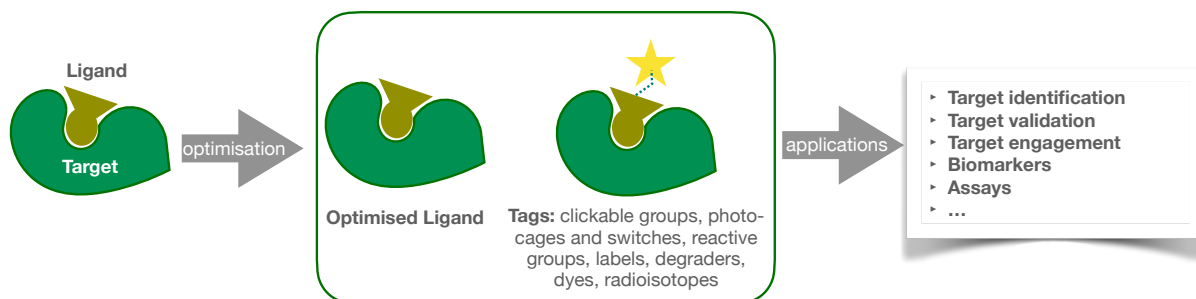
In summary, biomedical research approaches leveraging chemical probes allow to identify, validate and confirm novel targets for therapeutic applications, enable the development of *drug candidates*, and open the way to *new therapeutic strategies*, *vaccines* and also *diagnostic tools*. The present Special Issue highlights the role of chemical probes in biomedical discovery today and aims at identifying emerging trends and technologies in the discovery of the next wave of drug targets that will advance medical progress in the next decade.

**Keywords:** chemical biology, chemical tools, detection, omics technologies, mechanism of action, novel targets, best stories; Perturbation atlas  
Industrial, Academia, networks

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Chemical probes allow to identify, validate and confirm novel targets for therapeutic applications, enable the development of *drug candidates*, and open the way to *new therapeutic strategies, vaccines and diagnostic tools*.

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