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The Chemical Biology-Medicinal Chemistry continuum: EFMC's vision

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Abstract: The European Federation for Medicinal chemistry and Chemical biology (EFMC) is a federation of learned societies. It groups organizations of European scientists working in a dynamic field spanning chemical biology and medicinal chemistry. New ideas, tools, and technologies emerging from a wide array of scientific disciplines continuously energize this rapidly evolving area. Medicinal chemistry is the design, synthesis, and optimization of biologically active molecules **aimed at discovering new drug candidates – a mission that in many ways overlaps with the scope of chemical biology**. Chemical biology is by now a mature field of science for which a more precise definition of what it englobes, in the frame of EFMC, is timely. This article discusses chemical biology as currently understood by EFMC, including all activities dealing with the design and synthesis of biologically active chemical tools and their use to probe, characterize, or influence biological systems.

Introduction

The European Federation for Medicinal chemistry and Chemical biology (EFMC) is composed of national learned societies representing scientists active in the chemical biology - medicinal chemistry continuum. EFMC's mission is to advance science by promoting connectivity and cooperation among scientists in Europe and across the world, by supporting national adhering organizations and facilitating communication. EFMC fulfils these objectives by organizing symposia and short courses, by sponsoring scientific meetings, medicinal chemistry and chemical biology schools, as well as by publishing a newsletter,^[1] sharing information, and providing scientific recognition in the form of awards and prizes. Detailed information is available from the EFMC web site: www.efmc.info.

Chemical biology belongs to the scope of EFMC, and to emphasize this, we integrated it in the name of the federation, which until 2020 was the "European Federation for Medicinal Chemistry" (Fig. 1). Similarly, we recently changed the name of EFMC's newsletter, previously MedChemWatch, to MedChemBioWatch. In fact, chemical biology has long been included in EFMC's events and in its membership. For instance, the EFMC-International Symposium on Medicinal Chemistry (EFMC-ISMC) has three streams: one on chemical biology, one on medicinal chemistry, and one covering associated technologies. EFMC members include associations such as the Division of Medicinal Chemistry and Chemical Biology of the Swiss Chemical Society, or the Division of Medicinal Chemistry and Chemical Biology of the Royal Dutch Chemical Society. Like others, they consider both disciplines as part of a continuum. In some countries however, chemical biologists and medicinal chemists tend to remain in separate networks. The EFMC adapted its name to include chemical biology visibly, and in order to clarify its scope and the fact that it represents all members of this extended community.



Figure 1. The 2020 update of the EFMC logo and new name of the newsletter, now emphasizing the importance of chemical biology.

While there are multiple definitions of chemical biology,^[2] none of them are definitive or universally applicable. The challenge in identifying a bridging definition led many scientists to design their own description of chemical biology for teaching, communication or administrative purposes. It is, of course, complex to establish a consensus definition in a constantly developing scientific environment. EFMC therefore decided to come up with a description of what it understands as being the part of chemical biology that falls under its umbrella of activities. The authors of this article are members of EFMC's Chemical Biology Initiative, and consulted with many colleagues across the chemical biology community in Europe.

Medicinal chemistry and chemical biology

EFMC sees chemical biology and medicinal chemistry as part of a scientific continuum.^[3] It has its own definition of medicinal chemistry, largely including chemical biology activities:

"Medicinal chemistry is concerned with the design and synthesis of biologically active molecules. It aims at creating new chemical structures to better understand and influence physiological and/or pathological systems. Ultimately, it allows the discovery and optimization of novel drugs to address unmet medical needs."

CONCEPT

Chemical biology is interdisciplinary, involving the development and use of chemical tools to explore and modulate biological systems in a precise and controlled approach. The methods and compounds involved in this discipline are very diverse, including small molecules, natural products, molecular glues, covalent modifiers, peptides, and other pharmacologically active molecules, as well as molecular probes derived from these compounds. In the field of drug discovery, it sets the scene for medicinal chemistry by identifying and validating therapeutic targets, on the way to the discovery of clinically useful drugs. Chemical biology also enhances drug discovery by developing and employing chemical proteomic methods to identify novel chemical starting points and to study target engagement and proteome-wide selectivity of drug candidates in biological systems.

Clearly, the continuum of medicinal chemistry and chemical biology leads to an overlap of techniques and research activities (Fig. 2). This overlap creates opportunities for new ideas and synergies, bringing together scientists with different backgrounds and experience. Drawing on scientific diversity is essential in medicinal chemistry and chemical biology, because biology is so complex. A broad palette of ideas and skill sets are critical for facilitating the translation of ideas from basic research to applied science.

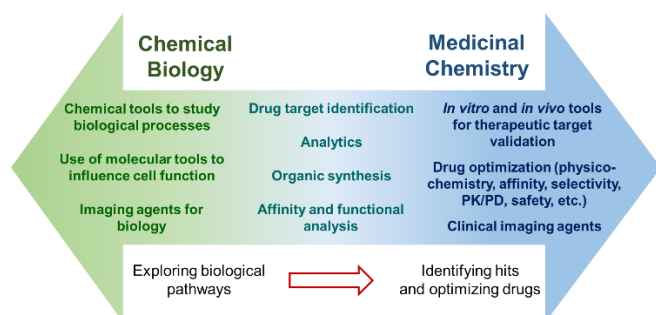


Figure 2. A simplified representation of the medicinal chemistry and chemical biology continuum. PK: pharmacokinetics; PD: pharmacodynamics.

Chemical biology uses techniques spanning many disciplines, and so it is common that many in the field do not define themselves solely as chemical biologists. The EFMC provides a community for an extended group of scientists who share an interest in bringing the power of chemistry to the study of biological systems, allowing multidisciplinary and synergistic studies.

In an effort to clarify the scope of chemical biology as seen by EFMC, Table 1 illustrates chemical biology and medicinal chemistry activities, in a non-exhaustive manner. Many of them intersect and overlap, illustrating the continuous nature of this field.

Table 1. Examples of activities that illustrate both sides of the chemical biology and medicinal chemistry continuum

"Chemical biology"-like	"Medicinal chemistry"-like
Designs and develops bioactive molecular tools to modulate and study biological processes.	Designs and optimizes bioactive molecules by modulating their activity and properties, to identify new drugs.
Optimizes chemical probes and imaging tools (e.g. fluorescent molecules) to explore biological systems.	Optimizes imaging agents (e.g. PET tracers) ^[a] as clinical biomarkers.
Uses synthetic biology to access new molecular scaffolds and selectively labeled molecules.	Uses synthetic chemistry to discover and optimize drug candidates.
Uses the tools of biology to develop high-throughput screening (e.g. DEL). ^[b]	Optimizes hits from screening campaigns (e.g. DEL screening).
Uses proteomics and metabolomics to identify a compound's effects on native proteins expression and function or the biomolecular target of a small molecule.	Uses proteomics to optimize the selective effect of drug candidates.

Develops chemical tools for molecular target identification and complex studies.

Uses nanotechnological tools in biology and single-molecule methodologies.

Develops strategies to access novel chemical space and bio-orthogonal chemistry.

Develops drug candidates for clinical proof of concept.

Develops nanotechnologies for nanomedicine and personalized medicine.

Develops synthetic strategies to access novel chemical space for drug discovery.

[a] PET: Positron emission tomography. [b] DEL: DNA-encoded libraries

Chemical biology, biology and biochemistry

The increasing interplay between chemistry and other sciences led to a blurring of traditional boundaries between disciplines. A helpful delineation is that medicinal chemistry and chemical biology create new molecules to study or influence biological systems, whereas biology and biochemistry are concerned with the study of living organisms, including their development and evolution, as well as of their anatomy, biochemical processes and physiological mechanisms.

While these disciplines all aim at new insights in biology, chemical biology does so through chemical intervention. It includes chemical reactions *in vivo*, the use of chemical probes (e.g. small molecules, peptides, natural products), or physical chemistry (e.g. radioactive, fluorescent or photo-activated agents). Complementary to chemical biology and biology, biochemistry characterizes biological processes based on the description of substances and chemical processes that occur within living organisms. Table 2 illustrates some examples characterizing these domains.

Table 2. Examples of activities that fall under EFMC's understanding of chemical biology, vs biology and biochemistry.

"Chemical biology"-like	"Biology and biochemistry"-like
Studies cellular pathways using chemical probes.	Study cellular pathways using biological techniques.
Creates or artificially modifies existing molecules to influence cellular processes.	Study how biomolecules produced by living organisms participate in cellular processes.
Uses structural biology to explore biomolecule-ligand interactions.	Use structural biology to characterize novel biomolecules & their function.
Uses proteomics to identify a compound's effects on native proteins expression or the biomolecular target of a small molecule.	Use proteomics to identify the interaction partners of a native protein.
Studies the function of proteins and cellular pathways by screening chemical libraries (chemical genetics).	Exploit genetic screening identify genetic mutations associated with function or disease.
Uses phenotypic screening to identify substances that alter the phenotype of a cell or organism.	Use phenotypic screening to identify genetic mutations leading to a specific phenotype.

Very often, exploiting the information a technique provides, rather than the use of a specific technique, defines what is or is not in the scope of chemical biology. As an illustration, the determination of the structure of a native protein by cryo-electron microscopy is not considered a chemical biology endeavor, in contrast to the use of the structural information gained by this technique to optimize a chemical probe or when using fluorescent probes in correlative light electron microscopy experiments.

There are many examples of such techniques supporting chemical biology and medicinal chemistry research. Their scientific value is irreplaceable, and they are undoubtedly connected to the realm of chemical biology and medicinal chemistry. While critically important to science as a whole, they remain parts of scientific disciplines such as cell and structural biology, pharmacology, or physics, and stand on their own, outside the scope of EFMC's activities in chemical biology.

Conclusion

No description of a discipline can claim perfection, and it is not the purpose of this essay to provide an ultimate definition of chemical biology. Its ambition is rather to provide a common ground to the chemical biology and medicinal chemistry community, and in particular to EFMC's present and future membership. We hope that this exercise will provide some guidance on the activities EFMC strives to support. Naturally, this scope will evolve to include the emerging interests of the scientific community embraced by EFMC, and future developments in the chemical biology – medicinal chemistry continuum. New ideas, new tools, and new methods will open novel possibilities and constantly redefine the vibrant research area at the chemistry-biology interface.

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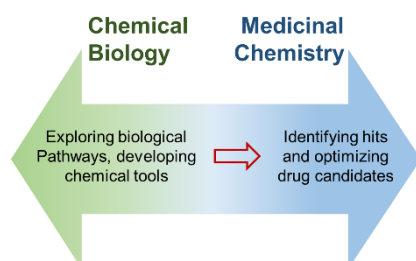
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Keywords: chemical biology • medicinal chemistry • EFMC

- [1] <https://www.efmc.info/medchemwatch>
- [2] See e.g. a) https://en.wikipedia.org/wiki/Chemical_biology; b) Voices of chemical biology. *Nat Chem Biol* 11, 378–379 (2015).
- [3] A. T. Plowright, C. Ottmann, M. Arkin, Y. P. Auberson, H. Timmerman, H. Waldmann. *Cell Chem. Biol.* 2017, 24(9), 1058-1065.

CONCEPT

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A scientific continuum? EFMC covers the field of chemical biology to medicinal chemistry. What are these disciplines, and how do they differentiate, if at all? This article discusses EFMC's current understanding of chemical biology as currently understood by EFMC, and its relation to medicinal chemistry, biology and biochemistry. Chemical biology includes many activities dealing with the design and synthesis of biologically active chemical tools, and their use to probe, characterize or influence biological systems.

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