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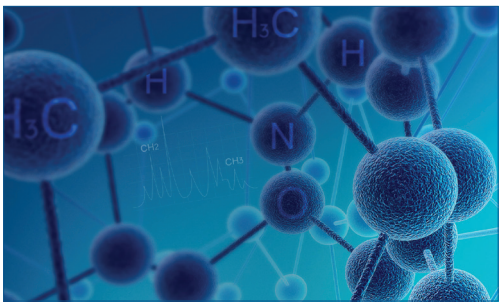
WHAT'S IN A NAME: *CHEMICAL* BIOLOGY OR CHEMICAL *BIOLOGY*?

Since when it was coined over two decades ago, the expression* chemical biology *has been widely debated for the semantic importance of the noun and the attribute. Yet, rather than being a kind of "applied chemistry" or "another branch of biology", chemical biology is a truly interdisciplinary science that requires both components and is related to medicinal chemistry more than any other discipline.

"*There should be no problem with biology driving science unless perhaps you happen to be a chemist!*"
Since the very first time I read it in the *Chemical and Engineering News* paper by Stuart Schreiber entitled "The small-molecule approach to biology", this sentence always fascinated and inspired me (and I often used it in talks).
Indeed, the last decades have witnessed tremendous developments in biology. Technological advances across all scientific disciplines are creating ever-increasing opportunities to enhance our knowledge of biological systems and how they relate to human diseases. As the world population increases and ages further, patients will be in need of novel innovative agents to treat their aliments. This situation creates an incredible opportunity and necessity for scientists to drive forward our biological understanding and discover novel medicines which truly differentiate from the current standard of care and cure disease.
One of the hallmark disciplines involved in drug discovery efforts over the past 100 years has been medicinal chemistry. The design and synthesis of new chemical entities targeting known biological systems, or those discovered from phenotypic screening, has been a central driving force in discovering new medicines. However, as the number of well-validated molecular targets is limited, the hurdles for differentiation over current treatments has increased, and a much greater emphasis is being placed upfront on the understanding of the relevance of new potential therapeutic targets, and this has required medicinal chemistry to develop and branch out into new areas.
If medicinal chemistry can apparently no longer meet the requirements of the post-genomic era in the traditional paradigm of drug research, namely those associated with delivering new structures with unique profiles of action within short periods of time, what kind of strategies do we need to address this problem in a sustainable way in the long term? In view of the complex situation at the outset, short-term patent remedies are not possible. The only solution is to use and implement the rapidly developing knowledge about biological principles in a strategic manner. However, this can only be done by using an interdisciplinary approach between chemistry and biology.



Over the past two decades "chemical biology" (term coined by Schreiber and Nicolaou in 1996) has emerged as a major

discipline which, as the name suggests, employs the methods and techniques of chemistry for the study of biological phenomena. Or, better, it could be defined as the design and use of molecules as tools to probe biological systems, from protein structure and function, to cellular pathways, to complex organisms. Chemical biology sits at the interface of many disciplines, bridging chemistry, biology, and biophysics, in an ideal case under the roof of one research laboratory, but more frequently by means of collaboration between research groups with complementary expertise. While it was originally confined to academic institutions it is now becoming more widespread and an integral part of drug discovery.

Beside the semantic discussion between the importance of the noun and the attribute in the term "chemical biology", the interdependency of chemistry and biology in it has been shown to be of great synergistic value. A relatively obvious example is the development of click chemistry and the plethora of applications in biology ranging from purification tools to the efficient preparation of bioactive ligands. These and many other examples show the usefulness and enormous significance of chemistry for biology.

The chemical biological approach to research in the life- and biosciences harbors the potential to gain insights into biological processes not accessible by means of biology techniques alone, and is, thereby, complementary to established biology methods. Although seemingly a "no-brainer", appropriate valuation and recognition of the individual contributions of the subdisciplines might be a matter of debate. Thus, chemical biology is neither a kind of "applied chemistry" nor "another branch of biology". Instead, it is a truly interdisciplinary science requiring both components. Bringing chemistry and biology much closer and at an earlier stage is creating new opportunities to probe and understand biological systems, often directly in human cells, and to validate the relevance of molecular targets to human diseases far earlier than before. In a time when the number of highly differentiating molecular targets is limited, the synergy of chemistry and biology creates new options for target discovery, and allows a more thorough investigation of molecular pathways and of the molecular mechanism of action (MMOA) of new molecules. Nowhere is this more evident than in cancer biology and drug development. Major challenges lie ahead of chemical biology research. The analysis of dynamic biological systems by means of selective, reversible, gradable, and conditional temporary perturbations (which cannot be achieved by means of genetic methods) provides one particularly relevant and timely example, and "systems chemical biology" clearly is on the horizon. To meet this challenge, the development of the chemical compounds needed to perturb dynamic biological systems and the development of the required biology techniques (e.g., new microscopy, targeting and visualization methods) need to go hand-in-hand in a truly trustful manner that fairly recognizes and values the contributions of both disciplines. In this interplay, it is the enabling ability to design, synthesize, characterize, and use tailor-made molecules (be they drug-like small molecules, modified proteins, oligo- or polynucleotides, saccharides, lipids, metal complexes or conjugates thereof or others, be they organic or inorganic) in well-chosen biochemical and biological experiments that defines the key expertise of chemical biology and distinguishes it from biochemistry and molecular biology. If research in chemical biology maintains this interdisciplinary character and balances the chemistry and the biology components well, it will establish itself as a key science in the study of complex and dynamic biological systems and phenomena.

In other words, despite the advances and impact of chemical biology, in my opinion the need for medicinal chemistry is as strong, if not stronger, than ever before. Initial hit molecules need to be effectively optimized against multiple parameters, challenging targets require a highly entrepreneurial mindset and optimization strategy, high toxicology hurdles and a defined mechanism of action (for target validation) places a great emphasis on the required compound selectivity. In addition, drug candidates still need the appropriate pharmacokinetic parameters to allow effective dosing in patients.

The following papers in this issue of *La Chimica e l'Industria* will outline how the combination of chemical biology and medicinal chemistry can ultimately foster science advance and impact diseases.