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# Drug Discovery … The Third in the Band!

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> *"La chimie crée son objet. Cette faculté créatrice, semblable à celle de l'art lui-même, la distingue essentiellement des sciences naturelles et historiques."*
>
> Marcelin Berthelot, *La Synthèse chimique*, Alcan, Paris, 1887

This famous quote from Marcelin Berthelot (its English translation is "Chemistry creates its object. This creative faculty, similar to that of art itself, distinguishes it essentially from natural and historical sciences.") exemplifies like no other the ability of the chemist to create new molecules with novel structures and, following therefrom, novel properties. Because of this creative power, chemistry, and in particular synthetic chemistry, has been assigned multiple enabling roles and several of its sister disciplines have grown "chemical" branches such as "chemical physics".

## Chemical Biology Is Rooted in Organic Synthesis

Among these disciplines, "chemical biology" is a younger cousin. While the name was coined at least four decades ago,[1] the current understanding of the term was shaped only within the last two decades. The field evolved from bioorganic chemistry, biochemistry, cell biology, and pharmacology, but synthetic organic chemists played a leading role in its inauguration. For instance, Stuart L. Schreiber and K. C. Nicolaou served as Editors of the journal *Chemistry & Biology*, "*the first journal dedicated to the expanding intellectual area in which chemical approaches and biological disciplines overlap.*" As they stress in their inaugural Editorial in the first issue: "*Both of us started professional life as strict organic chemists, with little knowledge of biology and not much expectation that we would ever need to know any.*"[2] Since then, the development and application of organic synthesis methodology to achieve a greater understanding of biology at the molecular level has emerged as one major area of research in chemical biology. For instance, labeling of biomolecules has greatly advanced in the last decades, based largely on the development of novel biomacromolecule synthesis and ligation techniques, which are often rooted in classical organic synthesis methods such as the Huisgen 1,3-dipolar cycloaddition and the Staudinger reaction.

## Chemical Biology and Organic Synthesis Are Brothers-in-Arms

Among the various applications of organic synthesis methodology in chemical biology research, it is most likely that the use of small-molecule probes as tools for unraveling and manipulating the inner workings of the cell (chemical genetics) today is commonly associated with the term "chemical biology". While major studies and efforts have been made during the last decades to fill the chemical toolbox required to meet this daunting task and to equip the chemical biologist with the right "tools" in the struggle to decipher the secrets of nature, this endeavor has only just begun. Notably, although large compound libraries are commercially available these days, their structural complexity and diversity remain fairly limited, and in high-content assays, their performance often leaves room for substantial improvement.

Higher structural complexity and incorporation of stereogenic centers often positively correlate with bioactivity, thus calling for the synthesis and application of complex compound classes in chemical biology research that expand the currently accessible tool and probe candidates to novel scaffold classes. This demand can only be met by the continuous introduction of novel synthesis methodology and the development of creative solutions to the problem of making increasingly complex compounds available with higher efficiency and practicability in the formats of compound-collection synthesis.

Therefore, the synthesis of structurally and stereochemically complex molecular architectures is at the heart of chemical biology research. Chemical biology needs continuous input from organic synthesis, and organic synthesis may find challenging and unprecedented synthesis targets with an immediate application in the problems faced by chemical biologists: chemical biology and organic synthesis are brothers-in-arms!

Ideally, to lend the brotherhood strength and to develop it to maximum impact, both chemical and biological expertise should be established under one roof, that is, within a given research group. As ideal as it would be, such an interdisciplinary team is hard to estab-

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lish. Limitations arise on one hand from the different cultures of the two sciences and the core expertise of the leading scientists, who usually were trained and started their career in either chemistry or biology. On the other hand, establishing and operating a full chemistry and biology infrastructure is very cost-intensive, and funds on the required scale often are simply not available. Hence, only few groups worldwide can fulfill these requirements.

Alternatively, collaboration between different research groups is necessary in chemical biology research, and, indeed, many of the best results obtained in this science represent multiteam efforts. If productive collaborations with mutual appreciation of the partners and their scientific contribution can be established, from a scientific point of view, this brotherhood may actually be the better approach to tackle demanding scientific problems. The combined expertise of the partners in chemistry and biology usually will allow deeper insights to be obtained and high-quality research in both sciences to be performed.

## Chemical Biology Fuels Drug Discovery

This brotherhood may prove vital to yet another sector of science in the near future, that is, to drug discovery. Chemical biology is partly rooted in cell biology and pharmacology, and its repertoire of methods extents into small-molecule synthesis, determination of bioactivity, and identification and validation of small molecule cellular targets. If the small molecules employed in chemical biology research have druglike properties, and modulation of the activity of their cellular targets can be tied to a disease-modifying effect, the link to drug discovery is obvious. In fact, fully fledged chemical biology research programs have the potential to simultaneously produce novel insights into fundamental biological mechanisms, deliver new targets, and supply small-molecule modulators of target activity. Therefore, major challenges in drug discovery may inspire chemical biology research and by extension, organic synthesis endeavors. Conversely, the outcomes of a chemical biology investigation may fuel efforts in drug discovery.

## The Third in the Band

This alliance may prove instrumental as a key driver for future research in the pharmaceutical industry. Facing major challenges, pharmaceutical companies very recently have increased collaboration with academic institutions far beyond the occasional support of individual smaller projects (see, for example, reference [3]). In so doing, the industry may be well advised to listen to its own opinion leaders. In June 2011, Mark Bunnage (Pfizer) wrote: "*This change in model reflects the reality that the vast majority of the initial breakthroughs in target biology research occurs in the academic research environment. It is thus considered essential for pharmaceutical companies and their scientists to become better connected with the external research environment and develop a more extended network of partnerships and genuine collaborations with academia. … It is thus essential for medicinal chemists in industry to increase their awareness of chemical biology approaches and build these into their armamentarium to enable drug discovery.*" [4]—He is right!

A successful and seminal example of such a fruitful collaboration between academia and industry is the Chemical Genomics Centre (CGC) of the Max Planck Society (Max-Planck Gesellschaft, MPG). The CGC was established in 2005 as a joint initiative of the MPG, Merck KGaA, Schering AG, Bayer CropScience AG, and Organon B.V. Research in the CGC is focused on challenging unsolved problems in chemistry and biology of major relevance to drug discovery, such as stabilization of protein–protein interactions by small molecules and the development of allosteric kinase inhibitors. Both the companies and the MPG funded independent research groups that developed the basic science and transferred it to the companies. If appointment of the group leaders to professorships and integration of the developed technologies into the internal project pipelines of the companies are accepted as stringent criteria for measuring success from both the academic and the industrial point of view, then the establishment of the CGC was a major success.

Accordingly, after the first funding period of the CGC (2005–2010) the MPG and Merck KGaA, AstraZeneca AB, Boehringer Ingelheim Pharma GmbH & Co. KG, Bayer Pharma AG, and Bayer CropScience AG have established "CGC II", and the first research group leaders have been appointed very recently.

The success of the CGC and related initiatives suggests that it may be more than advisable to those engaged in drug discovery to take the final verses of Schiller's poem "The Hostage" to heart (translation by Scott Horton):[5]

*He gazed upon them long in amazement,*
*And then spoke: "You have succeeded,*
*You have turned my heart,*
*In truth, fidelity is no idle delusion,*
*So accept me also as your friend,*
*I would be—grant me this request—*
*The third in your band!*"

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[3] A. Mullard, *Nat. Rev. Drug Discovery* **2012**, *11*, 6–8.
[4] M. E. Bunnage, *Nat. Chem. Biol.* **2011**, *7*, 335–339.
[5] *Harpers Magazine*, Sep 16, 2007.