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Synthetic biomolecules: from blind watchmakers to synthetic biologists

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Johan Winne has been Assistant Professor at Ghent University since 2015. There, he leads an organic synthesis research group, consisting of chemists fascinated by terpene natural product families, modular heterocyclic building blocks, and cycloadditions. Next to these research lines, he also actively collaborates with research groups active in polymer chemistry, pharmacy and plant biology. Such collaborative efforts include the development of new dynamic covalent chemistries and click-type bioorthogonal reactions, useful for the functionalisation of (bio)macromolecules.

Annemieke Madder was promoted Full Professor at Ghent University in 2014. She heads the Organic and Biomimetic Chemistry Research Group specialized in the design and synthesis of modified peptides (peptide cyclisation, scaffold decoration and peptide stapling), nucleic acids (modified backbone (PNA), base modifications, interstrand crosslinking) and methods for their conjugation and labeling. The research team works towards applications in antisense and antigene strategies, protein and miRNA/lncRNA target identification and receptor pulldown.

Synthetic chemistry and biomolecules have a long and closely intertwined history. The purposeful transformation of one natural substance into another (known) product was for a long time the most powerful way to elucidate and confirm the structural identities of new substances that were isolated from living organisms. Next to chemical degradation studies, aimed at breaking down complex substances into their simpler building blocks, the inverse process also gathered interest among chemists, especially over the course of the second half of last century, thus quickly building a toolbox that can tackle almost any synthetic challenge. It has been argued that synthetic chemistry today stands at a level of sophistication that should allow the directed synthesis of any biomolecule, including all biomacromolecules, and even any imaginable derivative, conjugate or mimic thereof. In practice, however, time and cost considerations will not always make such endeavours worthwhile or even sensible.

In the last few decades, the research focus on what (bio)molecules to choose as targets for synthetic chemistry, and on how to make them in the most efficient way, is slowly disappearing. Certainly not everything in synthetic chemistry is a solved problem, but a lot of the classical research questions in this area have become technical challenges rather than scientific ones. At the same time, the research questions surrounding the structures of biomolecules, and on how to determine them, are becoming less and less important for biochemistry and biology. These classical biochemistry or structural biology research questions, although certainly not always trivial, are indeed now also mainly situated in the area of technical challenges. However, one type of research questions both in biomolecular synthesis as well as in biochemistry or biology have remained as a major scientific challenge, and have even grown more pressing in the light of the vast quantity of available intimate structural insights into biomolecules. With the 'what' and the 'how' mostly covered, science needs to focus on the 'why' questions. The question of why a given biomolecule has a certain structure is of course closely related to the functional role of that biomolecule. Working out the various functions of biomolecules, including their interplay with other biomolecules within a cellular or even wider context, is still a major scientific challenge.

So far, synthetic biomolecules have proven to be highly valuable tools in biological research aimed at why-type questions. By purposely altering the chemical composition of a living organism, either by adding synthetic biomolecules or by adding synthetically modified versions thereof, the observed effects can often be rationalized in terms of biological functions and processes. The blind 'hit and hope' strategies, amplified by modern high throughput screening strategies, have already provided scientist with a

wealth of insights and are also greatly contributing to transformative applications in medicine and agriculture. The directions forward in these areas for synthetic chemistry not only lie in technological innovations to facilitate and automate synthetic processes to speed up discovery and serendipity, but will also include innovative chemical strategies to probe, understand and ultimately control biological processes. Resulting from the understanding of the biological functions of biomolecules, altered and potentially improved versions thereof can be generated by combining more traditional biomolecule synthesis procedures with novel chemical protocols, thus allowing to expand the chemical biology toolbox.

For this year's *Synthetic Biomolecules* section in *Current Opinion in Chemical Biology*, we have invited and encouraged leading scientists to write contributions for their respective fields of expertise, annotating the most recent and most relevant literature, with a focus on the outstanding challenges and promising new directions for research, offering authors the freedom to also include speculations and opinion. Traditionally, the Synthetic Biomolecules section focuses on biopolymers such as peptides, nucleic acids, carbohydrates, lipoproteins, glycoproteins, etc. In the current issue focus lies on the use of synthetic chemistry to construct mimics or modified versions of naturally occurring biomolecules allowing exploitation of the resulting constructs in biology but also in various fields beyond biology including development of next-generation therapeutics, material design, catalyst design and diagnostic developments. Furthermore, this year, we also wanted to include some perspectives from the 'small molecule' side of synthetic chemistry. Natural metabolites or synthetic protein ligands are certainly the oldest class of chemistry tools used in biology research, but new concepts and applications are still being developed today. The 'comeback' of small molecules and natural products chemistry in biology and biomedicine has been consistently predicted over the last few decades, but the truth of the matter is that they have never left the scientific scene, and are in fact stronger than ever, and any reports of their demise or decline have thus been greatly exaggerated.

Margaret Brimble and Emma Davidson offer the readers a selection of current synthetic work aimed at using natural products (or specialized metabolites) as a starting point for the development of new medicines. Although this strategy has fallen out of favor in industry, it is still strong and productive in academia, and natural products remain a stronghold to find new interesting biological activities. Alessio Ciulli and Chiara Maniaci present an overview of a concept that is rapidly gaining momentum in the small molecule field, aimed at bringing together disparate proteins with heterobifunctional chemical probes made up of two different small molecule protein ligands, which opens up very attractive applications for biology research, but also for novel therapeutic strategies such as targeted protein degradation. Lee *et al.* outline the state-of-the-art in our understanding of the bacterial cell membrane and how properties are affected by their lipid diversity. Membrane properties are very important to understand for the development of antibiotics, but even determining their exact phospholipid structures and composition is a very challenging task, given the wide structural diversity found therein. Small molecules and proteins have always been a good match, and the conjugation of proteins with small molecules is now also a well-known strategy. For many applications, a dynamic or reversible conjugation can be much more attractive. Christian Hackenberger and Alice Baumann describe examples of novel protein conjugation strategies that can allow a selective cleavage of protein conjugates within cells.

Resulting from the understanding of biological function and the interplay between structure and properties, methodologies that allow *de novo* design of proteins have gained momentum. Dawson *et al.* describe how starting from increased knowledge on protein dynamics and through a combination of minimal, rational and computational design, functional de novo proteins can be evolved that can tightly bind to small molecules or catalyse small molecule chemical transformations. On a smaller scale, conformational stabilization of peptides and peptidomimetics has become of prime importance in peptide-based drug design. While helix stabilization has been discussed at many previous occasions, in this issue Sandrine Ongeri *et al.* describe the state of the art in the design of conformationally stabilized linear and cyclic peptide and peptidomimetic inhibitors of PPIs involving β-sheet structures. The usefulness of peptides in a material science context becomes more and more apparent and while self-assembly of certain peptide sequences can result in materials with polymer-like properties, an alternative and original approach consists in the combination of peptides and silicone. Martin *et al.* provide an overview of strategies for the construction of peptide-biofunctionalized PDMS that finds different applications in silicone-based devices. Next to peptides and proteins, nucleic acids represent one of the other major classes of biomolecules with widespread applications. The application of enzymatic and synthetic procedures to obtain highly functionalized nucleic acids has been reviewed by Hocek *et al.* who provide an impressive account on the scope and limitations of an extensive series of selected chemical reactions for nucleobase modification, along with an overview of potential applications of such multiply modified nucleic acid sequences. In a related nucleic acid context, Darwinian selection methods have allowed the identification of nucleic acid enzymes that catalyze a broad range of transformations. The application of post-SELEX processing of existing nucleic acid catalysts as well as the use of modified triphosphates during selection procedures is described by Hollenstein, hinting towards the extensive range of applications of such constructs as

therapeutic agents in biosensing devices or as imaging reagents. Combining the best of both worlds in terms of stability, functionalization and base-pairing possibilities, Saarbach *et al.* review this most successful class of oligonucleotide mimetics and uncover an exciting series of high-end applications in gene-editing, nucleic acid detection and sensing and programmable supramolecular assembly for drug and protein organisation, heralding the bright future that such highly evolved biomolecular structures promise to have.