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Editorial

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Art, Architecture, and the Molecular Frontier

Guest Editorial for the Accounts of Chemical Research special issue on "Synthesis, Design, and Molecular Function".

The science of synthesis has been transformed in the last two centuries from its initially uncertain role in the preparation of natural products to its often overwhelming success in doing so. The seminal synthesis of the natural product urea by Wöhler in 1828 and other syntheses of that period forever changed how we think about the molecular world and our ability to impact it. Justus von Liebig captured the early optimism of that time, noting in 1837 that "*The extraordinary and to some extent inexplicable production of urea without the assistance of vital functions, for which we are indebted to Wöhler, must be considered one of the discoveries with which a new era in science has commenced.*" Some years later, Berthelot took this optimism to another level declaring in 1855 that "*we may, I say, claim to form anew all substances which have been developed since the origin of things*". The realization that natural substances could be made in a laboratory opened new areas of research that have since transformed our world in ways previously unimaginable. The reach of synthesis now extends from the scalable production of many natural compounds to designed molecules with new or improved functions, collectively impacting the whole of science, our economy, medicine, energy, materials, art, architecture, food, fashion, culture, and our standard of living. The impact has been fundamental, consequential, and not always fully appreciated. Before 1856, colorants, for example, were derived largely from natural sources. William Perkin changed that. His accidental synthesis of mauve, a light purple dye, influenced not only the fashion of the time, but gave birth to the dye industry and among other impacts forever changed the artist's palette. It also drew attention to the view that *non-natural* products could exhibit new and desirable functions. Enabled by the improving ability to create new chemical entities, the pharmaceutical and polymer industries emerged soon thereafter and the technical terms "antibiotic" and "nylon" became common words in most languages. Chemistry has since become an enabling partner in the whole of molecular science from anthropology to zoology. From "nanotech" to "nascent tech", Liebig's "new era in science", driven by our ability to design and make molecules with function, marked the beginning of what has since become a molecular revolution of unprecedented global significance.

Today we can indeed "form anew" most chemical entities, given, of course, sufficient time, funding, and peer and institutional support. Steroids, terpenes, alkaloids, carbohydrates, polyketides, peptides, proteins, and nucleic acids among other natural compounds are now accessible through synthesis. This has hugely beneficial environmental consequences as the reproducibility and scalability of chemical synthesis often avoids massive harvesting of scarce natural agents from their delicate marine and terrestrial ecosystems. The fusion of synthesis and engineered biosynthesis has created powerful additional ways to access complex natural molecules and their derivatives. For many natural targets, the challenge of synthesis has thus changed in recent years from whether the target can be made to whether it can be made in a supply-impacting and timely fashion. Syntheses are now increasingly measured not by prior art but by how close they come to more aspirational "green" if not ideal goals: one step, 100% yield, simple, safe, resource and time efficient, and environmentally sound. As evident in contributions in this special issue, chemists have impressively risen to meet these challenges and opportunities with powerful new reactions and strategies that have improved access to many molecules once thought impossible to make. Wöhler's one-step synthesis of urea set the bar high, but the science of synthesis driven by new reactions and innovative thought has moved us closer to that ideal.

For many targets, the design and development of a supply-impacting synthesis or even scalable harvesting from natural sources can take time. For many targets, that wait is unacceptable due to clinical or other time-sensitive needs. This has indeed turned some away from natural products and increasingly toward screening more synthetically accessible libraries. Screening has its merit in many situations especially in early stage research when leads are absent. There is however another option for many natural, even complex, therapeutic leads. Through synthesis-informed design, one can create simplified and thus accessible targets often exhibiting superior function. Given that often only a simple subunit of a complex structure is needed to achieve sought-after function, a designed, more synthetically accessible, simplified system can replace the more complex target. Target design thus becomes an initial synthesis priority. Synthetic chemists are ideally suited for this function-oriented design and synthesis approach as it extends the logic of retrosynthetic analysis to that of retrofunctional analysis, that is, creating structures with function through a knowledge of physical properties, mechanism, and reaction science. Examples of this approach are increasingly reported and are exemplified in this issue. The capability of computers to create and analyze structures for desired function, in essence digitally guided "isolation and assay", is also having a huge impact on this approach and the field, as it provides an amazingly rich and, for small molecules, an exhaustive source of new structures including those found in nature and beyond.

So where are we now? In 1996, a snapshot of the evolving field of synthesis was provided by many of its thought leaders (*Chem. Rev.* **1996**, *96*). This *Accounts of Chemical Research* special issue on "Synthesis, Design, and Molecular Function" is directed at providing a sequel now from a postmillennial perspective. It explores many representative new advances and challenges associated with designing and making molecules in the 21st century. It features contributions from thought leaders in the field directed at new reactions, reagents, and catalysts;

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total, automated, chemoenzymatic, and biomimetic syntheses; photocatalysis; photopharmacology; process technologies; screening strategies; computational approaches to vast new structural collections; and the collective impact of these remarkable advances on the design and synthesis of molecules that exhibit function from materials to devices and from molecular probes to new medicines and vaccines. At the suggestion of the editors (Ken Houk, Cynthia Burrows, Scott Miller, Laura Grünwald), who inspired and guided this effort, I have refrained from providing an overview of each contributed article. However, I do wish to extend my thanks to the editors and to those who made this special issue possible, imaginatively capturing the inspiring science and perspectives from the groups of Baran, Barrett, Boger, Brummond, Burke, Cossy, Danishefsky, Francis, Gademann, Glorius, Hudlicky, Lee, Ma, Micalizio, Movassaghi, Reymond, Scheidt, Seeberger, Sherburn, Sodeoka, Stephenson, Stoltz, Trauner, Trost, Wender, Wipf, Wong, and Yu. These remarkable, "must read" contributions inform and inspire, collectively illustrating the rich diversity of directions, orientations, and impacts associated with modern synthesis and the aspirational goal of achieving function through synthesis-informed design. While space constraints precluded broader participation (the original author list was well over 100), the science presented by the current contributors is a fascinating and inspiring Account of a remarkable and ever-evolving field that has changed and will continue to transform science and our world.

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Notes

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