CHEMICAL BIOLOGY OF NATURAL PRODUCTS

EDITED BY
DAVID J. NEWMAN
GORDON M. CRAGG
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CHEMISTRY

CHEMICAL BIOLOGY OF NATURAL PRODUCTS

This unique, long-awaited volume is designed to address contemporary aspects of natural product chemistry and its influence on biological systems, not solely on human interactions. The subjects covered include discovery, isolation and characterization, biosynthesis, biosynthetic engineering, pharmaceutical, and other applications of these compounds.

Each chapter begins with a brief and simple introduction to the subject matter, and then proceeds to guide the reader towards the more contemporary, cutting-edge research in the field, with the contributing authors presenting current examples from their own work in order to exemplify key themes.

Topics covered in the text include genome mining, heterologous expression, natural product synthesis, biosynthesis, glycosylation, chemical ecology, and therapeutic applications of natural products, both current and potential.

FEATURES:

- Contributions from leading scientists in the field
- Focuses on the chemical biology and biological chemistry of natural products
- Covers the discovery and modification of novel natural product chemotypes from multiple sources and interactions with biological processes
- Addresses a relatively neglected area of scientific publishing in book format

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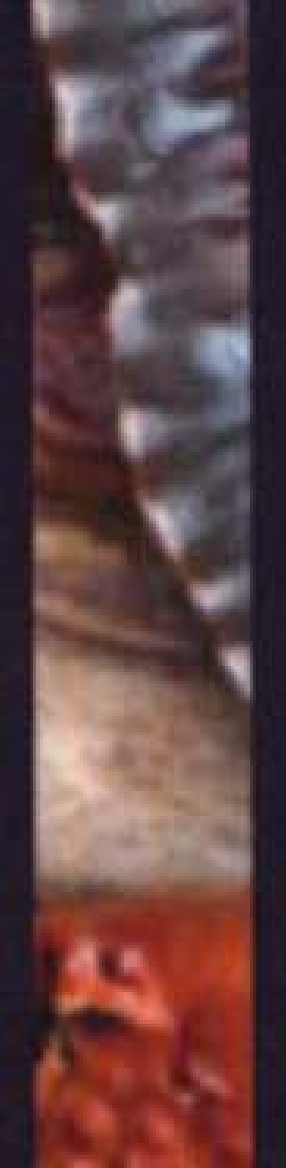

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Chemical Biology of Natural Products

Preface

Chemical biology, biochemistry, and biological chemistry? So what, if anything, are the similarities and differences? One easy definition of the first and last terms would be that *Chemical biology = The biology of chemicals*, whereas *Biological chemistry = The chemistry of biology*, and *Biochemistry is the study of the chemistry of living systems*.

This definition dilemma is further illustrated by the fact that there are eminent universities across the United States where there are chemical biology programs in the College of Chemistry (Berkeley, for example*), but also biochemistry in the same university but housed in the College of Letters and Science†; and at the University of Pennsylvania, the Chemistry Department has a Biological Chemistry Resource Center‡ and a chemical biology postgraduate program,§ with a biochemistry program included within the Medical School.¶ We should add that one of the editors practiced as a *biological chemist* in the U.S. pharmaceutical industry 45 plus years ago, studying the effect of small synthetic molecules on oxygenation of hemoglobin. Today, he might well have been practicing chemical biology!

The Broad Institute, based in Cambridge, Massachusetts,** defines chemical biology as "the science of small molecules in the context of living systems to discover and to elucidate molecular pathways fundamental in cellular, developmental and disease biology."††

Furthermore, a survey based on *leading journals at the interface between chemistry and biology*, conducted by the American Chemical Society (ACS), of 4000 scientists working at the interface of chemistry and biology, indicated that natural products did not feature in the top eight disciplines (bioorganic chemistry, medicinal chemistry, molecular biology, enzymology, biophysics, biotechnology, cell biology, and structural biology) selected as being linked to chemical biology.‡‡ Interestingly, when natural products was used as the *lead* term, the survey selections indicated that they were linked in decreasing order to medicinal chemistry, bioorganic chemistry, chemical biology, plant science, and pharmacology, but not to microbiology.

Attempting to separate the three *disciplines* mentioned in the first paragraph is probably an exercise in frustration. However, what intrigues us about the Broad

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* http://chemistry.berkeley.edu/ugrad/degrees/chembio.

† http://mcb.berkeley.edu/undergrad.

‡ https://www.chem.upenn.edu/content/penn-chemistry-biological-chemistry-resource-center.

§ https://www.chem.upenn.edu/content/graduate.

¶ http://www.med.upenn.edu/biocbiop/.

** https://www.broadinstitute.org/chembio-therapeutics.

†† http://www.broadinstitute.org/scientific-community/science/programs/csoft/chemical-biology/chemical-biology-program.

‡‡ http://pubs.acs.org/bio/.

Institute definition and the results of the ACS survey discussed above is the apparently widespread lack of appreciation of the role played by natural products in the area of chemical biology. Even more puzzling is the apparent failure to link natural products to microbiology. We therefore decided that a volume highlighting the role of natural products in *chemical biology* would be an enlightening undertaking and that such a volume should include examples of all three methods of interrogating Mother Nature in individual chapters.

The 15 chapters in this book range over the gamut of the definitions alluded to above and serve to emphasize the dominant role played by microbes in the production of bioactive metabolites. On the chemical biology front, they include the chemical biology of cyanobacteria, combinatorial biosynthesis, including synthetic biology, target identification from natural product inspired structures, and syntheses devised around active natural product structures. Moving to secondary metabolites that may be used in the future to *probe biological systems* or are themselves the products of complex interactions, there are discussions covering materials from insect–microbe symbioses, compounds from plant–endophytic microbes and rhizosphere interactions, and the coculture of microbes to induce production of fungal metabolites. Also covered are secondary metabolites from extremophilic sources, including toxic lakes and deep-sea sediments and vent organisms, and a chapter covering genomic mining of microbes to find novel bioactive natural products. Finally, moving closer to biological chemistry and/or biochemistry, there are significant discussions of neurotoxins from venomous *Conus* species and the somewhat similar active cyclic sulfide-bridged peptides from plants and animals.

There are many other very interesting topics at the interface of chemistry and biology, in particular if one looks at the burgeoning reports related to the actual sources of secondary metabolites in marine-related organisms, and perhaps in some cases, in plants as well. What has now become quite evident is that the majority of bioactive natural products described from the *Porifera* (sponges), and almost certainly in other marine phyla as well, are almost certainly produced by as yet uncultured microbes, whose secrets are now being revealed by the combination of genomic analyses of single microbial cells coupled to very sophisticated physicochemical techniques.

As an example, the story of the pederin–mycalamide–onnamide locus is one that even a few years ago would have been science fiction but is now recognized as being correct. This story, in an abbreviated form, leading from the *Paederus* beetle toxin, via a German entomologist's suggestion that a microbe was involved, through the work done by Piel and his collaborators on an as yet uncultured *Entotheonella* species, was recently reported by one of the editors in an open-access paper.*

That the investigation of biological phenomena now requires a multidisciplinary approach, where chemists and biologists need to work together to uncover Mother

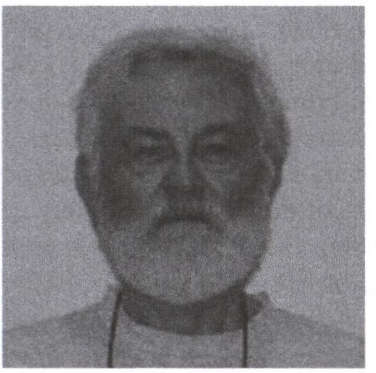
* Newman, D.J., The influence of Brazilian biodiversity on searching for human-use pharmaceuticals, *J. Braz. Chem. Soc.*, 2017, in press (http://jbcs.sbq.org.br/imagebank/pdf/160478RV_Biota.pdf).

Nature's secrets, has become evident today, and it is our hope that the examples in this book will further encourage scientists, be they chemical biologists, biochemists, biological chemists, or just *plain chemists and biologists*, to work together in order to further discover novel agents and their interplay, with the potential that some may lead to new treatments for human diseases.

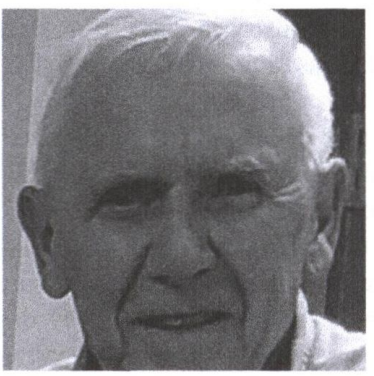
Our sincere thanks to all who have participated in this project!

David J. Newman
Gordon M. Cragg
Paul G. Grothaus

Editors

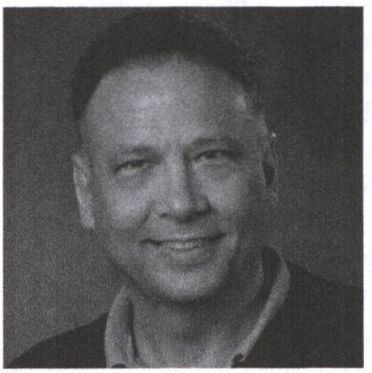


David J. Newman retired from the position of chief of the Natural Products Branch (NPB) in the Developmental Therapeutics Program at the National Cancer Institute (NCI) in Frederick, Maryland, in early January 2015. Born in Grays, Essex, United Kingdom, in 1939, he received an MSc in synthetic organic chemistry from the University of Liverpool in 1963. Following time as a synthetic chemist at Ilford, Ltd., he joined the Agricultural Research Council's (ARC) Unit of Nitrogen Fixation at the Universities of London and Sussex, as a research assistant in metallo-organic chemistry, transferring to the microbial biochemistry group in early 1966 as a graduate student and being awarded a DPhil in 1968 for work on microbial electron transport proteins from *Desulfovibrio*. He moved to the United States in 1968 as a postdoc in the Biochemistry Department at the University of Georgia, working on protein sequencing of *Desulfovibrio* ferredoxins, and then in 1970, he joined Smith, Kline & French (SK&F) in Philadelphia as a biological chemist. At SK&F, most of his work was related to antibiotic discovery, and in 1985, when the antibiotic group was dissolved, he left SK&F. For the next six years, he worked in marine and microbial discovery programs at Air Products, SeaPharm, and Lederle, and then in 1991, he joined the NPB as a chemist responsible for marine and microbial collection programs. He was given the National Institutes of Health (NIH) Merit Award in 2003 for this work, and following Gordon M. Cragg's retirement from the position of chief of the National Products Branch of the National Cancer Institute (NPB/NCI), at the end of 2004, he was acting chief until appointed chief in late 2006. He is the author or coauthor of over 180 papers, reviews, and book chapters (and an editor, with Gordon M. Cragg and David Kingston, of *Anticancer Agents from Natural Products*) and holds 18 patents, mainly on microbial products. He is still associated with the NPB/NCI as a special volunteer and also has a small consulting business to *occupy his spare time!*



Gordon M. Cragg obtained his undergraduate training in chemistry at Rhodes University, South Africa, and his DPhil (organic chemistry) from Oxford University. After two years of postdoctoral research at the University of California, Los Angeles, he returned to South Africa to join the Council for Scientific and Industrial Research. In 1966, he joined the Chemistry Department at the University of South Africa, and he transferred to the University of Cape Town in 1972. In 1979, he returned to the United States to join the Cancer Research Institute at Arizona State University, working with Professor G.R. Pettit. In 1985, he moved to the National Cancer Institute (NCI), National Institutes of Health (NIH), in Bethesda,

Maryland, and was appointed chief of the NCI Natural Products Branch in 1989. He retired in December 2004 and is currently serving as an NIH special volunteer. His major interests lie in the discovery of novel natural product agents for the treatment of cancer and AIDS, with an emphasis on multidisciplinary and international collaboration. He has been awarded NIH merit awards for his contributions to the development of the anticancer drug Taxol (1991), leadership in establishing international collaborative research in biodiversity and natural products drug discovery (2004), contributions to developing and teaching NIH technology transfer courses (2004), and dedicated service to the NCI as a member of the PDQ Complementary and Alternative Medicine Editorial Board (2010). In 1998–1999, he was president of the American Society of Pharmacognosy and was elected to honorary membership in 2003 and named as a fellow in 2008. In 2006, he was given the William L. Brown Award for Plant Genetic Resources by Missouri Botanical Garden, which also named a recently discovered Madagascar plant in his honor, *Ludia craggiana*. He has established collaborations between the NCI and organizations in many countries, promoting drug discovery from their natural resources. He has authored or coauthored over 180 papers, reviews, and book chapters related to these interests.



Paul G. Grothaus earned a BSChem from Creighton University in 1977 and his PhD from Purdue University in 1983, where he completed the first enantiospecific total synthesis of a trichothecene mycotoxin, anguidine. His education was followed by a postdoctoral stint at the University of Washington, investigating the synthesis of germacrolides. In 1984, he joined the Natural Products Group in the Plant Sciences Division of Monsanto Agricultural Company, where he investigated the synthesis and structure–activity relationships of agriculturally useful natural products. In 1988, he became the head of chemistry at Hawaii Biotech, Inc., in Aiea, Hawaii, where he worked on drug discovery based on both terrestrial and marine natural product leads. In 2002, he joined the Medicinal Chemistry Department of Celera Genomics, Inc., in South San Francisco, California, and rose to become an associate director of medicinal chemistry in 2005. Research at Celera focused on the development of protease and kinase inhibitors and activity-based probes for chemical proteomics studies.

At Celera, Dr. Grothaus led the chemistry group that designed and synthesized irreversible and reversible inhibitors of Bruton's tyrosine kinase (BTK), culminating in the discovery of ibrutinib (CRA-32765/PCI-32765), a first-in-class, oral, once-daily therapy that inhibits BTK, a key protein in the B-cell receptor signaling complex. Following further preclinical and clinical development by Pharmacyclics, Inc., Ibrutinib received three Oncology Breakthrough Therapy Designations by the Food and Drug Association and was approved for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma in 2014, mantle cell lymphoma in 2013, and Waldenstrom's macroglobulinemia in 2015.

In 2007, he joined the Natural Products Branch of the National Cancer Institute in Frederick, Maryland, where he coordinates biomass collections, biological screening of extracts, and collaborations with external natural product researchers. Dr. Grothaus is the author or coauthor of 24 papers, reviews, and book chapters and holds 5 patents.

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