Microbial Diversity and Bioprospecting
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EDITED BY Alan T. Bull
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This is an exciting time for those involved in bioprospecting, especially in the pharmaceutical area; indeed this field is at a crossroads in its development. Whereas ingenuity, innovation, and product introduction have been deaccelerated by the mega mergers of the pharmaceutical industry, the new opportunities now available for the development of new drugs are staggering. Indeed, the high cost of these novel opportunities to “big pharma” has in part contributed to the downgrading of natural product research and development. The loss of interest in this most important aspect of new drug innovation is of course only temporary because its replacement by combinatorial chemistry, genomics, and high-throughput screening has not been productive. This opinion is not a conclusion arrived at by biologists; rather, it has been stated publicly by prominent medicinal chemists. So what is to be done? The answer is a synergistic combination of the traditional and the new, i.e., combining intelligent bioprospecting of nature’s diversity with the novel techniques of genomics, proteomics, metabolomics, metagenomics, combinatorial chemistry, combinatorial biosynthesis, high-throughput screening, and bioinformatics. We are fortunate that, during this period of downgrading of natural products by the major drug companies, a number of smaller biotechnology companies have picked up the slack by entering the arena of natural product discovery. They are using some of the newer techniques in their efforts as well as expanding the search to relatively ignored environments such as the ocean.

When one speaks about natural products, included are biopharmaceutical (i.e., erythropoietin) primary metabolites such as amino acids and vitamins, secondary metabolites (penicillin G), products discovered in nature but made by chemical synthesis (thienamycin), and chemical derivatives of natural products (clarithromycin). Successful applications have included antibiotics, antitumor agents, enzyme inhibitors, antiparasitic agents, bioherbicides, algicides, and bioinsecticides. Of great importance for pharmaceutical discovery are new targets such as receptor-ligand binding, reporter genes, adhesion, proteosome action, signal transduction, and cell-to-cell communication. For antitumor agents, recent targets have included protein kinase C, farnesyl protein transferase, P53-related targets, proteosomes, and telomerase.

Many of the new developments in industrial microbiology derive from the birth of molecular biology in the 1950s and of recombinant biotechnology in the 1970s. Of special interest is the area of industrial enzymes that has made major strides because of cloning and the complementary techniques of protein engineering and directed molecular evolution. These enzymes have great use in food processing, detergents, cleaning of contact lenses, biosensors, and molecular biology (DNA polymerase for the polymerase chain reaction, and restriction enzymes). Enzymes and cellular bioconversions have been applied in the preparation of chiral drugs that are currently desired by industry and health authorities. Many industrial enzymes are derived from thermophilic, alkaliphilic, or psychrophilic microbes (“extremophiles”) from areas of high biodiversity interest. Environments of interest for bioprospecting are soil, the marine environment including the deep biosphere, the icy biosphere, marine sponges, and insects. Plants harbor many microbial symbionts that are a good source of alkaloids and other drugs, biocontrol agents, plant growth stimulators, agents protecting plants from abiotic stress, and for ecosystem restoration. Other current or potential benefits of exploring microbial diversity include (i) the economical and environmentally important replacement of chemical processes by biological procedures in the manufacture of riboflavin, acrylamide, 7-aminoccephalosporanic acid, and 7-aminoacetoxycephalosporanic acid; (ii) control of agricultural pollution by the use of feed enzymes such as...
phytase; (iii) replacement of petroleum, plastics, and other materials by bioprocessing of renewable raw materials; (iv) bioremediation and biodegradation of polluting materials; (v) discovery of new plant growth promoting microbes; and (vi) novel antifoulants and antibiofilm agents. In relation to the antifoulants, it was surprising for me to read in the present book that biofouling, i.e., the colonization of surfaces in aqueous environments by living organisms, costs the shipping industry over five billion dollars per year!

There is no doubt that biodiversity is being lost throughout the world. This is unfortunate because we need biodiversity to provide novel microbes and novel products. We are told that only 0.5 to 1% of living bacterial species and 5% of living fungal species have been cultured. Of great interest are new methods that allow isolation of previously uncultured microbes, e.g., low-nutrient media, long incubation times, dilution to extinction, ecosystem mimicry, syntrophy, and cell-to-cell communication. Of use in these efforts have been micromanipulation, optical tweezers, atomic force microscopy, and density gradient centrifugation. The newly cultured species may not do very well in industrial fermentors, but cloning of their production and regulatory genes into industrial bacteria and fungi would allow scale-up and industrial production. The metagenomics approach is a complementary development that allows expression of environmental DNA and mRNA. This very exciting area has already yielded known antibiotic products such as violacein, indirubin, and fatty dienic alcohols and new antibiotics such as acyltyrosines, terragine, and turbomycin. In addition to these secondary metabolites, new enzymes, antiporter and antibiotic resistance determinants, have been isolated from environmental nucleic acids.

It is clear that the large pharmaceutical companies will soon adapt their genomic, combinatorial chemistry, and high-throughput screening efforts to new natural product scaffolds. Such novel structures are sorely needed and will be provided by the proper utilization of biological diversity. It is extremely fortunate for the field that this book has been assembled at this time with contributions from the desks of the world's best minds of microbial diversity and bioprospecting. Of course, microbes are not the only source of remarkable drugs, but inclusion of plants and other life forms would have required much greater time and effort and would have delayed publication of this useful compilation, which is needed Now!

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PREFACE

ORIGINS

This book is born out of a lifetime’s fascination for microorganisms, a fascination that has been nurtured by many people and many experiences and, not the least, by undergraduate courses in systematic biology, an increasingly rare feature of degree curricula. Serendipity, I freely confess, has played a major role in sustaining this fervor for microbiology, and a significant turning point came in the 1970s when I joined the then Panel on Applied Microbiology of the United Nations Environment Programme and the United Nations Educational, Scientific, and Cultural Organization. This U.N. involvement enabled me to work with a group of extraordinarily committed humanitarian and knowledgeable microbiologists from the world over. The effect of working with Martin Alexander, Goran Heden, Roger Porter, David Pramer, Maurits la Riviere, Jacques Senez, and H. Taguchi, and others too numerous to name, was electrifying and permanent in so many ways but especially in revealing how microbiology can be developed for the common good. The panel experience had a variety of consequences for me, among them an entrée into international science and opportunities to see first hand a wide range of microbial technology being exploited in developing countries for both traditional and innovative processes. Years later this amalgam of experience led to two particular opportunities to bring microbial diversity and bioprospecting together in quite dramatic fashion—one in Indonesia that was relatively low tech and the other in Japan that was decidedly high tech.

Alfred Russel Wallace, “one of the neglected giants of the history of science and ideas,” has long been one of my heroes, for, as Peter Raby concludes in his splendid biography of Wallace (P. Raby, Alfred Russel Wallace: A Life, Princeton University Press, 2001), “There is, finally something heroic about a man who independently constructs a theory of natural selection . . . and spends the rest of his life proclaiming the ideals of co-operation and altruism as the way to hasten the perfecting of the human.” Consequently the chance to retrace a few of Wallace’s steps in the Malay Archipelago intermittently over a period of 15 years, but collecting microorganisms rather than insects or birds of paradise, came as a piece of tremendous good fortune. Results of the ensuing biotechnology training and research program, which included mycorrhizal inoculant technology, bioremediation, biopesticides, and applied microbial taxonomy, are summarized elsewhere (Indones. J. Biotechnol., Special Issue, June 2000), but the enduring memory is of the spectacular biodiversity of that remarkable archipelago. At the westernmost peninsula of Java, facing the Sunda Strait, lies Ujung Kulon, an area that was inundated by 10- to 15-m tidal waves in 1883 following the eruption of Krakatau. Ujung Kulon now is a national park devoid of human inhabitants and notable for containing the remaining (very small) population of Javan rhino. It was here some years ago that I witnessed a glittering display of bioluminescence. Our camp, where evenings were shared with an assortment of macaques, deer, monitor lizards, geckos, and bats, was close to the shore which, on one occasion, was intensely illuminated as teeming populations of microinvertebrates were oxygenated in the breaking tide. However, a few years later even this microbiological display was eclipsed by the coral reef communities off the north coast of North Sulawesi. These reefs are one of the most spectacular in the whole Indo-Pacific region, and the realization that a very high proportion of their invertebrate biomass comprised microorganisms about which so little was known was a forceful reminder of how fragmented and incomplete was our knowledge of microbial diversity. The English naturalist Sidney Hickson, following his observations of these ecosystems, wrote “A coral reef cannot be properly described. It must be seen to be thoroughly appreciated” (Hickson, A Naturalist in North Celebes,
Murray, 1889); how right he was! Readers will not be surprised to find marine invertebrates and their microbial symbionts featured in this book. Geothermal and other extreme environmental locations also are common in many parts of the archipelago and have provided further insights to the diversity of the microbial world. However, the opportunity to prospect microorganisms of truly extreme habitats was presented when Koki Horikoshi invited us to collaborate with the DeepStar program of the Japan Marine Science and Technology Agency (http://www.jamstec.go.jp). Our interest has been on the actinomycete diversity in very deep-sea sediments including those below the seafloor, where the extent of taxonomic diversity again is remarkably high. The exploration of these newly discovered biospheres is exciting and promising for bioprospecting, and various aspects of this novel field are contained in this book.

Edward Wilson probably has done more than any other individual to awaken the interest of both scientists and the public in biodiversity and why it should be promoted to a front page issue. His writings are rich in knowledge, challenging questions, and memorable imagery, and provide an especially pervading sense of wonder. Wonder, that emotion excited by what surpasses expectation and the desire to know, is something I very much hope that readers will encounter throughout the course of this book, for, as Francis Bacon declared, “For all knowledge and wonder (which is the seed of knowledge) is an impression of pleasure in itself” (F. Bacon, Proficience and Advancement of Learning Book I, 3, 1605).

**REVOLUTION**

During the lifetime of my generation there has occurred an unprecedented change in which biological systems—from cell to biome—are viewed and investigated. As I attempt to show in chapter 24, this has been a revolution of genuinely Kuhnian proportions. Within the span of 50 years we have progressed from speculative debates about the organization of DNA in bacteria (see, for example, E.T.C. Spooner and B.A.D. Stocker [eds.], Bacterial Anatomy, Cambridge University Press, 1956) to a position in which students can manipulate, with facility and rationality, the DNA within and between species, and even domains! The introduction and adoption of the techniques of molecular biology have occurred with unbelievable rapidity and ease such that they now permeate the whole spectrum of biological research. Questions can now be posed, and answered, that were inconceivable and/or had minimal expectation of being resolved prior to the molecular biology era. The impact on our approach to and understanding of phylogeny and evolution, biodiversity and ecology, infection and therapy has been immense; the impact on the ways in which we exploit genetic resources in the context of biotechnology is no less impressive. In short we are of a generation that has seen the emergence of a new and powerful discipline, albeit with ill-defined boundaries, called bioinformatics. A word of caution is necessary here: bioinformatics, powerful though it is, is not the sole technoscientific driver of biotechnology; innovative developments in chemistry, chemical and biochemical engineering, computer science, and nanotechnology, for example, all have engaged with biology in transforming the search for novel drugs, chemicals, materials, and so on. Nevertheless, there has been a demonstrable paradigm shift in the way in which we do, or can do, search and discovery in biotechnology, that is, the shift from traditional biology based on specimen collection, observation, and experimentation to bioinformatics based on data collection, storage, and mining. One of the questions emerging from this paradigm shift is whether bioinformatics, in concert with approaches such as combinatorial chemistry, will displace the traditional biological approach or will exist in synergy with it. Present evidence strongly suggests that a synergy will become established.

The extent to which we are able to integrate diverse technical and analytical capabilities will be critical for the future of microbiology and biotechnology. The multidisciplinary approach has long and widely been appreciated as an essential underpin for successful biotechnology, but a comparable recognition in microbiology and among microbiologists has been slower to emerge. Recently this point was made very clear by Ed DeLong, who concluded that, “The challenge to future microbial biologists is that they must become as conversant in Earth science as nanotechnology, as familiar with systems ecology as genomes, and as well versed in global information systems as bioinformatics” (E. F. DeLong, Towards microbial systems science: integrating microbial perspective, from genomes to biomes. *Environ. Microbiol.* 4:9–10, 2002). Just as integrated technology approaches are seen as increasingly necessary for addressing the big questions in microbiology, there is a growing sense that severe reductionist science, epitomized by molecular biology, has deflected attention away from an understanding of the complexities of biological system properties. I am pleased, therefore, that many of the contributions in this book directly confront or elude to these issues of technology integration and the holistic perspective.
MICROBIAL DIVERSITY AND
BIOPROSPECTING

Although this book has had a long gestation, now seems to be the appropriate time to bring together its principal themes and ideas. Equipped with a formidable set of new tools based on molecular biology, chemometrics, computing, statistics, and so on, and firmly fixed in the postgenomics era, we can begin to evaluate the effects that developments made possible by these tools are having on the way we go about exploring microbial diversity and searching for exploitable biology. The scope of this book is broad so that, in addition to those topics that might be anticipated, the reader will find other topics that are rarely considered in the context of microbial search and discovery, among them questions of biogeography, extinction, and the value of biodiversity. We also consider the implications of the Convention on Biological Diversity for microbial prospecting activities.

The book is organized in nine sections that deliberate on biotechnology and the case for natural product discovery; the resource that the microbial world presents for biotechnology; why it is important to take an ecological perspective when engaging in search and discovery; the distribution of microorganisms at the global scale and early attempts at microbial biocartography; the paradigm shift embodied in bioinformatics; some illustrations of microbial prospecting activities and their results in a range of high and not so high-added-value industries; the loss of evolutionary history and the conservation of microbial gene pools; microbiology, biotechnology innovations, and the Convention on Biological Diversity; and, finally, what we perceive as the value of biodiversity and how valuations might be made. Such a book is very unlikely to be exhaustive in its coverage; this one naturally reflects a personal survey of the landscape, and I would be pleased to have readers' thoughts on omissions and amendments that might be made. Readers also will be aware of the problems that often beset multiauthored books. Consequently, with the exception of the first and last sections, I have attempted to set the scene and provide continuity within and between the sections by way of short preambles. A few topics and authors have been lost along the way, but overall it has been possible to keep to the original plan and content.

QUAERENDO INVENIETIS!

If the reader will indulge me briefly, I wish to switch, finally and hopefully to some purpose, from microorganisms to music and in particular to Johann Sebastian Bach. A significant part of Bach's life overlapped with those of van Leeuwenhoek and Linnaeus, but this narrative concerns Frederick the Great rather than either of these notable biologists. Bach enthusiasts will recall that Frederick and Bach eventually met at Potsdam in 1747 and how the king invited Bach to improvise on a "royal theme," the result being one of the grandest and most complex inventions in the history of music—*The Musical Offering*. This composition of two fugues, ten canons, and a trio sonata was inscribed *Regis Jussu Cantio Et Reliqua Canonica Arte Resoluta* (at the king's command, the song and the remainder resolved with canonic art). The acrostic of Bach's dedication reveals "ricercar," the term for an earlier composition in the style of a fugue incorporating the most extreme devices of counterpoint, but also an adroit message in Italian—to seek out, with an implication of effort required in the search. The second ricercar of *The Musical Offering* is an astonishing six-part fugue, astonishing to the extent that Douglas Hofstadter likened it to "the playing of sixty simultaneous blindfold games of chess, and winning them" (D. Hofstadter, *Gödel, Escher, Bach*, Vintage Books, 1980). Moreover, among the canons, which were presented to the king as uncompleted musical puzzles, is one marked *quaerendo invenietis*—by seeking, you will discover. I like to think of the totality of this musical composition as the apt metaphor for biodiversity, biocomplexity, and bioprospecting, the more so because Bach and many of his contemporaries regarded music as a science; indeed Bach became a member of Lorenz Mizler's Society for Musical Sciences at the time of the *Offering's* composition. This exhortation is emphasized by Bill Strohl in the epilogue to his chapter and this, in essence, is the theme of this book.
ACKNOWLEDGMENTS

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The enthusiastic interactions that I have enjoyed with the contributors to this book have been marvelous, and I am greatly indebted to them for preparing such thoughtful and timely accounts of their specialist subjects—my warmest thanks to you all. It is a pleasure to acknowledge the support for my own research into microbial diversity and biotechnology, some of which is mentioned in this book, from the Biotechnology and Biological Sciences Research Council and the Natural Environment Research Council (U.K.), The British Council, the Department for International Development (U.K.), the International Institute for Biotechnology, and the Japan Marine Science and Technology Center.

Greg Payne has been the ideal editor with whom to work—ever solicitous, patient, and enthusiastic; to him and the production team at the ASM Press I wish to convey very special thanks and appreciation for all their efforts in bringing this book to fruition.

Finally, I want to dedicate this book to my wife Jenny for her steadfast support over the years and not the least during the preparation of this book.

Alan T. Bull
Canterbury, January 2003
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