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GUEST EDITORIAL

Chemical Biology of Signal Transduction

Chemistry is often referred to as the Central Science.[1] This point, typically made by those of us who dabble in the Chemical Sciences, simply serves to remind everyone that chemistry is the nexus through which all scientific endeavors are inextricably linked. As a consequence, the Chemical Sciences are often profoundly influenced by major scientific discoveries in other disciplines. This special issue of *Accounts of Chemical Research* is devoted to one such discovery, whose impact has reverberated throughout the many sub-disciplines of chemistry. Signal transduction is the biochemical mechanism by which information (e.g., the binding of a growth factor to a cell surface receptor, the presence of nuclear DNA damage, etc.) is transmitted and subsequently acted upon within a cell. The discovery of signaling pathways has not only transformed our understanding of how cells operate, it has had an enormous impact on the development of new therapeutic approaches for the treatment of nearly every human disease. Indeed, the recent introduction of Gleevec,[2] which targets a signaling protein and is used for the treatment of chronic myelogenous leukemia, has been hailed as the first in a new generation of drugs.[3] Every major pharmaceutical company, as well as a large fraction of the biotechnology community, now devotes a sizable portion of their R&D budget to programs that tap into the therapeutic potential of signaling proteins.

The emphasis on signal transduction by the pharmaceutical/biotechnology industry is not surprising, given the fact that cell signaling permeates nearly every aspect of modern biology. Consequently, chances are pretty good that a newly minted Ph.D. chemist, who enters the world of biomedical research, will find him or herself engaged in some aspect of signal transduction. For most individuals, this will be a rude awakening, since learning the terminology of another discipline in general, and cell signaling in particular, can be an extraordinarily painful experience. A good introduction to the general topic of signal transduction can be found in any introductory biochemistry text. Furthermore, reviews have been written on nearly every aspect of signal transduction. However, despite the obvious role that chemistry has and will continue to have in signaling, the chemist's perspective has not received its full due, particularly from the academic lab's point of view. This special issue of *Accounts* has been assembled to rectify this oversight. The articles in this compilation describe the application of tools from a variety of sub-disciplines (analytical chemistry, physical organic chemistry, organic synthesis, and enzymology) to some of the key issues that encompass signal transduction. In addition, relevant articles by Kishi and Rando[4] and Hengge[5] have appeared in recent issues of *Accounts*. The science described in these papers is representative of the impact that the Chemical Sciences has had in this burgeoning area of biological research.

Decades ago, enzymes were isolated on the basis of their activity and were appropriately christened. Names such as ATPase and lactate dehydrogenase are terms most chemists immediately understand. However, in the intervening years, molecular biologists have taken over the task of identifying gene products, often before the activity of the protein has been revealed. Consequently, the nomenclature associated with the proteins of signaling pathways is frequently chaotic. For example, the protein defective in the Wiskott–Aldrich Syndrome is known as WASP (where the final P stands for protein).[6] Regrettably, the term WASP is not a particularly enlightening appellation for a protein that happens to be a key player in the signaling pathway responsible for cell motility. To make matters worse, a recently identified yeast homologue of WASP was named after a fellow Hymenopteran: Bee.[7] Unfortunately, this kind of fanciful nomenclature is all too prevalent in the signaling world. The waters are muddied

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even further by the fact that two or more competing acronyms are often assigned to a single protein. This is in part due to the not uncommon situation in which a newly named protein identified in one specific context is found to be identical to a previously reported protein that has its own unique acronym. One might hope that, with the ready availability of online databases, the assignment of multiple monikers would cease. However, although the structure and function of many proteins are conserved from yeast to man, the scientists who practice their art in such organisms as worms, flies, and mammals feel compelled to employ a nomenclature that is not the least bit conserved across the borders of different species. In short, one scientist's CED-9 (worm) is truly another scientist's Bcl-2 (mammals). Finally, given the enormous number of acronyms that permeate biology (and the fact that our alphabet is limited to 26 letters), it is not surprising that proteins that have absolutely nothing in common often share the same name. Fpr is a family of FKBP proline rotomases. Unfortunately, Fpr is also the formyl peptide receptor and ferredoxin-NADP reductase.

Although chemists have IUPAC nomenclature rules and biologists do not, we chemists should not feel too smug. Organic chemists have Name Reactions, and terms such as the Ciamician−Dennstedt rearrangement can befuddle even the best of us. However, most Name Reactions can be found in a glossary in the back of the Merck Index (or in books devoted to the topic[8] as well as at various web sites[9]). It is in this spirit that a glossary is provided for the articles that comprise this special issue of *Accounts*. A glossary follows this Editorial, for those of you who are reading the hard copy. In the on-line version, there will be an electronic link to the glossary at the top of every paper.

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