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Preface to the First Edition

The ability of all living cells to sense and interact with their environment is certainly a prerequisite for life. Single cell organisms depend on these contacts for such functions as locating nourishment, reading reproductive cues, and mounting defense mechanisms. In multicellular species, the signaling mechanisms are more diverse as the amount and type of information received is necessarily more complicated, and this tends to increase as the organisms themselves get more complex. Thus, higher eukaryotes, including humans, possess very intricate extracellular signaling systems at the cellular level with additional layers of complexity at the organ and whole-organism levels. Simply identifying all of the players and their cognate pathways, defined in large part by protein–protein interactions, is a formidable task not yet achieved in any cellular paradigm. Furthermore, when one factors in the effect of time (as is required to relate induction, expression, interaction, posttranslational modification, and degradation as the result of stimulation), then signal transduction becomes, for the present at least, an incalculably greater, perhaps infinite, problem.

How then to organize such a large, multifaceted topic into a compendium that is timely, useful, and user friendly? The answer lay in using a combination of approaches. In the first place, we chose to subdivide the general topic of cell signaling into five sections that roughly parallel the events associated with the approach of a ligand to a cell and the subsequent events that result. Thus, this approach yields (1) ligand and receptor characterization including complex formation, (2) intracellular signaling events, (3) transcriptional and posttranscriptional modulation and nuclear events, (4) cellular responses, and, finally (5) phenotypic responses. These topics are not necessarily equal in size, and the first three topical sections conveniently lend themselves to division into numerous subsections. The second section is about twice as large as the others, perhaps reflecting the diversity of intracellular signaling mechanisms and the fact that numerous advances have been made in understanding these events, particularly in the past few years. At the same time, ligand/receptor interactions and transcriptional/posttranscriptional control are prime areas for drug discovery, and knowledge in these areas will surely grow significantly as

well. In the future, we see an expanding interest in and the ability of investigators to explore cellular and phenotypic responses, and we predict substantive growth in our understanding of nuclear and cellular organelle signaling events and their extension to cell–cell, organelle, tissue, and whole-organism systems biology, especially as they apply to the understanding and treatment of human disease.

Within this “physiological flow” model, we have not made any attempt to sort topics by paradigms or animal models. The majority of the information described is for higher eukaryotes but not exclusively so. Furthermore, it is not a complete description of any model or cell line. Signaling advances have come from the study of many different cells and systems and that will continue to be true. A large-scale academic effort is underway to describe signaling in two cell models very completely, and this is an important task; however, even assuming that these studies will be highly successful, they will not offer a full understanding of signal transduction, and the information on more diverse cells and systems will still be of great significance. Because the Handbook is intended to serve a broad audience, maintaining its catholic nature was an important consideration.

Our second organization decision was not to try to cover everything, but rather to place the focus, to the extent possible, on new advances rather than cataloging well-known information. We recognized, of course, that to the novice in the field or the expert from another field, that which is “well known” might not apply to them. We have addressed this issue by attempting to weave a very tight net across the field of cell signaling, at the expense of some inevitable redundancy, so that even well-known material will at least be alluded to and therefore searchable in our indices. From these locations, the interested reader can go backward through the references, if the description of the material they seek is not sufficient. In taking this approach, we have made room for material that is at or near the cutting edge of our understanding of this rapidly moving field. Also germane to the issue of timeliness is the web-based version of the Handbook, which we expect will be a highly used form. All of the editors and associate editors felt that this represented an extremely attractive part of this enterprise. The reasons include ease of access

(via desktop computing), hyperlinking to facilitate index interrogation and gain ready access to portions of the literature cited, the potential to update and add individual articles in the future, and the possibility of incorporating additional information, such as movies, at a later date.

In organizing this Handbook, we have been fortunate to assemble an extraordinary cast of editors, associate editors, and authors who represent the world leaders in this field and no better authoritative stamp could be provided than their respective bylines. Our editors, Jim Wells, Tony Hunter, Michael Karin, Marilyn Farquhar, and Brad Thompson, expended a considerable amount of effort on their sections, including challenging brainstorming and planning meetings, pressure phone calls with associate editors and authors, and skillful editing of manuscripts. Their associate editors, Tom Alber, Michael J. Berridge, Henry Bourne, Lewis Cantley, Jackie Corbin, Jack Dixon, Albert J. Fornace, Jr., Heidi Hamm, Marc Montminy, Tony Pawson, Michael G. Rosenfeld, John D. Scott, Nahum Sonenberg, Robert Stroud,

Geraldine Weinmaster, and Ian A. Wilson, were equally diligent in carrying out the organization and solicitations for their subsections. We wish to thank them all for their time and effort, without which this project could not have been completed. However, in the end, it is the content that matters, and for this we must profusely thank our many, many authors for their scholarly contributions.

Thanks also go to the staff of Academic Press (now Elsevier) for all of their help and assistance and their rising to the challenge of creating the first large-scale and comprehensive web-based work of this type to accompany a traditional print copy by a commercial publisher. Of particular note are Jasna Markovac, with whom the idea of a signaling handbook originated; K. Noelle Gracy, who got the initial stages off the ground; and Mica Haley, who shouldered the project in midstream and tirelessly shepherded it to completion.

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