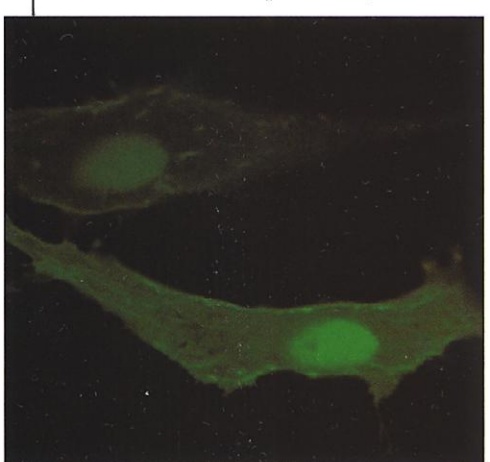
INTRODUCTION

Orienteering Strategies For a Signaling Maze

This joint Special Issue by *Science's Signal Transduction Knowledge Environment* (STKE) and *Science* presents important developments in the sprawling field of signal transduction. (Signal transduction refers to the processes by which cells perceive their environment or internal status and react to such stimuli with appropriate physiological responses.) The Viewpoints in this issue of *Science* provide authoritative syntheses that are accessible to the nonspecialist, explaining what a signaling pathway does and why it does it. Furthermore, this issue highlights new ways in which *Science's STKE* is working with authors to efficiently convey complex information. At *Science's STKE*, readers can delve deeper into the topic and take advantage of special electronic features, particularly the "Connections Map" database in which the details of the signaling pathway are dynamically displayed and annotated. (STKE is the first of a series of Knowledge Environments published by AAAS. These electronic publications gather a comprehensive set of resources to enhance access to information in a fast-moving field like cell signaling.)



Advances in information technology are required in the biological sciences to cope with the amount and complexity of information that must be handled in the postgenome era. Thus, *Science's STKE* has explored a new way of organizing, storing, and communicating the essence of our current understanding of signaling mechanisms. The Connections Maps are an interface to a database of authoritative information on signaling molecules and their relations with one another.* The reader accesses information through a Web interface that displays dynamically generated maps of the pathways (created in real time from the database, so there is no lag while an artist works on updating a drawing). Symbols in the maps represent signaling components or the relations between them, and users can access more information just by clicking on these symbols.

*Access to the Connections Map database is free to all registered users of *Science's STKE*; the full-text features within *Science's STKE* require an individual or institutional subscription.

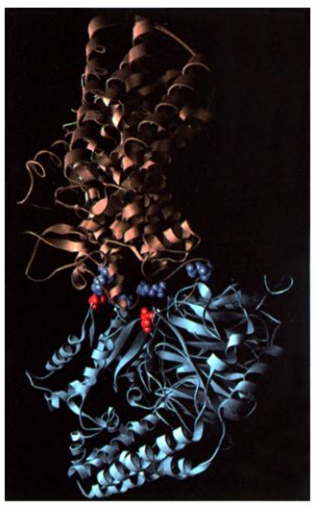
The Connections Maps are identified as either "canonical" or "specific." The canonical maps show the generic pathway module—a sort of consensus view. This type of pathway is useful for understanding the general signaling principles of the pathway and how modules are adapted to distinct functions, but are not intended to represent the situation in a real cell at a particular point in time. The specific pathways, on the other hand, depict real molecules and only those relations that are experimentally supported for a particular species, tissue, and cell type. Thus, components in the specific pathways can be linked to a defined entry in existing databases that catalog sequence information on individual genes or proteins.

The information in the database and maps is highly reliable. This quality is derived from the efforts of leading authorities recruited from many areas of signaling, who frequently update the database. These contributing authorites also provide an evaluation of the quality of the evidence for any given relation in the maps. We wanted to bring the diversity, importance, and—as one author says—the "beauty" of these signaling mechanisms that underlie so many aspects of biology to all of the readers of *Science*. Therefore, we invited the pathway authorities who author and curate the Connections Maps to write short Viewpoints that capture the essence of their pathway in this issue of *Science*. (Both the Viewpoints and the pathways at STKE were critically evaluated by peer review.)

We take a broad view of signaling at STKE and, therefore, have represented many sorts of pathways. Some paths can be deadly, like those emanating from members of the tumor-necrosis factor receptor family (Chen and Goeddel, p. 1634 and Wajant, p. 1635), but only when the balance is tipped away from growth-promoting or survival signals sent from the same receptors. The T and B cell antigen receptors are at the heart of the body's defenses, and unraveling their signaling mechanisms has revealed much about immunodeficiencies and autoimmune disorders, as well as the function of the healthy immune system (Singer and Koretzky, p. 1639, and Gauld *et al.*, p. 1641). Estrogen, a steroid hormone, doesn't bother much with signaling intermediates and makes its way right to the nucleus. But how does it interact with one receptor to produce so many different effects (McDonnell and Norris, p. 1642)? Many pathways have important roles in cellular transformation, like the Wnt/β-catenin pathway that also has critical roles in development (Moon *et al.*, p. 1644), or the JAK-STAT pathway, better known for mediating signals from interferons and other cytokines (Aaronson and Horvath, p. 1653). The signal from transforming growth factor receptors seem simple enough—just modify a SMAD protein and send it

off to regulate transcription in the nucleus. But nature has found room for plenty of interaction with other pathways and other modulation along the way (Attisano and Wrana, p. 1646).

The Connections Maps are not limited to the animal kingdom, but include plant signaling as well. Unlike vertebrate hormone receptors, plant receptors for cytokinins are histidine kinases that control many aspects of growth and development (Sheen, p. 1650). The lipid jasmonate is a key regulator in plants impacting processes like reproduction and stress responses. Although the biochemical pathway to synthesize these bioactive lipids is well delineated, many genetic components are waiting to be discovered (Liechti and Farmer, p. 1649).



Vaudry *et al.* explore how the same signal can be used to promote proliferation in one instance and differentiation in another. The phosphoinositide 3-kinase pathway uses changes in lipids at the cell membrane to recruit appropriate signaling molecules that ultimately control growth, survival, migration, and other responses (Cantley, p. 1655). G protein pathways are targets of the majority of therapeutic drugs currently available, and Neves *et al.* (p. 1636) highlight several such pathways that regulate fundamental processes from metabolism to learning and memory. Martin *et al.* (p. 1652) take us to "infinity and beyond," seeking understanding of how signals are generated by integrins, proteins that are literally so important that cells cannot live without them.

Please explore the beauty and complexity of these pathways and augment your reading of *Science* with the innovative tools available online at *Science*'s *STKE*. Think of *Science*'s *STKE* as a "GPS" enhancement to *Science*'s Compass. You'll never lose your way.

–L. BRYAN RAY AND NANCY R. GOUGH

Science

CONTENTS

VIEWPOINTS AND CONNECTIONS MAPS