Into unknown territory

The Alliance for Cellular Signaling is exploring new frontiers, both in fundamental scientific terms and in the way in which research in cell biology is conducted. Alison Abbott reports.

"We are exploring a vast, vast, vast continent," pronounces cell-signalling guru Henry Bourne of the University of California, San Francisco, "and we know only a few ports, a handful of rivers and a couple of mountain ranges."

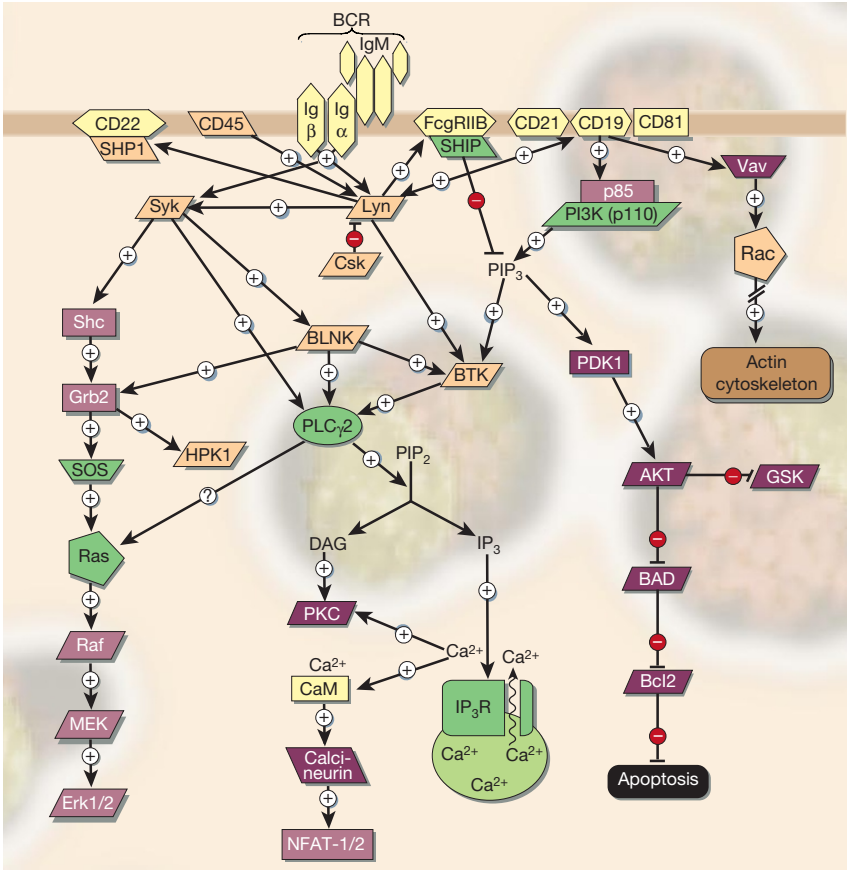
The dark continent that Bourne refers to is the labyrinth of overlapping biochemical signalling networks through which our cells make sense of the diverse internal and external signals that constantly bombard them. He is one of the founders of the Alliance for Cellular Signaling (AfCS), a 'big biology' project established to explore and colonize this territory.

This week, the project's leaders plant a flag in a newly constructed frontier fort. Together with *Nature*, the AfCS is launching the Signaling Gateway, an online resource that will combine news and reviews with scientific databases. The project's goals are also discussed in a series of articles in this issue (see page 703).

The intended beneficiary of the AfCS's colonial venture is the wider community of cell and molecular biologists. As yet, few outside the project are aware that it is already generating data and making them freely available — or that the AfCS is soon to offer a range of research materials, including complementary DNA (cDNA) clones representing genes for signalling proteins.

So what is the AfCS, and what are its aims? The brainchild of Al Gilman of the University of Texas Southwestern Medical Center in Dallas, winner of a Nobel prize in 1994 for his discovery of G proteins and identification of their role in cell signalling, the AfCS has the grand vision of creating a 'virtual cell' — a complete model of its biochemical behaviour. By mapping signalling networks, it should theoretically be possible to predict exactly how cells will respond to particular combinations of signals. It sounds simple enough, but the task is almost infinitely complex, and some experts predict that it may defeat even the grand alliance of specialists that Gilman has assembled.

Cell biologists now realize that they have oversimplified the biochemistry of signalling pathways. They have long hypothesized that a signal, such as a hormone binding to its receptor, initiates a wave of excitation through a simple, linear chain of proteins. But it has become clear that the proteins don't work individually, but instead assemble fleetingly into molecular machines, the components of which are shared between pathways (see *Nature* **417,** 894–896; 2002). "The inside of a cell is a thick soup of proteins talking to each other in ways we just don't understand," observes Robin Irvine, a pharmacologist at the University of Cambridge, UK.



Protein puzzle: this simplified flurry of signals is just one of many hundreds of interacting pathways in mouse B cells (pictured in the background), highlighting the sheer scale of the alliance's endeavour.

Signal strength

Gilman and his colleagues have produced a two-pronged plan for the AfCS's immediate future. First, they will collate existing information about components of signalling pathways, standardizing its format in a database of 'Molecule Pages' that will present key data on thousands of proteins involved in cell signalling. Second, they will generate robust new data about pathways in two types of mouse cell — B lymphocytes and cardiac muscle cells — in a consistent way. The project's funding comes from one of the 'Glue Grants' awarded for multi-site projects by the National Institute of General Medical Sciences in Bethesda, Maryland, expected to total $25 million by 2005, and from pharmaceutical companies. The latter have all signed up to the AfCS's core philosophy that all data, plus as many research tools as possible, should be made immediately and freely available to all scientists.

Early versions of the Molecule Pages are now available on the Signaling Gateway. There is a page for each signalling protein that has been identified in the mouse — currently more than 3,000 — containing information imported automatically from gene and protein databases such as GenBank and SWISS-PROT. Each page includes information such as the protein's molecular mass and isoelectric

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Rally the troops: Al Gilman (foreground) has assembled a crack squadron of cell-signalling specialists, marshalled by teleconferencing. The team aims to generate data on signalling in two model cell types.

point — the pH at which its net charge is zero — as well as its sequence, and the sequences of its counterparts in other species.

Within the next few months, when all of the interfaces are ready, it will be possible to interrogate the data. If you know some of the characteristics of an unknown protein, the Molecule Pages database will be able to deliver a list of all the possible candidates. "It's a very good place to start when you need a quick entry into the properties of a protein you have just come across," says Bob Michell, a cell-signalling biochemist at the University of Birmingham, UK, who is not involved in the AfCS.

Over the next few months, these basic data will be supplemented by around 1,000 experts, each of whom will author one or a few Molecule Pages, adding information on each protein, including its functions and known interactions. Peer review will be organized by *Nature*'s editors in London, independently of the AfCS. In addition, associate editors drawn from the research community will help to oversee dozens of pages in their particular areas of expertise.

"Eventually, the Molecule Pages will be important in putting together the whole picture of how a cell functions — something we can't even conceptualize yet," says Irvine, associate editor for some 80 pages on signalling pathways that depend on molecules called inositol lipids. "But in the meantime they will be a remarkable source of information."

Being an author of one of the Molecule Pages, which will be updated annually, will be time-consuming. So Gilman says it is essential that the effort should be recognized by faculty committees and granting bodies, in much the same way that they consider the value of authoring a widely cited review article. "If large-scale collaborations in biology are going to work, the community will have to change its ways of evaluating effort," he says.

In parallel to developing the Molecule Pages, the alliance has set up eight US laboratories, with almost 40 scientific staff, to generate signalling information on the two types of cell chosen as models. A further 40 or so scientists serve on committees that direct this research through teleconferencing.

The labs are now beginning to generate data that are being placed on the web. These include a screen for protein–protein interactions involving, so far, 30 signalling proteins in B lymphocytes, conducted in collaboration with Myriad Genetics of Salt Lake City. Another study is using a variety of techniques to study changes in gene expression, lipid biochemistry and other parameters in B lymphocytes exposed to 32 different ligands — small molecules that activate the cells. Eventually, the data being generated by the labs will be integrated into the Molecule Pages.

Admiring the view

"The collection of so much data on two model cell types is the most innovative part of the project," says Walther Rosenthal, head of the Research Institute for Molecular Pharmacology in Berlin, who is not part of the AfCS. "Nowhere else can you find this integrative view of the cell."

Anyone may publish analyses of the AfCS's data in the usual way — but the project's own scientists must wait a month after the data are posted on the web before submitting a paper to a journal. "This means that the alliance's scientists have no special privileges," says Gilman. For Alex Brown, who runs the AfCS lipidomics laboratory at Vanderbilt University in Nashville, Tennessee, the controls on publication are not important. Lipidomics — the high-throughput analysis of large numbers of lipid compounds at a time — is a new field, he says, "so I'm just grateful to have the opportunity to develop the technology".

Some AfCS labs are dedicated to the development of molecular tools, such as double-stranded RNAs for use in RNA-interference gene-silencing experiments, and cDNA clones. As soon as they have been fully catalogued, such tools will be made available at cost price to the scientific community through the American Type Culture Collection in Manassas, Virginia.

Highly specific antibodies targeted at signalling proteins, meanwhile, are being developed at the AfCS Antibody Laboratory at the Southwestern Medical Center, in collaboration with companies that will manufacture and sell them. A current priority is the development of antibodies that can distinguish between active and inactive signalling proteins, which often differ only in the presence of a single phosphate group.

"Access to better reagents will be important, since this is what is most limiting to research at the moment — many reagents that you buy just don't work," says Julian Downward, who heads the signal transduction laboratory at Cancer Research UK's London Research Institute.

Like all large projects, the AfCS has met its share of obstacles. Database interfaces designed to make it easy for authors to feed information to the Molecule Pages, and for users to quiz the data, are not yet ready. "The bioinformaticians in the collaboration were far too optimistic," says Gilman, who adds that bioinformatics will have a greater share of resources in future. The bioinformatics bottleneck has delayed the cataloguing of molecular tools, which is postponing their availability.

But despite such setbacks, those who are familiar with the AfCS are optimistic about its prospects. "The alliance will eventually develop a new language to allow us to describe the large networks of signalling pathways whose complexity already has us throwing up our hands in despair," says Michael Berridge, head of the signalling programme at the Babraham Institute in Cambridge, UK, and one of the few Europeans who sit on an AfCS advisory committee.

For now, producing a complete model of cell signalling is a distant dream. And the project's leaders accept that there is a chance that gathering data on such a massive scale will not yield advances of the interest and importance that they hope for. "We believe intellectually that this is the right thing to do, but there can be no guarantees," says Gilman.

"The collaboration itself is the biggest experiment of all," suggests Bourne. "After all, the scientific culture of biology is traditionally very individualistic, and it will be interesting to see if scientists can work as a large and complex exploratory expedition." ■

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www.signaling-gateway.org