Will cell alliance breed bureaucracy and leave contributors out?

Sir — A recent News story reported that a US-based "multi-laboratory, multidisciplinary initiative" called the Alliance for Cellular Signalling (AFCS) seeks to provide a more integrated view of cell-signalling pathways (*Nature*, **402,** 219; 1999). To accomplish this, the AFCS hopes to "map how molecules in a cell interact" without bias towards particular proteins, through the collaborative efforts of systems engineers, biologists and informaticists. This project is to have a budget of approximately US$100 million provided over ten years by the National Institutes of Health (NIH) and private companies.

We would like to express concern regarding both the outline of the experimental systems and the structural organization of the proposed alliance. Despite planning an integrative approach, the organization's website (http://afcs.swmed.edu) says that "the experimental efforts of the alliance will be focused on two cells that display interesting and important G-protein-regulated phenomena: the B lymphocyte ... and the cardiac myocyte". Although these cell types are of obvious biomedical and pharmaceutical relevance, how can such a biased and limited view contribute to a more global perspective on cell signalling? Such an endeavour is structured without consideration of additional cell types, model systems and other interesting signalling phenomena not necessarily involving G-protein-mediated processes.

We are concerned that the hierarchical structure of this initiative creates an unnecessary division of labour and multiple layers of bureaucracy with too many committees and directors. After a selection process (based on "recognition of valued accomplishments", according to the website) each member will be required to "contribute detailed, standardized, and quality-controlled information (from the literature) about their assigned molecules". Besides defining "new molecules of interest", the governing committees ("whose chairs and members have already been chosen") will decide on the termination of membership based on an undefined concept of "failure to perform".

It seems to us that this Orwellian structure minimizes the possibility of innovation and creative approaches towards a real understanding of cellular signalling. Furthermore, a 'one-member—one protein' paradigm monopolizes the contributions and marginalizes investigators in the field who are not members.

Members will be required not to publish their results in journals but rather deposit the data on the alliance's website in the form of a "molecule page" bearing their name. Although such an approach may be an efficient means of disseminating information, we feel that eliminating the impartial process of outside peer review is unsound and unacceptable. Moreover, it is unclear to us how the efforts of students and postdocs involved in the actual work will be acknowledged.

Finally, we are most concerned that this "new way of doing business [sic] that requires collaborators to act altruistically", is restricted to a network of laboratories in North America. As stated, "collaborators cannot be spread across too many time zones", because the alliance plans to hold teleconferences using Internet 2, which does not yet exist outside the United States. We find this reasoning shallow — and insulting to the international scientific community. The proposed research does not have to be communicated in real-time, and the Internet has worked very well for other large-scale collaborative efforts, notably the sequencing of genomes.

In view of these concerns we question whether the alliance, as it stands, deserves the genuine interest of the scientific community and the requested funding by the NIH, and whether it is such a "new research initiative" after all.

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Bourne and Gilman reply — Haggarty and Ramalho-Santos have misunderstood the goals, organization and scientific approach of the Alliance for Cellular Signalling. We urge readers to visit the alliance website and decide for themselves whether the critics are right.

Haggarty and Ramalho-Santos say that the alliance's decision to emphasize signalling in only two kinds of mouse cells is "biased and limited". But an intense focus (highly reproducible observations on a few systems) is essential to obtain complete sets of quantitative data for sophisticated mathematical modelling and systems analysis. Any criticism should be in the other direction: for hedging our bets by choosing two cell types rather than one. We plan to look at all signalling inputs to these cells, not just those initiated by G-protein-coupled receptors.

Our critics have failed to distinguish between participating investigators in the alliance and alliance membership. Participating investigators (currently 51 at 21 different research institutions) will collaborate to run the scientific programmes of the alliance. Members of the B-lymphocyte and cardiac myocyte committees will prioritize work in seven alliance laboratories (not their own laboratories), and will make resultant data and analysis publicly available on the Internet so that all cell-signalling researchers can join in the effort. Our intention is to supply leads — for example the results of yeast two-hybrid screens and protein-interaction traps — for others to pursue and substantiate or discard.

A critical factor is Internet 2, which will permit real-time audio-visual communication with sharing of virtually any software application. We do not need to disseminate data in real time, but we must interact freely and regularly, as do the members of any research group.

We solicit members to act as consultants and to represent molecules by authorship of molecule pages as the core element of a signalling database. The job of authorship is the equivalent of writing and maintaining a structured review of the literature. Molecule pages can be collaborative; they will be peer reviewed and include comments and feedback. By facilitating bioinformatic searches for emergent properties of signalling networks, the standardized format of molecule pages should foster — not "minimize" — innovation and creativity. To date, we have received 180 applications for membership from residents of 15 countries, and we welcome and can accommodate many more. The list of molecules that need champions is a long one.

Conventional publication of data from the laboratories of participating investigators or members is not prohibited. The data to be placed on the Internet will be produced in dedicated alliance laboratories staffed by fully trained, full-time research scientists and technicians, not postdocs or students.

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Proteins suggest form of their own database

Sir — A recent News report in *Nature*[1] mentioned a workshop that we organized at the National Institutes of Health concerning the prospects for databases that describe signal transduction pathways, and more specifically that define protein–protein interactions.

The complete genomic DNA sequence of an organism in principle yields its full coding potential, and gives the possibility of describing in a comprehensive fashion the structures and functions of proteins, and their organization into the pathways and networks that control cellular behaviour[2]. The vast literature on these topics seems likely to grow exponentially with the refinement of tools for rapid proteomic analysis. We feel that the value of this information, and its ability to serve as the basis for modelling of cellular responses to external signals, will depend on its organization into a readily accessible electronic format.

One approach to such a database makes use of the observation that a common theme in cellular events is the assembly of proteins into complexes, through specific modular interactions[3]. A growing number of such interactions use domains and recognition motifs that can be readily identified by primary sequence analysis, and are therefore predictable[4]. This notion can be extended to encompass the interactions of distinct types of macromolecules with one another, and with small molecules. Although not all cellular phenomena can be described in these terms, the concept provides a useful starting point from which to organize data.

The purpose of the workshop was to explore continuing efforts to design databases of protein–protein interactions, and to solicit input as to the best way forward. We considered the creation of a centralized, freely available, public submission database as an achievable and highly desirable goal for the next generation of cellular analysis. Such an undertaking will be complex and prone to numerous pitfalls, but we believe it is an inevitable evolution of current biological databases. Furthermore, we consider it essential if we are to understand more fully how cellular function is controlled.

A transcript of the workshop will be posted on the NIGMS website. As this initiative proceeds, we will solicit broader input from the scientific community.

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Debating controversies can enhance creativity

Sir — I could not agree more with the author of your Opinion "Resolution to enhance confident creativity" (*Nature* **403,** 1; 2000) that "there will always be established and influential scientists who ... are resistant to looking beyond their long-held scientific assumptions". I also agree that "too many of today's creative scientists lack long-term security" and that "good but unconventional ideas are probably falling by the wayside".

Peer review is important for ensuring the quality of published work and proposed studies. This quality check can prevent false information being disseminated and funds being wasted. But peer review can also restrict creativity. What can be done to improve the system?

With the emergence of electronic publications, which do not have to rely on a fixed format, the reviewing/citation components can now be integrated into publications. Supplemental information and hyperlinks can be added to electronically published papers to connect them with related information — a review or a follow-up research article, say. In this way, the value of the published work is automatically revealed through the reading of linked literature. Ultimately, pre-publication review might even be eliminated and replaced with continuous post-publication review, creating a free atmosphere for expressing creative ideas.

I have started such an experiment and created an electronic journal, *Logical Biology* (http://logibio.com), dedicated to debating controversial issues and promoting logic as a tool for scrutinizing long-held conventional views in biology: for example, the nature of bacterial life. Some people may dismiss this type of publication, but, in the interest of fostering creativity, isn't it worth a try? The primary goal of scientific publication is, after all, not validation but communication.

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Time for an aspirin

Sir — I found it painfully hard to read the first of the "Timescales" pages in the Impacts of Foreseeable Science supplement (*Nature* **402** (suppl.), C17; 1999). The vaguely coloured and seemingly meaningless background combined with the rather small compressed and low-contrast typeface gave me a headache. It's ugly, besides.

Artists should be on tap, not on top.

Marvin Minsky

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The myth of well-funded German research

Sir — You reported on difficulties in financing genome research in Germany (*Nature* **402,** 706; 1999). Two pages later, we read: "Lots more cash for UK universities". These articles are symptomatic of the current funding crisis in German research. Because of the country's past successes and its relative wealth, it is not generally known that research in Germany is no longer well funded. None of the *Länder* (states) provides enough funds to replace equipment in university laboratories — my institute has averaged less than 1 per cent of equipment costs per year for the last 20 years. Even before reunification in 1990 placed serious pressure on public funding, increases in federal support for the Deutsche Forschungsgemeinschaft (DFG) were very small.

In my field, biomedicine, research funding trails that of competing countries. In the United Kingdom, support from all sources in 2000 amounts to at least US$24 per head of population, compared with $15 in Germany. In the United States, biomedical funding from the National Institutes of Health (NIH) and Howard Hughes Foundation alone represents $74 per head of population — five times higher than all such funding in Germany. Japan intends to double its science budget and the NIH has started very well on its target of doubling US biomedical research funds within five years. In the United Kingdom, funding by the private Wellcome Trust alone exceeds all equivalent funding from the DFG. Although the DFG has given out 59 per cent more for standard grants over the past ten years, this is no increase at all when corrected for inflation and increases in population.

Germany has few natural resources and relies on its best minds to produce knowledge and wealth. It needs a huge increase in public spending on research and a massive infrastructure-replacement fund from federal and state governments. It is time for scientists and learned societies to begin lobbying much more intensively: German science will only be able to compete if funding is tripled or quadrupled in the next five years.

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