Taussig is New AfCS Associate Director

The Alliance for Cellular Signaling (AfCS) is pleased to announce the establishment of a major new position, Associate Director, and the recruitment of Dr. Ronald Taussig to fill this important job. The need for the equivalent of a Chief Operating Officer became clear as the seven AfCS Laboratories became fully operational and nearly ready to unleash a torrent of data. With the full support and help of the AfCS Steering Committee, Taussig was recruited from the Department of Biochemistry at the University of Michigan, where he was an Associate Professor.

One particularly attractive aspect of this choice is that Taussig and AfCS Director Al Gilman have had a positive and productive relationship since Taussig was a post-doctoral fellow in the Gilman lab from 1988 to 1993. Gilman is “extremely pleased and even relieved” that Taussig decided to join the AfCS and describes Taussig as “an individual with impeccable scientific credentials, innovative insights, excellent judgment and superb administrative and personal skills.”

As Associate Director, Taussig will chair the Experimental Design Committee, which helps develop strategies and maximize experimental outputs. He will also be closely involved in the planning done by the B Cell and the Cardiac Myocyte Committees. To implement experimental plans, Taussig will work directly with Alliance Laboratory Directors and Lab Leaders and will coordinate data management among the labs. “I am pleased to be back in Dallas and am particularly excited to be working with the Alliance,” said Taussig. “The opportunity to work with this extremely talented group of investigators and to apply a host of techniques to unravel the intricacies of signaling networks was too good to pass up.” Taussig was introduced to AfCS Laboratory Directors and Committee Chairs during the October 3, 2001 videoconference.

Taussig will also hold a position as an Associate Professor of Pharmacology at UT Southwestern

Al Gilman (left) and Ron Taussig attend an AfCS videoconference

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Medical School and maintain a small research group.

**The AfCS/Nature Signaling Gateway**

The AfCS and the Nature Publishing Group (NPG) have signed a Letter of Intent to establish the AfCS/Nature Signaling Gateway. The Gateway will be a Web site that will include the Homepage, Signaling Update Pages, the AfCS Molecule Page Database, the AfCS Experimental Databases, and a Data Analysis Center. NPG will create the Homepage and the Signaling Update Pages and will provide editorial and peer review services for the AfCS Molecule Pages. The AfCS will create and host the Molecule Page and experimental databases and the Data Analysis Center. The AfCS will also host the Signaling Gateway in San Diego and will control access to the site, which will be free to all users.

Peer review of AfCS Molecule Pages is an essential element in their acceptance as scholarly works by the scientific community. This process will help to ensure the high quality of the AfCS Molecule Page database that we believe will set it apart from those created by automated literature searching or hired curators. Peer review is also necessary for the ultimate indexing of AfCS Molecule Pages as NPG publications and, subsequently, their retrieval by any of the usual mechanisms for searching the literature. This process will ensure that authors receive the credit they deserve for preparation of the equivalent of a review article in a prestigious journal.

The AfCS and NPG plan to launch the Signaling Gateway in phases during the spring and summer of 2002.

**Ligand Screen to Begin**

The first major experimental project of the AfCS, the ligand screen, is about to begin using both primary cultures of resting splenic B lymphocytes and established cultures of a mouse B cell line, WEHI-231. These cells will be exposed to ligands for most cell-surface receptors that they express (at least those known to us), and a variety of responses will be measured. The screen will be conducted in two major phases. Single ligands will be tested during phase 1, while combinations of ligands will be examined in phase 2.

The purpose of the ligand screen is first to define with some thoroughness the pattern of response to each ligand. How many patterns can we discern? Are any two ligands truly identical in the responses that they elicit? But the deeper purpose of this substantial exercise is to examine the cellular responses to combinations of these ligands. We expect to find many instances of interactions between ligands, defined as energetic nonadditivity of their responses (where the parameter to be added is \( \ln x / x_0 \); \( x \) is the response measured). These nonadditive responses will be the focus of detailed mechanistic studies that we will perform later. They will
show us the points of intersection of signaling modules and thus the sites at which network complexity is generated.

We will attempt to measure as many responses as possible during the ligand screen. The emphasis is on techniques of genomics and proteomics: the use of DNA microarrays to determine mRNA profiles and 2D protein gels to assess covalent modifications and changes in protein abundance. Second messenger concentrations will also be measured.

Data from the ligand screen will be posted as soon as experiments are replicated and should begin to appear in January 2002. The images below provide evidence that the AfCS staff in the Cell Preparation Laboratory in Dallas is practicing their assembly line for the launch.

Zhen Yan (working) and Jody Girouard (posing) in the Dallas Cell Preparation Lab

The Dallas assembly line

Strategy for Use of DNA Microarrays in the Ligand Screen. The strategy for use of DNA microarrays has been much discussed, since this technology is developing rapidly. We plan to use rather extensive arrays of spotted cDNAs for the single ligand screen. We want to give ourselves the greatest possible opportunity to detect changes in gene expression. We expect to see many changes in transcription after exposure to cytokines or ligation of the B cell receptor. But we do not know how many messages will be altered after exposure of cells to ligands usually thought to initiate relatively short-term signaling events.

The need for arrays will be much greater when combinations of ligands are tested, and expense will become a major factor. We are exploring the use of arrays of spotted oligonucleotides for this phase of the screen, and we may hone in on a smaller number of genes, concentrating on those whose expression was altered most dramatically in phase 1. However, when interesting combinations of interacting ligands are detected, we hope to study the
transcriptional consequences of these interactions in detail. We anticipate the availability of arrays capable of monitoring transcription of every exon in the mouse genome.

The Aspen Workshop on Cellular Signaling

Contributed by Rama Ranganathan (UT Southwestern)

As we all know, the ultimate goal of the AfCS is to understand quantitatively the response of a complete signaling network to physiologically relevant inputs and to pathological perturbation. We have stated (though not with true clarity) that this will involve the reduction of the large mass of AfCS experimental data into a set of interacting theoretical models that describes and predicts cellular signaling. But how should this goal impact the AfCS effort in the short term? Is our immediate experimental plan appropriate for achieving this goal? What, if any, is the role of theoretical modeling in the early stages of the AfCS project? In a recent two-week workshop at the Aspen Center for Physics (8/19-8/31), a group of 12 AfCS scientists and 12 scientists drawn from the mathematics/physics/computer science communities met to probe these questions.

The specific goals of the workshop were predicated on a fundamental hypothesis of the AfCS that the signaling network in a cell is comprised of modular units that represent specific irreducible functional properties. The hierarchical organization of modules then allows new and more complex functions to emerge from the connectivity of modules. In this view, understanding signal transduction amounts to identifying and understanding these modules and then mapping the circuitry by which modules are specifically connected. Since the number of components and reactions is large, we expect that understanding these systems will require the powerful tools of mathematical modeling and simulation.

A first step in generating an experimental plan based on this hypothesis is a careful examination of the hypothesis itself. Is there support in the literature for the concept of modules, and what are some specific examples? The first week of the Aspen meeting involved studying a number of well-understood examples of proposed signaling modules. The systems we reviewed were bacterial chemotaxis (Naama Barkai, John Doyle), G-protein mediated signaling (Elliott Ross), the MAP kinase phosphorylation switch (Jim Ferrell), and both vertebrate (Lubert Stryer, Sharrad Ramanathan) and invertebrate (Rama Ranganathan) phototransduction. The detailed study of these model systems provided good evidence that signaling can be treated in a modular representation. For example, the adaptation and amplification systems in chemotaxis, the G-protein complex, the phosphorylation cascade in MAP kinases, and several aspects of visual signaling seemed to be well represented as subsystems that could be individually subjected to mathematical modeling. In this regard, we noted that these modules of signaling could be dye-
namic properties of the process itself, so that a functional module could be created upon stimulation of a receptor and then broken down rapidly upon termination of signaling. These observations were kept in context of the AFCS work by Al Gilman and Henry Bourne, who reviewed basic properties of signaling in the cardiac myocyte and B lymphocyte, respectively.

The next interesting issue discussed was how to recognize such modules of signaling without detailed knowledge of kinetic parameters and equilibrium constants of all reactions. Can signaling modules be recognized as such through architectural features alone (physical association of proteins, co-expression of genes encoding signaling proteins, co-modification of proteins, co-localization in cells, etc.)? This question is a difficult one with regard to biological systems because of a lack of experimental data, but it is a central one for the AfCS effort. Adam Arkin discussed a general computing environment for storing many types of experimental data and systematic testing of different theories for consistency with experiment. Such an environment may be suitable for addressing these questions. For example, we might begin by modeling a relatively simple module that has been studied in great detail (e.g., the G protein) to see how dependent the models are on knowledge of detailed biochemical parameters. With regard to AfCS data, Shankar Subramaniam presented the development of a scalable relational database specifically tailored for storing and retrieving the diversity of data we expect. The smooth interaction between this database and Adam Arkin’s computing environment will begin the process of linking the experimental and theoretical aspects of the AfCS.

In summary, the Aspen workshop represented an initial attempt to begin a dialog between several disciplines that must ultimately unite to turn the AfCS goals into practical reality. In the short term, our goals should include specific plans to incorporate modeling into the experimental cycle of the AfCS both through initiation of projects within the Alliance and through stimulation of external groups that are interested in theoretical understanding of biological systems. The many personal interactions that were initiated at the Aspen workshop between experimentalists and theorists may represent the beginning of this task. Happily, not all of the interactions during the intense two weeks in Aspen were confined to intellectual pursuits.

(Left to Right) Al (spotted photographer; showing off) & Kathy Gilman, Henry Bourne, Gil Sambrano & Rama Ranganathan. No one perished.
A Short Course on Mathematical Modeling of Signaling Mechanisms in Biology

A short course on modeling was presented at the AfCS Annual Meeting in Bethesda on May 24, 2001. The course was presented by Drs. Adam Arkin (U. of California Berkeley and Lawrence Berkeley National Laboratory) and John Doyle (California Institute of Technology) in six segments over a total of 4 1/2 hours. The original presentation was broadcast live on the Internet and is archived at the NIH videocast site http://videocast.nih.gov/default.asp. Unfortunately, the video quality is poor and it is difficult to see the slides. Thanks to the considerable efforts of Hugo Pons and Andy Guynn in the Video Production and Technical Operations Center at UT Southwestern Medical Center, the presentation is being repurposed, synchronizing full views of the PowerPoint slides with the audio recording, enabling the student to view and review each slide.

This course is an introduction to the basic mechanics of modeling and its uses. In brief, the six segments cover the following:

1. Arkin, 38 min: What is a model and what are modeling objectives?

2. Doyle, 57 min: The utility of modeling in the biological context.

3. Arkin, 50 min: The basic mechanics of physical modeling.

4. Arkin, 35 min: Step by step model building simulation with lambda phage.

5. Doyle, 61 min: Model validation and the experiment/theory cycle.

6. Arkin, 24 min: Role of experimental data in building and validating a model.

The first of these segments will be available on the AfCS Web site in the very near future. The others will follow as they are recast. We are most grateful for Pons’ and Guynn’s expertise and fortitude and are confident that the availability of this course on the AfCS Web site will benefit the entire cell signaling community.

Available Now on the AfCS Web site

http://cellularsignaling.org
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- The AfCS Protein List: a searchable, object-relational database of approximately 3000 signaling proteins: sequences, Blast searches, links
to NCBI, links to a growing collection of AfCS Mini Molecule Pages, biochemical classification.

- The AfCS Mini Molecule Pages: a searchable database of basic information on approximately 400 signaling molecules. These Mini Molecule Pages are the precursors of the AfCS Molecule Page Database, to be launched in 2002.
- Email forms: forms for suggesting new molecules, correcting errors, volunteering to author AfCS Molecule Pages.
- Signaling Maps: chemotaxis, BCR signaling, IL4 signaling, CD40 signaling, insulin signaling, cyclic AMP signaling, Ca$^{2+}$ signaling. These maps will evolve in time into more complex and useful formats.

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We hope to add additional collaborators to this list.