

**NEWS OF
THE
ALLIANCE
FOR
CELLULAR
SIGNALING**

We are launching at this time a Newsletter to help keep all who are connected with the Alliance up to date and involved. We must communicate with a diverse group, including Members, Sponsors, our External Advisory Committee, Employees (Laboratory Scientists, Technical Staff, Administrative Staff), and the Participating Investigators. *The total number of people currently involved is approaching 400 and growing rapidly.* We hope to produce a new letter every two months and, in time, to make this a web-based resource with links to items of particular interest within the AFCS site. For now, Volume 1, No. 1 will be plain vanilla. Our over-worked programming staff has more urgent assignments. Bear with us. A few of us are a bit overwhelmed.



Wendy Deane, Alliance Administrator

For those not familiar with the organizational structure of the Alliance, please see the document entitled **Administrative Management Plan** at <http://afcs.swmed.edu>.

PERSPECTIVE

The Participating Investigators in the AFCS are working hard to launch this ambitious project, and we are excited and enthusiastic about our efforts. The Alliance is indeed a large-scale collaboration: roughly 50 Participating Investigators at 20 Universities and Research Institutes, a membership of over 250, 50 employees (on our way to 100), 11 sponsors, and a growing list of important industrial collaborators. Our program will succeed if we can muster the energy and talents of people in all of the groups listed above; it will fail if we cannot.

Our organizational structure is unique. We do not offer conventional rewards to the Participating Investigators, such as money for individual laboratories or publications that bring special recognition to established individuals. We do offer a plan intended to advance the field of cellular signaling dramatically and a structure that we firmly believe will benefit everyone in the field who pays attention.

Our literature-derived database, contributed by experts in the form of Molecule Pages, will be a unique resource. It will require a significant but not prohibitive effort by our Membership (see below). If the Membership responds, this database will constitute detailed, high-quality annotation of 5-10% of the mammalian genome. As such, it

will serve as a model for what **must** also be accomplished by other similar groups. *Please think about this.* “Annotation jamborees” or databases prepared by computers or non-experts are only a quick fix. The research community will not benefit greatly from hasty, non-judgmental surveys. Our database will be built on the best efforts of those who have a stake in accurate and critical evaluation of the current and future state of knowledge.

We are also committed to providing exciting research opportunities for the entire signaling research community. The Molecule Page database is the beginning. Our experimental efforts will follow quickly. Consider this example: We must identify all of the molecular players in cellular signaling systems. To do this, we must first identify all of the molecular interactions that involve the identified players. We will perform all possible screens to identify such interactions, including newly developed techniques that we hope to apply. But we do not have the capability or capacity to perform the critical follow up on the interactions that we detect. Are they real? What are their molecular consequences? Is there physiological significance? We leave these questions to be answered by any member of the research community. We will do this by placing all of our data and analyses in the public domain on our web site. Data will be posted immediately. No insider will have an advantage. We require nothing in return except dissemination of your findings in conventional ways. We leave it to you to determine if the employees of Alliance laboratories should be acknowledged in your publications or included as authors. You should not include Alliance Participating Investigators in such considera-

tions. We must leverage your interest and talents in this effort. This is the heart of our strategy.

Please address comments to Al Gilman at the University of Texas Southwestern Medical Center, Dallas, TX: alfred.gilman@UTSouthwestern.edu

MEMBERSHIP AND MOLECULE PAGES

Preparation, editing, and publication of Mini Molecule Pages (first) and then of full-length Molecule Pages are critically important tasks; these are our most visible initial efforts. Pat Casey at Duke, Chair of the Alliance Membership and Editorial Committee, is spearheading this job, and it is a formidable one. Our Members are obviously essential for success here, **and we beg for your timely help.**

- Recall. Mini Molecule Pages are a jump start – an abbreviated version of the real product, the full-length Molecule Page.
- Pat Casey has assigned roughly 400 pages and, to date, approximately 50 Mini Molecule Pages have been received. **Please do this job as promptly as possible.** We do not think that it should take more than a few hours.
- Mini Molecule Pages are being posted (after review) at our new web site: <http://cellularsignaling.org>. We are also in the process of incorporating information from the old site (<http://afcs.swmed.edu>) into the new site, which will be maintained at

the San Diego Supercomputer facility.

- More assignments will be made in the near future.
- **Many more Members are needed!** Please help us to recruit qualified individuals. An application will be found at <http://afcs.swmed.edu>
- The Mini Molecule Pages will provide critical information for the Alliance laboratories, and in time the searchable Molecule Page Database will be an unmatched, superb resource for the entire signaling research community.
- We have initiated this effort with a list of molecules suggested by our Participating Investigators and by Alliance Members. We continue to welcome new suggestions. Our molecule list will also be expanded by addition of interacting molecules noted in the Molecule Pages, by bioinformatic analysis of genomes, and by experimental data (our own and others).
- This list of molecules will soon appear on our web site as an index to the Molecule Page database. The list will be sortable and searchable. It will show Molecule Page assignments as well as molecules still in need of volunteers.
- We are working on the form for submission of full Molecule Pages.
- We are negotiating with Science/STKE (Signal Transduction Knowledge Environment) for collaborative publication of Molecule

Pages. We envision the relationship as follows: Molecule Pages will be reviewed by peers. If members agree, they will also prepare a very brief summary of the Molecule Page as a “component description” for STKE pathway maps. Members will also prepare the brief description of relationships that are elements of the STKE database. In turn, authors will receive named credit at STKE, and the full Molecule Page will be incorporated into STKE with links to the searchable Alliance database. STKE and the Alliance will lobby the National Library of Medicine to index these contributions, such that they will be found in conventional searches of the published literature. We believe that this will make a Molecule Page the full equivalent of a peer-reviewed scholarly publication. **We request and welcome your feedback on this plan.**

- Pat Casey will be appointing additional people to serve as members of the Editorial Board of this virtual journal.
- **Please address comments and suggestions to Pat Casey at Duke University:** casey006@mc.duke.edu

ALLIANCE LABORATORIES

There are seven Alliance Laboratories, and most of our budget supports the research in these dedicated facilities. Participating Investigators in the Alliance are Directors, Co-Directors, or Associate Directors of each laboratory. Laboratory staff includes Ph.D. scientists, technical staff, and administrative personnel.

Bioinformatics. University of California, San Diego. Shankar Subramaniam, Director

Cell Preparation and Analysis. University of Texas Southwestern Medical Center. Paul Sternweis, Director; Donald Hilgemann and Richard Scheuermann, Associate Directors.

Assay Development. University of California, San Francisco; San Francisco Veteran's Administration Medical Center. William Seaman, Director; Paul Simpson, Co-Director.

Molecular Biology. California Institute of Technology. Melvin Simon, Director.

Protein Chemistry. University of Texas Southwestern Medical Center. Marc Mumby, Director; Yingming Zhao, Associate Director.

Microscopy. Stanford University. Tobias Meyer, Director; Stephen Smith, Associate Director.

Antibodies. University of Texas Southwestern Medical Center. Susanne Mumby, Director.

All of the lab directors have been working to recruit the necessary staff for these new facilities. Importantly, Lead Scientists have been recruited for all of the laboratories, and the remaining staff is being hired at an excellent pace. It is no small trick to fill the approximately 100 necessary positions with quality individuals, but we are making great progress.

Experimental efforts are being ramped up rapidly as the staff is trained.

In future versions of this letter we will provide links to Alliance data on our web site. For now, we note a few highlights.

- Murine splenic B cells are being prepared routinely; the yield and purity of cells are consistent with values discussed in our application for funding (<http://afcs.swmed.edu>)
- Murine cardiac myocytes are being prepared routinely; the yield and purity of cells are consistent with the experience of most others, based on the literature. We will contact the very few who appear to do better.
- Cell culture conditions are being explored for optimal maintenance of viability of both B cells and cardiac myocytes. This is a significant issue. It is difficult to sustain these cells, particularly myocytes, for an extended period of time in culture. We must evaluate the temporal changes that occur during culture using a variety of techniques. We must ascertain the optimal condition and time for initiation of our experimental manipulations.
- 2D gel technology for analysis of the B cell and cardiac myocyte proteomes is being optimized. We hope to adopt the Amersham/Pharmacia Biotech DIGE system for 2D gel analysis of stimulus-induced changes in the pattern of protein expression and migration. Briefly, this is a two color, ratiometric system for analysis of changes in 2D gel patterns. Experimental and control samples are labeled with two different fluorescent dyes, mixed, and run on the same gel. The major advantage is

elimination of inter-gel variation, which is substantial.

- The Alliance mass spectrometry facility has been established under the direction of Dr. Yingming Zhao. The first two mass spectrometers have been installed, and their performance is being optimized.
- Many assays are being optimized for use with B cells and cardiac myocytes. To date these include Ca^{2+} fluxes, cyclic nucleotides, 2D-gels of proteins (with emphasis on phosphoproteins), immunoblotting of selected proteins of interest (including blots using phospho-specific antibodies), and mass spectrometric analysis of B cell and myocyte proteins.
- We are establishing and evaluating a variety of techniques for analysis of mRNA transcripts in B cells and cardiac myocytes. We will have the capacity to prepare and analyze DNA microarrays prepared by spotting cDNAs. Extensive collections of mouse cDNAs have been obtained. We are attempting to negotiate a collaborative agreement with Rosetta/Agilent for production and use of oligonucleotide arrays that will represent all of the genes of interest to the Alliance. We hope to facilitate commercial production of such arrays. These will constitute enormously valuable reagents for the entire signaling research community.
- At some sites Alliance laboratories will be housed in completely renovated facilities. Construction is nearing completion for the three Alliance labs at UT Southwestern, to be

occupied in January. The photos below are proof of progress.



9/00: Susie Mumby, Al Gilman, Paul Sternweis, and Marc Mumby start the demolition.



12/00: Al and the Electricians: Pam Sternweis, Dianne DeCamp, Susie Mumby

SYSTEM COMMITTEES

The B Cell Committee (chaired by Henry Bourne) and the Cardiac Myocyte Committee (co-chaired by Shaun Coughlin and Jim Stull) have been meeting regularly since the establishment of the Alliance in September. Starting in December, these meetings and all others will take place using our newly installed Picture Tel 960 teleconferencing systems. Running over Internet2, these systems permit high quality audio and visual communication with simultaneous sharing of any Windows NT computer application. These sys-

tems will also be installed in all of the Alliance laboratories, permitting constant interactions among our scientists.

The two System Committees have been concentrating their efforts on prioritization of signaling modules for initial attention and on the construction and prioritization of lists of signaling molecules. These lists will guide production of antibodies and vectors, design of DNA microarrays, etc. As mentioned above, the Molecule List will be available soon as an index to the Molecule Page database. We also intend to post pathway maps of signaling modules. We draw these with complete awareness of their limitations and with assurance that they will contain errors. Despite these drawbacks, they will provide convenient points of reference. By sharing them with the research community, we hope to stimulate suggestions and elicit comments about additional molecules to be considered.

EXTERNAL ADVISORY COMMITTEE

We have appointed an External Advisory Committee. These individuals will attend the annual meeting and offer advice on large scale issues. They are an outstanding group:

Joan Brugge, Department of Cell Biology, Harvard Medical School

Tony Pawson, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto

Harold Varmus, Memorial Sloan Kettering Cancer Center

ANNUAL MEETING

The first annual meeting of the Alliance will take place at the Natcher Building Conference Center at NIH in Bethesda, Md. on May 24 and 25, 2001. All who receive this newsletter are most welcome to attend, although we must note that funds available to us will support travel and accommodations only for our Participating Investigators and the Alliance Laboratory Scientists.

It is possible that we will broadcast the meeting on the Internet for those who are unable to come.

We will supply information on the meeting schedule, hotels, etc. in the not too distant future.

LOGO

Some have suggested that the Alliance *must* have a logo. Others wonder why! Creative, artistic suggestions are welcome. There will be a prize (proportional to the quality of the effort) if the winning entry is submitted by an Alliance employee.

SPONSORS

Thanks to the generosity (and wisdom!) of our sponsors, we have raised funds sufficient for our first year of operation, and most of our sponsors have committed funds for our first five years. The budget for year 1 amounts to approximately \$10M. We acknowledge, with gratitude:

The National Institutes of Health:

The National Institute of General Medical Sciences.

The Alliance Project was conceived under the NIGMS Glue Grant Initiative. See: www.nigms.nih.gov/funding/gluegrants.html

The National Institute of Allergy and Infectious Diseases

The National Cancer Institute (Pending)

The Pharmaceutical Industry:

Eli Lilly and Co.

The Merck Genome Research Institute

Aventis Pharmaceuticals, Inc.

Johnson & Johnson

Novartis Pharma AG

Chiron Corporation

It is notable that these corporate sponsors support the investigative aims of the Alliance in full compliance with our policy on Intellectual Property (see <http://acfs.swmed.edu>). No sponsor views Alliance data before it is posted on the public Internet.

Philanthropic Foundations:

The Agouron Institute

Anonymous Foundation, Dallas TX

Others:

The University of Texas Southwestern Medical Center

We have established collaborative relationships with the following entities:

Isis Pharmaceuticals, Inc.

Myriad Genetics, Inc.

Amersham-Pharmacia Biotech UK Ltd.

These relationships involve either (1) collaborative research agreements in which services are performed for the Alliance at cost or below (with full and prompt disclosure of data) or (2) substantial reductions in pricing for equipment and/or reagents with the hope that successful use of these technologies by the Alliance (and promulgation of such data) will encourage widespread adoption of relevant technologies.

We hope to add additional collaborators to this list.