
Twelfth Annual

# Biotechnology Training Retreat

Christian Brothers Retreat Center
Napa Valley

Saturday, March 29, 2003

*Co-Sponsorship by the NIH Training Grant in Biomolecular Technology (NIH-1-T32-GM08799-01A1), the UC BioSTAR Program, and the UC Davis Biotechnology Program.*

# *Welcome to the Twelfth Annual Biotechnology Training Retreat*

As we gather on this day in the beautiful hills of the Napa Valley, we are delighted to: announce the funding of the NIH Training Grant in Biomolecular Technology; introduce the directors; showcase our 2002-2003 fellows and their faculty preceptors and offer networking opportunities for our Designated Emphasis in Biotechnology (DEB) pre-doctoral students.

It is an honor to receive one of these highly competitive fellowships, so we want the biotechnology community to meet these scholars and share in their exciting research projects. Our NIH fellows include: Chad Green (preceptor is Scott Simon); Ryann Muir (preceptor is Abhaya Dandekar), Marisa Wong (preceptor is Juan Medrano); and Scott Wong (preceptor is Kit S. Lam). Amanda Ellsmore (preceptor is J. Clark Lagarias) and Larry Joh (preceptor is Jean VanderGheynst) are Biotechnology fellows (industry and campus fellowships). We would also like to recognize our first year fellows: Craig Blanchette (Biophysics); Lucy Stewart (Plant Biology), and Clyde Washington (Chemical Engineering). Due to the limited time for oral presentations, we will also showcase research performed by additional students in the DEB program in the poster session. Please congratulate these outstanding predoctoral candidates.

As most of you know, The UC Davis Biotechnology Program (established in 1986) is the administrative home for the NIH Training Program in Biomolecular Technology as well as the Designated Emphasis in Biotechnology (DEB) Graduate Program. Although not required, all of our current fellows are also members of the DEB. The number of DEB students has more than doubled in the last year to close to 40 active members. We had a number of graduates in 2002. Aaron Nguyen (Microbiology) is now at Scios, Inc. Melody Trexler (Chemical Engineering) recently accepted a position at Genentech. Jeffery Murrell (Chemistry) joined the chemistry faculty at Sonoma State University. Mary Kalamaki (Ag & Environmental Chemistry) returned to her home in Greece. Tao Li (Chemical Engineering) also received his PhD and was planning to do post doctoral research in academia.

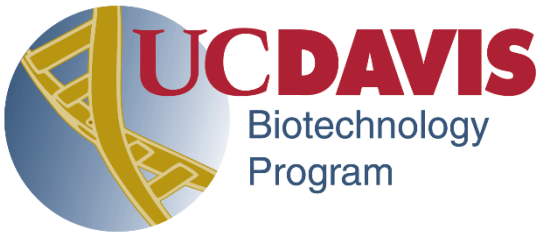
This annual event is a great time to officially thank our company affiliates for their support in the form of: fellowships; internships; participation on advisory boards; Picnic Day donors; and guest lectures for seminars and summer short courses. The education of our interdisciplinary pre-doctoral students is dependent on the support of our industrial partners. Thank you for your continued support. We also welcome our invited companies to become more deeply involved in our training program.

This daylong gathering gives us an opportunity to network with fellow scientists in a number of ways. We have formal scientific presentations and posters, a leisurely luncheon with Hess Select wines and scenic gardens. Good science and delicious food & wine are great ways to get communications flowing. Bon Appetit!

Last but not least. We would like to thank Prof. Karen McDonald for co-sponsoring this academic-industrial outreach event through a BioSTAR opportunity award. We want to also thank Prof. John Yoder for offering stimulating bioethics questions for our consideration. As for handling the logistics of the retreat, Jennifer Lee deserves our kudos.

We hope you have a wonderful day!

*Judy Kjelstrom, acting director and the staff*
*The UC Davis Biotechnology Program*




# NIH Training Grant in Biomolecular Technology

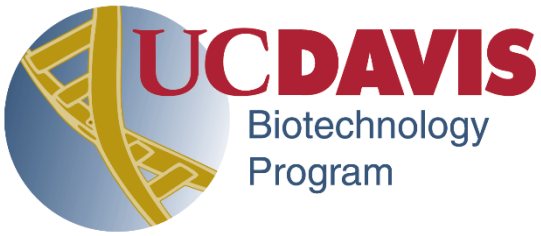
Bruce D. Hammock, Director
Martina Newell-McGloughlin, Co-Director
Rosemary Smith, Co-Director

**Executive Committee**

**Faculty:**
George Bruening (Plant Pathology)
Dan Gusfield (Computer Science)
Ian Kennedy (Mechanical & Aeronautical Engineering)
J. Clark Lagarias (Biochemistry & Molecular Biology)
Kit Lam (MED: Internal Medicine (Hem/Onc)
John Yoder (Vegetable crops)

**Company Representatives:**
Monsanto, Calgene campus: Nordine Cheikh
Novozymes Biotech: Joel Cherry
Scios: designee TBA

Judith A. Kjelstrom, Program Coordinator
Cathy Miller, Grant Administrator
Jennifer Lee & Gail Stroup, Administrative Assistants




## Designated Emphasis in Biotechnology (DEB) Executive Committee

Abhaya Dandekar, Chair
Karen McDonald
Robert Rice
David Rocke

## UC Davis Biotechnology Program

Acting Director
Judith A. Kjelstrom
(DEB Program Coordinator & Ex-Officio Member
of the DEB Executive Committee)

Jennifer Lee, Administrative Assistant

# UC Davis Twelfth Annual Biotechnology Training Retreat
# March 29, 2003
# Christian Brothers Retreat & Conference Center

**PROGRAM OVERVIEW**

| | **Abstract** |
|---|---|
| 8:15 am | Registration & Continental Breakfast |
| 8:30 am | Welcome by Bruce Hammock, Director<br>NIH Training Program in Biomolecular Technology |
| | **Morning Session Chair- Martina Newell-McGloughlin, Co-Director**<br>NIH Training Program in Biomolecular Technology |
| 8:45 – 9:05 | Abhaya Dandekar/Ryann Muir |
| 9:10 – 9:30 | **Aaron Nguyen (Scios)** |
| 9:35 – 9:55 | Kit Lam/Scott Wong |
| 10:00 – 10:20 | Juan Medrano/Marisa Wong |
| 10:25 – 10:40 | Break/poster viewing |
| 10:45 – 11:00 | Scott Simon/Chad Green |
| 11:05 – 11:25 | **Joel Cherry (Novozymes Biotech)** |
| 11:30 – 11:50 | Clark Lagarias/Amanda Ellsmore |
| 11:55 | John Yoder- Bioethics Question (Handout) |
| 11:55 – 2:00pm | Lunch/poster viewing |
| | **Afternoon Session Chair- George Bruening**<br>Biotechnology Advisory Committee-Chair |
| 2:00 – 2:15 | John Yoder- Bioethics Question (Discussion) |
| 2:15 – 2:35 | Jean VanderGheyst/Larry Joh |
| 2:40 – 2:55 | Break/poster viewing |
| 2:55 – 3:15 | **TBA (Genentech)** |
| 3:20 – 3:25 | Kay Nelson (Internship and Career Center) |
| 3:30 – 3:40 | Julio Baez (FibroGen) |
| 3:45 – 3:55 | Jing Zhu (Ciphergen Biosystems, Inc.) |
| 4:00 – 4:10 | David Hirschberg (Agilent Technologies) |
| 4:15 – 4:25 | Pete Smietana (BioXing, Inc.) |
| 4:30 – 4:40 | Keith Ball (Large Scale Biology) |
| 4:45 | Close |
| 5:00pm | Bus Departs |

## POSTER TITLES

A. "Regulation of the PYP1 Tyrosine Phosphatase in Response to Heat Shock"
**John I. Yoder, Denneal Jamison*, Manuel Torres*, Quy Ngo, Jean-Michel Petit, Natalya Tomilov, and Alexey Tomilov**

B. "Microbial Community Composition on a Harsh Soil Environment: Life with Heavy Metals, Nutrient Deficiency, and Drought on Serpentine Soils"
**Shira H. DeGrood*, Victor P. Claassen, and Kate M. Scow**

C. "DNA Damage Checkpoints and Recombinational Repair"
**Edwin Haghnazari*, Vladimir Bashkirov, and Wolf-Dietrich Heyer**

D. "Lack of Catabolite Repression in a Lactic Acid Bacterium: A New Opportunity to Maximizing Efficiency of Biomass Utilization"
**Jae-Han Kim, David A. Mills, David E. Block, and Sharon P. Shoemaker**

E. "Putative *in silico* Mapping of DNA Sequences to Livestock Genome Maps Using SSLP Flanking Sequences"
**Charles R. Farber and Juan F. Medrano**

**See pages 24 to 29 for abstracts.**

*Member of DEB graduate group

# Oral Presentation Abstracts

OVERVIEW OF LAB RESEARCH: Abhaya Dandekar/Ryann Muir

## Dandekar Laboratory

**Abhaya Dandekar**
Professor of Pomology
University of California, Davis

The research in my laboratory has focused on understanding the relationship between genes and expressed traits. Most horticultural important traits are ultimately the manifestation of gene regulation and allelic diversity of orthologous or paralogous gene sequences. These traits determine productivity, quality and food safety of fruit and nut tree crops important to the economy of California and many parts of the world. Our experimental strategy has involved analyzing both novel and endogenous genes using molecular and transgenic approaches to validate the relationship between genes and traits.

NIH FELLOW: Ryann Muir

**"Inhibition of Aflatoxin Production: Synthesis of Hydrolysable Tannins in Plants"**

**Ryann M. Muir*, Abhaya Dandekar**
Department of Pomology
University of California, Davis

Plants exhibit an innate defense mechanism such that defensive compounds are constitutively present in all plants. One such strategy for this innate response is the accumulation of a specific group of polyphenolic compounds, the hydrolysable tannins (HTs). Via precipitation of herbivore, microbial and fungal proteins, HTs interfere with the digestion and nutrient absorption of pathogens. We have data suggesting that a precursor and/or breakdown product of HTs (i.e. gallic acid) also imparts a type of fungal resistance. Gallic acid prevents formation of the fungal contaminate, aflatoxin. Therefore, we have been investigating the synthesis of gallic acid and the synthesis and breakdown of HTs. Two walnut cultivars (i.e. *Juglans regia* ssp. Chandler and ssp. Tulare) exhibit variable levels of gallic acid within their seed coat tissues. Thus comparison between these two lines will serve as a novel means by which to identify HT specific genes. Current technology will be employed including two dimensional gel electrophoresis, electron spray ionization - mass spectrometry (ESI-MS-MS) and *Agrobacterium* mediated plant transformation. This research potentially furthers the understanding of the regulation of tannins and their complex role in plants.

*** Member of the DEB graduate group**

COMPANY AFFILIATE: **SCIOS, INC.**

## "TGFβ1 Induced Los of β-Adrenergic Response in Human Bronchial Smooth Muscle Cells (hBSMC) is Dependent on TGFb-RI Kinase: Potential Therapeutic Application in Treating Airway Diseases"

**Aaron Nguyen****
Scientist
Scios, Inc.
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E-mail: nguyen@sciosinc.com

β-adrenergic agonists cause smooth muscle relaxation and are effective ronchodilators. TGF β1 is known to down-regulate β2-adrenergic receptor (β2AR) numer and function in human airway smooth muscle cells. Transgenic overexpression of β2AR in airway smooth muscle increases β2AR signaling and improves function. Thus, inhiition of TGFβ signaling to increase β2AR response presents a novel treatment paradigm.

**Methods:** β2AR expression and function were studied in primary hSMC using real-time RT-PCR, radioligand inding, and agonist induced cAMP accumulation. Smad2/3 phosphorylation, nuclear translocation, and β -AR signaling molecules were analyzed using Western or immunofluorescence. SD-208 is a novel, selective chemical inhiitor of the TGF β-RI kinase with an IC50 of 37 nM.

**Results:** TGF β 1 (1 ng/ml) exposure induced down-regulation of β2AR expression in hSMC, including mRNA and β-AR inding site levels, which was locked y SD-208 at 200nM. The inhiitor also prevented TGF β1 induced loss of the β-agonist response resulting in restored β 2AR mediated cAMP production. TGF β1 treatment induced Smad2/3 phosphorylation and nuclear translocation, which were inhiited y 200 nM SD-208. In addition, Smad3 expression was reduced at 24hr after TGF β1 exposure, indicating a negative feedack loop of TGF β signaling in hSMC.

**Conclusion:** TGF β1 treatment induces Smad2/3 activation and translocation and decreases β2AR expression and signaling in hSMC. TGF β-RI inhiitor SD-208 reverses these effects, thus providing potential therapy for ronchoconstrictive diseases.

**** Received his Ph.D. in Microbiology with a Designated Emphasis in Biotechnology in 2002.**

OVERVIEW OF LAB RESEARCH: Kit S. Lam/Scott Wong

**Lam Laboratory**

**Kit S. Lam**
UC Davis Division of Hematology/Oncology

**Kit Lam's Lab is well equipped for drug development research. There are 18 full time researchers in the laboratory. Active projects include:**

1. **Application of combinatorial library methods for basic research and drug discovery.**
2. **Development of new techniques in peptide and small-molecule combinatorial chemistry.**
3. **Protein tyrosine kinases, biochemistry and drug development.**
4. **Development of peptide-targeted therapy for cancer.**
5. **Development of novel anti-HIV agents.**
6. **Proteomics, application of combinatorial chemistry for drug targets and drug leads identification.**
7. **Chemical Microarray Technology Development.**

NIH FELLOW: Scott Wong

## "Identification of Small Molecule Inhibitors for the Simian Immunodeficiency Virus Protein NEF and the Cellular PROTEIN P21-Activated Kinase"

**Scott Wong*, Ruiwu Liu[2], Erwin Antonio[1], Alan Lehman[2], Michael Ye[1], Earl Sawai[1] and Kit Lam[2]**
Department of Medical Pathology[1], Division of Hematology/Oncology[2]
University of California, Davis

The Simian Immunodeficiency Virus (SIV) protein Nef is able to enhance virion infectivity, downregulate of CD4 and Major Histocompatibility complex class I protein (MHC-I) from the cell surface and participate in cellular activation. One way Nef increases cellular activation is by binding and activating the cellular protein p21-activated kinase (PAK). Regions of Nef required for PAK binding are selected for *in vivo* and results in increased viral replication. To further study this interaction *in vivo*, we will develop small molecules that inhibit the Nef-PAK interaction. First, wild-type SIV Nef with a poly-histidine tag attached to the C-terminus, was cloned and expressed in *E.coli*. Recombinant SIV Nef was used to screen encoded one-bead one-compound small molecule combinatorial libraries to identify ligands that bind Nef. In these libraries, each compound-bead contains a small molecule on the bead surface and an $\alpha$-amino acid containing a peptide tag in the bead interior. Then by sequencing the interior peptide tag with an automatic microsequencer, the identity of the exterior small molecule can be determined. Screening was performed by incubating the beads with Nef, followed by anti-His tag Mab-alkaline phosphatase conjugate and the substrate BCIP. Beads that interact with Nef will turn turquoise. In our preliminary experiment, several small molecules that interact with Nef were identified. Work is currently underway in confirming their binding specificities and their anti-viral effects in SIV infected cell culture. If these small molecules are active in cell culture, they will be tested in vivo and eventually developed into inhibitors for Human Immunodeficiency Virus (HIV). If successful, Nef inhibitors may become a new class of HIV therapeutic.

*** Member of the DEB graduate group**

OVERVIEW OF LAB RESEARCH: Juan Medrano/Marisa Wong

## Animal Genomics Laboratory: Animal Growth, Milk Composition, and Sex Determination in Sturgeon

**Juan Medrano**
Professor of Animal Science
University of California, Davis

**Animal Growth:** We have characterized the *high growth* (*hg*) mutation in the mouse that results in increased growth and efficiency of growth, without producing obesity. The mutation is due to a deletion[1] including the *Socs-2, Raidd/Cradd* and *Plexin C1* genes. The loss of Socs-2, a negative regulator of cytokine signaling, prolongs activation of the growth hormone (GH) and IGF-1 signaling, leading to an overgrowth phenotype. Our current work is directed towards: 1) Understand the effect of the genes within the *hg* region in relation to the expression of the phenotype; 2) Identify epistatic/modifier genes of *hg*; 3) Examine structural variation of *Socs2* in mammalian species and determine if this variation is associated with growth enhancing phenotypes. 4) Develop a transgenic approach to regulate the postnatal expression of *Socs2* in other species than the mouse.
**Milk composition:** Our interest is to increase cheese yield and modify the fatty acid[2] composition of milk. We have studied the structure and expression of the milk casein and whey[3] protein genes in dairy cattle and have identified genetic variants that have a close association with cheese yield and quality. Genetic selection for these variants can increase cheese yield 5%.
**Sex determination in sturgeon:** We are interested in identifying molecular markers that could be used for sexing fish and to study the mode of sex determination in sturgeon[3].

[1] Wong, M.J., A.D. Islas-Trejo, S. Horvat and J.F. Medrano 2002. Structural characterization of the mouse High Growth deletion and discovery of a novel fusion transcript between suppressor of cytokine signaling-2 (*Socs-2*) and viral encoded semaphoring receptor (*Plexin C1*). Gene 299:153-163.
[2]Mistry, D., E.J. DePeters and J.F. Medrano 2002. Comparative Composition of Total and sn-2 Fatty Acids in Bovine and Ovine Milk Fat Le Lait Dairy Science and Technology 82:255-259
[3]Folch, J.M., P. Dovc and J.F. Medrano. 1999. Differential expression of bovine β-lactoglobulin A and B promoter variants in transiently transfected HC11 cells. J. Dairy Research 66:537-544.
.[4]Van Eenennaam, A.L., J.P. Van Eenennaam, J.F. Medrano and S.I. Doroshov. 1999. Evidence of female heterogametic genetic sex determination in sturgeon. Journal of Heredity 90:231-233

NIH FELLOW: Marisa Wong

**"Expression Profiling of Genes Involved in the HG Deletion"**

**Marisa Wong* and Juan F. Medrano**
Department of Animal Science
University of California, Davis

The *high growth (hg*) mutation in the mouse is a valuable model for investigating genes involved in regulating mammalian growth. The *hg* phenotype is characterized by a 30-50% increase in the body size of homozygous animals, as well as atypical growth hormone secretion and increased plasma IGF-I. This mutation is due to a 450Kb deletion of mouse chromosome 10. We have shotgun sequenced the corresponding region in wildtype mice and identified three genes, *Socs-2* (suppressor of cytokine signaling-2), *Raidd*/*Cradd* (CASP2 and RIPK1 domain containing adaptor with death domain), and *Plexin C1* (also known as vespr, or viral encoded semaphorin protein receptor) which all fall within the *hg* deletion. The two deletion breakpoints lie within *Socs-2* and *Plexin C1,* causing a fusion of the two that is transcribed but most likely not translated. Socs-2 belongs to a family of proteins which negatively regulate cytokine signaling, such as growth hormone, prolactin and interleukins, by inhibiting the Janus kinase (JAK)/signal transducer and activators of transcription (STAT) signal transduction pathway. Activation of the JAK/STAT pathway through cytokine signaling leads to Socs expression, which demonstrates how *Socs* genes act in a classic negative feedback loop. The lack of Socs-2 causes the characteristic increased growth phenotype, which is hypothesized to be due to prolonged activation of the transcription factor STAT5b. We are currently creating detailed mRNA expression profiles of these three genes and the *Socs-2/Plexin C1* fusion transcript by assaying nine different tissues over three embryonic and four adult ages in both wildtype and *hg* mice using real time PCR. We have also created assays of other Socs family members that are known to be induced by STAT5b. A preliminary northern blot indicated the fusion transcript is expressed similarly to *Plexin C1* (rather than *Socs-2*), and our latest real time PCR results confirm that the fusion transcript is expressed similarly but not identically to *Plexin C1.* These results will help determine if the prolonged STAT5b activity has any biological consequence by causing an up-regulation or increased expression of downstream targets. In addition, we plan to use this information to aid in the identification of other effects the *hg* mutation has aside from increased growth, as well as study the regulation of *Socs-2* and *Plexin C1*.

*** Member of the DEB graduate group**

COMPANY AFFILIATE: **NOVOZYMES BIOTECHNOLOGY, INC.**

## "Directed Evolution of Industrial Enzymes"

**Joel Cherry**
Research Manager, BioEnergy Group
Novozymes Biotech, Inc.
1445 Drew Ave.
Davis, CA 95616
E-mail: cherry@novozymesbiotech.com

Directed evolution is playing an increasingly important role in the development of industrial catalysts. Enzymes are ubiquitously used as processing aids in the production of a wide variety of commercial products including laundry detergents, soft drinks, clothing, wine and animal feed. In this talk I will discuss the process of enzyme discovery, application testing, and commercial deployment and how the directed evolution of enzymes has been used to improve the speed or feasibility of enzyme commercialization.

OVERVIEW OF LAB RESEARCH: Scott Simon/Chad Green

## Molecular and Biophysical Mechanisms Regulating Leukocyte Recruitment in Inflammation and the Development of Rational Therapeutics to Block Their Inappropriate Adhesion During Diseases Including Myocardial Infarction and Sepsis

**Scott Simon**
Professor of Biomedical Engineering
University of California, Davis

Research activities in my laboratory are focused on defining the molecular and biophysical mechanisms regulating leukocyte recruitment in inflammation and the development of rational therapeutics to block their inappropriate adhesion during diseases including myocardial infarction and sepsis. Neutrophils constitute the largest component of white blood cells and are the body's primary defense against bacterial and pathogenic invasion. They traverse the circulation and are extremely efficient at homing to sites of infection and tissue injury where their functions are crucial to host defense and wound healing. Accumulation of neutrophils at sites of tissue injury is a finely balanced process, in some ways analagous to a double-edged sword. Pathologic conditions favoring their accumulation in oxygen-deprived or infected tissue and can lead to irreversible organ damage.

One scientific objective has been to elucidate the molecules and biophysical mechanisms underlying neutrophil adhesion by assembling unique experimental and computational tools. We have designed and fabricated rotational and straight channel shear flow chambers that allow us to simulate hydrodynamic conditions within the circulation. These shear chambers allow us to scale the shear rate and drag forces acting on cells. These chambers are directly coupled with optical microscopy and fluorescence flow cytometry to provide the means to evaluate the dynamic changes in the molecules supporting cellular activation and intercellular adhesion. Mathematical models based on two-body collision theory are applied to analyze and predict the relationship between physical parameters such as fluid shear and cell geometry, and the biological process of adhesion receptor-ligand bond formation and intercellular adhesion. This marriage of methodology, technology, and computational modeling has allowed us to publish our work in high quality journals and successfully compete for NIH funding.

<u>Laboratory Facilities</u>
*Cell adhesion laboratory*

Instumentation includes phase contrast and fluorescence optics microscopy and high speed video imaging of cell adhesion in parallel plate flow chambers. Micromanipulation apparatus consisting of an inverted optical microscope equipped with automated micromanipulators, two chambered manometers with precise pressure control and detection by pressure transducers, and image analysis. This allows application and detection of nano-forces with μsec resolution. Tissue culture facility including incubators and hoods for production and maintenance of endothelial and hematopoetic cell lines.

NIH FELLOW: Chad Green

**"Adhesion Receptor Dynamics on Neutrophils in Shear Flow"**

**Chad E. Green*, David N. Pearson and Scott I. Simon**
Department of Biomedical Engineering
University of California, Davis

Accumulation of neutrophils at sites of vascular injury is thought to occur via a sequential multistep process of capture and rolling followed by firm adhesion and extravasation. During an inflammatory response, various cytokines attract neutrophils to injured or activated vascular endothelium where brief encounters between sialylated and fucosylated sugars on the opposing surface initiate the process of neutrophil capture and rolling. This process appears to be mediated by E- and P-selectin on the endothelium and L-selectin and P-selectin glycoprotein ligand-1 (PSGL-1) on neutrophils. Once sufficient cell braking has occurred, $\beta_2$-integrin (CD18) receptors on neutrophils mediate firm arrest by engagement of intracellular adhesion molecule-1 (ICAM-1) on the endothelial surface. In the current study we show that E-selectin rapidly activates CD11b/CD18 dependent adhesion through multi-valent recognition of sialyl-lewis$^x$ (sLe$^x$) sugars on the neutrophil membrane. In addition, two sLe$^x$ decorated sugars, L-selectin and PSGL-1, colocalize in large clusters on the neutrophil surface following exposure to E-selectin in shear flow but not under static conditions. This coincided with the recruitment of active CD18 to the site of contact between the neutrophil and the endothelium, as detected using an antibody specific to the high affinity, ligand binding conformation of CD18. Adhesion signaled via E-selectin binding was inhibited 75% when blocking p38 and p42/44 mitogen-activated protein kinases (MAPK). This correlated with decreased expression and clustering of high affinity CD18. Together, the data demonstrates that E-selectin binding L-selectin and PSGL-1 rapidly induces receptor redistribution, directly resulting in $\beta_2$-integrin activation and clustering over a time frame relevant to neutrophil recruitment in shear flow.

*** Member of the DEB graduate group**

OVERVIEW OF LAB RESEARCH: J. Clark Lagarias/Amanda Ellsmore

## The Lagarias Laboratory

**J. Clark Lagarias**
Professor of Molecular and Cellular Biology
University of California, Davis

Plants possess photoreceptors which enables them to adjust to frequent fluctuations of intensity, direction and spectral quality of light in their environment. Research in my lab focusses on the biosynthesis, structure, function and molecular evolution of the plant photoreceptor phytochrome, a photoactivatable biliprotein that plays a central role in a plant's response to its light environment. The molecular basis of phytochrome action depends upon its ability to photointerconvert between two stable isomers, the red light absorbing Pr form and the far-red light absorbing Pfr form. This novel property of the phytochrome molecule is conferred by a linear tetrapyrrole (bilin) prosthetic group that is covalently bound to the phytochrome apoprotein via a thioether linkage.

Project 1. Through purification, biochemical and biophysical characterization of phytochromes from evolutionarily diverged organisms, structural features which may confer common and unique functions can be determined. These studies seek to define the structural basis for both photosensory and regulatory functions of the phytochrome photoreceptor mainly utilizing biochemical and molecular biological approaches. Our studies exploit the genetic diversity of this ancient family of bilin- and light-regulated receptors which are found in plants, crytogams, cyanobacteria, some nonphotosynthetic bacteria and fungi.

Project 2. Since light perception by all phytochromes depends upon the presence of the linear tetrapyrrole prosthetic group phytochromobilin, understanding the metabolic processes involved in its synthesis and assembly with apophytochrome are of fundamental importance to light-mediated plant growth and development. Using biochemical and molecule genetic approaches, we have characterized the pathway of bilin biosynthesis and its attachment to the phytochrome apoprotein. We have exploited this knowledge to regulate the light responsiveness via expression of enzymes that alter the structure of the bilin precursor in transgenic plants. The long term goal of these investigations is to rationally alter yield-reducing light responses in agronomically important plant species.

Project 3. A third project has been initated which exploits our ability to reconsitute photoactive and fluorescent phytochromes in living cells. Through directed evolution of phytochrome and bilin biosynthetic enzyme genes, bioorganic chemistry and *in vivo* functional screens, we ultimately seek to develop novel phytochrome-based fluorescent and photochromic biomolecules tailored for use as novel molecular tags and/or as regulators of gene expression in living plant, microbial and animal cells.

BIOTECHNOLOGY FELLOW: Amanda Ellsmore

## "Directed Evolution of Phytochrome"

**Amanda J. Ellsmore*, William J. Coleman, Mary M. Yang, and J. Clark Lagarias**
Plant Biology Graduate Group, Section of Molecular and Cellular Biology
University of California, Davis

Phytochromes are biliprotein photoreceptors that exist in two photointerconvertible forms - the red light absorbing Pr form and the far-red light absorbing Pfr form. We previously showed that unnatural bilin precursors yield strongly fluorescent adducts with apophytochromes in living cells [1]. These fluorescent phytochrome adducts, known as phytofluors, hold great promise for numerous cell biological applications, however, unlike the green fluorescent protein (GFP), exogenous unnatural bilin-precursors are needed for phytofluor formation in cells.

A directed evolution approach was undertaken with the goal of creating fluorescent phytochrome mutants that utilize endogenous bilin precursors found in plants and cyanobacteria. Our strategy employed error-prone PCR for generating point mutations at random positions within the domain adjacent to the bilin binding domain of the cyanobacterial phytochrome 1 [2]. The P4 domain was chosen for mutagenesis because it is critical for the formation and spectroscopic properties of the Pfr form of phytochrome [3, 4]. We hypothesize that alterations in the P4 domain will result in spectrally shifted holophytochrome mutants that are 'locked' in either the Pr or Pfr form, thereby enhancing their red and far-red fluorescence.

Phytochrome proteins with mutated P4 domains were expressed in different bilin producing strains of *E.coli* [5] and screened for spectral abnormalities using digital imaging spectroscopy. Multiple classes of mutants with altered spectral properties were identified and sequenced. These studies showed that mutations throughout the P4 domain led to spectrally altered holoproteins. The most common spectral mutant possessed 10 nm blue shifts for both Pr and Pfr forms that is similar to the spectra of Cph1 proteins which lack the P4 domain altogether. These results suggest that the P4 domain in these mutants is 'uncoupled' from interacting with the bilin prosthetic group. Two other mutant classes were observed, i.e. blue-shifted mutants altered individually in the Pr or Pfr forms. The correlation of observed spectral changes with specific amino acid residues in Cph1 requires construction of individual point mutations - experiments that are in progress. Fluorescence screening of the mutant library is also under way, however methods for reducing the background fluorescence will be required to increase the efficacy of this screen.

### References

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2. E. Henke, U. T. Bornscheuer (1999) Biological Chemistry 380 (7): 1029-1033
3. J.R., Cherry, D. Hondred, J. M. Walker, J.M. Keller, H. P. Hershey, R. D. Vierstra (1993) Plant Cell 5 (5): 565-575
4. S. H. Wu, J. C. Lagarias (2002) Biochemistry 39 (44): 13487-13495.
5. G. Gambetta, J.C. Lagarias (2001) PNAS 98 (19): 10566-10571.

Supported by grants from the USDA (AMD-0103397) and the UCD Biotechnology Program.

*** Member of the DEB graduate group**

OVERVIEW OF LAB RESEARCH: Jean VanderGheynst/Larry Joh

## VanderGheynst Laboratory

**Jean VanderGheynst**
Associate Professor of Biological & Agricultural Engineering
University of California, Davis

Our laboratory research area is Bioprocess Engineering with an emphasis on agricultural and environmental biotechnology. She is particularly interested in the application of biological engineering to the production and delivery of microbial agents for the control of plant pathogens and insects, and in value-added processing of plant biomass for production of high-value proteins and commodity chemicals.

BIOTECHNOLOGY FELLOW: Larry Joh

## "Value-Added Processing of Tomato for Production of Monoclonal Antibodies"

**Larry Joh*, and Jean S. VanderGheynst**
Department of Biological and Agricultural Engineering
University of California, Davis

The demand for existing biopharmaceuticals and new therapeutic proteins discovered through genomics research is expected to rise considerably in the future. Large-scale production of antibodies and other proteins in transgenic plants has been proposed as a cost-effective option for meeting this demand. Antibodies are relatively large and complex molecules that are not made well in many conventional systems such as *E. coli* and yeast but are typically made well in plants. The plant system of interest for our research is the UC82b processing tomato. Tomato provides several advantages over other plant expression systems, including amenability to large-scale greenhouse production and potentially simpler purification due to lower native protein content. Although a number of different biopharmaceutical proteins have been expressed in transgenic plants, surprisingly few reports have been published on protein extraction and purification, collectively termed downstream processing. Purification is likely to represent most of the cost of biopharmaceutical production in plants. We are using statistically designed experiments to develop and optimize the extraction and purification processes, and will use the computer software package SuperPro Designer (Intelligen, Inc., Piscataway, NJ) to estimate economics and scale-up the optimized bench-scale process to a 10 kg/yr base-case commercial antibody production unit. Our initial experiments have focused on extraction of soluble proteins from tomatoes, separation and concentration of protein extract from tomato pulp, and purification of immunoglobulin G (IgG) from native tomato proteins. We have observed that protein extraction yield from tomato is quite sensitive to extraction conditions and to unit procedures involved with blending and solid separation. To prevent fouling of filtration membranes and clogging of chromatography columns, a two-step process of centrifugation and microfiltration was needed. The microfiltered extract was then concentrated by ultrafiltration to reduce the size of chromatography columns. We have found that Protein A chromatography is very effective in separating IgG from a concentrated solution of IgG and native tomato proteins.

*** Member of the DEB graduate group**

COMPANY AFFILIATE: **GENENTECH**

**TBA**
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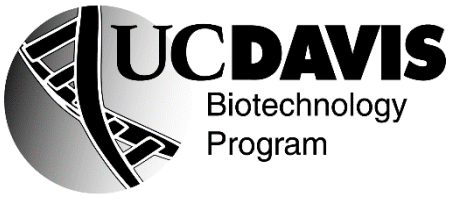


# Poster Abstracts

## A. "Plant-Plant Interactions in the Rhizosphere"

**John I. Yoder, Quy Ngo, Manuel Torres*, Denneal Jamison*, Jean-Michel Petit, Natalya Tomilova, Alexey Tomilov, Russell Reagan, Marta Matvienko**
Department of Vegetable Crops
University of California, Davis

Parasitic plants fulfill at least some of their nutritional requirements by robbing other plants. The effect on the parasitized host can be debilitating and some of the world's worst agricultural pests are parasitic weeds. The control point in the evolutionary origin of plant parasitism is the ability to recognize and attack an appropriate host plant. Parasitic species in the Scrophulariaceae use phenolics released by host plant roots to initiate the switch from autotrophic to heterotrophic growth, an event earmarked by the development of invasive haustoria on the parasite roots. We are using the common, springtime wildflower Triphysaria to dissect the signal pathway associated with host root recognition by parasitic plants. Triphysaria is a hemiparasitic plant that parasitizes a broad range of host plants, including maize, Arabidopsis: indeed, the only plants we have identified not infected by Triphysaria are other Triphysaria. We sequenced a cDNA library enriched for transcripts upregulated in Triphysaria root during early stages of host signal transduction and haustorium development. Haustorial enriched ESTs were assembled into 1385 assemblies of at least 50 bases comprised of 426 multiple read contigs and 959 singletons. We used Perl to search and cross-reference functional annotation data derived from multiple BLAST similarity searches of sequences in public databases, including the Gene Ontology (GO) Consortium, and archived the results in a MySQL database that is accessible over the web at http://pscroph.ucdavis.edu. Several transcripts have been identified for functional studies based on their putative functions following trans-annotation and RNA expression analyses. Biochemical studies of two distinct quinone oxidoreductases and one transcription factor are underway following expression of these proteins in heterologous systems. Transformation systems for Triphysaria are being developed to investigate the role of these genes in parasite development. Characterization of the genetic pathways regulating plant-plant interactions may suggest novel strategies for engineering crops for increased competitive performance against agricultural weeds.

*** Member of the DEB graduate group**

**B. "Microbial Community Composition on a Harsh Soil Environment: Life with Heavy Metals, Nutrient Deficiency, and Drought on Serpentine Soils"**

**Shira H. DeGrood* Victor P. Claassen, Kate M. Scow**
Department of Land, Air, and Water, Soils and Biogeochemistry
University of California, Davis

Serpentine soils, found throughout the world, are formed from hydrated magnesium silicate rocks. They contain high levels of heavy metals, low levels of macronutrients, and a low Ca:Mg ratio. Plant communities are known to differ substantially between serpentine and adjacent nonserpentine soils and plant that hyperaccumulate heavy metals have been well documented. Heavy metal concentrations of serpentine soils may also have serious implications for public health. To truly understand the mechanisms for these processes, it is important to understand the microbial community. Also, serpentine soils may also be a benchmark for revegetation and restoration of other heavy metal contaminated sites, such as mine spoils. Again, knowledge of the microbial community could provide valuable insight into the ecosystem processes. However, almost nothing is known of serpentine microbial communities. We compared soil properties and microbial communities in 562 samples of serpentine and nonserpentine soils at McLaughlin Natural Reserve in the California Coastal Range and at a restoration site in Colusa County, Ca. Using correspondence analysis, it was possible to see that serpentine soils were high in Mg and low in Ca, positively correlated with Co, Ni, and pH levels, but negatively correlated with Fe, P, Na, Mn, Zn, K, Cu, H, S, B, and organic matter. Microbial communities (by phospholipid fatty acid analysis) differed substantially between serpentine and adjacent nonserpentine soils. Serpentine communities had a high relative proportion of actinomycete and a low proportion of fungal biomarkers. These results suggest the chemistry and vegetation of serpentine soils select for unique microbial communities. Future work will examine nitrogen cycling on serpentine soils.

*** Member of the DEB graduate group**

## C. "DNA Damage Checkpoints and Recombinational Repair"

**Edwin Haghnazari*, Vladimir Bashkirov, and Wolf-Dietrich Heyer**
Sections of Microbiology and of Molecular and Cellular Biology,
Center for Genetics and Development
University of California, Davis

DNA damage and replication block checkpoints serve as surveillance mechanisms that sense alterations in the integrity of the DNA and, in response to such DNA damage, coordinate the subsequent cellular events. Among other cellular events, these checkpoints are required for cell cycle arrest, transcriptional induction of DNA repair genes, and slowing down of late-firing DNA replication origins. These checkpoint-mediated processes ensure the proper and accurate repair and propagation of the genetic material, an absolute requirement for the continuity of life.

Of the different types of damage that the DNA of all living organisms is subjected to daily, double-strand breaks (DSBs) are the most detrimental. DSBs arise when both strands of the double helix are broken in close vicinity. If not repaired, this type of genotoxic lesion will result in chromosome loss and death. DSBs are repaired by several different pathways, and we focus on one of the pathways; the evolutionary conserved *RAD52* recombinational repair pathway.

It was discovered in our laboratory that one of the repair proteins in this pathway, the *Saccharomyces cerevisiae* Rad55 protein, becomes phosphorylated in response to damage, and we further showed that this phosphorylation is checkpoint-dependent. To further investigate the direct involvement of DNA checkpoints in recombinational repair, we utilized a plasmid double-strand gap repair assay. We have found that checkpoint mutants, in particular *mec1* and *rad53*, two conserved kinases in the damage signaling cascade with human homologs ATR and CHK2, respectively, are defective in the efficiency of the gap repair. We also discovered that checkpoint mutants alter the outcome of the repair products: whereas in wild-type cells most repair events occur through gene conversion not associated with crossover, in *mec1*and *rad53* cells most of the events occur with crossovers. We are currently trying to identify the kinase target(s) involved at the resolution stage of the Holliday junction, a late intermediate that can be resolved alternatively. Our data suggest a direct and active role for DNA damage checkpoints in the efficiency and outcome of recombinational DNA repair.

*** Member of the DEB graduate group**

## D. "Lack of Catabolite Repression in a Lactic Acid Bacterium: A New Opportunity to Maximizing Efficiency of Biomass Utilization"

**Jae-Han Kim, David A. Mills, David E. Block, and Sharon P. Shoemaker**
Department of Food Science and Technology, Department of Viticulture and Enology, and California Institute of Food and Agricultural Research
University of California, Davis

Microbial production of lactic acid by stirred tank fermentation has been extensively studied but only recently from carbon sources derived from biomass. In contrast to the cornstarch based biomass, lignocellulosic polysaccharides comprises not only glucose in the form of cellulose but also a considerable amount of pentoses from hemicellulose. Therefore, the use of biomass-derived polysaccharides requires that the fermentation microorganism co-utilize both hexoses and pentoses without carbon catabolite repression. After screening of several lactobacillus isolates, *Lactobacillus brevis* was found to co-utilize both glucose and xylose. Further evaluation showed that multiple independent isolates of *L. brevis* possess this trait. Moreover *L. brevis* apparently co-ferments with glucose any sugar which it can ferment as a sole carbon source. This observation suggests that *L. brevis* does not have obvious carbon catabolite repression. In studies with mixtures of glucose, xylose and arabinose, *L. brevis* was shown to simultaneously utilize all three carbohydrates. Total carbohydrate utilization rates and cell growth rates were not affected by the composition of carbohydrates. Fermentations using rice straw hydrolyzate also exhibited the co-utilization pattern observed in rich media. In conclusion, *L. brevis* was found to utilize all of the sugars present in rice straw hydrolysate simultaneously and the total utilization rates and fermentation behavior were not affected by the presence of other plant constituents in the culture medium.

This research has been supported by a grant from the U.S. Department of Energy Office of Biomss Program.

## E. "Putative *in silico* Mapping of DNA Sequences to Livestock Genome Maps Using SSLP Flanking Sequences"

**Charles R. Farber and Juan F. Medrano**
Department of Animal Science
University of California, Davis

In this study, an *in silico* approach was developed to identify homologies existing between livestock microsatellite flanking sequences and GenBank nucleotide sequences. Initially, 1955 bovine, 1570 porcine and 1121 chicken microsatellites were downloaded and the flanking sequences were compared to the nr and dbEST databases of GenBank. A total of 74 bovine, 44 porcine and 37 chicken microsatellite flanking sequences passed our criteria and had at least one significant match to human genomic sequence, genes/expressed sequence tags (ESTs) or both. GenBank annotation and BLAT searches of the UCSC human genome assembly revealed that 38 bovine, 13 porcine and 17 chicken microsatellite flanking sequences were highly similar to known human genes. Map locations were available for 67 bovine, 44 porcine and 21 chicken microsatellite flanking sequences, providing useful links in the comparative maps of humans and livestock. In support of our approach, 112 alignments with both microsatellite and match mapping information were located in the expected chromosomal regions based on previously reported syntenic relationships. The development of this *in silico* mapping approach has significantly increased the number of genes and EST sequences anchored to the bovine, porcine and chicken genome maps and the number of links in various human-livestock comparative maps.

UCDAVIS Biotechnology Program

# Company Affiliates

Company Affiliates* Support Biotech at UC Davis

- Genentech
- Monsanto, Calgene Campus
- Novozymes Biotech, Inc
- Scios, Inc.

*These Biotechnology companies have donated at least $15,000 per year for a Biotechnology fellowship, have offered an internship site for our Biotechnology graduate students and have presented at the annual Biotechnology Training Retreat. Company representatives also serve as advisors for training grants and other educational programs.

**The success of our programs depend on the continued support of our affiliates and the Biotechnology Program would like to thank them for their continued support.**

**Genentech**
Contact: TBA
1 DNA Way
South San Francisco, CA 94080-4990

Founded in 1976, Genentech was the pioneer in the field of biotechnology. Thirteen of the approved products in biotechnology stem from our science. Genentech, Inc. was founded by venture capitalist Robert A. Swanson and biochemist Dr. Herbert W. Boyer. In the early 1970s, Boyer and geneticist Stanley Cohen pioneered a new scientific field called recombinant DNA technology.

Fourteen of the approved products in biotechnology stem from Genentech science. Genentech manufactures and markets nine protein-based pharmaceuticals. Some are listed below:

**I. BioOncology:**

Herceptin®(Trastuzumab) Anti-HER2 antibody: For the treatment of metastatic breast cancer in HER2 overexpressed tumors.

Rituxan (Rituximab) Anti-CD20 antibody: For the treatment of relapsed or refractor low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma.

**II. Cardiovascular:**

TNKase™ (Tenecteplase)
Single-bolus thrombolytic agent: For the treatment of acute myocardial infarction (AMI).

Activase®(Alteplase, recombinant) A tissue-plasminogen activator: For the treatment of AMI, acute ischemic stroke and acute massive pulmonary embolism.

**Mosanto-Calgene Campus**
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Calgene was founded in 1980 and is perhaps best known for the development of the first commercialized genetically engineered food, the FLAVR SAVR tomato. Monsanto acquired Calgene in 1997 and it is now a research and development site within Monsanto AG. Current research at Calgene focuses primarily on improving quality traits for feed and food, as well as nutritional approaches for the enhancement of health. Calgene has approximately 100 employees and it is the primary site within Monsanto for the canola biotech pipeline. Current projects include increasing the value of field crops by optimizing the micronutrient and oil profile of the grain. Several genomic-based approaches are being utilized for gene discovery. Functionality of candidate genes is then assessed in model systems. Examples of the use of genomic-based approaches to identify interesting gene leads will be presented.

**Monsanto provides a wide array of integrated solutions to help meet the needs of growers and commercial customers who need to control unwanted vegetation safely and effectively. Monsanto also provides products to the dairy industry to increase the efficiency of milk production, and seeds for several cropping systems.**

**Novozymes Biotech, Inc**
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Enzymes are the natural solution to industrial problems. With enzymes we can reduce the consumption of water, energy and harmful chemicals and still make production more efficient. Novozymes is the world leader in enzyme solutions. Based on an advanced biotech platform we produce and sell more than 500 enzyme products in 120 countries. Since 1941 Novozymes has introduced almost every new industrial enzyme on the market, making us the world's largest manufacturer of enzymes today. With our minds set on innovation, we will continue to be so in the future.

Novozymes has introduced, with few exceptions, every new enzyme to the industry, from lipases, which remove grease stains during washing, to amylases, which are used to manufacture sweeteners. In our work we use the following technologies: microbiology, bioinformatics, gene technology, protein chemistry, computer chemistry, directed evolution, fermentation and recovery technology.

**Scios, Inc.**
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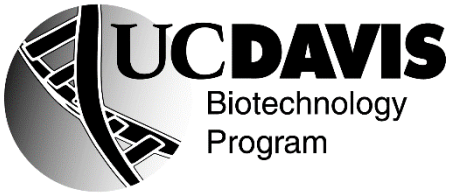
The overall objective of Scios' research program is to discover innovative new treatments for specific cardiorenal and inflammatory diseases and Alzheimer's disease. These disease areas are associated with substantial unmet medical needs. Scios scientists have developed an in-depth understanding of the molecular basis of these diseases and have discovered numerous product candidates, including those currently in the Scios clinical development pipeline.

The application of advanced technologies in the traditional areas of cellular and molecular biology, protein chemistry, medicinal chemistry, and pharmacology supports the ongoing discovery process. Over recent years, the Company has taken steps to develop and apply state-of-the-art platform technologies to facilitate the discovery of naturally occurring proteins and novel small molecules that can serve as potential new therapeutic agents. These technologies include genomics, combinatorial chemistry, high throughput screening and advanced models of diseases of interest. The application of these technologies has factored centrally in our success with numerous projects, like our P38-Kinase inhibitor program. In less than two years, our scientists have applied these

advanced methods to identify highly potent and selective inhibitors of this key pro-inflammatory enzyme.



# Invited Companies (prospective affiliates)

**Agilent Technologies**
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## Fingerprints of Pathology: The Use of Protein Arrays to Characterize Auto-Antibody Responses from Human Sera

The causes of many autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus are unknown and there are currently no definitive diagnostic tests. Furthermore, there are no known markers for these diseases that can be monitored in real time to assess the effect of any treatment. These diseases probably represent a collection of defects that give rise to similar symptoms. Simultaneous and serial measurements of hundreds of proteins in the blood are needed to make a differential diagnosis and to discover novel patterns that would define the disease. Protein arrays offer an elegant approach to accomplish this.

Agilent is one of the few companies with the raw resources and talent to optimize protein arrays in a very short time frame and we can only accomplish this with interactions with academic thought leaders and content providers. A protein array platform would complement our existing DNA and oligonucleotide technologies as well as create more accessibility of our existing gas chromatography and mass spectrometry technologies to the molecular medicine community.

We have made arrays containing peptides, and antibodies, that can detect markers for autoimmune diseases in humans and in animal models. In addition, we have used these arrays to detect many markers for other pathologies such as stroke and myocardial infarction, demonstrating known and novel makers.

**BioXing, Inc.**
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## Integrated Informatics Data System Architectural Requirements and Bottlenecks

Advanced genomic and proteomic technologies have dramatically increased the amount and complexity of statistical data. Requirements for validating these statistical results include performing orthogonal experiments, advanced analysis tools and electronic management of the entire laboratory workflow. Improving the speed and efficiency of analyzing data and correlating information requires integration, flexibility and control of experimental design and data derived from multiple instruments, data types and different locations. An overview of the architecture for the next generation informatics data system that provides an umbrella for combining laboratory tracking across multiple instrument technologies with an electronic laboratory notebook that supports annotation, data mining from disparate data sets and linking to knowledge databases will be presented. The role of XML and XSL/XSLT to help remove workflow automation bottlenecks will also be presented.

References:
Smietana, P; Mansfield, E; Current Requirements for Informatics Data Systems for Drug Discovery and Development. *PharmaGenomics* **2003**, *Volume 3 Number 1:* 38-48.

**Ciphergen Biosystems, Inc.**
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510-364-3155
jzhu@ciphergen.com

## ProteinChip® TECHNOLOGY – AN INTEGRATED PLATFORM FOR PROTEOMIC RESEARCH

**Jing Zhu, Tracey Kalb-Scherer**
Ciphergen Biosystems, Fremont, CA, 94555

ProteinChip® technology, also known as Surface Enhanced Laser Desorption/Ionization, or SELDI, is a sensitive and versatile protein analysis tool for clinical, basic and process proteomic research. The SELDI platform is composed of ProteinChip® arrays and the ProteinChip® Reader, which is a laser desorption/ionization time of flight (LDI-TOF) mass spectrometer for protein detection, and the ProteinChip® Peaks Software. The ProteinChip® arrays utilize various chemistries and biologically active surfaces to capture proteins of interest. Crude biological samples are spotted directly on to the arrays. Proteins are selectively retained on the array surfaces by retentate chromotography along with the use of various buffers to remove unbound proteins and other elements of the original sample. The retained proteins are then detected in the ProteinChip® Reader and the spectra read and analyzed with the ProteinChip® Peaks Software. The entire process takes roughly 2 to 3 hours. The technology is unique in its ability to analyze trace analytes (low femtomole) from crude, low-volume samples. It can also be use to develop sensitive, quantitative and high throughput assays. ProteinChip® technology enables fast and reproducible studies for biomarker discovery, validation, identification and characterization, to answer a wide variety of biological and clinical questions.

**FibroGen, Inc.**
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jbaez@fibrogen.com

## Fibrogen

FibroGen, Inc., is a private biotechnology company developing novel drugs to arrest fibrotic diseases in both chronic and acute conditions, such as renal and liver fibrosis, as well as the fibrotic complications of diabetes, for which there are no therapies today. Additionally, leveraging its knowledge of extracellular matrix biology, FibroGen has developed the only known commercially viable method for production of recombinant human collagens as well as specific synthetic gelatins based on portions of collagen molecules. Collagens and gelatins are sourced today from animal tissue and are widely used by the pharmaceutical, medical device, technology and food industries.

**Large Scale Biology Corporation**
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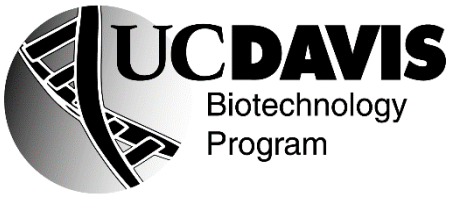
## NaviGene™: A Visual Analysis Tool for Genetic Reassortment

We introduce NaviGene™, a flexible Web-based visual analysis tool for nucleotide and protein sequence comparisons that may be readily applied as a user front-end to a wide range of applications. NaviGene™ features the flexible upload and retrieval of data through file upload, Web forms, or direct database access. It integrates sequence alignment and translation to afford simultaneous analysis of nucleotide sequence and its corresponding protein translation, which can then be correlated with assay data to establish structural and functional relationships. Further structural analysis is provided through a visual display of the amino-acid inheritance pattern mapped onto three-dimensional protein structure. By interfacing to a relational database containing all relevant experimental information, NaviGene™ also produces views of chromatograms and Phred scores by which the quality of candidate information transfer regions can be readily assessed, assisting in the selection of ideal candidates for further exploration.
Here, we illustrate the utility of NaviGene™ in the visual analysis of genetic reassortment, or "DNA shuffling" experiments. Even with very large data sets, the user may see at a glance both the nucleotide and translated protein sequence alignments. Results are presented both in an overview and in detailed views. The overviews allow immediate comparisons of the daughters to each other, while separate detailed views provide a comparison of each daughter to its parents. With this combination of views, the user can readily identify areas of information transfer marking the boundaries of nucleotide blocks inherited from different parents, indicating the degree of shuffling of each sequence. In addition, statistics are compiled and displayed for degree of shuffling, sequence identity scores, and mutation frequencies. This combination of visual tools affords a quick analysis of the experimental results, and rapid identification of promising new sequences with desired genetic properties.




# Participants

## Participants

| NIH Fellows (2002-2003) | Department/Organization |
|---|---|
| Chad Green | Biomedical Engineering |
| Ryann Muir | Pomology |
| Marisa Wong | Animal Science |
| Scott Wong | Med: Pathology |

| Biotech Fellows (2002-2003) | Department/Organization |
|---|---|
| Amanda Ellsmore | Molecular & Cellular Biology |
| Larry Joh | Biological & Agricultural Engineering |

**Graduate students/post docs**

| | |
|---|---|
| Michelle Adams | Division of Infectious Diseases & Immunity |
| Tiffany Chaddock | Division of Infectious Diseases & Immunity |
| Debra Conte | Division of Infectious Diseases & Immunity |
| Shira DeGrood | LAWR |
| Melissa Dominguez | Division of Infectious Diseases & Immunity |
| Charles Farber | Animal Science |
| Mary Guadalupe | Comparative Pathology |
| Angelica Giuffre | Comparative Medicine |
| Edwin Haghnazari | Microbiology |
| Ashley Harvey | Chemistry |
| Ze He | Chemistry |
| Lei Hua | Food Science & Technology |
| Shanna Iudice | Division of Infectious Diseases & Immunity |
| Jae-Han Kim | California Institute of Food & Agriculture Research, CIFAR |
| Viyada Kunathigan | Viticulture & Enology |
| Rhond McNeely | Division of Infectious Diseases & Immunity |
| Marcus Newman | Division of Infectious Diseases & Immunity |
| Kazunari Nozue | Molecular & Cellular Biology |
| Ahn Phung | Med: Internal Medicine |
| Vidhaya Ramakrishnan | Viticulture & Enology |
| Russell Reagan | Vegetable Crops |
| Juan Silva | Division of Infectious Diseases & Immunity |
| Lucy Stewart | Plant Biology |
| Mars Stone | Microbiology |
| Jennifer Taylor | Comparative Pathology |
| Alexey Tomilov | Vegetable Crops |
| Natalia Tomilova | Vegetable Crops |
| Manuel Torres | Vegetable Crops |
| Paulo Verardi | Vet Med: ILMB |
| Jennifer Weidhaas | Civil & Environmental Engineering |

| | |
|---|---|
| Qing Xie | Chemical Engineering & Materials Science |
| Melinda Zaragoza | School of Med: Internal Medicine |

**Faculty**

| | |
|---|---|
| George Bruening | Plant Pathology |
| Dan Chang | Civil & Environmental Engineering |
| Gussie Curran | UC Systemwide Biotechnology Research and Education Program |
| Abhaya Dandekar | Pomology |
| Katyoon (Katy) Dehesh | Plant Biology |
| Bruce Hammock | Entomology & Cancer Research Center |
| Clark Lagarias | Plant Biology |
| Kit Lam | Hematology & Oncology |
| Juan Medrano | Animal Science |
| Karen McDonald | Chemical Engineering & Materials Science |
| Kay Nelson | Internship & Career Center |
| Martina Newell-McGloughlin | UC Systemwide Biotechnology Research and Education Program/Plant Pathology |
| Jean VanderGheynst | Biological & Agricultural Engineering |
| Tilahun Yilma | Vet Med: ILMB |
| John Yoder | Vegetable Crops |

**Affiliated Companies**

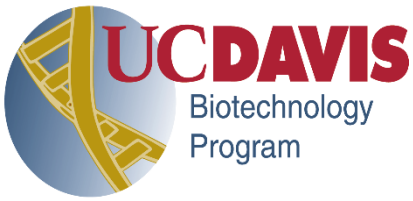
| | |
|---|---|
| Genentech | TBA |
| Novozymes Biotech, Inc. | Joel Cherry |
| Scios, In. | Aaron Nguyen |

**Guests**

| | |
|---|---|
| Agilent Technologies | David Hirschberg, Xiaohua Huang, Khanh Nguyen, Maggie Ostrowski, Uyen Truong |
| BioXing, Inc. | Pete Smietana |
| California Department of Food & Agriculture | Mimi Sen |
| California Institute of Food & Agricultural Research, CIFAR | Sharon Shoemaker |
| Ciphergen Biosystems, Inc. | Tracy Kalb-Scherer, Jing Zhu |
| Division of Infectious Diseases & Immunity, Modesto Community College | Doug Kain, Carmen Rexach-Zellhoefer |
| FibroGen | Julio Baez |
| Large Scale Biology | Keith Ball |

**UC Davis Biotechnology Program (Coordinators of the Retreat)**

| | |
|---|---|
| Judith Kjelstrom | Acting Director |
| Jennifer Lee | Event Manager |




www.biotech.ucdavis.edu

The Mission of the Biotechnology Program:

To assist in the organization of University activities related to biotechnology and to coordinate such activities with other efforts on the Davis campus, a Biotechnology Program was created. The Program's missions include:

- Promoting and coordinating the development of biotechnology and biotechnology-related research on the campus;
- Assisting with development of new and improved facilities for biotechnology research;
- Promoting research interactions between faculty and private industry and public agencies;
- Recommending and implementing curriculum development and training in biotechnology;
- Serving as an information and education resource on biotechnology for the campus and the public.

**Biotechnology Program Office**:

Dr. Judith Kjelstrom, Acting Director, and the staff run the program from the offices in 301 Life Sciences Addition.

Telephone: (530) 752-3260
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Email: biotechprogram@ucdavis.edu

# *Interested in Biotechnology?*

## *Award of NIH Training Grant in Biomolecular Technology*
## *July 1, 2002*

UC Davis has been awarded a prestigious NIH training grant in biomolecular technology in recognition of the quality of multidisciplinary research and training provided by the campus. The grant is under the directorship of Bruce Hammock, Department of Entomology, and The Cancer Research Center with co-directors Rosemary Smith, Department of Electrical and Computer Engineering; and Martina Newell-McGloughlin, UC Systemwide Biotechnology Program, and Department of Plant Pathology.

The name, Biomolecular Technology, is chosen to reflect the emphasis of the program as an area of scientific endeavor which is characterized by the following three elements:

1. emphasis on the analysis of model systems of obvious significance to medicine and biotechnology;
2. the synthesis of information and research approaches from disciplines such as cellular physiology, genetics, physical biochemistry, and chemical engineering; and
3. the translation of biological information into a quantitative framework.

Through this focus the program provides well-coordinated multidisciplinary training of predoctoral graduate students in critical areas of biotechnology research and a structure for interdisciplinary research environments that integrate basic biological science and engineering disciplines as well as academic and industrial experiences. The program is designed to recruit and support trainees who show exceptional promise coupled with the drive to reach out across disciplines and forge new research directions in biotechnology.

## Designated Emphasis in Biotechnology
### *http://www.deb.ucdavis.edu*

The Designated Emphasis in Biotechnology (DEB) is an inter-graduate group program that allows Ph.D. students to receive and be credited for training in the area of biotechnology. The UCD Biotechnology Program is the administrative home for this program. You may become a member of the DEB Program even if you are not funded on the NIH Training Grant.

DEB Mission:

- To provide well-coordinated, cross-disciplinary training of graduate students in critical areas of biomolecular technology research.
- To promote interdisciplinary research environments that integrate basic biological science, engineering and computational disciplines.
- To allow cross-disciplinary training and trainee experience in cross-college or biotech company laboratories.

Students come from a wide array of disciplines: Biochemistry & Molecular Biology, Biological & Agricultural Engineering, Cell & Developmental Biology, Chemical Engineering, Comparative Pathology, Entomology, Genetics, Microbiology, Plant Biology, Plant Pathology, Statistics, etc. This program supplements a student's Ph.D. curriculum and those completing the DEB program will obtain an official designation on their diploma & transcript indicating a qualification in biotechnology. Example: Doctoral Degree in Microbiology with a Designated Emphasis in Biotechnology

For more information, please contact
Dr. Judith A. Kjelstrom, Program Coordinator
(530) 752-8228 or at jakjelstrom@ucdavis.edu.

# *NIH Training Grant Faculty*

Directorship of Bruce Hammock. Co-Directors are Rosemary Smith and Martina Newell-McGloughlin

Gary Anderson (Animal Science)
Matthew Augustine (Chemistry)
Enoch Baldwin (MCB/Chemistry)
Craig Benham (Mathematics/Biomedical Engineering)
George Bruening (Plant Pathology)
Alan Buckpitt (Vet Med: Molecular Biosciences)
Kenneth Burtis (MCB-Molecular & Cellular Biology)
Daniel Chang (Civil & Environmental Engineering)
Abhaya Dandekar (Pomology) [also DEB chair]
Michael Denison (Environmental Toxicology)
Bryce Falk (Plant Pathology)
Katherine Ferrara (Biomedical Engineering)
Andrew Fisher (MCB/Chemistry)
Jeff Gregg (MED: Pathology)
Daniel Gusfield (Computer Science)
Alan Jackman (Chem Engineering & Materials Science
Ian Kennedy (Mechanical & Aeronautical Engineering)
Hsing-Jien Kung (MED: Internal Medicine)
J. Clark Lagarias (MCB)
Kit Lam (MED: Internal Medincine (Hem/Onc)
K. C. Kent Lloyd (Vet Med: Anatomy, Physiology & Cell Biology)
Karen McDonald (Chem Engineering & Materials Science)
Claude Meares (Chemistry)
Juan Medrano (Animal Science)
Richard Michelmore (Vegetable Crops)
James Murray (Animal Science)
Martin Privalsky (Microbiology)
Robert Rice (Environmental Toxicology)
David Rocke (Applied Science. MED: Epidemiology & Preventative Medicine)
Kate Scow (Land, Air & Water Resources)
Scott Simon (Biomedical Engineering)
Jean VanderGheynst (Biological Systems Engineering)
Craig Warden (NPB/ MED: Pediatrics)
David Wilson (MCB)
John Yoder (Vegetable Crops)

# *NIH Training Program in Biomolecular Technology*

- The DEB is a **formal training program** for the NIH Training Grant.
- The DEB provides **training and a structure for interdisciplinary interactions**, in addition to our established graduate programs.
- The DEB provide a **formal accreditation** (on diploma & transcript) to reflect biotechnology training in cross-disciplines.
- Not all the DEB students will be part of the NIH Biotechnology Training Program. The fellows are a **select subset** based on a highly competitive nomination & selection process:
  - –Nomination by a Faculty Trainer and completion of an application by the student
  - –Ranking by the Executive Committee of the Program. It is based on: **academic merit; quality of the research; interdisciplinary nature of research; and willingness to complete an internship.**

# *Designated Emphasis in Biotechnology Program (DEB)*

**Description**

The Designated Emphasis in Biotechnology (DEB) is an inter-graduate group program that allows Ph.D. students to receive and be credited for training in the area of biotechnology. The UCD Biotechnology Program is the administrative home for this program.

DEB Mission:

- To provide well-coordinated, cross-disciplinary training of graduate students in critical areas of biomolecular technology research.
- To promote interdisciplinary research environments that integrate basic biological science, engineering and computational disciplines.
- To allow cross-disciplinary training and trainee experience in cross-college or biotech company laboratories.

Students come from a wide array of disciplines: Biochemistry & Molecular Biology, Biological & Agricultural Engineering, Cell & Developmental Biology, Chemical Engineering, Comparative Pathology, Entomology, Genetics, Microbiology, Plant Biology, Plant Pathology, Statistics, etc. This program supplements a student's Ph.D. curriculum and those completing the DEB program will obtain an official designation on their diploma & transcript indicating a qualification in biotechnology.

Example: Doctoral Degree in Microbiology with a Designated Emphasis in Biotechnology

## For more information

**DEB program: www.deb.ucdavis.edu**
**UC Davis Biotechnology Program:** www.biotech.ucdavis.edu

# *Designated Emphasis in Biotechnology Program (DEB) Curriculum*

MCB/ECH 294 Seminar Series (3 quarters)* – Current Progress in Biotechnology - to introduce students to vocabulary. *MIC 292 may substitute for 1 quarter.

MCB 263 - Biotechnology Fundamentals & Application

GGG 296 – Scientific Integrity & Professionalism

MCB 282 – 3-6 month Internship (usually completed after qualifying exam). Biotech Company is preferred site.

The DEB program offers guidance and assistance in career development, oral presentations, editing of cover letters and curriculum vitae, and acts as ombudsman to help resolve other issues that arise during the student's tenure.

# *DEB Program Students 2002-2003*

| | |
|---|---|
| Shira Bell-DeGrood | Land, Air and Water |
| Kenneth Chan | VM: PMI/ILMB |
| Blythe Durbin | Statistics |
| Amanda Ellsmore | Plant Biology |
| Amanda Enstrom | MED: Internal Med: Hem/Onc |
| Brian Gierhart | Electrical Engineering |
| Angelica Giuffre | Microbiology |
| Chad Green | Biomedical Engineering |
| Moraima Guadalupe | Med. Microbiology & Immunology |
| Edwin Haghnazari | Microbiology |
| Ashley Harvey | Chem Eng & Materials Science |
| Ze He | Chemistry |
| Laura Higgins | Physiology |
| Alberto Iandolino | Viticulture & Enology |
| Aminah Ikner | Microbiology |
| Denneal Jamison-McClung | Vegetable Crops |
| Larry Joh | Bio & Ag Engineering |
| Kyung-Don Kang | Entomology |
| Kavita Karighattam | Plant Biology |
| Susanne Kuhlman | Microbiology (medical) |
| Viyada Kunathigan | Viticulture & Enology |
| Young Lee | MED:Hem & Onc |
| Artem Loukoianov | Agronomy and Range Sciences |
| Leah McHale | Veg Crops |
| Ryann Muir | Pomology |
| Sinyoung Park | Chem Engr & Materials Science |
| Anh Phung | MED: Internal Medicine |
| Vidhya Ramakrishnan | Viticulture & Enology |
| Wade Reh | Animal Science |
| Sheetal Singh | Food Science & Technology |
| Yuan (Sophia) Tang | Electrical Engineering (BioMEMS) |
| Jennifer Taylor | MED: Internal Medicine |
| Manuel Torres | Vegetable Crops |
| Wei Wan | VM:PMI |
| Jennifer Weidhaas | Civil and Environmental Engineering |
| Marisa Wong | Animal Science |
| Scott Wong | MED:Pathology |
| Melinda Zaragoza | Microbiology |

# *DEB Participating Faculty*

**Agricultural & Environmental Chemistry**
Everett Bandman
Andrew J. Clifford
J. Bruce German
You-Lo Hsieh
Annie J. King
Bruce Hammock
Fumio Matsumura
Tadeusz Molinski
David S. Reid
Dewey Ryu
Kate Scow

**Biochemistry & Molecular Biology**
Everett Bandman
Alan Bennett
Linda Bisson
Richard Bostock
George Bruening
Ken Burtis
Ronald Chuang
Gino Cortopassi
Michael Dahmus
Michael Denison
Roy Doi
Paul FitzGerald
Charles Gasser
Bruce Hammock
John Harada
Jerry Hedrick
John Hershey
Michele Igo
Thomas Jue
Clarence Kado
Hsing-Jien Kung
John Labavitch
Clark Lagarias
Kit Lam
Harry Matthews
Claude Meares
Stanley Meizel
Tadeusz Molinski
Marty Privalsky
Kathryn Radke
Robert Rice
Pam Ronald
Robert Rucker
Dewey Ryu
Kazuhiro Shiozaki
Frederic Troy
Brett Tyler
Thea Wilkins
Valerie Williamson
David Wilson
John Yoder

**Biological Systems Engineering**
*(formerly "Biological & Agricultural Engineering")*
Michael Delwich
John Krochta
David Slaughter
Jean VanderGheynst
Ruihong Zhang

**Biomedical Engineering**
Craig Benham
Fitz-Roy Curry
Katherine Ferrara
Jeffery Gibeling
Ian Kennedy
Tonya Kuhl
Kit Lam
Marjorie Longo
Dewey Ryu
Scott Simon
Rosemary Smith

**Biophysics**
Enoch Baldwin
Abdul Barakat
Ron Baskin
Craig Benham
E. Morton Bradbury

# *DEB Participating Faculty*

R. David Britt
Tsung-Yu Chen
Daniel Cox
Stephen P. Cramer
John H. Crowe
Thorsten Dieckmann
Robert H. Fairclough
William H. Fink
Andrew Fisher
Ching Yao Fong
Jerry L. Hedrick
Michael F. Insana
Niels Jensen
Thomas Jue
Stephen C. Kowalczykowski
Tonya Kuhl
Gerd N. LaMar
Janine LaSalle
Marjorie Longo
Pamela Pappone
Atulh N. Parikh
Carl W. Schmid
Scott I. Simon
Rajiv R. Singh
Alexei Stuchebrukhov
Steven M. Theg
Michael D. Toney
Frederic Troy
John V. Voss
David Wilson
Yin Yeh

**Cell & Developmental Biology**
Gary Anderson
Everett Bandman
Ron Baskin
Paul FitzGerald
Jerry Hedrick
Stanley Meizel
James Murray
Charles Plopper
Robert Rice
Reen Wu

**Chemical Engineering & Materials Science**
Stephanie Dungan
Ben McCoy
Karen McDonald
Ron Phillips
Dewey Ryu

**Chemistry**
Matthew Augustine
Alan Balch
Enoch Baldwin
Thorsten Dieckman
Andrew Fisher
Bruce Hammock
Susan Kauzlaurich
Mark Kurth
Carlito Lebrilla
Claude Meares
Tadeusz Molinski
Krishnan Nambiar
Ben Shen
Michael Toney
David Wilson

**Civil & Environmental Engineering**
Daniel Chang
Jeannie Darby
Timothy Ginn
Stefan Wuertz

**Comparative Pathology**
Naomi Balaban
Peter Barry
Jeff Gregg
Rivkah Isseroff
Kit Lam
Rance LeFebvre
Bruce Madewell
Stuart Meyers

# *DEB Participating Faculty*

Thomas North
Jay Solnick
Alice Tarantal
Jose Torres
Tilahun Yilma

**Entomology**
Bruce Hammock
Robert Page
Diane Ullman

**Environmental Toxicology**
Michael Denison
Fumio Matsumura
Barry Wilson

**Food Science**
Douglas Adams
Everett Bandman
Diane Barrett
Linda Bisson
David Block
Charles Bamforth
Christine Bruhn
Stephanie Dungan
J. Bruce German
David Ogrydziak
Robert Powell
Chester Price
David Reid
Dewey Ryu
Paul Singh
Gary Smith
Glenn Young

**Genetics**
Ursula Abbott
Alan Bennett
Linda Bisson
George Bruening
Ken Burtis
Robert Cardiff
Michael Dahmus
Abhaya Dandekar
Mary Delany
Charles Gasser
Paul Gepts
Robert Gilbertson
David Gilchrist
Tom Gradziel
John Hershey
Michele Igo
Clarence Kado
Bill Lucas
Paul Luciw
Harry Matthews
Bernie May
Richard Michelmore
James Murray
Marty Privalsky
Kathryn Radke
Pam Ronald
Michael Syvanen
Brett Tyler
Thea Wilkins
Valerie Williamson
Reen Wu
John Yoder

**Immunology**
Hilary Benton
Patricia Conrad
Eric Gershwin
Kit Lam
Paul Luciw
Dick Robbins
Jose Torres
Tilahun Yilma

**Mechanical & Aeronautical Engineering**
Ralph C. Aldredge
Abdul I. Barakat
Harry A. Dwyer
Ian Kennedy

# *DEB Participating Faculty*

Bahram Ravani
Nesrin Sarigul-Klijn
Anthony S. Wexler

**Microbiology**
Blaine Beaman
Linda Bisson
George Bruening
Robert Cardiff
Ronald Chuang
Patricia Conrad
Michael Dahmus
Satya Dandekar
Roy Doi
Eric Gershwin
John Hershey
Michele Igo
Clarence Kado
Paul Luciw
Karen McDonald
John Meeks
Thomas North
David Ogrydziak
Bennie Osburn
Niels Pedersen
Chester Price
Marty Privalsky
Kathryn Radke
Dewey Ryu
Kate Scow
Kazuhiro Shiozaki
Jay Solnick
Michael Syvanen
Jose Torres
Frederic Troy
Tilahun Yilma

**Molecular, Cellular and Integrative Physiology** *(formerly "Physiology")*
Gary Anderson
Hilary Benton
Fitz-Roy Curry
James Jones
Barry Wilson
Reen Wu

**Nutrition**
Chris Calvert
Quinton Rogers
Robert Rucker

**Pharmacology & Toxicology**
Hilary Benton
Ronald Chuang
Gino Cortopassi
Michael Denison
Teresa Fan
Bruce Hammock
Gary Henderson
Dallas Hyde
Hsing-Jien Kung
Jerold Last
Fumio Matsumura
Isaac Pessah
Charles Plopper
Robert Rice
Robert Rucker
Barry Wilson
Reen Wu

**Plant Biology**
Alan Bennett
Richard Bostock
Katayoon "Katie" Dehesh
Don Durzan
Charles Gasser
Paul Gepts
Tom Gradziel
John Labavitch
Clark Lagarias
Bill Lucas
Terence Murphy
Vito Polito
Michael Reid

# *DEB Participating Faculty*

Pam Ronald
Brett Tyler
Thea Wilkins
Valerie Williamson
John Yoder

**Plant Pathology**
Richard Bostock
George Bruening
David Gilchrist
Pam Ronald
Brett Tyler
Valerie Williamson

**Statistics**
Rahman Azari
Andrew J. Clifford
Juanjuan Fan
Shu Geng
Richard Levine
David Rocke
Jessica Utts

BIOTECHNOLOGY AT THE
UNIVERSITY OF CALIFORNIA

# *BioSTAR*

(Biotechnology Strategic Targets for Alliances in Research)

Biotechnology Strategic Targets for Alliances in Research (BioSTAR): launched Summer 1996, invests $12 million in Industry, State, and University funds in 40-45 new research partnerships every year focused on healthcare, agriculture, and natural resource

**Technology transfer & conference awards:**
Small seed grants of up to $15,000 to support activities that communicate developments in Biotechnology research at UC and in California firms, or enhance faculty, student, and staff understanding of commercial Biotechnology research, technology transfer, and opportunities for cooperative research with private sponsors, or assess and improve university approaches to technology transfer and administration of industry-sponsored research.

**Research matching grants:**
The UC BioSTAR solicits proposals for basic to proof-of-concept research in the field of Biotechnology. Applications are encouraged for new projects and for competitive renewals. All proposals will include a binding letter from a Private Sponsor, who will provide required matching funds.

**For additional information on the BioSTAR program, please see their we page at: http://www-biotech.berkeley.edu**

**UC Davis representative:**

| | |
|---|---|
| **David E. Block** | deblock@ucdavis.edu |

**Or Contact:**

| | |
|---|---|
| **David Gilbert** | dgilbert@uclink.berkeley.edu<br>(510) 643-5542 |