SEVENTH ANNUAL
BIOTECHNOLOGY
TRAINING GRANT RETREAT
CHRISTIAN BROTHERS RETREAT CENTER
NAPA VALLEY
FEBRUARY 21, 1998

PROGRAM OVERVIEW

8:15 am	Registration
8:45 am	Introduction by Dewey Ryu, Co-Director of the Training Grant
9:00 - 11:30 am	Company presentations may include brief overview of the company's mission, their research and development along project lines and/or a more in depth coverage of specific research projects. (Calgene, Chiron, Genentech, Novo Nordisk Biotech, Roche Bioscience)
11:30 - 2:00 pm	Poster Session & Lunch: Posters will be presented by new trainees, trainers and other students from trainer laboratories. There also will be opportunity for the trainees, first year fellows and other students to intermingle with the company trainers and gain a greater insight into research in the private domain and also, to develop ideas for suitable internship projects.
2:00 - 5:30 pm	Each of six faculty trainers and their present trainees will present an overview of their research projects, beginning with a short overview of the lab focus by the trainer (5 mins) and continuing with a more detailed description by the trainee (15 mins) of his/her research and ending with five minutes for questions.
5:35pm	Close

COMPLETE PROGRAM

8:15 am	Registration	
8:45 am	Introduction	— Dewey Ryu, Co -Director, Training Grant

COMPANY PRESENTATIONS

Chair	**Dewey Ryu, Chemical Engineering & Material Science**	
9:00 am	An overview of research at Calgene	— Vic Knauf, Principle Scientist, Calgene, Inc.
9:30 am	Chiron: A diversified biopharmaceutical company	— Steve Rosenberg, Senior Director, Research
	A protein fragment which functions as an angiogenesis inhibitor	— Wendy Fantl, Senior Scientist, Chiron Technologies
10:00 am	Break	
10:10 am	Genentech 1998: a view from the department of recovery sciences	— David Kahn, Senior Scientist, Genentech
10:40 am	A mycologists perspective of life as part of a multi-national biotechnology company	— Wendy Fantl, Senior Scientist, Fungal Genetics & Molecular Biology, Novo Nordisk Biotech
11:10 am	Research at Roche Bioscience	— Jim Barnett, Roche Bioscience
11:40 am	Presentation of Posters	
12:00 pm	Lunch, Discussion & Posters	
(12:45 pm	Executive Committee Meeting)	

TRAINEE AND TRAINER LAB PRESENTATIONS

Chair:	**Pat Conrad, Vet Med: Pathology, Microbiology & Immunology**	
2:00 pm	Colloidal diffusion in polymer solutions and gels	— Ron Phillips Chemical Engineering
	Diffusion of nonionic surfactants in nonionic gels	— Kristan Buck Chemical Engineering
2:25 pm	Plant defense proteins: novel	— Karen McDonald

	production methods and potential applications	Chemical Engineering
	Expression and characterization of plant defense proteins in transgenic tobacco	— Raj Krishan Chemical Engineering
2:50 pm	Overview of research	— Marty Privalsky Microbiology
	A conformational switch in nuclear hormone receptors is involved in coupling hormone binding to corepressor release	— Ben Lin Microbiology
3:15 pm	Control of growth and apoptosis by intracellular calcium signals	— Michael Hanley MED: Biological Chemistry
	Characterization of LNCaP prostate cancer cell apoptosis induced by SERCA pump inhibition	— Ingrid Wertz MED: Biological Chemistry
3:40 pm	Break	
Chair:	**George Bruening, CEPRAP**	
3:50 pm	Plant – plant communication	— John Yoder Vegetable Crops
	Subterranean plant - plant interactions: differential recognition of phenolic rhizosphere signals by parasitic plants	— Denneal Jamison Vegetable Crops
4:15 pm	What's going on in the lab.	— Bruce Hammock Entomology and Environmental Toxicology
	Insects and juvenile hormone	— Tonya Severson Entomology and Environmental Toxicology
4:40 pm	Cytoplasm to vacuole protein transport in yeast	— Daniel Klionsky Microbiology
	Characterization of the cytoplasm to vacuole targeting and autophagy pathways in *Saccharomyces cerevisiae*	— Michael George Microbiology
5:05 pm	Conclusion	— Dewey Ryu
5:30 pm	Bus departs	

POSTER TITLES

A. ENZYMATIC CONVERSION OF CELLULOSIC MATERIALS IN A CONTINUOUS STIRRED TANK REACTOR WITH AN ULTRA-FILTRATION MEMBRANE

Hanshu Ding[1], Elena Vlasenko[2], Charles Shoemaker[1] and Sharon Shoemaker[2]
1 Department of Food Science and Technology, University of California, Davis
2 California Institute of Food and Agricultural Research, Davis, CA

B. DEVELOPMENT OF NEW AFFINITY PURIFICATION OF PLANT SOLUBLE EPOXIDE HYDROLASES

Christophe Morisseau* and Bruce D. Hammock
Departments of Entomology and Chemistry, University of California, Davis

C. PESTICIDE FLUOROIMMUNOASSAYS IN ORGANIC SOLVENT, REVERSE MICELLAR SYSTEM AEROSOL OT/n-OCTANE

Evgenia G. Matveeva
A. N. Bakh Institute of Biochemistry, Russian Academy of Sciences, Moscow, Russia.
Department of Entomology and Environmental Toxicology, University of California, Davis

D. CONSTRUCTION OF RECOMBINANT BACULOVIRUS EXPRESSING INSECT SELECTIVE NEUROTOXIN FOR EFFECTIVE PEST MANAGEMENT

Rajendra Wudayagiri[1], Kevin J. Hackett[2], and Bruce D. Hammock[1]

[1]Department of Entomology, University of California, Davis
[2]Insect Biocontrol Laboratory, Beltsville, MD, 20705

E. DEVELOPMENTAL REGULATION OF INSECTS FOR APPLICATION IN BIORATIONAL PEST CONTROL.

Terri E. Young*, Andrew C. Hinton* and Tonya F. Severson
Department of Entomology, University of California, Davis

Oral Abstracts

AN OVERVIEW OF RESEARCH AT CALGENE

Vic Knauf
Vice President, Research
Calgene LLC, A Wholly Owned Subsidiary of Monsanto

Calgene was founded as an independent biotechnology company focused on higher plants and agriculture in 1980 by a Silicon Valley venture capitalist and a UCD professor. It was a publicly traded company for a little over ten years before being acquired by Monsanto in May 1997. While Calgene remains a legal entity as a wholly owned subsidiary, most activities at the Davis facility are now integral parts of Monsanto sector businesses and are principally research and development in nature. The research scientist staff will grow by about 25% in 1998. We will likely break ground on new greenhouse facilities in 1998 as part of a long range plan for a new & larger laboratory facility to be operational by years 2001-2002. University-owned land remains one option for the eventual location of the new "West Coast" research center for Monsanto. This presentation will outline some of the current research capabilities and objectives in two sectors, Nutrition & Consumer Products and Agriculture, and the role of the Calgene campus supporting these objectives in collaboration with sister labs in St. Louis, Chicago, and San Diego.

CHIRON: A DIVERSIFIED BIOPHARMACEUTICAL COMPANY

Steve Rosenberg
Senior Director, Research
Chiron Technologies

A PROTEIN FRAGMENT WHICH FUNCTIONS AS AN ANGIOGENESIS INHIBITOR

Wendy Fantl
Senior Scientist
Chiron Technologies

Chiron is a diversified biopharmaceutical company with businesses in vaccines, diagnostics, and therapeutics, with a focus on infectious diseases, oncology, critical care, and cardiovascular disease. Chiron's central research effort, Chiron Technologies, uses three methodologies, recombinant protein production, gene therapy, and combinatorial chemistry to discover and develop new products for unmet medical needs. The targets for these efforts are discovered using high throughput functional gene discovery. In addition, this group has the mandate to develop new technologies which can be used in the diagnosis, prevention, and treatment of human disease. Examples of both present products and future directions will be presented.

GENENTECH 1998: A VIEW FROM THE DEPARTMENT OF RECOVERY SCIENCES

David Kahn
Senior Scientist
Genentech

This talk will attempt to present an overview of the current R&D pipeline for Genentech. An update regarding Genentech's marketed products, as well as the status, and rationale, behind molecules which are currently in clinical trials will be presented. Current areas of focus for discovery research will also be discussed.

In addition to the broad discussion outlined above, the second portion of the talk will attempt, more specifically, to relate the perspective and role of the Recovery Sciences department. The primary responsibility of this group is the development of scalable purification (recovery) processes. Recovery Sciences is uniquely positioned within Genentech in that we deal routinely with scientists early in the development process (i.e. discovery research) as well as teams of scientists and engineers involved in implementing our processes in a manufacturing facility. It is hoped that profiling the challenges and responsibilities of this position will serve the useful purpose of exposing biotechnology students to alternate career paths appropriate for their training.

A MYCOLOGISTS PERSPECTIVE OF LIFE AS PART OF A MULTI-NATIONAL BIOTECHNOLOGY COMPANY

Wendy Yoder
Senior Scientist,
Fungal Genetics & Molecular Biology,
Novo Nordisk Biotech

Novo Nordisk Biotech, Inc., located in Davis, California, is a wholly-owned research and development subsidiary of Novo Nordisk A/S, the world's largest producer of industrial enzymes. Novo Nordisk A/S is also the world leader in the development and manufacturing of insulin as well as other diabetes care product products.

Established in 1992, Novo Nordisk Biotech, Inc., is the U.S. research arm of Novo Nordisk A/S 's Enzyme Business. Novo Nordisk Biotech, Inc. employees scientists in the fields of molecular biology, protein chemistry, microbiology, and microbial physiology. Novo Nordisk Biotech, Inc. emphasizes research in identifying and engineering new industrial enzymes as well as improving the manufacturing process for new and existing enzymes. Novo Nordisk Biotech, Inc. collaborates with other Novo Nordisk A/S research groups in Denmark, the United States, and Japan. The company also has collaborations with University of California, Davis as well as with other academic labs world-wide.

Head quartered in Denmark, Novo Nordisk A/S employs approximately 13,200 people in 53 countries and markets its products in 140 countries.

RESEARCH AT ROCHE BIOSCIENCE

Jim Barnett
Research Section Leader
Roche Bioscience

Roche Bioscience is a research-based, business-oriented enterprise dedicated to the discovery of innovative pharmaceutical products that significantly improve the quality of human life. Our mission is to lead the industry in this effort through research excellence and the cost-effective, timely delivery of novel drugs.

Roche Bioscience was formed in 1995 following the acquisition of Syntex Corporation by Roche Holding Ltd. Established in 1944, Syntex was best known for innovation in the synthesis of steroidal and nonsteroidal compounds. Syntex scientists were world leaders in the research and development of corticosteroids to treat dermatological conditions and for the synthesis of compounds leading to the development of oral contraceptives.

COLLOIDAL DIFFUSION IN POLYMER SOLUTIONS AND GELS

Ronald J. Phillips
Department of Chemical Engineering and Materials Science, University of California, Davis

The diffusion of globular proteins, colloidal particles and colloidal aggregates (i.e., micelles) in polymer solutions and gels is of central importance in many bioseparation and controlled release strategies. The diffusion process itself can be separated into two components: a thermodynamic driving force (i.e., the gradient in the chemical potential) that causes solute to move from regions of high concentration to low concentration; and a hydrodynamic drag force or resistance that results from the solute moving through a viscous fluid. In a pure solvent at very low solute concentrations, this representation of diffusion leads to the well-known Stokes-Einstein equation. However, for diffusion in media that consist of a solvent plus crosslinked polymer (i.e., a polymer gel) or uncrosslinked polymer (i.e., a polymer solution), and for non-dilute solute concentrations, both the thermodynamic driving force and hydrodynamic resistance are altered. In our research group, we are performing experiments and doing theoretical calculations to develop a fundamental understanding of how diffusion is affected by such complex environments. Our experiments consist of directly measuring rates of diffusion in polymer solutions and gels. We are also observing the effect of dissolved polymer on the motion of large, macroscopic particles in order to isolate and examine the hydrodynamic problem alone. For our theoretical work, we are using the principles of fluid mechanics to study the effect of crosslinked and uncrosslinked polymer on solute motion.

DIFFUSION OF NONIONIC SURFACTANTS IN NONIONIC GELS

Kristan K. S. Buck*, Stephanie R. Dungan, Ronald J. Phillips
Department of Chemical Engineering and Materials Science, University of California, Davis

Our lab is studying the properties of micelles in polymeric hydrogels. Gel/micelle materials have the potential to be very useful in the extraction and controlled release of hydrophobic solutes, such as toxic hydrocarbons, water-insoluble food compounds and pharmaceuticals. To enable the design of such systems, a fundamental understanding of the effects of micelle-gel fiber interactions on micelle thermodynamic and transport properties is required. We are conducting holographic interferometry experiments to measure diffusion coefficients of micelles in hydrogels. Our experimental results indicate solute concentration has an enhanced effect on diffusion in gel over its effect in solution. We compare our results with diffusion measurements in gels of proteins of comparable size to the micelles. This comparison allows us to determine whether the enhanced concentration effect can be understood by treating the micelles as "hard spheres," or whether surfactant-specific interactions are present. We hypothesize that the gel fibers serve to augment the thermodynamic influences which enhance diffusion at higher concentrations, while reducing hydrodynamic interactions which retard that diffusion. We are testing this hypothesis by comparing our experimental data with a new theory we are developing for the diffusion of “hard spheres” in fibrous media. By identifying features of micelle diffusion which can be treated with hard sphere models, the presence of any micelle-specific effects of size, electrostatic charge and hydrophobicity on the thermodynamic and transport properties of micelles in gels can be determined.

PLANT DEFENSE PROTEINS: NOVEL PRODUCTION METHODS AND POTENTIAL APPLICATIONS

Karen A. McDonald*, Alan P. Jackman, Abhaya M. Dandekar† and Rajesh Krishnan
Department of Chemical Engineering and Materials Science, University of California, Davis
†Department of Pomology, University of California, Davis

Although plant cell culture bioprocesses have been developed for large-scale production of plant secondary metabolites (e.g. paclitaxel, shikonin, berberine), very little research has been done on the production of proteins using plant cell cultures. In our laboratories, we are studying the production of two classes of natural plant defense proteins, ribosome inactivating proteins (RIPs) and chitinases from plant cell cultures. RIPs are believed to play a role in plant defense based on their potent ability to destroy ribosomal function in procaryotes and eucaryotes, their wide distribution throughout the plant kingdom and the fact that RIP expression is induced by exposure to microbes and viruses. As an enzyme class, they are attracting attention due to their wide range of potential commercial application including their use as broad-spectrum antiviral therapeutics, immunotoxins for treatment of cancer and other diseases, and genetic engineering of crops for improved pest and/or disease resistance. Plant chitinases, a diverse group of hydrolytic enzymes that cleave chitin, are classified as an important class of pathogenesis-related proteins.

In our laboratories we have discovered four new RIPs from plant cell suspension culture broths of Agrobacterium rhizogenes transformed T. kirilowii.1,2 Three of these proteins have both RIP and chitinase activities.3 These proteins may be particularly valuable as antifungal agents and we are currently studying their antifungal properties. In addition, we have studied the kinetics of extracellular RIP production from nontransformed T. kirilowii plant cell suspension cultures in 5L bioreactors.4 We have also isolated new RIPs from a wild Oregon cucumber, Marah oreganus and are working to establish cell cultures of this plant. The overall goals of our research are to fully characterize these novel plant defense proteins in terms of their physical and biological activities, and to develop efficient plant cell culture production systems.

1. Shih, N.-J. R.; McDonald, K.A. Purification and Characterization of Chitinases from Transformed Callus Suspension Cultures of Trichosanthes kirilowii Maxim. J. Fermentation and Bioengineering. 1997, 84: 28-34.
2. Shih, N.-J.R.; McDonald, K.A.; Dandekar, A.M, GirK. A. McDonald, A.M. Dandekar, Girbés, T.; Iglesias, R.; Jackman, A.P. A Novel Type-1 Ribosome-Inactivating Protein Isolated from the Supernatant of Transformed Suspension Cultures of Trichosanthes kirilowii", Plant Cell Reports (In Press).
3. Stoner, M.R.; Humphrey, C.A.; Coutts, D.J.; Shih, N.-J.R.; McDonald, K.A.; Jackman, A.P. Kinetics of Growth and Ribosome-Inactivating Protein Production from Trichosanthes kirilowii Plant Cell Cultures in a 5 Liter Bioreactor", Biotechnol. Prog. 1997, 13: 799-804.
4. Shih, N.-J.R.; McDonald, K.A.; Jackman, A.P.; Girbés, T.; Iglesias, R. Bifunctional Plant Defense Enzymes with Chitinase and Ribosome Inactivating Activities from Trichosanthes kirilowii Cell Cultures. Plant Science (In Press).

EXPRESSION AND CHARACTERIZATION OF PLANT DEFENSE PROTEINS IN TRANSGENIC TOBACCO

Rajesh Krishnan*, Abhaya M. Dandekar†, Alan P. Jackman, and Karen A. McDonald
Department of Chemical Engineering and Materials Science, University of California at Davis
†Department of Pomology, University of California at Davis

The focus of my research is the expression and characterization of two classes of plant defense proteins in tobacco suspension cultures and ultimately in transgenic tobacco plants. The two proteins to be studied are: 1. trichosanthin, a type I ribosome inactivating protein (RIP), and 2.a novel bifunctional chitinase/RIP from the plant *Trichosanthes kirolowii.* The proteins are instrumental in the defense of plants against fungi and bacterial parasites, as well as for the development of antiviral therapeutics and genetic engineering of crops.. The tricosanthin, like all RIPS, deactivates ribosomes by removing an adenine residue at a conserved site on prokaryotic and eukaryotic rRNA, thus halting protein synthesis. Chitinase is a hydrolytic enzyme that cleaves chitin, a biopolymer found in many fungi and insects. Different constructs of the structural genes for the proteins (specifically combinations of the N-terminal, coding region, and C-terminus sequences of each) were inserted into specially-designed binary vectors for *Agrobacterium tumefaciens*-mediated transformation and expression in tobacco plant leaves. From the transformed leaf tissue, I will develop tobacco cell cultures for enhanced protein production. In addition, transgenic tobacco plants, expressing the plant defense proteins, will be cultivated . These proteins will be isolated and characterized for their enzymatic function and kinetics, as well as for any antiviral/antifungal activities.

OVERVIEW OF RESEARCH

Marty Privalsky
Section of Microbiology, University of California, Davis

Our general interest is in the mechanisms by which proliferation and differentiation is regulated in normal cells, and in the abnormal processes that occur in neoplasia. Our specific goal is a better understanding of the actions of the nuclear hormone receptors in normal cells and in oncogenesis. Nuclear hormone receptors are a family of ligand-regulated transcription factors, and include the steroid, retinoid, and thyroid hormone receptors. These receptors directly modulate gene expression in response to hormones of extracellular origin, and play critical roles in metazoan homeostasis, differentiation, and reproduction. In addition, aberrant nuclear hormone receptors have been implicated as causal or contributory factors in a variety of human and non-human cancers. My research seeks to exploit these aberrant oncogenic receptors, both to better elucidate the actions of their normal counterparts, and to determine the molecular pathways that operate in neoplasia.

A CONFORMATIONAL SWITCH IN NUCLEAR HORMONE RECEPTORS IS INVOLVED IN COUPLING HORMONE BINDING TO COREPRESSOR RELEASE

Benjamin C. Lin*, Suk-Hyun Hong, Sheryl Krig, Sunnie M. Yoh, and Martin L. Privalsky
Section of Microbiology, University of California, Davis

Nuclear hormone receptors are ligand-regulated transcription factors that modulate gene expression in response to small, hydrophobic hormones, such as retinoic acid and thyroid hormone. The thyroid hormone and retinoic acid receptors typically repress transcription in the absence of hormone and activate it in the presence of hormone. Transcriptional repression is mediated, in part, through the ability of these receptors to physically associate with ancillary polypeptides called corepressors. We wished to understand the mechanism by which corepressors are recruited to unliganded nuclear hormone receptors and are released on the binding of hormone. We report here that an a-helical domain located at the thyroid hormone receptor C terminus appears to undergo a hormone-induced conformational change required for release of corepressor and that amino acid substitutions that abrogate this conformational change can impair or prevent corepressor release. In contrast, retinoid X receptors appear neither to undergo an equivalent conformational alteration in their C termini nor to release corepressor in response to cognate hormone, consistent with the distinct transcriptional regulatory properties displayed by this class of receptors.

CONTROL OF GROWTH AND APOPTOSIS BY INTRACELLULAR CALCIUM SIGNALS

Michael R. Hanley
Department. of Biological Chemistry, School of Medicine, University of California, Davis

The group has two major research interests in the area of cell signaling. The first is the molecular cloning and characterization of G-protein coupled receptors and analyzing their signal transduction pathways, emphasizing regulation of growth and apoptosis by calcium mobilizing receptors. The second is the molecular biology of the endoplasmic reticulum in calcium signaling and calcium storage. An emerging interest is a novel network of intracellular signaling events, including alterations in gene exprssion and ion channel activity, elicited by depletion of Ca2+ stores. Themes common to both interests are the roles of specific receptors or signal transduction genes in human disease, particularly prostatic cancer and novel molecular probes for manipulation of signaling events.

THAPSIGARGIN-INDUCED APOPTOSIS OF LNCaP PROSTATE CANCER CELLS IS NOT INHIBITED BY bcl2.

Ingrid E. Wertz, Xu-Bao Shi, Sabine Ottilie*, Scott P. Amdahl, Paul H. Gumerlock, Larry Fritz*, Ralph W. deVere White, and Michael R. Hanley
Departments of Biological Chemistry, Internal Medicine, and Urology, University of California, Davis, School of Medicine
*IDUN Pharmaceuticals, La Jolla, CA.

The *BCL2* oncogene is over-expressed in many human cancers, including prostatic adenocarcinoma (CaP). Bcl2 inhibition of CaP apoptosis may promote tumorigenesis and thus participate in the resistance of CaP tumors to therapeutic interventions. A novel candidate chemotherapeutic, thapsigargin (TG), has recently been shown to induce apoptosis in prostatic cancer cells. TG is a potent and selective inhibitor of ER Ca^{2+} ATPase pumps, and may therefore identify a new molecular target for chemotherapeutic intervention. We have investigated whether bcl2 prevents TG-induced apoptosis in the human CaP cell line LNCaP, which over-expresses bcl2. In response to TG treatment (100nM), apoptosis was detected by 24 hours as determined by DNA fragmentation, flow cytometric, and electron microscopic analyses. These results indicate that bcl2 does not prevent TG-induced apoptosis of LNCaP cells.

To investigate this further, we transfected LNCaP cells with sense and antisense bcl2 constructions, and generated clones over-expressing (clone 22-1) or under-expressing (clone 17F) bcl2 relative to the parent cell line. Both transfectant clonal lines, a control vector-transfected clone, and the parent LNCaP cells responded similarly to TG. Because bcl2 has been reported to modulate intracellular Ca^{2+} stores involved in apoptosis, we performed cell population fluorescence ratio measurements using the Ca^{2+} indicator dye Fura-2. No differences in TG-releasable Ca^{2+} stores or Ca^{2+} homeostasis were noted between the parent LNCaP cell line and clone 22-1.

The intracellular distribution of bcl2 has been reported to be critical for its anti-apoptotic function. To visualize bcl2 distribution in living cells, we prepared a fusion protein of enhanced green fluorescent protein (eGFP) linked in-frame to the C-terminus of murine bcl2. Functional testing of the bcl2•eGFP construct was compared to wild-type bcl2 in protecting against two models of experimental apoptosis. The first was killing HeLa cells using FAS antibody plus cycloheximide, and the second was killing HeLa cells with etoposide. No functional differences between the wild-type bcl2 and bcl2•eGFP construct were noted. As a negative control, a G145A point mutation was introduced in the fusion construction--a known inactivating mutation--and the resulting variant was completely inactive. The bcl2•eGFP construct therefore appears to be functionally similar to wild-type bcl2. As with clone 22-1, no differences in Ca^{2+} stores were detected between wild-type LNCaP and the bcl2•eGFP-transfected LNCaP cells, and no protection was afforded by the bcl2•eGFP construct against TG-induced apoptosis.

The bcl2•eGFP fusion protein was stably transfected in LNCaP cells. Using confocal microscopy, bcl2•eGFP was localized to endomembranes. Interestingly, treatment with TG resulted in intracellular redistribution of bcl2•eGFP to vesicular structures by 24 hours, the time point at which apoptosis was first detected in the parent cells by DNA laddering analyses. Intracellular localization of bcl2•eGFP was compared to other pro-apoptotic treatments. For example, treatment with 100 nM taxol, a chemotherapeutic known to phosphorylate and inactivate bcl2, induced apoptosis of LNCaP cells in a similar time frame to TG, but did not result in intracellular redistribution of bcl2•eGFP. Thus, phosphorylation is not a likely mechanism leading to relocalization of bcl2•eGFP induced by TG. In contrast, treatment with 10 nM phorbol 12-myristate 13-acetate (PMA), which has also been shown to induce apoptosis in LNCaP cells, caused a redistribution of bcl2•eGFP to non-vesicular endomembrane cisternae.

In sum, these results suggest that differential bcl2 trafficking may be correlated with evasion of the bcl2 blockade to TG-induced apoptosis. This has important implications for developing effective chemotherapeutic strategies against therapy-resistant CaP.

PLANT – PLANT COMMUNICATION

John Yoder
Department of Vegetable Crops, University of California, Davis

The recognition of host plants by parasitic plants offers a unique opportunity to investigate plant-plant signaling. Phenolic molecules released by host roots trigger the development of haustoria in parasitic plants. Haustoria are globular outgrowths on parasite roots whose functions are to attach the parasite to the host, invade the host root cortex, and establish a vascular continuum through which the parasite robs host resources. The impact to the host plant can be debilitating, and agriculturally parasitic plants are devastating. In Africa, over two thirds of the 73 million hectares cultivated in cereals and legumes are infested with Striga. The FAO estimates that the lives of over 100 million Africans in 25 countries are threatened by crop losses by Striga. In the United States, dwarf mistletoe (Arcethobium) is estimated to destroy up to 3.2 billion board feet of lumber per year in western forests. Understanding the genetic mechanisms governing host recognition and haustorium development should enable us to develop rational strategies for engineering host resistance against parasitic weeds. We are using the parasitic plant Triphysaria to define the genetics of host recognition and haustorium development. Triphysaria is useful for these studies because it is a facultative parasite whose host range includes Arabidopsis, it is a simple diploid amenable to genetic analyses, and, haustorium development can be monitored in vitro. Using geographically defined ecotypes of Triphysaria, we have identified heritable variation in three parasite specific phenotypes; spontaneous haustorium formation, sibling recognition, and, responsiveness to exogenous phenolic signals. These may represent recognition races for different signal molecules. We are also using suppressive subtraction to identify cDNAs differentially abundant in Triphysaria roots after treatment with haustorial inducing factors. Sequence comparisons are being used to assign tentative functions. Gene expression is being characterized in Triphysaria and the closely related, non-parasite Antirrhinum by in vitro and in situ hybridizations. Multi-array technology is being used to examine the global expression pattern of HIF induced genes in both parasites and non-parasites. A long-term objective is to assign biological functions to cloned genes by combining our genetics and molecular approaches.

SUBTERRANEAN PLANT-PLANT INTERACTIONS: DIFFERENTIAL RECOGNITION OF PHENOLIC RHIZOSPHERE SIGNALS BY PARASITIC PLANTS

Denneal Jamison*, Madeline Le, Marta Matvienko, Russell Wrobel, and John Yoder*
Department of Vegetable Crops, University of California, Davis

Parasitic plants recognize molecular signals in the rhizosphere in order to direct developmental events critical to the parasitic lifestyle. These signals, exuded by the roots of host plants, lead to the formation of the haustorium, the root organ, which attaches, penetrates, and forms a vascular continuum between the parasite and host roots. Triphysaria is an annual, parasitic angiosperm common in California grasslands. Haustorium development in Triphysaria roots can be monitored in vitro and occurs in response to several phenolic molecules. We used dimethoxy-benzoquinone (DMBQ) and hydroquinone (HQ), to stimulate haustorium development in three species of Triphysaria. Each of the three species displayed a distinct response to these inducers. Differences in responsiveness to the inducers were also observed in genetically defined families within a self-pollinating population. F1 analyses suggest that response to the phenolic signals is dominant. The phenolic responsiveness loci will be further defined in F2 mapping populations, with the long-term goal of cloning the relevant genes. Understanding the molecular genetic mechanisms governing plant responses to rhizosphere signals may lead to novel strategies for engineering allelopathic ability in crop plants.

WHAT'S GOING ON IN THE LAB.

Bruce D. Hammock
Departments of Entomology and Environmental Toxicology, University of California, Davis

The lab is composed of three complementary divisions: immunoassay, insect group, and mouse group. The immunoassay division is involved in designing and testing methods of detecting hazardous compounds such as pesticides, metals and other toxic substances as well as their metabolites. Immunoassay provides an attractive method for noninvasive detection of vanishing quantities of toxic substances with the specificity afforded by antibodies. Careful design allows discrimination between parent compounds and metabolites. The mouse group is involved in studying the mechanisms of toxicity and metabolism of toxic substances, and examines the role of epoxide hydrolases and carboxylesterases in detoxification of chemicals, and in activation of toxicity of others through metabolism. The bug group primarily focuses on developing insect selective alternatives to chemical insecticides and studying regulation of gene expression. The baculovirus expression system affords an insect-selective means of delivery of proteins that affect insect development (e.g. juvenile hormone esterase) and peptides such as insect-specific neurotoxins. These are being developed for potential use in control of agriculturally important insect pests, and as tools to dissect mechanisms involved in insect development.

INSECTS AND JUVENILE HORMONE EPOXIDE HYDROLASE

Tonya F. Severson*, Marvin Goodrow, Christophe Morisseau, Deanna L. Dowdy, and Bruce D. Hammock
Departments of Entomology and Environmental Toxicology, University of California, Davis

Epoxide hydrolases are enzymes which hydrolyze a variety of compounds containing epoxide moieties. Hydrolysis of epoxides proves in many instances a key step in the elimination of harmful substances. In insects, however, degradation of juvenile hormone plays an important part in regulation of development. Although degradation of JH by JH esterase has been well established as an important element of insect development, an additional possible route of degradation is hydrolysis of the epoxide moiety of juvenile hormone by a specific JHEH to produce an inactive metabolite. In order to examine the necessity or involvement of JHEH in insect development, we wish to block the active site of the enzyme and assess concomitant physiological consequences. To that end, we are screening a panel of potential inhibitors (available from commercial sources or synthesized within the lab). Comparison of the inhibition data among soluble and microsomal EHs from insects, mice, humans, and rats (and eventually plant EHs) may lead to greater predictive understanding of the structural bases for EH substrate selectivities and allow for the design and synthesis of even more effective inhibitors.

CYTOPLASM TO VACUOLE PROTEIN TRANSPORT IN YEAST

Daniel J. Klionsky*, Valerie M. Dalton, Kip P.-T. Eggerton, Michael D. George, Ann Hefner-Gravink, Maria U. Hutchins, John N. Kim and Sidney V. Scott
Section of Microbiology, University of California, Davis

Eukaryotic cells contain a variety of discrete membrane-enclosed organelles. This highly compartmentalized organization is essential to the normal functioning of the cell. The vacuole/lysome is the major organelle responsible for intracellular degradation in eukaryotic cells. Our goal is to develop a precise understanding of the molecular events involved in the recognition, targeting and transport of proteins to this organelle using yeast as a model system. While most characterized vacuolar proteins transit through the secretory pathway, aminopeptidase I (API) reaches this organelle through an alternative mechanism; API enters the vacuole directly from the cytoplasm. This suggests that API utilizes components of the subcellular sorting machinery that are distinct from those used by secretory pathway-mediated vacuolar proteins. Recently we have demonstrated that the mechanism of API import partially overlaps with that of autophagy. Both processes involve the formation of double membrane vesicles in that sequester proteins from the surrounding cytosol. Upon completion of formation, the vesicles target to the vacuole, fuse with the membrane and deliver a single membrane vesicle that is subsequently degraded, allowing access to the lumenal contents. However, there are distinct differences between autophagy and API import, again suggesting a unique set of targeting components is needed for API delivery. We are using a combined genetic and biochemical approach to characterize the import of API. First, we have identified a vacuolar targeting signal in the propeptide of API that is required for membrane binding and import. One of these mutants confers a temperature sensitive targeting phenotype. We used this propeptide mutant to demonstrate that precursor API transits to the vacuole as a dodecamer. The large size of the precursor complex would necessitate transport via a vesicular intermediate. Second, we have isolated a set of mutants that are specifically defective in vacuolar localization of API. Most of these mutants accumulate precursor API that is incorrectly localized to the cytoplasm. In one case, the precursor protein accumulates with subvacuolar vesicles. These mutants will allow us to define components of the sorting and transport apparatus that recognize and target this protein to the vacuole. Third, we have initiated the reconstitution of API targeting *in vitro* to allow the assignment of a biochemical function to cytosolic or membrane components that are required for its localization. A characterization of the proteins involved in API recognition and delivery will further our understanding of vacuolar/lysosomal protein targeting and biogenesis.

CHARACTERIZATION OF THE CYTOPLASM TO VACUOLE TARGETING AND AUTOPHAGY PATHWAYS IN *Saccharomyces cerevisiae*

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In their natural environments, most microorganisms must endure periods when the external nutrient supply is limited, or non-existent. Accordingly, eukaryotic cells have evolved mechanisms for delivering intracellular proteins, membranes, and organelles to specialized recycling compartments. In *Saccharomyces cerevisiae*, the vacuole is the primary site of macromolecular degradation during nutrient starvation. Autophagy is the process by which cells package and deliver bulk cytoplasm to this organelle. Most of the vacuole's resident hydrolytic enzymes are imported through the secretory pathway. The protease aminopeptidase I (API) bypasses this route, however, and is delivered by the cytoplasm to vacuole targeting pathway (Cvt). Recent studies indicate that autophagy and the Cvt pathway share common machinery to package and deliver their cargo. The characterization of these two pathways and their relationship to each other is the major focus of research in our lab. One of the more intriguing questions about autophagy and the Cvt pathway is how their characteristic double-membrane transport vesicles are assembled. Preliminary evidence indicates that the *APG5* gene product is a required component of both pathways, and that it may be involved in vesicle formation. *apg5* mutant strains are unable to survive periods of nitrogen starvation, and microscopy studies suggest they are blocked at the step of vesicle formation. In an $apg5^{tsf}$ strain, API is imported with wildtype kinetics at the permissive temperature (24°C), while transport is essentially blocked at the nonpermissive temperature (38°C). Moreover, API precursor molecules are sensitive to Proteinase K digestion at the restrictive temperature, indicating that completely enclosed Cvt vesicles have not formed. Biochemical evidence suggests Apg5p is a peripherally associated membrane protein. Treatment of cell lysates with high salt concentrations, high pH, and mild detergent release Apg5p from the membrane. Future studies will utilize biochemical, genetic, and cytological techniques to more precisely localize Apg5p, identify and characterize its interactions with other proteins, and determine the molecular role of this protein in vesicle formation. The characterization of Apg5p function will, in turn, provide vital insights into the mechanisms utilized for the biosynthetic transport of API to the vacuole, as well as those used to package and deliver bulk cytoplasmic material by autophagy.

Poster Abstracts

A. ENZYMATIC CONVERSION OF CELLULOSIC MATERIALS IN A CONTINUOUS STIRRED TANK REACTOR WITH AN ULTRA-FILTRATION MEMBRANE

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A continuous stirred tank reactor (CSTR) equipped with an ultrafiltration (UF) membrane was assembled and evaluated for enzymatic hydrolysis of pure cellulose (Solka Floc™) and lignocellulosic material (acid-pretreated mixed urban waste). An enzyme preparation, consisting of two commercially available cellulases, Spezyme CP® and Novozym 188®, was used for hydrolysis. Low molecular-weight hydrolysis products were continuously removed from the reactor through the membrane, thereby relieving end-product inhibition. Insoluble cellulosic material (substrate) and high molecular-weight cellulase (enzyme) were retained within the membrane reactor. Fresh substrate was added to the reactor about every 24 hours as the hydrolysis proceeded toward completion. The parameters of the reaction were compared for the membrane reactor and shake flask reactions, as carried out in a substrate-feeding mode.

Continuous removal of glucose from the membrane reactor reduced end-product inhibition of cellulases and provided 1.8-2.0 times higher conversion of both substrates compared to the results in shake flask. When pure cellulose was used as substrate in the membrane reactor, the cellulases efficiently hydrolyzed subsequent additions of substrate. However, when a lignicellulosic material was used in a substrate-feeding mode, the degree of substrate conversion rapidly decreased and the efficient use of enzyme was not achieved. This is likely due to accumulation of the insoluble lignin residue in the reaction mixture and the irreversible adsorption of cellulases onto lignin residue. The amount of enzyme required to produce 1 gram of glucose was 5.7 times lower in the membrane reactor compared to shake flask for Solka Floc™ cellulose, and 2.5 times lower in case of the acid-pretreated material.

Since the product stream from the membrane reactor gave a low glucose concentration, the technical feasibility of using reverse osmosis to concentrate glucose solutions for subsequent microbial fermentation is being pursued.

Key words: Cellulose, mixed urban waste, cellulase, enzymatic hydrolysis, membrane reactor, ultrafiltration

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B. DEVELOPMENT OF NEW AFFINITY PURIFICATION OF PLANT SOLUBLE EPOXIDE HYDROLASES

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Epoxide hydrolases (EH) are enzymes present in numerous organisms, that catalyze the hydrolysis of epoxides or arene oxides to their corresponding diols. Their role in mammals have been well studied[1], but little is known about the role of EH in plants. Recently, EHs from potato and cress have been cloned in our laboratory.[2-3] To study their biologic role and mechanism of action, it is necessary to obtain them in a pure form. Previously, our laboratory has developed an affinity purification method for mammal soluble epoxide hydrolases.[4] However, this chromatography method doesn't give good results with the plants EH: low yield (< 5 %) and bad purity (< 70 %). Here we describe the synthesis of new sets of inhibitors and chromatographic gels. New couples of inhibitor and gel has been defined for the both enzymes which allow to obtain pure enzymes (>95%) with a ten fold increase of the yield.

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C. PESTICIDE FLUOROIMMUNOASSAYS IN ORGANIC SOLVENT, REVERSE MICELLAR SYSTEM AEROSOL OT/n-OCTANE

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Polarization fluorimmunoassay (PFIA) is a homogeneous competition method based on detection of the difference of fluorescence polarization between a small fluorescence-labeled haptene and its immunocomplex with specific antibody. In a similar manner, quenching fluoroimmunoassay (QFIA) is based on the detection of the difference of fluorescence intensity. We developed PFIA and QFIA for atrazine[1], propazine[2], and 2,4-dichlorophenoxyacetic acid (2,4-D) both in non-polar organic solvent, *n*-octane, and in water (that the entrapment of proteins into reverse micellar systems leads to protein-sized, optically clear solutions, with retention of biological activity of proteins). The sensitivity (detection limit) of both PFIA and QFIA in presented reverse micellar system to 2,4-D was about 0.1 μg/L which is several times better if compared to aqueous medium by using the same reagents and equipment. Pesticides can be added to reverse micellar system when dissolved in octane, or chloroform. This makes possible the use for the analysis directly the pesticide extracts in non-polar organic solvents.

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D. CONSTRUCTION OF RECOMBINANT BACULOVIRUS EXPRESSING INSECT SELECTIVE NEUROTOXIN FOR EFFECTIVE PEST MANAGEMENT

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Viral insecticides, particularly baculoviruses (NPV), are becoming increasingly attractive as alternatives to chemical insecticides, since they are nonpathogenic to beneficial insects and other non-target organisms including mammals. However, the agricultural use of viral insecticides has been limited due to their relatively slow action on crop pests compared to classical insecticides. In an attempt to enhance the insecticidal efficiency of baculoviruses, a variety of strategies have been adopted by constructing recombinant baculoviruses expressing insect selective toxins (Maeda *et al*., 1991; Mc Cutchen *et al*., 1991; Stewart *et al*., 1991; Tomilski and Miller, 1991, 1992) and enzymes involved in insect metabolism (Hammock et al., 1990; Bonning and Hammock, 1992) which showed increased insecticidal properties compared to wild type viruses. Since the expression of insect selective neurotoxins appears to be highly promising for improving insecticidal activity, an attempt is made in the present investigation to construct recombinant baculovirus expressing an insect selective toxin derived from the South Indian red scorpion, *Buthus tamulus.* Insect selective neurotoxin (BT-IT) is isolated from the venom of *Buthus tamulus,* using ion-exchange chromatography and RP-HPLC, which was found to induce paralysis in *Heliothis virescens* but was non toxic to *Sarcophaga falculata* (blow fly) larvae and mice.. The toxin gene, deduced from the toxin's amino acid sequence, was constructed with a bombyxin signal sequence. The recombinant polyhedrin positive *Autographa californica* NPV (AcNPV) expressing insect selective toxin (BT-IT) was constructed under the control of P10 promoter. Bioassay with recombinant baculovirus on 2nd instar larvae of *Heliothis virescens* demonstrated a significant decrease in the median lethal time (LT_{50}) as compared to wild type AcNPV indicating that recombinant baculoviruses were able to efficiently control the crop pests.

E. TITLE: DEVELOPMENTAL REGULATION OF INSECTS FOR APPLICATION IN BIORATIONAL PEST CONTROL.

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Juvenile hormones (JH) along with ecdysteroids are important regulators of the development of insects from egg through adult stages. Titres of JH are regulated via synthesis and degradation by enzymes such as Juvenile Hormone Esterase (JHE) and Juvenile Hormone Epoxide Hydrolase (JHEH). This enzymatic degradation of JH is associated with both cessation of feeding and subsequent pupation of the larvae, and thus utilization of these enzymes to manipulate JH levels has been considered as a potential tool for insect control. One demonstration of this idea is the development of a recombinant baculovirus expressing JHE as a plausible alternative to environmentally disruptive chemical pesticides. Three projects exhibited here are focused on understanding and improving the role of JH degradative enzymes for endocrine disruption in lepidopteran pest control. 1) The JHE gene from *Heliothis virescens* has been mapped and the upstream region sequenced for promoter analysis. This study aims to understand the regulation of JHE transcription for improvement of JHE expression using recombinant baculovirus. 2) JHE is being purified and cloned from other insect species (i.e., *Manduca sexta, Tenebrio molitor, Anthonomus grandis*) so that the structural/functional similarities and differences may be determined. This knowledge will be applied to genetically engineer the structure of the enzyme to make it more stable in vivo. 3) The role of JHEH in insect development is being assessed and investigated for the potential to disrupt insect development. By understanding the basic structure, function and regulation of JH degradative enzymes, we can provide insight into the physiological and endocrinological processes of major insect pests and effectively utilize this information in improvement of biorational pesticides.

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