SIXTH ANNUAL
BIOTECHNOLOGY
TRAINING GRANT RETREAT
CHRISTIAN BROTHERS RETREAT CENTER
NAPA VALLEY
MARCH 8, 1997

PROGRAM OVERVIEW

8:15am	Registration
8:45am	Introduction by Roy Doi, Director of the Training Grant
9:00 - 11:30am	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 - 2:00pm	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 - 5:30pm	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 by Roy Doi.

COMPLETE PROGRAM

8:15am	Registration	
8:45am	Introduction	- Roy H. Doi, Molecular and Cellular Biology, Training Grant Director

COMPANY PRESENTATIONS:

CHAIR: Roy Doi, Molecular and Cellular Biology

9:00am	The future of Calgene research and product development	- Katie Dehesh, Principle Scientist, Calgene Inc.
9:30am	Chiron, a diversified biotechnology company	- Steven Rosenberg, Research Director, Chemical Therapeutics Group Chiron Technologies
10:00am	BREAK	
10:10am	Research and development at Genentech	- Randy Mrsny Senior Scientist, Genentech
10:40am	Overview of enzymes in commercial processes	- Alan V. Klotz, Department of Protein Chemistry, Novo Nordisk Biotech
11:10am	The role of tyrosine 194 in the collagenase selectivity of indolactam matrix metalloproteinase inhibitors	- Robert Martin, Roche Bioscience
11:40am	Presentation of Posters	
12:00pm	LUNCH, DISCUSSION & POSTERS	

TRAINEE AND TRAINER LAB PRESENTATIONS:

Chair: George Bruening, Plant Pathology/CEPRAP

2:00pm	Overview of research	- Marty Privalsky, Microbiology
	Plasticity of tetramer formation by retinoid X receptors, an alternative paradigm for DNA recognition	- Ben Lin, Microbiology

2:25pm	Cellular regulation of bovine leukemia virus (BLV) replication	- Kathryn Radke, Avian Sciences
	Host cell state and BLV expression	- Ed Fulton, Avian Sciences
2:50pm	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
3:15pm	Overview of research	- Pat Conrad, VM:PMI/ - Phyllis Whiteley Inflammatory Disease Unit, Roche Bioscience
	Activation of the MAP kinase p38 in LPS-stimulated cells	- Ruth Hemmer Vet Med: Pathology, Microbiology and Immunology
3:35pm	BREAK	

TRAINEE AND TRAINER LAB PRESENTATIONS:

Chair: Kathryn Radke, Avian Sciences

3:45pm	Overview of research	- Dewey Ryu Chem Eng./ Jim Barnett, Molecular Biology Roche
	Development of a novel bioreactor for high value phospholipic synthesis	- Rajesh Krishnan, Chemical Engineering
4:15pm	Extraction and controlled release technologies using micelles and microemulsions	- Stephanie Dungan, Chemical Engineering
	Cholesterol-Saponin interactions: micellar and solubilization properties	- Shuman Mitra, Chemical Engineering
4:45pm	Colloidal diffusion in polymer solutions and gels	- Ron Phillips Chemical Engineering
	Diffusion of nonionic surfactants in nonionic gels	- Kristen Buck Chemical Engineering
5:15pm	Conclusion	- Roy H. Doi, Training Grant Director

5:30pm Bus departs

POSTER TITLES

A. DIFFERENTIAL EXPRESSION OF FRUCTOKINASE GENES AND THE MODIFCATION OF TOMATO FRUIT SUGAR COMPOSITION BY ANTISENSE ENGINEERING

Yoshinori Kanayama, Yasutaka Kubo, Ann Powell, Alan Bennett
Department of Vegetable Crops, UC Davis

B. POLYGALACTURONASE GENE EXPRESSION AND PECTIN DISASSEMBLY DURING CHARENTAIS MELON FRUIT SOFTENING

Kristen A. Hadfield, Jocelyn K. C. Rose, and Alan B. Bennett
Department of Vegetable Crops, UC Davis.

C. PRODUCTION OF PLANT DEFENSE PROTEINS FROM PLANT CELL CULTURES

N.-J. Remi Shih, Karen A. McDonald and Alan P. Jackman
Department of Chemical Engineering and Materials Science, UC Davis

D. EXPRESSION OF ALCOHOL OXIDASE AND PHOSPHOLIPID ENZYMES IN THE YEAST *PICHIA PATORIS*

Rajesh Krishnan
Biochemical Engineering Program, UC Davis

E. THE MAMMALIAN SPERM GLYCINE RECEPTOR/CHLORIDE CHANNEL

Carman Melendrez and Stanley Meizel
Department of Cell Biology and Human Anatomy, UC Davis, School of Medicine

ORAL ABSTRACTS

THE FUTURE OF CALGENE RESEARCH AND PRODUCT DEVELOPMENT

Katie Dehesh
Principal Scientist
Calgene Inc.

Plant biotechnology is entering into a new phase of its development. For the past 15 years this field has resided in the realm of science. In the mid-1990's it finally entered the realm of commerce. Products ranging from insect resistant cotton to modified canola oils to tomatoes which have better improved flavor are being sold to farmers and consumers. Calgene too is evolving rapidly with a new corporate partnership and a significant repositioning of its produce research program. This presentation will summarize briefly the industries progress in commercializing GE plants with focus on Calgene's activities. Secondly, a status report on Calgene's research programs in oils, fiber and produce will be provided.

CHIRON: A DIVERSIFIED BIOPHARMACEUTICAL COMPANY

Steve Rosenberg
Research Director
Chemical Therapeutics Group
Chiron

Chiron is a diversified biopharmaceutical company with businesses in vaccines, diagnostics, and therapeutics, with a focus on infectious diseases, oncology, critical care, and ophthalmology. 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. 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.

RESEARCH AND DEVELOPMENT AT GENENTECH, INC.

Randy Mrsny
Senior Scientist
Genentech, Inc.

Genentech, Inc. is a pioneer biotechnology company using human genetic information to discover, develop, manufacture and market pharmaceuticals that address significant unmet medical needs. Genentech commits itself to high standards of behavior in contributing to the best interests of patients and the medical profession, and makes its products available to all patients who need them, regardless of their ability to pay. The company has headquarters in South San Francisco and is traded on the New York and Pacific Stock exchanges under the symbol GNE.

Genentech's most important asset is its science. The company's research has led to ten - almost half - of biotechnology-based products on the market today. Genentech is the only biotechnology company to have taken five of its own products from the laboratory to the marketplace

Science at Genentech focuses on six areas of medicine: Cardiovascular/pulmonary, cancer, immunology/allergy, endocrinology, neuroscience and blood cell formation. Nurturing quality research through a commitment to basic science, the company encourages scientists to pursue their own interests with time for discretionary research.

Genentech manufactures five products and markets them in the United States: Protropin® (somatrem for injection) human growth hormone for treating children with growth hormone inadequacy (GHI); Nutropin® (somatropin for injection) human growth hormone also for treating GHI in children and for treating growth failure in children due to chronic renal insufficiency (Nutropin also comes in a liquid version, Nutropin AQ™); Activase® (Alteplase, recombinant) tissue-plasmogen activator to dissolve blood clots in the arteries of patients with acute myocardial infarction (heart attack) and patients with acute massive pulmonary embolism (blood clots in the lungs); Actimmune® (interferon gamma-1b) for treating chronic granulomatous disease, a rare, inherited deficiency of the immune system; and Pulmozyme® (domase alfa) DNase, the first new therapeutic approach for cystic fibrosis in 30 years.

Some other potential products Genentech is investigating in clinical trials are the HER2 humanized monoclonal antibody, a potential treatment for severe cases of breast and ovarian cancer; and insulin-like growth factor (IGF-1) as a possible treatment for diabetes. Other indications targeted by the many new products in Genentech's pipeline include: other cancers, various side effects of cancer chemotherapy, asthma and a type of acute renal failure.

Genentech is also evaluating three of its marketed products for new indications: Activase for ischemic stroke, for which the company is awaiting regulatory approval; Nutropin for

growth hormone inadequacy in adults and for short stature associated with Turner's Syndrome; and Actimmune for metastatic renal cell carcinoma (kidney cancer)

Genentech and Roche are collaborating on several R&D projects to maximize complementary scientific strengths. These collaborations utilize advanced technology to develop potential new pharmaceuticals for untreated medical conditions.

Genentech also has R&D agreements with several biotechnology companies studying related technologies. An example of these is its relationship with IDEC Pharmaceuticals to develop a monoclonal antibody, IDEC-C2B8, currently in Phase III trials for non-Hodgkin's B-cell lymphoma. Genentech continues to seek out and develop strategic alliances with other companies when a synergistic fit exists.

OVERVIEW OF ENZYMES IN COMMERCIAL PROCESSES

Alan V. Klotz
Department of Protein Chemistry
Novo Nordisk Biotech

Enzymes are used as industrial catalysts to substitute for conventional chemical reagents in a growing number of commercially significant processes. This presentation will outline the opportunities for enzyme applications in commercial processes featuring the enzymes advantages of modest temperature, intermediate pH, and minimal side reactions. Specific examples will be discussed in the detergent, baking and animal feed industry sectors to describe how enzymes can functional as environmentally-friendly substitutes for harsh traditional chemicals thereby changing the ways in which people live and work.

THE ROLE OF TYROSINE 194 IN THE COLLAGENASE SELECTIVITY OF INDOLACTAM MATRIX METALLOPROTEINASE INHIBITORS

Robert Martin
Roche Bioscience

Potent collagenase inhibitors which contain a novel indolactam macrocycle have been reported (Castelhano, et. al., *Biorg. & Med. Chem. Letters,* **5**, 1415-1420). These compounds are low nanomolar inhibitors of the three reported human collagenases while they are low micromolar inhibitors of human stromelysin-1. Using a known stromelysin-1 structure and a modeled structure of collagenase-3, we investigated the collagenase selectivity of these compounds via site-directed mutants of both enzymes. We believe that the selectivity arises due to the interaction between the indolactam and a hydrophobic pocket on the collagenase enzyme. The bottom of this hydrophobic pocket is occupied by TYR-194. This tyrosine is conserved in all three collagenases as well as in the gelatinases. Mutating this tyrosine to phenylalanine had no effect on potency. If the tyrosine is mutated to threonine (the amino acid at this same position in stromelysin-1) there is a marked reduction in potency of the inhibitors. The corresponding T194Y mutant in stromelysin-1 had the reverse effect, *i.e.,* an increase of inhibitor potency. (Supported by NIH grant GM27939)

OVERVIEW OF RESEARCH

Marty Privalsky
Section of Microbiology
Division of Biological Sciences
UC 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.

PLASTICITY OF TETRAMER FORMATION BY RETINOID X RECEPTORS, AN ALTERNATIVE PARADIGM FOR DNA RECOGNITION

Benjamin C. Lin, Chi-Wai Wong, Hong-Wu Chen, and Martin L. Privalsky,
Section of Microbiology
Division of Biological Sciences
UC Davis

Nuclear hormone receptors function as hormone-regulated transcription factors that serve to regulate cell growth and differentiation, homeostasis, and metabolism in multicellular organisms. Most nuclear hormone receptors can bind to DNA as protein homodimers or heterodimers and are, therefore, traditionally viewed as being able to regulate the transcription of adjacent target genes in this manner. We have previously demonstrated, however, that DNA recognition by retinoid X receptors (RXRs), a member of the nuclear receptor superfamily, can occur by an unanticipated mechanism in which receptor tetramers and higher order oligomers are cooperatively formed on hormone response elements (HREs) containing suitably reiterated half-sites (specifically the CRBP-II element which contains four half-sites). We report here that RXR tetramers exhibit significant functional plasticity, forming with high cooperativity on a number of response elements that have a variety of nucleotide spacings between half-sites as well as a variety of half-site orientations, as determined by electrophoretic mobility shift assay (EMSA). Intriguingly, the spacing and orientation requirements for tetramer formation are non-equivalent at the different half-sites in the HRE. These results suggest that at least two protein-protein interfaces may be responsible for RXR tetramer formation and that at least one of these interfaces is likely to be non-identical to those previously implicated in RXR dimer formation. The formation of RXR tetramers and related oligomers appears to contribute to the synergistic transcriptional activation observed when multiple, spatially separated response elements are introduced into a single promoter. Oligomer formation may therefore be a common paradigm for DNA recognition and combinatorial regulation by several distinct classes of transcription factors.

CELLULAR REGULATION OF BOVINE LEUKEMIA VIRUS (BLV) REPLICATION

Kathryn Radke
Department of Avian Sciences
UC Davis

Our research focuses on how retroviral gene expression alters host cell function and on how host cells regulate viral gene expression. Bovine leukemia virus (BLV) is closely related to human T-cell leukemia viruses-1 and -2, and is an important model for learning how retroviral gene expression is regulated in cells that host silent infections *in vivo*. Knowing how viral latency is maintained and then is broken is necessary to understand how these viruses spread within the host and how they induce cancers. We investigate the regulation of viral gene expression and the production of viral particles using peripheral blood mononuclear cells with silent infections - the characteristic state of most infected cells in the infected individual. The stimuli encountered by host lymphocytes when participating in immune responses are thought to be important regulators of viral gene expression. Since B lymphocytes are the predominant host cells for BLV *in vivo*, signal transduction pathways specific to B cells are likely to play key roles in viral expression. Our long-term goal is to understand how the state of cellular activation supports BLV replication, expression, and virus production. Peripheral blood mononuclear cells from sheep in known stages of infection are manipulated in culture to elicit BLV expression. The genetic basis for altered envelope protein function of a natural BLV variant is being determined and the signal-transducing capacity of the BLV envelope protein complex is being explored. The research Ed will discuss is directed toward determining whether cells already activated *in vivo* preferentially support BLV expression in culture and whether BLV infection of the host animal alters the activation state of both infected and uninfected B cells.

HOST CELL STATES THAT FAVOR BOVINE LEUKEMIA VIRUS EXPRESSION

B. Edward Fulton Jr.∗ and Kathryn Radke
Microbiology Graduate Group∗ and Department of Avian Sciences,
UC Davis

Bovine leukemia virus (BLV), an oncogenic retrovirus related to the human T-cell leukemia viruses (HTLVs), infects cattle and can experimentally infect sheep. These retroviruses appear to be silent in host cells *in vivo*, demonstrating little or no viral mRNA or protein expression. The host cell lineages and activation states that are required for viral entry, provirus synthesis and integration into the cell genome, and later viral expression are not known.

Our goal is to determine what lineages and activation states of BLV-infected PBMCs (peripheral blood mononuclear cells) from experimentally infected sheep are most prevalent early and later in infection. Previous results with immunocytochemistry suggested that PBMCs that had recently undergone S phase *in vivo* were not more likely than non-cycling cells to express viral capsid protein (CA) in culture. However, identification of a cell as a cycling cell was limited to those that had been in S phase during a pulse of BrdU (5-bromo-2'-deoxyuridine) that was injected 18 hours before blood was drawn. Experiments are being designed to utilize flow cytometry to examine cell lineage, cell cycle status, and presence of viral proteins either individually or together in double-labeling or triple-labeling techniques.

We have also used immunocytochemistry to measure the effect of stimulation in culture on the timing of activation of host cells from BLV-infected sheep. PBMCs from BLV-infected sheep are more likely to enter S phase in response to 20 hours of LPS (lipopolysaccharide) stimulation in culture than are cells from uninfected sheep. The majority of the cells from the infected animals that entered S phase early in culture in response to LPS were B cells. These stimulation experiments are being extended to more fully characterize the timing of entry into S phase by infected cells. Some preliminary flow cytometry results using DNA staining techniques will be presented.

CONTROL OF GROWTH AND APOPTOSIS BY INTRACELLULAR CALCIUM SIGNALS

Michael R. Hanley
Department. of Biological Chemistry
School of Medicine
UC 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 capacitative calcium entry, elicited by depletion of Ca^{2+} 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.

CHARACTERIZATION OF LNCaP PROSTATE CANCER CELL APOPTOSIS INDUCED BY SERCA PUMP INHIBITION

Ingrid E. Wertz, Paul H. Gumerlock, Jared T. Muenzer, Philip C. Mack, Arline D. Deitch, Ralph W. deVere White, and Michael R. Hanley.
School of Medicine
UC Davis

Successful treatment of prostatic adenocarcinoma (CaP) is thought to eliminate cells via apoptosis, a mechanism of regulated cell death. Our goal is to understand the apoptotic pathways in the CaP cell line LNCaP, which expresses the anti-apoptosis oncogene *BCL2*. Thapsigargin (TG), an inhibitor of sarcoplasmic/endoplasmic reticulum (ER) localized Ca^{2+} ATP-ase (SERCA) pumps, induces depletion of ER Ca^{2+} stores and sustained elevation of cytosolic Ca^{2+}. TG has been reported to induce apoptosis of other CaP cell lines. We therefore treated LNCaP cells with 100 nM TG and extracted DNA at 12-hour intervals. Inter-nucleosomal DNA fragmentation characteristic of apoptosis was detected at 36 and 48 hours after treatment. Electron microscopic and flow cytometric analyses confirmed that TG-induced death was apoptotic.

To characterize the Ca^{2+} signaling pathways in TG-induced apoptosis, we loaded LNCaP with the Ca^{2+} chelator 1,2-bis(*o*-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid (BAPTA). 10μM BAPTA, which did not interfere with the growth of LNCaP cells, abolished the TG-induced increase in cytosolic Ca^{2+} as indicated by the Ca^{2+} indicator dye Fura-2. However, 10μM BAPTA failed to protect against TG-induced apoptosis. 100μM BAPTA, which may itself deplete ER Ca^{2+} stores, induced LNCaP cell death. These results suggest depletion of ER Ca^{2+} stores rather than elevation of cytosolic Ca^{2+} promotes apoptosis in LNCaP cells. We therefore used cyclopiazonic acid (CPA), a SERCA pump inhibitor structurally unrelated to TG. Like TG, 1μM CPA elevated cytosolic Ca^{2+} and depleted ER Ca^{2+} stores as confirmed by Fura-2 Ca^{2+} measurements, and 100μM CPA induced DNA fragmentation and LNCaP apoptosis in a similar time course as TG. lOμM BAPTA also failed to protect against CPA-induced apoptosis, consistent with the hypothesis that ER Ca^{2+} store depletion is a critical signal for LNCaP cell apoptosis.

To investigate the genetic regulation of TG-induced LNCaP apoptosis, we analyzed the phosphorylation state of the Retinoblastoma (Rb) protein, which showed progressive hypophosphorylation from 12 to 36 hours of TG treatment. Decreased Rb phosphorylation suggests an arrest in the G1 phase of the cell cycle, consistent with flow cytometric analysis of TG-treated LNCaP cells. Western blot analysis of the cyclin-dependent kinase inhibitor of Rb phosphorylation Cdkn1 (p21) showed increased p21 expression at 24 hours of TG treatment. Association of p21 with proliferating cell nuclear antigen (PCNA), a component of DNA replication and repair machinery, is thought to delay progression through S phase. A dramatic increase of p21/PCNA complexes was

detected at 12 hours of TG treatment. These results suggest that p21 plays a pivotal role in TG-induced cell cycle arrest of LNCaP cells.

In summary, these results suggest that TG-induced apoptosis of LNCaP cells is: 1. Dependent on ER Ca^{2+} depletion; 2. Independent of cytosolic Ca^{2+} elevation; and 3. Related to the p21-induced arrest of the cell cycle. Further elucidation of the specific mechanisms and genes involved in this apoptotic pathway may identify targets for pharmacological intervention to improve CaP therapy.

PURSUING EMERGING PROTOZA

Patricia Conrad
Vet Med: Pathology, Microbiology and Immunology
UC Davis

Research efforts focus on protozoal parasites of veterinary and human health importance, specifically *Babesia, Toxoplasma, Neospora and Cryptosporidium*. We have identified what appears to be a new species of human *Babesia* and are currently studying the molecular pathogenesis and epidemiology of this parasite. This work involves in vitro cultivation, as well as antigenic and genotypic characterization of new *babesial* isolates from humans and wildlife. In addition, we have a significant colloborative research program on *Neospora*, a newly recognized and important cause of abortion in cattle which we have also shown to be infective for primates. Our *Neospora* research (CMI) in cattle and primates, parasite biology, development of serologic and molecular diagnostic assays and evaluation of potential vaccines. *Cryptosporidium* research is currently focused on the molecular characterization of isolates.

ACTIVATION OF THE MAP KINASE P38 IN LPS-STIMULATED CELLS

Ruth Hemmer, Mary Welch, Jose Freire and Phyllis E. Whiteley
Inflammatory Disease Unit
Roche Biosciences

Proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) are secreted proteins produced by monocytes and other cell types in response to many inflammatory stimuli. Therapeutic agents that can selectively inhibit the biosynthesis of proinflammatory cytokines would be highly advantageous in diseases such as rheumatoid arthritis, osteoporosis and asthma. However, it is imperative that these therapeutics be selective for proinflammatory cytokine production and not inhibitory of homeostatic processes. A central focus of this laboratory is to define the signaling pathways that are responsible for the production of cytokines such as TNFα and IL-1 during an inflammatory response. Mitogen-activated protein (MAP) kinases are known to play a central role in the biosynthetic pathway of TNFα. A direct link between activation of the MAP kinase p38 and TNFα production has been established. The goal of these experiments is to develop a biochemical assay to measure the activation of p38 in LPS-stimulated THP-1 cells. Once established, this assay will be used to investigate other MAP kinase and tyrosine kinase signaling pathways (e.g. IL-2 production in T cells) to determine if p38 is activated in these pathways. This data will be used to evaluate which cell signaling pathways involve p38. Currently we are developing the imunoprecipitation and kinase assay for p38 activity in cell lysates. We have demonstrated that we can specifically immunoprecipitate p38. We have also shown an induction of p38 activity in LPS-stimulated THP-1 cells. Future experiments will test the cellular selectivity of the p38 signaling pathway.

OVERVIEW OF RESEARCH

Dewey Ryu
Chemical Engineering, UC Davis

Major research interests are in the area of biochemical and biomolecular process engineering dealing with genetically engineered recombinants, biologically active molecules, enzymes , and other gene products. Specific examples of current research programs include:

1) Biomolecular process engineering and recombinant bioprocess technology: Improvement of gene expression and secretion with a focus on efficient transcription and post-translational protein processing (i.e., vector system design, analysis of promoter regulation, protein folding, kinetics of peptide assembly). Genetic and metabolic flux analyses of recombinant bioprocess systems for optimal design and process improvement based on quantitative physiology and metabolic regulation.

2) Biotransformation and enzymatic synthesis of biologically active compounds, antibodies, amino acids, fine chemicals, pharmaceuticals, and agrochemicals of economic importance based on biocatalysis using enzymes and whole cells

3) Cell cultivation technology and optimization of staged (i.e., two-stage) continuous or fed batch bioreactor systems as applied to cultivation of recombinant cells including immobilized cells and enzymes, microorganisms, and plant and animal cell lines for production of gene products and secondary metabolites of medical and economic importance. Also, design and optimization of novel bioreactor systems for plant, animal and insect cell cultivation.

4) Bioseparation of biologically active high value gene products in low concentration using immunoaffinity purification methods with a focus on interactions between the monoclonal antibody and antigen, ligand matrix, their binding kinetics, distributed equilibrium parameter, elution techniques, and scale-up problems.

EXPRESSION OF ALCOHOL OXIDASE AND PHOSPHOLIPID ENZYMES IN THE YEAST *PICHIA PASTORIS*

Rajesh Krishnan
Biochemical Engineering Program, UC Davis

The ability of Pichia pastoris to metabolize methanol as its sole Carbon source is conferred primarily by the enzyme alcohol oxidase (AOX1 gene), which catalyzes the oxidation of methanol to formaldehyde using molecular oxygen. The AOX1 promoter is used in specific Pichia expression cassettes to drive expression of genes, encoding heterologous proteins of interest, selectively in methanol; the cells in turn can continue to grow during the induction period if the AOX1 gene in the host is not disrupted. Multiple copy integration of a specific chemokine into a Pichia host strain, while increasing the expression of the protein, resulted in a disruption of the host AOX1 gene; the resultant phenotype of the transformants was thus Muts (Methanol-utilization slow) and the cells were unable to grow appreciably during the induction period of chemokine gene expression. In order to further increase expression of the chemokine (by allowing cell growth during methanol induction), we are attempting to clone the AOX1 gene back into these Muts strains, while maintaining the multiple copies of the chemokine. The same technology will then be used for the construction of other Mut+ (able to metabolize methanol) strains with multiple copy integration of other heterologous proteins, specifically high value phospholipid enzymes from both yeast and bacterial sources.

EXTRACTION AND CONTROLLED RELEASE TECHNOLOGIES USING MICELLES AND MICROEMULSIONS

Stephanie Dungan
Chemical Engineering
UC Davis

Amphiphilic molecules will often form molecular aggregates known as micelles and microemulsions in solution, and these aggregates will extensively solubilize substances that are otherwise quite insoluble in the bulk solvent. This ability of surfactant aggregates to preferentially solubilize certain molecules can be utilized to design effective separation methods for valuable food/pharmaceutical components, or to enhance the controlled release rate of therapeutic molecules. In our laboratory we are measuring and modeling the ability of micelles and microemulsions to incorporate solutes such as whey proteins, cholesterol, and a variety of hydrophobic molecules, in order to employ these aggregates for extraction purposes. In addition, we are studying the solubilization behavior of these aggregates within complex systems such as emulsions and gels, with results impacting on the development of novel controlled release technologies.

CHOLESTEROL-SAPONIN INTERACTIONS: MICELLAR AND SOLUBILIZATION PROPERTIES

Shuman Mitra[§] and Stephanie R. Dungan[§†]
Department of Chemical Engineering and Materials Science[§]
Department of Food Science and Technology[†]
UC Davis

Quillaja saponins are naturally occurring surfactants used extensively in the food industry, and with interesting potential applications as pharmaceutical agents and in cholesterol extraction technology. In this study, the ability of quillaja saponins to form micelles in aqueous solution has been demonstrated using surface tension and dye solubilization measurements. The influence of temperature, pH and aqueous salt concentration on the critical micelle concentration (cmc) and size of these saponin micelles from different sources was explored, as well as their molecular properties at the air-water interface. Despite the fact that quillaja saponin is often regarded as a nonionic surfactant, its aggregation properties exhibit a significant influence of charge interactions.

This information on the micellar properties of quillaja saponin was further used in a study of aqueous saponin solutions containing cholesterol. To that end, we investigated the surface behavior of cholesterol saturated saponin solutions and found clear evidence of micellar aggregates. Interestingly, the properties of these micelles are different from those of pure saponin as far as the cmc, size and effect of temperature on the cmc are concerned. Temperature, salt concentration, pH, quillaja saponin source and micellar structure were all shown to affect cholesterol solubility. The knowledge gained from these studies of quillaja saponin solutions is useful in exploring their ability to extract solutes of biological significance, like cholesterol from animal fats and oils, and in understanding their use as pharmaceutical agents.

COLLOIDAL DIFFUSION IN POLYMER SOLUTIONS AND GELS

Ronald J. Phillips
Chemical Engineering and Materials Science Department

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
Chemical Engineering and Materials Science Dept., University of California, Davis, CA 95616

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.[1] 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 experiments to measure the diffusion coefficient of micelles and solutes in a hydrogel. This is done using holographic interferometry, a method used previously in this lab to study protein and micelle diffusion in destran solutions and in agarose gels.[2,3] A second experiment will be to measure the partition coefficient of micelles and solutes between a hydrogel and an external aqueous phase. The equilibrium distribution of surfactant between the gel and aqueous phases provides information on the energetic interactions present between surfactant and gel fibers, which in turn determine the number, size and shape of micelles formed within the gel. Preliminary experiments indicate surfactant concentration has an enhanced effect on micelle diffusion in gel over its effect in solution. By comparing experimental data with present theories for the diffusion of "hard spheres" in fibrous media, it will be possible to identify the thermodynamic and hydrodynamic contributions to this enhanced diffusion effect and also the presence of any micelle-specific effects of size, electrostatic charge and hydrophobicity and the thermodynamic and transport properties of micelles in gels.

POSTERS

DIFFERENTIAL EXPRESSION OF FRUCTOKINASE GENES AND THE MODIFCATION OF TOMATO FRUIT SUGAR COMPOSITION BY ANTISENSE ENGINEERING

Yoshinori Kanayama, Yasutaka Kubo, Ann Powell, Alan Bennett
Dept. of Vegetable Crops, Mann Lab, UC Davis

Sucrose, fructose and glucose are the predominant soluble sugars in ripening tomato fruit. The perceived sweetness of fructose is almost twice that of glucose. Because many fruit accumulate approximately equal amounts of the hexose isomers, glucose and fructose, metabolic engineering enhancing the fructose:glucose ratio has the potential to increase fruit sweetness by as much as 25%. Since metabolic modifications may impact constitutive respiratory pathways, hexose alterations are targeted to ripening fruit, a developmental period of the plant less sensitive to respiratory perturbation.

Fructokinase (Frk, EV2.7.14) plays an essential role in hexose metabolism in plant sink tissues by phosphorylating fructose and engineering suppression of this activity is predicted to increase the fructose:glucose ratio. Two cDNA clones (Frk1 and Frk2) were isolated from tomato and shown to encode genuine Frk by complementation of yeast mutants deficient in Frk. The Frk2 cDNA encoded a 328 amino acid deduced protein whose nucleotide and amino acid sequence was more than 90% identical to Frk from potato. In contrast, the Frk1 cDNA encoded a 347 amino acid deduced protein that is 55% identical to the potato Frk. Frk2 mRNA accumulates abundantly in enlarging tomato fruit, whereas Frk1 mRNA is more abundant in ripening fruit. Frk2 is less abundant in leaves than it is in stems and roots, but Frk1 mRNA is approximately equal in all three vegetative tissues. *In situ* hybridization shows that Frk2 mRNA accumulates in tissues involved in starch synthesis and seed development and Frk1 mRNA is widely distributed. These expression patterns could suggest that Frk1 is involved in general fructose metabolism and Frk2 functions in cells that import and utilize sugar.

To confirm the physiological role in plants of Frk1 and to test the feasibility of altering the ratio of hexoses in fruit, a 0.6 kb fragment of Frk1 inserted in the reverse orientation under control of the E8 promoter, specifying expression in ripening fruit, was introduced into tomato using *A. tumefacien*s. In the first generation, a maximum of 50% of the endogenous Frk1 mRNA was reduced by this strategy. Subsequent generations will be analyzed for further reductions in endogenous Frk1 mRNA, respiration rate, sugar composition, Frk enzyme activity, and amounts of Frk protein. An alternative approach, engineering a pathway novel to plants, using aldose reductase and sorbitol dehydrogenase in ripening fruit, may provide an alternative method to increase the fructose:glucose ratio by converting glucose to fructose through this pathway.

POLYGALACTURONASE GENE EXPRESSION AND PECTIN DISASSEMBLY DURING CHARENTAIS MELON FRUIT SOFTENING

Kristen A. Hadfield, Jocelyn K. C. Rose, and Alan B. Bennett
Department of Vegetable Crops, UC Davis.

Charentais melon fruit provide an excellent model system to study the regulation of ripening-associated cell wall disassembly due to the large and rapid decrease in firmness this fruit exhibits. Once softening is initiated, the fruit reaches a desirable texture usually within 24 hours and then begins to deteriorate. Associated with the deteriorative phase of fruit softening is a decrease in the molecular weight of pectic cell wall polymers and an increase in *in vitro* pectin degrading activity. We have identified three genes, MPG1, 2 and 3, that encode putative polygalacturonase (PG), a cell wall hydrolase that depolymerizes polyuronides. The accumulation of MPG1, 2 and 3 mRNAs differ temporally and in terms of abundance with MPG1 being the most abundant and MPG3, the least. Based on deduced amino acid sequence comparisons, MPG1 and 2 are evolutionarily related to a gene encoding a peach fruit ripening specific PG and MPG3 is closely related to the tomato fruit ripening PG. In order to biochemically characterize the proteins encoded for by MPG1, 2 and 3, experiments have been initiated with researchers at Novo Nordisk Biotech to express these genes in the filamentous fungus, *Aspergillus oryzae*, an organism used to express large amounts of protein for industrial uses. Substrate specificity and mode of action are among the properties we wish to establish using the protein obtained from this heterologous expression system.

PRODUCTION OF PLANT DEFENSE PROTEINS FROM PLANT CELL CULTURES

N.-J. Remi Shih, Karen A. McDonald and Alan P. Jackman
Department of Chemical Engineering and Materials Science, UC Davis

We are studying the production of plant defense proteins from plant cell suspension cultures in shake flasks and bioreactors. Of particular interest are the ribosome-inactivating proteins (RIPs), specific rRNA glycosidases, which have a variety of potentially useful pharmaceutical activities such as antiviral, antitumor, abortifacient and immunomodulatory activities. Trichosanthin, a 27 kDa protein isolated from *Trichosanthes kirilowii*, a Chinese cucumber found in China, Japan and Korea, has gone through phase II clinical trials as an AIDS drug. Because RIPs are believed to be produced from a multigene family, we have studied the expression of related proteins from *T. kirilowii* plant cell cultures. We have purified several basic proteins from the plant cell culture broths; these proteins possess the specific rRNA N-glycosidase activity which is characteristic of RIPs.

We have investigated the kinetics of growth and RIP production of *T. kirilowii* plant cell suspension cultures in 5 L bioreactors under well controlled conditions of temperature, dissolved oxygen concentration and aeration. We have found that the cultures exhibited a long lag phase and a doubling time of less than 2 days during the exponential growth phase. RIP production was observed in the culture broths during the exponential growth phase and reaches a level of 25-30 units/ml.

RIPs have also been identified from tissues and seeds of a native wild cucumber found on the Oregon coast. These proteins are similar to trichosanthin in terms of N-terminal sequence and ribosome inhibitory activity.

EXPRESSION OF ALCOHOL OXIDASE AND PHOSPHOLIPID ENZYMES IN THE YEAST *PICHIA PASTORIS*

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The ability of Pichia pastoris to metabolize methanol as its sole Carbon source is conferred primarily by the enzyme alcohol oxidase (AOX1 gene), which catalyzes the oxidation of methanol to formaldehyde using molecular oxygen. The AOX1 promoter is used in specific Pichia expression cassettes to drive expression of genes, encoding heterologous proteins of interest, selectively in methanol; the cells in turn can continue to grow during the induction period if the AOX1 gene in the host is not disrupted. Multiple copy integration of a specific chemokine into a Pichia host strain, while increasing the expression of the protein, resulted in a disruption of the host AOX1 gene; the resultant phenotype of the transformants was thus Muts (Methanol-utilization slow) and the cells were unable to grow appreciably during the induction period of chemokine gene expression. In order to further increase expression of the chemokine (by allowing cell growth during methanol induction), we are attempting to clone the AOX1 gene back into these Muts strains, while maintaining the multiple copies of the chemokine. The same technology will then be used for the construction of other Mut+ (able to metabolize methanol) strains with multiple copy integration of other heterologous proteins, specifically high value phospholipid enzymes from both yeast and bacterial sources.

THE MAMMALIAN SPERM GLYCINE RECEPTOR/CHLORIDE CHANNEL

Carman Melendrez and Stanley Meizel
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The mammalian sperm acrosome reaction is essential to fertilization. It is known that this exocytotic event in the sperm head can be initiated by the egg zona pellucida and requires chloride. Immunochemical and/or pharmacological evidence published by my laboratory has demonstrated that neuronal-type glycine receptor/chloride channels are present in porcine and human sperm and that such receptor/channels participate in the mechanism of the zona pellucida-initiated porcine acrosome reaction.

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Yoder, John I.	Professor	Vegetable Crops

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Jean C. Kridl	Senior Scientist	Calgene
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UNIVERSITY OF CALIFORNIA, DAVIS
GRADUATE TRAINING PROGRAM
IN BIOTECHNOLOGY

TRAINEES 1996-97

CONTINUING TRAINEES

Trainee	Preceptor	Department
Ed Fulton	Kathryn Radke	Avian Science
Ruth Hemmer	Patricia Conrad	VM: Immunology
Rajesh Krishnan	Dewey Ryu	Chemical Engineering
Benjamin C. Lin	Martin Privalsky	Microbiology
Shuman Mitra	Stephanie Dungan	Food Science & Technology/ Chemical Engineering

NEW TRAINEE

Ingrid Wertz	Michael Hanley	Biological Chemistry

UNIVERSITY OF CALIFORNIA, DAVIS
GRADUATE TRAINING PROGRAM
IN BIOTECHNOLOGY

First Year Fellowship Awards Fall 1996

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Buck, Kristan*	Chem Engineering	Colo. School of Mines	Genentech
Huxsol, Christopher	Physiology	UC Davis	Roche Bioscience
Kahn, Elaine	Biochem/Mol Biol	U of San Francisco	UC Davis
Kessler, Sharon	Plant Biology	University of Illinois	Calgene
Ramos, Jason	Plant Biology	UC Davis	UC Davis
Thomas, Kimberly	Biochem/Mol Biol	Texas A&M	Chiron
Wong, Edith	Biochem/Mol Biol	Wellesley College	Novo Nordisk Biotech
Zenser, Nathan	Plant Biology	Purdue	UC Davis

*Second year student supported by Genentech Fellowship

Biotechnology Training Grant
Executive Committee
1996-97

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Anderson, Gary	Professor	Animal Science
Bruening, George	Professor	Plant Pathology
Carlson, Don M.	Professor	Molecular & Cellular Biology
Hanley, Michael R.	Professor	MED: Biological Chemistry
Meares, Claude	Professor	Chemistry
Privalsky, Marty	Professor	Microbiology
Yilma, Tilahun	Professor	VM: PMI
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