Fourth Annual Biotechnology Training Grant Retreat
Mondavi Winery, Napa Valley
February 25, 1995

1. Program Overview

8:45 am	Introduction by Roy Doi, Director of the Training Grant
9:00 - 11:45 am	Company presentations may include brief overview of the company's mission, their research and development along project lines and/or a more indepth coverage of specific research projects. (Calgene, Chiron/Protos, Entotech, Genentech, Syntex)
11:45 - 2:30 pm	Poster Session & Lunch: Posters will be presented by trainers and other students etc. from trainer laboratories. Trainees may also present posters especially trainees whose company internship research differs from their thesis project. There will also be opportunity for the trainees, first year fellows and other students to interact with the company trainers and gain a greater insight into research in the private domain. Also, perhaps, develop ideas for suitable internship projects.
2:30 - 5:45 pm	Faculty trainers, company trainers and their trainees will present an overview of their research projects, beginning with a five minute overview of the lab focus by the trainer and continuing with a more detailed (10 min.) description by the trainee of his/her research and ending with five minutes for questions.
5:45 pm	Close by Roy Doi.

2. Complete Program

8:30	Registration	
9:00	Introduction	- Roy H. Doi, Mol & Cell Biology Training Grant Director

COMPANY PRESENTATIONS:

CHAIR:	**Roy Doi, Molecular and Cellular Biology**	
9:00	Calgene research and product development	- Luis Perez-Grau, Senior Scientist, Calgene Fresh
9:30	Chiron Company, a diversified biotechnology	- Steven Rosenberg, Research company Director, Chemical Therapeutics Group, Chiron
10:00	BREAK	
10:15	Overview of Entotech Research	- Chi Li Liu, Manager Microbiology Dept. Entotech
10:45	Overview of Genentech Research	- Dick Vandlen, Director, Protein Chemistry, Genentech
1 1 :1 5	Production of Monoclonal Antibodies Using A Secretion Capture Report Web	-Jack Dunne Department of Analytical and Structural Biology, Syntex
1 1 :45	POSTERS	
12:00	LUNCH, DISCUSSION & POSTERS	

NEW TRAINEE AND TRAINER LAB PRESENTATIONS:

CHAIR:	**George Bruening, Plant Pathology/CEPRAP**	
2:30	Cellular regulation of bovine leukemia virus (BLV) replication	- Kathryn Radke, Avian Sciences
	BLV expression and the cell cycle	- Ed Fulton, Avian Sciences
2:50	Extraction and controlled release technologies using micelles and microemulsions	- Stephanie Dungan, Chem. Eng.
	Solubilization properties of ♌-lactoglobulin and ♋-lactalbumin in reversed micelles	- Lynne Kawakami, Chem. Eng.
3:10	Molecular mechanisms of dioxin action	- Mike Denison, Env. Tox.
	Cloning and characterization of the 5'-flanking region of the human aromatic hydrocarbon (Ah) receotor gene	- Selwyna Tetangco, Env. Tox.
3:30	Mapping the high growth locus in mice/sheep Genome Mapping	- Juan Medrano, Animal Sci.
	Molecular sexing of white sturgeon	- Alison van Eenennaam Animal Science
3:50	BREAK	

CONTINUING TRAINEE AND TRAINER LAB PRESENTATIONS:

CHAIR: **Gary Anderson, Animal Science**

4:00	1. Macromolecular structure 2. Drug delivery	- Claude Meares, Chemistry
	Mapping the surface of *E.coli* RNA polymerase	- Douglas P. Greiner, Chemistry
4:20	Function of the *vif* gene of simian immunodeficiency virus (siv)	- Paul A. Luciw, MED: Pathology
	Mechanism of Simian Foamy Virus (SFV-1) Transcriptional Transactivation	- June X. Zou, MED: Pathology

COMPANY INTERN PRESENTATIONS:

4:40	Receptors and Signal Transduction Growth control by G-protein linked receptors	- Patricia Olson, Chiron (Michael R.Hanley, MED: Biological Chemistry)
	Roles of C-Terminal Domain in a Peptide Receptor Subfamily	- Chris Haskell, MED: Biological Chemistry
5:00	Modification of the fatty acid composition of rapeseed using geminivirus-derived gene expression systems	- Jean Kridl, Calgene (George Bruening, Plant Pathology /CEPRAP)
	Modifying plant fatty acid composition with geminivirus-derived vectors	- Bill Johnson, Plant Pathology
5:20	Bacillus thuringiensis delta endotoxin insect receptors	- Ildeyka Zimani, Entotech (Sharman O'Neill, Plant Biology)
	Identifying the causes of Bacillus thuringiensis loss of bioactivity on cotton	- David Van Tassel, Plant Biology
5:40	Conclusion	- Roy H. Doi, Training Grant Director

3. POSTER TITLES

A. THE USE OF SIZE EXCLUSION CHROMATOGRAPHY COMBINED WITH MULTI-ANGLE LASER LIGHT SCATTERING TO CHARACTERIZE ENDO-1,4-β-GLUCANASES ON CARBOXYMETHYLCELLULOSE

E. Yu., Vlasenko, S.P. Shoemaker, and C.F. Shoemaker
CIFAR and Department of Food Science and Technology, University of California, Davis, CA 95616

B. EFFECT OF LIGHT ON THE PRODUCTION OF SULFOLIPIDS FROM ANABAENA 7120 IN A FED BATCH REACTOR

Shivaun D. Archer*, Karen A. McDonald and Alan P. Jackson
Department of Chemical Engineering, University of California, Davis, CA 95616

C. PGIP - ITS ROLE IN COLONIZATION OF FRUIT BY SOFT-ROT FUNGI SECRETING POLYGALACTURONASES

A.L.T. Powell*[1], G. D'hallewin[3], H. Stotz[2], K. Sharrock[4], J. M. Labavitch[2], A.B. Bennett[1]
Department of Vegetable Crops[1], and Department of Pomology[2], UCD, Davis; CSIR, Sassari, Italy[3]; Horticulture & Food Research Institute, Auckland, New Zealand[4]

D. THIOESTERASE PRODUCTION IN PLANT PROTOPLASTS USING GEMINIVIRUS-DERIVED GENE EXPRESSION SYSTEMS

William K. Johnson*[1], Jean C. Kridl[3], Reggie Reymundo[1], and George Bruening[1,2]
CEPRAP[1] and Department of Plant Pathology[2]; Calgene, Inc.[3]

E. EXPRESSION OF HUMAN DOPAMINE BETA HYDROXYLASE IN DROSOPHILA CELLS

Jim Barnett, Stan Tsing, Alan Kosaka, Binh Nguyen, Eric Osen, Chinh Bach, Hardy Chan and Bin Li
Biotechnology Unit, Syntex Research, 3401 Hillview Ave., Palo Alto, CA 94304

F. THE REQUIREMENT FOR VIF IN SIVmac REPLICATION IS CELL-TYPE DEPENDENT

June X. Zou and Paul A. Luciw
Department of Medical Pathology, Univeristy of California, Davis, CA 95616

G. IDENTIFICATION OF RANDOM AMPLIFIED POLYMORPHIC DNA (RAPD) GENETIC MARKERS IN SHEEP

William T. Cushwa* and Juan F. Medrano
Department of Animal Science, University of California, Davis, CA 95616

H. CALIFORNIA INSTITUTE OF FOOD AND AGRICULTURAL RESEARCH

Sharon Shoemaker, Director
University of California, Davis, CA 95616

I. BIOTECHNOLOGY PROGRAM

Martina McGloughlin, Associate Director
University of California, Davis, CA 95616

ORAL PRESENTATION ABSTRACTS

CALGENE, INC. - RESEARCH AND PRODUCT DEVELOPMENT

Christine K. Shewmaker*
Calgene Fresh, Inc. - Research and Development

Calgene, Inc. is an agricultural biotechnology company headquartered in Davis, California. Research and development focuses on using genetic engineering technologies to improve product quality and agronomic characteristics as well as producing new or different products. Presently, research is focused on three crops: tomato, cotton and rapeseed (canola). A brief description of product development in each of these crops will be given followed by a discussion of the new areas of research.

CHIRON: A DIVERSIFIED BIOTECHNOLOGY COMPANY

Steve Rosenberg*
The Chemical Therapeutics Group, Chiron.

Chiron is a diversified biotechnology company with interests in vaccines, diagnostics, and therapeutics, with a focus on infectious diseases, oncology, critical care, and ophthalmology. Chiron's products to date have been proteins manufactured using recombinant DNA methods. Recently, we have combined a variety of state–of-the–art technologies to develop a program in molecular diversity, with the goal of improving the methods for discovering small molecule pharmaceuticals. The design and synthesis of libraries of compounds using robotic methods, and the identification of novel drug candidates in the G-protein coupled receptor family will be described.

Entotech

Novo Nordisk Entotech, a subsidary of Novo Nordisk's Plant Protection Division, which started in September 1990 in Davis, CA is working on research and development of biological pesticides. Entotech has 40 fulltime and 10 part-time employees. Research consists of two major projects: discovery of new and better strains of Bacillus thuringiensis and discovery of insecticidal/ nematicidal natural products from microorganisms.

Novo Nordisk A?S is the world's largest producer of industrial enzymes and the world leader in the development and production of insulin and diabetes care products. Headquartered in Denmark, Novo Nordisk employs more than 10,000 people and markets products in 130 countries. Novo Nordisk markets a broad range of *Bacillus thuringiensis* based-biopesticides: Biobit^{TM}, Bactospeine^{TM}, Florbac^{TM} for caterpillar pests of vegetables and other crops, Foray^{TM} for gypsy moth and other forest caterpillar pests, Novodor^{TM} for Colorado potato beetle, and Bactospeine^{TM} for mosquito and blackfly control.

GENENTECH

Dick Vandlen, Director, Protein Chemistry, Genentech, Inc., 460 Point San Bruno Blvd., South San Francisco, CA 94080

Genentech is a research and development company using genetic engineering techniques to produce therapeutic substances for human and veterinary use. Areas of interest include fibrinolectics, urokinase, human blood factors, growth hormones including human growth nerve factor, somatomedin, gonadotrophin, alpha and beta interferon, lymphokines including tumor necrosis factor, calcitonin, proinsulin, renin, factor VIII, protropin HGH, activase TPA, antitrypsin, human vaccines against herpes, AIDS and hepatitis, bovine interferons, animal growth hormones and vitamin C. Genentech's TPA is FDA approved for treating heart attacks. They have developed a recombinant cloning process for microbial polypeptide expression.

Activase" (Alteplase recombinant) sales for 1993 reached $236.3 million. Tissue-plasminogen activator increased its market share to more than two thirds since the results of the GUSTO trial showed a significant life-saving advantage to using activase t-PA over other thrombolytic regimens studied in the trial. Genentech was also granted a permanent injunction against Welcome Foundation that prevents Welcome from marketing t-PA in the United States until Genentech's patent expires in 2005.

Protropin " (somatrem for injection) human growth hormone sales for 1993 reached $216.8 million. Also filed a patent infringement which the International Trade Commission is investigating.

Actmmune " (Interferon gamma) licensed to Boehringer Ingelheim International received approval for treating chronic granulomatus disease (CGD) in six new countries. The products is now approved in 17 countries. Genentech began Phase III trials to investigate the use of Actimmune in treating metastic renal cell carcinoma.

Nutropin "(somatropin (rDNA origin) for injection) human growth hormone. Genentech received approval from the FDA in March 1993 to market Nutropin for the treatment of growth failure in children with chronic renal insufficiency before kidney transplantation. They completed US regulatory submission in 1993 for approval to market Nutropin to treat growth hormone inadequacy in children.

Pulmozyme " (dornase alfa inhalation solution) DNase received marketing approval from regulatory agencies in the US and Canada, three European countries and New Zealand for the treatment of cystic fibrosis (CF). Pulmozyme received unanimous recommendation for approval by the European Community for proprietary Medicinal Prooducts for this indication. Genentech introduced the Pulmozyme Patient Pledge so that qualified CF patients in the US who need Pulmozyme can obtain it. Completed Phase II trial in certain hospitalized chronic bronchitis patients.

Phase I trial results of gp120 AIDS vaccine (based on MN strain of HIV-1) reported at the IX international conference on AIDS showed that gp120 is safe and that it elicits an immune response against certain laboratory isolates of HIV-1 in both healthy individuals and HIV-1-infected individuals who have not yet developed AIDS. Genentech began Phase II clinical trials with gp120 as a therapeutic for HIV-1-infected people.

Insulin-like growth factor (IGF-1) . Genentech completed patient treatment in Phase II trial for the treatment of AIDS wasting syndrome and provided IGF-1 for physcian sponsored clinical studies in both Type I and Type II diabetes.

Genentech completed enrollment in Phase I trial of Nerve growth factor for peripheral neuropathies. Data analysis to be completed in April 1994. Genetech began Phase I safety trials of Ant-IgE humanized antibody in January 1994 in allergy patients. Genentech filed an investigational New Drug application for Transforming growth factor-β_1 (TGFβ_1) for chemotherapy mucositis.

Genentech has entered into agreements with GenVec, Inc. to license all of its cystic fibrosis gene therapy products worldwide, and made an equity investment in the company; with Texas Biotechnology Corporation for it to develop argatroban for cardiovascular indications, with Connective Therapeutics Inc. for it to develop relaxin for non-reproductive indications such as treating dermatological and connective tissue disorders, with Escalon Ophthalmics Inc. for TGF-β_1 regarding ophthalmic indications.Genentech also extended its relationship with Glycomed Incorporated through 1997 to develop carbohydrate-based therapeutics for inflammatory disorders such as rheumatoid arthritis and asthma, and made additional equity investment in the company. It collaborated with Roche reagrding orally active antagonists to platelet gpIIb/IIIa for

cardiovascular indications, to LFA/ICAM and interleukin-8 (Il-8) for chronic inflammatory disorders, and to RAS farnesyltransferase for certain cancers.

PRODUCTION OF MONOCLONAL ANTIBODIES USING A SECRETION CAPTURE REPORT WEB

John S. Kenney*, Forest Gray, Marie-Hélène Ancel[1] and John F. Dunne

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Monoclonal antibody technology has provided key reagents for the study of immune mechanisms. However, conventional techniques are inherently limited by inefficient detection of rare valuable hybridoma clones producing the desired antibody. We describe the production of monoclonal antibodies using a Secretion Capture Report Web. Following HAT selection in bulk culture, individual hybridomas are encapsulated in biotinylated agarose drops. Antibody secreted by the hybridoma is captured within the agarose drop using an avidin bridge and biotinylated anti-mouse immunoglobulin. The secreted antibody is detected by a fluorescent reporter which can be either a second antimouse antibody or an antigen. The binding of the reporter can be quantitated and the desired hybridoma directly cloned by flow cytometry. Multi-parameter (i.e., two-color) reporter analysis can also be used to selectively enrich and clone rare hybridomas secreting antibodies directly to unique epitopes. The method allows the characterization of thousands of clones per second and the isolation of hundreds of clones per day.

CELLULAR REGULATION OF BOVINE LEUKEMIA VIRUS REPLICATION

Kathryn Radke*, Department of Avian Sciences, University of California, Davis, CA 95616-8532

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 I and II, and is an important model for learning how viral 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 differentially supports BLV expression at transcription and translation of viral mRNAs and at 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 goal of the project Ed will discuss today is to determine whether cells already activated *in vivo* preferentially support BLV expression in culture.

BLV Expression And The Cell Cycle

B. Edward Fulton Jr.* and Kathryn Radke
Microbiology Graduate Group* and Department of Avian Sciences,
University of California, Davis, CA 95616

Bovine leukemia virus (BLV), an oncogenic retrovirus related to the human T-cell leukemia viruses (HTLVs), infects cattle and can experimentally infect sheep. BLV and HTLV have the unique feature of appearing silent in host cells *in vivo*, where little or no viral mRNA or protein is expressed. We are trying to determine how BLV infection is maintained in this seemingly dormant state and what conditions favor its expression. Therefore, we assessed the mitotic cell cycle and activation state of host cells to test the hypothesis that activated B lympho-cytes preferentially support virus expression. In experiments performed by pulse-labeling BLV-infected sheep with 5-bromo-2'-deoxyuridine (BrdU), circulating lymphocytes that had recently traversed S phase showed greater expression of BLV protein than other lymphocytes, but B cells were not more likely than any other mononuclear cell to have cycled through S phase. We plan to test other markers for host cell activation to be able to simultaneously measure viral expression, cell cycle state, and lymphocyte type.

EXTRACTION AND CONTROLLED RELEASE TECHNOLOGIES USING MICELLES AND MICROEMULSIONS

Stephanie R. Dungan, Departments of Food Science/Technology and Chemical Engineering and Materials Science, University of California, Davis, CA 95616

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 modelling 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.

SOLUBILIZATION PROPERTIES OF BETA-LACTOGLOBULIN AND ALPHA-LACTALBUMIN IN REVERSE MICELLES

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University of California, Davis, CA 95616

Reverse micelles are surfactant stabilized droplets of water dispersed within an organic medium. Proteins have a tendency to solubilize in the reverse micellar phase by partitioning into the water droplets, leaving other constituents behind. The solubilization behavior of proteins is affected by system conditions such as pH, ionic strength, and surfactant concentration and type. As individual proteins demonstrate varying degrees of solubilization in this system, reverse micellar systems have proven useful in the selective extraction of proteins from synthetic mixtures[1] and fermentation broths[2]. Here, we extend the application of reverse micelles to the extraction of alpha-lactalbumin and beta-lactoglobulin from cheese whey. We have recently characterized the solubilization behavior of alpha-lactalbumin and beta-lactoglobulin in reverse micelles of the surfactant sodium di-2-ethylhexyl sulfosuccinate (Aerosol OT) in isooctane. These proteins exhibit significant solubilization over a wide range of pH's and ionic strengths. Our results also suggest that hydrophobic forces, as well as electrostatic forces, play a dominant role in the solubilization of alpha-lactalbumin and beta-lactoglobulin.

[1]Goklen, K.E.; Hatton, T. A. (1987) Liquid-Liquid Extraction of Low Molecular-Weight Proteins by Selective Solubilization in Reversed Micelles. *Separation Science and Technology*, *22*: 831-841.

[2]Rahaman, R. S.; Chee, J. Y.; Cabral, J. M. S.; Hatton, (1988) T. A. Recovery of an Extracellular Alkaline Protease From Whole Fermentation Broth Using Reversed Micelles. *Biotechnology Progress*, *4*: 218-224.

MOLECULAR MECHANISMS OF DIOXIN ACTION

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Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin) the prototypical and most potent HAH, produces a wide range of species- and tissue-specific toxic and biological effects including: tumor promotion, hepato- and immuno-toxicity, teratogenesis and lethality. Many, if not all, of these effects are mediated by a soluble intracellular protein, the aromatic hydrocarbon receptor (AhR) to which these chemicals bind with high affinity. The AhR is a ligand-dependent transcription factor that modulates gene expression via its interaction with a specific DNA recognition site. The focus of our research group is directed toward examining the molecular mechanism(s) by which the AhR, in combination with other trans-acting DNA regulatory factors activates gene expression and the role of these events in the myriad of responses resulting from exposure to these chemicals.

CLONING AND CHARACTERIZATION OF THE 5'-FLANKING REGION OF THE HUMAN AROMATIC HYDROCARBON (Ah) RECEPTOR GENE

Selwyna C. Tetangco* and Michael S. Denison
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The aromatic hydrocarbon receptor (AhR) is a soluble intracellular protein known to mediate many of the toxic and biological effects of halogenated aromatic hydrocarbons such as chlorinated dibenzo-p-dioxins and biphenyls. Although the AhR has been recently cloned and its functional domains are being characterized, little is known about what regulates expression of the AhR gene itself. Here we describe studies directed toward the isolation and characterization of the 5'-flanking region of the human AhR gene. Utilizing a fragment from the 5'-end of the murine AhR cDNA as the probe, we have isolated three unique genomic clones from a EMBL3 human genomic DNA library. Restriction mapping of the genomic clones is currently being carried out along with Southern Blot analysis, using oligonucleotides prepared against the 5'-end of the human AhR cDNA, to identify a fragment containing the upstream regulatory region. Once the desired fragment is isolated, it will be sequenced and the regulatory regions of the AhR gene determined using deletion and transfection experiments.

GENE MAPPING AND GENE EXPRESSION

Juan F. Medrano, Department of Animal Science, University of California, Davis, CA 95616

Genetic and physical mapping of the *high growth* locus (*hg*) in the mouse: The *hg* locus was found in a strain of mice selected for high 3-to-6-wk post-weaning weight gain. This locus produces a 30-50% increase in postweaning growth rate and mature body size, and has a general influence on all chemical components of growth without dramatically altering overall body composition. We have localized *hg*, by interval mapping, to the distal half of mouse chromosome 10 and developed a fine genetic map (< 0.3 cM resolution) of the *hg* region. We are currently working in the physical mapping of this locus. (Student: Simon Horvat)

Milk protein gene expression: The amount of casein protein in milk is of great interest to the dairy industry because of its importance in cheese manufacturing. We have found that two allelic variants of important milk proteins, kappa-casein and beta-lactoglobulin (ß-LG), show a differential expression at the protein level. We have concentrated our work in studying alleles A and B of ß-LG. Higher amounts of ß-LG A whey protein are found (50% more), compared to ß-LG B whey protein in the milk of heterozygous ß-LG AB cows. We have looked for polymorphisms in the promoter of the ß-LG gene and identified seven mutations within the effective promoter region of this gene. Using mobility shift assays and footprinting, we have demonstrated that one mutation occurs at the binding site of an AP2 transcription factor. AP2 appears to bind preferentially to the ß-LG A promoter, suggesting that a delayed binding of AP2 to the mutated sequence could decrease mRNA synthesis in the ß-LG B allele. In order to more clearly understand the effect of the ß-LG promoter mutations on gene transcription, we are currently using COMMA-1D mammary cells to express reporter gene constructs of the ß-LG promoter. (Student: Lorraine Lum; Visiting Scholar from Slovenia: Dr. Peter Dovc)

Sheep genome mapping: see abstract by William T. Cushwa and J. F. Medrano.

Molecular Sexing of White Sturgeon: see abstract by Alison L. Van Eenennaam and J. F. Medrano.

MOLECULAR SEXING OF WHITE STURGEON (*ACIPENSER TRANSMONTANUS*)

Alison L. Van Eenennaam*, and Juan F. Medrano
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The sexual monomorphism of white sturgeon presents a problem for the emerging domestic caviar industry. The current diagnostic technique for sex identification requires a surgical biopsy of sexually-differentiated gonads. The availability of an age-independent, DNA-based sex identification procedure would enhance the economic feasibility of caviar production systems. We screened male and female pools of DNA derived from 30 unrelated sturgeon using the Randomly Amplified Polymorphic DNA (RAPD) PCR application called bulked segregant analysis[1]. Two of approximately 1,200 RAPD primers produced a sex-associated PCR amplification product. These two amplification products were cloned and sequenced to allow the 10 bp RAPD primers to be converted into pairs of strand-specific 20-22 bp Sequence Characterized Amplified Region[2] (SCAR) primers. Amplification of male and female DNA with these SCAR primers did not result in sex-specific amplification patterns. This suggests that the sex-associated polymorphisms originally detected in the screen were not located on the heterogametic sex chromosome or linked to a sex-specific chromosomal region. We now plan to screen sex-specific pools of DNA from a newly-constructed full-sib family. This full-sib design will increase the size of the chromosomal region(s) that are in linkage disequilibrium with sex-specific loci.

References:

[1]Michelmore, R. W., I. Paran, and R. V. Kesseli, (1991) Identification of markers linked to disease-resistance genes by bulked segregant analysis. A rapid method to detect markers in specific genomic regions by using segregating populations. *Proc. Natl. Acad. Sci. U.S.A.*. *88*: 9828-9832.

[2]Paran, I, and R. W. Michelmore. (1993)Development of reliable PCR-based markers linked to downy mildew resistance in lettuce. *Theor. Appl. Genet. 85*: 985-993.

MACROMOLECULAR STRUCTURE

Claude F. Meares, Chemistry, University of California, Davis, CA 95616

Our lab focuses on improving our understanding of biological processes at the molecular level by using the tools of chemistry to design and prepare probe molecules suited to a particular problem. Monoclonal antibody technology allows the specifity of an antibody for its antigen to be used in targeting cancer cells. The conjugation of metals--particularly radionuclides such as ^{90}Y or ^{67}Cu-- to monoclonal antibodies results in agents for radiometals with high stability under physiological conditions are essential to avoid excessive radiation damage to nontarget cells. To elucidate the molecular interactions during gene transcription, a method was developed to quantify the photoaffinity labeling produced by an aryl azide photoprobe positioned at the leading (5') end of the nascent RNA.

MAPPING THE SURFACE OF *E. COLI* RNA POLYMERASE

Douglas P. Greiner*, Karin A. Hughes, Angelo H. Gunasekera, and Claude F. Meares
Department of Chemistry, University of California, Davis, CA 95616

A new approach to 'protein footprinting' to map protein domains involved in macromolecular interactions has been applied to the CRP protein-DNA systems.[1] We have begun to explore the applicability of this approach for mapping interactions between the subunits ($\alpha_2\beta\beta'\sigma$) of *E. coli* RNA polymerase. Our procedure utilizes pre-formed Fe(III)-EDTA, in the presence of ascorbate and H_2O_2, as a non-specific protein cleaving reagent. This is followed by SDS-PAGE separation and electroblotting of the resulting protein fragments. Visualization is accomplished by immunostaining with antibodies specific to a C-terminal, 14mer peptide of the subunit of interest. Comparison of the cleaved fragments of the β' subunit from the core ($\alpha_2\beta\beta'$) vs. the holoenzyme (core + σ) shows that loss of σ is associated with appearance of several cleavage sites on β'. The most prominent protected site produces a C-terminal fragment with MW □ 97 kDa. Visualization of the holo enzyme with the anti-σ antibody produces a second, unique pattern of fragments, while visualization with the anti-α antibody fails to reveal any distinct fragments under identical cleaving conditions. These results are consistent with the larger subunits (β' = 155 kDa and σ = 70 kDa) having a greater reagent-accessible surface area than the α subunits (MW = 35 kDa).

References:

[1]Heyduk, E.; Heyduk, T. (1994) Mapping Protein Domains Involved in Macromolecular Interactions: A Novel Protein Footprinting Approach. *Biochemistry*, *33*; 9643-9650.

FUNCTION OF THE *VIF* GENE OF SIMIAN IMMUNODEFICIENCY VIRUS (SIV) AND PATHOLOGY

Paul A. Luciw, Department of Medical Pathology, University of California, Davis, CA 95616.

Regulation of retroviral gene expression *in vitro* and *in vivo*. Mechanisms (molecular) of viral pathogenesis. Members of my laboratory are using molecular genetic approaches to investigate the regulation of viral gene expression and to elucidate mechanisms of viral pathogenesis. The following viruses are being studied: simian immunodeficiency (SIV), simian foamy virus (SFV), rhesus cytomegalovirus (rhCMV), and feline immunodeficiency virus (FIV). Several *in vitro* systems are used to define cis-acting elements in viral promoters and to characterize viral-coded transacting factors (transactivators). The roles of host cell factos on viral transcription are also being investigated. To identify functional domains, mutations in viral promoter elements and in viral transactivator genes are made by site-apecific mutagenesis methods that employ synthetic oligonucleotides. Specific mutations are introduced into molecular clones of viral genomes and the consequences of these alterations on viral replication and pathogenesis are evaluated in both tissue culture and animal systems**.**

GROWTH CONTROL BY G-PROTEIN COUPLED RECEPTORS

Michael R. Hanley*
Dept. of Biological Chemistry, UCD School of Medicine, Davis, California 95616-8635

Neuropeptides which act on G-protein coupled receptors have been recognized as mitogens on a variety of cultured cell types, but the mechanisms and significance of these observations are unknown. The availability of cloned neuropeptide receptors now permits ectopic expression in heterologous hosts as model systems. We have used the family of mammalian tachykinin receptors expressed in NIH3T3 cells to investigate growth control. The NK3 tachykinin receptor, preferring neuromedin K, is largely localised to the nervous system and has no effect on proliferation. On the other hand, the NK2 tachykinin receptor, preferring substance K, is not expressed constitutively in brain but causes both ligand-dependent proliferation and malignant transformation. A third pattern of growth effects is observed with the NK1 tachykinin receptor, preferring substance P. The NK1 receptor is expressed in both neural and extraneural sites and causes ligand-dependent proliferation, but not malignant transformation. Intriguingly, truncation of the C-terminal tail of the NK1 receptor, which selectively abolishes a form of specific receptor adaptation, leads to the acquisition of malignant transforming activity. We are examining the molecular mechanisms underlying differences in growth responses, as well as the physiological importance of such pathways.

ROLES OF THE C-TERMINAL DOMAIN IN A PEPTIDE RECEPTOR SUBFAMILY

Chris Haskell*
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The tachykinin receptors comprise a family of three related seven-transmembrane-segment proteins that are defined on the basis of high-affinity recognition of the neuropeptides substance P, substance K, and neuromedin K. My broad goal is to characterize and compare the functional domains of the intracellular C-termini ("tails") of this family of receptors. To date, my studies have focused on the rat neuromedin K receptor (NKR); a neuronally-expressed G-protein linked receptor coupled to phosphoinositide hydrolysis for generating intracellular messengers. I have generated a set of four tail truncation mutants which have been expressed in both NIH3T3 cells and *Xenopus laevis* oocytes. Results of these studies on the NKR, as well as those on the substance P receptor (SPR) indicate that the tail is potentially an information rich region and may encode multiple regulatory functions. While removal of the SPR tail reduces the receptor's ability to signal and desensitize, removal of the NKR or SKR tails leaves the receptor fully functional in cell expression systems. This process of desensitization, the rapid reduction of signal upon sustained or repeated application of ligand, has been demonstrated in analogous systems to occur via phosphorylation events on the C-terminal tail. Within the tachykinin family, this variable role of the tail in desensitization could be an indicator of divergent receptor regulatory pathways. The existence of naturally-occurring tail-less SPRs also point to a potential role of desensitization resistant tachykinin receptors *in vivo.* In addition, C-terminal tail extension mutants have been generated. A six residue poly-histidine extension was designed to facilitate rapid isolation of the receptor on nickel-chelate affinity columns. This technique will enable investigation of receptor post translational modifications. In an attempt to assay receptor localization and turnover in a real time manner, chimeras of the SPR and green fluorescent protein have been generated.

MODIFICATION OF THE FATTY ACID COMPOSITION OF RAPESEED USING GEMINIVIRUS-DERIVED GENE EXPRESSION SYSTEMS

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Current research effort is focused on cloning and expression of plant genes intended to increase the saturated fatty acid content of canola oil. The genes under investigation include acyl-ACP desaturases and acyl-ACP thioesterases from a variety of plant sources. Genes are cloned either by a combination of protein purification, amino acid sequencing and PCR generation of probes or by exploiting homologies of previously characterized sequences. Isolated genes are characterized for their activities by expression in *E. coli*. Appropriate genes are then cloned between seed-specific expression sequences and transferred to *Brassica napus* via *Agrobacterium*-mediated transformation. Transgenic plants are analyzed for alteration in oil composition as well as for expression characteristics of the transferred genes. I also have a continuing interest in optimization of seed-specific gene expression in *Brassica*. Isolation and testing of new promoters as well as an investigation of a geminivirus gene expression system is ongoing.

MODIFYING PLANT FATTY ACID COMPOSITION WITH GEMINIVIRUS-DERIVED VECTORS

William K. Johnson*[1], Jean C. Kridl[3], and George Bruening[1,2]
CEPRAP[1] and Department of Plant Pathology[2], UC Davis; Calgene, Inc.[3]

The primary objective of this project is to construct and test African cassava mosaic geminivirus (ACMV)-based gene expression systems designed to modify the fatty acid composition of rapeseed. In the conception of these systems, the seed-specific acyl carrier (ACP) promoter drives synthesis of the viral AC2 protein, which is known to activate transcription of the viral coat protein gene, AV1. A C_{12}-specific thioesterase (TE) gene derived from the California bay tree is placed under the control of the AV1 regulatory elements. Since geminiviral DNA can replicate and generate multiple copies in the host cell nucleus, a high level of TE synthesis should be achieved, but only in the organs and at the developmental stages where the ACP promoter is active, namely developing seeds. ACMV DNA a-derived vectors (having one and one-third A-genome component equivalents to allow for replicational release) containing the TE gene were assayed for vector replication and TE expression. Protoplasts transfected with the ACMV-TE construct displayed increased levels of C_{12}-specific thioesterase activity when compared to both control protoplasts and protoplasts transformed with a non-replicating, double CaMV 35S promoter-driven TE vector. To test for the extent of transactivation of TE production by AC2 protein produced *in trans*, protoplasts were also co-transfected with the ACMV DNA A-derived vector having the chloramphenicol acetyltransferase ORF and another vector containing the TE ORF under the control of AV1 regulatory sequences. Three types of replicating vectors are being constructed for *Agrobacterium*-mediated T-DNA transformation of rapeseed plants, in addition to a non-replicating vector having only an ACP promoter-driven AC2 gene and the TE ORF controlled by AV1 regulatory sequences. The resulting transgenic plants will be tested for the extent of C_{12} fatty acids in seeds. If successful, the described geminivirus systems should find application in other plant species where the production of a large amount of a desired gene product is required using a specifically-regulated but weak promoter.

Bt DELTA ENDOTOXIN INSECT RECEPTORS

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To understand the mode of action of biological insecticides, including clarification of the mode of action of *Bacillus thuringiensis* S - endotoxin, and designing novel targets for insecticidal activity. The research involves receptor binding, amino acid transport studies, SDS-PAGE, fluorescent video - imaging, in vivo and ex vivo experiments, cell cultures, fluorescence population studies and spectrophotometric enzyme measurements.

IDENTIFYING THE CAUSES OF BT LOSS OF BIOACTIVITY ON COTTON

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Novo Nordisk Entotech Inc., 1497 Drew Avenue, Davis, CA 95616

Field tests and laboratory bioassays have shown that Bacillus thuringiensis delta endotoxin loses bioactivity when applied to cotton. Two different interactions have been postulated to account for this loss of activity. Because of cotton's unusually high leaf surface pH (9-11) the crystal toxin may degrade rapidly on the leaf as the aqueous suspension of protein crystals dehydrate following conventional foliar application. Cotton leaves are also recognized for their high concentration of aldehydes, terpenoids, alkaloids, phenolics, tannins, and other phytochemicals. It has been suggested that some cotton leaf phytochemicals may have an antagonistic effect on B.t. when the crystalline toxin and these compounds are ingested simultaneously by the insect. In order to identify phytochemicals which interact with B.t., a bioassay was developed. We found that it was possible to incorporate lyophilized, powdered plant material into an artificial insect diet. Incorporated cotton material antagonizes the effect of B.t., consistent with the observed effects of cotton in field trials, or on foliar bioassays. Broccoli material incorporated into the diet had no such effect. We are now in the process of narrowing down the classes of phytochemicals which may be contributing to the cotton antagonism, by determining what treatments of the cotton material are sufficient to degrade or extract the active components. It is hoped that once the mechanism by which cotton material antagonizes the action of B.t. is known, options for overcoming this problem can be explored.

POSTER ABSTRACTS

A. THE USE OF SIZE EXCLUSION CHROMATOGRAPHY COMBINED WITH MULTI-ANGLE LASER LIGHT SCATTERING TO CHARACTERIZE ENDO-1,4-β-GLUCANASES ON CARBOXYMETHYLCELLULOSE

E. Yu., Vlasenko, S.P. Shoemaker, and C.F. Shoemaker, CIFAR and Department of Food Science and Technology, University of California, Davis, CA 95616

Enzymatic hydrolysis of renewable cellulosic materials appears to be one of the most promising ways to produce liquid fuels and other useful products. Endo-1,4-β-glucanases are important components of the multi-enzyme cellulase system. They are characterized by essentially random hydrolysis of internal β-1,4- glucosidic linkages of substituted and unsubstituted cellulosic substrates.

Traditional methods of measuring endoglucanase activity, such as by viscometry and reducing sugars (RS), have not proven ideal for characteriz- ation of endoglucanases. Reductometric assays allow expression of enzymatic activity as the number of glycosidic bonds hydrolyzed per unit time during the initial period of hydrolysis, but do not distinguish the position along the polymer chain where the linkage is broken. Viscometry, on the other hand, provides such information, but does not allow for direct measurement of molecular weight. Although basically simple, the viscometric determination of endoglucanase activity requires fairly complex mathematical analysis of the change in viscosity with time in order to express the results in terms of the change in molecular weight of the substrate.

High pressure size exclusion chromatography, in conjunction with multi-angle laser light scattering (HPSEC-MALLS), is a relatively new method which provides reliable molecular weight measurements of polysaccharides without the need for calibration standards [1]. In our studies, HPSEC-MALLS technique has been used for the direct measurement of number-average molecular weight (Mn) of carboxymethylcellulose (CMC) during hydrolysis by endo-1,4-β-glucanase I (EGI) and endo-1,4-β-glucanases II (EGII) from *Trichoderma reesei*. The decrease of molecular weight of CMC was related to number of glycosidic bonds broken (measured as RS concentration) and to decrease of hydrolysate viscosity.

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B. EFFECT OF LIGHT ON THE PRODUCTION OF SULFOLIPIDS FROM ANABAENA 7120 IN A FED BATCH REACTOR

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Sulfolipids have recently emerged as promising anti-HIV and anti-tumor therapeutics. These lipids have been found in association with the photosynthetic apparatus in most photoautotrophic organisms. To date there has been no quantitative studies on the effect of environmental factors on the production of sulfolipid. In this study, we are investigating the effect of light on the production of sulfolipids using the cyanobacteria *Anabaena 7120*. The cyanobacteria are grown in a fed-batch 2 liter bioreactor at various light intensities. Total lipids are extracted using the Folsch procedure and sulfolipids are quantified using thin layer chromatography and scanning densitometry. We have been able to achieve a maximum of 13 mg sulfolipid/g dry weight of cell. Our results indicate that there are two stages in the specific rate of production of sulfolipid, one in the late exponential growth phase of the cells and the other in the light-limited stage of growth.

C. PGIP - ITS ROLE IN COLONIZATION OF FRUIT BY SOFT-ROT FUNGI SECRETING POLYGALACTURONASES

A.L.T. Powell*[1], G. D'hallewin[3], H. Stotz[2], K. Sharrock[4], J. M. Labavitch[2], A.B. Bennett[1]
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A glycoprotein inhibitor of polygalacturonases (Pgs) from softrotting fungi has been identified in tissues of several plants, including pear and tomato fruit. Polygalacturonase inhibitor protein (PGIP) is an abundant protein in the cell wall extracts of mature green pear fruit, and is a less abundant component of mature green tomato fruit. These PGIPs are present constitutively. Pear PGIP loses its cell wall association as ripening proceeds and concurrently, fruit become more susceptible to rotting, suggesting that PGIP is involved in limiting rot development until seed maturation is complete. Endogenous fruit Pgs are not inhibited by PGIP so ripening-associated pectin metabolism probably contributes to PGIP solubilization. PGIPs are much less abundant in leaves and roots, but their expression can be induced by fungal infection or by wounding, suggesting that in these plant tissues, PGIP can be part of an induced defense response. The coding sequences for all PGIPs identified contain 24 amino acid leucine-rich repeats (LRRs) found in other plant genes encoding race-specific resistance factors to microbial pathogens. The fruit sequences have several potential sites for N-glycosylation clustered in a conserved pattern in the LRRs and conserved cysteines grouped at the terminal.

Expression of pear PGIP under the control of the 35S promoter in transgenic tomato was used to evaluate the role of PGIP in resistance of fruit to several PH-producing fungi. The specific activity of *Botrytis cinerea* PG inhibition is about 20-fold greater with purified pear PGIP than with purified tomato PGIP. Fruit from greenhouse-grown plants primary transformants and their progeny expressing pear PGIP abundantly showed increased resistance to B. cinerea colonizaiton of ripe fruit.

D. THIOESTERASE PRODUCTION IN PLANT PROTOPLASTS USING GEMINIVIRUS-DERIVED GENE EXPRESSION SYSTEMS

William K. Johnson*[1], Jean C. Kridl[3], Reggie Reymundo[1], and George Bruening[1,2]
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The primary objective of this project is to construct and test African cassava mosaic geminivirus (ACMV)-based gene expression systems designed to modify the fatty acid composition of rapeseed. In these systems, the seed-specific, acyl carrier (ACP) promoter drives synthesis of the viral AC2 protein, which is know to activate expression of the viral coat protein gene, AV1. A C_{12}-specific thioesterase (TE) gene derived from the California bay tree is placed under the control of the AV1 regulatory elements. Since replicating geminiviral DNA generates multiple copies in the host cell nucleus, a high level of TE synthesis should be achieved, but only in the organs and at the developmental stages where the ACP promoter is active, namely developing seeds. Initial experiments were directed at optimizing protocols for inoculating tobacco and rapeseed protoplasts and detecting TE production using enzyme assays and Western blotting. Transformation of tobacco protoplasts with a non-replicating vector containing the TE ORF driven by a double CaMV 35S promoter yielded a five-fold increase in C_{12}-specific thioesterase in the transformed protoplasts using Western blotting were inconclusive. Co-transformation of protoplasts with an ACMV DNA A-derived vector (having one and one-third A-genome equivalents to allow for replicational release) containing the CAT gene and another vector with the TE ORF under the control of AV1 regulatory sequences should determine the extent of transactivation of TE production by AC2 protein. Replication of the TE vector in the transformed protoplasts may also occur, since that vector contains the ACMV A-genome common region. In addition, a T-DNA vector having only an ACP promoter-driven AC2 gene and the TE ORF controlled by AV1 regulatory elements is being prepared for *Agrobacterium*-mediated transformation of rapeseed plants, which should determine the effectiveness of using non-replicating ACMV sequences to increase C_{12} fatty acid levels in a tissue-specific manner.

F. THE REQUIREMENT FOR VIF IN SIVmac REPLICATION IS CELL-TYPE DEPENDENT

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The *vif* gene (viral infectivity factor) of the human immunodeficiency virus (HIV) is present in almost all members of lentiviruses and is highly conserved among different HIV isolates, implying an important role in the pathogenesis of lentiviruses. To analyze the role of Vif in SIVmac replication and infection, three SIVmac *vif* mutants have been constructed by introducing site-specific mutations or deletions into *vif* of the pathogenic molecular clone SIVmac239. The effect of Vif on SIVmac239 replication in T-cells was examined by transfecting equal amounts of either *vif*-positive or *vif*-negative viral DNA into SupT1, CEM-SS and H9 cells. Reverse transcriptase (RT) and p27gag antigen assays of supernatants from transfected cultures revealed that both SupT1 and CEM-SS cell lines supported replication of all three *vif* mutants to a level comparable to the parental *vif*-positive virus whereas *vif* mutants failed to replicate in H9 cell. Our results demonstrate that the requirement for Vif in SIVmac replication is cell-type dependent and both N-terminus and the C-terminus of Vif are required for its function. The requirement for Vif for the establishment of infection in primary lymphocytes with cell-free virus was examined by infecting primary cultures of human PBMC with equivalent amounts of *vif*-positive and *vif*-negative virus derived from transfected SupT1 and CEM-SS cells. *vif*-defective viruses failed to infect primary T-lymphocytes whereas both *vif*-positive and *vif*-defective viruses established productive infection in CEMX-174 cells. This finding indicates that Vif plays an important role in viral replication *in vivo*.

G. IDENTIFICATION OF RANDOM AMPLIFIED POLYMORPHIC DNA (RAPD) GENETIC MARKERS IN SHEEP

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DNA samples from the sires and dams of eight AgResearch International Mapping Flock (IMF) pedigrees were screened with 130 random amplified polymorphic DNA (RAPD) primers. An average of 85 parental polymorphisms (range: 76 to 96) was identified in each of the pedigrees. The segregation of the RAPD polymorphisms was investigated in five of the pedigrees. On average, 70% (range: 56 to 80%) of the parental polymorphisms were also polymorphic in the progeny. Polymorphisms that were monomorphic in the progeny were assumed to be the result of parental homozygosity for the dominant RAPD allele. Parental polymorphisms that visibly segregated in the progeny of three or more IMF pedigrees were scored, confirmed, and utilized as genetic markers for genome mapping. Thirty-five RAPD markers have been submitted to AgResearch and thirty of these markers show significant linkage (i.e. LOD ³ 3.0) to other markers previously mapped in the sheep genome. The thirty markers are distributed among fifteen autosomes and the pseudoautosomal region of the sex chromosomes. Three Y chromosome-linked RAPD markers have also been identified, and these polymorphisms appear to be conserved in a number of sheep breeds. One of these RAPD markers was converted to a single-locus marker and was physically mapped to the Y chromosome by *in situ* hybridization. These results demonstrate that the RAPD assay can be very useful for identifying polymorphic markers in domestic animals and that these markers can be utilized for physical mapping. We are continuing to screen these pedigrees with the objective of contributing approximately 50 RAPD markers to the sheep genetic linkage map.

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Anne Gillen	Genetics	Rutgers	UC Davis
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