Summer Student Fellowship, Continued from page 1

Requirements for eligibility are:
- Incumbent must be an undergraduate or graduate student
- Incumbent must be available to work full time for 8 weeks during the summer under supervision of Center member
- Project must be related to the pathogenesis of alcoholic liver or pancreatic diseases
- Incumbent must present work accomplished at Progress Report meeting in September and our symposium in December.

Interested candidates, please e-mail Anne Taguchi (ataguchi@usc.edu):
- Title of project
- Summary of project
- Mentor name
- Mentor's supporting letter (fax – 323-442-3126)

Selected Publications by Center Members
Spotlight on...

Hal F. Yee, Jr.
University of Southern California

Hal Yee is Assistant Professor of Medicine and of Physiology at UCLA, a member of the Research Center for Alcoholic Liver and Pancreatic Diseases and a very active member of the Cirrhosis Research Program. Hal Yee is the ideal physician scientist, combining day-to-day patient care, teaching and clinical as well as bench research.

Hal was born in San Jose, but grew up in Honolulu. Four years as an undergraduate at Brown University in Providence, Rhode Island followed. Hal was then ready to come back to California, to UCLA to attend Medical School and work towards a Ph.D. investigating the relationship between contractility and calcium in cardiac myocytes with Dr. Glenn Langer as advisor.

The residency years were at UCSF. In 1992 when it was time to choose a fellowship program Hal chose and was accepted in the Gastroenterology Program at UCSF: a big loss to cardiology but a great gain for us interested in liver! During the fellowship Hal developed his clinical skills in hepatology in general and in the liver transplantation unit in particular. This clinical work resulted in a number of publications together with Terry Wright and Steven Liodsky. At the same time, research wise, during a postdoc with Dr. Steven Liodsky Hal cloned a potassium channel from liver.

Pinzani Guest Lecturer at Cirrhosis Workshop

By Hide Tsukamoto
University of Southern California

On February 28, 2002, the Research Center had the pleasure of having Massimo Pinzani, M.D., Ph.D. (Professor of Medicine at the University of the Studies of Florence, Italy) speak for the Cellular Homeostasis Lecture series. His lecture was entitled, “Cellular and molecular mechanisms of liver fibrosis: Focus on intracellular signaling.” This stimulating lecture was followed by a fibrogenesis mini-workshop sponsored jointly by the Center’s Southern Alcohol Research Group (SCARG) and the Cirrhosis Research Group (CRG). This informal session consisted of presentations by Hal Yee, Saswati Hazra, EunDuk Kay, Ilya Gukovsky and Aurelia Lugaia on the cellular and molecular mechanisms underlying fibrogenesis in various organs such as the liver, eye and pancreas.

Dr. Pinzani also participated in Rancho Los Amigos Medical Center’s Liver Grand Rounds with a talk entitled, “Hepatic fibrosis: Diagnostic and therapeutic implications.”

Pilot Project Investigators Explore Innovative Alcohol Research

The Center is proud to support the exploration of new directions in alcohol research. The following investigators obtained pilot project funding for 2002.

Guenter Dennert, Ph.D., (USC) Alcohol and its effects on immune mediated liver injury The goal of this project is to examine the effects of alcohol in a small animal model on lymphocyte immunity in the liver.

Chih-Lin Hsieh, Ph.D., (USC) Impact of alcohol on chromosome integrity and DNA modification in the liver cells This project examines the potential links between alcohol and chromosome breaks and DNA methylation.

Bruce Ranyon, M.D. (Rancho Los Amigos Med. Ctr.) A randomized, double-blind trial comparing efficacy of prednisone plus nutritional supplementation vs pentoxifylline plus nutritional supplementation in patients with severe alcoholic hepatitis

The goal of this study is to compare the use of corticosteroids versus pentoxifylline in the treatment of patients with severe alcoholic hepatitis. Survival will be the primary end point of this study.

Yvonne Wan, Ph.D. (Harbor-UCLA Medical Center) Retinoid signaling in alcohol induced liver injury The goal of the project is to determine the impact of interfering retinoid signaling at the receptor level on alcoholic liver disease.

Zhiqun Tak, M.D., Ph.D. (USC) Ub+1 and Ub-proteasome system in alcoholic liver injury The overall goal of this project is to elucidate the mechanism of ethanol-induced hepatocyte death relevant to abnormalities of the ubiquitin (Ub)-proteasome pathway.

Center Supports ALF, Continued from page 4

If you are interested in getting some sun and exercise, and most of all, if you are interested in having some fun by supporting a worthy cause, please contact Anne Taguchi at ataguchi@usc.edu or Gloria Mota at gmoata1@hotmail.com to join Team USC.

For more information about the Liver Walk in general, please contact Isabel Velasquez at (310) 670-4624 or visit their website at www.liver411.com.

We look forward to seeing you there! ♦

3rd Annual Symposium, Continued from page 1

Hazra, and the Best Poster Awards were shared by Fawzia Bardag-Gorce and Victoria Nguyen. Many thanks to Drs. James Ou and Maria Runnegar for making some tough decisions, and congratulations to the winners!

We were very fortunate to have Jonathan Fielding, M.D., M.P.H., the Director of Public Health of Los Angeles County participate in our symposium. He provided insightful comments to the presentation by Nico Tao on epidemiology of alcoholic liver and pancreatic diseases in Los Angeles and shared a few words with us concerning the County’s outreach and preventive programs.

Postdoc Beth Miller studies posters during the lunch break.

LA County Public Health Director, Dr. Fielding.

Scientific Advisory Board Members: ChrcuZ. Dr. Steve Pandol, Hide Tsukamoto, Fred Goresick, Jackie Maher, David Brenner, Bob McCuskey and Tom Budgar.

Drs. Bob McCuskey and Laurie DeLeve; and L-R: Dr. Jose Fernandez-Checa, Dr. Steve Pandol, Yoon Jung, Dr. Steve Sussman.

Center supporter, Tony Lee and his wife; Drs. Maria Runnegar and Michel Mendler.

www.usc.edu/medicine/alcohol_center

www.usc.edu/medicine/alcohol_center
Spotlight on Hal Yee, Continued from page 2

Hal Yee presented a summary and update of his work elucidating the signal transduction pathways that determine, or at least influence activation of stellate cells together with the functional properties of these activated cells.

The model used in Hal Yee's laboratory is the rat hepatic stellate cell isolated from normal rats. Prolonged culture and/or addition of serum result in changes characteristic of activation, these include cell spreading, loss of vitamin A droplets and the formation of cytoplasmic fibers of actin and myosin. With the expression of these cytoskeletal components cells become contractile. It is generally accepted that this contractility modulates sinusoidal resistance and hence blood flow. In an elegant study Hal Yee and coworkers quantitated the contractile capacity of activated stellate cells. Stellate cells were suspended in a three-dimensional collagen gel attached to an isometric force transducer. They measured the force generated when cells were exposed to serum or varying concentrations of the agonist endothelin-1. Endothelin-1 is a vasoconstrictor in vivo and was known to cause contraction of stellate cells. Through these measurements they estimated that the contractile force generated by a single cell is sufficient to produce a pressure of 14,000 dyn/cm² in a rat sinusoid. This is well above the sinusoidal resistance that has been measured even in cirrhotic rats. These calculations showed that the contraction of stellate cells alone can account for the changes in pressure and blood flow seen in cirrhosis. Since contractility was easily reversed by removal of the agonist, it was also concluded that stellate cells may play a role in the normal physiological changes of hepatic blood flow.

Endothelin-1 has been shown to not only control cytoskeletal rearrangement and contractile force generation but also proliferation, fibrogenesis and cell migration in stellate cells indicating an interconnection between all these properties. How these processes occur and what are the signals that regulate them, is the focus of research by many groups. Hal Yee and his group study the intracellular signals that regulate contractility and cell migration. As already stated, on activation of stellate cells there is a large increase in the expression of the cytoskeletal proteins alpha-smooth muscle actin and myosin II. These form a complex network of fibers that can be seen by fluorescence microscopy when actin is labeled with rhodamine phalloidin (see Figure). The mechanical force needed for contraction and for motility is mediated by the function of the actomyosin complex. The actin-myosin interaction is regulated by the phosphorylation of the 20-Kda light chain of myosin by a calcium/calmodulin-dependent enzyme myosin light chain kinase (MLCK). Contractility in smooth muscle has been shown to be mostly regulated through a calcium mediated pathway of activation of MLCK. In order to determine whether the same control mechanisms apply to non muscle cells Hal Yee and coworkers investigated the effect of changes in calcium on the contractility of chicken embryo fibroblasts. Applying the experimental approaches that had been used to elucidate the role of calcium in smooth muscle contractility they found that in fibroblasts changes in cytosolic calcium concentrations did not correlate with myosin light chain phosphorylation (necessary for force production) or with the ability to contract. The conclusions from these results were that one or more other signaling pathway(s) play a role in myosin phosphorylation and contraction.

Rho, a small monomeric guanosine triphosphate–binding protein from the ras superfamily, had been shown by other workers to increase phosphorylation of myosin light chain through the activation of rho kinase in a calcium independent manner. This activation resulted in morphological and motility changes. Hal Yee proposed that this pathway may also control the morphological changes seen in stellate cell activation. He went on to show that stellate cells express rho and that inhibition of rho by the C3 transferase (a specific inhibitor of rho) prevented and reversed the cytoskeletal changes of activation. The next step was to determine more directly whether rho signaling affected the functions of activated stellate cells. If control of contractility and motility are mediated through rho signaling rather than calcium then inhibition of the rho pathway would result in decreased contractility and migration. To test this hypothesis Hal and coworkers used a very specific inhibitor of rho kinase Y-27632. In this work they developed an experimental approach that allowed them to measure directly the ability of stellate cells to migrate and accumulate in areas of injury in response to an endothelin stimulus. They found that addition of the rho kinase inhibitor dose

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Ron Thurman Memorial to be held at RSA Meeting

By Hide Tsukamoto
University of Southern California

We reported in our last newsletter that our beloved friend and colleague passed away last summer. In an effort to honor Ronald G. Thurman, Professor of Toxicology and Pharmacology at the University of North Carolina, the Bowles Center for Alcohol Studies of UNC is hosting a symposium entitled, “Alcohol and the liver: a memorial for Ron Thurman” on June 28, 2002 at the Research Society on Alcoholism - ISBRA meeting in San Francisco. We hope that those planning on attending the RSA meeting will be able to join this symposium which will include various speakers presenting their cutting-edge research on the effects of alcohol and the mechanisms of liver disease and how they relate to Ron's legacies.

The symposium will be from 8:00 AM - 5:00 PM on June 28, 2002 at the Hyatt Regency in San Francisco. Registration is free. For more information, please contact Fulton T. Crews, Ph.D. at (916) 966-5678 or ftcrews@med.unc.edu.

Spotlight on Hal Yee, Continued from page 3

dependently inhibited the ability of stellate cells to migrate to a wounded area firmly establishing a role for rho signaling in stellate cell activation.

In addition to the very productive research in liver Hal and coworkers are also looking at signal transduction in the intestinal tract. They showed that endothelin caused contraction and migration of human colonic fibroblasts, as in liver through myosin phosphorylation, suggesting a role for these cells in intestinal wound repair. These findings are consistent with previous in vivo work where it had been shown that inhibition of endothelin activity affected colonic wound healing in rats. In a very recent publication, Hal together with coworkers at UCLA, described the signaling steps that lead to proliferation following exposure to vasopressin in intestinal epithelial cells. Findings that indicate a possible role of vasopressin in the repair of the intestinal mucosa following injury.

Hal's interests and success are not limited to the lab. Hal is a physician scientist and as such values his clinical work. He runs a clinical program at UCLA that focuses on the problem of fatty livers and NASH (non-alcoholic steatohepatitis), conditions that affect primarily obese and diabetic patients. This study under the auspices of National Institute of Health is a collaboration between UCLA, UCSF and Kaiser. In addition Hal teaches GI and liver physiology and helps supervise and train residents.

Lastly but certainly not least, Hal is happily married to Frances a nurse practitioner in the LA county system. They are the proud parents of Maxwell a very lively 18 month old boy.

Center Supports the American Liver Foundation: Greater Los Angeles Chapter

By Hide Tsukamoto
University of Southern California

In support of the American Liver Foundation: Greater Los Angeles Chapter, the Center will be donating the $25 registration fee for each participating staff member.

The 10K run & 5K walk will be on June 1, 2002 at Griffith Park in Los Angeles. The start time is at 8:00AM. In addition to walking for a great cause, we are looking forward to entertainment, food, beverages, prizes and awards.

Center Supports the Ron G. Thurman Lecture-ship Award

By Hide Tsukamoto
University of Southern California

The Bowles Center for Alcohol Studies at the University of North Carolina has established the Ron G. Thurman Lectureship Award. This endowed award will establish a fund to cover scientists with travel and honorarium support. The hope is that this lectureship award will focus attention and excitement to the type of research that Ron was so excited about himself.

Please support this lectureship award by making a contribution to the fund.

The Center will match dollar for dollar any donation that you make!!

Please contact Anne Taguchi at ataguchi@usc.edu for information on how to make a donation.

www.usc.edu/medicine/alcohol_center
In 1996 Hal returned to UCLA where he joined the faculty of the Division of Digestive Diseases. Hal saw that in liver he could build on his expertise from previous work on the contractility of cardiac myocytes and apply it to stellate cells. These cells encircle the sinusoids, are normally quiescent but in chronic liver disease assume a myofibroblast-like phenotype. These “activated cells” begin secreting components of the extracellular matrix and developing contractile properties.

The premise for this research is that activation of these cells resulting in increased contractility, proliferation, migration and deposition of extracellular matrix is the major determinant of the development hepatic fibrosis and ultimately cirrhosis in chronic liver disease. Cirrhosis results in most cases from the prolonged, excessive intake of alcohol but can also result from chronic Hepatitis C viral infection. At present there is no successful treatment for cirrhosis, a very often fatal condition, short of a liver transplant.

The long term goals of Hal Yee's research are to develop strategies for the prevention and treatment of hepatic cirrhosis. Since the activation of stellate cells is central to the development of cirrhosis it is necessary to understand the molecular triggers and factors that control the progression of this change. Towards this aim Hal's laboratory is using a variety of molecular, biochemical and cellular methods to begin to understand the intracellular signals that control the activation process.

At a recent mini-symposium on Hepatic Cirrhosis held February 28th, 2002 to coincide with Dr. Pinzani's visit, Hal shared his progress with the audience.

**Pinzani Guest Lecturer at Cirrhosis Workshop**

By Hide Tsukamoto
University of Southern California

On February 28, 2002, the Research Center had the pleasure of having Massimo Pinzani, M.D., Ph.D. (Professor of Medicine at the University of the Studies of Florence, Italy) speak for the Cellular Homeostasis Lecture series. His lecture was entitled, “Cellular and molecular mechanisms of liver fibrosis: Focus on intracellular signaling.” This stimulating lecture was followed by a fibrogenesis mini-workshop sponsored jointly by the Center's Southern Alcohol Research Group (SCARG) and the Cirrhosis Research Group (CRG). This informal session consisted of presentations by Hal Yee, Sasawati Hazra, EunDuk Kay, Ilya Gukovskiy and Aurelia Lueja on the cellular and molecular mechanisms underlying fibrogenesis in various organs such as the liver, eye and pancreas.

Dr. Pinzani also participated in Rancho Los Amigos Medical Center's Liver Grand Rounds with a talk entitled, “Hepatic fibrosis: Diagnostic and therapeutic implications.”
The Center is pleased to announce that the program is now an annual opportunity for graduate and undergraduate students. Up to $1,000 is available for students interested in pursuing a summer research project.

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Center Offers Summer Student Fellowship
By Anne Taguchi
University of Southern California

Following the success of last year’s summer student fellowship program, the Center is pleased to announce that the program is now an annual opportunity for graduate and undergraduate students. Up to $1,000 is available for students interested in pursuing a summer research project.

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3rd Annual Symposium a Success!
By Hide Tsukamoto

Once again, we had a wonderful program, and I thank all those who participated in our all-day symposium. We had a full day of fascinating lectures, including special lectures by Jose Mato, Ph.D. of the University of Navarra, Spain, Yvonne Wan, Ph.D. of Harbor-UCLA Medical Center, Jose Fernandez-Checa, Ph.D. of the University of Barcelona, Spain, and Scientific Advisory Board member, Jacquelyn Maher, M.D. of the University of California, San Francisco. These special lectures will be available for viewing on our website following our upcoming redesign!

This year we invited junior investigators, graduate students and trainees to compete for two $300 prizes for a submitted abstract (poster or oral presentation) at a national meeting on topics related to the Center’s theme, “Elucidation of the mechanisms by which ethanol sensitizes and primes the liver and pancreas to diseases.” The Best Abstract Award went to Saswati

Drs. Neil Kaplowitz and Jose Mato catch up during the lunch break.

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