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CONTACTS:

Hide Tsukamoto, Director
htsukamo@usc.edu
323-442-5107

Anne Taguchi, Administrator
ataguchi@usc.edu
323-442-3120

Fax: 323-442-3126

Web:

www.usc.edu/schools/medicine/research/alcohol_center

Today

Center Organizes First Community Seminar

By Anne Taguchi
University of Southern California

On December 5, 2003, the lay public got its chance to meet the doctors involved in research on liver and pancreatic diseases in a lunchtime seminar hosted by the Center. With 30 people in attendance, the speakers spoke on alcohol and nutrition, hepatitis virus, obesity, and the pancreas. In this session, the audience had access to some of the most prominent M.D.'s in their respected areas – Dr. Stephen Pandol (UCLA), Dr. Shelly Lu (USC), Dr. Michel Mendler (USC) and Dr. Sumita Verma (USC). The session was also videotaped for local access cable. Please refer to local listings.

Due to its success, the Center will host another seminar this year, held on its own special day, Saturday, December 4, 2004, and with a format change which we hope will allow for greater audience participation. The session will be held in a "talk show" type format, and the doctors again will be available for questions by the audience. Please check back with TODAY for further information in the next issue.

The Center thanks Pharmavite, Genova, Fujisawa, Gilead and VWR for making this event possible. ♦

Hide Tsukamoto shares his view of the community seminar: "The Center is committed to education and training, and ultimately, our goal is for our research to benefit the public. The first community seminar has been a great step in our outreach efforts, to get the word out to patients and the lay public, and to bring the doctors within reach to them. We feel that this sharing of knowledge is an important mission of the Center."

Director's Note The Center's Second Phase of Growth

By Hide Tsukamoto
University of Southern California

I am delighted to report to you that our NIAAA center grant has successfully been renewed for 5 more years until the end of 2008. It provides us the total funding of \$8.3 million of which \$5.8 million are total direct costs. This success is truly a reflection of outstanding collective efforts by all center members during the past funding cycle. The summary statement for the reviewers' comments on our application, highlights several major strengths that the center has built. A 6-fold increase in the acquisition of NIH grants by the center members was considered as a remarkable outcome directly facilitated by the center's support mechanisms such as the pilot project program, cores, and collaborations. Accordingly, all three core components (administrative, animal and morphology) and pilot project program received outstanding scores. The reviewers all praised the center's evolution to a multifaceted program that encompasses cutting-edge basic and clinical

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Spotlight on...**Gunther Dennert**

By Maria Runnegar
University of Southern California



Gunther Dennert is Professor of Molecular Microbiology and Immunology at USC, and an active Member of the USC-UCLA Research Center for Alcoholic Liver and Pancreatic Diseases.

Gunther Dennert's interest in science began early from his father who was professor of Biology at the University of Bonn, Germany. In the sixties Gunther, with the idea of following in his father's steps, started undergraduate studies in Zoology and Botany at the University of Bonn. At the time these disciplines as formally taught were rather descriptive and could not satisfy Gunther's curiosity of the whys and hows of Biology. Graduate studies towards a PhD turned to phage genetics and the gene regulation of the pyruvate dehydrogenase complex in *E. coli* with Wulf Henning at University of Cologne. In the late sixties gene sequencing was only a hope for the future rather than the reality of the day. This meant that only purely genetic studies were possible.

Then serendipity stepped in the form of an exciting guest seminar by Niels Jerne on lymphocytes and their newly described roles in the immune system. Gunther was hooked to immunology: a discipline at the time progressing in leaps and bounds.

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Center Offers Lee Summer Student Fellowship

In the summer of 2001, the Center instituted the Lee Summer Student Research Fellowship Program to promote involvement of undergraduate and Master's students in research on our Center's theme. The program is named after Dr. S.P. Lee who made a donation toward this noble cause. Currently there is an opportunity for 4-5 undergraduate or Master's students slots with a stipend of \$800-\$1000 each for students interested in pursuing a summer research project.

Requirements for eligibility are:

- Incumbent must be an undergraduate or Master's student
- Incumbent must be available to work full time for 8-10 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 the Progress Report meeting in August or our symposium in December.

Interested candidates, please e-mail Anne Taguchi (ataguchi@usc.edu):

- Title of project
- Summary of project
- Mentor name and supporting letter (fax – 323-442-3126)

Spring Seminar Series Once Again a Big Success

By Rosy Macias
University of Southern California



*William Parks,
James Darnell
Atsushi Miyajima
R: Randall Moon
with Path 575
students*

This year's Cellular Homeostasis Lecture Series was kicked off with a lecture entitled, "How We Sense Infection: Answers from the Forward Genetic Approach" by Bruce A. Beutler, M.D. of The Scripps Research Institute. Other prominent speakers who were invited to participate in the Lecture Series, included William Parks, Ph.D. from Washington University School of Medicine who talked on "Control of Repair and Inflammation by Extracellular Proteolysis"; James Darnell, M.D. from Rockefeller University who discussed "STAT 3: Transcription and Cancer"; Atsushi Miyajima, Ph.D. of the University of Tokyo who spoke on "Roles of Cytokines for Liver Development and Regeneration."



Graduate students and postdoctoral fellows supported by the Center's institutional training program, have also taken this lecture series as a 2-unit pathology graduate course (Pathology 575: Frontiers of Pathology).

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progressing in leaps and bounds. He joined Klaus Rajewsky at the Institute for Genetics in Cologne. When considering the next step in 1970 it was clear that San Diego was the place to be for cutting edge immunology research. The Salk and Scripps Institutes as well as UCSD were attracting the brightest young scientists from Europe as well as the US. At the Salk Gunther started his seminal work in the study of the innate immune response.

Innate immunity provides an immediate response to infection against pathogens and enhances the specific T-cell mediated adaptive immune response that follows. Many cell types are involved in innate immune responses including macrophages, dendritic cells, natural killer (NK) cells and natural killer T (NKT) cells. Gunther was the first to successfully maintain permanently in culture cytotoxic T cells (CTL) and NK cells thereby disproving the then accepted dogma that in normal cells death occurred after a finite number of cell divisions. His lab was also the first to identify NKT cells as a subset of NK cells with expression markers both of NK cells and T cells allowing them to specifically recognize glycolipids and thereby become activated. Other pivotal findings included the identification of perforin by which NK cells and CTL kill infected cells.

Although life in the lab was very exciting for Gunther, he made time for the outdoors: camping trips to the desert, scuba-diving in the ocean, horse riding in Mexico together with many of the young scientists attracted to the vitality of the San Diego institutions. A love for the outdoors that continues today. Gunther had the opportunity to return to academia in Germany but the California hold after a ten-year stay was too strong. The opportunity to remain permanently in Southern California while facing new challenges came as an offer to join the faculty of the Department of Microbiology at USC. Here he could combine research with teaching, which had not been possible at the Salk.

An intriguing observation: the fact that the liver has the greatest number of NK and NKT cells in the body led Gunther's studies of innate immunity to this organ. The experimental model for this was the mouse. This was a lucky choice as in the intervening years knowledge of the mouse genome, the development of various knockout as well as the characterization of strains with spontaneous or induced mutations resulting in defects in the function of NK and NKT cells has led to amazing progress in the understanding of the mechanisms that determine the function of the immune system.

Gunther and his coworkers found that NK and NKT cells respond to viral infections. If these cells are inactivated

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5th Annual Symposium

By Anne Taguchi
University of Southern California

Our symposium in December of 2003, represented the last one for our 5-year funding period, and we had a wonderful turnout for the all day event. Thank you to all who participated. In addition to Fellows Brian Soreghan, Yan-Ling Wan, Balaka Das, Taunia Lee and Andy Melton, pilot project PI's, Yuan-Ping Han and Aurelia Lugea, reported on their progress. Our keynote speakers were Scientific Advisory Board member, Tom Badger, who spoke on "Alcohol and Endocrine-Regulated Gene Expression" and Prof. Hiromasa Ishii who came all the way from Japan to speak on "Genetic polymorphism of alcohol metabolizing enzymes and its relation to carcinogenesis of digestive tracts."

*Hide Tsukamoto
presents the
Outstanding
Service Award to
Dr. Qinggao Deng
at the dinner
reception*



This was the first year we held a community seminar during the symposium lunch break. (Please see cover story for more information.)

And once again 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 was given to Andy Melton and Two Best Poster Awards were given to Fawzia Bardag-Gorce and Mouad Edderkaoui. Many thanks to Drs. Hal Yee and Maria Runnegar for making some tough decisions, and congratulations to the winners!

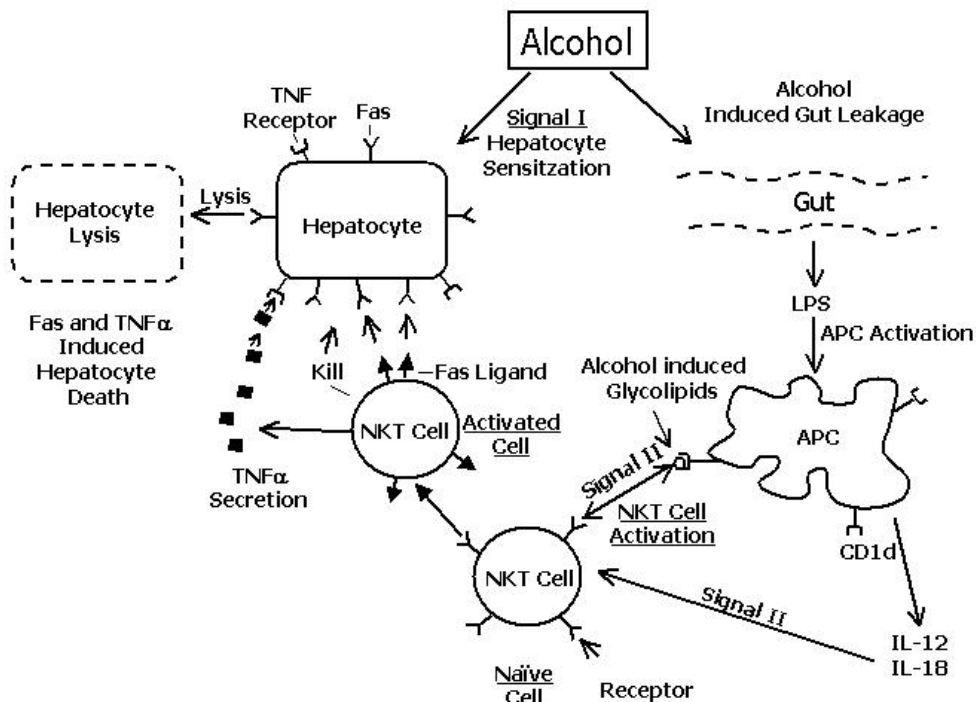
In the evening, we all retired to the Faculty Center for a delicious meal and a string quartet from USC's Music School. Two surprise awards were given to Prof. Ishii in recognition of longstanding contributions to alcohol research and to Dr. Qinggao Deng for his seminal contributions to the Animal Core Facility. Jerry Reilly, CEO of the Organs for Life Foundation graciously hosted the reception dinner. ♦

Gunther Dennert, Continued from page 3

then the subsequent adaptive immune response is greatly decreased indicating the close interaction between the two responses. The NK cells stimulate T-cells to more efficiently respond to virus-infected cells. This "sensitization" of the cell mediated T cell response is most likely through cytokines such as interferon alpha and chemokines that attract to the liver virus-specific T- cells.

There are recent reports that also indicate that NK and NKT cells play a major role in regulating autoimmune responses. Changes in the number and function of NKT cells have been shown to be associated with insulin-dependent diabetes, systemic sclerosis and lupus erythematosus in mice.

It has been known that chronic excessive alcohol consumption renders the liver more susceptible to viral infections such as chronic HCV with more severe progression. It is this background that initially interested Gunther to look at the innate immune response in an alcoholic liver disease model: the intragastric infusion mouse model. This work was facilitated by a pilot project grant from the Research Center for Alcoholic Liver and Pancreatic Diseases. One of the first findings was that alcohol feeding even for just a week significantly increased NKT cells in liver and ALT (measure of hepatocytes damage) in the serum. NKT cells are likely to be at least partially activated given that fatty liver changes can unmask glycolipids in the antigen-presenting cells (see diagram). To show that it is their degree of activation that determines outcome mice fed alcohol were dosed with a stimulating glycolipid that has been shown previously to fully activate NKT cells. The result was fulminant hepatitis. Since fulminant hepatitis does not follow glycolipid exposure in a control mouse led Gunther and coworkers to conclude that alcohol makes hepatocytes more susceptible to injury. Alcohol could well cause an increase in the production of cytokines capable of inducing at least partial activation of NKT cells.



The next question Gunther and colleagues then went on to ask was what is the mechanism that leads to the massive loss of hepatocytes when NKT are activated in an alcohol-treated mouse. They demonstrate that death of hepatocytes is likely due to increased susceptibility of hepatocytes to apoptotic signals mediated through the innate response. FasL (Fas ligand) at the cell surface of NKT cells kills hepatocytes by interacting with Fas present on the hepatocytes. This mechanism is substantiated by showing that *lpr* mice (Fas defective mice) will not die and will have a reduced ALT increase when stimulated with the glycolipid. Gunther and co-workers showed that TNF alpha induced cell death also plays a role in alcohol caused liver damage. Mice deficient in TNFR1 (TNF receptor 1) are partially protected from alcohol-induced injury. Serum levels of TNF alpha are increased while TNF alpha mRNA is induced in activated NKT cells. They showed that expression of both Fas and TNF alpha signaling pathways is necessary for maximal liver injury. Finally they propose a role for Kupffer cells. This work is currently in press in *Gastroenterology*.

Altogether the very interesting work of Gunther and coworkers in the study of alcoholic liver disease clearly shows the significant contribution of the immune system. Many questions have been answered but it is far from the end of the story and in the near future, as this work progresses, we will have many more intriguing findings. Overall this work clearly emphasizes the complexity of alcoholic liver disease: where a chemically simple molecule causes so many disparate responses. ♦

Pilot Project Investigators Explore Innovative Research

The Center is proud to support the exploration of new directions in research on the Center's theme. The following investigators obtained pilot project funding for 2004.

Yuan-Ping Han, Ph.D. (USC) - Cytokine regulation of MMPs and TIMPs by alcoholic liver

The goal of this project is to test whether MMP-9 is essential for HSC activation and liver fibrosis; to understand mechanism of dual signals from collagen and IL-1 α are required for induction of proMMP-9; and to delineate the molecular mechanism of collagen and TIMP-1 on maintenance of quiescence of hepatic stellate cells.

Aurelia Lugea, Ph.D. (UCLA) - Plasminogen system and alcohol-induced pancreatic fibrosis

The goals of the project are to determine the effects of ethanol on the course of cerulein-induced pancreatitis in plasminogen sufficient and deficient mice, and to examine the expression and effects of the plasminogen system on cultured pancreatic stellate cells and determine the effects of ethanol and its metabolites on cultured PSC responses to components of the Plg system.

Ite Laird-Offring (USC) - HuR-regulation of TNF alpha in alcoholic Liver Disease

The goal of this study is to determine whether methylation of HuR occurs in liver macrophages and is elevated in cell isolated from ethanol-treated rats.

Jian-Min Yuan (USC) - Risk factors for alcoholic liver disease in Los Angeles

The aims of the study are to assess the association between self-reported alcohol consumption and the risk of ALD; to determine the modifying roles of obesity, cigarette smoking, and dietary intake of antioxidants, fat and iron in the alcohol-ALD association; and to determine the modifying role of acetaminophen on the alcohol-ALD association.

Director's Note, Continued from page 1

research as well as undergraduate, graduate, post-doctoral training and public outreach components. The center is also regarded as a unique and invaluable resource because our animal core and non-parenchymal liver cell core (funded separately by NIAAA) extend their highly specialized services to investigators across the nation. Our postdoctoral training program is another strength and has incorporated the enlightening curriculum including the Spring Cellular Homeostasis Lecture Series, that has become one of the most attended seminars on campus.

Our center is the only NIAAA/NIH-funded center of excellence in the country that devotes to promotion of cutting-edge research on the pathogenesis of alcoholic liver and pancreatic diseases, and cirrhosis, as well as dissemination of newly generated information on the diseases. Our mission is to develop new therapeutic and preventive modalities based on the cellular and molecular understanding of how alcohol and secondary genetic or environmental factors make the liver and pancreas vulnerable to progressive damage. Even though we are far from achieving this ultimate goal, science pursued by the center investigators is beginning to shed critical insights into this central question. They are briefly summarized in our newsletters, also online at (http://www.usc.edu/schools/medicine/research/alcohol_center).

Our outreach efforts now include community seminars. The first center-supported community seminar was successfully held in conjunction with the annual symposium last December, where the center members gave short lectures to a lay audience on the interactions between alcohol and nutrition, hepatitis virus, obesity, and pancreas. The next one is scheduled on December 4, 2004 and will take a format of Q&A sessions in an open forum moderated by Jerry Reilly, CEO of Organs for Life Foundation and liver transplant recipient. We believe this type of direct outreach activity most efficiently disseminates cutting edge science information by the center-supported research to local community.

As the center enters the second cycle of the funding, it focuses on a qualitative growth of the center components that have been firmly established and effectively expanded for the past 5 years. We expect to see more investigators with their unique expertise introduced into our field and successfully competing for NIH grants. We expect to see more interactions between the diverse specialties for multidisciplinary and innovative approaches to basic and translational research. This second phase of the growth will only be possible when active participation by the center members continues as it did for the successful renewal. Congratulations to you all. ♦

Spring Seminars, Continued from page 2



Don Rockey at mini-conference

Dr. Parks and Dr. Rockey also stayed for mini-conferences after their seminar talk. The conferences were held in an informal, lab meeting style to exchange up-to-date research information among the center members who are currently engaged in research on matrix biology (Parks) and stellate cells (Rockey). ♦

Most Recent Publications by Center Members

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