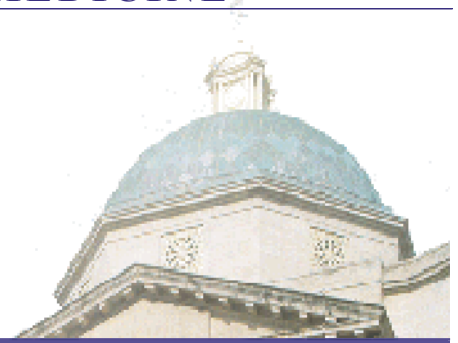


THE DEPARTMENT OF
**INTERNAL
MEDICINE**



Newsletter of the Department of Internal Medicine

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The Yale Liver Center: An Overview and History

The Yale Liver Center is an NIH Digestive Disease Research Core Center, established in 1984. It is now in its 20th year of consecutive funding having successfully competed for another five years of support from the National Institutes of Diabetes, Digestive and Kidney Diseases. From its inception, the major goal of the Center has been to bring together clinical and basic science faculty at Yale to focus on the common goal of understanding liver structure, function and disease. The leadership of the Center includes James L. Boyer, M.D., Ensign Professor of Medicine who is the Center Director, and Roberto J. Groszmann, M.D. and Michael H. Nathanson, M.D., Ph.D. who serve as Deputy Directors. The Center is governed internally by an Executive Committee that also includes: Drs. Tommy Cheng (Pharmacology), Dr. Richard Flavell (Immunobiology) and Dr. Guadalupe Garcia-Tsao (Internal Medicine).

Currently about 36 independent investigators are members of the Center, representing 13 departments at Yale: Cell Biology; Cellular and Molecular Physiology; Comparative Medicine; Epidemiology and Public Health; Human Genetics; Immunobiology; Laboratory Medicine; Internal Medicine; Molecular Biophysics and Biochemistry; Molecular, Cellular

and Developmental Biology; Pathology; Pediatrics; Pharmacology; and Surgery.

The Liver Center is formally constructed around four core facilities that contain: 1) an Administration Core, 2) a Cellular and Molecular Physiology Core, 3) a Morphology Core and 4) a Clinical Core. Since July 2003, Liver Center Administrative and Core Facilities have relocated to the Anlyan Center, which has expanded and consolidated the Center's physical space at the School of Medicine. The Administration Core supports the center administrator (JoAnn Sullivan), an accountant (Julie Scocozza) and the center coordinator (Ann Thompson). Together with the Center Director they are responsible for overall organization, general planning and fiscal management of the Center.

The Cellular and Molecular Physiology Core, directed by Dr. Boyer, provides three separate functions: 1) Isolation of hepatocytes, and non-parenchymal cells (bile duct epithelial cells, Kupffer cells, endothelial cells, stellate cells and lymphocytes) from rats or mice on a daily basis as needed. Kathy Harry provides expert technical assistance for these procedures. 2) A facility for maintaining rat or mouse livers in an isolated state. 3) A molecular component providing quantitative PCR technology, densitometry equipment and access to molecular services at the Keck Center.

The Morphology Core, directed by Dr. Nathanson, is a multi-service facility with major emphasis on confocal fluorescence microscopy. Additional morphologic techniques include epifluorescence microscopy, electron microscopy, video microscopy and two-photon



James L. Boyer, M.D.
Center Director

microscopy. State of the art image processing and analysis software is available.

Finally, the recently reorganized Clinical Core, directed by Dr. Garcia-Tsao, supports a clinical study coordinator and part time biostatistical support to assist investigators with protocol development, compliance with NIH, IRB and HIPAA policies as well as patient recruitment and storage of clinical samples of serum, liver biopsies and DNA. The Clinical Core is a hallmark of our Center, emphasizing translation of clinical science to the bedside.

The Yale Liver Center research base spans a broad range of basic and clinical investigation. Major research themes include: 1) Cellular and Molecular Biology of the Liver; 2) Hepatic Transport Mechanisms; 3) Basic Biology of Disease Processes; 4) Studies of the Splanchnic Circulation; 5) Liver Immunology; and 6) Clinical Hepatology. The total research base (sum of digestive disease related grants awarded to Center Investigators) is approximately \$15 million.

One of the most important functions of the Center, in addition to the services provided by the Core Facilities, is the **Pilot Feasibility Program, which provides funds for new and unfunded initiatives.** Each December a call goes out to the entire Yale biological sciences faculty soliciting letters of intent for applications for funding for new projects. Awards range from \$10,000 - \$25,000, and are primarily designed to support senior postdoctoral fellows and junior faculty to enable them to obtain sufficient data for initial R01 applications. More established investigators from outside the digestive disease community are also eligible for funding if they can apply their area of expertise to a new liver related project. Finally, current Center members can also apply for this start up funding if their project represents a new, as yet unfunded, direction. Applications are submitted on abbreviated NIH forms and are reviewed for eligibility and scientific merit by two experts, usually from within the Yale community. After this initial review, worthy applications are submitted to the Center's seven-member External Advisory Board who visits Yale on an annual basis in the spring. The board judges these applications for scientific merit, usually after a scientific presentation from the applicants. This year 12 applications were reviewed and 5 were awarded funding. These include grants to Anton Bennett, Ph.D. (Pharmacology),

"Regulation of Metabolic Homeostasis by MAPK Phosphatases in the Liver"; Jonathan Dranoff, M.D. (Internal Medicine), "Novel Mechanism to regulate Bile Duct Proliferation"; Michael J. Kozal, M.D. (Internal Medicine), "Development of DNA Microarrays to Detect HCV Drug Resistance"; Wajahat Mehal, M.D., Ph.D. (Internal Medicine), "Regulation of Stellate Cell Apoptosis by Adipokines"; and Mark Parker, Ph.D. (Cellular and Molecular Physiology), "Regulation of Intracellular pH in Hepatocytes: a Proteomic Approach".

During the past five years, more than \$500,000 was awarded in pilot funding to 31 individual investigators from 11 different departments. Seventeen were senior fellows or junior faculty and only 9 awards were given to faculty at the Professor rank, emphasizing that this program primarily supports young as opposed to established investigators. Subsequent successful applications from NIH and other sources based on pilot support research have already amounted to a 15-25-fold return on this investment.

Significant Scientific Accomplishments:

A few examples of some of recent scientific accomplishments of Liver Center investigators include: 1) Discovery of genes responsible for Polycystic Liver Disease by Dr. Somlo's group (*Am. J. Hum. Genet.* 72: 691-703, 2003; and *Nature Genetics* 36:575-577, 2004). 2) Evidence from Dr. Boyer's group that Mrp3 (*Abcc3*), the multidrug resistance protein 3 is transcriptionally induced in the liver, thereby providing a protective mechanism that diminishes bile salt induced liver injury in obstructive cholestasis (*J. Biol. Chem* 278:36688-36698, 2003). 3) The demonstration that the loss of inositol 1,4,5-trisphosphate receptors from bile duct epithelia is a common event in cholestasis that results in loss of Ca^{2+} mediated bicarbonate secretion by Dr. Nathanson's group (*Gastroenterology* 125:1175-1187, 2003). 4) The highly novel observation that calcium signals in the nucleus are regulated by a nucleoplasmic reticulum, again from Dr. Nathanson's group (*Nature Cell Biology* 5:440-446, 2003). 5) The demonstration that Kupffer cells are required for high affinity peptide-induced deletion but not retention of activated CD8⁺ T cells in mouse liver from Dr. Mehal's group (*Hepatology* 39:1017-1027, 2004). 6) The important finding that the phosphatidylserine receptor is required for the clearance of apoptotic cells from Drs. Flavell and Mehal's groups (*Science* 302:1560-1563, 2003).

7) Evidence that bacterial translocation in cirrhotic animals leads to endotoxemia and upregulation of GTP-cyclohydrolase 1 in the mesenteric vasculature further enhancing vascular NO production and aggravating vasodilatation in cirrhosis by Dr. Groszmann's group (Hepatology 38:1508-1515, 2003).

Since its inception, the Yale Liver Center has been characterized by several distinctive features: 1) Strong basic science collaborations, particularly in the Departments of Cell Biology, Cellular and Molecular Physiology, Immunobiology, and Pharmacology. 2) Important national and international collaborations that bring an added dimension to the Center and its research base and reputation. Some of these collaborations have been continual since the start of the Center in 1984. 3) Continued excellence as a national and international center for pre- and post-doctoral investigative training in Hepatology and its basic science disciplines. 4) A broad research base that features both basic science and clinical investigation, and provides a setting in which we continue to strive to bridge these disciplines. **The Center continues to be an important focus for pre- and post-doctoral training.** Approximately 20 to 25 pre- and post-doctoral M.D. and Ph.D. fellows train within the central Digestive Disease Center laboratories on Center-related projects each year. In addition to trainees from the United States, post-doctoral trainees have come from a number of different countries during the past five years including Brazil, Canada, China, England, Germany, Japan, Korea, India, Italy, Pakistan, Spain, Switzerland, Taiwan, Thailand and Turkey.

The clinical activities of the Center focus primarily on translational research in chronic liver disease. These studies are carried out both at the West Haven VA Hospital and the Yale School of Medicine and are designed to access: a) the role of pharmacological therapy in the treatment of portal hypertension supported by a multi-national NIDDK trial; b) the management of complications in chronic liver disease such as ascites and bacterial peritonitis; and c) therapy for chronic cholestatic liver disease including a multi-center trial that examined the role of methotrexate in addition to ursodeoxycholic acid in patients with primary biliary cirrhosis. These studies also benefit from the Clinical Research Center facilities at Yale New Haven Hospital.

New Initiatives: Several new programmatic initiatives have developed from Center activities during the last several years. These involve a program project in signal transduction within the nucleus, directed by Dr. Michael Nathanson; a new Viral Hepatitis C Center, based at the West Haven Veterans Administration Hospital, directed by Dr. Garcia-Taso; a National Gaucher Center, directed by Dr. Pramod Mistry; and a Comparative Toxicogenomics Database under development at the Center's satellite facility at the Mt. Desert Island Biological Laboratory and directed by Dr. James Boyer.

Community Activities: The Liver Center also sponsors local community based physician and patient oriented activities organized by the Connecticut chapter of the American Liver Foundation. Members of the Section of Digestive Diseases, their friends and families turned out in force to participate in the American Liver Foundation's Annual "Walk for Life" (see photo left). The event was held at Hammonasset State Park on October 3 and drew participants from throughout the state. Some of the participants chose to run the 5K course. Yale's entries placed first (Chuhan Chung, not pictured) and third (Charles Nathanson, pictured in the center).

Additional Information about the Liver Center is available at the website: <http://livercenter.yale.edu>



Nancy Berliner, M.D. named Chair of the Department's Appointments and Promotions Committee



Dr. Nancy Berliner, Professor of Internal Medicine in the Section of Hematology, was named Chair of the Department's Appointments and Promotions Committee effective November 1, 2004. Dr. Berliner has served on the Appointments and Promotions Committee for several years. She will bring considerable organizational skills and experience to this new role. The Department is fortunate to have Dr. Berliner in this critical position. She is replacing Dr. Mary Tinetti who was recently appointed Associate Chair for Clinical Research in the Department. In addition to Dr. Berliner, the Department's 2004-05 Appointments and Promotions Committee is comprised of Drs. Margaret Bia, Linda Bockenstedt, Edward Chu, David Coleman, Gary Desir, Erol Fikrig, Rosemarie Fisher, Patrick O'Connor, Mary Tinetti, and Lawrence Young.

New Faculty

Xuesong Chen, Ph.D. appointed Associate Research Scientist in the Section of Endocrinology

Dr. Chen received his Ph.D. from the Chinese Academy of Medical Science and Peking Union Medical College. His studies concerned the mechanism of gene regulation in human T cells, and the critical role for STAT1 and STAT3 in regulating Heat Shock Protein 90 alpha (hsp90alpha) gene expression. After one year of postdoctoral training at Children's Hospital Boston/Harvard Medical School, Dr. Chen joined the laboratory group of Dr. Arthur Broadus at Yale. He began work on a NIDDK funded project concerning the role of parathyroid hormone-related protein (PTHrP) and bone mechanical signal transduction. He developed data clearly indicating PTHrP as a candidate endogenous mediator of the anabolic effects of mechanical force on bone. This data is critical to understanding the molecular mechanism of bone remodeling and highlight the importance of PTHrP as an effective skeletal anabolic agent for the prevention and treatment of osteoporosis. Based on the merit of his study, Dr. Chen was selected to receive the Young Investigator Award by The American Society for Bone and Mineral Research (ASBMR) in 2004. He is utilizing PTHrP knock-in mice to further explore the role for PTHrP in bone mechanotransduction in vivo.



Dr. Chen currently lives in New Haven.

Susan Hardy, M.D. named an Instructor in Geriatrics



Dr. Hardy obtained her undergraduate degree in history from Princeton University and her medical degree from the University of Pittsburgh. She received her Internal Medicine training at Duke University, and came to Yale in 1999 as a Robert Wood Johnson Clinical Scholar. Upon completing the Clinical Scholars program, she embarked upon a three-year fellowship in Geriatric Medicine at Yale, during which she also earned her Ph.D. in Investigative Medicine (to be awarded in December).

Under the guidance of Drs. Thomas Gill and Mary Tinetti, Dr. Hardy examined recovery from disability in basic activities of daily living among older persons in her dissertation research. She focused on the recurrent nature of disability,

and is currently the recipient of a Pfizer/AGS Foundation for Health and Aging Junior Faculty Scholar Award to further pursue her research on transitions between states of disability and independence.

Dr. Hardy and her husband Larry live in New Haven, where they enjoy attending the theater.

Carolyn Macica, Ph.D. appointed Assistant Professor in the Section of Endocrinology

Dr. Macica obtained her master's degree and Ph.D. in Pharmacology from New York Medical College. She pursued her graduate work in the laboratory of Dr. Wenhui Wang on the regulation of the ROMK kidney epithelial potassium channel. She subsequently completed her post-doctoral graduate training in the laboratory of Dr. Leonard Kaczmarek in the Department of Pharmacology at Yale University where she studied the modulation of ion channel activity required to preserve high-fidelity firing in the auditory brainstem.

Dr. Macica currently conducts research in the field of nerve injury and regeneration and is interested in the role that Schwann cells play in the regenerating nerve following axotomy. While working in the laboratory of Dr. Arthur Broadus, she identified parathyroid hormone-related peptide as a key Schwann cell-derived factor involved in promoting nerve re-growth. She participates in the collaborative Multiple Sclerosis Research Center Award, directed by Dr. Jeffery Kocsis, in which different facets of tissue damage that occur in MS are explored in order to promote novel therapeutic approaches designed to improve nerve function.

Her interests include gardening, sewing, cooking and running and she is an active member of her local garden club. Her husband, Matthew, is a self-employed web designer and artist and is an avid golf enthusiast. They have a daughter, Sarah Ann, whose interests include soccer, drawing, writing, and she recently made her theatrical debut as "Queen Ant".



New Grant Awards

The focus of part of the Craft lab is upon understanding the mechanisms of loss of immune self-tolerance in systemic lupus erythematosus (SLE). They have found that T cells from lupus-prone mice are intrinsically (genetically) hyper-responsive following stimulation via their T cell receptor, and that this hyper-responsiveness contributes to loss of self-tolerance and subsequently to the disease phenotype. Similar events occur in T cells from patients with SLE. The lab has recently been awarded two grants to further investigate the biochemical and



genetic bases of these abnormalities. **Dr. Craft** was awarded a continuation of an R37, or MERIT (Method to Extend Research in Time) Award, entitled "Immune Responses in Lupus". MERIT Awards are given to provide long-term grant support to select investigators, and extend in duration beyond the usual length of an R01. Investigators do not apply for these awards; rather, the appropriate National Advisory Council based upon review of funded competing grant applications chooses them. Dr. Craft was awarded a MERIT Award from the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) in 2000, and this award was recently administratively continued in 2004 to provide 10 years of stable funding until July 2010. In addition, Dr. Craft was awarded an R21 grant from NIAMS, "T Cell Activation in Lupus: Proteomic Characterization" to use state-of-the art protein profiling to dissect signaling abnormalities in lupus T cells. R21 grants are focused, high-risk applications that support novel, potentially high yield ideas.



MARK J. MAMULA, PH.D., Associate Professor in the Section of Rheumatology, has recently been awarded two new grants from the National Cancer Institute of the NIH to study novel peptide vaccine candidates for the treatment of cancers in animal models. The grants entitled “Modified Her-2 Tumor Antigens for Vaccination in Cancer” and “Isoaspartyl Modified Tumor Antigens for Vaccination” are studies in collaboration with L2 Diagnostics at Yale University. Dr. Mamula has had a long-standing interest in investigating the early events involved with the induction of autoimmunity. More recently, Dr. Mamula has also been applying some his studies towards developing “autoimmune” responses against tumor tissues, in particular, murine models of melanoma and breast cancer. His laboratory has identified post-translational protein modifications that are known to be important in breaking immune tolerance to self proteins. His new grants are based on studies that demonstrate specific peptide immunization with peptides of either TRP-2 or

Her-2/neu elicit B and T cell anti-tumor immunity in models of melanoma and mammary carcinoma, respectively. These immunization strategies cause cytotoxic T cell infiltration of the solid tumor and generate high titers of anti-tumor antibodies. The goals of Dr. Mamula’s studies are to exploit strategies that break tolerance to self proteins in autoimmune diseases in eliciting immunity to self tumor tissues.



DR. MARGARET PISANI, Assistant Professor in the Section of Pulmonary and Critical Care Medicine, has received a five-year K23 Mentored Career Development Award from the NIH. Her primary mentor on this award is Dr. Sharon Inouye, Professor of Medicine. Dr. Pisani’s research focuses on the “Impact of psychoactive drugs on delirium in ICU patients.” The thrust of this research project is three-fold and will determine the association of psychoactive drugs with persistent delirium in post-ICU stay patients. Dr. Pisani’s group plan to identify leading drugs or drug combinations associated with the highest risk of persistent delirium. They will determine the independent contribution of psychoactive drugs to persistent delirium after controlling for other delirium risk factors. The ultimate goal of this research is develop specific interventions in ICU drug therapy vital to the care of more than four million critically ill patients in the United States.

Announcements

Position Available, Medical Director, Medical Service, Yale-New Haven Hospital

The position of Medical Director for the Medical Service of YNHH was recently established through funding provided by YNHH and the Department of Internal Medicine. The Medical Director will be responsible for overseeing the design, implementation, and measurement of policies to improve the quality and efficiency of care in the Medical Service of YNHH. The initial focus will be on the medical floors in the East Pavilion. The Director will be involved in teaching house staff and students, as well as close collaborative work with Nursing, Social Work, Pharmacy, Discharge Planners and the Quality Assurance Staff of YNHH. The Medical Director position is fully funded and will be a full-time faculty member. Any faculty interested in being considered for this position should send their CV and letter of interest to Rosemary Slattery in the Departmental office.

Training Program in Geriatric Clinical Epidemiology and Aging-Related Research

The Division of Geriatrics offers a two-year training program in Geriatric Clinical Epidemiology and Aging-Related Research, sponsored by the National Institute on Aging. The goal of the program is to provide highly qualified subspecialty fellows with research skills in geriatric clinical epidemiology and an intensive research experience under the mentorship of experienced investigators in geriatric medicine and gerontology. Subspecialty fellows will have access to resources and expertise through the Geriatric Medicine Program, the Program on Aging/Claude D. Pepper Older Americans Independence Center, the Robert Wood Johnson Clinical Scholars Program, and the Investigative Medicine Program. The deadline for applications for the 2005 academic year is January 31, 2005. Candidates should be committed to an academic career in aging-related research and must have completed clinical training in their subspecialty field by June 30, 2005. Application materials can be obtained from Ms. Karissa Stolzman at 203-688-3344 or from the web at <http://info.med.yale.edu/intmed/geriatrics/fellowship/T32application.htm>. Information about the Geriatrics Section and Research Programs in Aging may be found at: <http://info.med.yale.edu/intmed/geriatrics/index.html>

Medical Grand Rounds

November 25, 2004	No Medical Grand Rounds – Happy Thanksgiving!!
December 2, 2004	<i>“The Womens’ Health Initiative (WHI): Last Word on HRT or Just Another Beginning?”</i> Frederick Naftolin, M.D., Professor of Obstetrics and Gynecology Director, Center for Research for Reproductive Biology
December 9, 2004	<i>“Hemochromatosis”</i> Professor Tim Cox Department of Medicine, Cambridge University Medical School
December 16, 2004	<i>“A 34 year old Brazilian Man with Fever and Paraplegia”</i> Vincent Quagliarello, M.D., Professor, Section of Infectious Diseases
December 23, 2004	No Medical Grand Rounds – Recess
December 31, 2004	No Medical Grand Rounds – Recess

Grand Rounds begins at 8:30 a.m. in the Fitkin Amphitheatre.

Special Lectures

November 22, 2004

Junior Faculty Development Series

“HOW TO WRITE A GOOD PAPER”

Jerome L. Kassirer, M.D.

Professor Adjunct – Department of Internal Medicine

12:00 noon, Fitkin Amphitheater – lunch will be served

Book signing and reading from his new book

“ON THE TAKE: HOW MEDICINE’S COMPLICITY WITH BIG BUSINESS CAN ENDANGER YOUR HEALTH”

Jerome L. Kassirer, M.D.

Professor Adjunct – Department of Internal Medicine

7:00 p.m. - RJ Julia Booksellers, Madison, CT

Contact information: – 245-3959, call for a reservation

November 29, 2004

Seminars in Clinical Investigation

“SAMPLE SIZE AND POWER ESTIMATION”

Peter Peduzzi, Ph.D.

Associate Professor (Adjunct), Internal Medicine and

Assistant Professor (Adjunct), Epidemiology and Public Health

2:00-4:00 p.m. - Investigative Medicine Conference Room, ESH B18

Contact information: Pamela Fucci – 785-6842

December 2, 2004

Program for the Humanities in Medicine – 2004 Robert Penn Warren Lecture

“POETRY AND PAIN”

John Hollander, Ph.D., Sterling Professor Emeritus

Department of English, Yale University

5:00 p.m. – Beaumont Room in SHM, 333 Cedar Street

Contact information: Deborah Finger – 786-6102

December 6, 2004

Seminars in Clinical Investigation

“HOW TO FIND FUNDING SOURCES: RESEARCH AND CAREER GRANTS”

Penrhyn Cook, Executive Director

Melanie S. Glogower, Coordinator

YSM Grants and Contracts

2:00-4:00 p.m. - Investigative Medicine Conference Room, ESH B18

Contact information: Pamela Fucci – 785-6842

Special Lectures (continued)

December 20, 2004

Seminar in Biomedical Research

To be announced

12:00 noon, Fitkin Amphitheater – lunch will be served

Junior Faculty Development Series

“AUTHORSHIP ISSUES”

Mary Tinetti, M.D.

Gladys Phillips Crofoot Professor of Medicine, Section of Geriatrics

12:00 noon, location to be announced – lunch will be served

Contact information: Rosemary Slattery – 785-4119

THE DEPARTMENT OF INTERNAL MEDICINE

Yale University School of Medicine

<http://info.med.yale.edu/intmed/newsletter/>

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