Research Interests of Participating Faculty

Jody L. Baron, M.D., Ph.D.

The Baron research group studies mechanisms involved in the immunopathogenesis of hepatitis B-related liver disease as well as the basic principles of innate and adaptive immunity to viral pathogens in general. Work relevant to hepatitis B is based on the observation that liver disease in HBV-infected individuals is immune-mediated rather than cytopathic. Because natural hepadnaviral infections occur only in humans and other species whose immune systems vary from individual to individual (outbreeding), it is difficult to study immunopathogenesis in these hosts. To circumvent this limitation, the lab developed a novel transgenic mouse system that models the immune response to hepatitis B that would occur in the setting of natural infection. This mouse model has the potential to elucidate the basic mechanisms involved in immunopathogenesis of acute and chronic hepatitis B infection. In addition, the model holds promise for illuminating the fundamental aspects of innate and adaptive immunity to viral pathogens. Experiments are designed to use and extend the model to identify the mechanisms involved in acute and chronic hepatitis with the long-term goal of developing a comprehensive understanding of the role of innate and adaptive immunity in HBV clearance and virus-induced liver damage. Work to date has uncovered a function for Natural Killer T lymphocytes (NKT cells), a population of innate-like lymphocytes whose role was previously unclear. Continued research in this area should enhance our understanding of the ligands for and regulation of these unusual lymphocytes and their restriction element, the MHC class I-like molecule, CD1d.

Publications:
Baron JL, Gardiner L, Nishimura S, Shinkai K. Locksley R, Ganem D. Activation of a nonclassical NKT cell subset in a transgenic mouse model of hepatitis B virus infection. Immunity 2002;16:583-94.

Nathan M. Bass, M.D., Ph.D., Professor of Medicine; Medical Director Liver Transplantation, UCSF
Dr. Bass conducts a number of clinical and translational research projects relevant to patients with chronic liver disease or with liver transplants. One focuses on the role of renal microvascular vasoconstriction in salt and fluid retention in end-stage liver disease. Using spectral and power Doppler ultrasound measurements, Dr. Bass and his colleagues have shown that the degree of renal cortical vasoconstriction correlates with the severity of ascites. Ongoing work is directed toward determining the specific role of potent vasoconstrictor eicosanoids in the renal microcirculatory derangements in ascites and the impact of transjugular intrahepatic portacaval shunting (TIPS) on the renal production of these mediators. Independent research by Dr. Bass and collaborators assesses treatment for liver disease, including a therapeutic trial of octreotide in patents with hepatorenal syndrome and a multicenter Phase IIIB randomized clinical trial of transfusion with photochemically-treated, S-59-reduced, fresh frozen plasma for correction of multiple coagulation factor deficiencies. In collaboration with Drs. Terrault, Peters and Merriman, Dr. Bass contributes to therapeutic and epidemiological studies of patients with chronic viral hepatitis pre- and post-liver-transplantation. In collaboration with Drs. Bull and Merriman, Dr. Bass is exploring the role of PFIC/BRIC gene mutations in the pathogenesis of inherited and acquired cholestatic liver diseases and documenting the natural history of nonalcoholic steatohepatitis (NASH) as well as the role of mutations in genes regulating fatty acid oxidation pathways in the pathogenesis of NASH.

Publications:
Yao FY, Terrault NA, Freise C, Maslow L, Bass NM. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched untreated cohort. Hepatology 2001;34:411-416.
Yao FY, Bass NM, Ascher NL, Roberts JP. Liver Transplantation for hepatocellular carcinoma: lessons from the first year under the Model of End-Stage Liver Disease (MELD) organ allocation policy. Liver Transpl 2004;10:621-630.

D. Montgomery Bissell, M.D., Professor of Medicine; Chief, GI Division and UCSF Liver Center
The Bissell lab has a longstanding interest in the fibrogenic response to liver injury and defined the role of a pericyte population, termed stellate cells, in this process. Another important component of the injury response is hepatocyte replacement and tissue remodeling. Lab members have shown that cell replacement occurs not only because of division of mature hepatocytes but also through expansion of a progenitor cell compartment. In recent work, the laboratory has begun to define the role of progenitors known as "oval cells" in the repair response. Oval cells can be isolated and, with expansion in culture, could be useful for cell-based therapy of a variety of liver diseases. The Bissell group together with collaborators recently identified a cytokine belonging to the TNF-α family that appears to be a specific growth factor for a subset of hepatic oval cells. Researchers in the lab are currently characterizing the cells that respond to this factor.
A second project in the Bissell lab addresses the influence of hepatitis C virus gene products on hepatocyte metabolism. Until recently, most of the tissue injury in HCV infection has been attributed to the immune response. However, using transgenic mice with conditional expression of the HCV core (nucleocapsid) protein, the lab has found that core binds to mitochondria causing oxidant stress and, ultimately, apoptosis. This may be directly relevant to the progression of chronic injury and tumor formation, which is a frequent event in chronic hepatitis C infection.

Publications:
Chang ML, Chen JC, Alonso CR, Kornblihtt AR, Bissell DM. Regulation of fibronectin splicing in sinusoidal endothelial cells from normal or injured liver. Proc Natl Acad Sci USA 2004;101:18093-18098.
Kikuchi S, Griffin CT, Wan SS, Bissell DM. Role of CD44 in epithelial wound repair: migration of rat hepatic stellate cells utilized hyaluronic acid and CD44v6. J Biol Chem 2005;280:15398-15404.
Jakubowski A, Ambrose C, Parr M, Lincecum JM, Wang MZ, Zheng TS, Browning B, Michaelson JS, Baetscher M, Wang B, Bissell DM, Burkly LC. TWEAK induces liver progenitor cell proliferation. J Clin Invest 2005;115:2330-2340.

Laura N. Bull, Ph.D., Associate Professor of Medicine; Member UCSF Human Genetics Program
The goal of research in the Bull laboratory is to advance understanding of hereditary cholestatic diseases as well as determine the role of genetics in more complex cholestatic disorders. Several diseases are under study simultaneously, including progressive familial intrahepatic cholestasis (PFIC), familial hypercholanemia, Aaegenes' syndrome and intrahepatic cholestasis of pregnancy. In the case of the first two diseases, Dr. Bull identified the genes responsible and is actively pursuing disease mechanisms using cell biological and whole-animal approaches. Researchers in the Bull lab generated mice with a mutation in *atp8b1*, the gene linked to PFIC. These animals exhibit defective regulation of intestinal reabsorption of bile acids, and develop cholestasis when challenged with bile acids. Notably, the cholestatic phenotype appears to depend upon strain background, and if confirmed, the lab intends to pursue genetic mapping of modifier loci responsible for the inter-strain differences in phenotype. Studies of hypercholanemia in the Bull lab indicate that 2 genes are responsible (TJP2 and BAAT) and that the disorder lies in a border zone between simple and complex genetic traits. Intrahepatic cholestasis of pregnancy is being investigated by sequencing candidate genes from Chilean and American patients while establishing a larger-scale study of the incidence and genetics of the disorder in other populations.

Publications:
Klomp LW, Vargas JC, [et al], Bull LN. Characterization of mutations in ATP8B1 associated with hereditary cholestasis. Hepatology 2004;40:27-38.
Pawlikowska L, Groen A, Eppens EF, Kunne C, Ottenhoff R, Looije N, Knisely AS, Killeen NP, Bull LN, Elferink RP, Freimer NB. A mouse genetic model for familial cholestasis caused by ATP8B1 mutations reveals perturbed bile salt homeostasis but no impairment in bile secretion. Hum Mol Genet 2004;13:881-892.
Carlton VE, Harris BZ, Puffenberger EG, Batta AK, Knisely AS, Robinson DL, Strauss KA, Shneider BL, Lim WA, Salen G, Morton DH, Bull LN. Complex inheritance of familial hypercholanemia with associated mutations in TJP2 and GAAT. Nat Genet 2003;34:91-6.

Nigel Bunnett, M.D., Professor of Surgery and Physiology in Residence
Projects:
1) Examination of mechanisms by which proteases signal to protease-activated receptors on enteric and primary spinal afferent neurons to induce hyperexcitability and pain.
2) Investigation of the contribution of neuropeptides to inflammation and pain transmission.
3) Regulation of trafficking and signaling of G-protein coupled receptors for proteases and neuropeptides.
Selected Publications:
Amadesi S, Nie J, Vergnolle N, Cottrell GS, Grady EF, Trevisani M, Manni C, Geppetti P, McRoberts JA, Ennes H, Davis JB, Mayer EA, Bunnett NW. Protease-activated receptor 2 sensitizes the capsaicin receptor TRPV1 to cause thermal hyperalgesia. J Neurosci 2004;24:4300-4012.
Jacob C, Cottrell GS, Gehringer D, Schmidlin F, Grady EF, Bunnett NW. c-Cbl mediates ubiquitination, degradation, and down-regulation of human protease-activated receptor 2. J Biol Chem 2005;280:16076-87.

Douglas Corley, M.D. Research Scientist II, Kaiser Permanente Division of Research; Assistant Clinical Professor of Medicine, UCSF
Projects:
1) Evaluation of risk factors for Barrett's Esophagus.
2) Evaluation of surveillance for Barrett's Esophagus and Esophageal adenocarcinoma
3) Evaluation of adverse effects from proton pump inhibitor use
Techniques:
1) Case-control and cohort studies

Selected Publications:
1) Corley DA, Katz P, Wo JM, Stefan A, Patti M, Rothstein R, Edmundowicz S, Kline M, Mason R, Wolfe MM. Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. Gastroenterology. 2003 Sep;125(3):668-76.
2) Corley DA, Kubo A. Influence of classification on cancer incidence rates: an analysis of gastric cardia carcinomas. JNCI 2004; 96:1383-7

Dr. Jason Cyster, Ph.D., Professor, UCSF, Dept of Microbiology and Immunology, Investigator, Howard Hughes Medical Institute
Projects:
The Cyster laboratory studies the cues guiding lymphocyte migration during the adaptive immune response. They have identified and characterized a subset of the chemokine family known as lymphoid or homeostatic chemokines that are constitutively expressed in lymphoid tissues but that can also become induced at sites of inflammation. The lab is interested in examining the expression pattern of lymphoid chemokines (BLC/CXCL13, SLC/CCL21, ELC/CCL19 and SDF1/CXCL12) in the intestine during chronic inflammatory conditions and in the stomach during the response to Helicobacter. Work is also on-going to determine the chemokine and chemokine receptor requirements needed for recruitment of lymphoid tissue inducer cells (LTIC) to the embryonic intestine during the formation of Peyer's patches. Preliminary results have revealed an unexpectedly important role for SDF1 and CXCR4. Finally, the lab is working on the mechanism by which cells egress from tissues. In recent work we demonstrated an important role for sphingosine-1-phosphate (S1P) receptor-1 in lymph node and Peyer's patch egress. In future studies we will examine whether the large population of lymphocytes and dendritic cells that are present within the gut mucosa are able to exit from this compartment and whether this requires the function of S1P receptor-1.

Publications:
1) Lo CG, Xu Y, Proia RL, Cyster JG. Cyclical modulation of sphingosine-1-phosphate receptor 1 surface expression during lymphocyte recirculation and relationship to lymphoid organ transit. .*J. Exp. Med.* 2005;201:291-301.
2) Kabashima K, Banks TA, Ansel KM, Lu TT, Ware CF, Cyster JG. Intrinsic lymphotoxin-b receptor requirement for homeostasis of lymphoid tissue dendritic cells. *Immunity* 2005;22(4):439-450.

Elizabeth A. Holly, PhD, MPH, Professor and Cancer Epidemiology Division Head, Department of Epidemiology and Biostatistics
Projects:
Molecular epidemiology, large population-based case-control and cohort studies; clinic-based studies; population-based molecular-epidemiologic studies of genetic polymorphisms
Research resources potentially available to mentees:
Data bases for non-Hodgkin lymphoma, melanoma, pancreatic cancer, oral and anal cancer precursor lesions in men and women
Publications:
1) Da Costa MM, Efird JT, Holly EA, Palefsky JM. Association of HPV 16 copy number with progression to anal high-grade squamous intraepithelial lesions and validation of semi-quantitative testing methods. J Infect Dis In Press
2) Valery PC, Holly EA, Sleigh AC, Williams G, Kreiger N, Bain C. Hernias and Ewing's sarcoma: Pooled and meta analysis. Lancet Oncology In Press (on-line e-pub June 2005 prior to print version)

John M. Inadomi, M.D., Associate Professor of Clinical Medicine, Director, GI Outcomes and Health Services Research, UCSF, Chief, Clinical Gastroenterology, San Francisco General Hospital
Projects:
1) Economic impact of screening for colorectal cancer, 2) Patient- and systems-based barriers and facilitators to colorectal cancer screening, 3) Implementation of colorectal cancer screening in lowincome, under-insured populations.
Techniques:
1) Prospective cohort analysis, including IRB/HIPAA regulations, subject recruitment and follow-up, database construction and validation, statistical analysis of acquired data, 2) Descriptive analytic techniques, 3) Decision analysis, meta-analysis and cost-effectiveness analysis, 4) Univariate and multivariable regression analysis, 5) Cox proportional hazards modeling.

Publications:
1) Inadomi JM, Fennerty MB, Bjorkman D. The Economic impact of irritable bowel syndrome: a systematic review. Aliment Pharmacol Ther 18(7):671-82, 2003.
2) Shaheen NJ, Inadomi JM, Overholt BF, Sharma P. What is the best management strategy for high grade dysplasia in Barrett's esophagus? A cost-effectiveness analysis. Gut 53(12):1736-44, 2004.

Michael Korn, M.D., Assistant Adjunct Professor of Medicine, Mt. Zion
Projects:
Major aim of our work is the rational design of targeted combination therapies for GI cancer. The projects exploring the systems biology of cancer and have a strongly translational angle. We utilize cutting edge technologies and collaborate with leading scientists to design novel cancer therapies based on an in-depth understanding of cancer signal transduction networks. There are currently two main research tracks: (1) Analysis and prediction of pathway responses to targeted inhibition of the EGF-receptor pathway in esophageal and breast cancer. Computer models of signaling networks are being developed and the anti-tumor efficacy of inhibition of critical molecules within these networks is being explored. 2) Regulation and function of the human coxsackie-adenovirus receptor CAR. We discovered novel mechanisms of regulation of CAR, which is mission-critical for the success of adenovirus-based cancer treatments. We are investigating the possibility of pharmacological receptor restoration on cancer cells in order to increase the therapeutic efficacy of these viral agents.
Techniques:
Cancer Cell culturing, recombinant DNA technology, PCR, FISH, RNA-expression analysis including Northern-blotting, RT-PCR, TaqMan-PCR, luciferase promoter reporter assays, Affymetrix expression arrays, Western-blotting including co-immunoprecipitation, FACS, immune-fluorescense, confocal microscopy, immunohistochemistry , reverse-phase protein arrays, Cellomics high content image analysis, siRNA and shRNA mediated gene knock-down, controlled virus infection, CPE- and plaque assays.

Publications:
1) Korn WM, Prevention and Management of Early Esopahgeal Cancer. Current Treatment Options in Oncology, 2004, 5: 405-416

2) Au T, Thorne S, Korn WM, Sze D, Kirn D, Reid T. Minimal hepatic toxicity following infusion of adenoviral vector: spatial restriction of CAR receptor in normal liver. Cancer Gene Therapy, 2005 In press.

Uri Ladabaum, M.D. M.S., Assistant Clinical Professor of Medicine, UCSF, Director, GI Motility Program, UCSF
Projects:
1) Effects of antidepressants on visceral sensitivity, including IBS/citalopram study. 2) Observational study of clinical practice relating to IBS. 3) Decision analysis/cost-effectiveness analysis (focus on colon cancer screening; other current: treatment of ulcerative colitis). 4) Intervention to increase colorectal cancer screening in primary care. 5) Appropriate projects to be designed with interested fellow.
Techniques:
1) Barostat-controlled distension of viscera. 2) Clinical trials, double-blind administration of pharmaceuticals, data analysis (SAS software). 3) Decision analysis/cost-effectiveness analysis. 4) Database/observational studies.
Publications:
1) Mein, SM, Ladabaum U. Serologic testing for celiac disease in patients with symptoms of irritable bowel syndrome: A cost-effectiveness analysis. Aliment Pharmacol Ther 2004;19(11):1199-210.
2) Ladabaum U, Song K, Fendrick AM. Colorectal neoplasia screening with virtual colonoscopy: When, at what cost, and with what national impact? Clinical Gastroenterology and Hepatology 2004;2(7):554-563.

Lewis Lanier, M.D., Professor of Medicine, UCSF; Vice-Chair, Department of Microbiology and Immunology
Projects:
NK cell receptors in viral immunity, tumor immunity, and autoimmunity
Immune responses are regulated by membrane receptors that serve to activate or inhibit cell proliferation and clonal expansion, cytokines production, and cell-mediated cytotoxicity. Our lab focuses on the human and mouse activating and inhibitory receptors that are predominantly expressed by Natural Killer (NK) cells, but are also present on subsets of effector/memory T cells and some myeloid cells. We are particularly interested in the activating NK receptors that signal by associating with two distinct signaling adapter proteins named DAP10 and DAP12.
The DAP10 signaling adapter associates with the NKG2D receptor on NK cells and T cells, and DAP10 initiates signaling through the PI3-kinase pathway. We have implicated the NKG2D-DAP10 receptor in NK cell and T cell-mediated immune responses against certain tumors and viruses, but also demonstrated a detrimental role of this receptor in autoimmune diseases, e.g. type I diabetes.
The DAP12 signaling adapter associates with many different human and mouse receptors, including activating KIR, Ly49, CD94/NKG2C, and several myeloid receptors. Like the CD3 subunits of the T cell antigen receptor, DAP12 has an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. When a DAP12-associated receptor encounters its ligand, DAP12 is tyrosine phosphorylated, which results in the recruitment and activation of the tyrosine kinases ZAP70 or syk - initiating cytokine production and cell-mediated cytotoxicity. DAP12-associated receptors, such as Ly49H and Ly49P, are involved in immunity against cytomegalovirus infection.
The goal of our research is to understand the role of these NK cell receptors in immune defense against tumors and microbial pathogens, and explore their potential detrimental role in autoimmune diseases.

Publications:
1) Takaki R, Hayakawa Y, Nelson A, Sivakumar PV, Hughes S, Smyth MJ, Lanier LL. IL-21 enhances tumor rejection through a NKG2D-dependent mechanism. J. Immunol., 2005 In press.
2) Ogasawara K, Benjamin J, Takaki R, Phillips JH, Lanier LL. A role for NKG2D in bone marrow transplantation. Nature Immunology, 2005 In press.

Richard Locksley, MD, Professor, Medicine, Microbiology & Immunology
Projects:
Regulation of T cell polarized cytokine production. T cells are the critical effector cells of the adaptive immune response. To acquire effector functions, however, naive T cells undergo a complex differentiation process to become the mature cells capable of effecting host defense against microbial pathogens. Different pathogens require different types of effector cells that can have markedly different capabilities. The most widely disparate mature helper T cell populations, termed Th1 and Th2 cells, secrete distinct patterns of cytokines that orchestrate distinct types of immune responses. The Locksley laboratory melds molecular and cellular studies to investigate the signals that direct the differentiation of naive CD4+ T cells to their mature states. The current laboratory interests focus not only of T cell differentiation, but also on the acquisition of cytokine expression by innate cells of the immune system. Using a variety of genetically modified cells and mice, cytokine expression is studied *in vitro* and *in vivo*, using both infectious and allergic models. Major interests include understanding the primary regulation of IL-4 gene transcription in both T cells and non-T cells, and in exogenous signals that drive cytokine gene regulation at inflammatory foci.

Publications:
1) Xu M, Wang ZE, Locksley RM. Innate immune responses in peptidoglycan recognition protein-Ldeficient mice. Mol Cell Biol 2004;24:7949-57.
2) Voehringer D, Rosen DB, Lanier LL, Locksley RM. CD200R family members represent novel DAP12-associated activating receptors on basophils and mast cells. J Biol Chem 2004;279:54117-23.

Averil Ma, M.D. Associate Professor of Medicine, UCSF, Director, UCSF Center for Colitis and Crohn's Disease
Projects:
1) biology of cytokine signaling and inflammation, 2) regulation of signal transduction and mucosal immune homeostasis
Techniques:
1) gene targeting in transgenic mice, 2) intestinal models of inflammation, 3) molecular and cellular immunology

Publications:
1) Lee EG, Boone DL, Libby S, Chai S, Chien M, Lodolce JP, and Ma A. 2000. Failure to regulate TNF induced NF-κB and cell death responses in A20 deficient mice. Science 289;2350-2354.
2) Boone DL, Turer EE, Lee EG, Ahmad RC, Wheeler MT, Tsui C, Hurley P, Chien M, Chai S, Hitotsumatsu O, McNally E, Pickart C, and Ma A. 2004. The ubiquitin modifiying enzyme A20 is essential for terminating TLR signaling. Nature Immunology 5;1052-1060.

Jacquelyn J. Maher, M.D., Professor of Medicine, UCSF; Director, Rice Laboratory, SFGH
The Maher laboratory focuses on general mechanisms of liver injury as well as specific mechanisms of liver damage in the context of hepatic steatosis. General studies address cell death pathways in the liver (apoptosis/necrosis) and their connection to downstream events including inflammation and fibrosis. The laboratory has shown that apoptosis of liver cells prompts chemokine production, which in turn stimulates neutrophil recruitment to the liver. Notably, neutrophil influx in this context appears beneficial, because its blockade leads to worsening of liver injury. The laboratory also studies the connection between inflammation and fibrosis in the liver. Work in this area addresses whether disruption of hepatic inflammation (using leukocyte depletion or other models of immunodeficiency) alters progression to fibrosis in experimental models of liver disease. Results to date indicate that neutrophilic inflammation does not impact fibrogenesis, even when prolonged. Work on fatty liver disease is directed toward identification of the factor(s) that trigger progression from steatosis to steatohepatitis. For this work the laboratory utilizes a dietary model of steatohepatitis, in which mice are deprived of methionine and choline to block hepatic triglyceride secretion. When this methioninecholine-deficient (MCD) formula is enriched in simple sugar and fat, animals develop marked steatosis and steatohepatitis. Studies with this model show that hepatocellular death is related to accumulation of saturated fatty acids in the liver, whereas hepatic inflammation is a consequence of unsaturated fatty acid accumulation and resultant lipid peroxidation. The mechanism whereby saturated fatty acids kill hepatocytes is being explored in primary culture.

Publications:
Xu J, Lee G, Wang H, Vierling JM, Maher JJ. Limited role for CXC chemokines in the pathogenesis of alpha-naphthylisothiocyanate-induced liver injury. Am J Physiol 2004;287:G634-G741.
Hanson JC, Bostick MK, Campe CB, Kodali P, Lee G, Yan J, Maher JJ. Transgenic overexpression of interleukin-8 in mouse liver protects against galactosamine/endotoxin toxicity. J Hepatol 2005; epub July 18.
Rizki G, Arnaboldi L, Gabrielli B, Lee G, Yan J, Ng R, Fung A, Ginzinger D, Pitas RE, Maher JJ. Steatohepatitis in mice fed a methionine- and choline-deficient diet coincides with hepatic accumulation of toxic saturated long-chain fatty acids (submitted).

Raphael B. Merriman, M.D.
The principal focus of the Merriman lab is nonalcoholic fatty liver disease (NAFLD), a problem that is rapidly gaining prominence as a major cause of chronic liver injury. While it is clear that obesity and diabetes are important predisposing factors for NAFLD, genetic factors may be required for progression of NAFLD to clinically significant disease such as nonalcoholic steatohepatitis (NASH). The Merriman group is carrying out mutation analysis of several candidate genes related to lipid and lipoprotein metabolism and adipocyte function in patients with well-characterized NAFLD or NASH. Familial clustering and mode(s) of inheritance are being investigated in kindreds with NASH, and the biochemical effects of genetic variants are being investigated. The patient materials for this project come from a large clinical, tissue and DNA database that Dr. Merriman and his colleagues created, which includes morbidly obese patients seeking evaluation for gastric bypass surgery. In the latter group, they are examining the biochemical and histological consequences of weight loss. Finally, Dr. Merriman and Dr. Bass participate as a clinical center in an NIH-sponsored Clinical Research Network on NAFLD, which is currently enrolling patients in a trial to determine if treatment of insulin resistance (a hallmark of NAFLD) slows disease progression.

Publications:
Merriman RB, Aouizerat BE, Kane JP, Malloy MJ, Bass NM. A leptin variant with phenotype and genotype associations with NAFLD. Hepatology 2004;40:585A.
Merriman R, Aouizerat B, Bass N. Carnitine palmitoyl transferase-1A variants have phenotype and genotype associations with NAFLD. Hepatology 2005;42:612A.
Riley MR, Bass NM, Rosenthal P, Merriman RB. Underdiagnosis of pediatric obesity and underscreening for fatty liver disease and metabolic syndrome by pediatricians and pediatric subspecialists. J Pediatr 2005;147:839-842.

Marion G. Peters, M.D., Professor of Medicine, UCSF; Chief of Hepatology Research
Dr. Peters pursues clinical/translational studies of liver disease due to hepatitis B and C infection. Her group is particularly interested in viral hepatitis in complicated clinical settings, such as in patients with co-morbid conditions including alcoholism or HIV infection. In these complex situations the group focuses on immunology of the liver; they study the role of host responses to hepatitis virus infection, and examine the effect of alcohol or HIV on the progression of viral hepatitis and the response to antiviral therapy. The Peters group also addresses fundamental host-viral interactions in hepatitis C and hepatitis B infection. Specifically, they explore the role of inflammatory cytokines and their receptors in the pathogenesis of hepatitis using DNA polymorphism analysis and mRNA gene profiling. Clinical studies by Dr. Peters assess the outcome of hepatitis B and C in alcoholic or HIV-infected patients as well as the impact of these co-morbid illnesses on their response to therapy. Additional studies examine bone density in patients with chronic liver disease and after liver transplantation. Finally, Dr. Peters is investigating the recurrence of primary biliary cirrhosis (PBC) after liver transplantation, and the potential for ursodeoxycholic acid to modify post-transplant PBC.

Publications:
Guy JE, Qian P, Lowell JA, Peters MG. Recurrent primary biliary cirrhosis: peritransplant factors and ursodeoxycholic acid treatment post-liver transplant. Liver Transpl 2005;11:1252-1267.
Luetkemeyer A, Hare CB, Stansell J, Tien PC, Charlesbois E, Lum P, Havlir D, Peters M. Clinical Presentation and Course of Acute Hepatitis C Infection in HIV-Infected Patients. Journal of Acquired Immune Deficiency Syndromes. 2006;41:31-36

Buxbaum J, Qian P, Khuu C, Shneider BL, Allen PM, Peters MG. Novel model of antigen specific induction of bile duct injury (submitted).

Kathryn Phillips, M.D.
Projects:
1. Health services research, quantitative policy analysis, and applied health economics
2. Utilization and cost-effectiveness of preventive services (cancer screening) and pharmaceuticals
3. The impact of managed care on access to care and utilization of services
4. Economic implications of genetic screening and pharmacogenomics (the use of genetic information to individualize drug therapy)
5. Assessing patient preferences for care using willingness-to-pay methods
6. Women's reproductive health and access to contraceptives and abortion

Publications:
1) Phillips KA, Flatt SJ, Morrison KR, Coates TJ. Potential use of home HIV testing. NEJM. 1995;332(19):1308-1310.
2) Phillips KA, Lowe RA, Kahn JG, Lurie P, Avins A, Ciccarone D. The cost-effectiveness of HIV testing of physicians and dentists. JAMA. 1994;271(11):851-858.

Didier Y. Stainier, Ph.D., Professor of Medicine, UCSF; Member, UCSF Stem Cell Research Program
The goals of the Stainier laboratory are to identify and understand the function of genes regulating liver development. The group is conducting its investigations in zebrafish, a vertebrate model system well suited for embryological and genetic studies. Over the past few years the laboratory completed a detailed analysis of wild-type liver development in zebrafish, a study that should facilitate the use of the zebrafish system to identify and/or further analyze genes implicated in liver development. Specifically, researchers in the group found that the zebrafish liver develops very similarly to the mouse, chick and frog liver, indicating that the genes and molecular pathways of liver development are conserved among vertebrates. The lab has also conducted a large-scale forward genetic screen for genes regulating liver development using a transgenic zebrafish line expressing GFP in the endoderm and endoderm-derived organs. In order to further characterize these mutants, the lab has developed wholemount immunostaining techniques and generated specific transgenic lines.

Publications:
Field HA, Ober EA, Roeser T, Stainier DY. Formation of the digestive system in zebrafish. I. Liver morphogenesis. Dev Biol 2003;253:279-90.
Ober EA, Olofsson B, Makiner T, Jin SW, Shoji W, Koh GY, Alitalo K, Stainier DY. Vegfc is required for vascular development and endoderm morphogenesis in zebrafish. EMBO Rep 2004;5:78-84.

Margaret Tempero, M.D. Deputy Director and Director of Clinical Sciences, UCSF Comprehensive Cancer Center, Professor and Chief, Division of Medical Oncology
Projects:
We seek to identify new markers, which may permit earlier diagnosis in at-risk populations and thus allow earlier and more effective intervention. We need new and more accurate model systems for preclinical testing of promising new diagnostic and therapeutic tools. We are exploring the cell, developmental, and molecular biology of normal human and mouse pancreas cells. These studies are providing insight into the progenitor of pancreas cancer. In addition, using microarray technology, normal cells are being compared to pancreas cancer-derived cells to construct a catalogue of changes that take place in the transition of normal cells to a cancerous phenotype. Finally, we are deriving accurate mouse models that faithfully recapitulate the genetics and cell biology of the human disease in order to better understand its pathophysiology and to serve as a platform for the generation of new diagnostic and therapeutic agents.

Publications:
1) Ko, AH, Hwang, J, Venook, AP, Abbruzzese, J, Bergsland, EK, and Tempero, MA. Serum CA 19-9 response as a surrogate for clinical outcome in patients with advanced pancreatic cancer treated with fixed-dose rate gemcitabine. Brit J Cancer, Epub ahead of print, 2005.

2) Ko, AH, Dito, E, Schillinger, B, Venook, AP, Bergsland, EK, and Tempero, MA. A phase II study of gemcitabine given at fixed-dose rate infusion in combination with low-dose cisplatin for metastatic adenocarcinoma of the pancreas. Journal of Clinical Oncology, accepted for publication, 2005.

Jonathan P. Terdiman, M.D., Associate Professor of Clinical Medicine, MZH, UCSF Cancer Center, UCSF Center for Colitis and Crohn's Disease.
Projects:
1) Predictors of germline mismatch repair gene mutations in individuals with early onset colorectal cancer or a positive family history of the disease. 2) Array CGH to predict outcome in colorectal cancer. 3) Role of colonoscopy and chemoprevention in the prevention of colitis-related cancer. 4) Pathogenesis and treatment of collagenous and microscopic colitis. 5) Genomics of colitis-related cancer. 6) Identification of factors that are predictive of outcome in patients who present to the emergency department with gastrointestinal bleeding. 7) Assessment of the efficacy of a management guideline for patients with gastrointestinal bleeding.
Techniques:
1) Translational research with focus on the clinical and molecular epidemiology of colorectal cancer. 2) Clinical studies: randomized controlled trial, case-control, cohort and cross-sectional studies with a focus on colorectal cancer prevention and inflammatory bowel disease. 3) Outcomes research including decision analysis, meta-analysis.

Publications:
1) Velayos FS, Allen BA, Gum J, Truta B, Kim Y, Sleisenger MH, Terdiman JP. Rate of microsatellite instability in young patients with adenomas: assessment of the Bethesda guidelines to detect HNPCC. Am J Gastroenterol 2005;100:1143-1149.
2) Velayos FS, Williamson A, Lung E, Bostrom A, Weber EJ, Ostroff JW, Terdiman JP. Early predictors of severe lower gastrointestinal bleeding and adverse events: a prospective study. Clinical Gastroenterology and Hepatology 2004;2:485-490.

Norah A. Terrault, M.D., M.P.H.
A research objective of the Terrault group is to determine the risk factors that predict recurrence of hepatitis B or C in patients undergoing liver transplantation for end-stage disease due to these conditions. Another area of study is assessing the impact of specific interventions on the recurrence of viral hepatitis in transplanted patients. Ongoing studies address the efficacy of lamivudine or hepatitis B immunoglobulin + lamivudine in preventing recurrent hepatitis B and death in liver transplant recipients; these clinical endpoints are then correlated with patient-specific information regarding mutations in the surface, core, pre-core and polymerase regions of HBV. Utilizing the NIDDK-Liver Transplant Database (LTD), Dr. Terrault uncovered HCV as a precipitating cause of post-transplant diabetes mellitus. She is now using the NIDDK-LTD to explore whether liver transplant recipients with HCV are more at risk for chronic rejection than patients transplanted for other indications, and to assess the outcome of liver transplant recipients with recurrent HCV infection who require retransplantation. Dr. Terrault also oversees additional epidemiological studies of non-transplant-related liver disease as the UCSF representative to large cooperative groups (CDC cooperative studies). One involves the determination of factors associated with sexual transmission of hepatitis C virus among monogamous heterosexual couples, and the second is designed to establish the prevalence and incidence of specific chronic liver disease in the general population. Finally, Dr. Terrault in collaboration with Dr. Peters examines the role of alcohol in HCV disease expression.

Publications:
Khalili M, Lim JW, Bass N, Ascher NL. Roberts JP, Terrault NA. New onset diabetes mellitus after liver transplantation: the critical role of hepatitis C infection. Liver Transpl 2004 10:349-355.
Biggins SW, Rodriguez HJ, Bacchetti AP, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005;41:32-39.

Arthur Weiss, M.D., Professor of Medicine; Chief, Division of Rheumatology
The Weiss lab is interested in the biochemical signal transduction mechanisms that control T and B cell responses. The response to antigen by T lymphocytes involves complex molecular interactions involving multiple receptors.

The T cell antigen receptor (TCR) complex interacts with members of the Src, Syk and Tec families of cytoplasmic protein tyrosine kinases (PTKs) to initiate the activation of T cells. Studies are ongoing to understand how the TCR regulates these PTKs as well as the functions of their substrates.
CD45, a receptor protein tyrosine phosphatase (RPTP) expressed on hematopoietic cells, regulates TCR signal transduction by influencing the activity of Src PTKs. Dimerization of CD45 negatively regulates its function by blocking the PTP catalytic site. This contrasts with the activating effects of ligands for most receptors. Inactivation of this inhibitory mechanism for CD45 leads to lymphoproliferation and autoimmunity. Current studies are focused on regulation of CD45 dimerization and the effects of disrupting the dimerization-mediated inhibitory mechanism.
TCR stimulation alone is insufficient to activate T cells. Other interactions with molecules on an antigenpresenting
cell (APC) are required. CD28, a receptor on T cells, binds to the B7 molecules on APCs
and induces a signal involving the Akt and other kinases that activates the c-Rel and AP-1 transcription factors. These factors then bind to a transcriptional element in the interleukin-2 and other lymphokine genes. One goal of the lab is to understand the mechanisms underlying CD28 signaling and its contribution to T cell differentiation and activation.

Publications:
Roose JP, Diehn M, Tomlinson MG, Lin J, Alizadeh AA, Botstein D, Brown PO, Weiss A. T cell receptor-independent basal signaling via Erk and Abl kinases suppresses *RAG* gene expression. PloS Biol., 1:271-287, 2003.
Tomlinson MG, Kane LP, Su J, Kadlecek TA, Mollenauer MN, Weiss A. Expression and function of Tec, Itk, and Btk in lymphocytes: evidence for a unique role for Tec. Mol Cell Biol. 2004 Mar;24(6):2455-66

Hal F. Yee, Jr., M.D., Ph.D. Associate Professor of Medicine, UCSF; Chief, GI Division, SFGH
Projects:
Laboratory Research:
1) Molecular and cellular basis of hepatic fibrosis. 2) Molecular and cellular basis of intestinal fibrosis.
Clinical Research:
1) Access to subspecialty care and its impact on healthcare outcomes.
Techniques:
Laboratory Research:
High resolution transmission and epifluorescence microscopic imaging, standard molecular biological and protein methods, real-time assays for chemotaxis and contractile force generation, cell culture, and animal models of liver and gut injury.
Clinical Research:
Database development and analysis, and decision and cost analysis.

Publications:
1. Tangkijvanich P, Santiskulvong C, Melton AC, Rozengurt E, Yee Jr HF. p38 MAP kinase mediates platelet-derived growth factor-stimulated migration of hepatic myofibroblasts, J Cell Physiol, 2002;191: 351-361.
2. Chitapanarux T, Chen SL, Lee H, Melton AC, Yee Jr HF. C-type natriuretic peptide induces human colonic myofibroblast relaxation, Am J Physiol, 2004;286:G31-36.

T.S. Benedict Yen, M.D., Ph.D., Professor of Medicine; Vice-Chair of Pathology, SFVAMC
The Yen lab works on the regulation of gene expression by hepatitis B virus (HBV). One project examines the mechanism of action of the HBV posttranscriptional regulatory element (PRE), which is an RNA element that facilitates the cytoplasmic accumulation of viral mRNA. The PRE appears to be analogous to the Rev-response element of HIV-1, but depends solely on host proteins for its function. The group has found two cellular proteins that bind to the PRE; they and are now assessing the role of these proteins in PRE function. The Yen group is also characterizing the minimal cis-sequences required for PRE function, with the goal of producing a small functional cassette that can be used for maximizing gene expression for gene therapy and other medical applications. A second project in the Yen lab evolved from its discovery that one of the HBV envelope proteins causes stress in the endoplasmic reticulum, resulting in changes in both viral and cellular gene transcription. Researchers in the group are cataloging the cellular genes activated by this protein, as well as attempting to

characterize the signaling pathway from the endoplasmic reticulum to the nucleus. The eventual goal of these projects is to use the information gathered to devise novel therapeutic agents that can downregulate HBV in the infected liver.

Publications:

Foo ND, Ahn BY, Ma X, Hyun W, Yen TS. Cellular vacuolization and apoptosis induced by hepatitis B virus large surface protein. Hepatology 2002;36:1400-1407.

Schwer B, Ren S, Pietschmann T, Kartenbeck J, Kaehlcke K, Bartenschlager R, Yen TS, Ott M. Targeting of hepatitis C virus core protein to mitochondria through a novel C-terminal localization motif. J Virol 2004; 78:7958-7968.

Xu Z, Chen L, Leung L, Yen TS, Lee C, Chan JY. Liver-specific inactivation of the Nrf1 gene in adult mouse leads to nonalcoholic steatohepatitis. Proc Natl Acad Sci USA 2005;102:4120-4125.