

## RESEARCH ACTIVITIES OF UCSF GI & AFFILIATED FACULTY DIVISION OF GASTROENTEROLOGY

**James Allison, M.D.**, Clinical Professor of Medicine UCSF, Division of Gastroenterology SFGH, Adjunct Investigator Kaiser Permanente Division of Research

### Projects:

Screening for colorectal cancer, Northern California Kaiser Inflammatory Bowel Disease Registry, Dyspepsia, peptic ulcer disease and H.pylori.

### Techniques:

Clinical testing of new screening tests for colorectal cancer including unique immunochemical fecal occult blood tests and stool DNA tests, outcomes evaluation using large HMO databases.

### Selected Publications:

1. Allison JE, Hurley LB, Hiatt RA, Levin TR, Ackerson LM, Lieu TA. A Randomized Controlled Trial of Test-and-Treat Strategy for Helicobacter pylori. Archives of Intern Med.2003; 163
2. Herrinton L, Allison JE, Lowder JL, MD Natural History Of Patients With Severe Ulcerative Colitis Following Hospitalization in a Community-based Practice - abstract Gastroenterology May, 2005 in press.

**Jody Baron, M.D., Ph.D.**, Assistant Professor of Medicine, UCSF

### Projects:

We have now developed a novel transgenic mouse system that models the immune response that would occur in a natural primary Hepatitis B Virus infection. This model has allowed us to begin to address many of the unanswered questions relating to Hepatitis B Virus immunopathogenesis. Acute Hepatitis: 1) To identify the cytokines, and other molecules involved in the innate immune response to HBV in our transgenic mouse model. 2) To identify the ligand(s) recognized by the NKT cells in response to HBV (in the context of CD1d) : viral product being presented vs presentation of self (e.g. glycolipid). 3) To characterize the role of the innate immune response in the regulation of HBV replication. 4) To elucidate the mechanism of CD1d upregulation in the livers of HBV transgenic mice

Chronic Hepatitis: 1) To identify the immunologic mechanisms involved in the pathogenesis of chronic hepatitis B infection, and how these immune mechanisms involved in chronic hepatitis B differ from mechanisms involved in successful viral clearance. 2) To characterize the role of the innate immune response in the evolution of subsequent adaptive immunity. 3) To identify cell types, and cytokines that lead to chronic hepatitis versus clearance by deletion experiments using knock out mice (e.g. interferon gamma KO, CD8 KO, etc.) 4) To identify external interventions (e.g. immunization, cellular or cytokine therapy), which can be used to direct the innate and adaptive immune systems to resolve rather than cause disease.

### Techniques:

Molecular virology, transgenic and KO mice, cellular immunology, and Immunohistochemistry

### Selected Publications:

1. Cerwenka A, Baron JL, Lanier LL. Ectopic Expression of Retinoic Acid Early Inducible-1 gene (RAE-1) Permits NK Cell-mediated Rejection of a MHC Class I-bearing Tumor . Proc Natl Acad Sci. 2001;98:11521-6.
2. Baron JL, Gardiner L, Nishimura S, Locksley R, Ganem, D. Activation of a non-classical NKT cell subset in a transgenic mouse model of hepatitis B virus infection. Immunity. 2002;16:583-594.

**Nathan M. Bass, M.D., Ph.D.**, Prof. of Medicine; Medical Director, Liver Transplantation, UCSF

### Projects:

Clinical and translational studies on the pathophysiology and management of portal hypertension, fatty liver diseases, cholestatic and drug-induced liver diseases including: 1) Studies of the pathophysiological/genomic basis of nonalcoholic fatty liver disease through the National (NIH) Clinical Research Network for the Study of NASH. 2) Therapeutic trials of pharmacological agents and blood products in hepatic encephalopathy, ascites, hyponatremia, coagulopathy and primary biliary cirrhosis. 3) Long-term outcomes following liver transplantation through local and National (NIH) Liver Transplant Databases. 4) Studies of outcomes and therapeutic intervention trials (NAC and hypothermia) in acute liver failure through the National (NIH) Acute Liver Failure Study Group. 5) Studies of outcomes in hemochromatosis following liver transplantation through the National Hemochromatosis Transplant Registry (NHTR). 6) Therapeutic trials of intravenous albumin and terlipressin in the management of refractory ascites and hepatorenal syndrome.

### Techniques:

Patient-based physiological and hemodynamic studies; prospective, randomized controlled studies; prospective cohort studies; case control studies. Application of laboratory molecular technology to defining the pathophysiology of liver disease.

### Selected Publications:

- 1) Merriman RB, Aouizerat BE, Bass NM. Genetic Influences in Nonalcoholic Fatty Liver Disease. J Clin Gastroenterol 2005 (In Press).
- 2) Bass NM, Ahmed A, Johnson L, Gardner JD. Rifaximin Treatment is Beneficial for Mild Hepatic Encephalopathy. Hepatology 2004; 40:646A. (Presented, AASLD Annual Meeting, October, 2004).

**D. Montgomery Bissell, M.D.**, Professor of Medicine; Chief, Gastroenterology Division; Director, Liver Center, UCSF

### Projects:

1) The biology of hepatic fibrosis. 2) Cytokine regulation of the injury response; TGF-beta, its receptor(s) and signaling. 3) Pathogenesis of hepatocellular carcinoma.

### Techniques:

Isolation and primary culture of hepatocytes, stellate cells, sinusoidal endothelial cells and Kupffer cells; recombinant DNA-based analyses (PCR, cloning, sequencing, production of recombinant protein, mRNA by RNase

protection, etc.), western blotting, immunohistochemistry, cell migration and cell binding assays, affinity chromatography.

Selected Publications:

- 1) 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;101:18093-98.
- 2) Kikuchi S, Griffin CT, Wang SS, Bissell DM. Role of cd44 in epithelial wound repair: migration of rat hepatic stellate cells utilizes hyaluronic acid and cd44v6. J Biol Chem 2005;280:15398-404.

**David Boone, Ph.D.**, Assistant Professor of Medicine, UCSF

Projects:

Techniques:

Selected Publications:

- 1) **Boone DL**, Turer EE, Lee EG, Ahmad RC, Wheeler MT, Tsui C, Hurley P, Chien M, Chai S, Hitotsumatsu O, McNally E, Pickart C, Ma A. The ubiquitin-modifying enzyme A20 is required for termination of Toll-like receptor responses. Nat Immunol. 2004 Oct;5(10):1052-60.
- 2) Burkett PR, Koka R, Chien M, Chai S, Chan F, Ma A, **Boone DL**. IL-15R alpha expression on CD8+ T cells is dispensable for T cell memory. Proc Natl Acad Sci U S A. 2003 Apr 15;100(8):4724-9.

**Laura Bull, Ph.D.**, Assistant Professor of Medicine, SFGH

Projects:

- 1) Screening of the FIC1 and BSEP genes for mutations leading to hereditary cholestasis. 2) Study of the relationship between phenotype and genotype in patients with inherited liver disease. 3) Identification of the gene mutated in hereditary cholestasis with lymphedema. 4) Identification of genetic factors influencing susceptibility to cholestasis of pregnancy. 5) Genetic studies of familial hypercholestanemia. 6) Study of mouse models of hereditary cholestasis.

Techniques:

Mutation screening using DNA sequencing and DHPLC; gene mapping using genotyping of microsatellite DNA markers; generation and study of mouse models of hereditary liver disease, disease gene identification using database mining and gene identification programs.

Selected Publications:

- 1) Klomp LWJ, Vargas JC, van Mil SWC, Pawlikowska L, Strautnieks SS, van Eijk MJT, Juijn JA, Pabon-Pena C, Smith LB, DeYoung JA, Byrne JA, Gombert J, van der Brugge G, Berger R, Jankowska I, Pawlowska J, Villa E, Knisely AS, Thompson RJ, Freimer NB, Houwen RHJ, Bull LN. Characterization of mutations in ATP8B1 associated with hereditary cholestasis. Hepatology 2004;40:27-38.
- 2) Pawlikowska L, Groen A, Eppens EF, Kunne D, Ottenhoff R, Looije N, Knisely AS, Killeen NP, Bull LN, Oude-Elferink RPJ, Freimer NB. A mouse genetic model for familial cholestasis caused by ATP8B1 mutations reveals perturbed bile salt homeostasis but no impairment in bile secretion. Human Molecular Genetics 2004;13:881-892.

**John P. Cello, M.D.**, Professor of Medicine and Surgery, SFGH

Projects:

- 1) Randomized trial of Proton pump inhibitors vs. laparoscopic Nissen fundoplication for GERD. 2) Prospective cholangiographic and histologic evaluation of AIDS cholangiopathy. 3) Randomized, controlled clinical trial of ERCP plus laparoscopic cholecystectomy vs. laparoscopic cholecystectomy plus bile duct exploration. 4) Octreotide LAR vs placebo for variceal hemorrhage. 5) Heater probe vs. Argon plasma coagulation of upper GI bleeding.

Techniques:

- 1) Prospective randomized controlled trials. 2) Prospective open-label trials. 3) Retrospective consecutive patient reviews.

Selected Publications:

- 1) Cello JP. Capsule endoscopy features of human immunodeficiency virus and geographical diseases. Gastrointest Endosc Clin N Am. 2004 Jan;14(1):169-77.
- 2) Ko WF, Cello JP, Rogers SJ, Lecours A. Prognostic factors for the survival of patients with AIDS cholangiopathy. Am J Gastroenterol. 2003 Oct;98(10):2176-81.

**Timothy J. Davern, M.D.**, Adjunct Assistant Professor of Medicine, UCSF

Projects:

- Novel Methods of Gene Therapy for Liver Disease: 1) Development of adeno-associated vectors for treatment of metabolic diseases of the liver, 2) In vivo selection.
- Acute Liver Failure Study Group: 1) Define epidemiology of acute liver failure in the US, 2) Double-blind study of n-acetyl cysteine (NAC) for non-acetaminophen acute liver failure.
- Hepatotoxicity Clinical Research Network: 1) Define the epidemiology and clinical characteristics of drug-induced liver injury; 2) Pharmacogenomics.

Techniques:

- 1) Recombinant DNA technology. 2) Cell Culture. 3) Protein expression and purification. 4) Viral vector production. 5) Animal studies.

Selected Publications:

- 1) [Davern TJ 2nd](#). Acetaminophen hepatotoxicity. Hepatology. 2004 Oct;40(4):1021-2
- 2) [Wai CT, Fontana RJ, Polson J, Hussain M, Shakil AO, Han SH, Davern TJ, Lee WM, Lok AS; The US Acute Liver Failure Study Group](#). Clinical outcome and virological characteristics of hepatitis B-related acute liver failure in the United States. J Viral Hepatol 2005 Mar;12(2):192-8

**Mandana Khalili, M.D.**, Assistant Adjunct Professor of Medicine, SFGH

Projects:

1. Insulin resistance in hepatitis C. 2. HCV-induced alterations in glucose metabolism, 3. Determinants of severity of liver disease in patients with chronic hepatitis C and normal ALT (natural history study). 4. Safety and efficacy of combination antiviral therapy in patients with chronic hepatitis C

and genotype 1. 4. Role of new anti-viral therapy or combination therapy in patient with chronic hepatitis B. 5. Safety and efficacy of Pegylated interferon therapy in Latino patients HCV coinfection. 6. Antiviral therapy in patients with HIV/HCV coinfection.

Techniques:

1. Utilization of various techniques to measure metabolic abnormalities and insulin resistance in patients with hepatitis C. 2. Epidemiologic and natural history studies. 3. Clinical trials involving existing or new drugs.

Selected Publications:

1. Khalili M, Fisher E, Bernstein D, Lentz E, Baryliski C, Hoffman-Terry M. Peginterferon alfa-2a With or Without Ribavirin in HCV/HIV Coinfected Patients: Partially-Blinded and Randomized Multicenter Trial. Digestive Diseases and Sciences, In Press.

2. Shergill AK, Khalili M, Straley S, Bollinger K, Roberts JP, Ascher NA, Terrault N. Applicability and tolerability of preemptive antiviral therapy in hepatitis C- infected patients undergoing liver transplantation. Am J Transplant. 2005 Jan;5(1):118-24.

**Young S. Kim, M.D.**, Professor of Medicine and Pathology, DVAMC

Projects:

1) Molecular biology of colonic and pancreatic mucins in cancer and precancerous lesions. 2) Molecular genetic analysis of familial and sporadic colorectal cancers.

Techniques:

1) Regulation of mucin and trefoil factor gene expression using promoter reporter constructs in cultured cancer cells and in the development of animal models of colon cancer using promoter/SV40 Tag mice and APC min mice. Analysis of signal transduction pathways and transcription factors. 2) Microdissection of colorectal cancer and polyp tissue sections and cultured cancer cell lines; DNA and RNA extraction, RT-PCR, SSCP, LOH, analysis of mutation and microsatellite instability status; methylation analysis of promoters of hMLH1, P16, beta catenin and E-cadherin. 3) Apoptosis, cell proliferation, angiogenesis and invasion/metastasis assays, in situ hybridization and immunohistochemistry.

Selected Publications:

1) Ahn D-H, Crawley S, Hokari R, Kato S, Li J-D, Kim YS. TNF alpha activates MUC2 transcription via NF-kB but inhibits via JNK activation. Cell Physiol. Biochem., 15:29-40, 2005.

2) Deng G, Song G-A, Pong E, Sleisenger MH, Kim YS. Promoter methylation inhibits APC gene expression by causing changes in chromatin conformation and interfering with the binding of transcription factor CCAAT-binding factor. Cancer Res., 64:2692-2698, 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-fluorescence, 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.

Selected Publications:

1) Korn WM, Prevention and Management of Early Esophageal 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.

Selected Publications:

1) Mein, SM and 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.

**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

Selected Publications:

- 1) Lee EG, Boone DL, Libby S, Chai S, Chien M, Lodolce JP, and Ma A. 2000. Failure to regulate TNF induced NF- $\kappa$ B 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 modifying enzyme A20 is essential for terminating TLR signaling. *Nature Immunology* 5;1052-1060.

**Uma Mahadevan, M.D.** Assistant Clinical Professor of Medicine, Associate Director of Clinical Research, UCSF Center for Colitis and Crohn's Disease

Projects:

1) Pregnancy Outcomes in Women with IBD 2) Clinical Trials in biologic therapy for Inflammatory Bowel Disease; 3) The effects of IBD medications on male fertility and semen integrity

Techniques:

1) Endoscopy; 2) Colonoscopy

Selected Publications:

- 1) Mahadevan U, Terdiman JP, Aron J, Jacobsohn S, Turek P. Influximab and Semen Quality in Men with Inflammatory Bowel Disease. *Inflamm Bowel Dis.* 2005;11:395-399
- 2) Mahadevan U, Kane S, Sandbor W n, et al. Intentional Influximab Use During Pregnancy for Induction or Maintenance of Remission in Crohn's Disease. *Aliment Pharmacol Ther* 2005;15;21:733-8

**Jacquelyn Maher, M.D.**, Professor of Medicine, SFGH

Projects:

Studies investigating the cellular mechanisms of liver injury, inflammation and fibrosis. Experiments focus on:

- a) chemokine actions in liver;
- b) the pathogenesis of steatohepatitis; and
- c) the role of inflammatory cells in the pathogenesis of liver fibrosis.

Techniques:

1) Animal models of acute and chronic liver disease. 2) Primary liver cell culture. 3) Analysis of cell death pathways and inflammatory pathways in liver. 4) Histology, immunohistochemistry, in situ hybridization. 5) Gene transfer using recombinant adenovirus.

Selected Publications:

1) 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 Gastrointest Liver Physiol.* 2004 Sep;287(3):G734-41.

2) 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, in press.

**Antony F. McDonagh, Ph.D., M.R.S.C.**, Adjunct Professor of Medicine, UCSF

Projects:

- 1) Bile pigment transport, metabolism and toxicity - influence of three-dimensional structure and hydrogen bonding. 2) Photochemistry and photometabolism of bile pigments and porphyrins and mechanism of phototherapy of neonatal jaundice. 3) New therapies for neonatal jaundice. 4) Transhepatic transport mechanisms of bile pigments and related organic anions. 5) Acyl glucuronides - mechanism of formation and toxicity. 6) Antioxidant properties and physiologic role of bilirubin and biliverdin. 7) Metabolism of heme & sulfite in amphibians. 8) Gene therapy of inborn errors of bilirubin metabolism

Techniques:

Spectroscopy (UV-Vis, NMR, Circular Dichroism, Mass, Fluorescence). Molecular modeling. High performance liquid chromatography. Photochemical and photobiological techniques. Surgical techniques for i.v. infusion and bile collection in rats and frogs. Organic synthesis and stereochemistry. Breeding and maintenance of congenitally jaundiced (Gunn and TR-) rats. Measurement of bile pigment fractions in patients with liver disease. Porphyrin and heme biosynthetic enzyme assays.

Selected Publications:

1. Toietta G, Mane VP, Norona WS, Finegold MJ, Ng P, McDonagh AF, Beaudet AL, Lee B. Lifelong elimination of hyperbilirubinemia in the Gunn rat with a single injection of helper-dependent adenoviral vector. *Proc Natl Acad Sci.* 2005;102: 3930-3935.
2. Boiadjiev SE, Watters K, Wolf S, Lai BN, Welch WH, McDonagh AF, Lightner DA. pKa and Aggregation of Bilirubin: Titrimetric and Ultracentrifugation Studies on Water-Soluble Pegylated Conjugates of Bilirubin and Fatty Acids. *Biochem.* 2004;43:15617-15632.

**Kenneth R. McQuaid, M.D.**, Associate Professor of Clinical Medicine, DVAMC

Projects:

1. Accuracy of virtual colonoscopy versus conventional colonoscopy; 2. Colorectal neoplasia chemoprevention; 3. Colorectal neoplasia screening

Techniques:

Prospective randomized controlled studies; esophageal manometry and pH studies.

Selected Publications:

1. Sharma P, McQuaid K, Dent J, et al. A critical review of the diagnosis and management of Barrett's esophagus - the AGA Chicago workshop. *Gastroenterology* 2004; 127:310-30.
2. Rockey DC, Paulson E, Niedzwiecki D, Davis W, Bosworth H, Sanders L, Yee J, Henderson J, Hatten P, Burdick S, Sanyal A, Rubin D, Sterling M, Akerkar G, Bhutan MS, Binmoeller K, Garvie J, Bini EJ, McQuaid K, Foster B, Thompson B, Dachman A, Halvorsen R. Prospective comparison of colon imaging tests: a determination of the relative sensitivity of air contrast barium enema, computed tomographic colonography, and colonoscopy. *Lancet* 2005;365:305-11.

**Raphael B. Merriman, M.D.**, Adjunct Assistant Professor of Medicine, UCSF.

Projects:

- 1) Establishment of a clinical, tissue and DNA database of patients with various forms of fatty liver diseases (simple hepatic steatosis, NASH and fatty liver disease related cryptogenic cirrhosis)
- 2) Mutation analysis of several candidate genes related to hepatocyte lipoprotein, fatty acid and adipocyte metabolism, adipocytokines, insulin resistance and hepatic inflammation and fibrosis and their correlation with disease presence and severity in an attempt to elucidate the pathogenesis of this common complex metabolic disorder
- 3) Determine the hepatic biochemical, histological and protein expression consequences of weight loss after gastric by-pass surgery on morbidly obese individuals with non-alcoholic fatty liver disease
- 4) Participation as an co-investigator in the NIH-sponsored NASH Clinical Research Network, to define the pathogenesis, natural history and treatment of non-alcoholic fatty liver disease (NAFLD). This involves subjects accrual in various study components of the NASH CRN including the NAFLD Database and NASH adult and pediatric treatment clinical trials
- 5) The evaluation of novel MRI-based imaging modalities to permit the non-invasive evaluation of hepatic steatosis, inflammation and fibrosis
- 6) Determination of the effects of Nucleoside Reverse Transcriptase Inhibitors (NRTI) on mitochondrial DNA through inhibition of DNA polymerase gamma, to confirm the suspected pathogenesis of NRTI-induced steatosis and lactic acidemia
- 7) Evaluation of the effects of continuous epoprostenol on portopulmonary hypertension and hepatic function.

Techniques:

Mutation analysis through the use of DDGE, SSCP, fluorescence polarization genotyping and confirmatory nucleotide sequence analysis. Protein expression through ELISA assays and microarrays. Statistical methods of complex metabolic disease including linkage analysis and association studies. Ultracentrifugal quantification of lipoprotein fractions. Quantification of mitochondrial DNA using Southern Blot analysis. Hemodynamic studies permitting detailed patient-based prospective cohort analysis of the effects of epoprostenol on portopulmonary hypertension..

Selected publications:

- 1) Riley, M; Berquist, W; Rosenthal, P; Bass, N; Merriman, R. Failure To Diagnose Obesity And Screen For Fatty Liver Disease In Pediatric Practice. *Journal of Pediatrics* (In Press, 2005)
- 2) Merriman R, Bass N. Genetic Influences in Nonalcoholic Fatty Liver Disease. *Journal of Clinical Gastroenterology* (In Press, 2005)

**Alex Monto, M.D.** Assistant Clinical Professor of Medicine, UCSF, Gastroenterology Staff, SFVAMC and UCSF Gastroenterology Faculty Practice, 350 Parnassus.

Projects:

1. Hepatitis C and alcohol interaction in causing liver disease
2. Hepatitis C and steatosis
3. Predictors of liver histology in HIV-HCV coinfection
4. Liver disease natural history and clinical outcomes of hepatitis C-infected and hepatitis C and human immunodeficiency virus-coinfected individuals

Techniques:

Cohort studies

Selected Publications:

- 1) Monto A, Patel K, Bostrom A, Pianko S, Pockros P, McHutchison JG, Wright TL. Risks of a range of alcohol intake on hepatitis C-related fibrosis. *Hepatology* 2004;39:826-834.
- 2) Monto A, Dove LM, Bostrom A, Kakar S, Pien P, Wright TL. Hepatic steatosis in HIV-HCV coinfection: prevalence and significance compared to HCV mono-infection. *Hepatology* In Press.

**V. Raman Muthusamy, M.D.**, Assistant Clinical Professor of Medicine, Director, Endoscopic Ultrasound Program, UCSF

Projects:

- 1) Outcomes studies regarding the utility of endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration (EUS-FNA) in GI malignancies.
- 2) New techniques in the diagnosis of microlithiasis.
- 3) New Endoscopic Technologies/Techniques.

Techniques:

- 1) Endoscopic Ultrasonography with Fine Needle Aspiration.
- 2) Endoscopic Retrograde Cholangiopancreatography.
- 3) Chromoendoscopy.
- 4) Endoscopic mucosal resection.
- 5) Photodynamic therapy.

Selected Publications:

- 1) Visser BC, Muthusamy R, Mulvihill SJ, and Coakley, F. Diagnostic Imaging of Cystic Pancreatic Neoplasms. *Surgical Oncology* 2004;13:27-39.
- 2) Visser BC, Khawaja O, Muthusamy VR, Yeh B, Coakley F, Way LW. Diagnostic Evaluation of Cystic Pancreatic Lesions. *Archives of Surgery*, 2005 Accepted.

**James W. Ostroff, M.D.**, Clinical Professor, Medicine, UCSF

Projects:

- 1) Characterization of patients with pancreas divisum.
- 2) Morbid obesity and gastroesophageal reflux disease (GERD): prevalence of GERD symptoms

and changes in symptoms with behavioral weight loss and Roux-en-Y gastric bypass surgery. 3) Endoscopic management of end-stage sclerosing cholangitis as a bridge to liver transplantation. 4) Biliary anastomotic strictures after liver transplantation: non-invasive evaluation by MR cholangiography. 5) Endoscopic management of biliary complications after liver transplantation. 6) Tumor markers in pure pancreatic juice. 7) The endoscopic management of surgical strictures after Esophago-gastrectomy.

Techniques:

1) The characterization of biliary strictures with a high resolution small diameter per-oral cholangioscope. 2) Push enteroscopy with no overtube. 3) Use of enteral stenting in the pre-operative setting prior to colonic resection.

Selected Publications:

1) Ostroff JW. Endoscopic and Radiologic Management of Pancreatic and Biliary Tract Disease. Seminars in Gastrointestinal Disease, 2003;14:222-36. 2) Gugig R, Ostroff JW, Chen Y, Harrison M, Heyman MB. Gastric Cystic Duplications: A Rare Cause of Recurrent Pancreatitis in Children. Gastrointestinal Endoscopy 2004;59:592-594.

**Robert Owen, M.D.**, Professor of Medicine, Biostatistics and Epidemiology, DVAMC

Projects:

1) Role of intermediate filaments in uptake and transport of antigens and microorganisms by M cells in Peyer's patches. 2) Homing and localization of antigen processing cells and lymphocyte subsets in intestinal lymphoid organs. 3) Neuropeptide mediation of hepatic immunocyte migration and function. 4) Diagnosis and treatment of microsporidia and other protozoa in diarrhea and the wasting syndrome of AIDS.

Techniques:

Immunohistochemistry and in situ hybridization for localization of intermediate filaments, neuropeptides, their receptors, macromolecular antigens and microorganisms. Video microscopy and computer-assisted morphometric analysis of hepatic and mucosal lymphoid structures during mucosal immune responses. Ultrastructural immunolocalization of vimentin and correlation with transport function of rabbit and human M cells in Peyer's patch and appendix. Cloning and sequencing of rabbit vimentin. Measurement of mRNA for vimentin as an indication of M cell differentiation. Ultrastructural analysis of opportunistic protozoal, bacterial and viral pathogens in intestinal mucosal cells.

Selected Publications:

1) Fujimura Y, Owen RL: Tacrolimus (FK506) and cyclosporine reduce the uptake and transport of particles into rabbit Peyer's patches. Transplantation 2002;73:1049-1054. 2) Kato T, Owen RL: Structure and function of intestinal mucosal epithelium. In: Mucosal Immunology. Third Edition, J Mestecky, ME Lamm, W Strober, J Bienenstock, JR McGhee, L Mayer (eds), Academic Press, Orlando, FL. 2005:131-151.

**Marion Peters, M.D.**, Professor of Medicine, Chief of Hepatology Research, UCSF

Projects:

Laboratory based: The role of the immune system in biliary based inflammation and the importance of antigen location in immune responses in the liver. The laboratory has developed transgenic mice which express a foreign antigen on hepatocytes or biliary epithelium. These mice develop chronic active hepatitis and cholestatic liver disease after adoptive transfer of antigen specific CD4 and CD8 T cells. While antigen specific responses initiate disease, innate immune cells of the liver regulate the response. Our lab studies the role of antigen location, organ specific and innate immune cells as well as cytokines in the control of this inflammation.

Translational: Host-viral interactions in Hepatitis C and Hepatitis B infection. This project evaluates the role of inflammatory cytokines and their receptors using DNA polymorphism analysis and mRNA gene profiling. We will assess the effect of the host response in induction of disease and response to therapy including the effect of alcohol and HIV co-infection. Clinical: Clinical studies in the role of alcohol in Hepatitis C infection; Co-infection of HIV patients with Hepatitis B and C: these studies evaluate outcome and response to therapy; Bone density in patients with chronic liver disease and after liver transplantation; Recurrence of Primary Biliary Cirrhosis post liver transplantation and the role of ursodeoxycholic acid.

Techniques:

Laboratory studies: Development of transgenic mice techniques: construct preparation, screening of tails, breeding. Cell culture techniques of mouse and human mononuclear cells including cell isolation, cytokine and immune functional analyses; cellular immunology techniques; molecular techniques including analysis of gene expression at the protein and mRNA level; . Clinical studies: Design of clinical studies, data /statistical analyses and manuscript preparation.

Selected Publications:

1) Guy JE, Qian P, Lowell JA, Peters M, Recurrent Primary Biliary Cirrhosis: Peritransplant Factors and Ursodeoxycholic Acid Treatment Post Liver Transplant Liver Transplantation in press 2005. 2) Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, Peters MG, et al, for the A5071 Study Team. A randomized, controlled trial of PEG interferon alfa 2a plus ribavirin versus interferon alfa 2a plus ribavirin for chronic Hepatitis C virus infection in HIV co-infected persons: the US AIDS Clinical trials Group A5071 study team. N Engl J Med. 2004 Jul 29;351(5):451-9

**James C. Ryan, M.D.**, Associate Professor of Medicine in Residence, VAMC

Projects:

Characterization of a new family of natural killer lymphocyte receptors implicated in the recognition and lysis of neoplastic, foreign, and virally infected cells.

Techniques:

Molecular characterization of receptor-ligand interactions and activation pathways. Protein-protein interactions, transmembrane signaling, eukaryotic and prokaryotic protein expression and mutagenesis. Gene discovery through eukaryotic expression cloning and eukaryotic complementation.

Monoclonal antibody production.

Selected Publications:

- 1) Kveberg L, Ryan JC, Rolstad B, Inngjerdingen M. Expression of regulator of G protein signaling proteins in natural killer cells, and their modulation by Ly49A and Ly49D. *Immunology* 2005; 115:358-65.
- 2) Naper C, Dai KZ, Kveberg L, Rolstad B, Niemi EC, Vaage JT, Ryan JC. Two structurally related rat Ly49 receptors with opposing functions (Ly49 stimulatory receptor 5 and Ly49 inhibitory receptor 5) recognize nonclassical MHC class Ib-encoded target ligands. *J Immunol* 2005;174:2702-11.

**Janak Shah, MD**, Assistant Clinical Professor of Medicine, Dir. of Therapeutic Endoscopy, VAMC

Projects:

Clinical research interests in the areas of: 1) pancreaticobiliary endoscopy, 2) endoscopic ultrasound, 3) advanced endoscopic techniques, 4) GI bleeding, 5) comparison of endoscopic techniques for acute PUD hemorrhage, 6) EUS vs. MDCT for evaluating pancreatic adenocarcinoma, 7) role of endoscopy in diverticular hemorrhage.

Selected Publications:

- 1) Rodriguez H, Muthusamy VR, Shah JN. Endoscopic ultrasonography versus multidetector CT for the evaluation of pancreatic adenocarcinoma. *Gastroenterol* 2005; 128: A406.
- 2) Shah JN, Ahmad NA, Shetty K, Kochman ML, Long WB, Brensinger CM, Pfau PR, Olthoff K, Markmann J, Shaked A, Reddy KR, Ginsberg GG. Biliary tract complications following living donor liver transplantation: types and endoscopic management. *American Journal of Gastroenterology* 2004; 99: 1291-5

**Jonathan P. Terdiman, M.D.**, Associate Professor of Clinical Medicine, MZM, 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.

Selected 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 Terrault, M.D., M.P.H.** Assistant Professor of Medicine, UCSF

Projects:

- 1) Natural history and therapies to prevention complications of cirrhosis in patients with HCV and HBV.
- 2) Outcomes of HCV infection in dialysis patients and those undergoing kidney transplantation.
- 3) Natural history of post liver transplantation disease in patients with HCV infection, determinants of disease severity and management strategies for recurrent disease.
- 4) Therapeutic trials with new drugs to treat chronic HBV and HCV.

Techniques:

- 1) Population-based studies with sentinel surveillance for incident and prevalent cases. 2) Cohort and case control studies for in patients with chronic HBV and HCV. 3) Phase I, II, and III clinical trials

Selected Publications:

1. Shergill AK, Khalili M, Straley S, Bollinger K, Roberts JP, Ascher NA, Terrault NA. Applicability and tolerability of preemptive antiviral therapy in hepatitis C infected liver transplant recipients. *Am J. Transplant*, 2005;5:118-24.
2. Biggins SW, HJ Rodriguez, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum Sodium Predicts Mortality in Patients Listed for Liver Transplantation. *Hepatology*, 2005;41:32-39.

**Fernando Velayos, M.D.**, Assistant Clinical Professor of Medicine, Mt. Zion

Selected Publications:

- 1) Velayos FS, Allen BA, Conrad PG, Gum J, Karkar S, Chung DC, Truta B, Sleisenger MH, Kim YS, Terdiman JP. Low rate of microsatellite instability in young patients with adenomas: Reassessing the Bethesda Guidelines. *American Journal of Gastroenterology*. 2005 May; 100(5):1143-9.
- 2) Velayos FS, Terdiman JP, Walsh JM. Effect of 5-Aminosalicylate use on colorectal cancer and dysplasia risk: A systematic review and meta-analysis of observational studies. *American Journal of Gastroenterology*. 2005 June; 100: 1345-1353.

**Richard A. Weisiger, M.D., Ph.D.,** Professor of Medicine, UCSF

Projects:

Development of an integrated electronic medical record for use in the outpatient clinics at UCSF

Techniques:

1. Programming in various languages including Java, Oracle, Filemaker, AppleScript and Unix. Beta testing using selected faculty in the Department of Medicine. Working with the Breast Cancer Center for Excellence to develop an electronic medical record suitable for Breast Oncology.  
2. Regulation of fatty acid metabolism in hepatocytes with emphasis on the role of intracellular binding proteins and albumin. 2) Mechanisms of hepatic clearance and detoxification of organic anions. 3) Quantitative analysis of hepatic transport

Selected Publications:

1) Weisiger, RA. Mechanisms of intracellular fatty acid transport: role of cytosolic binding proteins. *J. Mol. Neurosci.* (in press) 2005.  
2) Wiesiger RA. Serum albumin. *Oxford Textbook of Hepatology*, 3rd Ed. Prof. Benhamou, ed, Blackwell Publishing, Oxford, England 2005

**Teresa L. Wright, M.D.,** Professor of Medicine; Chief, Gastroenterology Division, DVAMC

Projects:

1) Characterization of hepatitis B and C infection in patients with HIV infection. 2) Development of novel antivirals for the treatment of hepatitis B and C 3) Role of HCV variants in disease pathogenesis and treatment failure. 4) Molecular techniques to track transmission of HCV and/or HBV. 5) Epidemiology of hepatitis C and hepatocellular carcinoma in the Veterans Health Administration. 6) Genetic variables associated with natural history and treatment of hepatitis C.

Techniques:

Polymerase chain reaction amplification of hepatitis C RNA and hepatitis B DNA; Southern analysis; dot blot hybridization; asymmetric PCR for detection of positive and negative strands of HCV; HCV RNA quantification in collaboration with Chiron Corp. and Roche Molecular Systems; sequencing of HBV DNA and HCV RNA, heteroduplex analysis of HCV variants, phylogenetic analysis of relatedness of HCV quasispecies, heteroduplex analysis of HCV variants, large scale genetic screening of host genes.

Selected Publications:

1) Bini EJ, Bräu N, Currie S, et al, and Wright TL. Epidemiology of chronic hepatitis C and eligibility for antiviral therapy in the United States. *A J Gastroenterol*, 2005, In Press.  
2) Ku N-O, Lim JK, Krams SM, Esquivel CO, Keeffe EB, Wright TL, Parry DAD, Omary MB. Keratins as susceptibility genes for end-stage liver disease. *Gastroenterology* 2005, In Press.

**Francis Yao, M.D.,** Associate Medical Director, Liver Transplantation Program, Associate Clinical Professor of Medicine, Director for Community Liaison, UCSF

Projects:

1) Liver transplantation for hepatocellular carcinoma: A prospective study evaluating survival according to intention to treat analysis and drop-out from the waiting list. 2) A prospective evaluation for liver transplantation for hepatocellular carcinoma using the modified UCSF staging criteria. 3) Analysis of total tumor volume as predictor of outcome after liver transplantation in 100 consecutive patients undergoing liver transplantation for hepatocellular carcinoma. 4) Multi-center controlled trial for PEG-interferon versus lamivudine for chronic hepatitis B infection.

Techniques:

Clinical research data base, randomized controlled studies.

Selected Publications:

1) Yao FY, Kinkhabwala M, LaBerge J, et al. The impact of pre-operative loco-regional treatments on survival following liver transplantation for hepatocellular carcinoma. *Am J Transplantation* 2005;5:795-804.  
2) Cruz E, Ascher NL, Bass NM, Roberts JP, Yao FY. High incidence of recurrence and hematologic events following liver transplantation for Budd-Chiari syndrome. *Clinical Transplantation* (In Press).

**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.

Selected 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.