

**DEPARTMENT OF PATHOLOGY & LABORATORY MEDICINE
RESEARCH PROJECTS**

- 1) **PROJECT TITLE:** Chronic Anemia Post Gastric Bypass Surgery: Mimicking Myelodysplastic Syndrome: More than just Iron and Copper Deficiency

PRIMARY INVESTIGATOR: Mingyi, Chen, M.D., Ph.D./Assistant Professor of Pathology and Laboratory Medicine.

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

Collecting and analyzing the clinical data.

DESCRIPTION: Obesity is characterized by chronic, low-grade, systemic inflammation, which, in turn, has been associated with anemia of chronic disease. Bariatric surgery has been proved to be the most effective treatment for morbid obesity. Following bariatric surgery, chronic anemia is common due to micronutrient and vitamin (iron, folate, and vitamin B12) deficiencies despite oral supplementation. Iron deficiency develops in approximately 50 percent of gastric bypass patients, and is associated with anemia in a third of cases. Similar to iron deficiency, copper deficiency can cause hematological abnormalities with or without neurological complications. Some patients present with persistent anemia after bariatric surgery with normal concentrations of iron, copper, folate and vitamin B12. Bone marrow biopsy show hypercellular with overt dysplastic features and increased ringed sideroblasts, mimicking myelodysplastic syndrome. In addition, increased serum inflammatory cytokines including IL-6 and TNF- α were detected in majority of patient. The obesity related chronic inflammatory state superimposed upon the micronutrient and vitamin deficiencies remains an underappreciated cause of ineffective hematopoiesis. We recommend serum copper and erythropoietin level as well as inflammatory determination should be incorporated into the routine diagnostic workup for patients with suspected MDS including those with a history of gastric bypass surgery associated with obesity-related comorbidities.

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- 2) **PROJECT TITLE:** Therapy for HIV Latency in the Nonhuman Primate Model for AIDS; Clinical Proteomics

PRIMARY INVESTIGATOR: Paul Luciw, Ph.D./Professor, Department of Pathology and Laboratory Medicine, and Center for Comparative Medicine

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

Infectious disease studies in nonhuman primates; protein biomarkers for disease

DESCRIPTION:

Virology research: The main focus of my research, since joining UCD in 1986, has been on viruses that establish chronic infections in animal models. Studies on simian immunodeficiency virus (SIV) infection of rhesus macaques and AIDS pathogenesis have occupied the largest share of my research program. This animal model work, conducted at the California National Primate Research Center, has been extended to include analysis of SIV/HIV recombinant viruses (designated SHIV). Currently, we are using the SHIV/macaque model to identify latent reservoirs of the virus. Accordingly, the preclinical research in my lab in this animal model will be critical for testing and developing novel drug regimens for AIDS patients that are based on treating patients with agents that potentially eliminate latent viral reservoirs.

Clinical Proteomics: The DOPLM has established a Clinical Proteomics Program to support proteomics approaches and tools for investigating mechanisms of pathogenesis and developing novel diagnostics. Research activities are focused on the identification of clinically relevant protein biomarkers and development of appropriate assays for analyzing normal biological processes and pathologic conditions. There are 2 capabilities in this program: (1) multiplex microbead immunoassay for measuring biomarker proteins in body fluids, tissues, and cells, and (2) two-dimensional differential gel electrophoresis (2-D DIGE) for proteomic biomarker discovery. These capabilities have the potential to contribute to personalized medicine *via* application of clinical biomarkers to match therapies with specific patients. Current projects involve biomarkers for infectious disease (tuberculosis), cancer, and wound healing.

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- 3) **PROJECT TITLE:** Establishing Response Time (TAT) Standards for Multi-part Frozen Section Cases.

PRIMARY INVESTIGATOR: John W Bishop, M.D., Professor of Pathology and Laboratory Medicine

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

Collecting time motion data for the frozen section process from operating room hand off to call back, and analyzing the data.

DESCRIPTION: There are no standards for multi-part frozen section cases. Our institution, and perhaps the U.S. hospital community at large, could benefit from doing a time-motion analysis to construct an expected response time curve as a function of the number of blocks in the lab at any point in time. A further enhancement would account for time needed in dissecting larger specimens before samples could be frozen (as commonly happens in ovarian, uterine, and renal masses as examples). The data gathering for such studies is best done by someone who is not entangled in the process. Ideally the response time study should begin when the surgeon hands the specimen off the operating table, accounting for all process until reporting of results back to the operating room.

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4) PROJECT TITLE: Redefine the classification of endometrial carcinomas

PRIMARY INVESTIGATOR: Eric Huang, M.D., Ph.D./Assistant Professor of Pathology and Laboratory Medicine.

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

Collecting and analyzing the clinical data.

DESCRIPTION: Endometrial carcinoma is the fourth leading cause of cancer and eighth leading cause of cancer related mortality among women (SEER data 2004-2008). However, it is increasingly recognized that the current histologic classification of endometrial carcinomas does not adequately stratify tumors into biologically relevant subtypes. This failure reflects our limited understanding of endometrial carcinoma and the biology behind them, particularly high grade tumors. These high grade tumors have high mortality, and our lack of biological understanding contributes to our failure to develop effective therapies. We hypothesize that endometrial carcinomas carry “fingerprints” or “signatures” that cannot be identified based on conventional light microscopy. This study will first focus on classifying endometrial carcinomas using the established histomorphology and immunohistochemical profile. The endometrial carcinomas classified under the current morphologic and immunohistochemical criteria will undergo Raman spectroscopy and molecular sequencing searching for “fingerprints” or “signatures” that have not been previously identified. When these signals are found, we will attempt to reclassify the endometrial carcinomas with ambiguous features based on this new data. This study will contribute to a better understanding of the pathophysiology and molecular biology of endometrial carcinomas and better define the endometrial carcinomas with ambiguous features by using these objective techniques. We believe this new information will shed light into future therapy and leading to translational research and potential targeted therapy.

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5) **PROJECT TITLE:** Super-resolution microscopy of standard pathology specimens

PRIMARY INVESTIGATOR: Richard Levenson, M.D., Professor of Pathology and Laboratory Medicine and Vice Chair for Strategic Technologies

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

Imaging and analyzing data

DESCRIPTION: Super resolution techniques have been developed over the last few years that can take images with higher magnification and greater resolution than can be achieved with conventional microscopes. One such instrument is available at UC-Davis and has already been used to take very intriguing but preliminary images of formalin-fixed, paraffin-embedded sections of kidney. The resolution is above what has been seen previously with standard microscopy techniques, and the questions to be answered include: best ways to prepare and stain samples; what kinds of samples might benefit from such techniques; how can the software for imaging, image analysis and image display be optimized. This work would be done in collaboration with investigators at CBST, including Sebastian Wachsmann-Hogiu and Tim Zhang.

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6) **PROJECT TITLE:** iPad-enabled, video-enhanced consent forms for virtual autopsies

PRIMARY INVESTIGATOR: Richard Levenson, M.D., Professor of Pathology and Laboratory Medicine and Vice Chair for Strategic Technologies

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

Development and enhancement of content, including video content. Assessing patient and family acceptability.

DESCRIPTION: Virtual autopsies are a new approach to increasing the acceptability of autopsies for patients and families, as they combine the use of post-mortem CT exams with fairly broad tissue sampling for microscopic analysis. As the body is not disfigured and can be transferred to the funeral home quickly, it is expected that many more exams can be conducted, with benefits to patient care and research. Since this is a new concept, families will have to be informed about what the process will entail, and what kind of results and insights can be expected. They also have to provide their legal consent to permit the procedure to be performed. A recent development in electronic consent technology involves the use of iPads to communicate important and possibly technical information to patients and family effectively and in ways that cannot be later challenged in court. A proprietary solution that uses the camera on the iPad to document reading (via gaze tracking) and comprehension,

via mini-quizzes, is under development in cooperation with investigators at UC Davis. In addition to the documentation component, the iPad consent process can involve the presentation of video content to help patients and families understand all of the techniques that might be involved in a virtual autopsy.

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- 7) **PROJECT TITLE:** Advanced image-segmentation approaches to pathology diagnosis and quantitative assessments

PRIMARY INVESTIGATOR: Richard Levenson, M.D., Professor of Pathology and Laboratory Medicine and Vice Chair for Strategic Technologies

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

Explore and if appropriate extend software tools that can classify pathology-relevant regions in clinical histology specimens. Perform proof-of-concept experiments to determine the quality and applicability of such tools for clinical applications.

DESCRIPTION: New developments in machine-learning neural-net-based software tools are beginning to demonstrate that computers can perform useful high-level image “understanding” of digital pathology images. Some packages, including ones not publically available, can be used to explore the usefulness and limitations of such approaches. For example, we do not yet if their application will be limited to quantitative methods (counting mitoses, estimating areas of fibrosis or necrosis, etc.) or whether they can be used to make or at least suggest diagnosis or detect possibly missed rare events, such as isolated cancer cells or the presence of infectious organisms. Various on-line data sets which include digital tissue microarray images with accompanying outcome data, and/or locally scanned pathology specimens, will be used to explore computer-aided methods.

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- 8) **PROJECT TITLE:** Neuronal Anatomy on Autism

PRIMARY INVESTIGATOR: Verónica Martínez Cerdeño

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION: Processing and cutting human brain tissue, Golgi staining for neurons, microscopy, and Neurolucida analysis.

DESCRIPTION: Dendritic spines harbor the components that participate in the transmission of electrical signals between neurons. Many psychiatric and neurologic disorders are accompanied by alterations in dendrite and spine number and morphology. We hypothesize that an alteration in dendritic and spine number and morphology in pyramidal neurons in the cerebral cortex underlies cognitive deficiencies that are present in autism. A small number of previous studies suggest that dendritic branching may be affected in the cerebral cortex of subjects with autism. Nevertheless, a thorough study has not yet been performed on dendritic branching in human tissue. Furthermore, there is contradictory data about whether there is an increase or decrease in the number of dendritic spines. We will determine if there is an alteration in dendritic branching and spine number and morphology in area BA9 of prefrontal cortex of subjects with autism through Golgi staining and Neurolucida analytic methods. Exploring whether and how the number and morphology of dendrites and spines is altered in autism will open new lines of research that focus on the modulation of signaling factors and genes that control dendrite and spine development and plasticity, and on transmission of electrical signals between neurons in autism.

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- 9) **PROJECT TITLE:** Establishing a departmental tabulation of the prognostic results of breast cancer specimens

PRIMARY INVESTIGATOR: John W Bishop, M.D., Professor of Pathology and Laboratory Medicine

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

After obtaining the appropriate clearance and training, the resident/ medical student will conduct a records review to extract the information necessary for this database. For any medical student who should elect to take on this project, the PI shall provide training and access to the necessary records, as well as instruction on the scoring of IHC prognostic assays and Nottingham scoring. The student will be acknowledged in the intra-institutional report of findings as well as have co-authorship on any publishable manuscript arising from this effort.

DESCRIPTION: There is a new regulatory requirement for laboratory directors to tabulate and analyze annually the results of testing on all breast carcinomas examined in their laboratories. The laboratory results profile must be compared to published benchmarks. We do not yet have such a tabulation. Such a tabulation should include all breast carcinomas examined, the patient age, the Nottingham grade (preferably the full score), specification of any special type (v usual invasive ductal type), The ER, PgR, Ki-67, and Her2 IHC and/or FISH results. For many cases (ER positive, node negative) there is also the opportunity to compare results to an outside laboratory assay (Oncotype DX). While this new regulation places this study firmly in the quality assurance purview, the results may nevertheless be publishable either as a single institution comparison to Oncotype Dx or as part of a University of California multicenter comparison.

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ADDITIONAL RESEARCH PROJECTS

- 10) **PROJECT TITLE:**
Flow cytometry study on myeloma

PRIMARY INVESTIGATORS:
Joo Song, MD & Denis Dwyre, MD

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RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:
Collecting and analyzing the clinical data and preparing publication.

- 11) **PROJECT TITLE:**
Essential Thrombocytosis with ringed sideroblasts

PRIMARY INVESTIGATORS:
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RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:
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12) PROJECT TITLE:

Methotrexate induced MDS / AML

PRIMARY INVESTIGATORS:

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13) PROJECT TITLE:

Prevention of hemolytic disease of the newborn by plasmapheresis and intrauterine transfusions

PRIMARY INVESTIGATORS:

Leonor Fernando, MD; Denis Dwyre, MD; Hanne Jensen, MD

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

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14) PROJECT TITLE:

Prolonged necessity of plasmapheresis for resistant initial presentation of TTP

PRIMARY INVESTIGATORS:

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RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

Collecting and analyzing the clinical data and preparing publication.

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15) PROJECT TITLE:

Massive requirement of blood products to support an aplastic anemia patient

PRIMARY INVESTIGATORS:

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RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

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16) PROJECT TITLE:

Cryopreservation of leukopheresis products for aliquoting and storing as part of the bio-repository in order to make it available for research.

PRIMARY INVESTIGATORS:

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RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

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17) PROJECT TITLE:

Anaphylactic reaction to platelet transfusion on a patient with peanut allergy

PRIMARY INVESTIGATORS:

Leonor Fernando, MD; Jeremy Parsons, MD; Todd Nishimoto, MD

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:

Collecting and analyzing the clinical data and preparing publication.

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18) **PROJECT TITLE:**
Diagnosis of CLL on a pap smear.

PRIMARY INVESTIGATORS:
Denis Dwyre, MD; Alaa Afify, MD

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Collecting and analyzing the clinical data and preparing publication.

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- 19) **PROJECT TITLE:**
Treatment of Hyperlipidemia with ocular complications by plasmapheresis.

PRIMARY INVESTIGATORS:
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RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:
Collecting and analyzing the clinical data and preparing publication.

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- 20) **PROJECT TITLE:** Cancer Cell Biomarkers: Studies on Anomalies of Intracellular Signaling Proteins.

PRIMARY INVESTIGATOR: Imran H. Khan, Ph.D./Assistant Professor, Dept. of Pathology and Laboratory Medicine.

RESIDENT/MEDICAL STUDENT OPPORTUNITY FOR PARTICIPATION:
Performing experiments on cancer cells using immunohistochemistry to detect distribution and activation of intracellular signaling proteins.

DESCRIPTION:
With the advent of targeted therapeutics directed against cell signaling proteins, it has become important to understand the molecular mechanisms of their interactions with these key targets and the resulting effects on cell regulation and growth. Equally important is an understanding of off-target effects that may cause side effects. In cancer treatment, increasing numbers of inhibitor and/or antibody based therapeutics, targeting cell signaling proteins ranging from surface receptors (e.g., EGFR, Her3 etc.) to intracellular signaling proteins (e.g., PI3K, Akt etc.), are being introduced. We are developing panels of biomarker assays to study molecular mechanisms of activation of key signaling

molecules and their influence on the activities of other signaling proteins. Our aim is to use such biomarker panels to investigate molecular mechanisms of action of targeted therapeutics and develop tests for diagnosis, prognosis, patient stratification and monitoring efficacy of therapy. We have previously developed novel approaches to study signaling proteins and their pathways in cell lysates using relatively high-throughput multiplex microbead immunoassays (Khan et al., 2006; Khan et al., 2010; Campbell et al., 2010). In liquid tumors, where relatively pure populations of malignant cells can be obtained, such methods readily yield desirable results. However, in solid tumors, due to presence of other cells (e.g., stromal cells) in the vicinity of cancer cells, it is additionally important to develop assays to study cell signaling pathways directly in the malignant cells. In the current study we have used morphological methods employing fluorescent and electron microscopic analyses in combination with antibodies to label specific signaling proteins to investigate their resting and activated states. Protein specific anti-phospho antibodies and protein specific total antibodies were used to study active state and total amounts of each protein, respectively. We have optimized methods to label different signaling proteins, their phosphorylated forms (active) and downstream phosphorylation substrates in the relevant signaling pathways.

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