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Dear Friends,

As we embark upon another academic year in ECP, we look forward to the diversity of possibilities that come with a new beginning and to the task of building upon the carefully-laid foundations of previous years.

The continued dedication of the people who make up ECP has been vital to our success. ECP faculty consistently produce work of the highest caliber, receiving national and international recognition for their contributions, service, and expertise. With the help of dedicated staff and our driven students, we anticipate continued growth and opportunity, fueled in part by the addition of new faculty, graduate students, and staff.

The new Dean of the College of Pharmacy, Lynda Welage, Pharm.D., has joined our ECP faculty, as have Dr. Elizabeth Hirsch, Pharm.D., and Dr. R. Stephanie Huang, Ph.D. Graduate students Jay Wen and Shen Cheng have joined our Ph.D. program, and new staff member Becky Palapala will fill the role of Finance and Communications Specialist.

On behalf of the department, I am proud to extend the warmest possible welcome to our new students and coworkers and offer a sincere thanks to our dedicated colleagues, partners, and friends.

Sincerely,

Robert Straka, Pharm.D.
Department Head
Research Focus:

Using Community-Based Participatory Research to Address Health Disparities in Minnesota Hmong

Recent national and international conversations about access and equity have not been limited to politics and economics. In health sciences and research, precision medicine has received considerable attention as a means to address health disparities among underserved populations.

The Department of Experimental and Clinical Pharmacology (ECP) continues to leverage recent advances in technology that have made the exploration of genetic influence on an individual’s response to drugs—pharmacogenetics—both feasible and impactful. Consistent with ECP’s mission to “discover, disseminate, and apply new knowledge related to the safe, effective and economical medication use in patients,” ECP Department head, Robert Straka, emphasizes that “we can realize the full impact of this technology and discovery only if genetic results are explored, acceptable, and understandable to all members of society.” Currently, there are significant gaps in knowledge of potentially impactful information for select populations who traditionally do not engage in research.

Efforts aimed at involving special populations in pharmacogenomic research must navigate several unique challenges. Differences in language and education, perceptions of western medicine, and religious and other cultural differences can lead to a reluctance of communities to engage with researchers.

ECP’s well-trained faculty are engaged in translational research across an array of therapeutic areas from discovery to implementation. ECP’s strategic growth in this area uniquely positions the department to employ novel approaches and establish new collaborations. With these assets, ECP faculty and graduate students partnered with community researchers and members of the Hmong community in Minnesota using Community-Based Participatory Research (CBPR) principles to engage in pharmacogenetic explorations to address a problem of interest to the Hmong.

Who are the Hmong?

The Hmong are a unique Southeast Asian population with ancestral roots in Southeast China, Laos, and Thailand. Resettled to the United States in the 20 years following the end of the Vietnam War (1955-1975), the Hmong currently number over 260,000. Of those, over 64,000 currently reside in Minnesota, which is second only to California in total Hmong population. As with other unique populations, physiological, biological, dietary, religious and environmental factors may influence how healthcare professionals approach providing care to the Hmong. Generational differences add another layer of complexity—and opportunity—when considering how genetics may factor into optimal drug selection and use in this population.

The process of addressing these challenges began over 15 years ago when Dr. Straka, along with his community partner, Dr. Kathie Culhane-Pera, joined forces with other community members to develop and implement a Hmong Genomics Board. The board consisted of Hmong and non-Hmong professionals, lay people, and community leaders of diverse age and education level.
Guided by the board and using a culturally and linguistically appropriate informed consent process, Dr. Straka’s research team conducted a pilot study to collect genomic DNA and determine allele frequencies of a limited number of key genetic variants within pharmacogenes. Confident from the success and informed by the results of this early study, researchers were able to return to the Hmong community to ask what health concerns their community would like to address. Their answer: “Gout.”

Based on this feedback, the past 15 years of work has specifically addressed the Hmong’s recognition of their apparent and well documented higher prevalence and severity of gout relative to non-Hmong in Minnesota. Hmong face a two-fold increased risk of gout and a five-fold increased risk of gout-associated co-morbidities, as well as earlier presentation and severity, compared to non-Hmong.

Since the Genomics Board’s creation, Hmong-centric pharmacogenomics projects have been funded through several mechanisms, including Health Disparities Research grants, Office of Community Engagement (UMN CTSI) assistance, PCORI Tiers 1, 2 and 3 awards, and a current UMN Grand Challenge pilot grant.

The early analysis of genomic DNA from over 240 Hmong participants allowed researchers to focus on the prevalence of alleles associated with hyperuricemia—the precursor of gout—and identify the Hmong as having distinctly elevated levels of “risk alleles” for select drug transporters responsible for uric acid disposition. Armed with this knowledge, researchers were able to explore the impact of genetic variants for these transporters on the disposition and pharmacodynamic response to the commonly used drug—allopurinol—in Hmong individuals.

A Successful Model

Research has continued to expand upon early signals of the impact of select genetic variants on the pharmacokinetics and pharmacodynamics of oxipurinol (allopurinol’s metabolite). Specifically, early findings from our Genetics Of hyperUricemia and gout Therapy in Hmong (GOUT-H) study seem to suggest that although effective in most patients, some individuals with specific genetic profiles exhibit a diminished response to allopurinol.

The GOUT-H study was the main focus of Dr. Youssef Roman’s Ph.D. Thesis. Dr. Roman’s research experience exemplifies the positive results of equivalent partnerships between community and University-based researchers to recognize a common goal and create a CBPR program that answers pressing health questions. Researchers’ overall goal, and that of the Hmong Community, is to work to eliminate disparities in knowledge of the impact of pharmacogenomic advances for unique populations and, in this case, minimize suffering from gout.

This research journey represents a path that traverses the intersection of translational research and pharmacogenomics and demonstrates a method of partnering with community researchers and leaders within a unique population to advance knowledge that can one day help inform intelligent drug selection and use to achieve optimal outcomes for patients.

While researchers on the Hmong CBPR project knew that they were making important and pioneering inroads with the Hmong people of the Twin Cities, they were unprepared—very literally—for the depth of those inroads. When ECP Ph.D. candidate and researcher on the GOUT-H study, Youssef Roman, gave his dissertation defense on June 23, 2017, the attendance from local Hmong community members and academics was so high that the event had to be moved at the last minute to a twice-larger room than initially planned. The community members who attended did so not just out of curiosity about the results, but out of individual and personal support for both Dr. Roman and the UMN-Community researchers who continue to work with the Hmong community.

Dr. Roman, who has since graduated, has accepted an Assistant Professor position at the University of Hawaii. There, he will continue his innovative work using the CBPR, pharmacogenomic, and other methods he helped to pioneer at the U of M.
Education and Outreach


Mark Kirstein led the College of Pharmacy peloton in the University of Minnesota’s inaugural Chainbreaker bicycle ride for cancer research. ECP members Dr. Kirstein and Dr. Straka, along with other College of Pharmacy members, rode 100 miles, and the peloton raised over $15,000 for the Masonic Cancer Center at the U of M.

Melanie Nicol piloted her first offering of an International APPE Research Elective in Kampala, Uganda with PD4 student Amy Tran. They worked with Winnie Nambatya, pharmacist, of Makerere University to develop a research protocol to evaluate the dosing practices of phenytoin on the Neurosurgery Ward at Mulago Hospital.

Swayam Prabha participated in 5K run at the 18th annual HOM Teal Strides for Ovarian Cancer walk/run held on Saturday, September 16th in Edina’s Rosland Park.

Faculty Highlights

Grants

Lisa Coles and Jim Cloyd are Co-PIs on an NIH-NINDS R01 study: “Established Status Epilepticus Treatment Trial: Pharmacokinetic-Pharmacodynamic”

Michael Kotlyar received a 2-year, $230,375 grant from the National Institute on Drug Abuse for a study titled “Effect of Banning Menthol Flavorant on Cigarette and e-Cigarette Use.”

Ling Li (PI) received a two-year, $419,378 grant award from the National Institute on Aging (NIA), the National Institutes of Health (NIH) for the project entitled “Testing a Unique HDL Mimetic Peptide to Reverse ApoEα Lipidation Deficiency and Alzheimer’s Neuropathology.” Dr. Li also received a five-year, $1,875,864 grant award from the National Institute on Aging (NIA), the National Institutes of Health (NIH) for the project entitled “Dysregulation of Protein Prenylation in the Pathogenesis of Alzheimer’s Disease.” Mark Distefano in the Department of Chemistry is a Co-PI for the project.

Susan Marino and Angela Birnbaum are Co-PIs on a new investigator-initiated, 2-year grant for $1,178,022 from Supernus Pharma entitled, “Cognitive Effects of Immediate Release Topiramate (Topamax) vs Extended Release Topiramate (Trokendi XR) in Patients with Migraine.”

Susan Marino is also the recipient of a 2-year, $380,000 investigator-initiated grant from Veloxis Pharma for Comparison of the cognitive and motor effects of treatment between an immediate- and extended-release tacrolimus (Envarsus® XR) based immunosuppression regimen in kidney transplant recipients. Co-PI: Arthur Matas, MD.

Beshay Zordoky has been awarded a 1-year, $50,000 grant from the Rally Foundation for Childhood Cancer Research for his study “Role of Galectin-3 Signaling in Juvenile Doxorubicin-induced Cardiotoxicity.”

Swayam Prabha received a 1-year grant from the Minnesota Ovarian Cancer Alliance to support her work on Glyco-engineered Mesenchymal Stem Cells for Image-Guided Therapy of Ovarian Cancer. Dr. Prabha also received a $50,000 gift from alumnus Terry Noble and his wife, Bette, for the same project. The Nobles were inspired by Bette’s own battle with ovarian cancer to help save lives and reduce suffering for those diagnosed with the disease.

Grants
Recognition

Angela Birnbaum was inducted into office as the Chair of Graduate Education SIG of the American Association of Colleges of Pharmacy in July. Dr. Birnbaum was also named a Fellow of the American Epilepsy Society in December, 2016.

Angela Birnbaum, Ilo Leppik, and Jim Cloyd were recognized as co-inventors on U.S. Patent number 9,629,797 for Novel Parenteral Carbamazepine Formulation.

Scott Chapman was named Outstanding Reviewer by Pharmacotherapy Publications Inc., Board of Directors.

Jim Cloyd received the J. Kiffin Penny Award for Excellence in Epilepsy Care from the American Epilepsy Society (AES). Originally established in 1997 with a gift from Abbott Laboratories, the Penny Award is now supported through the J. Kiffin Penny Fund of AES. The award honors Dr. Penny’s lifelong focus on and genuine concern for the patient with epilepsy. It recognizes individuals (members or non-members) whose work has had a major impact on patient care and improved the quality of life for persons with epilepsy.

Betsy Hirsch was appointed to a one-year term as an Advisor of the Subcommittee on Antimicrobial Susceptibility Testing for the Clinical and Laboratory Standards Institute (CLSI), the organization responsible for developing and setting clinical breakpoints for antimicrobial agents.

Pamala Jacobson received honorable mention as a 2017 Clinical and Translational Science Institute (CTSI) Mentor of the Year. Mentor awards recognize outstanding research mentors, using nominations provided by the mentees themselves.

L’Aurelle Johnson was named Associate Director of Graduate Studies of ECP and will serve as Interim Director of Graduate Studies while Angela Birnbaum is on semester leave Fall 2017.

Reena Kartha was selected as the 2017 Clinical and Translational Science Institute (CTSI) Junior Mentor of the Year. Mentor awards recognize outstanding research mentors, using nominations provided by the mentees themselves.

Melanie Nicol became a member of the steering committee for a new INF (infectious disease) community of the American Society of Clinical Pharmacology and Therapeutics. The Infectious Diseases Community connects themselves.

Maha Elsayed presented “Monocarboxylate Transporter 1 (MCT1) in Brain: Possible Role in Drug Transport” (oral presentation) at the Cold Spring Harbor Laboratories Meetings. Dec 7-10, 2016 in Cold Spring Harbor, NY.

Vaishnavi Soundararajan completed an internship at OneOme in Minneapolis, MN.

A New Home for Pharmacogenomics

ECP Pharmacogenomics faculty Drs. Jeffrey Bishop, R. Stephanie Huang, and William Oetting moved to a new, expanded, and renovated laboratory suite in August.

The Department of Experimental and Clinical Pharmacology Pharmacogenomics Laboratory is located at B-150 Phillips-Wangensteen and can accommodate up to 4 PIs. It contains office space for twelve additional researchers (students/fellows/staff). It is comprised of over 3,000 square feet of main laboratory space, plus auxiliary lab rooms and conference space.

The pharmacogenomics laboratory is designed for targeted genotyping and functional characterization studies. This new, state of art laboratory is functionally divided into several work areas including those for molecular genetics, biochemical analysis, cell culture and analytical analysis. There is a dedicated biological safety cabinet for human biospecimen processing, particularly the collection of serum, plasma, and peripheral blood mononuclear cells (PBMCs) from whole blood. The laboratory specializes in the isolation of nucleic acids (DNA, RNA, protein) from various biospecimen types such as serum, plasma, whole blood, isolated PBMCs, fresh/frozen/paraffin embedded (FFPE) tissue, saliva, and buccal swabs using validated and standardized protocols, and is capable of high capacity biospecimen storage. The laboratory also houses a 365 square-foot in-vitro cell culture room containing four biological safety cabinets, two stacked incubators, and one HERAcell 150i CO2 incubator for functional characterization studies utilizing multiple cell modeling techniques.

Media

Angela Birnbaum’s article “Antiseizure, Antidepressant, and Antipsychotic Medication Prescribing in Elderly Nursing Home Residents” was highlighted with commentary by Clinical Edge Neurology as one of five must-read neurology articles in March, 2017.

Dr. Birnbaum’s articles, “Prevalence of Epilepsy and Seizures as a Co-morbidity of Neurological Disorders in Nursing Home Residents” were selected for coverage by Epilepsy Advisor and Redefining Seizure Care

Graduate Student Highlights

Ali Alhadab completed an internship at AbbVie in Waukegan, IL.

Sam Callisto completed an internship at AbbVie in Waukegan, IL this summer, where he worked on modeling and simulation of clinical trials. He also passed his preliminary examinations in spring 2017 to achieve doctoral candidacy.

Maha Elsayed presented “Monocarboxylate Transporter 1 (MCT1) in Brain: Possible Role in Drug Transport-Blood Brain Barrier” (poster) and “Monocarboxylate Transporter 1 (MCT1) - Role in Nutrient Drug Transport” (oral presentation) at the Cold Spring Harbor Laboratories Meetings. Dec 7-10, 2016 in Cold Spring Harbor, NY.

Vaishnavi Soundararajan completed an internship at OneOme in Minneapolis, MN.
ECP faculty Jeffrey Bishop and Richard Brundage mentored three of the University’s eleven Melendy Scholars over the summer, and Pamela Jacobson mentored a student through CTSI’s Advanced Pathways to Research program. CTSI/Melendy Scholarships provide research experience to professional and clinical-track students.

Chris Olson (Bishop): “Pharmacogenetics of dopamine genes and antipsychotic dosing in psychotic disorders.”

Summary: This project examined relationships between antipsychotic dosing and 5 functional dopamine receptor and transporter polymorphisms in patients who have reached clinical stability. Researchers assessed patients who were previously enrolled in the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) who had a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis. Patients who had detailed medication information and were clinically stable at recruitment were included our study.

Sofia Shrestha (Bishop): “Therapeutic potential of microRNAs as biomarkers for treatment response in psychiatric disorders.” Sofia’s poster for her project won a 2017 CTSI travel award, which will cover a portion of her expenses to travel to a national or international conference to present her work.

Summary: MicroRNAs regulate gene expression, participate in normal neuro developmental and physiological processes, and have recently been implicated in the pathogenesis of several psychiatric disorders. This project aims to examine the relationship between microRNA genetic variants and antipsychotic treatment response outcomes such as symptom severity and cognition in patients with first-episode psychosis. The goal of the project is to enhance our understanding of microRNAs as therapeutic biomarkers in psychiatric disorders and also help us learn more about the pathophysiology of psychotic illnesses.

Aileen Scheiberner (Jacobson): “Fludarabine and Cyclophosphamide Markers Predict Hematopoietic Cell Transplant Outcomes.”

Summary: This project looks at two chemotherapeutic drugs, Fludarabine and cyclophosphamide, that are used to prepare the patient’s body for bone marrow transplants. These drugs kill the existing bone marrow cells and suppress the body’s immune system. The pharmacokinetics of these drugs varies widely from patient to patient. However, with the current treatment protocol, all patients receive the same dose of these drugs regardless of how their body is processing it. Our research seeks to relate pharmacokinetics of these chemotherapeutics to clinical outcomes such as survival. This will help personalize drug doses for each patient to help maximize the probability of survival and minimize adverse events.

Thang Tran (Brundage): “Model-based Approach to Characterize the Underlying 24-hour Cortisol Circadian Rhythm in Children with Congenital Adrenal Hyperplasia.”

Summary: The goal of this project is to develop a pharmacometric model that includes both a cortisol PK model for exogenous HC dosing as well as an oscillating endogenous cortisol production rate. Understanding the dynamics of this step is necessary before constructing an integrated PKPD model that can be used to predict adrenal androgen concentrations in response to changes in HC dosing. The project sets an important step for the development of alternative dosing strategies for patients with the disease and might result in a new standard of care for those patients.