Second Annual Clinical Research Coordinator Research Excellence Award

The second annual Research Excellence Award honors UTMC clinical research coordinators who exemplify excellence in knowledge, skills, and acumen of the research profession. The Jacobson Center for Clinical and Translational Research (JCCTR) established the award that was presented to Stephanie Wilson for her outstanding performance last month.

Stephanie has been working as a clinical research coordinator in the Department of Neurology, Gardner-McMaster Parkinson Center for the last 13 years. She began her career at the former Medical College of Ohio in June 1991 before Dr. Elmer hired her as his research coordinator in May 2002. She has been involved in over 15 Parkinson's Disease and Huntington's Disease studies and has received numerous accolades throughout her career that include, having a 100% retention rate on all of her studies and being the highest enrolling U.S. site on two recent trials.

"I feel extremely honored to be chosen for the second annual Research Excellence Award. I am surrounded by an amazing group of research professionals who are all so deserving of this recognition as well, so I am humbled to be acknowledged in this way. Thank you to all of my co-workers in the GMPC, JCCTR, and coordinators who make this a great place to work.” —Stephanie Wilson

We congratulate Stephanie who continues to inspire us with her commitment toward research excellence!
Two-pronged host defense by IRF3. Virus infection is recognized by cellular sensors, which trigger two distinct antiviral pathways. My research is focused on the molecular details of these two pathways and how they protect from viral diseases in vivo. Viruses have also evolved with counteracting mechanisms against host responses.

For the past several years, my focus has been the IRF3 transcription factor, which upon virus infection is activated to transcriptionally induce interferons and many antiviral genes, also known as interferon stimulated genes, whose protein products inhibit various stages of the viral life cycle. In addition to the well-established transcriptional function of IRF3, my research has uncovered a novel antiviral pathway. In this pathway, IRF3 directly activates an apoptotic response in virus-infected cells by collaborating with the pro-apoptotic protein, BAX (Chattopadhyay et al, EMBO J 2010, Chattopadhyay and Sen, Cell Cycle 2010). We have established that this pathway is operational in both RNA and DNA virus-infected cells (Chattopadhyay et al, J. Virol 2011, Chattopadhyay et al., J. Virol 2013). The IRF3/BAX-dependent apoptotic pathway efficiently kills the virus-infected cells. A major question that we addressed in a recent study (Chattopadhyay et al, Immunity, in press) was the biological relevance of the newly discovered pathway in the whole organism. Using a newly generated knock-in mouse, we showed that in the absence of transcriptional activity, the apoptotic branch of IRF3 can protect the mice against respiratory viral pathogenesis. The IRF3/BAX-dependent apoptotic pathway is operational in other viral and non-viral diseases. It protects the primary human monocytes from human T-cell leukemia virus replication. Surprisingly, this pathway has been shown to promote alcoholic liver diseases. This clearly indicates a broader biological function of the IRF3-dependent apoptotic pathway, not only in viral infection, but also in other diseases.

Viruses have co-evolved with the host and, therefore, have come up with mechanisms to dampen the host responses to maintain productive replication. Such mechanisms are mediated by viral proteins, which target various components of the host defense machinery. Therefore, a tug-of-war is always in progress between the host and the virus; the timing and the strength of this battle determines the outcome of the overall response. Investigating these counteracting mechanisms is critical for the development of new therapeutic applications.

It has become increasingly clear that no one strategy can work against all viruses. Therefore, it is desirable to identify new host factors that inhibit specific viruses. Using respiratory virus infection as a model, I began a
high throughput approach to identify new viral restriction mechanisms. We will use both human and mouse respiratory viruses, which cause deadly diseases, and continue to investigate the biochemical mechanisms of antiviral protection. Using genetically modified cells and mice, we will address how a specific gene mutation can affect the overall antiviral response. I am looking forward to productive collaborations within the university to facilitate my research and also to expand my horizon.

New antigen in aortitis

Ritu Chakravarti, PhD
Assistant Professor
Department of Surgery

Aortitis, inflammation of the blood vessel wall, is more common than imagined. Individuals are often asymptomatic, adding to the difficulties in diagnosis. Aortitis can be classified as either infectious (IA), or non-infectious (NIA). NIA is more prevalent in recent times. About 20% of aortitis patients develop thoracic aortic aneurysms that can rupture or dissect, and therefore presents a life-threatening condition. Histologically, the vessel wall shows infiltration of immune cells, thickening of advential and medial layers with, quite often, necrotic regions. No specific serological test exists for the diagnosis of aortitis. Though both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are increased in the patients with aortitis, they often don’t correlate with the disease. IA can be treated using antibiotics; however, in the case of NIA, immunosuppression is the only strategy to control its symptoms. Absence of targeted therapy and serological markers to monitor the disease activity, significantly limit disease management strategies.

My group has been investigating the pathogenesis of NIA that leads to thoracic aortic aneurysms. In collaboration with surgeons, rheumatologists and clinical nurses, I started to collect discarded aortic tissues from aortic reconstruction surgeries to investigate the trigger of inflammation in NIA, primarily giant cell arteritis, Takayasu arteritis and idiopathic focal arteritis. Using sera as a natural source of antibodies, we started our exploration to find an antigen in the aortic tissues. Our results showed that one family of proteins, 14-3-3, turns antigenic in the case of aortitis. Sera from aortitis patients carry antibodies to 14-3-3 family proteins. Interestingly, these antigenic proteins also reside in the medial region of aortic wall where inflammation and damage is mostly observed (Chakravarti et al., 2015). These results opened a new path to continue our investigations to understand the reason behind these native proteins becoming antigenic, and importantly, to develop the first serological diagnostic test. This will not only help in the detection of aortitis but will also be of immense utility in measuring disease activity in the asymptomatic population. A model depicting our work plan is shown on the right.

As with other inflammatory diseases, the vessel wall of NIA patients face what is termed a cytokine storm, primarily dominated by IFN-γ & IL-17. Suppression of symptoms with glucocorticoid treatments has been shown to reduce IL-17 levels with no impact on the IFN-γ. We wonder what relationship these cytokines have on the antigenicity evolution of native proteins, and if there is any cross talk that supports sustained inflammation even in the presence of immunosuppressive treatment. Blocking the trigger may resolve the inflammation and therefore offers a viable therapeutic treatment. I am looking forward to collaborations with fellow scientists and clinicians with similar research interests, to make significant advancement in the understanding of a life threatening disease.

New Publication

A computational milestone for revealing blood relations from genomic data in humans
A recent publication from the UT bioinformatics lab describes a breakthrough in finding cryptic distant blood relationships between peoples. The manuscript “Atlas of cryptic genetic relatedness among 1000 human genomes” published in Genome Biology and Evolution is available from the Fedorov lab publications page. With this new approach, it is possible to find 20th order relatives and even beyond. You can now find out how much genetic similarity you share with people from other continents. All you need is your DNA sequence and the DNA sequence of the person/s you want to find similarity with. The novel method processes genomic sequence data with computer programs exclusively developed by Dr. Fedorov’s team and doctoral students in his lab.

This method promises to be a fascinating tool for revealing cryptic relatedness which is critical for understanding fundamental questions regarding human evolution and demographic history, as well as for practical purposes such as individualized medicine, forensics and identifying disease genes in clinical association studies. In the modern era of low cost genome sequencing, the UT bioinformatics lab predicts increasing importance of their new method for its inherent simplicity and considerably high computational speed. With an expected massive flood of genome sequencing in the next few years, we foresee hundreds of millions of novel genomic biomarkers becoming available which will require precise definition and cataloging for broad public usage. Keeping this in mind, our lab has set a long term goal of creating a public database of human biomarkers.

Ancestry plays a critical role in our genetic makeup and affects distinct traits in different ethnic groups. Two genomic segments are called Identical By Descent (IBD) if they share the same alleles inherited from a common ancestor. All individuals in a finite population are related if traced back long enough and will, therefore, share IBD segments. During gamete formation, IBD segments are broken up by recombination. The genome of every individual is a mosaic of IBD segments inherited from previous generations. Since real human populations have limited sizes and have frequently experienced admixtures, even apparently unrelated individuals from the same geographical region frequently share one or several IBD genomic segments transmitted from their common distant ancestors.

The simple computational method which we have developed calculates total number of differences in genetic variants between 1,191,372 human pairs and analyzes the distribution patterns of very rare genetic variants (vrGVs), which have minor allele frequencies of less than 0.2%. These patterns are then used for revealing cryptic blood relationships. We have shown that shared vrGVs between two individuals are clustered in a single or a few small regions in the genome. When two individuals share five adjacent vrGVs located in the same genetic region, the probability of this event occurring by random coincidence is equal to 0.0025, which is less than one in \(10^{13}\). Therefore, these clusters of shared vrGVs cannot result from coincidence. They are signatures of IBD genomic segments. Using this simple rationale, the paper describes exhaustive comparison of 100 people randomly selected from England with 100 Chinese from Beijing. The comparison allows us to determine a hundred English-Chinese pairs that share common ancestors about 2-3 thousand years ago. Similar comparisons have been carried out for 14 different populations from across the globe and possible related pairs have been identified. Some of the other distant common ancestors identified are the ancestors to European–African pairs who lived 118 generations ago or \(\sim 2,950\) years ago.

The large public database we plan to develop, containing submissions of human vrGVs will be greatly facilitated by the simplicity and computational speed of our new approach. It would find usage for large cohort and GWAS studies where thousands of sequenced genomes will be available.

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**New Patent**

**Sweet-P: Molecule for targeting human cancer**

Terry Hinds, Ph.D.
Assistant Professor
The Hinds Lab has discovered that the glucocorticoid receptor β (GRβ) causes migration (movement) of cancer cells, and have designed a new type of drug that we have named Sweet-P to target the gene. We designed the Sweet-P molecule as a peptide nucleic acid conjugated to the Trans-Activator of Transcription (TAT) protein from HIV (for cellular delivery) to specifically target the human GRβ gene. Sweet-P is the only compound that has been shown to regulate GRβ, and we have obtained a provisional patent from the Patent Office (see below). We have recently published the work in the high impact journal, Oncotarget. At this point, we have shown that the Sweet-P molecule suppresses GRβ in prostate cancer, lung cancer, and bladder cancer, as well as inhibits the ability of cancer cells to move. We will be testing the effect of the Sweet-P molecule on other types of cancer.

Applications: The Sweet-P molecule may be used for cancer treatment in bladder, prostate, lung, leukemia, and glioblastoma, in methods for hindering migration of such cancers and in inflammatory diseases such as lupus and asthma. Sweet-P is ready for commercialization and will not require an expensive and lengthy product development period.

D2016-49 – Provisional Patent Application Title: Targeting of Human Glucocorticoid Receptor Beta in Cancer
Inventors: Terry D. Hinds, Jr. (90%), Lucien McBeth (10%)
MST File No.: 1-57720

Clinical Research Snippets

Use of statins to reduce cardiovascular deaths in hypertensive patients

By: Imad M. Hariri, MD

Cardiovascular diseases remain the major cause of death across the world. The use of statins to reduce the risk of death from cardiovascular causes is well established in high risk patients with or without overt atherosclerotic cardiovascular disease. This month, we review results of the HOPE-3 trial which establishes the benefit of statins (cholesterol reducing medications) in patients with intermediate-risk and without apparent cardiovascular disease.

Heart Outcomes Prevention Evaluation (HOPE)-3 is a randomized double blinded placebo-controlled multicenter international trial that included an ethnically and racially diverse study population (29.1% Chinese, 27.4% Hispanic, 20.2% White, 1.8% Black) to distinguish itself from other studies that have shown benefits of the use of statins in white patients without cardiovascular disease, to maximize generalizability. Eligibility criteria included men 55 years of age or older and women 65 years of age or older who had at least one cardiovascular risk factor, did not have cardiovascular disease and were at intermediate risk for cardiovascular disease (annual risk of major cardiovascular events approximately 1%).

In this trial with a 2x2 factorial design, a total of 12,705 participants at 228 centers in 21 countries were randomized to receive daily 10 mg of rosuvastatin (n=6,361) or placebo plus daily combination of candesartan/ hydrochlorothiazide (16mg/12.5mg) (n=6,356) or placebo. The researchers followed the patients for a mean of 5.5 years for composite death as a first co-primary outcome and resuscitated cardiac arrest, heart failure and revascularization as a second co-primary outcome.
In one arm of the study, the first co-primary outcome was observed in significantly fewer participants taking rosuvastatin vs. those taking placebo (p-value = 0.0002), as was the second co-primary outcome (p-value <0.0001) with a 24% lower risk for cardiovascular events. In another arm, the first co-primary outcome was not significantly different in participants randomized to receive candesartan/hydrochlorothiazide combination vs. placebo. In a third arm of the study, participants were randomized to receive rosuvastatin plus candesartan/hydrochlorothiazide vs. rosuvastatin plus placebo vs. candesartan/hydrochlorothiazide plus placebo vs. two placebos. In this arm, the first co-primary outcome was observed in significantly fewer participants receiving both drugs vs. placebo (p-value <0.005).

The results of this trial show that patients with an intermediate risk for developing cardiovascular disease would benefit from rosuvastatin (10mg) compared to placebo, and that there would be the need to treat 91 patients to prevent 1 death and 73 patients to prevent 1 morbidity event. The use of antihypertensive medications in this patient population did not seem to have a statistically significant effect despite 37 percent of them having Hypertension as a risk factor.

These results were not met without criticism. The study arm did not include lifestyle modification. Application of the results from this study in the United States is compromised by the fact that less than 2% of the studied population was black. Additionally, advocating for the use of medications rather than recommending meaningful lifestyle modifications for patients at intermediate risk for cardiovascular disease may additionally ignite an already rampant culture of physicians pushing pills to their patients.

### New Clinical Trials

**An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson’s Disease Complicated by Motor Fluctuations.**
Dr. Elmer - Medicine

**A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of AB103 as Compared to Placebo in Patients with Necrotizing Soft Tissue Infections (NSTI).**
Dr. Nazzal - Surgery

**A Randomized, Double-Blind, Multicenter, Superiority, Placebo-Controlled Phase III Study of Pexiganan Cream 0.8% Applied Twice Daily for 14 Days in the Treatment of Adults with mild Infections of Diabetic Foot Ulcers.**
Dr. Nazzal - Surgery

### IRB Corner

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