Message from the Dean

The mission of The University of Toledo is to improve the human condition; to advance knowledge through excellence in learning, discovery and engagement; and to serve as a diverse, student-centered public metropolitan research university. Likewise, the mission of The University of Toledo College of Medicine is to improve the human condition. We do this by providing a world-class education for the next generation of physicians and scientists, by creating new knowledge that is translated into cutting edge clinical practice, and by providing the highest level of professionalism and compassion as we deliver university quality health care. The University Of Toledo College Of Medicine is a transformative force in medical education, biomedical research, and health care delivery in the region, nation, and world. Research is critical to our identity and our purpose at UT and especially in the College of Medicine and Life Sciences where translational research helps solve the problems that we observe in the care of our patients. These concerns are subsequently studied by researchers to discover how to fix or improve these problems which then leads to refined solutions which go back to benefit our patients. The ability to bring medical discoveries from the laboratory to patients in the community gives our clinicians and students the tools that they need to improve the human condition. Our discoveries will be so important in creating the future of health care. The demand for new therapies has markedly increased as the overall population expands and ages. We have made great improvements in medical care through research, but are left with many continuing problems and mysteries without solutions. We also know that a research experience is becoming a necessity for more and more of our students. A student’s involvement in research may not only aid them in obtaining a residency position but also provide them with a valuable experience to critically evaluate the medical literature during their future careers.

My vision for clinical and translational research at our College of Medicine and Life Sciences is aligned with the mission of our institution. In spite of the uncertainty of future funding by the NIH and the sequestration cuts which have had a significant negative impact on research funding, our mission remains clear. Clinical and translational research will continue to be an integral part of our institution, our community and our future. We will need to adjust to changes in traditional funding streams for research and be able to identify new partnerships to carry our mission forward. Clinical and translational research are uniquely adaptable to alternative funding paradigms. Even though I have been in my role as Interim Dean for a short time, I have been very impressed by the passion and energy of our research scientists, the clinical faculty and the leaders of the academic departments. I believe that our future is in the right hands as the winds of change continue to course through the landscape of university research.

Ronald McGinnis, M.D.
Interim Dean, College of Medicine and Life Sciences
New Investigator

Jyl S. Matson, Ph.D.
Assistant Professor
Department of Medical Microbiology and Immunology

I have been fascinated by organisms that cause human disease for as long as I can remember. Therefore, when I decided to go to graduate school at the University of North Dakota, it was an easy decision for me to join the new lab that studied *Yersinia pestis*, the bacteria that cause Bubonic plague. While working on the plague was a great experience (and a great topic of conversation), I realized that I wanted my future work to be on a disease that currently has a large human impact.

In 2003, I moved to the University of Michigan and began my postdoctoral studies on *Vibrio cholerae*, the bacteria that cause epidemic cholera. After my postdoctoral work, I transitioned into a research faculty position at UM, continuing to work in the same area. Last June, I joined the faculty at the University of Toledo in the Department of Medical Microbiology and Immunology.

While not a public health concern in the US, cholera is still widespread in the developing world, estimated to afflict approximately 5 million people each year. Cholera is a diarrheal disease acquired by ingestions of food or water contaminated with *V. cholerae*. Cholera can kill within hours without treatment, due to rapid dehydration. Treatment consists of oral rehydration therapy and antibiotics, however, due to the rapid emergence of antibiotic resistance, therapeutic options are becoming limited. One of the major goals of my research at UT is to characterize compounds that may be developed into new cholera therapeutics.

During my postdoctoral studies, I identified a proteolytic pathway responsible for halting production of virulence factors under conditions where they are unneeded [16254052](http://www.ncbi.nlm.nih.gov/pubmed/16254052). We predict that this pathway is activated when *V. cholerae* exits its human host and returns to the aquatic environment. Characterization of this pathway included working on components of the *V. cholerae* extracytoplasmic stress response pathway, which is required for virulence and overall fitness of the bacteria in the presence of extracellular stress. Recently, I developed and implemented a high throughput screen to identify inhibitors of this pathway in conjunction with the UM Center for Chemical Genomics. Ongoing work in my lab is to identify and characterize these small molecule inhibitors with the goal of developing the most promising compounds into therapeutic agents against cholera.

Another aspect of my research is using next generation sequencing (RNAseq) to uncover new knowledge about how bacteria respond transcriptionally to various types of stress. My lab is particularly interested in using this powerful technology to determine the function of previously uncharacterized *V. cholerae* proteins. Previously, I used genetic techniques to characterize genes that are involved in resistance to antimicrobial peptides [20154134](http://www.ncbi.nlm.nih.gov/pubmed/20154134). Advances in sequencing technologies have given us even more sophisticated and powerful ways to analyze these responses. Recently, we have performed RNAseq analysis on *V. cholerae* grown in the presence and absence of sublethal concentrations of antimicrobial peptides to determine the overall transcriptional response of the bacteria to this type of stress. We are currently using the results of this study to piece together uncharacterized pathways that allow the bacteria to sense and respond to stresses that they may encounter in the environment and in the human host.

New Publication

By David C. Allison, M.D., Ph.D.

Individual genes produce different mRNAs which, in turn, produce the protein effector molecules responsible for cell growth and behavior. Cancer cells often have extra gene copies, possibly selected to produce higher levels of the mRNAs favoring cancer cell growth. Gene expression arrays, and other powerful new methods, can simultaneously measure the mRNA levels of all cancerous and normal human genes. Surprisingly, these new methods have had little impact on guiding the treatments of most cancers, although these tests provide a convenient way to measure the mRNA levels for previously discovered breast cancer genes. David A. Weaver, Andrea L. Nestor Kalinoski, Kristen Craig, Matthew Gorris, Tejal Parikh, Helen Mabry, and David C. Allison of the Department of Surgery, Bioinformatics and Proteomics/Genomics Program, and the Advanced
Microscopy & Imaging Center have recently published an article entitled, “Corrections for mRNA Extraction and Sample Normalization Errors Find Increased mRNA Levels May Compensate for Cancer Haplo-Insufficiency” (http://onlinelibrary.wiley.com/doi/10.1002/gcc.22133/full).

Gene copy numbers predict mRNA levels within, but not between, cell types. A. Method for measuring HK gene copy numbers in cancer lines based upon identifying the genetic map positions of the abnormal cancer cell chromosomes. B. Gene mRNA levels correlate with gene copy numbers when measured in the same aneuploid cancer lines. C. Surprisingly, benign and cancer cells measured by standard gene expression arrays have identical mRNA levels, despite the cancer cells having significantly higher gene copy numbers.

This report describes a fundamental error in the current methods of measuring cellular mRNA levels found in a study of the mRNA levels of six cancer lines and four types of benign cells. The genetic map positions of the abnormal cancer chromosomes were found in the six cancer cell lines (Fig. 1A); this allowed determination that the cancer cell gene copy numbers were higher than those of benign normal cells. Also, the mRNA levels of cancer genes with only one (haploid), two (diploid) or three (triploid) copies clearly increased relative to each other when measured in the same tumor cells (Fig. 1B). Thus, the gene expression arrays gave accurate measurements of relative mRNA levels in individual mRNA samples. Surprisingly, the mRNA levels for a set of test genes in six cancer cell lines and the four types of benign cells were similar, despite the cancer cells having higher copy numbers of these genes (Fig. 1C). Thus, the mRNA level increases found with higher gene copy numbers in single cell types (Fig. 1B) were not seen in comparisons of cell types with different gene copy numbers (Fig. 1C). To explain this paradox, the authors compared the mRNA measurements of normal human lymphocytes with 1,040 test gene copies to the SUIT-2 cancer line with 2,045 test gene copies (both shown in Fig. 1C). The cartoon in Figure 2A shows the lymphocytes and SUIT-2 cells actually having differing test gene mRNA levels, but with the standard mRNA preparation methods currently employed for mRNA measurements destroying the mRNA differences.
Evidence for mRNA extraction and sample normalization errors distorting standard mRNA measurements. A. Prediction that separate purifications of mRNAs from a benign cell (cell A, or a lymphocyte) and aneuploid cancer cell (cell B or a SUIT-2 cancer cell) will produce the same amounts of labeled mRNA by gene expression array analysis. B. Gene expression array analysis of a 50:50 mixture of the separately purified SUIT-2 cancer cell and diploid lymphocyte mRNAs finds that both cell types have identical mRNA amounts. C. Prediction that the purification of mRNA extracted from a 50:50 mixture of intact SUIT-2 cancer cells and benign lymphocytes will find increased cancer mRNA levels. D. Gene expression array analysis of mRNA extracted from a 50:50 intact cell mixture of lymphocytes and SUIT-2 cancer cells shows the SUIT-2 cancer cells have ~three times as much mRNA as non-cancerous lymphocytes.

An expression array analysis performed on mixed samples of separately extracted lymphocyte and SUIT-2 pure mRNAs confirmed this prediction that equal mRNA amounts were found in 50:50 mixtures of pure mRNAs separately extracted from normal lymphocytes and SUIT-2 cancer cells (Fig. 2B). Figure 2C predicts that mixing equal numbers of intact SUIT-2 cells and lymphocytes together before mRNA extraction would accurately reflect the true mRNA levels in each cell type: This proved to be the case, as expression array analysis of mRNAs extracted from (50:50) SUIT-2 and lymphocyte mixtures found the SUIT-2 cells have a ~3.16 increase in mRNA levels compared to the lymphocytes (Fig. 2D). Thus, future correction of this sample preparation error in mRNA analyses may provide new insights into the biology and treatment of human cancers.

The Interprofessional Immersive Simulation Center: From Vision to Reality

By Pamela Boyers, M.A., Ph.D.
Executive Director, Interprofessional Immersive Simulation Center

A large percentage of avoidable medical errors are caused by communication gaps and well functioning teams result in better patient care outcomes. Thus, the current trend in healthcare education is towards the development of interprofessional simulation centers. Following
other high-risk industries such as aviation, oil and gas, and nuclear power, many medical and nursing schools, hospitals, health systems, and private clinics have, over the course of the last decade, developed simulation labs. More recently, demonstrating progressive skill development using simulation (for individuals or healthcare teams) is fast being required as an accreditation standard for the education of health professionals.

In 2009, there were five independent simulation centers on the UT Health Science Campus: The College of Nursing Learning Resource Center; the Ruth M. Hillebrand Clinical Skills Center, a College of Medicine Lab, an Orthopedic Simulation Lab, and a Urology Simulation Lab. With the overarching goals of transforming the learning environment for health care professionals and advancing interprofessional collaboration at every level of training, in full accordance with the Deans of the Health Science Campus, it was proposed that UT develop an interprofessional simulation center. In April 2010, a "prototype" center was created in a 12,000 sq. ft. space in the Collier Building. Over the last three years, clinical simulation has been rapidly adopted and, currently, UT students, residents, faculty and staff comprise 90% of the structured simulation activities. The center also holds courses for the Toledo Fire Department and several community health care facilities. The number of learners experiencing "hands-on" education has grown at a rate of 20% each year – recording a total of 14,695 learners, recruitment tours, and visitors in FY13.

Opening in April 2014, the new Interprofessional Immersive Simulation Center (IISC) is a transformational facility (65,000 sq. ft.) that places UT in a national and global leadership position. Through the development of highly technical learning environments that are designed to stimulate innovative ways of learning, teaching, and research, the IISC is creating a new paradigm for the education of healthcare professionals. The center provides experiential learning opportunities in a wide range of simulated healthcare settings, where almost any scenario can be created and rehearsed prior to taking care of real patients. To be successful, this paradigm shift requires significant interprofessional collaboration and practice, as well as a spirit of innovation. It is anticipated that the new state-of-the-art simulation center will create efficiencies in educating the future health care work force, improve patient care outcomes, and positively impact the recruitment and retention of students.

The IISC leadership team is currently working with leaders on the UT main campus to explore the establishment of a 3D and Virtual Immersive Reality (VIR) site in the Carlson Library. This integration of technologies would facilitate cooperation between the two UT campuses. In addition, the IISC is also engaged in several community relationships with the Toledo Fire Department, Toledo Zoo, and Toledo Museum of Art. Moreover, a training and research partnership has been established with the Wright Patterson Air Force Base. Please find below the major capabilities of the IISC. On April 21st, the IISC will be holding an Open House and tours of the facility.

First Floor: Virtual Immersive Reality Center - Widest array of 3D and Virtual Immersive Reality technology offering unprecedented opportunities for learning, teaching, research and advancing patient care.

1. First 5-sided, seamless LED immersive environment in the world
2. A 38M pixel curved CAD Wall
3. First Holographic Theater in the academic world
4. State-of-the-art 3D and VIR technology software
5. Global/Distance Learning Suites
6. Training in 3D & VIR technology, holographic technology and software development

Second Floor: Advanced Clinical Simulation Center - Improving Patient Outcomes through individual and team training using human patient simulators in virtual hospital settings.

1. Highly advanced virtual hospital (Elliptical Hospital)
2. Clinical skills area and Advanced Clinical Skills Room
3. State-of-the-art simulation models
4. Pre-briefing, debriefing and breakout rooms
5. Measuring human performance and effectiveness
Third Floor: Progressive Anatomy & Surgical Skills Center - Regional, national and global destination for surgeons to ensure competency in training and practice.

1. Sixteen surgical bays
2. Surgical skills labs
3. State-of-the-art surgical equipment
4. Fresh tissue labs
5. “Gallery” for historical displays and plastination models
6. R&D with industry collaborators

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**BRIM Connection Conference**

"Design of New Drugs to Target Cell Death Pathways in Glioblastoma"

12:00 - 1:00 PM on April 21, 103 Health Education Building

To be presented by:

Dr. William Maltese, Ph.D., Professor, Chairman & McMaster Endowed Chair in Biochemistry

Chris Trabbic, Research Associate, Pharm-Med/Bio Chem

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**IRB Corner**

By Carolyn Pinkston, M.P.H., R.N., C.I.P.

The University of Toledo recognizes and accepts its basic responsibility to assure the protection of any human subjects involved in research. To oversee the human research activities across both campuses, UT created the Department for Human Research Protections (DHRP) in 2007 and developed university-wide policies and procedures. UT holds an agreement with the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) called a Federal Wide Assurance (FWA), which is a commitment to the government that the institution will review and approve research involving human subjects in accordance with the ethical principles outlined in the Belmont Report and the DHHS regulations 45 CFR Part 46. The DHRP staff members function in an administrative capacity with the IRBs to process and track such research.

UT has registered two IRBs. The Biomedical IRB reviews all research designed to evaluate the safety, effectiveness, or usefulness of an intervention including research on therapies (e.g., drugs, diet, exercise, surgical interventions, or medical devices), diagnostic procedures (e.g., CAT scans), and preventive measures. The Social, Behavioral and Educational IRB reviews all protocols involving human subjects that generate data by means of questionnaires, observation, studies of existing records, and other experimental designs involving exposure to a non-biomedical stimulus or intervention. The Boards fulfill a very important role in the promotion and conduct of safe, ethical research, helping to assure that UT investigators are aware of and comply with, federal regulations. The Board clearly understands the pressure of conducting research in a competitive scientific and academic environment and the majority of Board members are investigators themselves. Regardless of the pressures to rush scientific proposals into action, the associated ethical concerns and regulatory requirements necessitate a careful and methodical examination of the research.

The primary responsibility of the IRB is to protect the rights and welfare of human research subjects and assure the ethical conduct of research. In accordance with DHHS and FDA regulations, the IRB reviews research proposals to ensure that risks have been minimized and the potential for benefit has been maximized before human subjects participate in the research. The authority conveyed to the IRB includes decisions to approve, disapprove, require modifications, monitor, suspend and terminate research projects involving human subjects.

The IRB also ensures that human subjects participate in research only after providing legally effective informed consent. Investigators may not solicit subject participation or begin data collection until they have received approval from the appropriate IRB or written concurrence that the research has been determined to be exempt from IRB review.

Certain populations may be particularly vulnerable in a research setting (e.g., children, prisoners, pregnant women, fetuses, persons with physical or mental disabilities, and economically or educationally
disadvantaged persons). In our institution, students and staff members are included in this category to avoid any undue pressure from authority figures. When reviewing research involving these subject populations, the IRB will apply additional protective safeguards as required by federal and state law, institutional guidelines, and any other applicable agency/entity regulations.

All research activities involving human subjects must be reviewed and approved by the IRB. Once research is approved, the IRB must review the study at least once a year to ensure the study continues to meet ethical guidelines and provide benefits. Importantly, the IRB cannot grant retrospective approval for research activities – it functions as an independent committee and its decision to not approve research cannot be reversed by administration.

The Biomedical IRB meets every month for approximately three hours to review new research proposals, amendments to research, and continuing reviews. In addition, the Board must review and acknowledge all Exempt and Expedited research that has been approved throughout the course of the month. Educational items and issues for discussion often round out the agenda.

The Biomedical IRB is currently comprised of 19 members representing various areas, including medicine, surgery, pharmacology, biochemistry and cancer biology, nursing, education, sociology, public health and the community. To allow for continuity, the members are appointed in staggered, three-year renewable terms. Importantly, membership on an IRB is on a volunteer basis. Their expertise in, and understanding of, the sciences, research methodologies, ethics, regulations and the human condition greatly contribute to the ethical conduct of research at our institution. If you have an opportunity to see one of these hard working individuals, please take a minute and thank them for their service to the UT research community.

RSP Corner

By Rick Francis, Ph.D., C.R.A.

The NIH salary cap affects many investigators at UTHSC. Do you know where it comes from?

The NIH salary cap limits the direct salary that NIH will pay an individual on an NIH grant. Every year since 1990, the cap has been legislatively mandated by Congress. For 1990 it was established at $120,000, but years later, in 1998, the move was made to tie it to a specific Federal Executive Level salary.

Initially it was tied to Executive Level III salary, then raised to Executive Level II for FY2000 awards, which resulted in a peak of $145,100. For FY2001 awards the cap was raised to the top level, Executive Level I, and it was tied to that level all the way to issue of FY11 awards, steadily rising to peak at $199,700.

However, for FY 2012, the Consolidated Appropriations Action, 2012 (Public Law 112-74) lowered the salary cap for the first time, from Executive Level I ($199,700) to Executive Level II ($179,700). At that time, additional agencies adopted the salary cap for the first time. Today the cap applies to grants from NIH, SAMHSA, AHRQ, CDC, and HRSA. In January 2014 the salary cap followed the annual Executive Level II COLA adjustment to rise to $181,500.

Many online sources explain the calculation of salaries on grant proposals subject to the cap, and you can
Hello to All My Friends and Colleagues at UTMC

As many of you know I will be retiring April 30, 2014, which is fast approaching. Even though I have been working here for only a short time, I feel that UTMC is “home” for me – what I mean is, when I was fortunate enough to get the job as Clinical Research Coordinator it felt as though I belonged to UTMC. It was 36 years ago when I earned my nursing degree from the University of Toledo Community & Technical College. (My oh my how time flies.) Over the years I have worked in a wide range of nursing jobs, including ICU/CCU, home health, and office. I have been in management roles and staffing roles and know well the ups and downs of each role. Throughout my career I have learned from each job what it means to be a nurse, because from a young age that is all I ever wanted to be.

I always say you must learn something new every day and I can certainly say that has been true with my job as a study coordinator. When I reflect on my time here, I have learned so much from everyone I have come in contact with. Sure, any job comes with ups and downs, but overall my experience here has been a positive one, and I thank each person I have worked with for that. I am proud to be a Clinical Research Coordinator and see, first hand, those advances in medicine happening all around us. I am astounded when I reflect on what medicine/nursing was 36 years ago and how it has changed so dramatically along with the new care and treatment of our patients over the years.

I have been privileged to work with a lot of very special people who have been part of my time at UTMC, including but not limited to: the registration staff, volunteers, physicians, nursing staff, fellows, clerical staff, leadership staff, and the individuals who I have been fortunate enough to enroll in studies. In retirement I will continue to be part of nursing by putting my Parish Nurse Certification to use. I plan to do lots of volunteer work in the community and in my church. I always said, “When I retire I want to have a fun job,” so I will make whatever I do fun. My husband and I have lots of travel destinations to visit, along with spending more time with our family and friends.

Always remember what we do as Clinical Research Coordinators, the work which touches lives now and through many years to come. Keep up the great work!

Thank you for my time at UTMC.

Adele Griffin, RN

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