It Takes a Highly Specialized Village to Train Graduate Students Within the Biomedical Science Program

Kandace Williams, Ph.D.
Associate Dean for UT College of Medicine and Life Sciences Graduate Programs

The Biomedical Science Program at the University of Toledo College of Medicine and Life Sciences (UT-COM & LS) is the structural umbrella over a training program that is comprised of four basic research tracks; Cancer Biology (CAB), Cardiovascular Biology and Metabolic Diseases (CVMD), Infection, Immunity, and Transplantation (IIT), Neurosciences and Neurological Disorders (NND), and two programs, Bioinformatics and Proteomics/Genomics (BPG) and the MD/PhD training program. Each of the research training tracks is closely aligned with the four basic research departments within the College of Medicine; Department of Biochemistry and Cancer Biology (CAB), Department of Physiology and Pharmacology (CVMD), Department of Medical Microbiology and Immunology (IIT), and Department of Neurosciences (NND). Each research track also has graduate faculty from many other academic and clinical departments within UT that help train our young scientists.

A director who is a graduate faculty member within the aligned department accomplishes student oversight within each track. The directors are Dr. Kandace Williams (CAB), Dr. Andrew Beavis (CVMD), Dr. Kevin Pan (IIT), Dr. Nicolas Chiaia (NND). Dr. Robert Blumenthal directs the BPG program, and Drs. Marlene Welsh and Randall Ruch co-direct the MD/PhD training program.

Admissions committees from each of the aligned departments screen applicants from all over the world. The number of applicants invited each spring for subsequent fall entrance depends on the number of research faculty currently with adequate funding, and a calculated guess of the number of faculty that will obtain adequate funding within the next 2-3 years. This decision-making approach is necessary because the major advisor pays the majority of the student’s stipend after the first year of graduate school.

During the first year of training, all students register for Biomedical graduate courses that are team-taught by the graduate faculty. Each student also undergoes 8-10 week rotations in research labs of individual faculty. By the end of the spring or summer semester of their first year, each student will be “matched” with a major
advisor for their thesis (MS degree) or dissertation (PhD degree) research project. Dr. Randall Ruch organizes
the rotation schedule, and matching process. Once a student has been matched with their major advisor, a
graduate faculty committee is then chosen. This committee serves to help and advise, and is the examining
committee for the student’s qualifying exam and for the final defense of the student’s research project.

After successfully passing the qualifying exam, the student will continue to spend the next 3-4 years in the
research lab learning to formulate hypotheses, plan experimental approaches, develop appropriate technical
skills, interpret results, construct posters and/or platform talks for scientific meetings, and prepare for
presenting research seminars. The student's progress is monitored carefully by the major advisor during
weekly lab meetings, one-on-one meetings, and meetings with the student’s committee. The major advisor
also helps the student write manuscripts of their results for submission to scientific journals.

When the student, major advisor, and committee all agree that the student has accomplished sufficient work
to qualify for a defense of their research, the student writes a thesis or dissertation and subsequently defends
this orally to the public, and immediately after to their committee behind closed doors.

Throughout the student’s graduate experience, the College of Graduate Studies (COGS) monitors overall
progress. Michelle Arbogast, Manager of Administrative Services, manages all administrative details. As
Associate Dean of UT-COM & LS Graduate Programs, I work closely with Michelle and with Dr. Thea Sawicki,
Associate Dean & Vice Chancellor for Graduate Health Science Studies, to ensure the smooth progress of each
of our Biomedical Science Program graduate students. From student orientation to graduation, the HSC COGS
office is essential to this program.

A major perk of my current appointment is the ability to address specific areas of concern for our Biomedical
Science Program students, such as different training opportunities and career options. Several of the graduate
students have expressed an interest in teaching careers, therefore Dr. Constance Shriner, Associate Provost
for Faculty Development, has agreed to offer a teaching workshop this summer for all interested graduate
students and postdoctoral fellows. Dr. Doug Leaman, Chair of Biological Sciences, has also offered weekly TA
opportunities this coming fall to all interested graduate students. To address our ever-growing concern of
public advocacy for biomedical research, the Blade has agreed to publish articles written by our Biomedical
Science Program students and postdoctoral fellows about their research. This is a challenging opportunity for
the students to learn how to describe their research to the public. Dr. Elsa Nadler from UT Research &
Sponsored Programs, and Meghan Cunningham, UT Media Relations Specialist, have offered to help proofread
our student’s stories. I am delighted to report that the first article by Akshada Sawant (Cancer Biology
student) was published May 5th in the Science and Health section of the Blade
(http://www.toledoblade.com/Medical/2014/05/05/UT-doctoral-students-fight-to-tame-cancer-gen.png). I
am also developing a new course “Scientific Communication Skills and Career Goals”, with financial support
from UT-COM & LS Academy of Educators. This course is planned for both graduate students and postdoctoral
fellows, to educate our new investigators with regard to key elements of scientific communication, and to help
identify and pursue different career opportunities.

In summary, the Biomedical Science Program has been purposefully designed to train graduate students to
understand and apply the scientific method of enquiry, regardless of specific biomedical research focus. The
Biomedical Graduate Executive Committee (basic science departmental Chairs, track directors, and Associate
Deans Sawicki and Williams) provides ongoing oversight, advice, and adjustments for program improvement.

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**New Grant**

**In Vivo Role of Platelets in Bacterial Blood Infection**

Randall G. Worth, Ph.D.
Assistant Professor, Department of Medical Microbiology and Immunology

You are probably familiar with platelets as the tiny cells that stop a cut from bleeding, by clumping together to
form a plug (also known as a "clot"). Platelets also clot in places where they are not supposed to, like within
veins and arteries, which can result in strokes, heart attacks or pulmonary embolism. We have a good
understanding of how platelets participate in clot formation, and even in repair of broken blood vessels.
Platelet-targeted anticlotting therapies have been developed that can often prevent or reverse these disorders,
and these therapies can involve pharmaceuticals as simple as aspirin or as complex as clopidogrel,
dipyridamole, and abciximab.

It has been known for many years that patients with certain autoimmune diseases and infections are more
prone to suffering strokes, heart attacks and other thrombotic abnormalities due to excessive platelet
activation. For example, my lab has demonstrated that Systemic Lupus Erythematosus patients exhibit
excessive platelet activation, which may lead to their susceptibility to thrombotic attack and production of immune cytokines (http://www.sciencedirect.com/science/article/pii/S0002944012007171). In many cases, the basis for this increased risk is unknown. However, there is evidence that platelets can recognize immune signals and infectious agents, thus leading to these unwanted thrombotic responses. To recognize infectious agents and immune signals, platelets express receptors commonly found on immune cells. When these receptors are activated, they can trigger the platelet to release substances that have potent immune-activating characteristics (http://www.sciencedirect.com/science/article/pii/S0008874910000717, http://cvi.asm.org/content/18/2/210.long); but the function of these molecules remains unknown.

For the past several years, my lab has worked to understand if blood platelets contribute to these situations of increased risk, in addition to responding to infections or inflammation. We have observed that human platelets are capable of killing bacteria (http://onlinelibrary.wiley.com/doi/10.1111/j.1574-695X.2012.00945.x/full). We know that to kill bacteria, platelets must first capture and then "eat" the bacteria through a process known as phagocytosis. If either capture or phagocytosis are blocked, the platelets can no longer kill bacteria. Phagocytosis is more typically associated with much larger cells, such as neutrophils and macrophages, and platelets have not typically been considered in studies of how the body clears bacterial infections. However, platelets outnumber neutrophils by about 100:1, so their overall defensive role may be much more important than has been appreciated.

We are actively trying to understand the mechanism(s) behind platelet antibacterial activity. We have performed many experiments in test tubes, using platelets isolated from fresh human blood (donors provide about 10 milliliters at a time). However, to see if platelets are truly important in antibacterial defenses, we needed to perform experiments in a living animal, and to do so with and without platelets present. For this purpose, we engineered a new strain of transgenic mice in which platelets can be depleted for extended periods of time without harming the animal. The time that the mice are deficient in platelets acts like a window of opportunity for us to perform experiments to determine how a mouse can battle infection without the help of platelets.

In selecting the initial bacterial infection to challenge our new platelet-depleted mice, we chose Staphylococcus aureus, which is the most common cause of blood infections in humans. This bacterium is commonly associated with skin infections and pneumonia, and has been extensively covered in the media because of a particular form known as methicillin-resistant Staph. aureus or MRSA. We obtained a strain of MRSA from a clinical study here at UTMC, and performed several experiments by infecting the mice via direct blood inoculation and observed that platelet-deficient mice are more susceptible to infection.

From these studies, we know that platelets are essential to mouse survival (and possibly our own) from S. aureus blood infection. Since platelets appear to play a major role in killing bacteria and regulating immune responses, we developed a grant proposal to determine how platelets protect our bodies from infectious agents like MRSA. We are very fortunate that the National Heart, Lung and Blood Institute of the National Institutes of Health funded this $1.5M grant. In the newly-funded studies, we will use genetic approaches to understand how platelets recognize, capture and kill the bacteria, which will allow us to understand the important platelet molecules involved in this process. We will be using a variety of techniques including intravital microscopy and whole-animal bioluminescence imaging to monitor the progression of disease in these animals, so we can determine how platelets participate in bacterial killing. In all, the experiments proposed in this grant will allow us to determine how platelets perform these essential activities and may provide new therapeutic targets that will allow more effective treatment of bacterial blood infections. It may also help to "fine-tune" antiplatelet therapies designed to reduce clotting, so that the therapies do not also affect the antibacterial platelet activities.
Electron microscopy images showing resting platelets (left) and platelets containing internalized IgG-coated nanoparticles (right). This was the initial evidence suggesting that platelets are capable of internalizing targets in a similar fashion as leukocytes and therefore may exhibit functions distinct from clotting.

**Department of Urology: Overview**

Steven Selman, M.D.
Professor, Clinical Director & Chairman; Director, Urology Residency Training Program

The Department of Urology was established in 1991. Previously, the Division of Urology existed as a surgical specialty unit within the Department of Surgery. Dr. Kenneth Kropp (KK) was the first chairman of the Division (1971) and the Department (1991) maintaining the chair until 2008. Early faculty included Jagdish Jhunjhunwala (JJ), a talented surgeon who trained as Dr. Kropp's first resident and subsequently first faculty hire. Both KK and JJ were participants in the first renal transplant performed in Northwest Ohio (1972). The kidney program continues to this day within the Department as a marquee service and recently reached the 2000 patients transplanted milestone. In 1981, Steven Selman (SS) joined Drs. Kropp and Jhunjhunwala as a member of the full time faculty, the faculty members being then identified as KK, JJ or SS. In addition to the full time faculty, a strong cadre of well-trained volunteer faculty at Toledo Hospital and St. Vincent’s hospital actively supported the residency training program. Two residents a year were accepted yearly for the 5 year and subsequently 6 year urology training program. In 1993 Dr. Jerzy Jankun assumed the position within the Department as the full time Director of Urologic Research. A research laboratory had earlier been established by Dr. Selman in conjunction with Mr. Rick Keck. Dr. Jankun was subsequently joined in 2002 by his wife Ewa as a second research position in the Department. In 1998, Michael Rees joined the faculty. Having completed a transplant fellowship in transplantation and Ph.D. in immunology in Cambridge, England, Dr. Rees energized the renal transplant program and established a laboratory in xenotransplantation.

New fellowship trained faculty have joined over the last 5 years including Khaled Shahrour, M.D., Director of Minimally Invasive Surgery and Stone Management, Samay Jain, M.D., Director of Urologic Oncology, Alice Bonnell, M.D., Director of Pediatric Urology and Ajay Singla, M.D., Director of Female Urology and Pelvic Reconstruction.

Residency Training: Accredited urologic training has been available in Northwest Ohio since the 1940's. Upon the establishment of a Division of Urology at MCO, the primary teaching site for residency education was transferred from St. Vincent’s Hospital to the present UTMC campus. Since 1971, more than 80 urologists have been successfully trained. Currently, one half of the practicing urologists in the Toledo metropolitan area are MCO/UTMC trained.

Clinical Programs: The Department offers clinical expertise in general as well as subspecialty urology. Included in the latter are pediatric urology (based at St. V's), urologic oncology, stone management, minimally invasive robotic surgery, female urology and pelvic reconstruction, men’s health and renal transplantation. The Kropp procedure for treatment of the pediatric neurogenic bladder was developed on campus. The renal transplant program is recognized internationally for its part in the development of Paired Kidney Exchange. The addition of new fellowship trained faculty has resulted in a 43% increase in patient visits to UTP/UTMC facilities over the last 3 years.

Research Programs: Research, both basic and clinical, has been a fundamental aspect of the Department's culture since its inception. Significant contributions to urologic oncology, pediatric reconstruction, paired renal transplantation, xenotransplantation, and female pelvic reconstruction have been recognized by the scientific community. Over 25 million dollars (est.) in extramural funding has flowed into the institution as a result of the Department's research endeavors. Current collaborative basic research includes work in castrate resistant prostate cancer, xenotransplantation, photodynamic therapy for bladder cancer, nutraceuticals for the management of urologic cancers, treatment evaluation for patients with interstitial cystitis and the science of paired kidney exchange.
Department of Urology: The Alliance for Paired Donation

Michael Rees, M.D.
Professor, Vice Chair and Medical Dir, Human Donation Science Program

The Alliance for Paired Donation was founded in 2006 by Michael Rees, MD, PhD to help kidney patients with willing, but incompatible living donors to exchange their donor’s kidneys to achieve compatible kidney transplants. These exchanges are known as kidney paired donation. The organization’s status as a charitable non-profit (501c3) was granted by the IRS in August of 2006. Initially available through several centers primarily in the Ohio area, the network of participating transplant centers has grown each year and now comprises close to 80 centers. The collaborative efforts of Dr. Rees and his colleagues has raised over $5 million of philanthropic and grant support to allow the APD to work toward achieving its mission “to save lives by securing a living donor kidney transplant for every patient who needs one.”

The APD is now in its seventh year. With a proven track record as one of the most innovative organization in the kidney transplant field, the APD was one of the first national organizations devoted to kidney paired donation (KPD), which has rapidly spread throughout the living kidney transplant field. APD was the first organization to pioneer Non–Simultaneous Extended Altruistic Donor (NEAD) chains, and today 75–80% of all KPD transplants are done through those chains. The University of Toledo in collaboration with the APD was the first organization to receive a federal grant to implement a national Standard Acquisition Charge (SAC), and now work is underway to revolutionize the way living kidney donation is financed.

The demand for kidney transplants continues to grow every year. In 2012, the number of people waiting for a
kidney transplant numbered 106,395. Over the same time period, 5,619 people received a living donor kidney transplant; 10,868 received a deceased donor transplant. Unfortunately, 4,527 people died while waiting for a kidney transplantation.

One of the major challenges for patients with kidney disease (End Stage Renal Disease, or ESRD) as well as for the health care system is the rapidly increasing costs associated with care and treatment. In the words of Dr. Rees, "increasing kidney transplantation is the place where true healthcare reform is possible: better care at lower costs." Transplants are better than dialysis for most patients while costing the government and private insurers significantly less money. 507,326 people were receiving dialysis service in 2011; one year of hemodialysis cost Medicare $87,945 in 2011 (the last year data is available from the 2013 USRDS Annual Report [http://www.usrds.org/atlas.aspx](http://www.usrds.org/atlas.aspx)), whereas one year of kidney transplantation cost Medicare $32,922. Over five years, transplanting a single ESRD patient rather than having them remain on dialysis saves Medicare $275,115. And the average patient that receives a deceased donor transplant lives 10 years longer than if they had remained on dialysis.

From the earliest days of the APD, Jonathan Kopke has served as software designer – taking the initial program, written by Dr. Rees’ father, Alan Rees, and transferring it to a web-based program. The APD clinical database is operated on a HIPAA-compliant server at The University of Toledo and made accessible to our member centers via a secure website. The software has undergone many enhancements throughout the years; in 2010 the way in which match runs are completed was radically changed, enabling staff to perform a match run in literally seconds. The APD’s Scientific Operations Committee works closely with the APD and with Jon to adjust the matching software as needed to reflect current priorities of creating the most transplants for the hardest to match recipients. In 2012, APD collaborator, Alvin Roth, was awarded the Nobel Prize in Economics, in part for his work with the APD in developing matching software for kidney exchanges. The APD’s optimization software is the result of this collaboration. Further improvements will be rolled out in 2014, including automated emails when potential donors are found, as well as automated match offers.

More recently the APD has partnered with UT Medical Microbiology and Immunology Professor Stanislav Stepkowski, PhD to develop innovative approaches to determine if a potential donor and ESRD patient are a match. This project was funded by the NIH and has resulted in the identification of an entirely new way to find matches for the most difficult to match patients. The University of Toledo transplant immunology laboratory provides the centralized laboratory for the Alliance for Paired Donation and is establishing the model for efficiently testing compatibility to speed the identification of suitable kidney exchanges. Additional collaborative research with the University of Michigan, also funded by the NIH, is using simulation and sophisticated statistical modeling to develop new algorithms to identify the solution most likely to lead to successfully completed KPD transplants.

**Department of Urology: Faculty Highlight**

**Interstitial Cystitis: Elucidation of Psychophysiologic and Autonomic Characteristics**

Ajay Singla, M.D.
Professor, Vice Chair, Urol Clin Aff, Assoc Dir, Urol Res Prog, Dir, Female Urol, PR Surg

Dr. Singla, Professor in the Department of Urology has been awarded NIH/NIDDK - RO1 grant as Co-PI to recruit patients who are suffering with Interstitial Cystitis. The University of Toledo Medical Center serves as an investigative site along with Case Western University Hospital.

Interstitial Cystitis/Painful bladder syndrome (IC/PBS) is a chronic condition with symptoms of urinary frequency, urgency, nocturia, bladder or pelvic pain. A large number of autonomic disorders have been identified which are clinically associated with IC. Despite extensive research, the etiology of IC/PBS remains elusive. As such, no successful long term therapy currently exists for treating IC/PBS. This study may provide a better understanding of common abnormalities found in autonomic activity in IC/PBS and associated disorders. The main objectives of the study are:

1. To differentiate the specific baseline neurophysiological abnormalities occurring in IC/PBS from healthy subjects, specifically bladder and pelvic floor afferent and efferent neural function.
2. To determine autonomic and pain response which may be common to IC/PBS and their relatives and which may differ from healthy subjects.
3. To provide an answer to the question of the clinical utility of lidocaine installation into the IC bladder.
This study is currently open to enrollment to all patients who have been diagnosed with IC or have a relative who has IC or has symptoms suggestive of IC. Initial visits are carried out at UTMC. All participants will go through the informed consent process and a screening visit. Based on inclusion/exclusion criteria the recruitment will be carried out. A number of questionnaires are used to assess IC/PBS. A full clinical evaluation to assess autonomic efferent, somatic afferent neural function and gastrointestinal function will be carried out. Subjects will be compensated financially at the end of study.

**Newly Enrolling Clinical Trials**

A Multicenter, Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Study to Evaluate the Safety and Efficacy of Intravenous Natalizumab (BG00002) on Reducing Infarct Volume in Acute Ischemic Stroke

Mouhammad Jumaa, MD - Neurology

**RSP Corner**

**Some Shortcuts Make the Route Longer**

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

In recent RSP Corner columns I've described the NIH salary cap, how the rollout of an online system for grant development, endorsement, and submission will help researchers at UT, and how researchers can gain from use of the NIH Reporter tool to become aware of funded research well before results are published. In this month’s RSP Corner I must address a problem that has caused a great deal of inefficiency and even some risk for the institution.

Institutional policy determines who is authorized to commit the university to a project or contract. In short, very few people can sign documents on behalf of the university. PIs cannot, chairs cannot, and deans cannot. The Vice President for Research is the person authorized to sign grant proposals, grant agreements, subcontracts, and non-disclosure agreements.

Some investigators are tempted to ignore the policy, and sign and submit documents as Authorized Institutional Officials. I suspect they imagine the policy is overly restrictive and unnecessary, and that a shortcut would simply save time and cut through bureaucratic red tape.

Unfortunately we have had a number of occasions to find out what really happens, and time-saving is NOT one of the consequences! What really happens is that -- at best -- account setup is delayed, and at worst, embarrassing exchanges with the sponsor result from misplaced agreements, misdirected checks, inaccurate proposal information, inability to document spending for reports, and legal agreements the university cannot honor and must negotiate and execute long after it was inappropriately signed and returned without review by RSP. Funds may have to be returned (!), and relations with sponsors may be soured for years. Moreover, if you as a UT employee sign a document without authorization, you are personally liable, and the university has no responsibility to defend you. In such a case one UT administrator had to pay thousands of dollars of his own money!

Fortunately the remedy is simple: contact RSP if you are submitting an application for funding for ANY sponsored project or gift, including training, fellowships, community outreach and education. We will help get it done right the first time, and save you time and problems while enabling the university to honor its commitments and maintain good relations with our sponsors.

**IRB Corner**

**Tips for working with the DHRP Office - Help Us Help You!**

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

The Department for Human Research Protections office is here to partner with University researchers in achieving a smooth application approval process. The
department staff members have encountered a few issues that impact the
course of the application review and we thought might be helpful to provide a
few tips to - help us, help you - and result in a more successful outcome.

Tip #1 - The DHRP staff, are not the IRB.

There is frequent confusion regarding the role of the Department for Human
Research Protections (DHRP) staff and the role of the Institutional Review
Board (IRB) members. Researchers, students and other support staff are often
under the impression that they can wait in the office while the DHRP staff
approve a research application. Contrary to that misconception, the DHRP staff
members are not committee members empowered to make decisions
regarding the approval of research but instead, function in an administrative
capacity supporting the board and processing research documentation. The
IRB is comprised of 19 members who meet on a monthly basis to review and
make decisions about research proposals.

Tip #2 - Please provide the basic study information when making inquiries.

When placing a call or visiting the DHRP office in regard to a study, please have available, the IRB number,
the name of the principal investigator or the study title. The office frequently receives calls regarding the
status of IRB applications without the pertinent information. The volume and complexity of research
applications submitted on a monthly basis makes it impossible to retain these details and many investigators
oversee multiple studies. Providing the basic information is very helpful in locating the correct study and
providing an accurate update.

Tip #3 - Training is a must!

Prior to submitting an application to the DHRP office, please verify that all research team members have
completed human subject research training, and HIPAA training if applicable. Applications will not be reviewed
until all training is complete and the lack of training can result in an unwanted delay, especially with student
research under a limited time frame. The CITI human subject research training is valid for three years. For
those who completed the original CITI course(s) a few years ago, the Refresher Course is now due. The
instructions are available at http://www.utoledo.edu/research/RC/HumanSubs/training.html Research
personnel tables on incoming applications will be checked for updated training.

Tip #4 - The more complete the application, the smoother the approval process.

A few of the most critical issues impacting the research approval process are; the submission of an incomplete
application, missing attachments or lack of research training. Submitting an application form without responses
to questions or a "NA" response is problematic. Please respond to application questions with a complete
sentence, otherwise the reviewer is left guessing your intentions and the application will be returned or an
inquiry sent via email. These omissions can add significant time to the application turn-around. Please include
all attachments as the reviewer cannot make a decision without looking at the material. Incomplete
applications hold up the review process as evidenced by the monthly 20-40 applications awaiting an
investigator’s clarification, personnel training or additional documentation.

Tip #5 – IRB members volunteer their time.

Another common misconception is that and IRB members are present in the DHRP office and available to make
decisions on a daily basis. The two University of Toledo IRBs, Biomedical and Social, Behavioral and
Educational, operate on a volunteer basis and meet once a month. IRB members are busy faculty and
community members who allocate time in their schedules to review convened research studies and attend the
three hour monthly meeting as a service commitment to the University. In addition to the IRBmeeting, there
are a handful of members who donate extra time to review exempt and expedited applications. While the
DHRP office attempts to maintain a monthly schedule of volunteer reviewers, there are occasions when
unexpected issues impact attendance. While we understand that investigators believe their research study
should be a priority, exempt and expedited applications are entered into a queue and are reviewed on a first
come, first served basis unless there is an over-riding patient safety issue constituting an emergency.

The DHRP office appreciates the opportunity to interact with University’s research community and keeping the
aforementioned tips in mind will help facilitate the process for everyone. Thank you.