A Message from the Chair of the UT Biomedical IRB

Why do we need an IRB?

Roland T. Skeel, MD
Chair University of Toledo Biomedical IRB

“We all are highly ethical and would never do anything to harm our patients, so why do we need an IRB to review our research?” While few would argue those who do human subject research deliberately intend to harm the subjects in their research, there is a long and ongoing history in the US and elsewhere of inadvertent, negligent, or conflict of interest-driven harm that supports the ongoing need for an independent ethical review of human subject research.

In this message to the UT community, I will focus on why an IRB or independent ethical review committee is needed. In later messages, I will discuss additional challenges for researchers, including how to put together an application that fully meets ethical standards and regulatory requirements.

Early historical events occurring in the US and elsewhere included

- 1932-1972 – The Tuskegee Syphilis Study
- 1939-1945 - Nazi “Medical Experiments” – forced surgery, poisons, viruses, ice water
- 1944-1974 - US Government Sponsored Human Radiation Experiments (4000), with no subject consent, no direct benefit
- 1946-1947 - Nuremberg Doctors’ Trial and Nuremberg Code – many were found guilty of crimes against humanity.

These were followed in 1948 by the UN Universal Declaration of Human Rights, and in 1964 by the Declaration of Helsinki, which stated “it is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.” It was a landmark international agreement adopted by the World Medical Association. This document recommends ethical standards in medical research, including the standard that “the benefits, risks, burdens, and effectiveness of a new method should be tested against best current... unless no proven... method exists”

Additional documents and regulations followed, most notably The Belmont Report in 1979, which established the three foundational principles for ethical research in human subjects:

- Respect for Persons
Beneficence

Justice

This was followed shortly by FDA Regulations in 1980 and “The Common Rule” in 1991, which was adopted by 16 Federal agencies. In 2000 – The Office of Human Research Protection (OHRP) was established in DHHS to replace NIH Office for Protection from Research Risks.

In spite of these declarations and regulations, there have been notable ongoing breaches in the protection of human subjects. In 1999 Jesse Gelsinger, an 18 year old with partial ornithine transcarbamylase (OTC) deficiency died at the University of Pennsylvania shortly after receiving normal OTC gene attached to a therapeutic virus. (DIC, Systemic Inflammatory Response Syndrome). The responsible researcher was charged with:

- Enrolling the subject despite being ineligible
- Misleading patients that FDA was comfortable with study
- Inadequate informed consent
- Misleading the IRB about eligibility testing

In 2001 at Johns Hopkins University (JHU), a 24-year-old lab technician who volunteered for a study died of respiratory and renal failure one month after inhaling hexamethonium by nebulizer. OHRP found that researchers should have known about potential lung toxicity and should have informed the patient. The issue here was an inadequate literature search. OHRP disagreed with JHU interpretation of regulations that the hexamethonium was not “investigational medication”. It resulted in a temporary suspension of ALL clinical research at JHU and a new JHU standard developed for an adequate and comprehensive literature search.

Recurrent issues of ethical concern:

- Vulnerable populations, such as elderly, children, students, employees, minorities or cognitively impaired.
- Absent or inadequate consent – the principle for respect for persons requires that subjects be appropriately informed that the study involves research, what will be done and why, how long their participation will be, that their participation is voluntary, what the alternatives are, and who to contact regarding questions or in case of injury.
- Justification based on good of society or governmental interests, despite potential harm to the individual subject.
- Arrogance of researchers (most often physicians) who think their research is so important that ethical principles do not apply to them or that rules can be bent
- Absence of scientific or inadequate ethical review. If it is poor science, it is not justifiable to subject anyone to the research. Inadequate review gives false assurances of benefit vs. risk
- Inadvertent harm done to subjects or to bystanders, including loss of confidentiality because of benign negligence or inadequate attention to details.

While the individual researcher has the primary responsibility to assure the protection of the research subjects, review by an independent group can go a long way to satisfy all interests that the researcher has considered the issues that will help protect the subject. Thus the IRB reviews the qualifications and training of the researchers, the purpose and justification for the study, the procedures used to identify and recruit subjects, the design and procedures of the study itself, the consent form and process, and the maintenance of confidentiality. This process of independent review, while not perfect – and at time laborious – thus far seems to be our best way to balance the scientific and educational need to conduct human subject research while protecting the rights and welfare of the subjects.

My Clinical Research

M. A. Julia Westerink, M.D.
Professor, Chief, Infectious Diseases Division

When we think of HIV, we tend to focus on increased susceptibility to a number of unusual pathogens. However, a rather common bacteria named *Streptococcus pneumoniae* is a major cause of illness and
death in HIV-infected individuals. It is the most common bacterial respiratory pathogen encountered in the HIV-positive population, and disease is frequently complicated by seeding of the bacteria to the blood and/or recurrences. Despite the widespread use of anti-HIV viral medications, HIV-infected individuals remain at a 35-50 fold increased risk of invasive pneumococcal disease compared to HIV-negative individuals. It is therefore recommended that all HIV-positive children and adults are vaccinated with either the pneumococcal conjugate (PCV) or with PCV followed by polysaccharide vaccine (PPV) respectively. These vaccines consist mainly of the sugar capsule or polysaccharide that surrounds the bacteria. Although vaccination is highly effective in preventing pneumococcal disease in small children and healthy young adults, the vaccines are much less effective in the high risk HIV-positive population.

Similarly, the pneumococcus is the most common bacteria isolated from elderly patients with community acquired pneumonia. It is recommended that the elderly receive pneumococcal vaccination but the vaccine is also less effective in this high risk group of individuals (Link1).

Our laboratory studies the immune response to pneumococcal vaccination in various populations. We initially looked at healthy young individuals who we know are well protected by the vaccine, to define what the ideal response looks like (Link2).

The most common method of studying how well a vaccine works is by measuring the amount of antibody a person makes after vaccination which can coat the bacteria and facilitate ultimate death. Unfortunately, this simple method does not consider the fact that sometimes antibodies that bind the polysaccharide capsule are in fact not useful in clearing the bacteria from the body. A second, more useful, method of evaluating how well a "pneumonia" vaccine protects is by studying how well the blood of a vaccinated person kills the bacteria. This is called opsonophagocytic activity. We use both methods to study vaccine responses. The antibodies that ultimately protect against pneumococcal infection are generated by immune cells called B cells. We postulated that there is a problem with B cells in elderly and HIV-positive individuals who are not adequately protected by the pneumonia vaccine. To study what these B cells look like in healthy young, elderly and HIV-positive populations, we have designed a method, using a fluorescently stained pneumococcal polysaccharide, to isolate these cells from the blood after vaccination.

To date we have studied B cells in healthy young adults and found that the majority of cells that respond after polysaccharide vaccination are so called IgM memory B cells (Link3), in sharp contrast to the B cells that respond to vaccination with proteins. Similarly, in HIV-positive individuals, many of the B cells that respond to the polysaccharide vaccine are IgM memory B cells, but they are much lower in number.

In recent years, HIV disease has been compared to a rapid aging process because they share many similarities in B cell dysfunction. Although elderly individuals had very low protective immunity following pneumonia vaccination, just as the HIV-positive individuals, we found that the B cells which respond to the vaccine were totally different than the responding B cells in both young and HIV-positive adults (Link4).

These findings suggest that we can probably not use the same approach in HIV-positive and elderly individuals to improve the response to the pneumonia vaccine as each of these entities, although similar in some aspects, are unique in nature.

In 2015, 50% of HIV-positive individuals in the US will be 50 years of age or older. This population, because of their age and their HIV status, forms a very distinctive group of individuals with a combined immune deficiency. Our laboratory is presently studying the immune response to the pneumonia vaccine in this group of individuals at depth under funding provided by NIH RO1A081558.

The ultimate goal of our studies is to lay the scientific foundation for the development of improved
pneumococcal vaccines for these high risk, poorly responsive populations.

## My Clinical Trial

### Clinical Trials for *Clostridium difficile*

Joan Duggan, MD.
Professor, Director, Ryan White HIV Center

Antibiotics are a well-known cause of diarrhea. One of the major - and most important - causes of antibiotic associated diarrhea (AAC) is the anaerobic gram positive bacillus *Clostridium difficile*, commonly known as C. diff. Infection with this organism can cause a severe form of colitis in which ulcerations occur on the surface of the colon which are covered with white plaques (called pseudomembranes) containing proteins, mucus, and inflammatory cells. The formation of these plaques on the surface of the colon with infection with *Clostridium difficile* is also the origin for another common name for this infection – pseudomembranous colitis. Infection with C. diff is one of the most common hospital acquired infections, and the incidence is increasing dramatically in both hospitalized patients and now patients in the community.

While most cases of C. diff can be successfully treated with antibiotics, patients with compromised immune systems may be at increased risk of severe infections which may be life-threatening. Traditional treatment for C diff usually involves the use of oral medications such as metronidazole or (Flagyl) or fidaxomicin (Dificid) for mild to moderate disease, and the use of vancomycin for severe disease. Unfortunately, despite the use of vancomycin, metronidazole, or fidaxomicin, approximately 25% of patients with C. diff will have a recurrence of infection, usually within the first month after stopping treatment. And if a patient has had a recurrence of C. diff, they have a 65% chance of subsequently having another relapse.

A new drug that is under investigation for infection with pseudomembranous colitis is surotomycin. Surotomycin is a non-absorbable antibiotic that in vitro is more potent than the preferred agent –vancomycin- against *Clostridium difficile*. In preliminary human trials, surotomycin not only had a higher cure rate for C. diff when compared to vancomycin, but also demonstrated a 50% reduction in recurrence. Surotomycin is now in a phase III multi-center clinical trial designed to evaluate superiority when compared to the competitor study drug, vancomycin.

The study ---Cubist LCD-CDAD---is now enrolling patients at UTMC. Inclusion criteria for the study include diarrhea with a minimum of 3 unformed stools per day that is proven to be due to *Clostridium difficile* by a positive test result for the C. diff toxin, and age >18 and <90. Patients enrolling in the study receive either surotomycin or vancomycin in a blinded fashion for up to two weeks.

If you are interested in obtaining more information about this clinical trial, please contact the UTMC investigators (Joan Duggan, Thomas Sodeman, Aijaz Sofi) or the study coordinators (Nicole Amadio, Mary Bowles) at 419 – 383 – 4387.

## New Grant

### Role of Complement Regulatory Proteins in the Interaction Between Platelets and Leukocytes

Viviana P. Ferreira, D.V.M., Ph.D.
Assistant Professor, Department of Medical Microbiology and Immunology

The complement system is composed of approximately 50 proteins that form a central part of our body's innate defense system against pathogenic microorganisms or cells. It can kill directly, and/or induce inflammation and mark the target with molecules that are recognized
by a more specialized defense system for elimination. Inflammation is a natural and beneficial reaction of the body to foreign agents and to other challenges; however, unchecked inflammation can destroy tissue and create permanent damage. In order to protect host cells from damage by complement activation, the complement system uses a complex set of regulatory molecules that are either bound to the surface of cells (DAF, CR1, CD59, and MCP), or that circulate in the blood (factor H, factor I and C4bp). My lab is working on understanding the molecular mechanisms of activation of the complement system. Specifically, we are elucidating (1) the means by which different targets are identified by complement, and (2) how complement is regulated by certain proteins, and how mutations in these regulatory proteins can lead to disease.

Factor H is the primary soluble regulator of activation of the alternative pathway of complement, an evolutionary ancient defense system that spontaneously activates at a low rate in humans. Factor H prevents activation of complement on host cells and tissues upon association with complement products that have bound to cells (such as C3b and iC3b) in combination with surface polyanions (including sialic acids, heparin, and other glycosaminoglycans) that are normally found abundantly on our cells and tissues. We have previously shown that the C-terminal end of factor H is essential for the ability of the regulator to recognize and protect cell surfaces ([Link1], [Link2], [Link3], [Link4]). Using gene engineering, we have developed a recombinant protein composed of the C-terminus of factor H as an antagonist to inhibit the interaction of factor H with cell surfaces. This approach has enabled us to further elucidate the molecular mechanisms by which factor H participates in preventing the pathogenesis associated with various chronic inflammatory diseases including age-related macular degeneration, arthritis, asthma and renal diseases ([Link5], [Link6], [Link7], [Link8]).

Although complement activation is normally tightly regulated, complement-mediated damage also contributes to the pathology observed in most chronic inflammatory diseases, including those mentioned above. Thus, under certain disease scenarios, our ability to limit complement-mediated damage on our cells and tissues becomes overwhelmed. Complement protein properdin is the only known positive regulator of complement activation and has the important role of stabilizing the enzymatic complexes that allow efficient amplification and function of the alternative pathway of complement. We and others have recently determined that properdin not only serves as a positive regulator of complement, but also selectively binds to certain pathogenic microorganisms as well as apoptotic and necrotic cells and initiates complement activation ([Link9], [Link10], [Link11]). We have also recently determined that activated platelets have the ability to bind properdin and activate the alternative pathway of complement on their surface ([Link12]), thus suggesting a role for properdin in the development of cardiovascular disease.

Cardiovascular disease is the leading cause of mortality in many countries. Platelets play a central role in vascular hemostasis and in disease-related thrombosis, as they are the first blood cells that rapidly adhere to tissue, to each other, and to white blood cells (leukocytes) in response to vascular injury. An increased number of activated platelets and platelet/leukocyte aggregates (PLA) are found in the blood of patients with inflammatory cardiovascular diseases such as atherosclerosis and acute coronary syndromes and are considered to play an important role in the initiation and progression of disease. My lab has recently been awarded a $1.85M R01 grant from the National Heart, Lung and Blood Institute of the National Institutes of Health to investigate the molecular basis of a novel mechanism whereby properdin binds to platelets and leukocytes and enhances their interaction, promoting the formation of PLA and thrombi in human whole blood. In addition, we aim to understand how factor H conversely limits platelet/leukocyte interaction. To complete these studies, we will use ex-vivo techniques that allow us to assess PLA formation in the fluid phase of human whole blood by flow cytometry as well as thrombi formation in human whole blood subjected to physiological and pathological shear stress, as would occur in blood vessels. We will also attempt to develop recombinant properdin fragment molecules with the ability to competitively inhibit the functions of properdin.

Understanding how the interactions between platelets and leukocytes are promoted and how they can be inhibited will lead to new treatments for important cardiovascular diseases. There are presently only two FDA-approved drugs that either inhibit or regulate the complement system, with many more drugs in various stages of development. The long-term goal of my lab is to contribute to the knowledge that will allow the design of drugs to control the complement system, either by inhibiting its pro-inflammatory and tissue-damaging
consequences in chronic inflammatory diseases or by enhancing its activity on unwanted cells such as microbes or cancer cells.

Acknowledgements: We are grateful for the continuous support that the American Heart Association has provided for our research during the past 6 years, as well as for the NIH American Recovery and Reinvestment Act grant, all of which have made the described studies possible.

The Investigational Drug Service (IDS)

Gregory Bartlett Siegel, JD, RPh, CGP
Clinical Research Pharmacist

Those of you who grew up at the same time as me will remember Bob Dylan’s song, “The Times They Are A-Changin.” Well, the times are changing in the IDS. I am retiring at the end of June 2014. Stepping in, with the advantages of youth and enthusiasm, to manage the IDS is Rachel Rarus, PharmD. Please join me in affording her a warm welcome.

Rachel graduated with her B.A. in English from the University of Michigan, Ann Arbor in 2009 and her PharmD with Highest Distinction from the University of Michigan College of Pharmacy in 2013. She is currently finishing up a PGY-1 Pharmacy Practice Residency at the University of Toledo Medical Center (UTMC). She is already familiar with our mission to advance knowledge and to improve the quality of patient care. Dr. Rarus will also serve as the UTMC Medication Safety Officer and membership on the University of Toledo Biomedical Institutional Review Board (IRB) is in the works.

Before going any further, Rachel and I would like to take this opportunity to thank all of those talented individuals promoting our clinical research programs at the University of Toledo. Examples include: Administration, Research and Sponsored Programs, the Department for Human Research Protection, the Jacobson Center for Clinical and Translational Research and especially our Investigators/Scientists and their teams. These people and others keep our University a major player in important and interesting research.

Currently, there are over one hundred clinical trials open at the University of Toledo. Many of these are drug studies. The IDS is responsible for providing support of these protocols. Examples include: (1) site qualification, (2) protocol and investigator brochure review, (3) collaboration with investigators and coordinators regarding blinding, randomization, dispensing and monitoring, (4) proper storage and security, (5) written in-service materials and training that allows for 24/7 pharmacy coverage of hospital studies and (6) familiarity with Good Clinical Practice guidelines and the ethical issues concerning human subject research.

The IDS also maintains a Biosafety Level-2 lab equipped with a certified biosafety cabinet and a minus 80 degree centigrade freezer. This facility is available to our investigators who may have an interest in the clinical application of biotechnology, such as stem cells or gene transfer therapies. Please let us know if you are considering this type of work so that we can work together to get up and running without unnecessary delay.

The Joint Commission (TJC) survey is expected soon. The accreditation standard that applies to investigational medications is MM.06.01.05. One element of performance requires that pharmacy control these agents. Please remember to keep these products separate and apart from regular inventory; keep them locked up and stored according to label directions. Daily temperature logs are required using a certified thermometer and accountability logs must be up to date. The IDS may do periodic inspections of investigational drug storage areas.

The IDS is also available to assist in investigator initiated studies. We can help with aspects of studies, such as blinding plans, randomization schedules, placebos and other drug protocol details. Contact us at (419) 383-3794 and we will help make sure you are in compliance with institutional requirements and our complex drug laws and regulations.

The IDS is funded in part by fees. Currently, the billing structure looks like this:
1. The initial pharmacy charge is $1,000.00. This applies only to funded extramural drug studies and is earned after IRB approval and contract reconciliation. This fee is not tied to enrollment. This is treated as a start-up expense and is paid by the sponsor.
2. There are also dispensing fees that are billed by the IDS. Oral, topical and inhaled dosage forms are $25.00 each and sterile products cost $75.00 (capped at $750.00 per subject per month).
3. For unusually complex protocols or intramural funded studies, please call us at 419-383-3794 and we will negotiate an agreement. Please be sure to budget appropriately.

In conclusion, the IDS is here to assist investigators in the study and management of investigational agents. From site qualification to study close, we look forward to helping our study teams in their delivery of world-class research. It is an honor to be a part of this noble endeavor that benefits science, our community, and our patients.

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Manuscripts in translational science requested for UT journal of medical sciences

Keith A. Crist *

*Editor, Translation

Translation: The UT Journal of Medical Sciences offers peer review by internal and external content experts and provides a citation for published work that is discoverable through Google Scholar. The journal accepts novel results from basic and clinical research, providing several advantages for projects having a limited time frame for completion.
- You do not need a large number of figures and tables
- Reviewers will not ask you to perform additional experiments
- The initial review is rapid, our goal is an initial 2 week cycle

Case reports will also be considered.

Currently, the average time for the first round of manuscript review is 14 days. Students, residents and faculty with applicable projects are encouraged to submit!

Starting in July, the journal will transition to its permanent home as part of the University of Toledo Digital Repository at utdr.utoledo.edu

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The Newly enrolling clinical trials

A prospective, multicenter, single blind, randomized, controlled trial comparing the lutonix drug coated balloon vs standard balloon angioplasty for treatment of femoropopliteal in-stent retenosis.
Dr. Burkett - Medicine

A Phase IIIb, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Alteplase in Patients with Mild Stroke: Rapidly Improving Symptoms and Minor Neurologic Deficits (PRISMS).
Dr. Zaidi - Neurology

A randomized, open label, parallel-group, multi-center trial to compare efficacy and safety of TachoSil® versus Surgicel® Original for the secondary hemostatic treatment of needle hole bleeding in vascular surgery.
Dr. Nazzal - Surgery

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Contact Us

Health Science Campus • Center for Creative Education Bldg.

2920 Transverse Drive, Floor 3 • Toledo, OH 43614

Phone: 419.383.6919 • ClinicalResearch@utoledo.edu