Rocket Science

Rocket Science is published annually by The University of Toledo College of Medicine and Life Sciences for alumni and friends of the college in cooperation with the UT Office of Marketing and Communication and the UT Alumni Association.

Editorial Board
Robert Mrak, MD, PhD, Editor-In-Chief
Esther Fabian
Howard Newman
Daniel Saevig

Writers
Meghan Cunningham
Cynthia Nowak
Jim Winkler

Photography
Daniel Miller

Design
Amanda Russell
Michelle Hoch-Henningsen
Creative Director

Rocket Science is supported by:
Division of External Affairs
Division of Institutional Advancement
Office of the Chancellor
Research Advisory Council

2011-2012 Board of Trustees
College of Medicine and Life Sciences Alumni Affiliate
Board of Trustees
Stephen Bazeley, MD (MED ’74)
Craig Burkhart, MD (MED ’75, EDU ’83)
Mark Burton, MD (MED ’74, Res ’77)
Heather Carone, MD (ARS ’97, MED ’01)
Andrew Casabianca, MD (MED ’88, Res ’92)
Kathy Franco-Bronson, MD (MED ’75, Res ’77)
Edward Goldberger, MD (MED ’86)
Randall King, MD, FACEP, (MED ’81)
Jason Levine, MD (MED ’00, Res ’05)
Thomas Padanilam, MD (MED ’91, Res ’96)
Kevin Phelps, DO (Res ’92)
Ralph Rosenberg, MD (MED ’79)
John Russ III, MD (MED ’80)
Shirish Shah, MD (Res ’78)
Beth White, MD, FACS (Res ’93)

To contact us
Editorial offices are located at UT’s Health Science Campus, 2280 Dowling Hall (attn. Dr. Mrak), Mail Stop 1090, 3000 Arlington Avenue, Toledo, Ohio, 43614. Please send story ideas or comments about the magazine to that address, or email them to cathie.harman@utoledo.edu.
Immunity, fighting infection...
See inside
1 HOW CAN WE MAKE EFFECTIVE DRUGS AND VACCINES AGAINST DANGEROUS MICROBES?

6 BETTER METHODS TO PROVIDE ORGAN TRANSPLANTS AND TO PREVENT THEIR IMMUNE REJECTION

10 CAMPUS CAPSULES

13 INFECTION, IMMUNITY & TRANSPLANTATION STUDENTS LEARN THROUGH DISCOVERY

14 BEYOND ALLERGY MEDICINE AND CREAMS FOR POISON IVY: CONTROLLING DISEASE BY TARGETING INFLAMMATION

19 FIGHTING DAMAGE IN THE FOURTH DIMENSION

22 CORE LABORATORIES PROVIDE STATE-OF-THE-ART INSTRUMENTS FOR CUTTING EDGE RESEARCH

24 EXPLORING THE REMARKABLE SURVIVAL SKILLS OF MICROBES

29 CLASS NOTES
This fourth issue of Rocket Science highlights some of the research being done at The University of Toledo that addresses immunity.

Research is so important to what we do in the College of Medicine and Life Sciences. Our faculty and students are engaged in research across disciplines and across institutions. Research is a part of the fabric of the university medical center — institutions like ours hold the future of health care in our hands.

As we continue our quest to become a member of the Club of 100 — the top university medical centers in the United States, research remains a vital stepping stone in getting there. The culture of these Health Science Centers is distinguished by:

• Shared mission, culture and values of excellence in all education, translational research and clinical care entities

• Stable economics and ongoing investment in sustaining and growing the culture of academic and clinical excellence

• Full-service and high-quality clinical and academic programs — the choice made by patients & students with choice

• Strong, synergistic and interlocking governance and senior leadership team structures with horizontal integration

• Tight alignment of university, hospital and physicians — all with a strong regional, national and international distinction

• World-class physicians and scientists working in quality facilities in an economically thriving community

In 2012 UT Medical Center was recognized by US News & World as the number one hospital in the region. Seven specialties were cited: Ear, Nose and Throat; Geriatrics; Kidney Disorders; Neurology and Neurosurgery; Orthopedics; Pulmonology; and Urology. Our impressive clinical outcomes, coupled with an unprecedented service-excellence program and facilities improvement initiative, make for an excellent patient experience rivaled by very few other health-care delivery systems.

Thank you for your continued interest in and support of The University of Toledo College of Medicine and Life Sciences. Please continue to share your own news and updates with us, and if you find yourself in the area, please stop by.

Sincerely,

Jeffrey P. Gold, M.D.

Chancellor and Executive Vice President for Biosciences and Health Affairs,
Dean of the College of Medicine and Life Sciences
How can we make effective drugs and vaccines against dangerous microbes?

By: Cynthia Nowak
If the body’s natural immune responses represent the first line of defense against dangerous microbes, drugs and vaccines represent the secondary line, the elite troops that boost the effects of the primary attack. Such designer drugs, based in large part on molecular research, would send pioneers of medicine like Pasteur into a swoon.

The vaccine Pneumovaxâ, commonly used against Streptococcus pneumoniae, is a case in point. As UT researcher Dr. M.A. Julie Westerink, professor in the Department of Medicine and chief of the Infectious Diseases Division, explains, “Pneumovax, which been on the market for decades, is a subunit vaccine consisting of an outer portion of bacterium that causes protective immunity acquired against pneumococcal pneumonia.”

The incidence for streptococcal pneumonia, she adds, is very high in infants, but this then declines dramatically and stays down until people reach about 50. At that time it slowly creeps up, spiking after age 70; thus the recommendation that all people over age 65 receive a pneumonia vaccine.

However, another population that began showing a dramatic rise in streptococcal pneumonia in the 1980s was HIV-infected individuals, who had a hundred-fold increase in incidence compared with non-infected people of their age group. The University of Toledo Medical Center treats approximately 750 HIV-infected individuals in northwest Ohio, the largest such population for any hospital in the city and surrounding area.

“We routinely give pneumonia vaccines to the elderly as well as to the HIV-infected,” Westerink says. “What’s paradoxical is that those are the two populations that historically don’t respond well to the vaccine; they still develop pneumococcal disease despite vaccination, and when you measure their antibody response by measuring the amount their bodies make, overall it’s not significantly different from healthy individuals of their age.

“When you look at how well the antibody works, though, you see a significant decrease. People who are older, or HIV-infected, make the antibodies in their systems, but the antibodies are not very active and do not protect well.”

Her lab is investigating why, with a goal of developing a method of changing the immune response for both groups. “It’s probably a different answer for each,” Westerink says.

The HIV-infected population poses a special challenge, she notes. “Although HIV is thought of as a T cell immunodeficiency disease, pneumococcal diseases, [where the immune response is] mediated by B cells, are the big exceptions. You don’t really need T cells to make an immune response to this. So why are people with HIV so susceptible?”

What HIV does, she explains, is to non-specifically stimulate a certain subpopulation of B cells, those characterized by having immunoglobulin belonging to the VH3 gene family on their surface. Through their continual stimulation, the cells begin dying off, leaving a gap in the immune system of the individual, who by this time has AIDS.

“They’re totally depleted of this specific subset of B cells that carry the VH3 immunoglobulin,” Westerink says. “VH3 is extraordinarily important in protection against [a number of] organisms that include streptococcus pneumonia.”

Streptococcus organisms carry important antigens made of carbohydrates, and VH3 is the predominant immune response in healthy individuals against carbohydrate antigens, so the loss of these VH3-positive B cells in HIV-positive individuals may explain their inability to respond well to the pneumonia vaccine.

When people become infected with HIV, there is an early disarray in the B cell immunity. There is stimulation of the subset of VH3-expressing B cells, which begin multiplying wildly while producing immunoglobulin. The immunoglobulin is not directed against any one specific protein or microbe or parasite; it’s nonspecific, providing no disease protection. These cells are stimulated, but the HIV infection progresses nonetheless.

Through their continual stimulation, the cells begin dying off, leaving a gap in the immune system of the individual, who by this time has AIDS. “They’re totally depleted of this specific subset of B cells that carry the VH3 immunoglobulin,” Westerink says. “VH3 is extraordinarily important in protection against the organisms that cause streptococcus pneumonia; against all carbohydrate antigens, VH3 is the predominant immune response.”

As a clinical practitioner as well as a researcher, the questions raised have immediate application for Westerink: “We know Pneumovaxâ doesn’t do very well, particularly in patients with a CD4 count lower than 200, which is called AIDS. The treatment recommendation is that they should be vaccinated with Pneumovaxâ as soon as possible; the question is whether it’s better to treat them with antiviral treatment before we vaccinate them.

“Will we get a much better immune response if we do that, then wait for half a year before vaccination? That means first we’d get rid of all the HIV virus circulating in their blood. Are they then better able to respond? Another important question is at what point do people lose their ability to respond to the vaccines?”
Could a vaccine be given right at the time we think there’s been a bioterrorist attack?

Dr. Jason Huntley, assistant professor of medical microbiology and immunology, adds, “There are probably a lot of good vaccines out there, many still in research and development, that are not 100 percent effective because they catch the individual at the wrong time — or they generate antibodies, but not the right ones.”

In vaccine development, he notes, a researcher may have a vaccine that is only moderately effective, but minor alterations can change the quality and quantity of antibodies produced in response to the vaccine, making the vaccine much more efficacious.

“So it’s become much more complex than taking a bacteria, killing it and injecting it,” he says. “Now we’re going down to the molecular level and identifying proteins we think might make a good vaccine. We look at the immune responses generated to those proteins — then, based on that, can we tilt the scales so we get more of a certain antibody type? This way, it becomes possible to turn an ineffective vaccine into an effective one. Even better, we can assess the immune situation of that person, and wait for the right time.”

His own work focuses on aspects of membrane proteins on the surface of the bacterium Francisella tularensis, which is high on the U.S. government’s list of Category A Select Agents, a group of high-threat agents that also includes anthrax, botulism and plague. Capable of surviving in species ranging from freshwater amoebae to flies, ticks, mammals and humans, F. tularensis is the cause of tularemia, which can kill an adult in as little as five days.

Researchers working with biodefense vaccines, Huntley says, have a sense of urgency: “Can we develop new vaccines that will very quickly elicit antibodies? Could a vaccine be given right at the time we think there’s been a bioterrorist attack? There are ways to do both, but it means once again going down to the molecular level, asking what immune responses are needed to kill the pathogen, and designing new vaccines so that we don’t get other immune responses that don’t matter.”

Vaccine development is thus a very targeted process, he says. Knowing what particular immune response is needed is one major focus. The second focus is to identify the neutralizing target(s) on the bacteria. Huntley’s lab studies molecules on the bacteria surface because these are most likely to promote virulence — including attachment and invasion of host cells, secretion of virulence factors or toxins, and disease progression.

“The theory is that if we study those particular molecules we can develop vaccines that will stimulate immune responses blocking virulence factor function and clear infections. Vaccines can also teach T cells how to recognize those virulence proteins and destroy the infected cells,” he says.

“Francisella is one example, but these techniques can be applied to any bacterial pathogen. They all have surface proteins. In fact, there are a lot of similarities between these surface proteins among bacteria, so sometimes the information we get from studying one bacteria can be applied to other bacteria, especially, say, for respiratory bacteria or gastrointestinal bacteria. If there’s a protective immune response that’s elicited by one vaccine, sometimes you can extend that to other bacteria.”
Dr. Richard Komuniecki studies many tropical diseases, many caused by parasites that exhibit substantial genetic variability.
he limitations of vaccines are a daily concern of Dr. Richard Komuniecki, Distinguished University Professor of Biological Sciences, as he continues his work on what he calls neglected tropical diseases: geohelminths, schistosomiasis, river blindness, elephantiasis and intestinal parasites.

Schistosomiasis alone affects at least 240 million people worldwide, and more than 700 million people live in endemic areas. This parasitic disease, like many that Komuniecki studies, causes chronic illness rather than immediate mortality.

“The World Health Organization uses the disability-adjusted life year (DALY) as a measure of overall disease burden, expressed as the number of years lost due to ill health, disability or early death,” he explains. Nearly three out of four countries with at least one neglected disease are visited by two or more of these diseases. Africa is believed to bear approximately 90 percent of the global burden of neglected diseases.

Komuniecki, who concentrates much of his work on parasitic worms, is all too aware of what vaccines can and cannot do to eradicate such diseases. “A few years ago, everyone decided that we’d have vaccines, so we wouldn’t need drugs for ongoing treatment anymore,” he says.

“But we have no vaccines today for many of these diseases, and we won’t in the near future. Many of these parasites exhibit substantial genetic variability, often as well as what’s called molecular mimicry. The parasites have lived in concert with their hosts for so long that many of their surface antigens have been selected to look like host antigens, and in some cases the parasites even stick host proteins to their surface, in effect camouflageing themselves.

“So vaccine development is a lot further away than we thought a few years ago.”

Whereas Komuniecki previously studied the parasites themselves, his lab now uses a dual-systems approach that relies on an easy-to-grow, free-living nematode called Caenorhabditis elegans. C. elegans is used as a model for human diseases such as Parkinson disease, and work on C. elegans has resulted in a number of recent Nobel Prizes in medicine.

Africa is believed to bear approximately 90 percent of the global burden of neglected diseases.

By applying knowledge of molecular genetics, Komuniecki and his team are working on identifying core signaling pathways in the nematode. Twice the Chair of the Tropical Medicine Study Section at the National Institutes of Health, he’s taking what has been learned from C. elegans and applying it to parasites — “because in the last five years a number of genomes have been sequenced from parasitic nematodes, so we can go in and see if core signaling drug targets are conserved across the phylum.”

He continues, “As we work to define the inner machinery that controls for locomotory decision-making in C. elegans, we’ve identified serotonin-like compounds that rapidly paralyze the worm, suggesting that the receptors for these compounds may be good targets for drug discovery. Current drugs cause either a spastic paralysis where the muscles clench and the worm goes stiff, or a flaccid paralysis where the muscles relax.

“The compounds we’ve developed here don’t do either — they do what I call confusion paralysis. The worm is not so much paralyzed as strongly convinced not to move. Part of the worm wants to move forward and the other part wants to move backward. The net result is that the worm is sitting there being ‘intellectually’ convinced by the drug not to move — if a worm with only 300 neurons can be intellectually convinced of anything.”

Their initial assumption has been shown as correct: Core signaling pathways are highly conserved across the phylum. “We can take a mutant gene in C. elegans and rescue it with a gene from a parasite. That’s sort of cool, because these nematodes diverged hundreds of millions of years ago; there’s almost as much diversity among [these organisms] as there is between the nematodes and humans.”

His lab has pioneered this dual-systems approach, with at least one grant sponsor calling the work a paradigm shift. In fact, as the C. elegans molecular tool kit has grown, Komuniecki has expanded his research into more cell-based approaches using direct imaging of live worms and electrophysiology to confirm his genetic observations on potential drug targets.
BETTER METHODS TO PROVIDE ORGAN TRANSPLANTS AND TO PREVENT THEIR IMMUNE REJECTION

By: Cynthia Nowak
Despite impressive new developments in transplantation technology, the numbers of people waiting for organ transplants continue to grow. Donate Life America offers startling statistics: More than 113,000 American men, women and children currently need life-saving organ transplants; every 10 minutes another name is added to the national organ transplant waiting list; and an average of 18 people die each day from the lack of available organs for transplantation.

Dr. Michael Rees, professor of urology, vice chair of Department of Urology, and director of the UTMC transplant program, cites more stats: “Every year in America, more than 120,000 people are diagnosed with kidney failure. In 2009, Medicare spent $29 billion treating people with end-stage renal disease, more than 6 percent of its entire budget.”

Rees’ name has become nationally linked with organ transplantation — specifically kidney transplants — through his creation in 2006 of the Alliance for Paired Donation Inc., which utilized an advanced computer program to match patients and donors.

Today, the alliance boasts 80 participating transplant centers in 30 states. “It has resulted in more than 120 kidney transplants that otherwise would not have been performed, with about 25 of them done at UTMC,” Rees notes.

In 2007, the alliance came up with a new concept: the non-simultaneous extended altruistic donor chain, featured in a the New England Journal of Medicine in 2009. The first transplant in this program garnered national attention in USA Today. The second pair of operations in this chain of transplants happened a week later at the UT Medical Center, with a crew from ABC World News with Charles Gibson at the hospital to cover it. In each instance, family members who weren’t able to donate a kidney to help their loved ones signed up to “pay it forward” by donating the organ to someone else in need.

The combination of the alliance’s computer program and the altruistic donors created the possibility of a “never-ending kidney transplant chain,” says Rees. The alliance now has 50 “bridge” donors who bridge the time gap between one series of “pay it forward” transplants and the next. What is unique about these bridge donors is that they have to be trusted to donate their kidney after their loved one has already received a transplant.

With national partnerships being forged yearly, Rees adds, these chains have become the most common way of doing kidney donations in America.

However, the donor gap is only one of the challenges associated with organ transplants. Allograft rejection by the recipient’s immune system has been a key problem since the earliest transplantation attempts. An allograft —the most common type of human tissue and organ transplant —is a transplant between two genetically non-identical members of the same species. Due to the genetic differences between the donated organ and the recipient, the recipient’s immune system will identify the organ as foreign and immediately attempt to destroy it, causing transplant rejection. Dr. Stanislaw Stepkowski, professor of medical microbiology and immunology, has devoted some 20 years to developing immunosuppressive drugs to prevent allograft rejection.

“Our immune systems begin to develop in the fetal stage,” he explains. “After birth, a body continues to learn how to accept own tissues. One might say that it’s educated in tolerance, based on recognizing its own tissue and rejecting those that are foreign. Because of this, we have to use immunosuppressive drugs following transplantation of hearts, kidneys and other organs to ensure that the foreign tissue is not rejected.”

Dr. Stanislaw Stepkowski’s research publication was recently accepted by the American Journal of Transplantation. His goal is to mimic the fetal re-education mechanism for the subset of the body’s immune system called T cells.

THE DONOR GAP IS ONLY ONE OF THE CHALLENGES ASSOCIATED WITH ORGAN TRANSPLANTS.
The development of such drugs, he says, exploded as researchers learned how to use them in combination with each other, increasing the effectiveness of the therapy as compared to therapy based on a single drug — while reducing the side effects of each drug.

At present, patients treated with drugs to prevent rejection must continue to receive them daily for the rest of their lives. Stepkowski hopes to develop a limited-time treatment to induce permanent acceptance, called transplantation tolerance, which would change the immune system so that an allograft would be accepted in the same way people accept tissues from their own body.

Equally important, however, is that the immune system remains intact to defend the body against viruses and bacteria. Theoretically, Stepkowski says, it is possible to totally destroy the immune system to create permanent acceptance of the allograft — “but that is not going to help us if we become infected with outside agents. So we have to very selectively induce this reprogramming so that only the foreign parts of the allograft will be accepted as our own cells.”

His lab’s approach — as elaborated in a publication recently accepted by the American Journal of Transplantation — is to mimic the fetal re-education mechanism for the allograft. The body’s immune system called “T cells” (the cells that actually recognize and destroy allografts), using a drug therapy with an anti-T cell receptor monoclonal antibody. This therapy forces the immune system to eliminate those T cells that recognize the allografts as foreign, at the same time expanding protective T cells called regulatory cells.

The uniqueness of this approach lies in the way it protects regulatory cells that maintain the balance of the immune system, while eliminating the aggressive T cells that are activated by the allograft. In the laboratory, a similar approach has been successful in preventing development of type 1 diabetes and blocking onset of disease in two mouse models. Although rejection of an allograft and development of type 1 diabetes seem very different, they possess a common mechanism, as both are mediated by T cells.

Stepkowski and Rees are collaborating on a project relating to T cells called regulatory cells. His lab’s approach — as elaborated in a publication recently accepted by the American Journal of Transplantation — is to mimic the fetal re-education mechanism for the allograft. The body’s immune system called “T cells” (the cells that actually recognize and destroy allografts), using a drug therapy with an anti-T cell receptor monoclonal antibody. This therapy forces the immune system to eliminate those T cells that recognize the allografts as foreign, at the same time expanding protective T cells called regulatory cells.

The uniqueness of this approach lies in the way it protects regulatory cells that maintain the balance of the immune system, while eliminating the aggressive T cells that are activated by the allograft. In the laboratory, a similar approach has been successful in preventing development of type 1 diabetes and blocking onset of disease in two mouse models. Although rejection of an allograft and development of type 1 diabetes seem very different, they possess a common mechanism, as both are mediated by T cells.

Stepkowski and Rees are collaborating on a project relating to T cells called regulatory cells. His lab’s approach — as elaborated in a publication recently accepted by the American Journal of Transplantation — is to mimic the fetal re-education mechanism for the allograft. The body’s immune system called “T cells” (the cells that actually recognize and destroy allografts), using a drug therapy with an anti-T cell receptor monoclonal antibody. This therapy forces the immune system to eliminate those T cells that recognize the allografts as foreign, at the same time expanding protective T cells called regulatory cells.

The uniqueness of this approach lies in the way it protects regulatory cells that maintain the balance of the immune system, while eliminating the aggressive T cells that are activated by the allograft. In the laboratory, a similar approach has been successful in preventing development of type 1 diabetes and blocking onset of disease in two mouse models. Although rejection of an allograft and development of type 1 diabetes seem very different, they possess a common mechanism, as both are mediated by T cells.

Stepkowski and Rees are collaborating on a project relating to T cells called regulatory cells. His lab’s approach — as elaborated in a publication recently accepted by the American Journal of Transplantation — is to mimic the fetal re-education mechanism for the allograft. The body’s immune system called “T cells” (the cells that actually recognize and destroy allografts), using a drug therapy with an anti-T cell receptor monoclonal antibody. This therapy forces the immune system to eliminate those T cells that recognize the allografts as foreign, at the same time expanding protective T cells called regulatory cells.
U.S. News names UTMC as area’s best hospital

U.S. News and World Report recognized The University of Toledo Medical Center as the best hospital in the Toledo metro area for 2011-12. The magazine ranked UTMC as a high-performer in seven clinical specialties, the most of any institution in the area.

“It is clear that U.S. News understands what the Toledo community already knows: The University of Toledo Medical Center offers patients superior care, a great experience and a higher degree of healing,” said Dr. Scott Scarborough, senior vice president and executive director of UTMC. “Caring for patients is a team effort, and this is an accomplishment that the entire team should be proud of,” Scarborough said.

U.S. News listed UTMC as a high performer in: Ear, Nose and Throat; Geriatrics; Kidney Disorders; Neurology and Neurosurgery; Orthopedics; Pulmonology; and Urology.

UTMC Wound Care and Hyperbaric Center opens

The University of Toledo Medical Center now offers the region’s first multiple patient hyperbaric chamber with the opening of the new Wound Care & Hyperbaric Center in February.

“The Wound Care and Hyperbaric Center brings together specialists from across UT Medical Center to provide patients with the best possible care for their wounds and ulcers,” said Dr. Munier M.S. Nazzal, medical director of the Wound Care and Hyperbaric Center and chief of the UTMC Division of Vascular and Endovascular Surgery. “The unique large hyperbaric chamber allows our center to treat more patients in a more comfortable environment with the latest technology available.”

Hyperbaric oxygen therapy is a treatment method in which the patient breathes 100 percent oxygen while at increased atmospheric pressure inside a hyperbaric chamber. The therapy is used for a variety of conditions, including diabetic ulcers, radiation tissue damage, and crush injuries and severed limbs, as well as emergency treatments for carbon monoxide and cyanide poisoning.

The new hyperbaric chamber at UTMC, Model OxyHeal 8000-10, is designed to treat up to 10 seated patients simultaneously. The “Omega” shaped geometry of the chamber also provides the option to treat up to four patients lying down.

The large chamber, which is 21 feet long and 10 feet wide, is the first of this type in the United States and the only multiple patient hyperbaric chamber in northwest Ohio.
Researchers’ new spinal implant device means minimally invasive surgery, faster recovery

Surgery to repair one of the most common causes of lower back pain will be shorter, have less risk of complications, and result in faster patient recovery times, thanks to a novel device developed at The University of Toledo.

UT researchers Dr. Mohammad Elahinia and Dr. Vijay Goel have created a minimally invasive intervertebral device that eliminates the need for a large surgical opening because of its new design, allowing surgeons to remove a much smaller portion of bone when performing surgical spinal implants, called a cage.

“Our cage is different because it is comprised of a chain of linked segments connected by hinges, and it is inserted vertically or horizontally into the inter-vertebral cavity one link at a time,” said Elahinia, lead researcher and UT associate professor of mechanical, industrial and manufacturing engineering who also serves as director of the Third Frontier Project Nitinol Commercialization Accelerator to advance the development of products made from the alloy of nickel and titanium.

“This allows for an incision as small as 6 millimeters wide and 10 to 20 millimeters high.”

Goel, UT professor and chair of orthopedic bioengineering, said the unique design of the cage is a clear improvement over current devices because it allows for easier insertion and faster, safer recovery for patients.

“Because of the smaller, single incision, this device minimizes the risks of spinal fluid leak and penetration of the dura, the outer layer of the spinal cord,” said Goel, who in addition to working with Elahinia serves as co-director of the Engineering Center for Orthopedic Research Excellence (E-CORE) in UT’s colleges of Engineering and Medicine and Life Sciences.

“It eliminates the need to remove all or most of the spinal and vertebral structures to operate and, therefore, it increases the overall structural stability and reduces risks.”
Scientists attend international plastination conference at UT

The University of Toledo was the center of international plastination technology in July when it hosted the 10th International Interim Conference on Plastination, which featured oral presentations, poster sessions and three half-day workshops for scientists and researchers from 23 countries and six continents.

Dr. Carlos Baptista, UT associate professor of neurosciences, serves as president of the International Society for Plastination and coordinated the conference, which also had special exhibitions open to the public.

Plastination is a technique by which bodies and body parts are preserved in plastic without destroying the composition and structure of the tissues. Plastinated specimens are used as models and teaching tools for students in any field requiring gross anatomical studies. They also can be used for training students in medical procedures or to show what actual body parts look like in comparison to imaging tools, such as computed tomography and magnetic resonance imaging.

UTMC receives recognition for stroke care

The University of Toledo Medical Center was recognized for the seventh consecutive year for its excellent care of victims who have suffered a stroke.

The University has received the 2011 Stroke Gold Plus Performance Award from the American Heart Association/American Stroke Association.

“The UT Medical Center was one of the first institutions to be recognized for meeting the standards in 2004, and we have continued to not only meet but exceed them for now seven consecutive years,” said Dr. Gretchen Tietjen, professor and chair of Neurology, and director of the Stroke Program and of the Headache Treatment and Research Program. “This is a measure of quality of care, and people can be assured by our track record and consistency in achieving this accomplishment.”

The award recognizes a hospital’s commitment to and success in implementing excellent care for stroke patients. Qualifying hospitals have achieved at least 85 percent or higher adherence to a set of guidelines in stroke patient care. The standards include treatments such as providing aspirin, blood thinners and cholesterol-lowering medicines to qualifying patients to lessen the impact of a stroke or prevent a recurrence, as well as education efforts, such as smoking cessation counseling, for the patient’s continued health.

The UTMC Stroke Program, established in 1994, was the area’s first such center and it now treats an average of 300 stroke patients each year.

UT announces advanced $36 million simulation center

The University of Toledo will commit to the development of a new multi-million dollar Interprofessional Immersive Simulation Center that will enable students and clinicians to use cutting-edge technology to allow teams to learn, enhance outcomes, and improve patient safety in a simulated, low-risk environment.

Working with the University’s economic development arm, Innovation Enterprises, UT will establish the Interprofessional Immersive Simulation Center that will be housed in a new three-story facility slated to open in 2012 next to UT’s Center for Creative Education Building on Health Science Campus.

The center will place UT among the first health-science campuses in the nation to incorporate I-Space, a four-sided virtual immersive room with 3-D computer-aided design walls. This technology can create an unlimited number of virtual images that allow learners to travel through the heart of a human body or experience being inside a human blood cell.

The new facility will be unique in that it will be comprised of three integrated simulation centers: a progressive anatomy and surgical skills center, an advanced simulation center, and the virtual immersive reality center. Typically, academic health centers offer only one type of simulation center.
Infection, Immunity & Transplantation students learn through discovery

By: Meghan Cunningham

The cure for type 1 diabetes could be right around the corner and Paul Schroder, a graduate student in the Infection, Immunity and Transplantation track in the UT College of Medicine and Life Sciences, wants to be part of its discovery.

Schroder, who is in the combined M.D./Ph.D. degree program, is working with Dr. Stanislaw Stepkowski, professor of Medical Microbiology and Immunology, to investigate T-cell directed therapies to prevent and cure type 1 diabetes.

T-cells — or T lymphocytes — are a major defense component of the human immune system that protects us from pathogen infections, but in some conditions such as type 1 diabetes or organ transplants, they play a role instead attacking a part of the body when they should not. The research underway at UT is investigating how to adjust or limit their responses.

“Type 1 diabetes is one of the most common illnesses and there is a cure on the horizon,” Schroder said. “Insulin therapy has existed for the past 60 years to control the illness, but there has to be a better way and I truly believe we are on the cusp of finding it. I want to be part of that discovery.”

All graduate students in the Infection, Immunity and Transplantation track work in the labs closely with researchers incorporating discovery into their education. The discipline investigates microorganisms that are relevant to human health and the immune system that allows humans to overcome infection.

David Leggat, who is pursuing his PhD, focuses his attention on B-cells, a type of immune cell that produces antibodies.

The standard vaccine for Streptococcus pneumoniae addresses the 23 most common disease causing strains associated with the bacteria and is recommended for adults over 65 years of age and people whose immune systems are compromised.

Leggat’s research with Dr. Julie Westerink, professor and chief of the Infectious Diseases Division, involves giving the vaccine to healthy young adults, the elderly and those who are compromised with HIV. Their goal is to compare these B-cells one week and one month later to test the immune response and the long-term effectiveness of the vaccine to improve vaccine strategies.

“Vaccines are interesting,” Leggat said. “Successful vaccines can protect people, a wide variety of people ahead of time. When they work, they work well.”

The myriad research projects in the Infection, Immunity and Transplantation track give graduate students a variety of avenues to explore.

JP Lavik, also in the combined M.D./Ph.D. program, is tracking how the bacterium Borrelia burgdorferi spreads through tissue to better understand Lyme disease.

Working closely with Dr. Mark Wooten, associate professor of Medical Microbiology and Immunology, Lavik visualizes how the bacterium moves through the skin of living mice in real time using a multi-photon confocal microscope in the Advanced Microscopy and Imaging Center.

There is a big difference between how a bacterium behaves in a test tube and in a living host, Lavik said, and observing its activity in anesthetized mice allows the research team to more accurately learn about the progression of the disease and the accompanying immune system response.

The complement system is the focus of research for Garpanna Saggu, who is pursuing her PhD. The complement system, a part of the innate immune system, is composed of a series of proteins in the blood that are essential for elimination of pathogens as well as dead and dying cells from our bodies.

Complement activation also leads to generation of pro-inflammatory mediators, which are essential in recruiting inflammatory cells to sites of infection or tissue damage. Although a controlled amount of inflammation is necessary for an immune response, it can become harmful if it is excessive. Certain blood proteins can regulate complement so that excessive pro-inflammatory products aren’t generated. In patients with myocardial infarction and other chronic inflammatory diseases, a lot of the tissue damage is due to complement activation.

Working with Dr. Viviana Ferreira, assistant professor of Medical Microbiology and Immunology, Saggu’s work centers on discovering and understanding molecular mechanisms of activation of the complement system, and how this activation can be inhibited to avoid potential pathological consequences of excessive inflammation.

Saggu, who received her undergraduate and master’s degrees in India, said she enjoys the hands-on research afforded to her in the UT program.

The Infection, Immunity and Transplantation track encourages researchers, including graduate students, to move their fundamental research findings from the lab to the hospital bedside to improve people’s health and well-being.
Beyond allergy medicine and creams for poison ivy:
BEYOND ALLERGY MEDICINE AND CREAMS FOR POISON IVY:
CONTROLLING DISEASE BY TARGETING INFLAMMATION

BY: CYNTHIA NOWAK
Inflammation as a physiological phenomenon remains a double-edged sword. Although inflammation is a natural and beneficial reaction of the body to foreign agents and to other challenges, unchecked inflammation can ravage tissue and create permanent damage.

Three University of Toledo researchers in the Department of Medical Microbiology and Immunology are focusing their work on the processes that create inflammation, applying that knowledge toward the control of specific diseases.

The studies of Dr. Viviana Ferreira, an assistant professor, center on a part of the innate immune system called complement. The complement system is comprised of a number of blood proteins and enzymes, and is essential for an effective immune response to invading microorganisms. The complement system is activated in a cascade-like process that leads either to direct killing or to opsonization of the pathogen. Opsonization is a process by which complement proteins are deposited on pathogens, allowing phagocytic cells to more readily engulf (and subsequently kill) the pathogen. This complement opsonization process is also essential for the removal of dead and dying cells from the body.

Another important consequence of complement activation is the generation of pro-inflammatory mediators such as C5a and C3a. These are cleavage byproducts of complement activation that are essential for recruiting inflammatory cells (such as neutrophils and macrophages) to sites of infection or tissue damage.

“Inflammation is one of the first responses of the immune system to infection or irritation,” Ferreira explains. “A measured amount of inflammation is acceptable and necessary for the immune response, but it can get out of control. Thus we have certain proteins in our blood and on our cells that allow us to control the formation of the pro-inflammatory complement-derived products so excessive inflammation is not generated.”

She points to patients who have suffered myocardial infarctions (heart attacks): “Their bodies form lesions produced when tissue is deprived of oxygen. It is known that complement activation is responsible for much of the tissue damage, but the specific mechanisms of why complement activation cannot be controlled at this stage remain largely unknown.”

Complement-mediated damage also contributes to the pathology observed in most chronic inflammatory diseases, including age-related macular degeneration, atherosclerosis, Alzheimer disease and rheumatoid arthritis.

Ferreira’s lab is working on understanding the molecular mechanisms of activation of the complement system: the means by which different targets are identified by complement, how complement is regulated by certain proteins, and how mutations in these regulatory proteins can lead to disease.

“The long-term goal of my research 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 or by enhancing its activity on unwanted cells such as microbes or cancer cells,” she says, noting that there are presently two FDA-approved drugs that either inhibit or regulate the complement system, with many more drugs in various stages of development.

Dr. Randall Worth, also an assistant professor, works on the autoimmune disease known as systemic lupus erythematosus, commonly called lupus. Although the cause of lupus is still unknown, what is known is that the immune system of lupus patients attacks the same body cells and tissues it should be protecting from foreign pathogens.

Once commonly fatal, lupus today can be controlled with steroid therapies, but it remains a periodic disease, with peaks and valleys of symptoms — among them a susceptibility to thrombosis. Worth’s area of study is the interface between thrombosis and inflammation.

He begins with platelets, the cells responsible for clotting. Produced in the bone marrow, platelets possess no nucleus, no DNA, no changing gene expression. They can, however, change the transcripts of messenger RNA molecules (mRNA), the key intermediaries in gene expression that translate DNA’s genetic code into protein-making amino acids.

Platelets also express a single FC-receptor, found only in humans, that detects and binds antibodies. Earlier researchers found this receptor, cloned it, and published the results, but then largely abandoned the subject. When Worth came across the literature, he says, he was intrigued: “As far as I knew, all platelets do is clot; why would they express a receptor for an antibody?”

Even more intriguing were the results when his lab added small groups of antibody complexes to platelets: “The platelets don’t activate, don’t get sticky like a clump or clot, but they
do produce very potent inflammatory cytokines that can affect [the inflammatory cells] B cells, macrophages and T cells.

“Platelets outnumber just about every type of cell in the blood. If you can start a reaction with the platelets, you’ll end up with many, many cytokines that could stimulate an immune response.” That quantity of platelets is important in lupus, he explains, because the disease is caused by the formation of immune responses resulting in antibodies that recognize and attack parts of a patient’s own body — including platelets.

In the blood of lupus patients, platelets possess numerous surface antibodies. Worth’s group is attempting to correlate the presence of the FC-receptor that recognizes antibodies with the antibody-antigen complexes found in the circulation of lupus patients. Presumably, Worth says, the anti-DNA antibodies that are found in the blood of lupus patients form complexes that bind onto platelets and trigger production of cytokines that begin activating cells around them.

Inflammatory cytokines are also central to the work of Dr. Zhixing Kevin Pan, professor and director of the Infection, Immunity and Transplantation Graduate Track, which focuses on new treatments for sepsis and septic shock.

The typical road to develop new medications used in treatments, he notes, is a long one that can cost billions of dollars and take decades of research. To bypass this process, his lab uses drug repositioning strategy. He explains, “Researchers take an existing drug and, by using the same dosages that are approved for clinical use by regulatory bodies, perform experiments to determine whether the drug can be used for other diseases. In these cases, because much of the work has already been done in approving the drugs, it becomes much easier for regulatory agencies to grant the use of an already approved drug for new purposes.”

His own researchers apply this strategy to their work in sepsis, a bacterial infection of the blood stream characterized by fever, hypotension, and a type of uncontrolled clotting known as disseminated intravascular coagulation (or DIC). Sepsis can lead to multi-organ failure and death. Approximately 750,000 cases of severe sepsis occur annually in the United States, with a mortality rate of around 30 percent.

“Every year we spend billions of dollars to manage this disease,” Pan says. “In addition, inappropriate antibiotic treatments have contributed to the worldwide emergence of antibiotic-resistant bacterial strains. Therefore, development of novel therapeutic strategies is urgently needed.”

Worth’s guess is that platelets may act as a catalyst for the entire process. In his lab, researchers use a normal clotting agent to stimulate platelets of both lupus patients and healthy subjects. He says, “When we added an antigen-antibody complex to healthy platelets, they responded just like lupus platelets. We think the presence of these immune complexes, in addition to producing these cytokines and participating in the inflammatory properties, puts the platelet in a state that’s hypersensitive to thrombosis, so any small change in normal thrombotic stimuli that wouldn’t affect a healthy platelet is causing the lupus platelets to form a clot. When we added an antigen-antibody complex to healthy platelets, they responded just like lupus platelets. This may be one explanation why lupus patients are predisposed to various clotting disorders.”

"DEVELOPMENT OF NOVEL THERAPEUTIC STRATEGIES IS URGENTLY NEEDED"
FIGHTING DAMAGE IN THE FOURTH DIMENSION

BY: CYNTHIA NOWAK
We do not yet understand how skin — the largest organ of our bodies — protects itself from disease.

Careful scrutiny of the skin will reveal a remarkable utilitarianism that borders on beauty.

Certainly the skin protects the body's internal environment from external damage rendered through physical injury, infections, toxic chemicals and ultraviolet radiation. Serving as a physical barrier, skin as well is a functional boundary, a role illustrated by a living network of entities called Langerhans cells: dendritic cells that are present in the outermost layer of skin. Although the precise function of dendritic cells is still debated, the specialized Langerhans cells in general are active in the capture, uptake and processing of antigens.

Studies of Langerhans cells conducted by Dr. Akira Takashima, professor and chair of the Department of Medical Microbiology and Immunology, have led to the development of a striking new scientific tool: four-dimensional, real-time color visualization of the movement of Langerhans cells.

"Initially we used transgenic mice, genetically engineered so that only Langerhans cells express enhanced green fluorescent protein, or EGFP," Takashima explains. EGFP is a protein composed of 238 amino acid residues that exhibits bright green fluorescence when exposed to ultraviolet blue light. This technique allows researchers to visualize Langerhans cells in real time in the skin of living mice. The researchers decode the microscopic images at regular intervals, combining the data to create a video.

"Using that model, we learned that Langerhans cells are anything but static or dead," Takashima says. "The cells extend their dendritic processes almost constantly. If you injure the skin, that motile behavior is significantly augmented, because the job of Langerhans cells is to monitor the unusual signals of the skin that signify some threat. The cells respond by changing their behavior."

A newer method now allows Takashima and his team to monitor Langerhans cells' behavior without using an animal model, he adds: "We injected wild-type animals with a yellow fluorescently-packed probe; it's actually material that would be internalized by Langerhans cells. After a few hours, you're able to see under the microscope only those cells that have incorporated the fluorescence."

Takashima, who also serves as director of the Ohio Center for Innovative Immunosuppressive Therapeutics, notes that although the probe-injection method hasn't yet been medically approved, its application potential is wide.

"My collaborator is a dermatologist in Arizona who studies photo-damaged skin and runs a clinic specializing in the treatment of skin cancer," he says. "One of his patients is funding a method to monitor the progress of sun-induced skin damage. What I suggested to him was to use the behavior of Langerhans cells as a way of monitoring that damage."
A fellow UT researcher who saw immediate potential in Takashima’s four-dimension visualizations is Dr. Mark Wooten, associate professor in the Department of Medical Microbiology and immunology and director for immunity and infection, and director of BSL3 Core Laboratory. One area of his research is Lyme disease, a persistent malady complicated by both a host infection with the spirochetal bacteria Borrelia burgdorferi and an excessive response of the host’s innate immune defenses to the organism.

“Lyme disease is far and away the number one vector-based disease in the United States,” Wooten explains. “One of the problems in understanding it is that B. burgdorferi is completely different from most bacteria. The spirochetes live differently, metabolize differently; they move differently and, to top it off, they’re obligate parasites — incapable of living outside a host animal. Everything they do is a reflection of their current host, because as they pass from a tick to a mammal, they have to quickly perceive what new host they are now in, and react to it.”

Their evasive responses do not occur all at once, he notes; B. burgdorferi does only what it needs to survive in that host. “Unfortunately, with B. burgdorferi, what we see in the test tube is not what we see when we look in a mouse or other animal. Thus we are desperate for a way to look down at the cellular level in a host animal to see why the organism is so good at what it really does.”

Takashima’s intravital imaging techniques provided Wooten with the jump in technology he needed. “We were able to engineer for the first time the spirochetes in different colors and inject them into the skin of mice, their natural environment,” says Wooten. “The spirochetes fluoresce when hit with these high-powered lasers, allowing us to actually view the bacteria within the intact skin of the anaesthetized mouse and watch what they do in real time.”

Those actions, he adds, are remarkable: “While many die very quickly due to the host immune defenses; a subset is properly prepared to survive. Within two days, they adapt to the host and figure out where they want to go, and they move — really move.”

Thanks to their shape and unique motility structures, B. burgdorferi become muscular corkscrews that are well adapted for moving through the dense skin tissues. With multiple motors for locomotion at each end, the bacteria can move a hundred times faster than any immune cells that migrate into the skin to contain them. As Wooten puts it, “Chased by the immune system, they can take off and completely outrun it.”

Most researchers have assumed that these spirochetes would migrate to some special protected area that would allow them to hide from the host’s antibodies and other developing immune responses. However, his team was surprised to find that B. burgdorferi remains in the open, always moving.

“This is a new paradigm, where constant motion can feasibly get them past the cellular immune response,” he says. “The immune cells coming into the infection site try to smell invaders, wrap them up and kill them. When something is constantly moving, though, they cannot accurately determine where the smell is coming from. Not only are they unable to quickly clear the bacteria, but with time they may get used to the smell and no longer chase the bacteria as aggressively.”

Interestingly, the antibodies produced by the host appear to be perfectly able to recognize the bacteria and should clear them, but somehow they are unable to work during the natural course of this infection.

To better understand this unique evasion, Dr. Wooten’s team has created different mutations in the bacteria’s genes that appear to be involved in both their motility apparatus and their chemical-sensing network, which helps the bacteria identify places in the host body that are attractive and those to avoid. (Wooten notes that recent research indicates approximately 8 percent of the genes essential to the bacteria — a huge allotment — have to do with these survival resources.)

“By seeing how mutations change the way they move, and how long they can persist, we learn what’s important in affecting the bug’s actions,” Wooten explains. “We can also monitor the actual immune cells by using special mouse lines that are engineered so that either the Langerhans cells or other immune cells that live in the skin environment fluoresce a different color, and then see how they react differently after the B. burgdorferi genes have been mutated. In this way, we can identify what things we may target to allow our own immune system to work better to clear these infections.”

THE SPIROCHETES FLUORESC WHEN HIT WITH THESE HIGH POWERED LASERS, ALLOWING US TO ACTUALLY VIEW THE BACTERIA WITHIN THE INTACT SKIN OF THE ANALIEUHETIZED MOUSE AND WATCH WHAT THEY DO IN REAL TIME.
CORE LABORATORIES provide state-of-the-art instruments for cutting edge research.

By: Meghan Cunningham
In a dark room on the lower level of the Paul J. Block Jr. Health Science Building a multi-photon confocal microscope assists researchers in the study of how Lyme disease spreads through tissue.

The bacterium Borrelia burgdorferi fluoresces red and the immune cells responding to it fluoresce green enabling real time tracking of the disease’s progression in an anesthetized mouse with the goal of identifying key targets for the development of more effective Lyme disease therapies.

The nearly $1 million multi-photon confocal microscope that allows this detailed study is one of a number of instruments in the Advanced Microscopy and Imaging Center at The University of Toledo. The microscope allows researchers to probe 400 microns deep and compose 3-D images from multiple planes, and it is used regularly by some 200 researchers across all departments at the University.

“Every user needs something different,” said Dr. Andrea Kalinoski, assistant professor of surgery and technical director of the Advanced Microscopy and Imaging Center. “Bioengineering faculty use the lab to assist with topography of metals or bacteria on biofilms, and neurosciences researchers have used our lab for their studies about the effects of methamphetamines using mice subjects. We work with everyone to advance their research.”

The advanced microscope and other instruments in the Advanced Microscopy and Imaging Center are available to researchers across both Main Campus and Health Science Campus through the network of Core Laboratories.

The Core Laboratories network includes seven labs with state-of-the-art instruments and cutting-edge technological services for important research. Millions of dollars have been invested in the lab areas to allow more researchers access to the latest technologies.

Also in the College of Medicine and Life Sciences are the Flow Cytometry Core and the Genomics Core. The Flow Cytometry Core allows measurement and purification of cell populations or particles of interest. As the cells pass in front of the lasers, they emit light in distinct wavelengths to excite the cell’s inherent qualities along with any dyes with which they have been stained. The Genomics Core provides researchers with microarray technology to track tens of thousands of molecular reactions in parallel to detect specific genes or to measure the activity of genes.

Main Campus is host to additional Core Laboratories, including the Center for Materials and Sensor Characterization in the North Engineering Building. At the heart of advanced materials research is the characterization of materials properties, and this Core Lab offers assistance with both materials and sensor characterization. The materials lab houses three electron microscopes and a cluster of other instruments in the Electron Microscopy and Materials Characterization Laboratory. The Environmental Sensor Testbed also is available for characterization of microfabricated sensors.

The remaining Core Labs are in Wolfe Hall and Bowman-Oddy Laboratories on Main Campus.

The Center for Drug Design and Development in Wolfe Hall assists with the design and development of potential small molecule diagnostics, biomarkers, therapeutics and prevention agents. Assistance is provided for drug design, chemical synthesis, bioanalytical chemistry, molecular biology, in vitro screen and in vitro testing.

The Nuclear Magnetic Resonance Facility, located in Bowman-Oddy, provides nuclear magnetic resonance spectroscopy to faculty members, as well as companies in northwest Ohio and southeast Michigan. NMR spectroscopy is a powerful tool to determine molecular structure and study molecular dynamics and the characterization of materials at the molecular level. The facility houses four NMR spectrometers.

For more than 25 years, the Instrumentation Center has supported faculty research and provided access for advanced training for graduate students. The state of Ohio appropriated money in 1985 for the Center in the Bowman-Oddy that provides access to X-ray diffractometers, thermal gravimetric differential thermal analyzer, and more advanced equipment.

“We have created the Core Lab Network to achieve several objectives. One is to make our cutting-edge research facilities more visible in the community and another is to improve the user-friendliness of our services,” Dr. Akira Takashima, professor and chair of the Department of Medical Microbiology and Immunology. “We are pleased with the number of researchers using the laboratories and want to make sure that all faculty and students know about these wonderful resources to advance their studies.”

For more information on the Core Labs visit utoledo.edu/corelabs
Exploring the remarkable survival skills of microbes

UT studies target mechanisms of antibiotic resistance

By: Jim Winkler
In the race between clever microbes and defenses against them, microbes seem to have the upper hand. They replicate rapidly on the skin and in the human body and in huge numbers. Adapting to new environments, they constantly change and produce stronger and smarter versions. Constant mutation makes infections difficult to treat because drugs designed to interrupt the infection process fail when their targets change, leaving physicians with fewer tools to fall back on. The battle never seems to end.

Enter University of Toledo College of Medicine scientists Robert Blumenthal, Ph.D.; Isabel Novella, Ph.D.; and Deepa Mukundan, M.D., whose labs are studying different aspects of the remarkable skills of bacteria and viruses and the genetic strategies they use to outwit physicians, and to survive and cause disease.

Dr. Blumenthal, a professor of medical microbiology and immunology, is examining an assortment of supervisory genes that control the activities of other genes in bacteria, while Dr. Novella, associate professor of medical microbiology and immunology, is exploring biologic mechanisms of mutation that lead to drug resistance. Dr. Mukundan, assistant professor of pediatrics, is conducting studies to better understand the evolution and resilience of the important drug-resistant bacteria called methicillin-resistant Staphylococcus aureus (MRSA) — studies that could pave the way for development of new therapies and vaccines.

Bacterial cells, which operate with some 5,000 genes, are simpler than human cells, which (surprisingly) only have around 20,000 genes. Genes, made of DNA, contain the instructions for producing proteins and RNAs that carry out most functions in cells. Of the 5,000-odd bacterial genes, just a small fraction operate at any one moment to orchestrate its activities and to help it survive and cause infection — following the instructions of so-called global regulatory genes, according to Dr. Blumenthal.

These master regulatory genes act as monitors, helping bacteria to discern and to adapt to new changing conditions such as temperature, nutrition and acidic pH, and to produce new sets of proteins at the right time and in the right amount that will allow the bacteria to survive and grow. By studying the bacteria’s elaborate genetic regulatory networks — and the mutations that occur — Dr. Blumenthal and his colleagues hope to further understand how bacteria develop resistance to antibiotics.

“The typical bacterium has around 5,000 genes, and you can’t have these genes turning on and off at random,” explained Dr. Blumenthal. “That would be chaotic. In a very competitive world, organisms like that would not survive. You have to make sure that every gene is on when it is needed and it is off when not needed, and you only make as much product as you need so you are efficient.”

To conduct his studies, Dr. Blumenthal is using Escherichia coli, one of the most-studied organisms in science, the sometimes harmless and sometimes deadly bacteria that live in the gut by the billions. It is an organism easy to work with in the laboratory, and its processes also happen in a wide variety of other bacteria. One of its amazing features is its ability to survive the variety of conditions in the human body such acidic pH conditions, digestive enzymes, antimicrobial peptides, and other hazards as they pass through the stomach and intestine to find a home in the gut.

Constant mutation makes infections difficult to treat because drugs designed to interrupt the infection process fail when their targets change.
Dr. Blumenthal’s studies focus on a unique gene that acts as a master regulator called leucine-responsive regulatory protein (Lrp). It works as a master switch, “turning on” hundreds of lower-level genes that hold instructions to create proteins for carrying out functions and processes in a number of different bacterial pathogens.

In Escherichia coli, Lrp controls several hundred genes, but in Haemophilus influenza, which causes a particular form of meningitis, it controls just a handful.

“We don’t yet know why a master regulator controls a large set of genes in one type of bacteria and the same regulator controls a small set in another type of bacteria,” Dr. Blumenthal explained.

Just how many master regulatory genes supervise activities in E. coli is unknown, but the top seven master regulator genes, including Lrp, control more than 50 percent of all the genes found in the bacterium. Once scientists know which genes and proteins help boost E. coli’s disease-causing potential, as an example, they can use the information to develop new strategies to combat E. coli’s deadly effects.

“It is very important to understand how these bacteria respond to their environment because we are running out of antibiotics and are looking for new ways to target bacteria that will not select for resistance,” Dr. Blumenthal said. “So what defines which regulators are master regulators? Why are they selected and how does that evolve? These master regulators are controlling so many different things and there is a lot of overlap. Some genes are controlled by three or four master regulators. So they are responding to a complex mix of conditions to get the right amount of expression.

“It also isn’t known whether gene networks controlled by Lrp have the same basic structure in all of these different bacteria,” Dr. Blumenthal explains. “If not, how has the structure changed? What are the implications of any changes found on bioinformatic predictions of gene regulation from genome sequences?”

A series of experiments conducted by his lab uncovered that Lrp appears to have expanded responsibilities (at least in E. coli), changing its activity in response to many other amino acids, just not leucine.

“This has changed how we think about what this gene is doing and when it is turning genes on and off,” he said. “But we also want to understand whether the Lrp proteins from different bacteria are responsive to different groups of amino acids, which is something we do not know.”

New biocomputing methods will allow the Blumenthal lab to discover additional sites that Lrp targets in bacterial-cell DNA. The amount of data is enormous, and may allow additional insights into how genes in different strains of bacteria are regulated by Lrp.

For his studies, Blumenthal will use the high throughput DNA sequencing facility at the Venter Institute in Rockville, MD. The lab’s automated workstations sample and run thousands of assays a day, sparing countless hours of human work and greatly speeds Dr. Blumenthal’s work.

He is also examining promoter sequences — upstream DNA that controls how much of the protein is expressed — that are controlled by Lrp.

Dr. Blumenthal’s studies have been funded by a National Institutes of Health grant with subcontracts to researchers at the University of Minnesota and Stanford University.

For scientists to determine how and why microbes evolve to cause disease, they need an ideal model to study.

D r. Isabel Novella is using vesicular stomatitis virus (VSV), a pathogen that infects farm animals, but rarely humans. Nevertheless, scientists study it because of its similarity to human viruses that cause influenza, measles, Ebola hemorrhagic fever, rabies, and dengue fever. In addition, it has many features in common with human viruses transmitted by mosquitoes.

VSV replicates quickly, but the copies are imprecise. In a day, a single virus produces billions of offspring particles, and hundreds of generations of viruses appear in a matter of weeks, making it possible to observe significant evolutionary change as it happens and to set up experiments to test ideas about how viral evolution works. And because the virus carries just a handful of genes, Dr. Novella can see if mutations result in new generations with genes that confer new properties such as higher virulence.

“Evolution, in my mind, is an extremely interesting topic and because this virus mutates so much, you can see evolution in real time,” she explained. “These viruses mutate so fast you can actually see things happening in a few days or few weeks.”

Her research measures how individual mutations affect the physical properties of VSV — things like how well the virus attaches to its cellular host and how quickly it reproduces inside the cell. She also is collecting data on how different environments alter the effects of mutations.
Dr. Novella also is studying how VSV can be used to target unwanted cells. VSV is a candidate virus for use as a way to attack cancer cells, provided that it can be engineered to be safe and selectively replicate within and proceed to kill cancer cells, leaving normal cells untouched. Such viruses are known as oncolytic viruses.

Cancer cells are not able to fight off an invading virus, nor are they able to respond to warning signals from neighboring normal cells and protect themselves. A virus can therefore potentially replicate and reproduce through the tumor, leaving the normal tissue uninfected.

Her second area of research is to identify mutations that enhance the replication of dengue virus. The disease is spread by the bites of mosquitoes.

Dengue fever is a mosquito-borne illness that can cause debilitating sickness and death. According to the World Health Organization, almost half the people in the world are vulnerable to the dengue virus. Currently there is no treatment for it and no way to prevent it, according to Dr. Novella.

Dengue is an emerging infectious disease with epidemics that are becoming more frequent and more severe, according to Novella, making it important to understand the mechanisms that are responsible for generating the epidemics.

Today, few bacteria have grabbed newspaper headlines more than the drug-resistant bacteria methicillin-resistant Staphylococcus aureus (MRSA). In the U.S., much of community-acquired MRSA infection is caused by a strain known as USA-300. Invasive MRSA infections are estimated to have caused more than over 15,000 deaths in 2008, according to the U.S. Centers for the Disease Control and Prevention.

While serving as a pediatric resident at the former Medical College of Ohio and later as infectious disease fellow at the University of Michigan in the mid-2000s, Dr. Deepa Mukunda began to see early signs of a troubling trend. Month by month, the number of otherwise-healthy children she was seeing with MRSA acquired outside of the hospital was growing. These were children who had never been hospitalized and so, previously, wouldn’t have been considered at risk of developing MRSA infections.

So she and her colleagues conducted a retrospective analysis of the incidence of children with MRSA infections seen at Mercy Children’s Hospital in Toledo from 2002 to 2007 and found a six-fold increase.

Staphylococcus aureus (“staph”) bacteria are ubiquitous. About 30 percent of healthy people carry staph in their nose or on their skin at any given time — a process known as colonization — but have no problems. However, problems arise when staph gains entry into the tissues or blood stream through a break in the skin. The infection causes unusually severe problems, including abscesses and skin ulcers as well as necrotizing fasciitis, giving them the popular name of flesh-eating bacteria. They can also cause pneumonia, damage the heart, and produce widespread infection through the blood.

MRSA is easily transmitted, passing from person to person through simple touch or the sharing of personal objects. Transmission can also occur indirectly through contact with contaminated items such as bandages, towels, or athletic equipment.

Dr. Mukundan cites the overuse of antibiotics in livestock as a contributor to the problem. She is trying to learn more about the genetic factors that make USA 300 MRSA so invasive, and about why the bacteria mutate and spread so rapidly in the community. To understand how USA 300 bacteria spread, she has taken samples of the strain from more than 100 pediatric patients and is sequencing their DNA.

“The question is whether this staph carries any unique genes that allow it to colonize on the skin so well, in addition to spreading from person to person so easily,” Dr. Mukundan said. “Can we identify any protein in the staph which makes this infection really serious, and can we then use it as a vaccine target to protect against invasive disease?”
Thomas Tulisiak MD (MED ‘80), vice president of operations at Medina Hospital, part of Cleveland Clinic Regional Hospitals, became Medina’s president Sept. 1. He’s been with the hospital for 28 years.

David L. Firkin MD (MED ‘84, Res ‘89), urologist with Marion General Hospital (MGH), was chosen as MGH Physician of the Year for 2011.

G. Alfred Dodds MD (MED ‘88), cardiologist for Michigan Heart PC at Saint Joseph Mercy Health System in Ann Arbor, Mich., is the 2011 chair of the Washtenaw County Heart Ball, a fundraiser to benefit the American Heart Association for cardiovascular research and children’s heart health initiatives.

Cheryl Bihn MD (MED ‘93) joined the physical medicine and rehabilitation department at Mayo Clinic Health System in La Crosse, Wis.

Samir R Patel, MD (MED ’95) is co-founder of SPEC Pharma, LLC and Digital Therapeutics, LLC. Prior to that he was a medical director with Centocor Inc./Johnson & Johnson. Dr. Patel was formerly in the staff of South Carolina Heart Center, which pioneered the MASH unit; he helped revolutionize the way heart disease is treated.

Death notices

Earl Freimer MD, Columbus, faculty member at MCO from 1968 until his 1997 retirement, May 23 at 84. He was hired as a professor and founding chair of the Department of Microbiology (now Medical Microbiology and Immunology), and was the founding chief of the Division of Infectious Diseases in the Department of Medicine. The Medical Microbiology and Immunology Department will name its annual award for a graduating medical student who shows exemplary performance in the infection and immunity block of the curriculum in Freimer’s honor. In addition, a scholarship fund is being established in his name.

John H. Hageman MD, Toledo, who played an integral role in the practice, education and advancement of vascular surgery for more than 40 years, March 30 at 76. He joined the MCO faculty in 1984 as an associate professor in the Department of Surgery and was promoted to professor in 1994. While there, he served as chief of peripheral vascular surgery and medical director of the surgical intensive care unit. After retiring in 1998, Hageman took a volunteer faculty position as clinical professor in the Department of Surgery; he held the position until 2006.

John M. Howard MD, Toledo, professor emeritus of surgery, March 16 at 91. He joined the MCO faculty in 1974 as professor of surgery. During the Korean War, Howard directed the U.S. Army’s Surgical Research Team, which pioneered the MASH unit; he received the Legion of Merit award from President Eisenhower for his efforts. Working with national trauma organizations, he also spearheaded the early development of a coordinated program for emergency care of the acutely ill and injured in northwest Ohio. When he retired in 1990, Howard was named professor emeritus. Ten years later, he established a fund, the John M. Howard Endowed Professorship of Surgery. He was a member of the Heritage Oaks Society.

William B. Kannel MD, renowned cardiovascular epidemiology medical researcher who received an honorary doctor of science degree from MCO in 1997, Aug. 20 at 87. He was associated with pioneering the Framingham Heart Study, which helped revolutionize the way heart disease is treated.

Michael J. Leslie MD (HS ‘96, MED ‘96), Sandusky, Oct. 20 at 43.

Lucien E. Morris MD, Rollingbay, Wash., faculty member at MCO from 1970 until his 1985 retirement who was named professor emeritus of anesthesiology in 1987, Nov. 15 at 96. In 1970, he was appointed founding chair of the Department of Anesthesia; he developed the private practice plan for clinical physicians, established the Anesthesia Residency Program and served as chief of staff of the hospital. Morris was known for designing a precision anesthesia vaporizer system known as the “copper kettle” that for more than two decades was used as a standard apparatus in most U.S. teaching hospitals. Morris received an honorary doctor of science degree from MCO in 1994.

Stuart K. Remley MD, Toledo, an endocrinologist who was an MCO volunteer faculty member, March 17 at 86. He was appointed a clinical associate in the Department of Medicine in 1970, and was a clinical instructor when his appointment ended in 1985.

Gerald P. Rosen MD, Ottawa Hills, Aug. 15 at 76. He joined the MCO Department of Surgery in 1993 and retired as associate professor of surgery/otolaryngology in 2003, at which time he took a volunteer position as clinical associate professor of surgery.

John T. Schauefele MD (MED ‘86, Res ’89), Toledo, clinical professor in the Department of Pediatrics since 1989, Oct. 19 at 57. He was one of six students in his class inducted into the Alpha Omega Alpha medical honorary society, and later was appointed chief pediatric resident. He became director of the Pediatric Student Program, received the Dean’s Award for Teaching Excellence in 1997, and was appointed the first endowed chair of pediatrics in 1998.

Michael A. Yanik MD (Res ‘81), Maumee, Aug. 8 at 63. A plastic and reconstructive surgeon, he gained a reputation as an expert in the care of catastrophic burn and trauma injuries, and launched the area’s first tissue bank.

Christin A. Waite MD (A/S ‘00, MED ‘03), Holland, April 16 at 33. She was serving an internal medicine residency at UTMC.