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Welcome to the 2014/2015 Department of Chemistry newsletter. It has been another outstanding year for the department, its faculty, staff, and students. It is also an exciting time of reflection at Vanderbilt with the university implementing its new strategic plan. As one of the biggest teachers of undergraduates and the largest graduate program on campus, the department finds itself at the heart of this process. While we develop our own departmental strategic plan for the coming decade, we are forging new trans-institutional initiatives, imagining immersion experiences, and exploring new ways to teach across the campus.

One of the constants in life is change. Last year, the department saw quite a bit of it with the retirements from teaching of Professors Ned Porter, Joel Tellinghuisen and Chuck Lukehart. The department also hired a new assistant professor, Steven Townsend, and a new senior lecturer, Susan Verberne-Sutton. Currently, we are looking to hire a new inorganic chemistry assistant professor in the area of catalysis.

A hallmark of our faculty is their dedication to research, teaching, and service. This faculty excellence is seen in the national awards that we earn. Examples include: Professors Jeff Johnston and Richard Armstrong were named ACS Cope Scholars for excellence in organic research. Professor John McLean was named an Agilent Thought Leader and his lab was recognized as a Waters Center of Innovation. The US-Israel Binational Foundation recognized Janet Macdonald with the Bergmann Memorial Award. Professor Sandra Rosenthal won the 2014 SEC Faculty Achievement Award for her recognized excellence in teaching and scholarship. Finally, I wish Professor Larry Marnett the best in his new role as the associate vice chancellor of research at VUMC.

We are proud of all of our students who come from across the U.S. and around the world. This past year, we graduated twenty students with ACS-certified bachelor’s degrees in chemistry, most of whom will pursue graduate or professional studies. We also graduated three students with the master’s degree and eleven students with the Ph.D. in chemistry. Our trainees were the recipients of a number of awards ranging from NIH training grant positions to the NSF Graduate Research Fellowship to an Eli Lilly Innovation Postdoctoral Fellowship.

The stories in the following pages will provide you with a snapshot of what researchers are doing, the changing faces of the department, the recognition that we continue to garner, and some insights into our students and alumni. We are redoubling our efforts to connect with you, our alumni, and hope that you will take the time to let us know what you are doing. We would love to hear about it.

David Wright
Stevenson Professor and Chair
Department of Chemistry
Vanderbilt University
Creating such a “microbrain bioreactor” is the challenge of a new $2.1 million research grant awarded to an interdisciplinary team of researchers from Vanderbilt University, Vanderbilt University Medical Center, the Cleveland Clinic and Meharry Medical College. The grant is one of seventeen that are being issued by the National Center for Advancing Translational Sciences at the National Institutes of Health as part of a $70 million “Tissue Chip for Drug Testing” program. The five-year program is a cooperative effort on the part of NIH, the Defense Advanced Research Projects Agency, and the FDA.

The reason for microfabricating organ simulators containing small populations of human cells—generally known as “organ-on-a-chip” technology—is to bridge the formidable gaps that exist between the models that researchers currently use to develop new drugs—cell cultures and animal and human testing. These gaps not only add substantially to the difficulty and expense of developing new drugs, but also contribute to the large number of experimental drugs that aren’t effective or have unacceptable side effects when they are finally tested on people.

“Given the differences in cellular biology in the brains of rodents and humans, development of a neurovascular model that contains neurons and all three barriers between blood, brain, and cerebral spinal fluid, using entirely human cells, will represent a fundamental advance in and of itself,” said John Wikswo, the Gordon A. Cain University Professor and Director of the Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE), who is orchestrating the multidisciplinary effort.

Vanderbilt Professors of Chemistry David Cliffel and John McKenzie, Ph.D., Cliffel Group

Take a millionth of a human brain and squeeze it into a special chamber the size of a mustard seed. Link it to a second chamber filled with cerebral spinal fluid and thread both of them with artificial blood vessels in order to create a microenvironment that makes the neurons and other brain cells behave as if they were in a living brain. Then, surround the chambers with a battery of sensors that monitor how the cells respond when exposed to minute quantities of dietary toxins, disease organisms, or new drugs under development.

Artist’s conception of the microbrain bioreactor. The upper chamber contains the neurons and an artificial capillary that carries blood to the brain surrounded by the cells that make up the blood-brain barrier. The lower layer is filled with cerebral spinal fluid (CSF) and contains an artificial choroid plexus (red) that makes CSF and a venule (blue) that carries blood away from the brain, along with a collection of cells that form the blood-CSF and CSF-brain barriers. Collectively, all these cells will reproduce the microenvironment found in the brain. The entire device will be about the size of a grain of rice. (Dominic Doyle and Frank Block / Vanderbilt)
McLean are leading the efforts to enable online analytical measurements from the developed organs, a key component to allow for automated monitoring of organ health before and after treatment with drugs undergoing investigation.

Professor David Cliffel and his group have been building miniature electrochemical sensors that measure cellular metabolism by tracking the consumption of glucose and oxygen and the production of lactate and changes in acidity, key molecules in the cellular energy cycle. By monitoring these analytes over time, it will be possible to gain insight into cellular health, as well as track how specific drugs may affect the ability of the organs to produce their own energy. When coupled with the novel instrumentation developed by VIIBRE, these sensors enable real-time and automated monitoring of cellular health. Says Cliffel, “Our key contribution is the continuous measurement of the major components of cellular physiology and bioenergetics common to all organs: glucose, oxygen, lactate, and acidification. Thus, we study a wide variety of organs including the brain, lung, liver, and even the lymph nodes.”

The electrochemical sensors are based on previous instruments developed by the Cliffel lab, but the collaboration with VIIBRE has sparked further research into development of additional sensors that could be employed. Student researchers from all different education levels, including undergraduate and graduate students, are working together to develop and test new metabolic sensors that can be used to monitor changes to the Neurovascular Unit-on-a-Chip.

While the Cliffel lab focuses on small metabolites which are detectable using electrochemistry, Stevenson Professor of Chemistry John McLean’s group has been leading the effort to connect these organs to sophisticated mass spectrometers that can identify in real time the presence of thousands of different proteins and other molecules that the cells produce. “It’s an exciting challenge to apply real-time analytics to decipher the molecular communication that takes place in the brain,” McLean said. When coupled with high-powered instrumental and data analysis techniques, McLean’s group is able to discern patterns within the thousands of signals to focus in on how concentrations of certain small molecules are changing over the course of a drug treatment.

Wikswor and his collaborators agree that this new type of brain model should provide new insights into how the brain receives, modifies, and is affected by drugs and disease agents. By replicating the forms of chemical communication and molecular trafficking that take place in the human brain, the device will allow them to test the effectiveness of various drug and nutritional therapies designed to prevent both acute injuries like strokes and chronic diseases like obesity and epilepsy, as well as uncovering the potential adverse effects of experimental drugs.

Once the microbrain bioreactor has been developed and tested, a team headed by Scott Daniels, assistant professor of pharmacology and director of drug metabolism and pharmacokinetics at the Vanderbilt Center for Neuroscience Drug Discovery, will collaborate with the Cleveland Clinic Foundation group to validate the chip technology by testing it with a number of clinically approved and experimental compounds that vary in their ability to penetrate the central nervous system. Daniels noted that “the brain-on-a-chip technology could enable the accurate prediction of human brain penetration by small molecule therapeutics and, therefore, bridge a critical translational gap in the drug discovery arena.”

Another group, headed by Associate Professor of Medicine Kevin Niswender, will be applying the new device to study the biology of stroke and the role that the brain plays in obesity. The system will allow his group to ask fundamental questions about how dietary macronutrients and inflammatory signals influence the various components present in the brain. Assistant Professor of Molecular Physiology and Biophysics Kate Ellacot will employ the system to understand how glial cells interact with neurons in the context of inflammation in obesity. In addition, the Cleveland Clinic has a large collection of samples from patients with these and other conditions. They will put cells from selected patients in the bioreactors and quantify how they respond to different treatments. “The ability to apply these precious samples entrusted to us by patients to a platform where we can literally measure hundreds of parameters is a dream come true,” said team member BethAnn McLaughlin, assistant professor of neurology and member of the Vanderbilt Kennedy Center. “We have enormous challenges in developing therapeutics to protect the brain from injury and this is a profound unmet need. Not a single drug has passed FDA approval to protect the brain from stroke, and we only have one that breaks up clots. We need to do better.”

This research is supported by the NIH National Center for Advancing Translational Sciences, Grants UH2TR000491 and UH3TR000491.
Vanderbilt University has been awarded a Cooperative Agreement with the Defense Advanced Research Projects Agency (DARPA) and the Army Research Office (ARO) that is worth up to $16.5 million over five years. The Vanderbilt Agreement is led by Richard Caprioli, Ph.D., Stanford Moore Professor of Biochemistry, Professor of Chemistry, and director of the Mass Spectrometry Research Center (MSRC), and principal investigator of a National Institutes of Health grant (GM103391) that in 2011 established a National Resource in Imaging Mass Spectrometry at Vanderbilt University. “In the second half of my career, I want to take some of the … really extraordinary things that can be done in research labs, and … bring them into the public domain on problems that can directly help (people),” said Caprioli, who joined the Vanderbilt faculty in 1998.

The Vanderbilt Agreement governs research that will be conducted in up to four phases. At the end of each one, the milestones and the metrics “get tougher and tougher,” said Caprioli, a pioneer in mass spectrometry techniques.

A transinstitutional effort, the Vanderbilt project consists of three teams: The analytics team—co-led by John McLean, Ph.D., Stevenson Professor of Chemistry, and Jeremy Norris, Ph.D., research assistant professor of biochemistry, who also serves as project manager. Other faculty team members include Brian Bachmann, Ph.D., associate professor of chemistry and biochemistry, and Kevin Schey, Ph.D., professor of biochemistry and director of the MSRC Proteomics Lab. The biology team—led by Eric Skaar, Ph.D., MPH, Ernest W.
“We’re going to grow human cells on slides ... and they’re going to be exposed to the toxins and will be analyzed using our scanning, laser-based mass spectrometry technologies ... to get a very rapid assessment of what’s going on in those cells at the molecular level,” he said. These include MALDI IMS, an imaging mass spectrometry technology developed at Vanderbilt that is being used to study how changing gene expression affects production of proteins and metabolites important in cellular function and regulation.

Instrumentation that will be used for these studies includes a new 15.5 tesla FTICR mass spectrometer that was installed in Caprioli’s lab on the ninth floor of MRB III last fall (15.5 tesla is roughly 200,000 times the strength of the earth’s magnetic field), and a 9.4 tesla instrument.

“The opportunity is amazing,” Caprioli said. “It makes you get up in the morning with great enthusiasm and say, ‘Let’s get there and do this. This is worth doing.’

This research was supported by a grant from the National Institutes of Health (GM103391).

Mapping Brain Membrane Proteins

MALDI imaging mass spectrometry (IMS) is a powerful tool for studying the spatial distribution of molecules directly within tissues. It has been applied to many different pharmaceuticals, metabolites, and small, soluble proteins. Large membrane-spanning proteins, however, have not been well studied by MALDI IMS because of analytical challenges related to their size and solubility.

Richard Caprioli, Ph.D., and colleagues have now developed a novel sample preparation procedure for MALDI IMS of transmembrane proteins directly from tissue. They used the method to assess the spatial distribution of myelin proteolipid protein and DM-20, two highly abundant transmembrane proteins within central nervous system myelin, throughout various regions of the rat brain.

The study also includes new processes for assessing fatty acid modifications and for on-tissue protein identification using a hydrogel containing proteases (protein “scissors”). The approaches, reported in the August 6 issue of Analytical Chemistry will enable further MALDI IMS studies of transmembrane protein distribution.
Fundamental Discovery of New Form of Crystalline Order

By Sandra Ford, with Janet Macdonald, Ph.D., Assistant Professor of Chemistry

Since the 1850s, scientists have known that crystalline materials are organized into fourteen different basic lattice structures. However, a collaborative team of researchers from three different backgrounds and from Vanderbilt University and Oak Ridge National Laboratory (ORNL) now reports that it has discovered an entirely new form of crystalline order. They saw crystals that simultaneously exhibit both crystal and polycrystalline properties, which they describe as “interlaced crystals” and hold promise for thermoelectric applications.

In the Nov. 14, 2014, issue of the journal, Nature Communications, the researchers describe finding this unusual arrangement of atoms while studying nanoparticles made from the semiconductor copper-indium sulfide (CIS), which is being actively studied for use in solar cells. The interlaced crystal arrangement has properties that make it ideal for thermoelectric applications that turn heat into electricity. The discovery of materials with improved thermoelectric efficiency could increase the efficiency of electrical power generation, improve automobile mileage, and reduce the cost of air conditioning.

“We discovered this new form while studying nanoparticles,” said Sokrates Pantelides, Ph.D., University Distinguished Professor of Physics and Engineering at Vanderbilt, who coordinated the study. “It most likely exists in thin films or bulk samples, but it has apparently gone unnoticed.” They also predict interlaced crystals are present naturally in a much broader class of materials.

Assistant Professor of Chemistry Janet Macdonald, Ph.D., explains, “In CIS, the sulfurs make these perfectly packed 2-D layers and the Cu and In ions lie in between, like jam in a sandwich. My postdoctoral student, Emil Hernandez-Pagan, was making nanoparticles of this material in the lab, but didn’t know if the Cu and In were ordered, or just randomly distributed in the “jam” layers. This is really important for the optical properties as disordered structures would have poor properties.”

She continues: “There was no easy way to tell if they were cation ordered or not using our usual tools for nanocrystals, as you have polycrystalline samples, there is strain or breaks at the edges between areas of crystalline order. However, there seemed to be no strain or breaks at the edges. Despite all of the little crystallites, the sulfur layers and the broader lattice of the crystal are completely ordered and needn’t shift or twist or break at all to accommodate all these changes in the cation layers.

Without strain or defects in the interlaced crystals, interlaced crystals should be great conductors of electricity, despite all these different regions of cation ordering. As Macdonald summarized the discovery, she said, “Electrons will have a smooth path. But, heat travels through atomic vibrations, and all of the grain boundaries in the cation layers will scatter these vibrations and hinder heat from flowing easily through the material. This is exactly what you want for a thermoelectric. I’m excited to see what comes out of thermoelectric studies.”

Research was funded by National Science Foundation grants DMR-0938330, EPS-1004083 and CHE-1253105; U.S. Department of Energy grant DE-FG02-0946554; Office of Science contract DE-AC02-05CH11231; and by ORNL’s Basic Energy Sciences/Materials Science and Engineering Directorate and Center for Nanophase Materials Sciences, sponsored by US DOE.
Vanderbilt University’s Richard Armstrong, Ph.D., is part of a multi-institutional research team that has found a new way to interrogate a “super-family” of enzymes involved in detoxification, cellular metabolism, and antibiotic resistance, which have many other as-yet-undiscovered functions.

Their approach, published in the current issue of the journal *PLOS Biology*, provides a “roadmap” for determining the function of enzymes from the genetic sequences that encode them and their three-dimensional structures.

“We don’t know what most of these proteins actually do. That’s the major challenge,” said Armstrong, professor of chemistry and biochemistry, who partnered in the research with Steven Almo, Ph.D., of Albert Einstein College of Medicine in New York, and Patricia Babbitt, Ph.D., from the University of California, San Francisco.

Once function has been determined, it may be possible to alter it in a way to prevent bacteria from becoming resistant to antibiotics, or boost the ability of other microorganisms to break down environmental pollutants, a process known as bioremediation.

The scientists focused on the super-family of cytosolic glutathione transferases (cytGSTs). Cytosolic means these enzymes are not bound to a cellular membrane. They act in concert with the antioxidant glutathione primarily to protect the cell from “oxidative stress,” detoxify harmful chemicals, and play other key roles in metabolism. From 13,000 non-redundant cytGST genetic sequences, the researchers generated “clusters” of similar sequences and structures. They crystalized representative samples from various clusters, and in so doing identified thirty-seven new molecular structures, or snapshots, of twenty-seven proteins in different states.

Using information from known enzymes in the clusters, and a high-throughput assay system for analyzing others, they were able to confirm cytGST-like activity in eighty-two enzymes that had not previously been characterized. This increased the number of known enzymes in this superfamily by about 50 percent.

That’s just the tip of the iceberg, of course. “One of the most important aspects of the bioinformatics is that it illustrates how much we don’t know,” Babbitt said. The challenge is not sequencing or determining protein structure through techniques like X-ray crystallography, which, in Almo’s lab, has become a heavily automated, high-throughput operation. “It’s the function, which is the most difficult and expensive thing to elucidate in the lab,” Armstrong said.

This is where the bioinformatics provided by Babbitt’s team was crucial. Almo’s lab provided structural context for the data coming out of her group, while Armstrong and his colleagues provided functional annotations of the proteins.

The research was funded through the Enzyme Function Initiative, supported by National Institutes of Health grant GM093342, and also by NIH grants GM060595 and GM103311.
Aflatoxin B1 (AFB1) is a fungal toxin which is a known carcinogen associated with early-onset hepatocellular carcinoma. Two new reports by Professor Michael Stone, Ph.D., and his collaborator, Professor R. Stephen Lloyd at the Oregon Health & Science University, confirm that both AFB1–N7-Gua and AFB1–FAPY are, in fact, highly mutagenic in primate cells into which either an AFB1–N7-Gua- or AFB1–FAPY-containing DNA substrate was introduced.

This work has been highlighted in the Spotlight section of the American Chemical Society journal Chemical Research in Toxicology http://pubs.acs.org/doi/abs/10.1021/tx500300x.

Liang Li, a Ph.D. student in Stone’s laboratory, synthesized a series of site-specific AFB1 lesions that were inserted into primate cells and replicated. The results of this research revealed that these AFB1 lesions were highly mutagenic, yielding replication error frequencies of 97 percent, with the predominant base substitutions being G to T transversions. These transversions are consistent with mutational data derived from aflatoxin-associated HCCs. The original research articles were published in the Journal of Biological Chemistry and in Carcinogenesis.

This research was supported by a grant from the NIH, National Cancer Institute, Grant R01-CA-55678

Michael P. Stone, Ph.D., Stevenson Professor of Chemistry, led the research on the Aflatoxin B1 (AFB1).
We now know that many serious diseases have genetic links that are present in an individual’s genome—the DNA double helix where our hereditary information is encoded.

Researchers know too that a protein protects our DNA, which is vulnerable to becoming entangled when it's unwound from the helix to be read, and also to being attacked by enzymes that damage the strands, thereby making the code indecipherable.

This precious protein is called Replication Protein A (RPA). If DNA was the words in a book, then the RPA protein makes sure the pages are kept in place when the book is open and that the reader reads the words in correct order.

As the primary ssDNA binding protein in humans, RPA is absolutely essential to virtually all processes that maintain and propagate our genomes.

"To be read, the DNA needs to be unwound from its familiar, double-stranded helical state into separate strands," explains faculty member and lead investigator Walter Chazin, Ph.D. "But single stranded DNA (ssDNA) has a strong tendency to become tangled and is also readily cut up by numerous nuclease enzymes. Every organism has evolved ssDNA binding proteins to protect the ssDNA and keep it untangled."

RPA functions by serving as a platform for the many, highly dynamic, multi-protein machines that perform these essential genetic processes. It not only manages access to the ssDNA, but also orchestrates the coming and going of the other proteins that make up the DNA processing machines.

Despite its central importance, little is known about how RPA molecules perform these complex roles. In a recent study, Chazin and collaborators used a fundamentally new approach to investigating the multi-stage process by which RPA engages DNA that can be applied to other biosystems. The studies combined data from X-ray scattering at the Advanced Light Source at Lawrence Berkeley National Laboratory, neutron scattering at Oak Ridge National Laboratory, and supercomputers at national facilities. The study was published as a featured article in *Nucleic Acids Research*.

The results altered the long-standing views of RPA. They contrast with previous models that had proposed that RPA initially binds ssDNA in a condensed state and becomes more extended as it fully engages the substrate. The work also revealed RPA undergoes two (not three) transitions as it binds ssDNA, with no evidence for an intermediate state.

These findings provided a new framework for understanding both how RPA works and how it is able to stimulate DNA processing machines. Further, it provides new insights into how one DNA processing pathway can be selected over others. Next steps are to use the new strategy they have developed to characterize how RPA configures itself when it performs different functions with human DNA, and when it repairs damaged DNA with the critical repair factor XPA.

These and related studies also set the stage for translation to clinical applications. In a joint effort with the laboratory of faculty member Stephen Fesik, Ph.D., Chazin is already involved in trying to evaluate the potential therapeutic value of inhibiting RPA with small molecules, as an adjuvant to current cancer chemotherapies.

*The RPA research was supported by NIH RO1 GM65484, RO1 CA092584, and RO1 EH1065561; training grant: T32 GM80320; Center in Molecular Toxicology grant no. P30 ES00267; and Vanderbilt-Ingram Cancer Center grant P30 CA068485.*
Vanderbilt scientists have discovered a series of small molecules that may help unlock the mystery of schizophrenia, a severe mental disorder that can cause disabling hallucinations, delusions, and disorganized thinking.

If they can refine the molecules into drug-like compounds, and pass the baton to a drug company for further development, the result could be a new class of drugs significantly more effective than current therapy and with fewer side effects. The work is slow going, and the risk of failure is high. Even if a candidate compound passes the rigorous safety and efficacy testing required of a potential new drug, it may be 2016 before it can be tested extensively in patients, and 2020 before it reaches the market.

But the project, conducted in collaboration with the global biopharmaceutical company AstraZeneca, represents a paradigm shift in the way novel drugs are discovered and developed. The hope is that such partnerships will significantly improve treatment of a host of disorders, from serious infections to cancer and diabetes.

That research is supported by the university, the National Institutes of Health (NIH), philanthropy and, increasingly, revenues from licensing agreements negotiated by the Vanderbilt Center for Technology Transfer and Commercialization (CTTC).

"If we don't invest in the basic science, we're not going to be successful," says Craig Lindsley, professor of chemistry and director of medicinal chemistry in the Vanderbilt Center for Neuroscience Drug Discovery; the William K. Warren Jr. Professor of Medicine; and professor of pharmacology.

"I feel schizophrenia is the scourge of all illnesses because of its devastating, vulnerable symptoms," says William K. Warren Jr., chairman emeritus of the Oklahoma-based foundation named for his father. "Other illnesses receive a lot more attention, but we must support 'deep biology' research to better understand and treat this horrific illness."

Schizophrenia affects an estimated one of every 100 adults. Current medications can keep hallucinations and delusions at bay but do little to address other symptoms, including cognitive difficulties and a tendency to withdraw from others. The drugs also cause side effects that can be devastating for patients and family members, including metabolic disorders and significant weight gain.

FREEDOM OF PURSUIT

"Clearly, there are huge unmet clinical needs," says Mark Duggan, vice president for neuroscience at AstraZeneca. "That's why we are continuing to invest in neuroscience but via external scientific partnerships with some of the best groups around the world, including Vanderbilt," adds John Dunlop, also a vice president of neuroscience at AstraZeneca. "Together we are aiming at getting a compound that could advance into clinical testing."

The target of the collaboration is the M4 muscarinic acetylcholine receptor, which in the brain binds the neurotransmitter acetylcholine. In animal models the Vanderbilt scientists have shown that "allosteric modulators" of M4 can "ramp up" the receptor's activity without affecting other signaling pathways. The result is an improvement in cognitive impairments and behavioral disturbances that, in humans, are associated with Alzheimer's disease as well as schizophrenia.

Craig Lindsley, along with P. Jeffrey Conn, Ph.D.—the Lee E. By Bill Snyder
Vanderbilt’s ranking in total spending on “chemical R&D” catapulted from 33rd place in 2010 to 12th place in 2011. Today Vanderbilt has one of the top drug-discovery programs in the country. – Chemical & Engineering News, December 9, 2013

PROGRESS IS FRAGILE
Vanderbilt's strength in drug discovery grew out of its early commitment to clinical pharmacology, the study of how drugs work in the body. These efforts weren't limited to the School of Medicine. The establishment of the Vanderbilt Institute of Chemical Biology (VICB) in 2002 under the direction of Lawrence Marnett, University Professor of Biochemistry and Chemistry, and the Mary Geddes Stahlman Professor of Cancer Research, demonstrated the university's encouragement of cross-campus, multidisciplinary collaborations.

When it comes to translating basic research discoveries into advances in clinical medicine, "chemistry is at the heart of it," says Marnett. "Chemists make new molecules that become drugs. Chemists develop analytical methods that are at the heart of biomarker development."

Medicinal chemistry is the stage at which compounds are identified, made, and tested for their ability to bind to, and affect the activity of, a target like M4. That's followed by molecular pharmacology, drug metabolism, and pharmacokinetics, and then behavioral pharmacology, to test their potential to become drugs.

The first stage—identifying drug-like compounds—has been accelerated dramatically in recent years through advances in high-throughput screening (HTS). Vanderbilt's HTS facility, established by David Weaver in 2005, has a "library" of 190,000 compounds and the ability to test tens of thousands of samples per day.

"One of my basic assumptions is that I don't understand too much about how the system works," says Weaver, assistant professor of pharmacology. So, he tries to develop "open-minded" assays, designed to let scientists detect unanticipated effects of a potential drug on a drug target, for example.

Fancy screening techniques aren't enough, of course. Potential drugs must show efficacy and safety in animal models before being tested in humans, and many a promising agent has failed when it got to the clinical trial.

The problem with schizophrenia, at least for would-be drug discoverers, is that, like cancer, it is not one disease but many. Its constellation of symptoms, behaviors, and cognitive impairments probably results from more than one genetic mutation affecting multiple proteins, receptors, and signaling pathways throughout the brain.

That's why some drugs work in some patients but not in others. If potential new drugs could be "matched" with research subjects most likely to respond to them based on their "genotype" or genetic makeup, the success rate for clinical trials would be much higher, Lindsley says.

"We need the right molecules for the right mechanisms in the right patients," agrees AstraZeneca's Dunlop. Thanks to advances in psychiatric genetics, that day is coming, and may arrive within the next decade, he says.

Vanderbilt is well positioned to translate these advances into tangible benefits for patients, if it continues to invest in new technologies, facilities, and people.

But scientific progress "is a very fragile thing," says Marnett. "Even though we've got a lot of people doing some really exciting things … if the garden isn't tended, it unravels pretty quickly."
Controversial Info Release Aids VUMC Bird Flu Research

Computational Models Prove Accurate

By Carole Bartoo
Vanderbilt University Medical Center research has produced reassuring results that address some fears about the pandemic power of avian influenza viruses (commonly referred to as “bird flu”) created in research labs.

H5N1 avian influenza virus essentially does not yet seem to transmit from person to person in nature, only directly from birds to people. However, in 2010, scientists in the Netherlands and at the University of Wisconsin found that when H5N1 avian influenza was passaged intentionally in the laboratory from ferret to ferret, the deadly virus could acquire aerosol transmissibility.

Now, the Vanderbilt work, published online Sept. 3, 2013, in the Journal of Clinical Investigation, shows that human antibodies to the natural strain of H5N1, induced in volunteers during experimental H5N1 vaccine testing, are able to kill the potentially more dangerous laboratory-created strain of the avian flu.

The work stirred fears in the scientific community of potential use of this information for bioterrorist purposes and led to the unusual step of journals temporarily withholding publication of the research. The sequences of the transmissible viruses eventually were published in the journals Science and Nature.

“The work we did was only made possible by the publication of the controversial sequences. The publications identified the mutations, and we were then able to go back and engineer them into our recombinant protein to determine if our antibodies might be effective against such aerosol transmissible viruses,” said Natalie J. Thornburg, Ph.D., a scientist in the Vanderbilt laboratory of James E. Crowe, M.D., Ann Scott Carell Professor, professor of pediatrics, professor of pathology, microbiology, and immunology, and corresponding author of the publication.

Then, because Vanderbilt is home to a National Institutes of Health (NIH)-funded Vaccine and Treatment and Evaluation Unit (VTEU), housed within Vanderbilt Vaccine Research Program, Crowe’s team was able to ask participants previously involved in an H5N1 vaccine trial to return and supply blood cells to the laboratory for isolation of antibodies they had produced in response to the vaccine.

“Fortunately, we discovered the antibodies we isolated from subjects immunized with the existing vaccine also would neutralize strains that had these specific new mutations,” Thornburg said.

Crowe and his team, in collaboration with David Nannemann, Ph.D., a postdoctoral student in the Department of Chemistry, and Jens Meiler, Ph.D., associate professor of chemistry and pharmacology, in the Center for Structural Biology, utilized a “hybrid approach” to describe the viral/antibody interactions.

“Hybrid modeling approaches bring together diverse sets of data from a number of fields, which alone tell a small part of the story, into a picture which can inform upon a more global hypothesis,” Nannemann said.

“Our images show that the antibodies are able to reach down into a protected area of the virus to bind to and neutralize it, despite the changes made in its structure of the virus that are in an adjacent area. These findings provide important information about immunity to these new viruses, and in this case the information is also reassuring,” Crowe said.

Some of the new computer-driven, virtual test models used in this study provide virus/antibody interaction snapshots that may be quicker and easier to capture than the classical method of crystallography of natural protein complexes.

The team has shown the models have a high degree of accuracy so far. However, he pointed out that it will be useful to compare the Vanderbilt results with traditional crystallography as the field progresses, which the team is pursuing with Ben Spiller, Ph.D., assistant professor of pharmacology, and his team.

Senior author James E. Crowe Jr., M.D., director of the Vanderbilt Vaccine Center and professor of pediatrics pathology, microbiology, and immunology, said the combination of the release of critical information from the 2010 research, and the use of highly developed biotechnology used in his laboratory shows this type of work can continue to inform vaccine and treatment development, even for pandemics that do not yet exist.

The team did not use the respiratory droplet transmissible viruses themselves; they used a noninfectious synthetic protein and added the controversial viral mutation sequences to the surface of the protein. This allowed the Crowe laboratory to study the effect of the mutations in virus structures safely through finely tuned experiments.

This work was supported by NIH grant R01 AI106002, NIAID contract HHSN272200900047C, the Vanderbilt NIH CTSA grant UL1 RR024975, and the DoD grant HDTRA1-10-1-0067.
The research of Vanderbilt Chemistry Professors B. Andes Hess, Jr., and Lidia Smentek provides fundamental new insight into a long-standing controversy regarding the mechanism of one of the most intriguing biological reactions, the conversion of the acyclic polyene, squalene, to an intermediate with four fused rings, which is the backbone of all steroids.

Previously, Hess had shown how the last ring of the four was formed in an unusual concerted manner starting from a three-ring intermediate [Hess, B.A., Jr., J. Am. Chem. Soc. 2002, 124, 10286-10287]. His was the first theoretical description of a type of reaction that has since been found by others to occur widely in nature.

In the new work [Hess, B.A. Jr., & Smentek, L., 2013, Angewandte Chemie Int. Ed. 2013, 52, 11029-11033.], Profs. Hess and Smentek demonstrate that the first three rings are formed in a completely concerted reaction, much like closing a zipper, that leads to an intermediate, which then undergoes the reaction to form the fourth ring. Their results suggest that the major role of the enzyme in this biosynthesis is to “cradle” the squalene molecule in the appropriate shape (conformation), which allows the reaction to occur. Understanding of this key biosynthetic reaction may allow the design of better drugs to thwart the biosynthesis of the steroid cholesterol in humans.

Professor B. Andres Hess, Jr., received his Ph.D. from Yale University in 1966 and joined the Chemistry Department at Vanderbilt in 1968. He served as chairman of the department from 1982 to 1994. In addition to his research, he was deeply involved in the realization, planning, and construction of the new Chemistry Building from 1992 to 1995.

Professor Lidia Smentek received her Ph.D. in physics from N. Copernicus University, Toruń, Poland. She completed her Habilitation in 1993 and was awarded the National Title of Professor of Physical Sciences in 2009 by the president of Poland. Professor Smentek's association with Vanderbilt goes back to 1982 when she spent a year as a postdoctoral fellow in computer sciences with Professor Charlotte Frose Fischer. She has held the title of adjoint professor of chemistry since 1994. She is an atomic physicist and quantum chemist.
Lawrence J. “Larry” Marnett, Ph.D., the Mary Geddes Stahlman Professor of Cancer Research, and University Professor of Biochemistry and Chemistry, has been named Vanderbilt University Medical Center’s next associate vice chancellor for research and senior associate dean for biomedical sciences, effective September 1, 2014.

Marnett will succeed Susan Wente, Ph.D., who held the position for the past five years, and was named provost and vice chancellor for academic affairs for Vanderbilt University.

Marnett, who is also director of the A.B. Hancock Jr. Memorial Laboratory for Cancer Research, director of the Vanderbilt Institute for Chemical Biology, and professor of pharmacology, has been a member of Vanderbilt’s faculty since 1989.

In his new role Marnett will support cross-institutional collaboration for shared institutes and centers. He will work closely with other institutional leaders on the university’s newly unveiled strategic plan and how it will strengthen basic sciences across the institution.

“I want to welcome Dr. Marnett into this new role. Larry possesses both a distinguished career as an investigator and a rich tradition as someone with a passion for nurturing young scientists. He also brings a wealth of institutional knowledge and proven leadership experience, essential for Vanderbilt in 1989.

Among the leadership positions he has held since joining Vanderbilt include associate director for Basic Research Programs for the Vanderbilt-Ingram Cancer Center from 1993 to 2002. In 2002, Marnett was named the founding director for the Institute of Chemical Biology and has held this position since.

Marnett’s research focuses on the role of the enzyme cyclooxygenase-2 in cancer and inflammation, as well as on the contribution of oxidative metabolism to the generation of DNA damage and mutation.

His laboratory has used structure-based approaches in conjunction with medicinal chemistry to design selective cyclooxygenase-2 inhibitors as potential anti-inflammatory, cancer preventive, and anti-anxiety agents.

Marnett is a Fellow of the American Association for the Advancement of Science and the American Chemical Society and is the author of more than 450 research publications and fourteen patents. He is the founding editor-in-chief of the American Chemical Society journal, Chemical Research in Toxicology. He has trained forty-two Ph.D.s and forty-nine postdoctoral fellows.

“I am grateful to Jeff Balser and his senior leadership team for this opportunity,” Marnett said. “Vanderbilt is one of the top academic medical centers in the world comprising exceptional investigators, departments and centers. We are also part of a great university that is committed to integration of basic research and education across campus. The recent strategic plan establishes fostering transinstitutional initiatives as one of its top four goals.

“The opportunity to participate in that effort at an institutional level and to help build a sustainable and robust model for basic biomedical research is exciting,” he said.
Richard N. Armstrong and Jeffrey N. Johnston
Receive Cope Scholar Award for Research Excellence in Organic Chemistry

Two organic chemists at Vanderbilt University are among the ten recipients of the 2014 Arthur C. Cope Scholars Award that recognizes and encourages excellence in the field of organic chemistry. The Arthur C. Cope Scholar Awards were established in 1984 by the American Chemical Society Board of Directors, under the terms of the will of Arthur C. Cope.

Vanderbilt’s Cope Scholar award winners are Richard N. Armstrong, professor of biochemistry and chemistry, and Jeffrey N. Johnston, Stevenson Professor of Chemistry.

Armstrong is being recognized for his significant contributions to understanding detoxification enzymes that are essential components in organisms’ ability to resist toxic chemicals. He has applied cutting-edge technology and chemistry to identify the molecular mechanisms that several of these enzymes use to metabolize foreign molecules. He has also investigated the manner in which disease organisms adapt detoxification enzymes to protect themselves from antibiotics—a process that contributes to the erosion of efficacy of antibiotics that has become a major public health problem.

Johnston specializes in building complex organic molecules from scratch using purely chemical means. He has led the development of a novel method for chemically synthesizing peptides that promises to lower the cost and increase the availability of drugs based on natural compounds. In addition, he has developed other chemical short-cuts that allow more efficient methods for synthesizing a promising new drug for Chagas disease and a novel therapeutic being tested for its anti-cancer properties.

JEFFREY N. JOHNSTON

The Johnston laboratory specializes in reaction development and target-oriented synthesis. At Vanderbilt University, his group develops innovative methods for enantioselective synthesis by employing novel organocatalysts. These developments are tools that enable concise routes to natural products and therapeutic molecules. Collaborating with a diverse set of colleagues in biochemistry, cancer biology, and drug development, the Johnston lab advances the field of chemical biology by providing access to small molecules used to illuminate our understanding of the pathology of disease, and ultimately treatments to improve human health.

New reaction development is not unlike paving roads through undeveloped land.

Natural products with underexplored biological activity are the destinations, including alkaloids ((+)-serratezomine A and the ambiguines) and peptides. In their development of new reactions, the Johnston lab often uses the opportunity to discover and leverage unusual reactivity. They discovered that aryl and vinyl radicals could add to azomethine with regioselectivity opposite to that observed in most every case. The resulting functionality was perfectly positioned to enable a highly convergent synthesis of indoline α-amino acids and several complex alkaloid natural products.

Similarly, an unprecedented amide-forming reaction was discovered in the Johnston lab and incorporated into a short sequence that allows the convergent preparation of amides and peptides from non-carboxylic acid substrates. The significance of this development is illustrated by the enantioselective preparation of α-aryl glycinamides, amides that normally suffer from stereo-
separated into the pure (−)-Nutlin-3 using supercritical chiral chromatography. The Johnston lab developed an efficient synthesis to enantiopure (−)-Nutlin-3 employing a unique BAM organocatalyst. The key step involves an aza-Henry reaction developed in the Johnston lab utilizing the BAM organocatalyst for the first highly diastereo- and enantioselective addition of aryl nitromethanes to aryl aldimines, granting access to the more potent enantiomer of Nutlin-3.

An Ohio native, Jeffrey Johnston received his B.S. degree in chemistry (summa cum laude) from Xavier University and his Ph.D. with Leo Paquette at The Ohio State University in 1997. He was an NIH Postdoctoral Fellow at Harvard with David Evans prior to his independent career at Indiana University, where he began in 1999 and was ultimately promoted to professor of chemistry with tenure. In 2006, he moved with his research group to Vanderbilt University where he is currently Stevenson Professor of Chemistry and a member of the Vanderbilt Institute of Chemical Biology.

RICHARD N. ARMSTRONG

Armstrong has long been interested in detoxification enzymes. “I actually became interested in the detoxification of toxic compounds from my days at NIH when I worked with Don Jerina on epoxide hydrolases. That was basically what got me into the detoxification chemistry. Then when I moved to Maryland as an assistant professor, I continued to do work in the field, mostly focusing on glutathione transferases,” says Armstrong.

In the laboratory, cutting-edge technology and chemistry are utilized to identify and understand the molecular mechanisms of glutathione transferases and how they interact with foreign compounds. Methods include the use of three-dimensional crystal X-ray structures, kinetic assays utilizing NMR, HPLC, and UV spectroscopy, as well as Hydrogen-Deuterium Exchange Mass Spectrometry to observe conformational changes and ligand binding.

One of the projects in the Armstrong laboratory investigates FosB, a detoxification enzyme in bacteria that results in bacterial resistance to the antibiotic fosfomycin. In the Armstrong lab, postdoctoral researcher Dr. Matthew Thompson and Chemistry graduate students Mary Keithly and Michael Goodman as well as other Vanderbilt researchers have been investigating the structure and function of the FosB enzyme from the Gram-positive pathogen S. aureus and how it interacts with fosfomycin, a broad-spectrum antibiotic. In the study, the three-dimensional X-ray crystal structure of FosB from S. aureus was determined to a resolution of 1.15 Å. Along with various kinetic studies, significant insights were revealed as to how the enzyme operates in the presence of particular metal ions and thiol substrates.

Another project in the Armstrong lab involves the investigation of glutathione transferase enzymes known as Membrane-Associated Proteins in Eicosanoid and Glutathione Metabolism (MAPEG). Kristin Droege is a third-year Chemistry graduate student investigating the chemical interaction and dynamics of the MAPEG protein 5-lipoxigenase activation protein (FLAP) and how it allows the enzyme, 5-lipoxigenase (5-LOX) to catalyze the conversion of the fatty acid, arachidonic acid, to its product 5-hydroperoxyeicosatetraenoic acid (5-HpETE). Hydrogen-Deuterium Exchange Mass Spectrometry (HDX-MS) is a highly sensitive method that investigates the exchange rates of hydrogens on the amide backbone of an enzyme for the purpose of detecting conformational changes and interactions with substrates and other proteins. These studies aim to provide a more dynamic overview of how this complex interacts, leading to novel therapeutics specific for the 5-LOX/FLAP complex.

One other ongoing project in the Armstrong lab involves the investigation of the chemical mechanism and inhibition of another MAPEG enzyme, microsomal prostaglandin E, synthase 1 (MPGES1). MPGES1 is the most prominent prostaglandin synthase expressed during inflammation and catalyzes the conversion of PGH, to the prostaglandin PGE2. It is a promising therapeutic target for the treatment of chronic inflammation and potential drug candidates have been pursued by the pharmaceutical industry. Little is known about the chemical mechanism of the enzyme, with no physical evidence to support it. However, glutathione (GSH) appears to participate as a cofactor in the reaction. Michael Goodman, a second-year Chemistry graduate student, is currently synthesizing the serine analog of GSH, γ-L-glutamyl-L-serylglutamate (GOH). This compound will be used with MPGES1 to investigate the kinetics of the enzyme, giving further evidence to the chemical mechanism of the enzyme through spectroscopic techniques.
The pace of scientific innovation is ever-increasing as the methodologies and instruments available to researchers continue to improve. The early adopters of new investigative technology are modern-day pioneers of science, finding applications for these new tools that even their inventors could not have foreseen. John McLean's laboratory is at the forefront of one of these wild frontiers of scientific inquiry where new methodologies, instrumentation, and applications are explored in the application of mass spectroscopy to biology and medicine.

Professor of Chemistry John McLean, Ph.D., and his colleagues have made quite an impact with their work at Vanderbilt. Their work in the field of mass spectroscopy has led Waters Corporation, a three-billion dollar developer and manufacturer of analytical instruments, to name his lab a Waters Center of Innovation, indicating their recognition of the research group as one of the leaders in the field of health and life science research.

Agilent Technologies, formerly the scientific development arm of Hewlett-Packard, has granted McLean the Agilent Thought Leader Award in recognition of his contributions to ion mobility mass spectrometry (IM-MS) focused on advanced applications, including comprehensive biomolecular systems analysis and synthetic and chemical biology.

Vanderbilt University is also proud to recognize the achievements of one of their own and have recently granted McLean the position of Stevenson Professor of Chemistry, one of the university’s distinguished endowed chairs.

A major goal of medical research in recent years has been the identification of biological molecules that indicate otherwise obscure disease states in patients. These molecules, called biomarkers, could be proteins, lipids, carbohydrates, or oligonucleotides that are all naturally present within a potential patient. A change in the health of the patient should be matched by a change in the concentrations of the many biomolecules present in the patient. If appropriate biomarkers are identified, they could be used for early detection of conditions such as various cancers, infections, and toxin exposures before symptoms are presented. Aided by emerging analytical techniques, the medical community stands at the edge of potential significant breakthroughs in diagnostic science.

The McLean laboratory takes a systems approach to biology. Systems biology is an attempt to understand living organisms by observing as much of the organism as possible. By monitoring many aspects simultaneously, it becomes possible to see how the diverse mechanisms of a living organism fit together and interact with one another. By developing instruments, methods, and analysis techniques capable of monitoring many biological molecules at once, scientists are provided with a big picture view of an organism without losing finer details. This approach requires investigators to be able to analyze samples and process data very quickly.

The McLean group uses ion mobility-mass spectrometry, or IM-MS, to identify potential biomarkers in biological samples. The field of ion mobility experiments, developed in the late 1800s, is itself experiencing something of a renaissance in recent years, as improvements in technology have enhanced the technique's power and compatibility with other devices. Because of the vast range of diseases investigated and the staggering number of unique biological molecules that must be observed for each disease, one of the major challenges faced by biomarker investigators is how to improve experimental throughput to handle the huge number of samples and amount of experimental data involved in the research. McLean’s research proceeds on several fronts: the development of more versatile IM-MS instruments, exploration and refinement of IM-MS techniques, and streamlining the interpretation of IM-MS experimental data.

The use of IM-MS has advantages over more traditional mass spectrometry approaches when it comes to handling large pools of samples. An IM-MS instrument can run a sample in fractions of a second whereas other related
techniques such as liquid chromatography-mass spectrometry require minutes to hours to complete their analysis. Reducing the time required to analyze a sample is essential to systems biology investigations. In some cases even a few seconds per sample may still be too slow to tackle the problem of biomarker identification as the IM-MS step is often a bottleneck in multiplexed studies in which multiple samples are prepared simultaneously. This problem is being addressed through the development of an eight-channel IM-MS instrument capable of conducting multiple experiments simultaneously and potentially speeding up research by nearly an order of magnitude. This device will streamline investigations involving large numbers of samples, such as in high-throughput screening of drug libraries.

The group is also preparing a variable temperature ion-mobility device to improve the scientific understanding of the relationship between temperature and molecular structure. This knowledge is expected to be extremely useful in understanding the interactions of various molecule classes such as the protein-ligand interactions which are responsible for the efficacy of the majority of pharmaceutical compounds.

Development of new instruments is by no means the only way to accelerate research. The McLean lab also excels in finding new ways to use the existing resources available to the field. In order to explore the theory that not only the concentration but also the location of potential biomarkers in the tissues is important, techniques for spatial resolution of tissues have been developed. In collaboration with Professors Richard Caprioli, Sharon Weiss, and Donna Webb and the National Research Resource for Imaging Mass Spectrometry at Vanderbilt University, the McLean group is using a technique called matrix-assisted laser desorption/ionization in conjunction with a moving sample platform to perform rapid IM-MS analysis across surfaces of entire organs or even organisms. This technique generates an atlas revealing the locations and identities of the many biomolecules in a sample and allows investigators to determine whether a given disease state causes unusual enrichments or depletion of potential biomarkers in specific organs with spatial resolution as small as a few micrometers. The research group has also developed an application of IM-MS to analyze the surfaces of metal nanoparticles too small for microscopy studies. These particles have broad application in both medical diagnostics and treatment strategies.

The final bottleneck in biomarker studies is data analysis. A single IM-MS analysis may reveal thousands to hundreds of thousands of different molecules at various concentrations and experiments may range from having dozens to thousands of samples, leading to the production of terabytes of data from a single experiment. The development of new approaches to process and understand this data is an important part of the McLean labs work. Members of the lab have developed and continue to work on a wide variety of approaches to this problem. Approaches include algorithms for the classification and eventual identification of the many unknown molecules in biological samples, as well as the application of tools borrowed from astronomy and Internet data mining to allow quick visual interpretation of vast quantities of data. These techniques allow the rapid comparison of samples, for example, by highlighting which of the many analyzed molecules are more or less prevalent in a cancer patient compared to a healthy patient.

Computer modeling is another tool utilized by the group to improve understanding of molecular structure. By comparing ion-mobility data to theoretically generated molecular structures, the lab helps determine a more comprehensive knowledge of how and why molecules take certain confirmations and consequently why those molecules interact with other molecules the way they do.

The ability to replicate real-world observations is a key test for scientific models. An emerging application of systems biology is the development of synthetic biological systems. The McLean group, in collaboration with Professors David Clifft in Chemistry and John Wikswo in Biomedical Engineering, as well as investigators at Harvard University and Los Alamos National Labs, are developing replicas of human biology for medical testing. It is hoped that these “organ-on-a-chip” platforms will provide realistic test environments for the efficacy of medical treatments and the effects of toxic compounds. The ability to build and model complex systems of multiple organs will be a profound milestone in human understanding of complex biological systems.

The new techniques and discoveries the lab and its many collaborators are responsible for are important advancements in systems biology. The McLean laboratory is making significant contributions to the omics fields involved in the search for new biomarkers and to the process of drug discovery. There can be no doubt that future developments in the research group will continue to excite the curiosity of and be of service to the research community.

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As of July 1, 2014, Steve Townsend joined the faculty of Vanderbilt University as assistant professor of chemistry. Townsend earned his Ph.D. at Vanderbilt in 2010, where he was a UNCF/Merck Predoctoral Fellow, under the advisement of Gary Sulikowski. His Ph.D. thesis was entitled “Studies Toward the Total Synthesis of Bielschowskysin,” and focused on the total synthesis of a member of the important furanocembrane class of natural products, which has known anti-cancer and anti-malarial properties. He concluded his time at Vanderbilt by spending six months in Craig Lindsley’s lab synthesizing potassium channel activators and glutamate receptor allosteric ligands.

In 2011, he began his postdoctoral work as a National Cancer Institute Postdoctoral Fellow under Samuel Danishefsky at the Memorial Sloan-Kettering Cancer Center and Columbia University in New York City, where he was involved in the total synthesis of erythropoietin and para-thyroid hormone related protein. He also synthesized the tumor-associated antigen GM2 for use in a vaccine against ovarian cancer that recently finished first-phase clinical trials.

At Vanderbilt, Townsend’s research will focus on the synthesis and evaluation of carbohydrates, proteins, and other compounds found in human milk. “Our global goal is to synthesize compounds that will allow us to take advantage of the benefits of human milk for use in infant formula and possibly adult supplements,” says Townsend. When his wife became pregnant, Townsend was appalled when he looked into the current practice in baby feeding.

“We only in the United States do the big pharmaceutical companies dominate public opinion so thoroughly that they have convinced most Americans that infant formula is just as good as breast milk. That simply isn’t the case,” he said. “Breast milk is a complete nutritional source for babies that can’t be adequately replaced by any other food, including infant formula.”

The current major project in the Townsend group focuses on...
components of human breast milk, known as human milk oligosaccharides (HMOs), which fall under the broader term “glycoconjugates.” HMOs are the third-largest component of human breast milk and are made up of long chains of individual sugar molecules. Even though HMOs make up a large percentage of human milk, they are largely indigestible by humans. This interesting fact has led to research indicating that HMOs are both useful as probiotics for beneficial bacteria in the human gut and as decoys to deter harmful bacteria from attaching to the intestinal wall. Since these discoveries, companies such as Abbott Laboratories have sought to take advantage of these biological benefits by including HMO analogs, known as galactooligosaccharides (GOs) in baby formulas.

“Because human milk features some pretty complex glycans, pharma attempts to mimic those structures in infant formula by utilizing GOs, which are easy to prepare. As you can imagine, these compounds are nothing like the complex compounds actually present in human milk,” says Townsend. Not only is human milk chemically complex, it also differs from woman to woman, and its chemical makeup varies over the course of breastfeeding an infant. He has begun developing novel ways for synthesizing HMOs and exploring their pro- and antibiotic properties.

There are currently few ways to artificially prepare specific oligosaccharides, and HMOs have a highly complicated composition. The combination of these two factors makes it difficult to study the behavior and biological properties of specific components of HMO mixtures. Townsend’s group aims to help counteract this methodological deficiency by developing state-of-the-art methods for assembling oligosaccharides like HMOs. “What [we want] to do is synthesize small HMOs and design methods to polymerize them, in order to make better GOs,” says Townsend. The synthesized glycoconjugates could then be used to study the specific effects of each substance in living beings. These techniques could ultimately be used to make glycoconjugates to help control biological phenomena such as the type and amount of gut flora in babies, and to help improve human health in general. His ultimate goal is to develop a new kind of infant formula that contains multiple HMOs that duplicate some of human milk’s nutritional and protective qualities.

The Townsend lab will also pursue projects concentrated on the development of techniques for site-specific protein modifications. Most of the chemical processes that occur in our bodies are performed by proteins. Major factors influencing how a protein does its job are post-translational modifications—modifications made to the proteins after they have been synthesized by our bodies. These post-translational modifications play direct roles in many metabolic processes; for example, modification of extracellular proteins with sugars is necessary for cellular recognition by the immune system. Despite the impact that these modifications can have on protein function, there are relatively few known ways to posttranslationally modify proteins in the lab, and these techniques are mostly restricted to specific amino acids such as lysine or cysteine. The Townsend group aims to expand these techniques to include additional amino acids. These developments will help enable site-specific amino acid modifications that could be leveraged to alter the structure and function of both natural and man-made proteins.

Currently, his research team consists of John Hayes and Dorothy Ackerman, both second-year graduate students.

Susan Verberne-Sutton Joins Vanderbilt Chemistry Faculty as Senior Lecturer

Susan Verberne-Sutton has joined the faculty in the Department of Chemistry as a senior lecturer. In addition to general chemistry courses, she will teach analytical chemistry as well.

Verberne-Sutton earned her bachelor of science degree in chemistry from Southeastern Louisiana University in Hammond, Louisiana, in 2000 and a master’s degree in chemistry, with an emphasis in inorganic chemistry, from the University of California, Davis, in 2004. While at UC-Davis, she completed a semester-long internship with a start-up electronics company, Kovio, Inc., in Sunnyvale, California.

Verberne-Sutton taught general chemistry courses at Southeastern Louisiana University before moving to Nashville, Tennessee, where she worked as an analytical chemist for Environmental Science, Inc. in Mount Juliet, Tennessee, where she operated ICP-OES instruments for ultra-low detection of trace metals. She became an instructor of chemistry and undergraduate laboratory coordinator at Tennessee State University, where she coordinated all undergraduate teaching laboratories and wrote new laboratory manuals with Web enhancement for four undergraduate chemistry classes, in addition to teaching general chemistry courses. Verberne-Sutton joined the Division of Research and Sponsored Programs at TSU, where she purchased, installed, and trained researchers on analytical equipment in the Nanoscience and Biotechnology Core Facility.

Upon deciding to complete her Ph.D. in 2012, she joined the Garno research group at Louisiana State University. Verberne-Sutton’s research focused on the development of a new sample stage for photocurrent measurements using scanning probe microscopy.
Ned Porter has been a member of the Vanderbilt Chemistry Department since 1998, when he joined the department as Stevenson Professor. While at Vanderbilt, he served as the chairman of the Department of Chemistry from 2003 to 2009, and was associate director of the Vanderbilt Institute of Chemical Biology from 2003 to 2012.

In fall 2013, Porter retired from teaching, and now maintains an active research program in the department as research professor, and gives occasional lectures in various graduate courses. He continues his research efforts with the support of grants from the NIH and NSF and is a member of the Vanderbilt Center for Molecular Toxicology and the Vanderbilt Kennedy Center.

Porter received his B.S. from Princeton University in 1965, where he majored in chemical engineering; his Ph.D. in chemistry was from Harvard University. He joined the faculty of the Department of Chemistry at Duke University in 1969, and rose through the ranks to James B. Duke Professor of Chemistry.

Over the years, Porter developed and maintains active research collaborations with colleagues from Vanderbilt, as well as at institutions around the world. He is the author of more than 280 publications and a book, *Control of Stereochemistry in Free Radical Reactions; Concepts, Guidelines, and Synthetic Applications*. He has been an Arthur C. Cope Scholar and a Norris Award winner of the American Chemical Society; a C. K. Ingold Prize winner of the Royal Society (Great Britain); an NIH Career Awardee; a Humboldt Senior Fellow (Germany); and an NIH MERIT Awardee. He is a Fellow of AAAS and the American Chemical Society. Over the years, Porter spent sabbaticals at Cal Tech, the University of Nijmegen (the Netherlands), the University of Freiburg (Germany), The Technische Hochschule at Darmstadt (Germany), The University of New South Wales (Sydney), and The Australian National University (Canberra).

His main research interests evolved from studies of mechanisms of free radical reactions, including the oxidation of lipids, to investigations of cholesterol biosynthesis disorders. These recent studies have focused on a human genetic condition called Smith-Lemli-Opitz Syndrome (SLOS), an inborn error of cholesterol synthesis. It is an autosomal recessive, multiple malformation syndrome caused by a mutation in the enzyme 7-Dehydrocholesterol reductase, or DHCR7. It causes a broad spectrum of effects, ranging from mild intellectual disability and behavioral problems to lethal malformations. His discoveries have identified SLOS as an oxidative stress disorder and they forge a direct connection between a highly oxidizable cholesterol biosynthetic precursor, 7-dehydrocholesterol, and SLOS pathology.

Among the many accomplishments of Ned Porter in the field of chemistry research, including studies of mechanisms of free radical reactions and SLOS, Porter mentored more than 150 graduate students and postdoctoral associates during his career. Larry Marnett (left) was his first graduate student, and Connor Lamberson (right) will likely be his last graduate student.

From First to Last, Ned Porter Nurtures Scientific Excellence

Among the many accomplishments of Ned Porter in the field of chemistry research, including studies of mechanisms of free radical reactions and SLOS, Porter mentored more than 150 graduate students and postdoctoral associates from 1969, when he joined the faculty at Duke University, to present, at Vanderbilt University.

After Porter joined the faculty at Duke, his first graduate student was Lawrence J. (Larry) Marnett. Marnett graduated from Rockhurst College in 1969, entered Duke University graduate program to pursue a Ph.D. in chemistry, and chose as his mentor Ned Porter, who had just joined the faculty at Duke as associate professor of chemistry. Marnett received his Ph.D. in 1973.

Since then, Marnett completed postdoctoral training at the Karolinska Institute with Bengt Samuelson and joined the faculty at Wayne State in 1975. He subsequently joined the faculty at Vanderbilt in 1989. He is the Mary Geddes Stahlman Professor of Cancer Research, director of the A.B. Hancock Jr. Memorial Laboratory for Cancer Research, director of the Vanderbilt Institute of Chemical Biology, and professor of chemistry. As of September 1, 2014, Marnett was named associate vice chancellor for research and senior associate dean for biomedical sciences.

Porter’s last graduate student will likely be Connor Lamberson. Lamberson came to Vanderbilt initially as a rising junior at Augustana College in South Dakota, through the VICB Research Experience for Undergraduates in the summer of 2009, and again in 2010. The first summer (2009), he worked with Ned Porter and Libin Xu, a research associate professor in Porter’s lab. The project involved synthesis of a specific product that was isolated from free radical oxidation of the 7-dehydrocholesterol, thought to be involved in the
Charles (Chuck) M. Lukehart Retires

Chuck Lukehart retired this year at the age of sixty-seven from his professorship position in the Department of Chemistry at Vanderbilt University. His long career at Vanderbilt started forty-one years ago in 1973, after receiving his Ph.D. from the Massachusetts Institute of Technology under Dr. F. A. Cotton. Lukehart was interested in organometallic chemistry of the transition metals. Since arriving at Vanderbilt, he has published nearly 200 peer-reviewed articles, edited three books, filed six patents, and mentored M.S. and Ph.D. students.

Lukehart has served Vanderbilt in many different roles in his career. He was the Department of Chemistry director of graduate studies for twenty-one years and chair or assistant chair of Chemistry for sixteen years; helped found the Interdisciplinary Graduate Program in Materials Science; and elected to the Arts and Science Faculty Council and the Faculty Senate. He has also served the chemistry community as chairman of the Nashville Section of the American Chemical Society.

Lukehart’s students remember him fondly, having established the Charles M. Lukehart Endowment Fund for Graduate Study in Chemistry in his honor in 1995. He received the 2009 College of Arts and Science Award for Excellence in Graduate Mentoring, and he was a three-time recipient of the American Chemical Society Student Affiliates Excellence in Teaching Award.

Joel B. Tellinghuisen Retires

Professor of Chemistry, Emeritus

Joel Tellinghuisen earned his A.B. from Cornell University in 1965 and his Ph.D. in chemistry from the University of California, Berkeley, in 1969. He did postdoctoral research in spectroscopy and chemical physics at the University of Canterbury (NZ), the University of Chicago (with Nobel Laureate Robert Mulliken) and, with the support of a National Research Council Fellowship, at the National Oceanic and Atmospheric Administration’s Aeronomy Laboratory in Boulder, Colorado.

Professor Tellinghuisen came to Vanderbilt University in 1975 as an assistant professor in the Department of Chemistry. He was promoted to associate professor in 1980 and professor in 1983.

Professor Tellinghuisen’s early research emphasized ultraviolet and visible spectroscopy relevant to the understanding and development of excimer lasers, like those now widely used in laser eye surgery. More recently he has focused on statistical data analysis methods of interest to experimental methods more commonly used in the life sciences, like titration calorimetry and quantitative real-time polymerase chain reaction procedures. With his professional and student collaborators, he has published more than 200 refereed papers and book chapters and has given more than 200 invited and contributed presentations on his work.

Professor Tellinghuisen has taught seventeen different courses in chemistry and has supervised undergraduate research projects by thirty students. The appreciative parents of one such student honored Tellinghuisen by endowing an award in his name, given each year since 2003 to a graduating senior in Phi Beta Kappa in recognition of outstanding performance in undergraduate research.
Professor David W. Wright has been named chairman of the Department of Chemistry, effective July 1, 2014. He will succeed Michael P. Stone, who served as chair from 2009 to 2014. Wright was also named a Stevenson Professor of Chemistry this spring.

Professor Wright completed his doctoral dissertation at the Massachusetts Institute of Technology under the late Prof. Orme-Johnson, where he made significant contributions toward elucidating the structure of the co-factor of the enzyme nitrogenase. Subsequently, he moved to Boston College for his postdoctoral research with Prof. William H. Armstrong on the structure and reactivity of the oxygen-evolving complex of Photosystem II.

In 2001, Wright was recruited to Vanderbilt University as assistant professor of chemistry. At Vanderbilt, his work is focused on the role of heme detoxification in the malaria parasite, leading to new approaches to drug discovery and low resource point-of-care diagnostics. The other area of his research is focused on the amazing structural processing of biomaterials in nature. He is interested in why beetle shells and butterfly wings are so iridescent, how diatoms make their intricate glass houses, and how these lessons can lead to new and revolutionary materials for applications such as biomedical sensors and next-generation batteries.

Wright has received a number of awards, including the Young Investigator Award from the Society of Infectious Diseases; a National Science Foundation CAREER award; and in 2011 was selected by the National Academy of Sciences and the Kavli Foundation as a Kavli Fellow at the Frontiers of Science.

The Stevenson Chair honors Eldon Stevenson Jr. (1893–1972), a member of the Vanderbilt Board of Trust and president of National Life and Accident Insurance Co. in Nashville. Generous gifts from Stevenson helped make possible the original construction of the Vanderbilt University natural science complex in the early 1960s.
John A. McLean Promoted to Stevenson Professor of Chemistry

Professor John A. McLean has been promoted to Stevenson Professor of Chemistry at Vanderbilt University. McLean completed his doctoral dissertation at the George Washington University with Prof. Akbar Montaser, where he made significant contributions in plasma spectrochemistry in the development of new technologies for the analysis of complex and limited radionuclide and biological samples. Subsequently, he performed postdoctoral research at Forschungszentrum Jülich in Germany with Prof. J. Sabine Becker, and then as a postdoctoral at Texas A&M University with Prof. David H. Russell in biological mass spectrometry.

Working with David Russell from 2001 to 2006, he constructed ion mobility-mass spectrometers capable of broad-scale analyses of extremely complex biological samples, termed “panomics,” on the basis of both molecular structure and mass. Sophisticated ion mobility-mass spectrometry platforms were subsequently released by multiple leading global scientific instrument manufacturers.

In 2006, McLean was recruited to Vanderbilt University as assistant professor of chemistry, through both the Department of Chemistry and the Vanderbilt Institute of Chemical Biology. At Vanderbilt, McLean and colleagues focus on the conceptualization, design, and construction of structural mass spectrometers, specifically targeting complex samples in systems, synthetic, and chemical biology as well as nanotechnology.

His group applies these strategies to forefront translational research areas in drug discovery, personalized medicine, and “human-on-chip” synthetic biology platforms. McLean and his group leverage these strengths with those across Vanderbilt, nationally, and internationally in academe, industry, and government through cutting-edge interdisciplinary collaborations.

McLean has received a number of awards, including the Agilent Thought Leader Award, Excellence in Teaching Award from the student members of the American Chemical Society, a Defense Threat Reduction Agency Research Award, an American Society for Mass Spectrometry Research Award, a Spectroscopy Society of Pittsburgh Award, an R&D 100 Award, and the Bunsen–Kirchhoff Prize from the GDCh (German Chemical Society), among others.

The Stevenson Chair honors Eldon Stevenson Jr. (1893–1972), a member of the Vanderbilt Board of Trust and president of National Life and Accident Insurance Co. in Nashville.

David E. Cliffel Promoted to Professor of Chemistry

David Cliffel has been promoted to professor of chemistry at Vanderbilt University. Cliffel’s promotion recognizes his internationally recognized research and scholarship in the field of analytical chemistry, as well as his outstanding undergraduate and graduate teaching.

In addition to his primary appointment in Chemistry, he has secondary appointments in the Department of Pediatrics and with the Diabetes Research and Training Center within VUMC. He is a faculty fellow in the Vanderbilt Institute for Integrative Biosystems Research and Education, and a member of the Steering Committee in the Vanderbilt Institute of Nanoscale Science and Engineering where he oversees the Biomolecular Nanostructures Laboratory Facility.

He received a B.S. in chemistry and a Bachelor of Electrical Engineering from the University of Dayton in 1992. Cliffel received an NSF Predoctoral Graduate Fellowship and earned his Ph.D. in chemistry in 1998 from the University of Texas at Austin, working with Professor Allen J. Bard. He did his postdoctoral work with Professor Royce W. Murray at the University of North Carolin, Chapel Hill, working on the electrochemistry of monolayer protected clusters. He received the Society of Electroanalytical Chemistry (SEAC) Young Investigator Award in 2005, and an ACS Younger Chemistry Committee Leadership Development Award in 2004.

Cliffel currently serves as a standing member of the NIH Review Panel for Nanotechnology in Biology and Medicine until the end of 2014, the SEAC Board of Directors until 2016, and two steering committees for the Electrochemical Society in physical and analytical electrochemistry and in organic and biological electrochemistry until 2015. His current research concentrates on the electrochemistry and analytical chemistry of nanoparticles and photosynthetic proteins, and his group has invented the multianalyte microphysiometer for metabolic profiling and toxicology.
American Society for Mass Spectrometry Recognizes Richard Caprioli for Distinguished Contributions

Richard M. Caprioli was awarded the 2014 ASMS Award for a Distinguished Contribution in Mass Spectrometry for the development of MALDI Imaging Mass Spectrometry and its application to molecular mapping of tissues in biology and medicine.

Caprioli’s work led to a new paradigm for molecular imaging of tissues, founded on the development of matrix assisted laser desorption ionization (MALDI) imaging mass spectrometry. This is now a burgeoning application of mass spectrometry whereby molecular measurements can be made directly from tissues, adding significantly to the information that can be obtained from these specimens.

This work has made significant contributions to the study of proteins, lipids, metabolites, and pharmaceutical compounds. Since publication of Caprioli’s seminal 1997 paper (Anal. Chem. 69(23), 4751-4760) showing the power of MALDI imaging mass spectrometry for tissue analysis, he has pioneered advancements in sample preparation, instrumentation, and informatics approaches that have considerably advanced the technology and made it accessible to hundreds of laboratories worldwide.

The impact of his work is evident in the numerous commercial platforms that employ this technology. Approximately 2,500 papers have been published to date on the subject of MALDI imaging mass spectrometry.

Caprioli is the Stanford Moore Chair in Biochemistry, professor of chemistry, and director of the Mass Spectrometry Research Center at Vanderbilt University.

Sandra Rosenthal Named Winner of 2014 SEC Faculty Achievement Award

Sandra J. Rosenthal, Jack and Pamela Egan Professor of Chemistry at Vanderbilt, is a recipient of the 2014 SEC Faculty Achievement Award. These annual awards recognize a faculty member from every Southeastern Conference university who demonstrates outstanding records of teaching, research, and scholarship.

To be eligible for the SEC Faculty Achievement Award, a professor must be a teacher or scholar at an SEC university; have achieved the rank of full professor at an SEC university; have a record of extraordinary teaching; and have a record of scholarship that is recognized nationally and/or internationally.

“The 2014 SEC Faculty Achievement Award winners are some of our nation’s most accomplished instructors, researchers, and scholars,” Jay Gogue, president of Auburn University and president of the Southeastern Conference, said. “It is my great pleasure to preside over an intercollegiate athletics conference that not only recognizes their work, but strives to support it as well.”

“These...professors positively represent the breadth and depth of education in the Southeastern Conference, and I want to congratulate each of them,” SEC Commissioner Mike Slive said. “The commitment to their students, universities, and communities is truly commendable.”

Selected by a committee of SEC provosts, the SEC Faculty Achievement Awards and the SEC Professor of the Year Award are part of SECU, the academic initiative of the Southeastern Conference, which sponsors, supports, and promotes collaborative higher education programs and activities involving administrators, faculty, and students at its fourteen member universities.

Craig Lindsley Wins John J. Abel Award in Pharmacology

Vanderbilt University’s Craig Lindsley, Ph.D., has won the 2014 John J. Abel Award in Pharmacology for young investigators from the American Society for Pharmacology and Experimental Therapeutics (ASPET).

Lindsley, director of Medicinal Chemistry and co-director of the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD), and William K. Warren Jr. Professor of Medicine, was honored for “his fundamental and transforming impact on pharmacology, medicinal chemistry, and drug discovery in the fields of neuroscience and cancer biology.”

The award, named for ASPET’s founder, was presented to Lindsley on April 26, 2014, during ASPET’s annual meeting in San Diego.

Lindsley’s award lecture, entitled “Exploiting Allosteric Sites for Target Modulation,” was given April 28.

He is the third Vanderbilt scientist to receive the award, which has been given sixty-seven times since 1947. F. Peter (Fred) Guengerich, Ph.D., won the award in 1984, and Lee Limbird, Ph.D., in 1987.

“Receiving this award is a great honor and a continued testament to the science, environment, and amazing colleagues here at Vanderbilt that made this possible,” said Lindsley, who is also professor of pharmacology and chemistry. Lindsley is widely recognized as a pioneer who brought technology-enabled synthesis to the forefront of drug discovery chemistry. Using the technology platform he developed, he has discovered and developed high-quality novel compounds in multiple therapeutic areas, from cancer to neuroscience, and pioneered the medicinal chemistry of allosteric modulation.
Assistant Professor Janet Macdonald recently travelled to the Israeli Embassy in Washington, D.C., to accept the Bergmann Memorial Award from the United States-Israel Binational Science Foundation (BSF). Said Yair Rotstein, executive director of the BSF, “We annually give out the Bergmann Memorial Award to a young scientist who offers an exceptional research proposal...[Macdonald’s] research into nanotechnology and its use in clean energy is very exciting.”

The BSF is a grant-awarding institution that promotes collaborative research in a wide range of basic and applied scientific disciplines, established in 1972 by an agreement between the governments of the United States and Israel. The BSF’s income is derived from interest on an endowment of $100 million which was established in equal parts by the United States and Israeli governments. The organization is governed by a Board of Governors consisting of five American and five Israeli members, appointed by their respective governments. The BSF’s base of operations is in Jerusalem, Israel.

The Bergmann Memorial Award, the award for promising young scientists, was established in February 1976 to honor Professor E.D. Bergmann, an organic chemistry researcher and one of the leaders who established the BSF.

The award comes with a grant to conduct collaborative research on hybrid nanoparticles with Professor Uri Banin from the Hebrew University, a previous winner of the Bergmann Award in 1997. Macdonald worked with him previously during her two-year postdoctoral position in Jerusalem.

Macdonald’s research focuses on the synthesis of nanoparticles, tiny bits of solids that are only hundreds or thousands of atoms large. Her aim is to solve problems in solar energy capture with nanoparticles that have two or more different types of materials connected on the same particle.

Her research group has been synthesizing nanoparticles of a new material called Wurtzite Copper Indium Disulfide which absorbs sunlight very strongly. The vision is that by adding reactive pieces of metal to the particle, sunlight can be used as energy to drive chemical reactions that make green fuels.

Macdonald and Ph.D. student Alice Leach of the Interdisciplinary Graduate Program in Materials Science at Vanderbilt travelled to Jerusalem to Banin’s laboratory in May. Their experiments there will discover the details of how the new nanoparticles absorb light and what happens to that energy.

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The realm of medical research is inundated with individuals whose sole goal is to formulate a single novel idea that may somehow shape the way future generations relate to the diseases that plague the human race. However, it has been seen time and again that nature has a way of creating therapeutics so robust and effective that they easily outstrip most synthetic medical remedies. Furthermore, many of the most effective synthetic and natural product molecules are exceedingly hydrophobic. The underlying issue which prevents these cures from being readily utilized today lies in the inherent desire of the human immune system to destroy any entity deemed foreign to the body. This dynamic system, which has evolved as a defense mechanism against disease, can wreak havoc on the therapeutics which have been found efficacious as treatments for many serious ailments that attack one's health. Whether this limitation arises from the rapid removal of the

Alternative Methods of Drug Delivery

By Benjamin Spears, Graduate Student, Harth Lab
therapeutics or an inability to remain in solution in physiological conditions, the solution is the same: alternative methods of delivery must be created.

Glycidol has been studied for some time as a viable candidate to form small molecule convoy systems. Its analogous structure to the currently implemented poly(ethylene glycol) (PEG), as well as its abundance of primary and secondary hydroxyl groups provides a system that is oxidatively and thermally stable, nontoxic, biocompatible, and exceedingly hydrophilic. The formation of single-step dendrimer-like macromolecules, that maintain the abilities of dendrimers without the painstaking process of dendrimer growth, have garnered much of the attention from those interested in the formation of poly(glycidol). The latent AB2 monomer characteristic of glycidol allows for additional control through a step-wise polymerization rather than a rampant polycondensation, which is the usual reaction mechanism seen with other AB2 type monomers. The capability of the glycidol monomer to suppress this AB2 characteristic until after the ring opens has contributed to the success of glycidol-based polymers. This added control allows the synthesized poly(glycidol) to maintain the benefits of other hyperbranched systems while affording macromolecules with polydispersity indices (PDIs) of 1.5 and lower, much more manageable than the PDIs of 5 or greater observed with other AB2 type monomers. Work in this field has been successful in forming hyperbranched poly(glycidol) systems, in varying sizes, with low polydispersity indices (PDIs) and controlled degrees of polymerization (DP). These systems could very well become advantageous as alternatives to multistep dendrimer species.

We discuss the formulation of the first notable method for the formation of semibranched poly(glycidol). These novel architectures afford a range of motion hitherto unachievable by the dendritic species. The structures exhibit a branched backbone, shown to be advantageous for biological applications, which the linear systems do not possess. Although the hyperbranched systems previously formed through the polymerization of glycidol have shown some applicability, the ability to form polymers with a controlled degree of branching is advantageous. These lower branching systems will retain the benefits of the hyperbranched system’s “fuzziness” while allowing for a wider range of subsequent reactions. It is hypothesized that this secondary reaction ability will impart a greater degree of versatility to the already robust poly(glycidol) architecture. This increase in post-modification capability will increase the viability of the synthesized polymer systems and allow for novel macromolecules.

In order to study the effect of this new class of poly(glycidol) polymers, protein polymer conjugates were formed using albumin from bovine serum. The resulting conjugates were characterized to confirm polymer attachment as well as size of the attached polymer species, and circular dichroism measurements were performed to validate the retention of the protein’s three-dimensional structure. Finally, the conjugate species were tested for their bioactivity. The results obtained were comparable to similar studies done with PEG-based structures. Future research is aimed at the formulation of biologically relevant glycidol-protein conjugates and the study of their in vivo pharmacokinetics and circulation time.

From the treatment of chronic hepatitis and types of lymphocytic leukemia to stimulation of the production of white blood cells, PEGylated proteins have had a dramatic impact on the treatment of some of the most devastating diseases. The advent of an analogous system, with increased modification potential, is an avenue that can lead to even more beneficial treatment options. The research being done is an exciting step towards new methods of combating the most deadly diseases plaguing our world today. Spears, Benjamin R.; Waksal, Julian; McQuade, Caitlin; Lanier, Laura; Harth, Eva M. Controlled branching of polyglycidol and formation of protein-glycidol bioconjugates via a graft-from approach with "PEG-like" arms. Chem. Commun. 2013, 49, 2394.
Using Deuterated Fatty Acids to Combat Oxidative Stress
Strong scientific attention has been directed to the free radical oxidation (or peroxidation) of polyunsaturated fatty acids (PUFAs) in recent years since the process has been associated with a variety of human pathologies, such as heart disease, environmental exposures, and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Natural antioxidants such as Vitamin E (α-tocopherol being the main component) are excellent inhibitors of these peroxidation reactions in solution. However, clinical therapies consisting of antioxidant treatment in patients with diseases associated with peroxidation have been underwhelming.

Due to the limited success of antioxidant therapies, a new strategy to diminish lipid peroxidation in vivo that is being pursued by our collaborators is to replace the reactive hydrogen atom of PUFAs with deuterium atoms. Deuterium is a heavy isotope of hydrogen, and much more difficult to remove via free radical species generated during peroxidation. The strategy has seen recent success: in one example, treatment of yeast with a small percentage of deuterated PUFAs increases resistance of the yeast to oxidative stress. Another report has shown that these compounds also diminish neurodegeneration in a mouse model of Parkinson's disease.

Ned Porter's lab has looked into the perceived “protective” effects afforded by these deuterated PUFAs. This is done by measuring rate constants of peroxidation for natural and deuterated PUFAs. Using these values we are able to calculate kinetic isotope effects (KIE), which ultimately gives us the relative oxidizability of the natural PUFA compared to the deuterated PUFA. Values for KIE are typically less than 7. Our initial experiments with the deuterated PUFAs resulted in measured KIEs of around 10, demonstrating that these compounds were some ten-fold less reactive than their natural counterparts when no antioxidants were present.

Since α-tocopherol is naturally abundant, the results above spurred us to broaden the study to oxidations in the presence of α-tocopherol. KIE values for these experiments reached as high as 36, far higher than the previous KIEs measured in the absence of an antioxidant! Why is this the case, and what are the implications?

Typical peroxidation reactions generate a carbon-centered lipid radical through the removal of one of the reactive hydrogen atoms on the PUFA. Once this radical is formed, molecular oxygen can rapidly add in to form a peroxyl radical. These peroxyl radicals propagate the reaction by abstracting another reactive hydrogen from a neighboring PUFA, generating a lipid peroxide and a new carbon centered lipid radical. Buildup of these peroxides is detrimental to health and is associated with the pathologies listed above. Antioxidants such as α-tocopherol donate a hydrogen atom to the peroxyl radical, effectively inhibiting the peroxidation reaction by eliminating the propagating species while at the same time reducing the overall levels of lipid peroxides formed. The newly formed tocopheryl radicals go on to terminate with another molecule of tocopherol or another radical in solution, effectively halting the free radical chain reaction. However, under certain conditions, such as in human low-density lipoprotein (LDL) and the conditions used in our experiments, tocopheryl radicals can survive long enough to initiate another round of chain oxidation, acting as a pro-oxidant. This process is called tocopherol-mediated peroxidation or TMP.

TMP has been suggested to play a key role in the oxidative modification of human LDL, which can eventually lead to atherosclerosis. The LDL particle itself contains a lipid core consisting mainly of cholesterol linoleate and various phospholipids, along with appreciable levels of α-tocopherol. When the LDL particle is hit by some external source of oxidative stress, the peroxidation process is initiated. As peroxyl radicals start to form, α-tocopherol begins to donate hydrogen atoms to these species in an attempt to halt the peroxidation. In LDL, however, the tocopheryl radical can survive for long periods of time without encountering another radical to terminate, eventually abstracting a hydrogen atom from another lipid molecule. This regenerates α-tocopherol and propagates the free radical chain reaction, thus furthering the oxidative modification of the LDL particle. The high KIE values indicate not only that the deuterated PUFAs are much less oxidizable than their natural counterparts, but also that powerful molecular forces are at work during hydrogen atom abstraction by tocopheryl radicals, further reinforcing the theory that TMP plays an important role in the oxidative modification of LDL and the eventual onset of atherosclerosis.

The research was supported by a grant from the National Science Foundation to NAP (NSF CHE-1057500).
DNA molecules are constantly exposed to endogenous and exogenous toxins. These toxins can give rise to about a million molecular lesions per cell per day in humans. DNA repair mechanisms are thus important for maintaining genomic health. Nucleotide excision repair (NER) is a type of DNA repair mechanism specialized to remove bulky DNA lesions from the genome. Defects in NER result in Xeroderma pigmentosum (XP), a spectrum of disorders characterized by hypersensitivity to sunlight and dramatically increased rate of skin cancer. There is currently no cure for XP. Understanding of the molecular details of human NER can potentially aid in the development of treatment for XP. However, the process of dissecting details of human NER had been slow as this is a multi-step mechanism involving more than thirty proteins.

XPA is one of the proteins involved in human NER. XPA serves as a scaffold for NER, interacting with several other NER proteins as well as the DNA substrate. The critical importance of XPA is underscored by its association with the most severe clinical phenotypes of the genetic disorder XP. Especially, those XPA mutations located at the putative DNA binding region lead to accelerated aging and neurological disorders, suggesting the importance of XPA-DNA interaction in human NER. Although XPA has been extensively studied for more than twenty-five years, the structural basis for its binding to DNA is not well understood.

A putative DNA-binding domain (DBD) was initially assigned to residues 98–219 of XPA (XPA_{98-219}) (Kuraoka et al. Mutat Res 1996). Subsequently, the solution NMR structures of a globular domain within XPA_{98-219} were determined (Ikegami et al. Nat Struct Biol 1998 and Buchko et al. Nucleic Acids Res 1998) and chemical shift perturbations induced by binding of a 9-nt ssDNA oligomer were measured (Buchko et al. Nucleic Acids Res 2001). However, we found that XPA_{98-219} lacks full DNA-binding activity as compared to full-length (FL) XPA. Detailed sequence analysis led us to generate a series of C-terminally extended constructs. XPA_{98-239} containing twenty extra residues, was identified as most stable of these and bound DNA substrates with the same affinity as FL XPA. We also show via NMR analysis that some of the extra C-terminal residues are likely to be directly involved in DNA binding. Together, we redefine XPA_{98-239} as XPA DBD which can now be used for structural investigation of XPA-DNA interaction to aid in the understanding of human NER.


Grants which supported this research include R01 ES1065561 (NIH); P01 CA092584 (NIH); P30 ES00267 (Vanderbilt Center in Molecular Toxicology); P30 CA068485 (Vanderbilt-Ingram Cancer Center).
Chemically modified inhibitors of the COX-2 enzyme relieve anxiety behaviors in mice by activating natural “endocannabinoids” without gastrointestinal side effects, Daniel Hermanson, Ph.D., reported in *Nature Neuroscience* in August 2013.

Endocannabinoids are natural signaling molecules that activate cannabinoid receptors in the brain, the same receptors turned on by the active ingredient in marijuana.

These receptors are also found in the gastrointestinal system and elsewhere in the body, and there is evidence that they play a role in a wide range of physiological and pathological processes, in addition to modulating stress and anxiety.

If the “substrate-selective” COX-2 inhibitors developed at Vanderbilt also work in humans without side effects, they could represent a new approach to treating mood and anxiety disorders, the researchers concluded. Clinical trials of some of these potential drugs could begin in the next several years, said Lawrence Marnett, Ph.D., director of the Vanderbilt Institute of Chemical Biology and the paper’s co-senior author with Sachin Patel, M.D., Ph.D.

The Vanderbilt scientists are pursuing other potential applications of activating endocannabinoids by substrate-selective COX-2 inhibition, including relieving pain, treating movement disorders, and possibly preventing colon cancer.

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) relieve pain and inflammation by blocking either or both of the cyclooxygenase (COX) enzymes, which produce pro-inflammatory prostaglandins.

It has been known for several years that COX-2 inhibition also activates endocannabinoids. Because the “substrate selective” inhibitors developed at Vanderbilt increase endocannabinoid levels in the mouse without blocking prostaglandin production, “we think (they) will not have the gastrointestinal and possibly cardiovascular side effects that other NSAIDs do,” said Marnett, University Professor and Mary Geddes Stahlman Professor of Cancer Research.

“We thought we knew everything there was to know about (COX-2 inhibitors) until about five years ago when we discovered the substrate selective inhibition,” he added. The approach used by the Vanderbilt team “is a really powerful way to help design the next generation of drugs.”

Daniel Hermanson, a former graduate student in Chemistry, was first author of the paper.

*The three-year-long study was supported by National Institutes of Health grants CA089450, GM015431, NS064278, DA031572, HL096967, HL109199, MH063232, NS078291 and MH065215.*
Christine Markwalter, a second-year graduate student, knew she wanted to devote herself to a medically oriented chemical research career when her husband, Daniel, now a medical student at Vanderbilt School of Medicine, suffered severe complications from Rocky Mountain spotted fever in 2012. The Graduate Program at Vanderbilt caught her eye because of its focus on medically relevant chemical research that positively impacts populations around the globe. Particularly interested in the diagnosis of infectious diseases, Markwalter joined Professor David Wright’s laboratory, where her initial research focuses on developing a robust and affordable diagnostic test for malaria using *Plasmodium* lactate dehydrogenase as a biomarker.

This year, Markwalter was awarded a National Science Foundation Graduate Research Fellowship (NSF GRF), a three-year support package, which includes a $32,000 annual stipend, education allowance for tuition and fees, and opportunities for international research and professional development.

Markwalter’s project employs aptamers—short, single-stranded oligonucleotides capable of recognizing nearly any class of target molecule with high affinity and specificity—as molecular recognition elements for diagnostic tests. She has proposed a novel aptamer selection protocol designed to select two aptamers with distinct binding sites against a single target. The NSF GRFP award provides Markwalter the opportunity to develop a fluorescent aptamer sandwich assay on magnetic particles to detect human secretory immunoglobulin A (h-SIgA), a biomarker for fecal contamination of drinking water.

In addition, Markwalter will be working on diagnostic tests for complications of pregnancy, including preeclampsia and chorioamnionitis, using protein and microRNA biomarkers. This research has the potential to improve outcomes for at-risk pregnancies in both developing and developed nations through early detection and intervention.

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Graduate Student Gabriel LeBlanc Participates in SciFinder Future Leaders in Chemistry Program

Last fall, Gabriel LeBlanc participated in the SciFinder® Future Leaders in Chemistry Program. This competitive travel grant program included graduate students and postdocs from across the world. The participants learned about the inner workings at Chemical Abstracts Services (CAS) and made recommendations for future products. They were additionally provided the opportunity to present their research at the national ACS conference in Indianapolis, Indiana. There, LeBlanc presented his thesis research conducted under the guidance of Professor David Cliffel. His work focused on an interdisciplinary project that looks to integrate materials directly from nature into next-generation solar energy technologies. Working with a number of collaborators, LeBlanc discovered that coupling an efficient protein from photosynthesis with semiconductor electrodes provided an incredible boost in the current that could be generated from these devices. Other work from this same research team has led to faster and less expensive device fabrication methods.

At the conference, LeBlanc also met his current postdoctoral advisor, Delia Milliron. Now at the University of Texas at Austin, LeBlanc is working with nanostructured materials and composites for battery and smart window applications.

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Steven Combs, Ph.D., Awarded Eli Lilly Innovation Postdoctoral Fellowship

Steven Combs, Ph.D., working with Associate Professor of Chemistry Jens Meiler, and Sergey Tsukanov, Ph.D., working with Jeff Johnston, Stevenson Professor of Chemistry, have received an Eli Lilly Innovation Fellowship. The Lilly Innovation Fellowship Award (LIFA) program was created to identify and foster exceptional postdoctoral scientists pursuing groundbreaking research projects. The LIFA program pairs postdoctoral scientists with their academic mentors and Lilly scientists, who serve as industry mentors, to advance innovative research proposals developed by the fellows. The goal of the LIFA program is to focus on research topics or “Grand Challenges” that will drive innovation in scientific areas of greatest strategic interest to Eli Lilly and Company, while remaining general enough to foster disruptive innovation. Fellowship awardees typically work at both their academic institutions and at a Lilly research site, with access to Lilly scientists and technologies, to advance their research plans.

Combs entered the Graduate Program in Chemistry in 2008, joining Jens Meiler’s research group. He received his Ph.D. in May 2014.
Graduate Students Noah Orfield and Darwin Fu Participate in Federal STEM Policy and Advocacy Workshop

Noah Orfield (Rosenthal Group) and Darwin Fu (Meiler Group) both Chemistry graduate students, participated with twenty-four other Vanderbilt students in the first Federal STEM Policy and Advocacy Program organized by the Vanderbilt University Office of Federal Relations October 16-17, 2014, in Washington D.C. The workshop was designed to explain and demonstrate federal STEM policy and advocacy processes, and introduce the students to potential government sector and related careers many had not considered or didn’t know existed.

Education in the STEM sciences provides a methodical way of thinking that allows the breakdown of complex policy questions to look for solutions. The student participants ranged from undergraduates to postdoctoral scholars and represented twenty academic fields of study, including environmental engineering, neuroscience, pharmacology, chemistry, biomedical engineering, chemical and biomolecular engineering, public policy studies, and medicine, health, and society.

The seminar featured eight panels with nineteen speakers, many of whom are Vanderbilt alumni. Speakers covered topics such as the history of U.S. science and technology policy, the federal budget process, and the role of coalitions in policy making. Several panels also addressed career-oriented topics such as the value of professional societies and fellowship programs, the experience of working on Capitol Hill, and career opportunities in science policy and advocacy.

Students participated in a mock congressional conference committee for the spending bill that funds many science-related agencies. As part of the simulation, participants role-played the part of senior legislators to produce an agreement that set funding levels and policy priorities for the coming year.

The original idea for the Vanderbilt workshop came from a similar program created and run by the American Association for the Advancement of Science.

2013–2014 Ph.D. Graduates

Amanda Blane Doody
Synthetic Pursuit of the Tridecapeptide Feglymycin and the Manzamine Alkaloid Kauluamine

Jay Garrett Forsythe
Advanced Strategies for Imaging Mass Spectrometry and Ion Mobility-Mass Spectrometry

Daniel John Hermanson
Substrate-Selective Inhibition of Cyclooxygenase-2 Molecular Determinants, Probe Development and In Vivo Effects

Kelly Marie Hines
Biomolecular Signatures of Disease via Ion Mobility and Mass Spectrometry Techniques

Gabriel Adrien LeBlanc
Biohybrid Electrodes Based on Photosystem I for Solar Energy Conversion

Marta Wieslawa SzuUik
Oxidation of Cytosine in DNA

Steven Combs
Identification and Scoring of Partial Covalent Interactions in Proteins and Protein Ligand Complexes

Oleg Kovtun
Probing Ensemble and Single-Molecule Behavior of Cocaine-Sensitive Dopamine Transporter with Antagonist-Conjugated Quantum Dots

Ian Roys Olmsted
Investigating Biochemical Interactions Relevant to Human Health Using Backscattering Interferometry

Michael Lawrence Schulte
Application of Organocatalysis to the Synthesis of Pharmacologically Relevant Scaffolds: Chiral Aziridines and B-Fluoroamines; Total Synthesis of Stemaphylline and Discovery of Selective Par4 Antagonists

Artez Laurant Sims
Development and Application of Dendritic Systems for Targeted Intracellular Delivery

2013–2014 Master of Science

Dain Bridgeon Beezer
Holly Marie Carrell
Nina Renee Collins
Have you considered applying your scientific training to a career with the U.S. government? Well, neither had Samantha Arnett when she graduated from Vanderbilt with a B.S. in 2002. Now, at thirty-four years old, she works at the U.S. State Department in the Biosecurity Engagement Program (BEP), which aims to keep terrorists and/or unstable governments from making or acquiring weapons of mass destruction.

Obviously, you don’t instantly go from being an undergrad at Vanderbilt to the BEP Deputy Team Chief and Program Officer for Iraq and South Asia at the State Department. Arnett graduated from Vanderbilt University in 2002, with a B.S. in chemistry, having done undergraduate research in the lab of Michael P. Stone, Ph.D. in physical chemistry, DNA damage and repair. She then entered graduate school at Johns Hopkins University, where she earned a Ph.D. in bio-organic chemistry in 2008 in the laboratory of Dr. Craig Townsend. While working toward her doctorate, she made time to volunteer with a local HIV testing clinic, which brought her to the realization toward the end of graduate school that she wanted to use her scientific skills to pursue her interest in the HIV field and infectious diseases. Her postdoc was at The Scripps Research Institute in the laboratory of Dr. Dennis Burton, where she integrated her knowledge of bio-organic and protein chemistry with the field of HIV vaccine development.

During her postdoc, she began exploring careers outside academia and applied for the American Association for the Advancement of Science and Technology Policy Fellowship, which is a highly competitive program that provides accomplished U.S. scientists and engineers the opportunity to contribute to the federal policymaking process, while learning firsthand about the intersection of science and policy. Arnett explains, “Scientists in the STEM sciences are sought after for the way they think, their stepwise approach to problem solving, and their ability to synthesize large amounts of information quickly…We need scientists in government positions to ensure that government policymaking and implementation are informed by the best available science. Scientists, and engineers, are imperative to addressing global policy issues such as climate change, national security, and global food security.”

The selection process for the fellowship introduced Arnett to a wide range of “alternative” career opportunities in the U.S. government where she could potentially utilize her scientific knowledge, method of problem solving, and analytical rigor away from the bench and laboratory. She was selected for (and accepted) a Program Officer position in the Department of State’s Bureau of International Security and Nonproliferation’s Office of Cooperative Threat Reduction (CTR). CTR programs—the Biosecurity Engagement Program (BEP), Chemical Security Program (CSP), and Partnership for Nuclear Security (PNS)—are aimed at reducing the threat posed.
by terrorist organizations or proliferant states seeking to acquire weapons of mass destruction (WMD) expertise, material, and equipment. At the conclusion of her two-year fellowship, Arnett was offered a full-time position in CTR where she continues developing and overseeing the implementation of programs that reduce the risk that a WMD comes to fruition.

"I have worked on both biological and chemical security issues during my time in CTR," continues Arnett, "but, I am formally on the BEP team. BEP reduces the threat of bioterrorism by preventing terrorist access to potentially dangerous biological materials, dual-use infrastructure and expertise, while supporting efforts to combat infectious disease and enhance public and animal health worldwide. As a Program Officer, I work with partner countries to design country-specific programs that strengthen biorisk management practices, enhance infectious disease detection and control, and support cooperative research and development to prevent terrorist and other non-state actors from gaining access to potentially dangerous biological agents. Each country is different, and our approach is shaped by each country’s unique culture, diplomatic and political relationship with the U.S., and biological science capacity."

As you might expect, no two days, two weeks, two months, or two years have been the same for Arnett. "I remember one week last year that took me from a business suit in D.C. to ballistic body armor and a headscarf in Afghanistan," she says. She left D.C. on a Friday evening after working all day to fix a budget issue and draft briefing material for senior officials. After two commercial flights, one contract fixed wing flight, one helicopter ride, and a ground movement with military convoy, she arrived in the southern province of Kandahar, Afghanistan, on Tuesday afternoon.

"My travels abroad are usually split between overseeing the implementation of a BEP threat reduction activity and meeting with host country partners. The identification and design of BEP activities are collaborative efforts with our partner countries. We literally sit down with Ministry officials, laboratory scientists, field technicians, animal and public health officials, law enforcement personnel, and biological professionals to identify areas of mutual interest and co-develop our bioengagement activities."

From a diplomatic and political standpoint, BEP works in some of the most difficult countries in the world which forces her team to do a lot of creative problem solving. She credits her scientific training with her ability to analyze any situation and identify a number of possible approaches, explanations, or solutions.

Arnett’s expertise in chemistry, biology, and infectious disease helps her to develop and advance efforts to prevent the weaponization of biological material. Furthermore, her knowledge of molecular biology, microbiology and vaccine design puts her in a unique position to help reduce the risk that dual-use technology and expertise are exploited for nefarious purposes.

Additionally, her scientific background makes it easier for her to relate to and build trust with international scientific partners. She gave the following examples: "I was able to initiate a strong relationship with a laboratory in Southeast Asia by helping a technician pour Agar plates. And on another occasion, I gained the trust and respect of a laboratory director in South Asia by fixing and calibrating a PCR machine that had been broken for several years. Neither of these laboratory skills are particularly impressive on a scientific level but they do give me credibility as a laboratory scientist, especially when I am not able to verbally communicate due to language barriers."

When asked what her most satisfying experience has been, Arnett quickly identifies the relationships built on the ground in Afghanistan. "Afghanistan," she continues, "is a war zone and personal safety and security are pivotal for BEP in-country. I work very closely with the State Department’s Regional Security Office as well as U.S. and Allied Forces to ensure we are working under the safest and securest conditions possible. My close coordination and open communication with security personnel have allowed me to creatively implement our programs within the parameters of the constantly changing security situation on the ground. These relationships have allowed me to proactively tailor our programs to build-in implementation flexibility in order to achieve our mission even in the most confining of circumstances."

As for the future, Arnett thinks she has found her niche in the national security sector, and says, "I enjoy applying my scientific background, diplomatic nature, and focused disposition to national security issues. I like working at the intersection of science and security and am interested in gaining more hands-on, technical experience in the field."

“As scientists, we are taught that there is always more than one answer, and this is true beyond the bench as well.”
As college-bound students interested in a career in the STEM sciences or medicine look at institutions they might attend, an important factor has become the prospect of working in a scientific and/or medical laboratory as part of their undergraduate experience. Those who choose Vanderbilt often do so on the strength of the research programs and the possibility of getting hands-on experience in a lab. Such experiences enhance their graduate school or medical school applications, and teach them to work independently in a lab and to have ownership in their projects. One thing Vanderbilt does particularly well is enable students to engage in research that crosses traditional disciplinary lines.

Chemistry majors work alongside fellow undergraduates, graduate students, and postdocs in the labs of Chemistry faculty. With access to state-of-the-art research facilities, they are able to carry out their own independent research projects, while getting hands-on experience in the lab. Doing research bridges the gap between something being very theoretical and academic, and something more practical and real. Vanderbilt provides them with an intersection between those two experiences.

Vanderbilt is both a top 25 research university and a top 25 undergraduate institution: with Vanderbilt Chemistry ranking twelfth in R&D funds from national research foundations.

In addition to working in a chemistry research lab during the school year, Vanderbilt also offers summer research experiences for Vanderbilt undergraduate students, as well as undergrads from other colleges and universities. Some of the programs are described below.

**BECKMAN SCHOLARS PROGRAM**
Arnold O. Beckman, founder and chairman emeritus of Beckman Instruments, Inc., represents nearly a century of outstanding scientific achievements. Considered one of the top five inventors of scientific instruments, Dr. Beckman created devices that revolutionized the study and understanding of human biology, ultimately saving countless lives around the world.

The Beckman Scholars Program, funded by the Arnold and Mabel Beckman Foundation, provides scholarships that contribute significantly in advancing the education, research training, and personal development of select students in chemistry; biochemistry; and the biological and medical sciences. The sustained, in-depth undergraduate research experiences and comprehensive faculty mentoring are unique in terms of program scope, content, and level of scholarship awards ($17,600 for two summers and one academic year).

This past year, Laura Mast participated in the Beckman Scholars Program in Chemistry, doing research with Professor Janet Macdonald. One of her projects involved synthesizing CuInS₂ nanocrystals. She presented her research at the Beckman Scholars Conference at CalTech in August 2014, which will be submitted for publication as part of a larger study in the Macdonald lab. Mast graduated in May 2014, and is now a graduate student at Georgia Tech.

**SUMMER RESEARCH EXPERIENCE FOR UNDERGRADUATES**
Each summer, undergraduates from across the country come to Vanderbilt to work in one of the numerous REU (Research Experience for Undergraduates) programs. Programs include the Vanderbilt Institute of Chemical Biology (VICB) REU Program, Summer Science Academy, Vanderbilt Undergraduate Summer Research Program, Vanderbilt Institute of Nanoscale Science and Engineering Program REU, as well as Summer Internships in faculty labs. At the conclusion of the ten-week program, a poster session is held with all programs participating.

**VICB REU**
During the summer of 2014, students from outside Vanderbilt participated in the Vanderbilt Institute of Chemical Biology REU program:

- **Amanda Clark** from the University of Central Michigan worked with Gary Sulikowski on the synthesis of oxidative metabolites of curcumin.
- **Corey Hayford** from the University of Texas at Austin worked with Carlos Lopez on mathematical modeling of progressing through the mammalian cell cycle.
- **Gabriel Pajares-Hurtado** from Georgia Tech worked on oxidative stress propagates methylglyoxal generation via inhibition of glyoxylase, in the lab of Larry Marnett.
- **Lidalee Silva** worked on the development of a catch and release diagnostic platform for the malarial biomarker PfLDH in David Wright's lab; she came from the University of Puerto Rico at Aguadilla.
- **Kari Stratton** worked with Ned Porter's research group on determining the propagation rate constants of biosynthetic precursors to cholesterol. She attends Texas A&M.
**TN SCORE REU**

As part of the grant awarded through the National Science Foundation's Experimental Program to Stimulate Competitive Research (EPSCoR) Research Infrastructure Improvement Program of Fall 2010, the TN SCORE (Tennessee Solar Conversion and Storage Using Outreach, Research, and Education) grant includes funding for Summer Research Experiences for Undergraduates. The research focus of TN SCORE is specifically advanced solar conversion and innovation, components and devices for energy storage and conversion, and nanostructures for enhancing energy efficiency.

Lucas “Louie” Thal began his foray into the field of science with a passion for the search for renewable energy. He is now an undergraduate senior at the University of Tennessee, Knoxville, working towards a dual chemistry and BCMB degree. This summer, Thal was invited to do research with David Cliffel as a TN-SHORE REU student. Thal’s project focused on a new solar energy concept in which solar cells are being integrated with the ever-abundant plant protein Photosystem I. More specifically, Thal worked to improve the photosystem I film orientation in biohybrid solar cells. This research project could not have been a better fit, as he was able to employ techniques and knowledge gained from his experience as a research assistant under biologist Barry Bruce at UTK, whose research is also centered around Photosystem I applications in solar conversion. This interdisciplinary experience enabled him to tackle problems in his summer project from both biological and chemical angles. In his final year at UTK, Thal will return to the Bruce Lab where he hopes to begin research on Photosystem I crosslinking. Afterwards, Thal plans to attend graduate school in a chemical biology Ph.D. program geared towards renewable energy.

**LEADERSHIP ALLIANCE**

Since 1992, the Leadership Alliance has encouraged students from groups traditionally underrepresented in the sciences, engineering, social sciences, and humanities to pursue research careers in the academic, public, and private sectors. SR-EIP is a rigorous ten-week summer research experience designed specifically for undergraduates interested in applying to Ph.D. or M.D.-Ph.D. programs. It provides undergraduates with training and mentoring in the principles underlying the conduct of research and prepares them to present competitive applications to graduate schools.

Vanderbilt University and the Department of Chemistry were host to Stephanie Castillo during the summer of 2014. She is currently working toward a B.A. in chemistry at the University of Central Florida. During the school year, she had the opportunity to work under Florencio Hernandez in his nonlinear optics and materials lab, where she observed the antioxidant properties of tea by using nanoparticles. In the summer of 2013, she conducted research for Marcelo Sousa’s structural biochemistry lab at the University of Colorado Boulder. She investigated the interaction of proteins within the beta-barrel machinery complex to better understand fundamental cellular processes.

This summer at Vanderbilt University, Castillo worked with a group of undergraduates in Janet Macdonald’s materials science lab. Their role was to understand the electronic properties of the new surface chemistry of quantum dots.

“I really enjoyed my summer here at Vanderbilt,” said Castillo. “Not only is the campus beautiful, but also Nashville itself is so beautiful. I was impressed with their attentiveness and the sense of community within my lab and the chemistry department... Researching at Vanderbilt opened my eyes to what it would be like as a grad student at their school. Getting that inside look from the grad students and my mentor reassured my decision to apply to grad school to pursue a Ph.D. in chemistry. I am looking forward to hopefully calling Vanderbilt my new home.”

**ENHANCING DIVERSITY IN GRADUATE EDUCATION (EDGE)**

Vanderbilt’s goal of recruiting and retaining talented young scholars in the STEM sciences from underrepresented groups is charged to the EDGE office, and Assistant Dean Don C. Brunson, Ph.D. These efforts are based on the university’s sincere desire to provide underrepresented students with access to the tools necessary to reach their professional goals, while creating a diverse learning community for all of our students.

One of the programs that EDGE sponsors is the VU-EDGE PhD Pre-VU Recruitment Event. In fall 2013, the Graduate Program in Chemistry was introduced to seniors Jade Bing and Jordan Rhodes, both from Rider University. Both applied to the Graduate Program in Chemistry, were offered admission to the program, traveled to Nashville for a second look at Vanderbilt in the spring of 2014, and ultimately accepted our offer and matriculated. Bing is interested in organic synthesis, while Rhodes is interested in alternative energy and solar cells.

“I have broadened and deepened my skills as a scientist ... Additionally, I learned how to adapt to a new environment, and personally grew through the experience of being immersed in a new place ...”— VICB REU Participant Amanda Clark
Undergraduate Awards in Chemistry

**Donald E. Pearson Award** for outstanding graduating senior majoring in chemistry, planning graduate work in chemistry — Jennifer M. Ruddock

**Merck Index Award** to the outstanding graduating senior going on to medical school — Jennifer Sun

**Distinguished Undergraduate Chemistry Research Award** — Alec J. Pawlukiewicz

**D. Stanley and Ann T. Tarbell Prize in Organic Chemistry** awarded to the graduating senior who has excelled in organic chemistry, either having earned the highest grades in the courses taken and/or having done outstanding research in organic chemistry — Alexander J. Levonyak

**Thomas W. Martin Award** for the outstanding graduating senior excelling in physical chemistry — Ruidan Ma

**Robert V. Dilts Award** for the outstanding graduating senior excelling in analytical chemistry — Virginia Ann Smith Liau

**Mark M. Jones Award** for undergraduate achievement in inorganic chemistry — Laura G. Mast

Honors Thesis and Adviser:

Alexander Levonyak — Ned A. Porter, Ph.D.

Virginia Liau — David E. Cliffel, Ph.D.

Ruidan Ma — Michael P. Stone, Ph.D.

Laura Mast — Janet Macdonald, Ph.D.

Alec Pawlukiewicz — David W. Wright, Ph.D.

Jennifer Ruddock — David E. Cliffel, Ph.D.

Jennifer Sun — Walter J. Chazin, Ph.D.

Schuyler Tang — Lawrence J. Marnett, Ph.D.

Eugene Yap — Sandra J. Rosenthal, Ph.D.

**Amanda Clark**

One of the participants in the fall 2013 Pre-VU Recruitment Event was Amanda Clark. As a junior at the time at Central Michigan University, she learned about the VICB NSF REU internship at Vanderbilt, applied, and was accepted into the program for the summer of 2014. She worked in the lab of Gary Sulikowski on the synthesis of oxidative metabolites of curcumin. In addition to new research skills, this gave her an expanded opportunity to explore all of the opportunities at Vanderbilt and the Department of Chemistry.

After her summer in the VICB REU program, Clark explained the significance that this research experience had on her life as a budding scientist: “In addition to conducting research, the program exposed me to research in other fields, and professional development topics during a variety of weekly seminars. I have broadened and deepened my skills as a scientist by performing research outside of my home institution. Additionally, I learned how to adapt to a new environment, and personally grew through the experience of being immersed in a new place with new people. After my time at Vanderbilt, I truly think I am more prepared to enter graduate school.”

Clark became involved in research at Central Michigan during her freshman year when she joined Choon Lee’s organic synthesis lab. As a first-generation college student, she developed strong interests in research and pursuing higher education, which led her to become a McNair Scholar at CMU. After joining the McNair Scholars Program, she completed her first summer research project on the organic synthesis of a second generation antioxidant dendrimer.

Clark’s long-term goals are to pursue doctoral training in chemistry or chemical biology at Vanderbilt. After obtaining her Ph.D., Clark would like to pursue a tenure-track faculty position and conduct research in the area of chemistry, applied to cancer biology topics.

**Class of 2014**

Ankerholz, Kevin
Donald John
Beiter, Eric Christopher
Chandler, Dustin
Couch, Andrew Lanier
Franklyn, Lindsey Anne
Kang, June Woo
Kee, John David
Levonyak, Alexander Joel
Liau, Virginia Ann Smith
Ma, Ruidan

Martin, Justin
Mast, Laura Guilia
Pawlukiewicz, Alec James
Pillai, Arjun Suresh
Ruddock, Jennifer Marie
Sun, Jennifer
Tang, Schuyler George
Wong, Jason Paul
Yap, Eugene (fall 2013)
Young, Rebecca Adair
The Chemistry Colloquium Series is a mainstay of VU Chemistry, broadening knowledge of emerging science and deepening connections between researchers at all levels. Following are 2013–2014 speakers.

**Mitchum E. Warren Jr. Lecture**
**Professor Daniel Nocera**
Harvard University, “The Artificial Leaf: Personalized Energy for 1 (× 6 Billion)”

**Bircher Lecture**
**Dr. John Rogers**
University of Illinois at Urbana-Champaign, “Materials for Electronics That Can Dissolve in Your Body”

**Sigma-Aldrich Lecture**
**Professor Daniel Romo**
Texas A&M University, “Natural Products Fueling Both Scaleable and Microscale Synthetic Methodology to Impact Biology”

**Professor Franklin Davis**
Temple University, “Asymmetric Synthesis of Homotroponines, Troponines, Tropanes and Cocaine Derivatives using Sulfinimines (N-Sulfinyl Imines)”

**Professor G.B. Hammond**
University of Louisville, “Does Pixie Dust Exist? Rethinking the Role of Counterions in Ionic Chemical Reactions”

**Professor Ken Hsu**
Faculty Candidate, “Lipid Metabolism in the Mammalian Immune Response”

**Professor Iyvlo Ivanov**
Georgia Tech University, “Structurally Distinct Complexes of Ubiquitin and Sumo-Modified PCNA Lead to Distinct DNA Damage Response Pathways”

**Professor Motomo Kanai**
The University of Tokyo, “Merging Organic Synthesis and Life Science with Catalysis: from Asymmetric Catalysis to Amyloid Oxidation”

**Dr. Laszlo Kurti**
University of Texas Southwestern, “Exploiting the Extraordinarily Versatile N-O Bond: Rapid Synthesis of Biaryls, Carbazoles, Aziridines and Primary Aromatic Amines”

**Professor Andrew Link**
Vanderbilt University, “Systems Analysis of Protein Complexes and Proteomes to Identify Regulatory Modules in the Biological Networks”

**Professor Taif Mahmud**
Oregon State University, “Mechanistic Understanding and Rational Engineering of Natural Products Biosynthetic Pathways”

**Dr. Charles Chusuei**
Middle Tennessee State University, “Increasing Amperometric Detection of H2O2 via Controlling ZnO Nanosized Morphology”

**Dr. David Cliffe**
Vanderbilt University, “Electrochemical Nanobiotechnology: Future Promises for Medicine and Energy”

**Professor Stephen Craig**
Duke University, “Mechanochemical Remodeling: From New Reactions to Adaptive Materials”

**Dr. Bryan Dickinson**
Faculty Candidate, “Molecular Imaging and Evolution Approaches to Probing the Chemistry of Living Systems”

**Dr. Joe Fox**

**Professor G. Ramarao**
University of Michigan, “Rational Engineering of Natural Products and Structure-Based Function Annotation”

**Dr. Charles Nocera**, Vanderbilt University, “A Chemist’s Journey in Structural Biology with a Special Emphasis on Chromatin Structure and Function, and Pharmacology”

**Dr. Michael Pollastri**, Northeastern University, “Target Repurposing Accelerates Drug Discovery for Neglected Tropical Diseases”

**Professor Jeremy Rawson**, Case Western Reserve University, “Harnessing Genomes and Building Molecules to Investigate Biosynthetic Mechanisms”

**Dr. Sarah Slavoff**, Faculty Candidate, “Discovery and Functional Characterization of Peptides Translated from Human Short Open Reading Frames”

**Dr. Steven Townsend**, Faculty Candidate, “Target-Oriented Total Synthesis: From Small Molecules to Biologics”

**Professor Rajesh Viswanathan**, Case Western Reserve University, “From Radicals to Magnetism, Coordination Chemistry and Catalysis”

**Dr. Martin Von Bergen**, Helmholtz Centre for Environmental Research, “Signaling in Proteomics and the Neglected Majority”

**Professor David Walba**, University of Colorado at Boulder, “Supramolecular Stereochemistry in Liquid Crystals: From Pico Projectors to the First Fluid Conglomerate to Organic Nanoparticles for Photovoltaics”

**Dr. A. Joshua Wande**, University of Pennsylvania, “Recent Advances in NMR Spectroscopy of Encapsulated Proteins & Nucleic Acids Dissolved in Low Viscosity Fluids”

**Professor Donald Watson**, University of Delaware, “Transition Metal-Catalyzed Methods for Introducing Heteroatoms into Hydrocarbon Frameworks”

**Professor Gavin Williams**, North Carolina State University, “Synthetic Biology Approach to Reprogramming the Biosynthesis of Natural Products”


**Dr. Yang Zhang**, University of Michigan, “Genome-Wide Protein Structure Prediction and Structure-Based Function Annotation”
1. Liquid Helium Fill/Vent Port
2. Liquid Nitrogen Fill/ Vent Port
3. Bore Tubes of Magnet
4. Sample
5. Superconducting Magnet
6. Outer Steel Shell
7. Vacuum Space/Radiation Shields
8. Liquid Nitrogen Reservoir (75l, 14 days)
9. Liquid Helium Reservoir (78l, 23 days)
10. Cryoshims and Associated Electronics

Magnet Data:
- 300MHz Oxford
- Built 1999
- Running until 2013
- 7.05 T, 300MHz, 39.77A