Graduate Program in Chemistry
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VANDERBILT UNIVERSITY GRADUATE PROGRAM IN CHEMISTRY

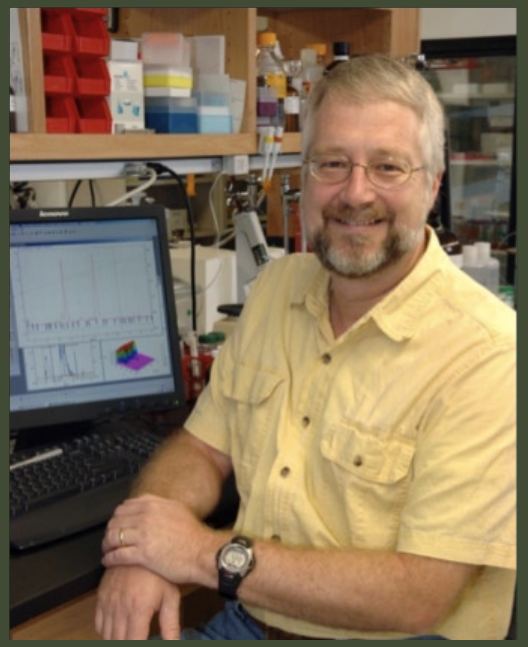
COLLEGE OF ARTS AND SCIENCE

Welcome to the Vanderbilt University Department of Chemistry!

Shortly after the American Civil War, Commodore Cornelius Vanderbilt's vision was to create an institution that would "contribute to strengthening the ties that should exist between all sections of our common country." Today, Vanderbilt University is renowned for its many interdisciplinary scientific research programs. Our students and faculty come from all across the United States and from around the world. Vanderbilt has the intellectual and financial resources to sustain an aggressive expansion in teaching and scientific research across the spectrum of disciplines in Chemistry. These include major research initiatives focusing on problems at the chemical biology interface, nanotechnology and materials science, and in structural biology.

As a prospective graduate student, I encourage you to explore the many possibilities as you consider how our academic programs might fit with your training, research interests, and career goals. You will find details of our graduate program, descriptions of the many interdisciplinary research opportunities available, and application instructions. I believe you will find that our Department is large enough to provide you with exciting opportunities and state-of-the-art facilities, yet small enough to treat you as an individual. We value each of our outstanding students! Selecting your intellectual environment is one of the most important decisions that you will make in your academic career. I hope you will seriously consider Vanderbilt Chemistry as your academic home.

Michael P. Stone



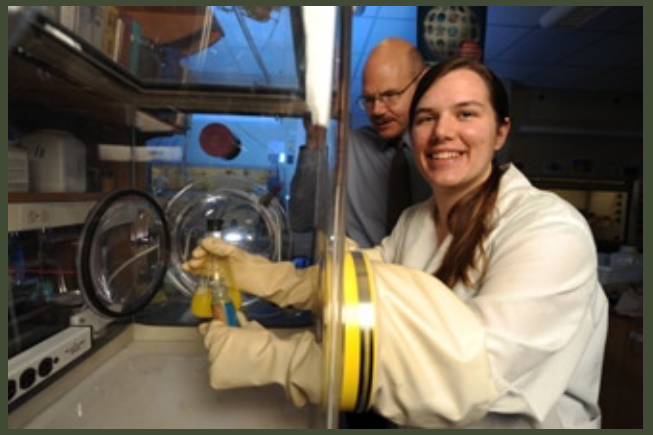
Michael P. Stone - Chairman

Vanderbilt offers...

to able and serious students a faculty that is active in research and deeply committed to the development of scholars. Students participate in classroom, laboratory, tutorial, and collegial modes of learning and in systematic independent inquiry, in a setting that allows them to see scholars at work, day in and day out, as an important means of learning the scholar's art. Students are in situations in which they are known personally and well, and concern for what happens to them is very strong.

Graduate Program in Chemistry

Graduate degree research has held a central place in the program of Vanderbilt University since it opened in 1875. The first Doctor of Philosophy degree was granted in 1879 in Chemistry, the 2000th in 1975, the university's centennial year. As of May 2009, 18,741 Doctor of Philosophy degrees have been awarded. By way of comparison, the first Ph.D. given by an American university was awarded in 1861 by Yale University. The second American institution to offer the degree did so in 1870.



VANDERBILT UNIVERSITY

Vanderbilt University

Graduate Program in Chemistry

Benefits 2009-2010

Stipend: $23,000

Guaranteed for up to 5 years

Tuition paid by Department of Chemistry: $37,632

Health Insurance Paid by Department of Chemistry: $2,021

Additional fellowships of $2,500 for one year to $10,000 for five years available to highly qualified applicants.

Admission to the Graduate Program in Chemistry

Qualified applicants with bachelor's degrees are eligible for admission to the Graduate Program in Chemistry at Vanderbilt University. Interested students should go to the Department of Chemistry Web page (http://www.vanderbilt.edu/AnS/Chemistry/grad/) and follow the instructions for completing the application and submitting required documents.

To be considered, students must

- officially submit an online application,
- submit official undergraduate and graduate, if applicable, transcripts
- submit three letters of recommendation from current or previous research mentors/advisors, instructors or supervisors.
- Submission of scores on the General Test of the Graduate Record Examination (GRE) is required as part of the application.
- A statement of purpose is highly recommended.
- International students must also present the results of the Test of English as a Foreign Language (TOEFL), unless they have earned a degree from an American or English-speaking institution.
- The application deadline for admission to our Fall class is January 15.

Applications may be reviewed as soon as they are complete. Thus, early application is encouraged, and often results in early recommendations for admission. The Graduate School makes all official decisions regarding admission. There is no application fee for applications completed online.

For further information about our graduate program, please email the Department of Chemistry Graduate Recruiting Office: chemgrad@Vanderbilt.edu

Financial Assistance

All applicants are considered for admission with a financial award in the form of either a teaching assistantship (TA) or research assistantship (RA). Both TAs and RAs receive the same, generous, twelve-month stipend, including annual incremental increases to this stipend. In addition, a full tuition scholarship and an individual health insurance policy are provided.

For the 2009/20010 academic year, these awards include:

- **Stipend of $23,000.00,**
- **Vanderbilt student health service benefits,**
- **Individual major medical insurance,**
- **Full tuition scholarship,**

…a total package valued at over $60,000 per year.

Additionally, prospective graduate students are considered for a number of University, College, and Departmental fellowships.

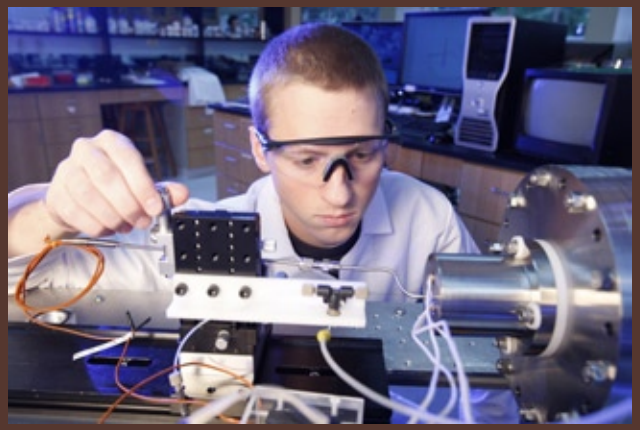
Teaching Assistants typically teach two 3-hour undergraduate laboratories per week, hold office hours, and grade laboratory reports and lecture course examinations. This Teaching Assistantship requires about of 12 hours per week.

Faculty research support typically provides for RA positions, which usually become available to students after the first year of study.

Merit Awards

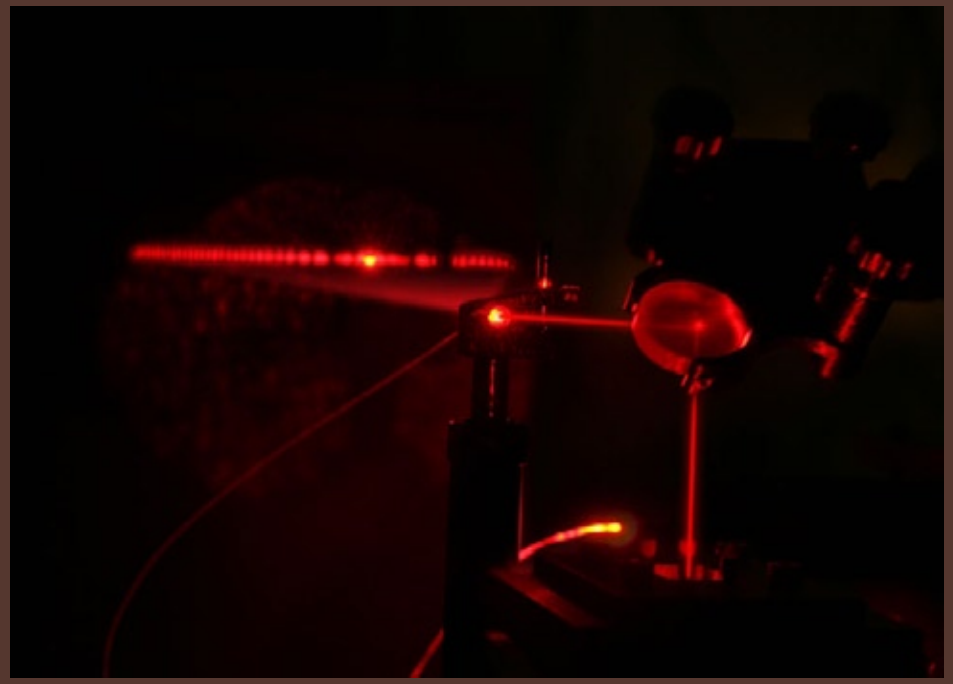
All applicants to the Graduate School are considered for merit awards, such as Honor scholarships, University Graduate Fellowships, and Provost graduate fellowships, which awards are granted by Vanderbilt University through competitive review. The Department nominates applicants for 5 year awards offered by the Graduate School (University Graduate Fellowship, Harold S. Vanderbilt Graduate Fellowship, Graduate Select Scholarship in Arts and Science, or the Dean's Graduate Fellowship), which add to a student's basic stipend.

In addition, the Department of Chemistry awards Mitchum Warren Fellowships and Hercules Fellowships to well-qualified students, which also add to a student's basic stipend for the first two years.



Ph.D. Program

The first Ph.D. given at Vanderbilt University in 1879 was in Chemistry. Vanderbilt continues to excel in research. The combination of cutting-edge research and a distinguished medical center creates an invigorating atmosphere where researchers collaborate to solve complex questions affecting our health, culture and society. From 2000 to present, Vanderbilt has led the country in the rate of growth for academic research funding. As a private research university, there are more than 5000 graduate and professional students at Vanderbilt, with more than 120 graduate students in the Department of Chemistry.



Course Work and Examinations

Prior to class registration, entering students take placement examinations to aid in selecting courses and possibly qualify to complete some courses by examination. Faculty research supervisors then assist students in selecting courses, which can include offerings from other graduate departments. Students complete at least 24 hours of course work including 3 seminar hours, normally finishing all course work within their first three semesters.

Ph.D. Program

Research Requirements

Ph.D. Program

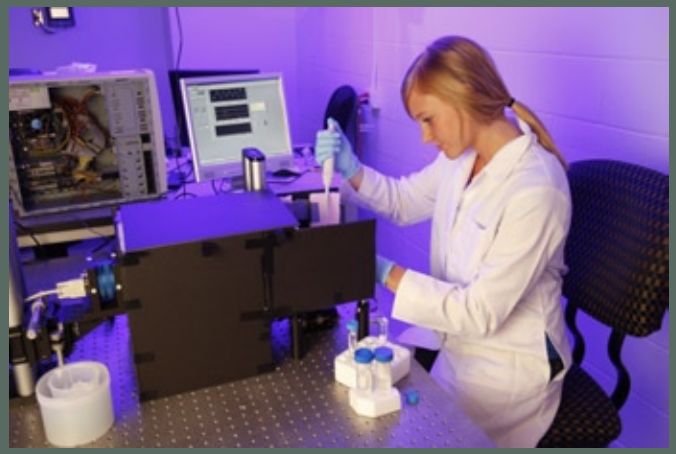
During their first year, students complete three lab rotations in research groups of their choosing, and then select a research adviser at the end of their second semester.

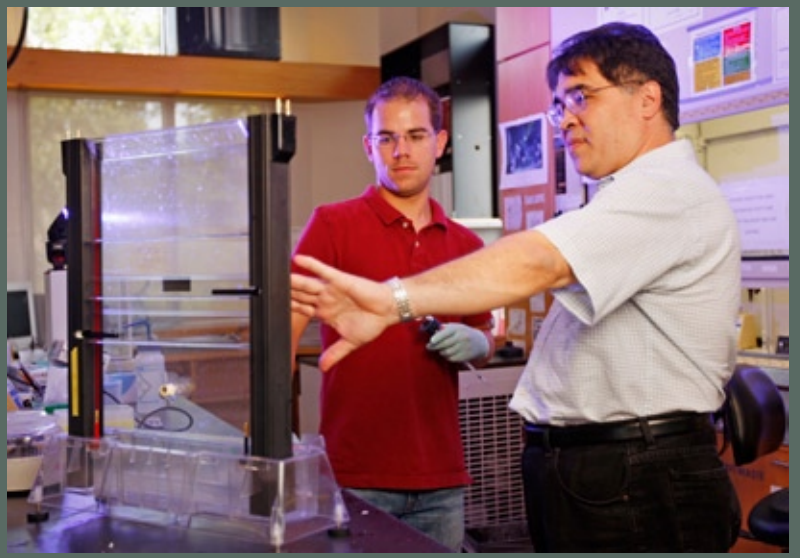
Students complete a Ph.D. qualifying examination, normally within their fifth semester of graduate study. Subsequently, they meet at least once with their Academic and Research Monitoring (ARM) Committee, which monitors their research progress. Students present their research results to date in a departmental seminar scheduled during their third year. During their fourth year, students present and defend an Independent Research Proposal.

The program design enables students to graduate with a professional degree within four years. Students conclude their Ph.D. program when they pass informal and public final defenses of research results.

M.S. Program

Students who pursue an M.S. degree in chemistry must complete a research thesis approved by two faculty members. The M.S. program of study closely parallels that of the Ph.D. program, thus allowing flexibility in selecting the final degree goal. No financial aid is available for the M.S. program.





Chemical Research Facilities

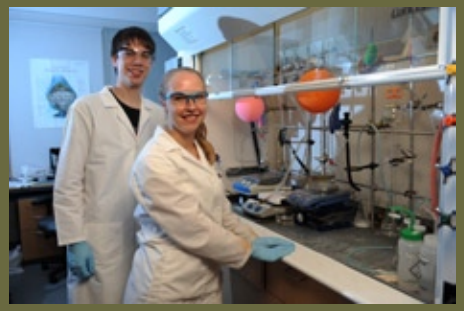
The outstanding research facilities at Vanderbilt University offer graduate students an excellent opportunity to gain hands-on experience in leading edge experimental techniques. As chemical research becomes more sophisticated and interdisciplinary, a broad range of instrumental techniques is required to advance scientific knowledge.

In Stevenson Center, the Chemistry Building and the Science and Engineering Building provide the Vanderbilt Department of Chemistry more than 100,000 square feet of space for wet chemistry teaching and research, and more than 130,000 square feet for physical and theoretical chemistry, biomedical engineering, microelectronics, and geology. Two additional research buildings are shared with the School of Medicine, Medical Research Building III and Medical Research Building IV, and give the Center for Structural Biology and Institute for Chemical Biology

53,000 additional square feet of modern research space on the Medical School Campus, immediately adjacent to Stevenson Center. Chemistry faculty also have offices and laboratories in the Preston Research Building and the Robinson Research Building, which are on the Medical School Campus.

State-of-the-art Laboratories

Vanderbilt University chemistry graduate students work in ultramodern laboratories as part of a curriculum combining solid research, intensive training, and exceptional education. This accelerated program enables graduated students to leave Vanderbilt with outstanding, ACS-accredited, professional degrees, well prepared for highly competitive careers in respected research universities, private and public sector laboratories, industry, and in other chemistry-related professions, such as patent law.



LABORATORIES

Vanderbilt University has a vast array of research instruments, which all students have access to use. Highly trained, full time instrumentation and research assistance is available for teaching how to use the equipment and expanding the research possibilities. Scheduling is done online by the student.

MASS SPECTROMETRY RESEARCH CENTER

The mission of the Mass Spectrometry Research Center (MSRC) is to bring state-of-the-art mass spectrometry expertise, methodology, and instrumentation to the research and clinical infrastructure of the Vanderbilt University Medical Center. Mass spectrometry is a powerful analytical tool that is used in the elucidation of the molecular weight and structure of a wide variety of molecules and has extensive applications in chemistry, biology, medicine, and forensics. Compounds ranging from small drugs and metabolites up to large biomolecules such as proteins can be characterized with attomole sensitivity and ppm mass accuracy.

Richard Caprioli is the Director of the MSRC. Dr. Caprioli is one of the top mass spectrocopists in the world. He has published over 300 scientific papers, including three books. He holds more than 10 patents in scientific achievement. In 2003, Dr. Caprioli received the Thomson Medal Award from the International Mass Spectrometry Society “for outstanding achievements in mass spectrometry and for distinguished service to international mass spectrometry.” He received the Field and Franklin Award from the American Chemical Society in April, 2006 for Outstanding Achievement in Mass Spectrometry. He has been named as one of the “Pioneers in Proteomics” by the National Institutes of Health.

Mass Spectrometry Home Page

MASS SPECTROMETRY RESEARCH CENTER

The MSRC at Vanderbilt University consists of the Proteomics Laboratory, the Mass Spectrometry Core, the Caprioli and Schey Research Labs, the Tissue Profiling and Imaging Core, and a Bioinformatics Group. The MSRC instrument facility currently houses 33 mass spectrometers, of which 18 have been assigned to the shared resource. Specialized instruments for imaging and proteomic studies are also available, such as high resolution matrix spotters, a cryomacrotome for whole animal imaging studies, a high resolution digital microscope for documenting histology data, a 2D gel fluorescence imaging and 2D gel processing robot. Fifteen mass spectrometers with specialized analytical capabilities are available in the research core. The cores are closely integrated and share methodologies and expertise.

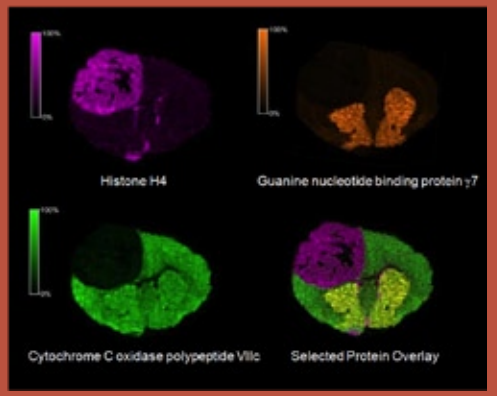


Figure 1. Selected images of proteins detected in a tumor-bearing mouse brain. Proteins are displayed which localize to the tumor, the straitum, and one that is present throughout all of the normal brain. Images courtesy of Sara Frappier.

NMR

Vanderbilt University has three NMR facilities, which house 9 state-of-the-art NMR spectrometers, which are available to all Vanderbilt faculty, staff and students. With these state-of-the-art instruments, atomic resolution structures of DNA and proteins can be obtained, the dynamics of these molecules studied or ligand interaction sites identified, as well as many other applications. Training classes in 1D, 2D NMR and 3D are available to all users and are typically held several times a year. These training classes focus on the practical aspects of acquiring and processing NMR data sets. In addition to the classes, three full time staff are available to assist students.

Small Molecule Facility

more info

MRB IV Facility

more info

Biomolecular NMR Center

more info

Biomolecular NMR Center

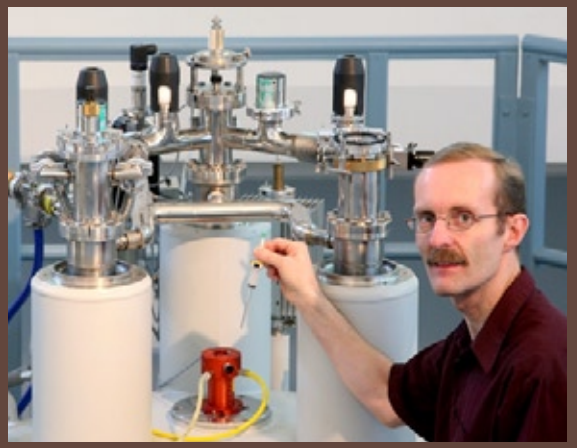
Nuclear Magnetic Resonance spectroscopy (NMR) is a powerful technique that can provide information on molecular structure and dynamics at the atomic level. The naturally-occurring 1H isotope is the most sensitive NMR reporter. However, the very large number of 1H nuclei in macromolecules, can make the 1H-NMR spectrum intractable. Fortunately, with the advent of multi-dimensional techniques and methods in molecular biology to incorporate 13C, 15N and 2H in biological macromolecules, it has become possible to probe the structure, dynamics and biochemistry of proteins, RNA, DNA, and carbohydrates with NMR. The Vanderbilt Biomolecular NMR center was created as a part of a transinstitutional initiative to develop structural biology on campus.

The Biomolecular NMR Center provides instrumentation and assistance in obtaining data on the structure and dynamics of biological macromolecules. The Facility houses four state of the art NMR spectrometers, which are available to all Vanderbilt faculty, staff and students, including one 500 MHz, two 600 MHz and one 800 MHz Bruker spectrometers. All instruments are equipped with four channels. Three cryo-probes, one at each field (500, 600, 800) drastically enhance the sensitivity of these spectrometers. A variety of training opportunities are offered, as well as assistance with
software and experimental design.

The facility is managed by the Director of Operations, Markus Voehler, Ph.D. (m.voehler@vanderbilt.edu)

600 Mhz Bruker Avance
FT-NMR spectrometer

500 MHz Bruker Avance FT-NMR
spectrometer with cryoprobe



800 MHz Bruker Avance FT-NMR
spectrometer with cryoprobe

Small Molecule NMR Facility

The small molecule NMR facility is equipped with 4 spectrometers. The facility is located in SC1119 and houses the following instrumentation:

•**300 MHz Bruker DPX FT-NMR Spectrometer** - This system is dedicated to "walk-up" use (quick 1H & 13C acquisitions) and is capable of acquiring multinuclear experiments such as 1H, 13C, 19F, and 31P with automatic probe switching between different nuclei.

•**400 MHz Bruker AVI FT-NMR Spectrometer**- This spectrometer is also capable of acquiring multinuclear experiments such as 1H, 13C, 19F, and 31P with automatic probe tuning/matching. It also is equipped with a sample changer that can accommodate 60 samples for automated acquisition. Users can set up multiple samples/experiments and have the results emailed to them when samples are completed.

•**500 MHz Bruker DRX FT- NMR Spectometer**- This spectrometer is optimized for 1H sensitivity which caters to users who need to run 2D experiments such as COSY, NOESY, HSQC and HMBC. This spectrometer is also equipped to run variable temperature experiments from -73 C up to 150 C.

•**600 MHz Bruker AVIII FT-NMR Spectrometer** - This spectrometer is the latest state-of-the-art instrument from Bruker Biospin. It features a 5 mm cryogenically cooled NMR probe for increased 1H & 13C sensitivity. The cryoprobe enables users to acquire data on low-microgram quantities of material for 1H and mid-microgram quantities for 13C. This spectrometer is also equipped with an LC-SPE-NMR accessory which enables users to separate and analyze their sample without having to handle the sample. Currently, Vanderbilt University is the only academic institution in the Southeast to house this cutting edge technology.

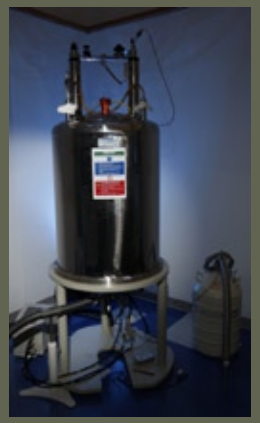
In addition to spectrometers, the Small Molecule NMR Facility at Vanderbilt offers the following:

•Training classes in both 1D & 2D NMR to all users - Training classes are typically held several times a year and focus on the practical aspects of acquiring and processing 1D & 2D NMR data sets.

•Campus wide site license for the Bruker NMR software TOPSPIN which allows users to access and process their data from any location on campus.

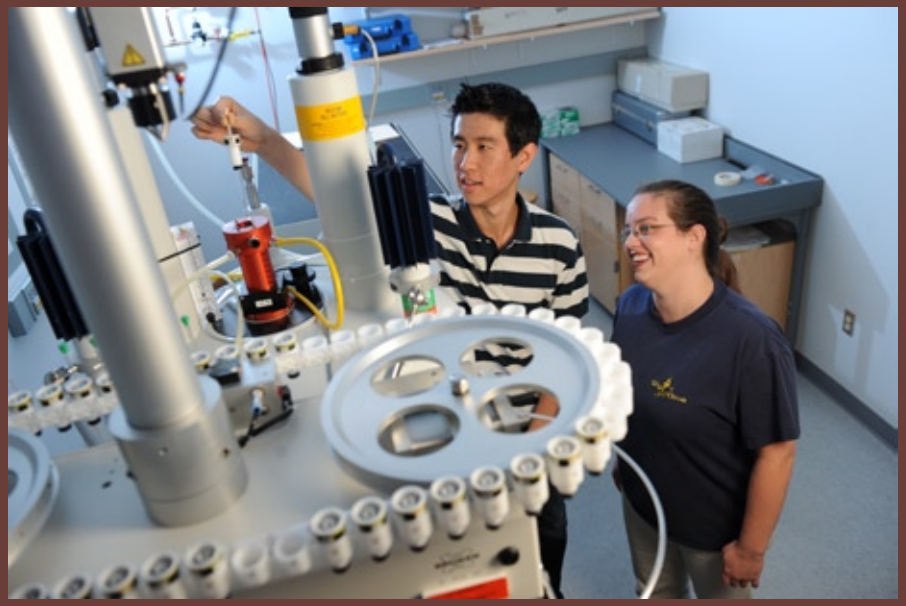
•Consultation with NMR Experts – users can receive additional training or consultation from two Ph.D. trained NMR spectroscopists

Don Stec, Ph.D., is the Director of the Small Molecule Facility.



MRB IV NMR Facility

The 12th floor of Medical Research Building IV houses a Bruker 400 MHz FT-NMR DRX spectrometer with sample changer (BACS 60) for the use of faculty and graduate students. Training classes are available through the Small Molecule Facility. The two staff spectroscopists are available for consultation or additional training.



400 MHz FT-NMR DRX spectrometer with sample changer (BACS 60)

High-Throughput Screening Facility

The High-Throughput Screening Facility utilizes state-of-the art lab automation for sample storage, retrieval, and liquid handling and high-throughput plate readers, data management and analysis software to screen and interrogate chemical libraries (150,000 compounds selected to represent the chemical diversity of more than 1,000,000 MRSF accessible compounds) and recombinant phage-displayed antibody libraries (~ 2.9 x 109 members) to identify reagents for use in research, diagnostic or therapeutic applications.

for more information, click here

The Instrument Laboratory

Equipment in the facility includes:

Saturn GCMS
Voyager DE-STR MALDI-TOF-MS
API 2000 LC/MS/MS
Cary 100 UV/Vis Spectrophotometer
HP GCMS,
Beckman HPLC,
Spectrofluoremeter,
Scanning probe microscope.

Additional resources are available to students:

- Center in Molecular Toxicology (http://www.toxicology.mc.vanderbilt.edu/)
- Vanderbilt-Ingram Cancer Center (http://www.vicc.org/)
- Vanderbilt Molecular Recognition and Screening Center (http://www.vanderbilt.edu/hts/)
- Center for Structural Biology (http://structbio.vanderbilt.edu/about.php)
- Computational Resources (http://structbio.vanderbilt.edu/comp/)

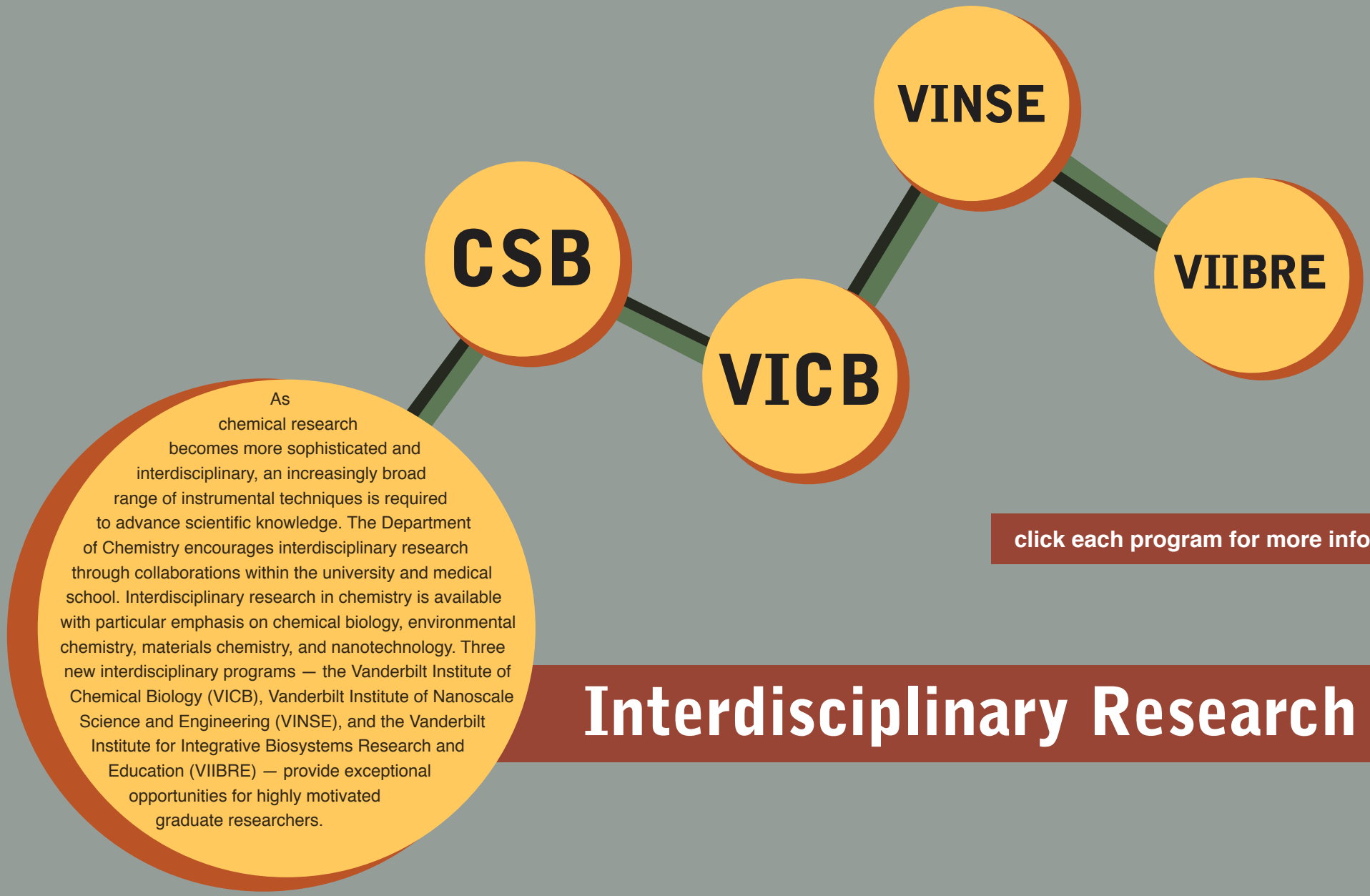
The X-RAY Diffraction Laboratory

The X-Ray Diffraction Laboratories are located in Medical Research Building III and Robinson Research Building. In addition, the lab has membership in the LS-CAT beamline at the Advanced Photon Source at Argonne National Laboratory.

Equipment in crystallography includes:

- 2 X-ray generators
- Bruker Microstar microfocus rotating-anode equipped with state-of-the-art Proteum CCD detectors mounted on kappa-axis goniometers, as well as a Bruker Bruno sample changing robot.
- Oxford Diffraction Xcalibur PX2 Ultra sealed-tube generator with a CCD detector and kappa-axis goniometer. All detectors are equipped with cryostats for cryogenic data collection.

- Hamilton Microlab Starlet liquid handling robot to set up crystallization screens and TTP LabTech Mosquito nanoliter dispensing robot to set drops for crystallization experiments.
- Crystallization incubators maintained at a variety of temperatures
- Two Leica MZ12 microscopes with polarizer/analyzer; one with a CCD camera for photographing crystals.
- Leica MZ6 microscope with polarizer/analyzer.



As chemical research becomes more sophisticated and interdisciplinary, an increasingly broad range of instrumental techniques is required to advance scientific knowledge. The Department of Chemistry encourages interdisciplinary research through collaborations within the university and medical school. Interdisciplinary research in chemistry is available with particular emphasis on chemical biology, environmental chemistry, materials chemistry, and nanotechnology. Three new interdisciplinary programs — the Vanderbilt Institute of Chemical Biology (VICB), Vanderbilt Institute of Nanoscale Science and Engineering (VINSE), and the Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE) — provide exceptional opportunities for highly motivated graduate researchers.

click each program for more info

Interdisciplinary Research

Vanderbilt University

Commodore Cornelius Vanderbilt, founder of Vanderbilt University, is considered to be the second wealthiest person in American history, after John D. Rockefeller. (Bill Gates ranks 6th.)

Cornelius Vanderbilt was an American entrepreneur who built his wealth in shipping and railroads. His second wife's cousin, Methodist Bishop Holland N. McTyeire, while staying with the Vanderbilts in New York following medical treatment early in 1873, convinced Vanderbilt to gift $1 million dollars to the founding of Vanderbilt University. It was McTyeire who made the decision to locate Vanderbilt in Nashville, his home town; he chose the site, supervised the construction of the buildings and personally planted many of the trees that now thrive on the Vanderbilt Campus. Sadly, Commodore Vanderbilt never visited the campus. He died in January, 1877 at the age of 89.

In the beginning, the university consisted of one main building (Kirkland Hall), an astronomical observatory, and houses for faculty. Landon C. Garland was named Vanderbilt's first chancellor serving from 1875 to 1893; he advised McTyeire in selecting faculty, arranged the curriculum, and set the policies of the university.

Initially, it was assumed that Vanderbilt University would be an all-male institution; however, the Board never enacted rules prohibiting women. At least one woman attended Vanderbilt classes every year from 1875 on. Most women came to classes by courtesy of professors or as special or "irregular" (non-degree) students. Vanderbilt women had full legal equality except for one respect – access to dorms – which they gained in 1901.

For the first 40 years, Vanderbilt was under the auspices of the Methodist Episcopal Church South. As a result of a dispute with the bishops over who would appoint university trustees, the Vanderbilt Board of Trust severed its ties with the church in June 1914.

The original Vanderbilt campus consisted of 75 acres. By 1960 the campus had grown to about 260 acres of land. In 1979, the George Peabody College for Teachers merged with Vanderbilt University and 53 more acres were added. Today the university occupies approximately 330 acres.

For virtual tour, **click here**

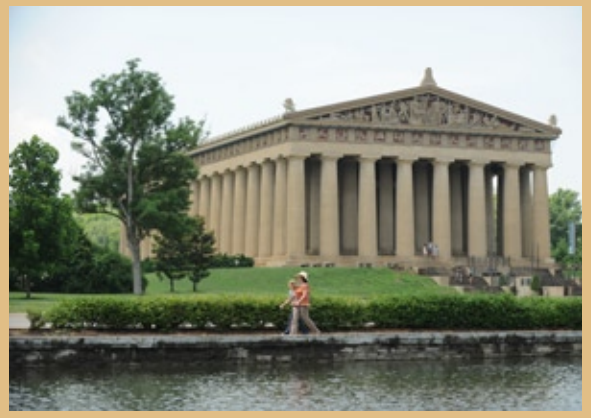
Nashville

Vanderbilt University is located in Nashville, Tennessee, a vibrant, engaging city that proudly exudes all of the charm and hospitality one expects from a Southern capital.

Nashville was settled in 1779, when Fort Nashborough, named in honor of the Revolutionary War general Francis Nash, was founded at the Great French Lick on the Cumberland River by James Robertson and John Donelson. Col. Donelson's daughter, Rachel, would become the wife of Andrew Jackson, the nation's seventh president.

In 1796, Tennessee became the 16th state of the Union, the name Tennessee being derived from a Cherokee word meaning "bend in the river" or "meeting place," and Nashville became the state capital in 1843. During the Civil War, the city's significance as a shipping port made it a desirable prize as a means of controlling important river and railroad transportation routes. As a result, in February 1862, Nashville became the first Southern state capital to fall to Union troops. Following the Civil War, Nashville quickly regained its importance as a trading and shipping place.

Nashville



The advent of the Grand Ole Opry in 1925, combined with an already thriving publishing industry, positioned Nashville to become “Music City USA.” As the “home of country music,” Nashville has become a major music recording and production center. All of the Big Four record labels, as well as numerous independent labels, have offices in Nashville, mostly in the Music Row area. Nashville has also become a hub for pop, rock, bluegrass, jazz, classical, contemporary Christian, blues, and soul music. Since the 1960s, Nashville has been the second biggest music production center (after New York) in the U.S.

The newly constructed Schermerhorn Symphony Center, home to the renowned Grammy-winning Nashville Symphony, anchors the downtown end of the recently designated Music Mile, a symbolic stretch of roadway connecting the Symphony Center with the music district of Music Row, the vibrant new entertainment venues on Demonbreun Street, the Frist Center for the Visual Arts, the Country Music Hall of Fame, the Music City Walk of Fame and Museum, and the Sommet Center.

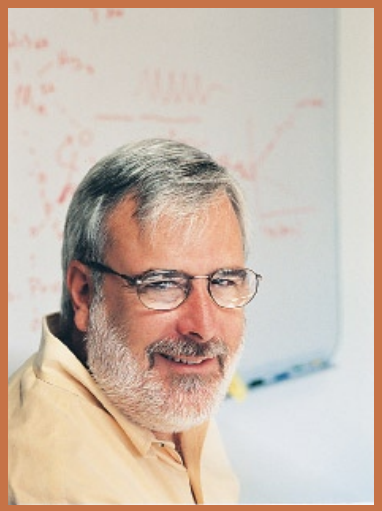
The city limits encompass 533 square miles with a population of more than 570,000. The greater Nashville area encompasses eight counties and has a population of more than 1.5 million. The city is known for its music, entertainment, financial, publishing, and health care management businesses, and is home to more than 20 institutions of higher learning.

While there are four distinct seasons, the weather is typically mild and pleasant, with only a few days of the year having either very hot or very cold conditions. One of the few cities to have two professional sports teams, Nashville hosts an NFL team (the Titans) and an NHL team (the Predators), as well as an AAA baseball team, the Nashville Sounds, farm team for the Milwaukee Brewers. In addition, Vanderbilt athletic teams provide a wide range of sports entertainment.

While music is the lifeblood of Nashville, it is also a city of culture and history, haute cuisine, pro sports, outstanding academics, natural beauty, and pure Southern charm.

Nashville: http://www.vanderbilt.edu/nashville


LEADERS
in Research



Richard N. Armstrong

Professor of Biochemistry & Chemistry
Ph.D., Marquette University, 1975

Email: r.armstrong@vanderbilt.edu
For more information and a list of recent publications, please go to www.vanderbilt.edu/AnS/chemistry/faculty/bio.php?ID=1

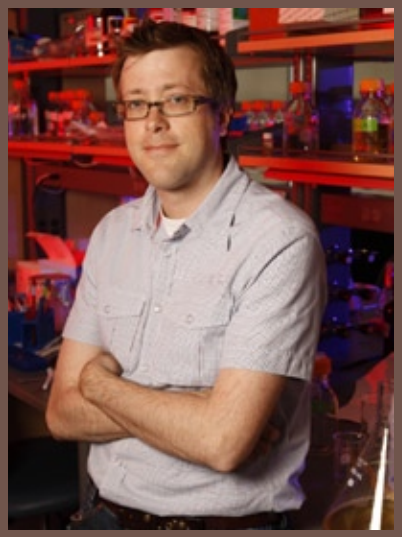
Structural and Mechanistic Enzymology

Research efforts in Professor Armstrong's laboratory are embodied in three projects directed at elucidating the mechanisms of action of enzymes involved in the metabolism of foreign or xenobiotic molecules. These catalysts, known as detoxication enzymes, are essential components of any organism's ability to resist chemical insult.

The first project is a study of glutathione transferases, a family of enzymes involved in the metabolism of electrophilic molecules such as expoxides, alkyl halides, and a,b-unsaturated carbonyl compounds. From studies of the physical organic chemistry occurring in the active site, aspects of the kinetic, chemical, and stereochemical mechanisms of these enzymes have been elucidated. In addition, high-resolution three-dimensional structures of several glutathione transferases have been solved and are being used as a guide in the construction of chimeric or hybrid enzymes with altered catalytic properties. The functional properties of the mutant enzymes provide insight into the specific role of various amino acid residues in the region of the active site. The site-general and site-specific incorporation of unnatural amino acids into this enzyme is being investigated as a tool to refine our understanding of the mechanism of catalysis.

Many detoxication enzymes are membrane-bound and pose unique problems for mechanistic analysis. In a second project, two membrane-bound detoxication enzymes, enzymes epoxide hydrolase and UDP-glucuronosyltransferase, are being investigated. Efficient expression systems are being developed for these enzymes to facilitate structural and mechanistic studies. The discovery that epoxide hydrolase proceeds via a covalent ester intermediate has aided in the identification of active site residues that participate in catalysis and has helped define the evolutionary relationship of this protein with other hydrolase enzymes.

Microorganisms also have detoxication enzymes which allow them to use many organic compounds as energy sources or to resist the toxic effect of antibiotics. This later phenomenon contributes to the erosion of the efficacy of clinically useful antibiotics and represents a serious human health problem. The objectives of the third research project are to elucidate the catalytic mechanisms and structures of enzymes involved in the resistance of microorganisms to the antibiotic fosfomycin. These objectives include, (i) the construction of high-level expression systems for fosfomycin resistance proteins; (ii) elucidation of the catalytic mechanisms of the enzymes, by spectroscopic, steady state, and pre-steady state kinetic techniques; and (iii) determination of the three-dimensional structures by X-ray crystallography. The information will provide a rational basis for the design of new drugs to counter antibiotic resistance.



Brian O. Bachmann

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Biosynthetic Science

The primary mission of the Bachmann Lab is to apply knowledge of the design rules for secondary metabolism at the chemical, biochemical and genetic levels toward the biosynthesis of “non-natural” compounds of high value to biomedical research and the clinic. Key to this program in “synthetic biology” is the dissection of the mechanisms by which life makes bioactive molecules in vivo. The lab is organized according to three interlocking research areas: Biosynthesis, Synthetic Biology, and Discovery. These subgroups each have basic research and applied components and overlap with one another both thematically and methodologically.

1. Biosynthesis. The focus of the biosynthesis research subgroup centers on investigating the biosynthesis of pharmacophores by microorganisms from a genetic to a chemical basis. In all cases, we target non-trivial biotransformations that have little or no precedent in prior research. To date, pathways have been targeted in the bacterial Order Actinomycetales (also called actinomycetes), one of the richest microbial sources of secondary metabololites.

2. Synthetic Biology. Synthetic Biology is a burgeoning field, the ambitious aim of which is to use the machinery of biological systems (DNA, RNA, proteins) for the production of synthetic compounds and materials of high value to research, medicine and human life. For small molecule synthesis, these methods offer totally new avenues for the production of compounds and an alternative to petrochemical-based chemical synthesis. We believe that the global societal impacts of synthetic biology will be far reaching in this century. The primary mission of the Bachmann lab is to apply this knowledge of the design rules for secondary metabolism at the chemical, biochemical and genetic levels toward the biosynthesis of “non-natural” compounds of high value to bio research and the clinic.

3. Drug Discovery. It is becoming increasingly apparent that natural products derived from microbes, plants and animals represent important contributors of chemical diversity for the development of sustainable drug discovery efforts. Brian Bachmann in his former (industrial) and current (academic) lab has developed a two-pronged approach for natural product discovery:

1. A strategy for leveraging microbial genomic sequence data to predict secondary metabolic potential of microorganisms and to utilizing these predictions to prioritize isolations, accelerate isolation and structural elucidations.

2. A strategy for integrating natural product discovery into contemporary high throughput screening technologies by A) rapid generation of natural product fraction libraries from unique biological sources and B) applied metabolomics technologies for the identification and discovery of antibiotic/cytotoxic compounds. Rapid identification of compounds correlated to a biological activity of interest drives the prioritization of a classic isolation/structure-elucidation cascade in the Bachmann lab.

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Analytical Chemistry

Our group interests center around multidisciplinary bioanalytical and biomedical research:

- the application of lasers to nanoscale chemical and biochemical analysis, and the use of micro-fluidics for onchip patterning, high throughput screening, proteomics and point of care analysis.
- the synthesis, characterization, and application of exogenous markers (particularly multi-modal signaling agents) for early disease detection, diagnosis, and in-vitro assays.

Back Scattering Interferometry (BSI) - Our group has developed a unique sensor, the Back Scattering Interferometor (BSI) and pioneered its use. This new Technology was reported in Science. For the first time, free-solution, label free detection of the interaction of molecules in a micro-chip format with zeptomole sensitivity is possible. BSI is ideally suited for measuring molecular interaction kinetics and performing quantitative, end point assays. The BSI platform can be used to discover new biomarkers, rapidly develop assays, and run routine / quantitative molecular based assays in seconds, at picomolar concentrations in either free-solution or surface-bound, label free modes. The BSI platform consists of a simple optical train employing a helium-neon laser like those used in grocery store scanners, a mirror, a CCD detector like those used in digital cameras and a special microfluidic chip.

Molecular Imaging/Chemical Synthesis - Multiple targets and various approaches to signaling and/or therapeutic intervention are under investigation. A main target of interest is the 18 kD protein, the Peripheral Benzodiazepine Receptor (PBR). PBR is found primarily in the mitochondria and is known to be associated with responsiveness to reactive oxygen species, apoptosis and steroidogenesis. PBR expression is upregulated in some cancers, and its density has been correlated with metabolic status of the cell. These observations make PBR an attractive target for the delivery of contrast agents and therapeutics to diseased tissue. Recently we prepared a PBR targeted imaging agent (1) {Eu-PK11195, Figure 1} based on our relatively unique lanthanide chelate chemistry (2). The lanthanides are brightly luminescent, show promise for early cancer detection (3) and can even be used as multi modal agents by simple exchange of the chelated lanthanide ion. In-vitro and in-vivo investigations along with new synthetic methodologies are being developed in our laboratory. Some of these new agents have also demonstrated promise as in-vitro diagnostic stains for use in histopathology. In addition, we are developing near-infrared fluorochromes (4), PET agents, and MR signaling agents that are smart, can precipitate selectively or can provide both a signature and a therapeutic effect. Also under intense investigation are the unique spectroscopic properties of the lanthanide chelates.

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Research in Biochemistry, Bioorganic, and Analytical Chemistry

Our research group is focused on understanding the roles of specific lipid molecular species and phospholipases in cellular functions and human disease. We combine systems biology approaches with mass spectrometry to profile changes in cellular lipid species (lipidomics). Much of our work is focused on understanding the role of phospholipase D (PLD) in growth factor and G protein coupled receptor (GPCR) signaling networks. With our collaborators we are developing novel chemical inhibitors of PLD and ancillary proteins in the signaling network to better understand the role of PLD in cancers and tumorigenesis, as well as to explore its therapeutic potential. Areas of current research include: structure and enzymology of PLD; defining the signal transduction networks from the receptor tyrosine kinases and GPCRs to PLD; mechanisms by which phosphatidic acid (PA) regulates cell cycle, growth, and proliferation; roles of PLD in zebrafish; developing novel probes for defining specific lipid binding targets; precursor-product relationships of lipid enzymes using mass spectrometry; lipid perioxidation and antioxidant mechanisms; and advanced methods in lipid mass spectrometry.

Signal Transduction Pathways of Phospholipase D.
Our laboratory has a long-standing interest in enzymes involved in cellular signaling and particularly the dynamic balance between PA and diacylglycerol (DAG). One of the major cellular pathways for direct production of PA is PLD. This enzyme is expressed in certain bacteria, viruses, yeast, and ubiquitously in mammalian cells. Defining the functions of PLD along with the pathways by which PLD is activated by cell surface receptors has been a challenging undertaking. We are particularly interested in defining the roles of PLD-generated PA in EGF receptor functions and have recently developed a system to define both protein and lipid participants in this pathway using a strategic combination of proteomic and lipidomic approaches.

Preclinical Drug Discovery: Design, Synthesis, and Evaluation of Novel Phospholipase D Inhibitors.
PLD has been implicated in a number of human diseases including diabetes, myocardial disease, neurodegenerative disorders, infectious diseases, and cancers. We have developed a platform to screen small molecule libraries for inhibitors of PLD and other lipid signaling pathways using both enzymatic- and cell-based assays. In collaboration with Craig Lindsley's group candidate small molecules are identified and compounds optimized to improve potency, isoform selectivity, and pharmacodynamic properties. Effective inhibitors are being used to define mechanisms of PLD action on cell growth, proliferation, and a variety of processes in cancer cells.

Structure and Enzymology of Phospholipase D.
The structure of a mammalian PLD phosphodiesterase has been elusive. Our goal is to understand how G proteins and kinases modulate the structure and catalytic activity of the enzyme in order to fully understand its molecular mechanism. We will use this information to further refine our cadre of inhibitors to be more specific and isoform selective.

Bioorganic Chemistry of Lipid Probes and Lipid Perioxidation
As a result of our detailed analysis of the lipid composition of macrophages, we have identified several atypical or novel species of glycerophospholipids. This includes plasmanyl and plasmenyl species of phosphatidic acid and phosphatidylinositols. The roles of these species in metabolism and cell signaling are currently not defined, but we are using state-of-the-art mass spectrometry to establish precursor-product relationships. This includes the perioxidation products of polyunsaturated fatty esters and determining mechanisms by which these species contribute to human disease. The focus of this project includes the study of products formed by perioxidation of different lipid classes, including electrophiles generated. In collaboration with the groups of Ned Porter and Larry Marnett in the Chemistry Program at Vanderbilt, we have developed a new class of lipid probe that is being used to track metabolic and signaling pathways through cells. These probes are being developed for both lipidomic and proteomic applications.

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The research interests of this laboratory are aimed at the investigation of biological processes involving the synthesis, modification, storage and degradation of certain peptides and proteins using modern mass spectrometric methods of analysis to follow molecular events. In recent years there has been a great amount of interest in investigating the biochemical events involved in the metabolism of peptides, primarily in the brain and gut of mammals, encompassing the enzymatic breakdown of these peptides, their production from peptide and protein precursors, and the disruption of these processes by certain xenobiotics. Modern mass spectrometric techniques are used in these studies, including electrospray and matrix-assisted laser desorption ionization mass spectrometry. This research is generally carried out with two experimental approaches.

The first involves in vivo metabolic studies in live animals (rats) using microdialysis sampling procedures together with molecular identification and quantitation by electrospray tandem mass spectrometry. This experimental approach allows us to measure metabolic events that occur in freely moving animals at a level of 50-100 attomoles in the tissue dialysate. Integrated technology for microdialysis/mass spectrometry utilizes quadrupole mass spectrometry (MS/MS) and micro-electrospray ionization (micro-ESI) for very high sensitivity measurements. The micro-ESI source has been optimized to produce ions from the electrospray process at sub-microliter per min flow rates. The application of combined microdialysis/ESI mass spectrometry is ongoing in four areas, i) Investigation of the kinetics and quantitative aspects of the in vivo metabolism of the neuropeptides and enkephalin neuropeptides, ii) Studies of the kinetics and differential processing of opioid peptide fragment precursors in vivo, iii) Investigation of the in vivo quantitative production and enzymatic degradation of N-acetylaspartyl-glutamate in seizure disorders using a rat model, and iv) Development and measurements of in vivo drug pharmacokinetics, using the drugs haloperidol, valproic acid, cocaine, amphetamine, and the new GABA antagonist n-butyl-3 aminopropylphosphinic acid.

The second experimental approach used in the study of cellular peptide metabolism utilizes new molecular imaging technology that is being developed in our lab. This method involves molecular mapping of animal tissue through the production of ion images obtained from the analysis of mammalian tissue slices by matrix-assisted laser desorption mass spectrometry (MALDI MS)12. This technique permits a tissue section to be mapped in multiple molecular weight values, localizing the molecules in an X, Y coordinate representation of the sample. Ion images are produced by repetitive exposure of the sample to the laser beam, where adjacent spots are irradiated, resulting in an ordered array of mass spectra that are keyed to specific locations in the sample. From one raster of the sample, a specific ion image, at any chosen m/z value, could be produced to give the spatial arrangement of molecules of interest. Current work involves; i) Instrument development involving modifications to an existing commercial MALDI (TOF) mass spectrometer, including changes to the laser optics, target movement system, and instrument control hardware and software, ii) Development of methods for sample preparation and target surface modifications to achieve high sensitivity and high image resolution, with molecular specificity, and iii) Applications to specific research areas involving questions about certain spatial distributions of molecules within specific tissues.

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Research in our laboratory seeks to characterize the structure and motions of proteins and nucleic acids, and the way in which they interact with other proteins, nucleic acids and drugs. We are in essence using the power of the chemistry approach to address key problems in biology and medicine. NMR spectroscopy is the primary experimental tool, though in studying these complex biomolecules, we make use of other biophysical and structural techniques, including X-ray crystallography, calorimetry, fluorescence spectroscopy and X-ray scattering.

The Structural Basis for Protein Function

One of the great challenges today is to understand how proteins act together to perform the major processes in a cell such as DNA replication. A process like DNA replication is complex, involving a sequence of many chemical steps. Our lab is trying to understand how these multiple steps (i.e. the activity of a number of proteins) are coordinated? Our lab currently studies two types of multi-protein machinery, one group involved in DNA replication, damage response and repair, and a second involved in protein ubiquitination.

Our studies have focused on structurally characterizing the contacts between specific RPA domains and the corresponding regions of the partner proteins. More recently, NMR and X-ray scattering studies have been undertaken on intact RPA and we have made considerable progress in understanding the global architecture of RPA and how this is changed upon binding DNA. By piecing together these aspects of RPA structure and interactions, we are building a basic understanding of how the RPA molecule functions in mediating DNA processes. In so doing, we are laying the foundation to determine how mutations in the constituent proteins cause defects that lead to cancer and other diseases.

Ca2+ Signal Transduction by EF-hand Proteins

Change in the level of calcium inside a cell is a common means for regulating biochemical signaling cascades and biomechanical actions- ranging from controlling the opening and closing of ion channels to the contraction of muscles. The EF-hand family of calcium binding proteins plays a central role in virtually every aspect of calcium signaling, so studies of how EF-hand proteins respond to the binding of calcium are the key to understanding how this ion influences so many aspects of health and disease.

Over the past few years we have been determining the structural basis for how changes in calcium levels in cells control inactivation of the human sodium cardiac channel Nav1.5. These studies revealed a complex mechanism involving an EF-hand domain in Nav1.5 that directly binds calcium, and an equally critical role for the ubiquitous EF-hand protein calmodulin. These two calcium sensing mechanisms act in concert to re-position a flap at the edge of the pore that controls movement of sodium ions from outside to inside the cell. Mutations in the corresponding regions of Nav1.5 have been shown to lead to cardiac arrhythmia syndromes and are being investigated in an effort to determine if new therapeutic strategies for these diseases can be developed based on our structural insights.

A second area of emphasis involves the unique S100 class of EF-hand proteins, the first structures of which were determined in our laboratory. These proteins are distinguished by their ability to exert activity both inside and outside cells. We currently focus on calprotectin (CP), a dimer of S100A8 and S100A9 that plays a role in mediating inflammation and serves as an integral part of the innate immune response. CP exhibits a remarkable ability to suppress infections by S. aureus and other bacteria by starving them of essential metals needed for survival. Our ultimate goal is to develop new approaches for antimicrobial agents that are based on the mechanism of action of CP.
A second CP project involves determining the structural basis of CP activity in inflammatory processes, which results from its ability to activate the cell surface receptor RAGE (receptor for advanced glycation end products). The structure of RAGE is not known, so characterization of RAGE alone is underway in parallel to analyzing the structural basis for RAGE activation by CP. These studies will provide critical insights for understanding chronic inflammation and atherosclerosis in diabetics and have the potential to reveal new avenues for treating these and other chronic inflammatory disorders.

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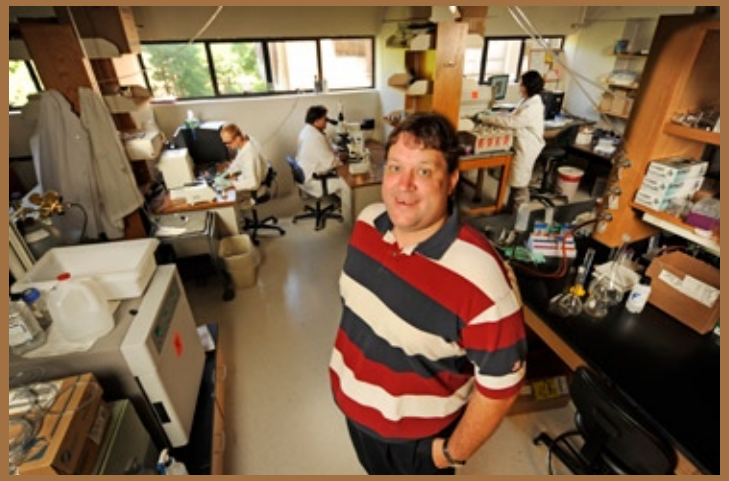

Specialties
Electroanalytical Chemistry
Bioanalytical Chemistry
Nanoparticle Biomimics

Multianalyte Microphysiometry

Analytical chemistry often leads the forefront of scientific discovery, as new instrumentation allows us to perform new experiments. Our group has created multianalyte microphysiometry by combining microfluidic technologies with electrochemical detection to study the dynamic behaviors of metabolic pathways. We are developing new multianalyte microphysiometry methods with applications in cancer, diabetes, and toxicology.

We have added electrochemical detectors for many metabolic analytes into the microfluidic chamber to give a complete dynamical picture of the live cell population.

Nanoparticle Biomimics

The ability to mimic biomolecular recognition requires the generation of nanoscale structures that faithfully reproduce the lock & key motif of protein binding. We have designed biomimics that present targeted linear and loop peptide structures on the surface of monolayer protected gold nanoparticles. These biomimics are useful for calibrating immunoassays, especially in our immunosensor work with the quartz crystal microbalance.

Electrochemistry on the Nanoscale

Electron transfer in nanometer-size chemical systems is an important process for the creation of macromolecular electronics. We are interested in the electrochemistry of metallic nanoparticles, redox proteins like Photosystem I, and other electroactive nanomaterials that bridge the gap between bulk solids and discrete molecules in the development of electronic devices using nanotechnology.

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Inorganic Chemistry

Use of ligand design to control the reactivity of main-group and transition metal organometallic and coordination complexes; investigation of steric effects on the reactivity and magnetic properties of metal complexes; synthesis of precursors to materials with desirable electronic/optical properties; computational investigation of bonding and structure in inorganic systems.

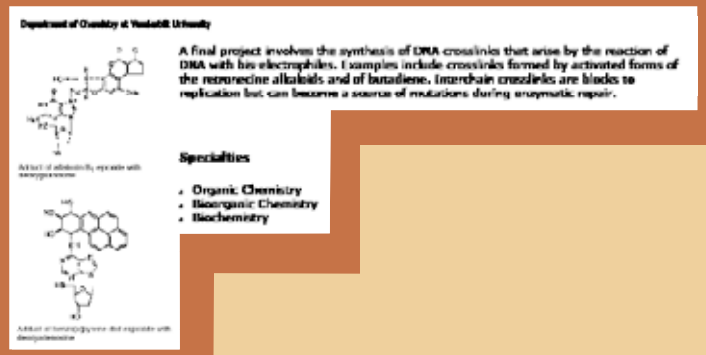
Molecular chemistry of the main-group metals: Our group has been developing ligand-based approaches to manipulating the structure and reactivity of main-group metals. The synthesis of volatile and/or liquid compounds that could be useful for the preparation of thin films of metal oxides and halides by chemical vapor deposition (CVD) methods is of particular interest. We have used large, sterically demanding cyclopentadienyl ligands to turn poly- or oligomeric compounds of the heavier alkaline-metals (Ca, Sr, Ba) into monomeric species, often dramatically lowering their sublimation temperatures or melting points. Aluminum alkoxides and alkyls are being designed to deposit stochiometrically precise films of alumina on silicon wafers for microelectronics applications.

Use of sterically bulky allyl ligands in catalysis and the study of non-covalent interactions: The compact size of the allyl anion ([C3H5]-) means that its transition metal complexes are often coordinatively unsaturated and prone to facile decomposition. We have used sterically bulky substituents (e.g., SiMe3) to produce pi-allyl transition metal compounds that have no unsubstituted analogues, such as the extremely electron deficient 12- and 14-electron species [1,3-(SiMe3)2C3H3]2Cr and [1,3-(SiMe3)2C3H3]2Fe. We are synthesizing new bis- and tris(allyl) metal complexes of the transition metals and lanthanides, and examining their ability to serve as initiators in polymerization reactions. Density functional calculations are being used to study conformational preferences in bonding. We are also examining the way that the double bonds of allyl ligands can engage in cation-pi interactions. These non-covalent interactions are important in biological systems, but commonly involve aromatic rings. We are examining non-aromatic cation–pi interactions such as that between K+ and the allyl ligands of the zincate complex at right. Our investigations are helping to identify the geometric features that can affect the strength of cation-pi attractions.

Symmetry effects on the magnetic properties of transition metal complexes: There is considerable interest in the synthesis of transition metal compounds whose magnetic properties can be influenced by external agents. In the case of spin-crossover complexes, transitions between high- and low-spin states can be induced by temperature, pressure, and light, and the effective control of such transitions could ultimately lead to applications in switching devices, magnetic storage, and photonic systems.

Metallocene-based complexes have been attractive in this regard, and variations in the metals, their oxidation states, and ring substituents have led to species displaying spin-crossover behavior, molecular ferromagnetism, and ferromagnetic/antiferromagnetic exchange. We have been studying bis(indenyl) metal complexes, which are relatives of metallocenes, but whose ligand conformations are sensitive to orbital occupancies.

Monomeric (1-RC9H6)2Cr (R = t-Bu, SiMe3) are staggered, high-spin complexes with 4 unpaired electrons. When additional bulk is added to the ligands (e.g., (1,3-R2C9H5)2Cr; R = t-Bu, SiMe3), however, rotation to a gauche (near 90) conformation is forced upon the molecule. Owing to increased metal-ligand orbital mixing, maintenance of the high-spin state is no longer possible, and the molecules adopt low-spin configurations with 2 unpaired electrons. This indicates that both steric bulk and electronic effects brought about by selective substitution of the indenyl ligand can be used to tailor the magnetic properties of the compounds, making them suitable as tunable sources of variable spin molecules. The spin state changes also suggest that there may be useful variations in the reactivity of the complexes, a possibility we are investigating.



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Bio-organic Chemistry

Dr. Harris is a member and currently associate director of Vanderbilt's Center of Molecular Toxicology. The chemical basis of the genotoxicity of man-made and naturally occurring environmental carcinogens is being investigated in his laboratory. A central thrust of the research involves devising strategies for preparation of DNA to which carcinogens are bound in a structurally specific manner. Additional interests include mechanistic studies of the reactions of carcinogens with DNA, structural studies of DNA bearing the carcinogen adducts, and the implications of these findings for the carcinogenic process.

One project centers on the fungal metabolite aflatoxin B1. This powerful carcinogen is a common contaminant of peanuts and other agricultural commodities. The goals of the project are to understand why the compound reacts so efficiently with DNA and why the adducts are so potently mutagenic. Dr. Harris has synthesized the long-sought active form, the 8,9-epoxide, and has been studying its interactions with DNA. These studies include determination of the structures of the various DNA adducts, 2-dimensional NMR studies of the adducts in duplexed DNA to elucidate conformations, and investigations of the mechanisms by which the adducts are formed.

Another project involves the carcinogenic polycyclic aromatic hydrocarbons (PAHs) formed during food preparation, cigarette smoking and from incomplete combustion of fuels. Synthetic strategies are being developed for preparation of oligonucleotides bearing regio- and stereospecifically placed adducts of PAH diol epoxides so that the effect of adduct structure on DNA conformation and replication fidelity can be assessed.

A final project involves the synthesis of DNA crosslinks that arise by the reaction of DNA with bis-electrophiles. Examples include crosslinks formed by activated forms of the retronecine alkaloids and of butadiene. Interchain crosslinks are blocks to replication but can become a source of mutations during enzymatic repair.

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Polymer, Materials, and Organic Chemistry

The overreaching goal of our research is the development of versatile platforms of innovative vectors for cancer therapeutics, vaccine development and imaging reagents in nanomedicine. With the growing sophistication of polymerization strategies, the implementation of functionality and utilization of macromolecular architectures will be key for many of the promising applications in nanotechnology related to the biomedical field and materials science. Thereby structural and functional fidelity compatible for bioconjugation is a focus in the design of the polymer topology.

Design and Synthesis of 3-D Multifunctional well-defined Nanoscale Objects. We develop multifunctional organic nanoparticles of degradable and non-degradable nature to enable the controlled attachment of targeting units, molecular transporter, therapeutics and/or imaging reagents.

A new Generation of Molecular Transporter. Considering the low efficiency of cellular transport, we investigate dendritic molecular transporter of unique design to allow the delivery of bioactive cargos specifically to the cytosol or nucleus without unwanted intracellular probe metabolism and transport.

The systemic combination of nanovectors with preferred therapeutics, targeting moieties and vectors for cellular uptake provides the opportunity to obtain a large number of personalized therapeutic reagents.

Towards organic ‘quantum dots- Approaches to novel semiconducting Nanoparticles. In demand of imaging probes correlated with the efficacy of drug carriers, well-defined nanoparticles are developed for in vivo imaging and device technologies. They contain fluorescent core units and are decorated with lanthanides to provide powerful bimodal imaging reagents and will vitalize the investigation of electronic properties through site-isolation effects of electroactive entities in well-defined nanoobjects.

Mass Spectrometry
Research in the Hercules group deals with the development of new instrumental analytical techniques. The major focus has been on application of novel method of mass spectrometry to the study of synthetic polymers and to biomedical, environmental and analytical chemistry.

The Hercules group is active in the characterization of polymers using mass spectrometry. The focus is both on surface analysis and bulk analysis. Surface analysis of polymers involves studying the surface segregation of one component of a block copolymer. For example, in a styrene-siloxane diblock copolymer, the surface layer will be entirely the siloxane component even though the bulk composition is 10% or less siloxane. The extent of surface segregation is measured by secondary-ion mass spectrometry (SIMS).

David Hercules

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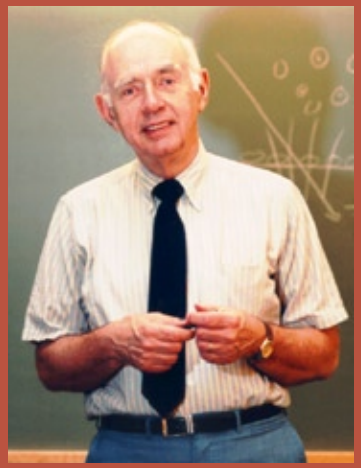
Matrix Assisted Laser Desorption/Ionization (MALDI)
MALDI mass spectrometry is being used for bulk analysis of copolymers. Of particular interest is determining the molecular weight distribution of a component of a block copolymer as it exists in the polymer chain. Polyurethanes are specific examples studied recently. Polyurethane properties are determined by the molecular weight of the soft block in the polymer chain. Combination of selective chemical reactions with MALDI permit measurement of the soft block (or hard block) molecular weight distributions in polyurethanes.

Single Molecular Weight (SMW) Oligomers
Synthesis of single molecular weight (SMW) oligomers of reasonable size (molecular weight >5000) is being pursued for a variety of reasons. SMW oligomers are important as calibration standards for polymer chromatography, as models to study fragmentation of polymers in mass spectrometry, and as model compounds for the behavior of intractable polymers in mass spectrometry. They are also valuable for comparing ionization processes in the different types of mass spectrometry.

Electrospray ionization (ESI)
ESI mass spectrometry is a particularly versatile method because one can inject solutions directly into the mass spectrometer. This allows one to determine the species of a given element in solution and to observe changes in speciation as solution conditions are changed. This is particularly attractive for environmental chemistry because the chemical behavior (toxicity) of an element varies significantly with its specific molecular form. Because ESI is a soft ionization method, non-covalent complexes can be observed and these can be used to measure the chirality of molecules, something almost impossible with other forms of mass spectrometry.

MALDI is very useful as a rapid screening, quantitative method which makes it ideal for use with combinatorial studies. Rapid screening in clinical and forensic chemistry is very important, and MALDI, coupled with solid-phase extraction, can be used to screen individual or multiple analytes. It is possible to screen for members of a given drug type (benzodiazepines) or a given clinical component (bile acids). Current research is focused on improved ways to use MALDI to accomplish rapid screening, coupled with chemically-selective solid-phase extraction methods for separation of trace analytes from complex matrices.



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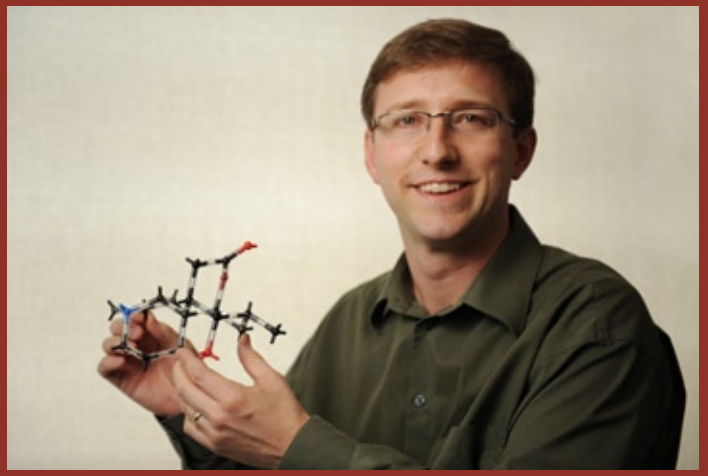

Our programs are tied by the common theme of organic synthesis, but can be expressed to reasonably diverse endpoints. Specifically, we are interested in the development of new reactions and reagents for natural product total synthesis, and in recent years have contributed a variety of new reactions to the chemist's arsenal: free radical-mediated aryl and vinyl amination, a Brϕnsted acid-catalyzed aza-Darzens, and a new acid catalyzed olefin aminoacyloxylation reaction, among others. We are now applying these reactions to the targets that inspired them. For example, our synthesis of mitomycin C uses the acid-catalyzed aza-Darzens reaction, in addition to a regioselective enamine-quinone coupling. As a result, we are able to synthesize an advanced intermediate with considerable brevity. An emerging area within our program is the use of indoline 'a-amino acids' made uniquely by our amination technology - for applications in bioorganic chemistry.

We have also advanced the concept and first embodiment of chiral proton catalysis. Reagents known as BAM-protic acid complexes are bifunctional, containing both a polar ionic hydrogen bond (a Brønsted acid) and a Brønsted base. These catalysts synchronize the activation of two substrates while orienting the electrophile for stereoselective addition. The net result is the ability to make a variety of products in enantioenriched form through carbon-carbon bond-forming reactions. From this perspective, these catalysts function in a chemically similar manner to enzymes. An underlying goal of our program is to understand how biological catalysts achieve substrate activation, and determine how this can be translated to small molecule catalysts.

Finally, we have ongoing internal and collaborative projects in organometallic catalysis that target reactions not amenable to protic acid catalysis. Our contributions in this area include the development of the first axially chiral

b-diketiminate (IAN amines), and the study of their coordination chemistry with group IV metals.

Through these studies, the student is trained how to think about problems in organic chemistry from an approach that involves extensive laboratory experimentation. Germane to this training is the routine use of spectroscopic (NMR, IR, mass spectroscopy, X-ray diffraction) and analytical (chiral stationary phase HPLC) techniques.

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Computational and Physical Organic Chemistry

Recent advances in computer technology have allowed many problems of interest to the organic chemist to be studied computationally. Described below is an application of computational chemistry to the study of the reaction mechanism of the recently studied biochemical transformation of squalene oxide to lanosterol.

Mechanism of the Conversion of Squalene to Lanosterol, the Precursor to all Steroids — It was suggested more than 50 years ago that in animals the acyclic triterpene squalene is converted enzymatically to lanosterol, a system containing four rings. What appears to be a very simple reaction on the surface has been described as one of the most complex reactions in biological systems. The formation of the tetracycle is thought to first involve epoxidation of one of the double bonds of squalene followed by protonation that leads to a "cascade" of reactions in which the four rings are formed:

Originally this cascade of reactions was proposed to proceed through discrete carbocationic intermediates with the stepwise formation of the first three rings (each giving rise to a tertiary carbocation). Although in the steroids these rings are all six-membered, in order to produce a carbocation from the formation of the third ring, a five-membered ring must form. It was thought that this five-membered ring then underwent an anti-Markovnikov ring expansion to give the six-membered ring followed by formation of the fourth ring, a cyclopentane ring. We have recently shown that the formation of these last two rings might very well involve a concerted ring expansion of the five-membered ring with the formation of the fourth ring by studying a model system as shown.The middle structure represents the transition structure for this concerted ring expansion and ring formation.

Recently we have turned our attention to whether the formation of the first three rings (6,6,5) in the cyclization of squalene is a concerted reaction or might involve discrete carbocation intermediates. It turns out that this problem initially reduces to one of studying the possible conformations of the individual carbocations that might be intermediates. This was done using model systems. In all cases it was found that the conformation that would lead to ring cyclization does not exist as a minimum on the potential surface, rather collapsing to the cyclic structure. This is strongly suggestive that the formation of at least the first three rings is concerted, and to test this we have undertaken calculations on model systems which involve the potential for a "double" cyclization. These cyclizations are studied by first finding an initial transition structure and then subjecting it to the intrinsic reaction coordinate calculations which follow the pathway downhill to product. Preliminary results obtained for the related cyclization of squalene to the hopanoids indeed confirm our conjecture of a concerted reaction. Along the pathway shown in the figure below, no intermediates were located, though it was found that the first ring is almost completely formed prior to the formation of the second ring.

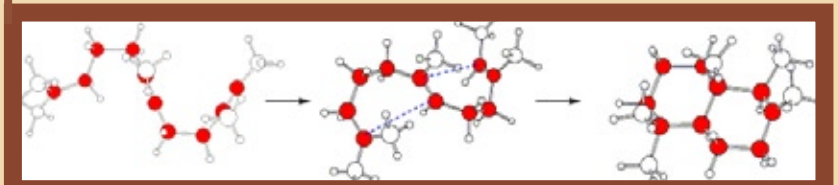

Figure 1. Concerted ring-closure of rings A and B of squalene.

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Nanotechnology and molecular electronics are rapidly growing interdisciplinary fields. However, there is a gap between the designs for nanodevices and available molecular building elements. Our goal is to fill this gap by providing rationally designed molecules, which would serve either as supportive elements, or as active components in molecular assemblies. In our lab, we work on challenging ring systems with unique geometries and structures that can be used to make attractive spacers for the construction of a molecular diode, a molecular shift register, or for the study of electron transfer processes in general.

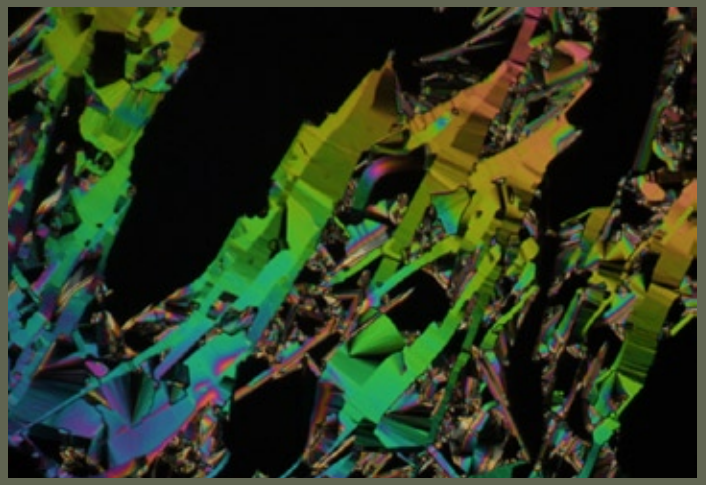
Molecular Materials

Development and application of materials with well defined molecular and bulk properties is becoming increasingly important for contemporary technologies. Our research addresses basic and applied problems and concentrates in three major areas of advanced organic materials. We design, synthesize, and characterize materials for optoelectronic applications, nanoscale construction, molecular electronics, and molecular magnetism. The desired electronic effects in organic molecules are engineered using main group elements such as B, Si, N, P, and S. Each project involves extensive computer-aided design of molecular systems, synthesis and study of the new materials, and comparison of the experimental results with theoretical predictions.

One of our group's major strengths is our considerable expertise in organic synthesis and in the properties of liquid crystals.

We are actively developing liquid crystalline materials with large positive dielectric anisotropies for applications in flat panel displays. The dielectric anisotropy is related to the distribution of dipole moments within the molecule and is essential for the electrooptical effect in liquid crystal displays in calculators, laptop computers, etc. In this context, we are exploring boron closo-clusters, such as p-carborane, as novel structural elements of liquid crystalline molecules.

The centerpiece of our design of potentially magnetic radical liquid crystals is the thioaminyl radical fragment which can be incorporated into aromatic rings (e.g. Figure 1) and thus into the rigid cores of a variety of mesogenic molecules. The design is general and, in principle, allows for engineering of almost all types of liquid crystalline phases and the study of electronic and magnetic phenomena in semiordered media. Using these materials, we hope to test the theory that molecular organic magnetism may be achieved through partially oriented fluids.



Craig W. Lindsley

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Associate Professor of Pharmacology
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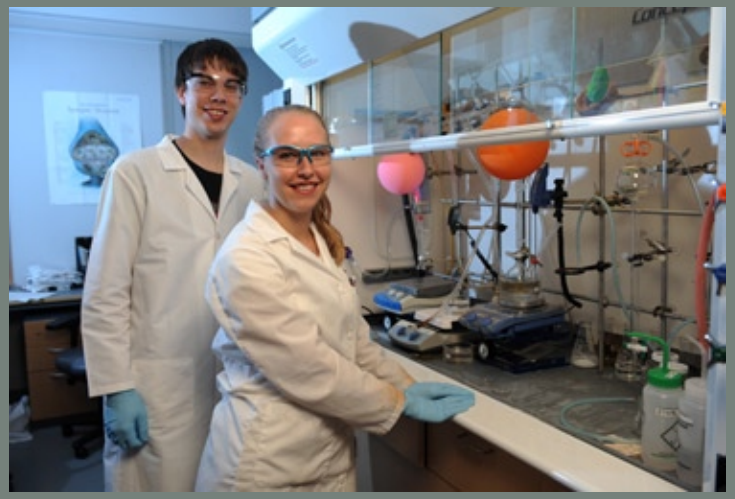
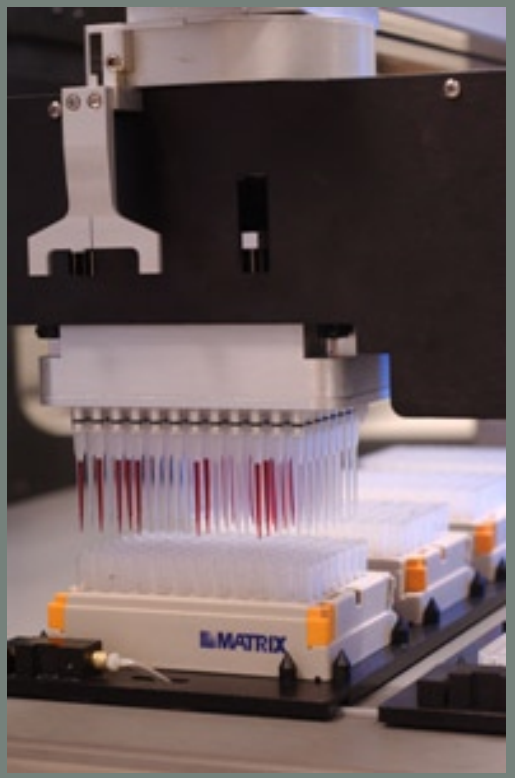


Medicinal Chemistry

The major focus of the Lindsley laboratory is drug discovery and medicinal chemistry. Students in my lab will collaborate with other members of the Pharmacology, Drug Metabolism and Clinical Pharmacology departments to pursue small molecule hits from high throughput screens, perform lead optimization studies to develop structure-activity-relationships (SAR) and ultimately deliver small molecules with acceptable properties to validate novel targets/mechanisms in in vivo animal models of target diseases. The molecular targets of interest are kinases, GPCRs, ion channels, nuclear hormone receptors and protein-protein interactions, with an emphasis on allosteric modulation as opposed to classical agonism/antagonism. Therapeutic areas of interest span cancer, neuroscience (schizophrenia, anxiety, pain, sleep, Parkinson's disease) and endocrinology (diabetes, obesity). Students will be exposed to every phase of classical drug discovery. As a member of ther Vanderbilt Institutue of Chemical Biology, training in my laboratory will be broad and involve organic synthesis, medicinal chemistry, pharmacology and drug metabolism. For many programs in the neuroscience area, students will have the opportunity to also develop radioligands for binding assay development and PET tracers for imaging studies.

Another focus in the group is parallel synthesis and the development of new technologies for library synthesis. The lab has state-of-the-art microwave synthesis technology, a mass-directed HPLC purification platform and a large collection of monomers and polymer-supported reagents. There are a number of projects directed at synthesizing libraries of small molecule protein-protein inhibitors, target family-directed libraries and other drug-like small molecule libraries for use in high throughput screening efforts.

The third area of interest in my group is synthetic organic chemistry. Students will have the opportunity to work on synthetic methodology projects as well as partial and total synthesis projects.



Charles M. Lukehart

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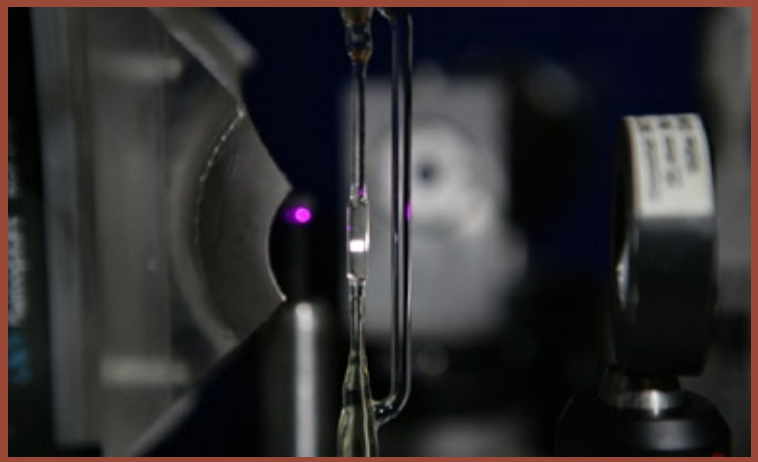

The Lukehart group discovers and develops new synthesis strategies for the preparation of inorganic materials that exhibit desired chemical reactivity or interesting physical properties. There is a special focus on the preparation of nanocomposite materials in which nanoparticles of a guest substance are highly dispersed either on a solid support or throughout a solid matrix. For many applications, single-source molecular precursors are used to control the elemental composition of the nanoparticle substance. Instrumental methods used by the Lukehart group for the characterization of the resulting nanocomposite materials include transmission electron microscopy (TEM), scanning electron microscopy (SEM), powder x-ray diffraction (XRD), scanning probe microscopy, thermogravimetric and surface-area analysis.

Specific research projects under active investigation include the following:

- Use of single-source or dual-source molecular precursors for the synthesis of metal or metal alloy/carbon nanocomposites for testing as supported catalysts in PEM fuel cells.
- Use of single-source or dual-source molecular precursors for the synthesis of superparamagnetic or ferromagnetic nanoparticles.
- Synthesis of graphitic carbon nanofibers (GCNFs) materials including GCNF pellets, GCNF/Si wafer mats, superhydrophobic GCNF/carbon felt mats, and metal/GCNF intercalates.
- Synthesis and characterization of graphitic carbon nanofiber and nanodiamond hybrid nanocomposite materials in which surface-modified GCNFs and nanodiamond particles, including polymer brushes, are covalently incorporated into organic polymer or ceramic matrices or function as sensors.

Terry P. Lybrand

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Computational and Biophysical Chemistry

In our laboratory, we utilize computational methods to study the properties and behavior of biomacromolecules and ligand-biomacromolecule complexes, and to aid in the design of small molecule ligands with desired binding properties for targeted receptors. Techniques used include quantum mechanical calculations, molecular dynamics and Monte Carlo simulation, and free energy perturbation methods. Computational methods complement experimental techniques and can enhance our understanding of biomacromolecular function.

Our current research interests are focused in several key areas. One area of research involves the use of computational methods to provide detailed molecular models for ligand-macromolecule recognition and binding processes. These studies can also suggest structural modifications for ligands (or biomacromolecules) that may enhance desired biological effects. For example, one active research project uses molecular modeling tools to help explain the molecular basis for the exquisitely tight binding of biotin to streptavidin. Collaborators are using site-directed mutagenesis, calorimetry, and x-ray crystallography to provide supporting data in these studies. Another project focuses on detailed study of cyclooxygenase structure-function relationships, reaction mechanism details, and inhibitor complexes.

A second area of research employs molecular modeling techniques, together with data from biochemical and biophysical studies, to generate three-dimensional models for proteins and protein-ligand complexes not currently tractable to direct experimental structural characterization. Most effort at present focuses on generation of 3D models for integral membrane receptor proteins that function in signal transduction pathways. One project involves an examination of structure-function relationships in bacterial chemotaxis receptors.

A final area of major research activity involves the development of new mathematical models and computer software to aid in modeling studies such as those outlined above. Much effort in recent years involves the development of methods to calculate free energy differences and solvation effects accurately in molecular dynamics simulations, as well as the development of algorithms for analysis and graphical display of simulation results.

Lawrence J. Marnett

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Organic, Bioorganic and Biochemistry
Our research group has interests in the areas of protein structure and function, nucleic acid chemistry, drug design and synthesis, and chemical genomics. Much of our work focuses on the biochemistry and molecular biology of oxidation of natural and synthetic chemicals. Areas of interest to us include: mechanisms of oxidation of arachidonic acid and endocannabinoids by cyclooxygenase and lipoxygenase enzymes, design, synthesis, and biochemical evaluation of lipoxygenase and selective cyclooxygenase-2 (COX-2) inhibitors; chemistry and biology of DNA damage by lipid oxidation products; and endogenous pathways of DNA damage in the genesis of human cancer.

The following studies are underway in our labs:

Structure and Function of Fatty Acid Oxygenases
Our laboratory has a long-standing interest in enzymes of arachidonic acid oxygenation. This includes lipoxygenases, which incorporate one molecule of O_2 into the carbon framework and cyclooxygenases, which incorporate two molecules of O_2. The products of both pathways of oxygenation are substrates for metabolizing enzymes that generate a panoply of lipid mediators. Leukotrienes and prostaglandins are involved in multiple physiological and pathophysiological events, and inhibition of their action is the molecular basis for the pharmacological activities of several important drugs. Foremost among these are non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors. We have conducted extensive functional studies with lipoxygenases and cyclooxygenases based on available crystal structures and employing exhaustive site-directed mutagenesis.

Design, Synthesis, and Evaluation of Novel COX-2 Inhibitors
Cyclooxygenase-2 (COX-2) is the molecular target of non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors. Our laboratory has combined structural analysis with functional studies to define the molecular determinants of the interaction of ligands (substrates and inhibitors) with COX-2. For example, we recently reported the identification of a critical H-bonding interaction that leads to the selectivity of aspirin for acetylation of Ser-530 in COX-2. Many NSAIDs are aralkyl carboxylic acids. Comparative analysis of the effect of site-directed mutation of active site residues on the binding of substrates and inhibitors to COX-1 and COX-2 led us to hypothesize that neutral derivatives of esters and amides would bind selectively to COX-2. We tested this hypothesis by synthesizing a series of neutral derivatives of NSAIDs and demonstrating increases in selectivity for COX-2 of several orders of magnitude. We are exploiting this discovery to prepare novel COX-2 inhibitors as anti-inflammatory drugs and cancer preventive agents.

Chemistry and Biology of Endogenous DNA Damage by Lipid Peroxidation Products
Our laboratory has focused on DNA damage by aldehydes produced endogenously in mammalian cells as a result of lipid peroxidation. Malondialdehyde is the major mutagenic product of lipid peroxidation and is produced ubiquitously in animal and human tissues. It reacts with DNA to form a series of adducts that we and others have identified. The major adduct is a pyrimidopurinone that we have abbreviated M_1G. This adduct possesses a blocked Watson-Crick base-pairing region so it is expected to be mutagenic. We have evaluated its mutagenicity by synthesizing viral genomes containing M_1G at defined positions. Following transfection into bacterial or mammalian hosts, the replicated genome is interrogated to determine the outcome of replication at the site of the adduct. These experiments indicate that M_1G is indeed mutagenic. We have used a variation of this approach to establish that M_1G is repaired by nucleotide excision repair. To support and extend these in vivo studies, we conduct experiments utilizing adduct-containing duplex DNA molecules or template-primers as substrates for purified DNA polymerases or repair enzymes. These investigations provide more detailed information about the structural and functional basis for induction of mutation. Our laboratory has had a long-standing collaboration with the Stone laboratory in the Chemistry Department at Vanderbilt, which has provided precise information about the structural perturbations introduced into DNA by adducts such as M_1G.

Signal Transduction by Lipid Mediators and Lipid Peroxidation Products
A relatively new area of research in the laboratory is the definition of signal transduction pathways stimulated or interrupted by lipid mediators or lipid peroxidation products. The work on lipid mediators is focused on endocannabinoid oxygenation products of COX-2 and 15-lipoxygenase whereas the work on lipid peroxidation products is focused on malondialdehyde, 4-hydroxynonenal, and structurally related molecules. We are particularly interested in events important in controlling the growth and metastasis of cancer cells such as proliferation, migration, apoptosis and angiogenesis.

Each of the projects utilizes a range of the outstanding core facilities available at Vanderbilt (microarray, proteomics, molecular recognition, and high throughput screening) and involves stimulating collaborations with colleagues at Vanderbilt and elsewhere.

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Theoretical and Computational Chemistry at the Molecular and Nano Scales

The focus of our research is the use of molecular modeling tools to understand and predict the thermodynamic and transport properties of complex fluids, nanomaterials, and biological systems. These tools include molecular dynamics and Monte Carlo simulations and molecular theory.

Current projects include:

Molecular Modeling of Nanoscale Systems
Molecular modeling is a particularly useful tool for studying nanoscale systems where experimental investigation is often difficult due to the time and length scales involved. In particular, we are interested in the study of nanoparticles, such as carbon nanotubes and polyhedral oligomeric silsesquioxanes (or more simply POSS molecules), and using molecular modeling to understand how the chemical structure and composition of nanoparticles and composite materials determines their properties.

Development and Application of Molecular Theories

The ability to accurately predict the thermodynamic properties of fluids is central to chemical product and process design. Our work focuses on the development and application of molecular based approaches to determine the thermodynamic properties and phase behavior of a wide range of fluids such as hydrocarbons, polymers, ionic liquids and electrolytes.

Improving the Efficiency of BioFuel Conversion

Biofuels are a very promising component of the solution to the problem of meeting the energy needs of the 21st century. However, the potential of biofuels is currently limited by low efficiencies and high cost. Our work in this area focuses on developing models and tools that can be used to understand the biological depolymerization of cellulose by cellulases, with the ultimate aim of providing molecular level insight to enable the design of more efficient and active cellulases.

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Bioanalytical and Biophysical Chemistry

Our research focuses on the design, construction, and application of advanced technologies for structural mass spectrometry, in particular, for studies in structural proteomics, systems biology, and biophysics. To identify and structurally characterize biomolecules from complex samples, we perform rapid (µs-ms) two-dimensional gas-phase separations using ion mobility-mass spectrometry (IM-MS) techniques. IM-MS provides separations on the basis of apparent surface area (ion-neutral collision cross section) and mass-to-charge (m/z), respectively. Biomolecular structural information is interpreted by comparing experimentally obtained collision cross-sections in the context of those obtained via molecular dynamics simulations.

In the analysis of complex biological materials, IM-MS provides a significant advantage over contemporary MS in that the regions in which signals appear in 2D conformation-space correspond with specific molecular class, i.e. the correlation of collision cross section with m/z varies as nucleotides/carbohydrates < peptides/ proteins < lipids/surfactants. Deviations from where a particular signal is predicted to occur can provide additional information including: (i) identification of sights of post-translational modification, (ii) characterization of secondary, tertiary, and quaternary structural motifs, and (iii) rapid screening for analyte-ligand binding interactions. The separation of analytes on the basis of molecular class provides significant advantages as a proteomics tool, because signals arising from concomitant, non-peptidic, materials are readily separated from the peptides of interest. Thus, signals arising from contaminants are resolved from peptides on the basis of structure and can thus be eliminated when searching peptide m/z signals against proteomic and genomic databases for high-confidence level protein identification.

Importantly, IM-MS can provide detailed structural information for conformational sub-populations of the same analyte (Figure 3), i.e. the relative abundances of different biomolecular conformations can be readily determined. By measuring the change in relative abundance of specific structural conformations as a function of IM separation temperature, thermodynamic and kinetic parameters can also be determined for structural sub-populations, or for structural transitions, respectively (i.e. via van't Hoff or Arrhenius plots). Note that this procedure can also be used to quantify the thermodynamic consequences of stepwise addition of solvent, or small molecules, on the prevailing molecular structure.

Key areas of investigation and development include:

- Investigation of the prevailing influences of post-translational modifications (e.g. glycosylation, phosphorylation, ubiquination, sumoylation, etc.) on protein secondary and tertiary structure?
- Development of imaging IM-MS instrumentation for multidimensional imaging/characterization of biomarker species from thin tissue sections and microarrays.
- Combining microfluidic separation strategies with IM-MS for fundamental biomolecular characterization in systems biology.
- Development of selective IM-MS shift reagents for high confidence level identification in proteomics, glycomics, lipidomics, and metabolomics.
- Development of molecular dynamics strategies for structural interpretation of complementary IM-MS collision cross sections.
- Construction of advanced laser optical strategies for high-throughput screening of drug-ligand interactions.

Jens Meiler

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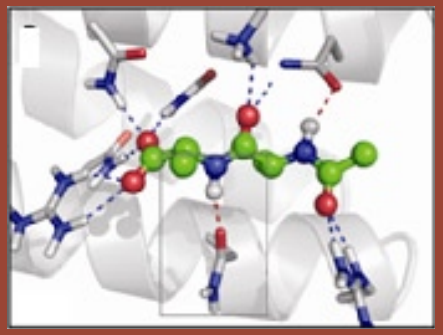

Computationally designed interface between target peptide and protein antibiotic

Structural and Chemical Biology

Research in our laboratory seeks to fuse computational and experimental efforts to investigate proteins, the fundamental molecules of biology, and their interactions with small molecule substrates, therapeutics, or probes. We develop computational methods with three major ambitions in mind: 1) to enable protein structure elucidation of membrane proteins – the primary target of most therapeutics – and large macromolecular complexes such as viruses; 2) design proteins with novel structure and/or function to explore novel approaches to protein therapeutics and deepen our understanding of protein folding pathways, and 3) understand the relation between chemical structure and biological activity quantitatively in order to design more efficient and more specific drugs. Crucial for our success is the experimental validation of our computational approaches which we pursue in our laboratory or in collaboration with other scientists.

Current research projects include:

Protein Structure Elucidation of EMRE. EmrE is a 12 kDa small multidrug resistant transporter (SMR) protein. It contributes to multidrug resistance in cancer and bacterial cells by removing compounds toxic to the cell such as the therapeutics. EmrE has been shown to contain four transmembrane α-helices and form a homodimer. While X-Ray crystallography and NMR spectroscopy frequently yield datasets for membrane proteins that are of lesser quality and/or sparse compared to soluble proteins, extensive Electron Paramagnetic Resonance (EPR) and cryo-Electron Microscopy (cryo-EM) datasets are available for EmrE. We develop computer algorithms tailored for determining the structure from these low resolution/sparse experimental data with the ultimate goal of solving the structure of EmrE and other membrane proteins. By determining the structure of EmrE, novel chemotherapeutic agents could be developed, including those to combat multidrug resistance.

Design of Protein Antibiotics. Gram positive bacterial infections are a significant global cause of human mortality. More than 125,000 people contract multidrug-resistant gram positive infections annually in the U.S. alone, resulting in more than 40,000 deaths per year. Vancomycin is the last-line antibiotic for gram-positive infections. It kills bacteria by binding the -D-ala-D-ala C-terminus of a key bacterial cell wall glycopeptide component, thereby inhibiting proper cell wall biosynthesis. The most common mechanism of acquired resistance is through the substitution of a -D-lac in place of the -D-ala at the C-terminus of the bacterial glycopeptide. The goal of this project is to explore a rational design approach to develop novel antimicrobial protein therapeutics capable of binding both the multidrug-resistant -D-ala-D-ala and vancomycin-resistant -D-ala-D-lac target peptides.

Novel Schizophrenia Therapeutics by Virtual High-Throughput Screening. Selective potentiators of the metabotropic glutamate receptor subtype mGluR5 have exciting potential for development of novel treatment strategies for schizophrenia. A high-throughput screen (HTS) for mGluR5 potentiators at Vanderbilt's molecular libraries screening center network facility revealed a large and diverse set of about 1,400 substances. We utilize the power of recent machine learning techniques such as Artificial Neural Networks (ANNs) and Support Vector Machines (SVMs) to model the complex relationship between chemical structure and biological activity of mGluR5 potentiators. These models will be used to virtually screen millions of compounds for activity and guide chemical synthesis of novel compounds.

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My current research focuses in two directions. In one direction, three dimensional molecular structures of chiral molecules, in the solution or vapor phase, are determined using chiroptical spectroscopic methods. This direction also involves developing new instrumental techniques and the use of quantum theoretical techniques. In the second direction, the secondary structures of biological molecules are determined. The specific areas of interest include: (1). vibrational circular dichroism (VCD), which measures the differential absorption of left versus right circularly polarized infrared radiation; (2). vibrational Raman optical activity (VROA), which measures the corresponding difference in vibrational Raman scattering; (3). optical rotatory dispersion (ORD), which measures the rotation of plane polarized light as a function of wavelength; (4). electronic circular dichroism (ECD), which measures the differential absorption of left versus right circularly polarized visible radiation. The first quantum mechanical predictions of VROA [J. Phys. Chem., 94, 8106-8112 (1990)] and of optical rotation [Mol. Phys. 91, 551-554 (1997)] carried out in this laboratory led to remarkable progress in these areas.

The research in my lab uses the experimental measurements in the above mentioned areas, and combines them with either corresponding quantum mechanical predictions or spectra-structure correlations (in the case of biological molecules) to establish the structures of chiral organic molecules and biological molecules in the solution phase.

Our research group has interests in the areas of mechanistic, synthetic and bio-organic chemistry. Most of our research has centered on free radical chemistry. Areas of interest to us include: the mechanisms of the free radical reactions of natural products, such as lipids and phospholipids with molecular oxygen (a process important in the degradation of fats and oils and implicated in vivo); mechanisms and utility of free radical reactions; and the control of chemical and biological processes by means of light.

These studies are underway in our labs:

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• We are exploring the free radical chemistry of organic compounds and molecular oxygen. This process is important in commerce because most commercial products are exposed to molecular oxygen and free radical initiating events. Of interest to these studies are the biologically important compounds that react readily with molecular oxygen, particularly unsaturated and polyunsaturated lipids. We are studying the mechanisms of the free radical oxidation reactions of lipids, known as lipid peroxidation, and we are developing methods for measuring the rates of free radical chain oxidation reactions by means of “free radical clocks”.

• We have established collaborative research projects with groups in the Biochemistry, Pharmacology and Clinical Pharmacology Departments at Vanderbilt. These collaborations are central to an NIEHS Program Project Grant on “Lipid Oxidation and Antioxidant Mechanisms”. One of the themes of this research is the chemistry of electrophiles that are generated in the decomposition of peroxide natural products formed in lipid peroxidation. These electrophiles react with nucleic acids and proteins and adducts formed have properties that are altered from the naturally occurring nucleic acids and proteins. We are developing procedures to prepare naturally occurring electrophiles derived from free radical oxidation of phospholipids and cholesterol esters and we are studying the reactions of these electrophiles with peptides and proteins. Critical to this research is the development of new strategies for identification of lipid-protein adducts by proteomics mass spectrometry methods.

• Another theme of our collaborative research is to define the products of polyunsaturated lipid oxidation and determine the mechanisms by which these compounds contribute to human disease. The over-arching hypotheses that govern the research are that the balance of competing oxidation pathways for different lipid substrates governs adaptation to oxidative stress and oxidative injury by controlling the distribution of bioactive lipid oxidation products. Analytical methods that make extensive use of HPLC MS/MS are being developed to help in the identification of lipid peroxidation products.

• We are studying the reactions of free radicals in lipoproteins and we are examining the effects of antioxidants on these processes. Polyunsaturated fatty acids and esters are important lipid constituents in biological membranes and in circulating lipid storage proteins, i.e. endogenous levels of lipoproteins such as LDL and HDL correlate with the development and progression of cardiovascular disease and peroxidation of lipids in these lipoproteins has been related to the advancement of disease processes.

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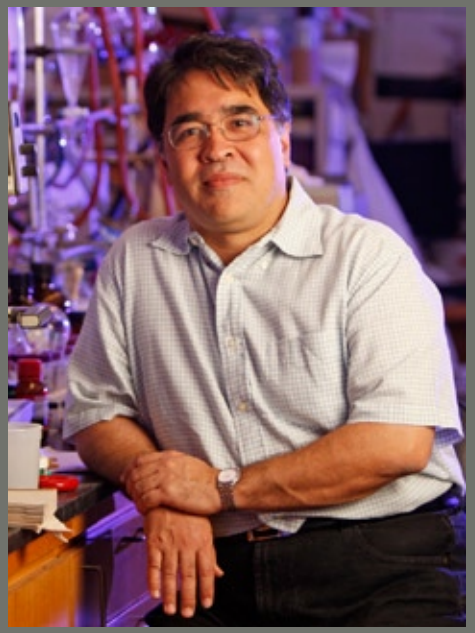
For more information and a list of recent publications, please go to www.Vanderbilt.edu/AnS/chemistry/faculty/bio.php?ID=36



Chemistry and Biology of DNA Damage.

Covalent modification of DNA by electrophiles is generally accepted as the initial event in chemical carcinogenesis. If these modifications are not repaired, they can compromise the fidelity of DNA replication leading to mutations and possibly cancer. To properly study the biological processing of pre-mutagenic DNA lesions, oligonucleotides containing structurally defined carcinogen adducts are required. Our laboratory develops synthetic strategies for the site-specific incorporation of nucleotides that are chemically modified by carcinogens into DNA. Once synthesized, the structure, replication and repair of the carcinogen-modified oligonucleotides are examined. Many of these studies are preformed in collaboration with other laboratories on Vanderbilt's campus and elsewhere.

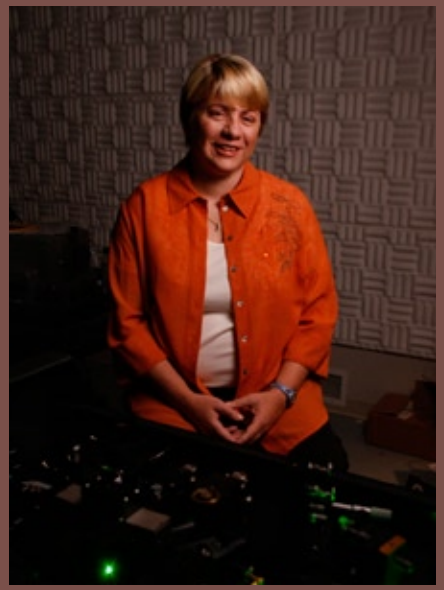
One specific project includes the preparation of the C8-deoxyguanosine adduct of 2-amino-3-methylimidazo[4,5-f]quinoline (IQ). IQ is a member of a family of highly mutagenic heterocyclic amines found in cooked meats. We found that the C8-IQ adduct adopts different conformations depending on the sequence of the adducted oligonucleotide and we have hypothesized that this sequence-dependent conformation plays an important role in the biological processing of the lesion. This hypothesis will be tested using in vitro and in vivo systems. The adduction of IQ with DNA also gives a minor N2-adduct of deoxyguanosine, which has not been extensively studied. We have recently completed a synthesis of the N2-adduct and have incorporated it into oligonucleotides.

A second major project in our lab involves DNA adducts derived from endogneous sources such as lipid peroxidation. Examples of such reactive electrophiles include alpha,beta-unsaturated aldehydes (acrolein, crotonaldehyde, and 4-hydroxynonenal), 2,3-epoxyaldehydes and dicarbonyl species (malondialdehyde and 4-oxo-2-nonenal).

Although these compounds are chemically simple, they react with DNA in a complex and diverse manner. We recently demonstrated that alpha,beta-unsaturated aldehydes can form inter- and intra-strand DNA crosslinks, which are a very severe but largely unstudied form of DNA damage. The crosslinking chemistry is highly dependent on the stereochemistry of the DNA adduct. In collaboration with other laboratories, we are studying the mechanism of the DNA crosslinking reaction and the biological processing of the DNA crosslinks.

Modern mass spectrometry and NMR are integral parts to all of our studies on DNA damage. We have convenient and open access to superb analytical facilities on Vanderbilt campus. Our laboratory is affiliated with the Vanderbilt Center in Molecular Toxicology, Vanderbilt Institute of Chemical Biology, and the Vanderbilt-Ingram Cancer Center.

SANDRA J. ROSENTHAL



Professor of Chemistry
Ph.D., The University of Chicago, 1993
For more information and a list of recent publications, please go to www.Vanderbilt.edu/AnS/chemistry/groups/rosenthal/

Nanocrystals

In the Rosenthal group we study semiconducting nanocrystals, a novel material whose optical properties and electronic structure can be precisely tuned by controlling the size of the nanocrystal. We are specifically interested in two applications exploiting the properties of nanocrystals: the use of nanocrystals as the light harvesting element in photovolatic devices and the use of fluorescent nanocrystals as biological probes for membrane proteins involved in neuronal signaling. We have also recently begun a program to explore the possible use of nanocrystals as a white light emitter for implementation in solid state lighting.

Solar Cells

Nanocrystals are an ideal light harvester in photovoltaic devices. The band gap can be exquisitely tuned by controlling the size of the nanocrystal,thus the proper choice of size and type of nanocrystal allows one to create a photovoltaic whose absorption spectrum matches the spectral distribution of sunlight. The nanocrystals absorb sunlight more strongly than dye molecules or the bulk semiconductor material, therefore high optical densities can be achieved while maintaining the requirement of thin films. Perfectly crystalline CdSe nanocrystals are also an artificial reaction center, separating the electron hole pair on a femtosecond timescale. The size-tunable band gap, large absorption coefficients, intrinsic electron hole pair separation, long exciton lifetime, and chemical robustness make nanocrystals the ideal material for solar cells. The photovoltaic devices we make in our laboratory could eventually be fabricated inexpensively at low temperatures and can cover large areas.

Biological Labs

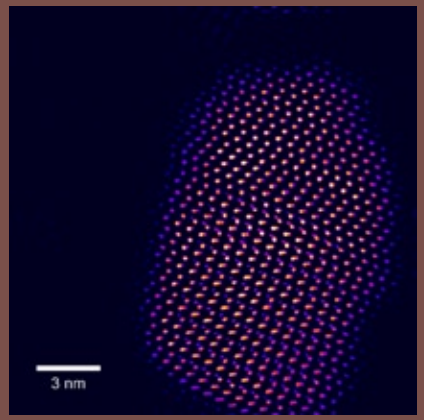
Fluorescent nanocrystals have several advantages over organic dye molecules as fluorescent markers in biology. They are incredibly bright and do not photodegrade. They have narrow, guaussian emission spectra enabling the co-localization of several proteins simultaneously. Drug-conjugated nanocrystals attach to the protein in an extracellular fashion, enabling movies of protein trafficking. With the drug-conjugated nanocrystals we will be able to map the distribution of these proteins and be able to determine mechanisms which regulate protein expression at the cell surface.

Solid-State Lighting

In response to ever increasing energy demands and subsequent costs, a tremendous emphasis is being placed on energy saving, solid state lighting devices in the form of light emitting diodes, or LED's. Specifically, a need exists for pure white-light LED's as a more efficient replacement for conventional lighting sources. Switching to solid state lighting would reduce global electricity use by 50% and reduce power consumption by 760 GW in the United States alone over a 20 year period. Semiconductor nanocrystals exhibit high fluorescence quantum efficiencies and large molar absorptivities. We have demonstrated white-light emission from ultra-small cadmium selenide (CdSe) nanocrystals. This raises the intriguing possibility of using these nanocrystals as a white-light phosphor.

Fundamental Studies

We also perform fundamental studies on semiconducting nanocrystals. We have pioneered the use of Rutherford backscattering spectroscopy and atomic number scanning transmission electron microscopy to determine atomic level constitution and structure of nanocrystals with unprecedented detail. We use ultrafast spectroscopy to map out the ultrafast carrier dynamics of electrons and holes inside the nanocrystals and to follow the charge transfer reactions of the nanocrystals inside the photovoltaics.



Michael P. Stone

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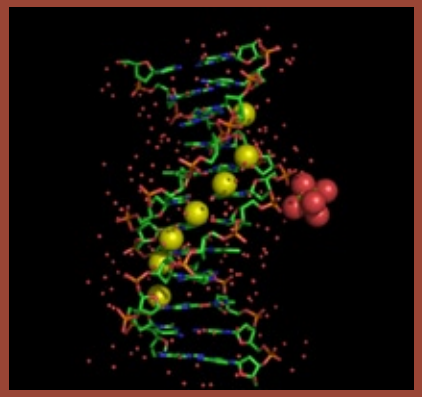

Biophysical Chemistry

DNA damage is believed to represent the initiating step in chemical carcinogenesis. Our laboratory seeks to understand how specific DNA adducts perturb DNA structure and how these structural interfere with the biological processing of DNA. One goal is to understand the basis whereby chemical modification of DNA triggers specific mutations. Some mutations, especially those occurring in proto-oncogene sequences or tumor suppressor gene sequences, play crucial roles in the process of chemical carcinogenesis. Some fundamental questions under study are:

• How do specific DNA adducts alter the three dimensional structure of DNA?

• How does adduction affect the biological processing of DNA during replication and repair?

• How do specific DNA adducts alter the three dimensional structure of primer-template complexes with damage bypass polymerases?

• What is the role of DNA sequence in modulating adduct conformation and biological processing?

Both NMR spectroscopy and X-ray crystallography play major roles in our research program. Our laboratory is affiliated with the Vanderbilt Center in Structural Biology. NMR spectroscopy is used to determine the three dimensional structures and dynamics of site-specifically adducted oligodeoxynucleotides in aqueous solution. Crystallographic approaches allow the structural determination of larger biomolecular complexes involving DNA processing enzymes.

Gary A. Sulikowski

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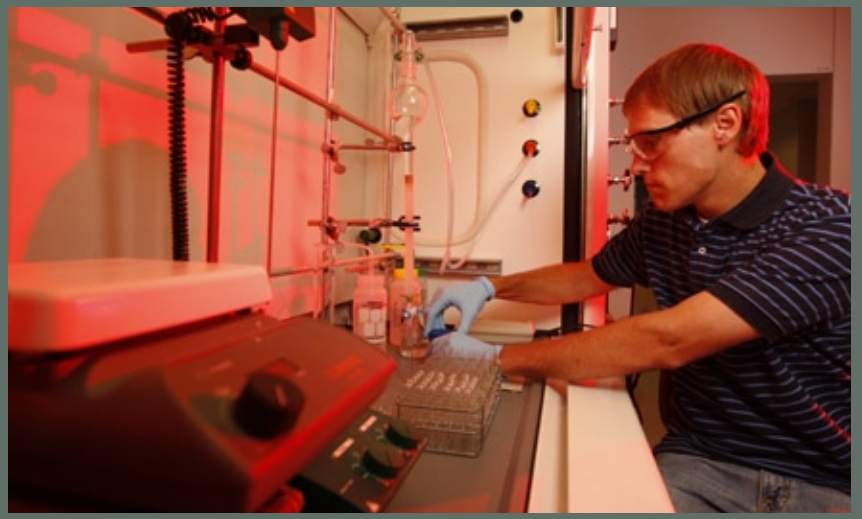

Total Synthesis of Natural Products

A major focus of our research group is the synthesis of structurally complex natural products. Frequently, research projects are initiated with the selection of a target structure (recently) isolated from various natural sources such as soil microorganisms, fungi, or plants. Criteria for the selection of molecular targets include structural novelty, unique biological activity and/or potential development of a new reaction in assembling a key structural feature contained within the natural product. Target structures of current interest to our group are shown below and represent a broad range of structural complexity and biological activity. Following the identification of a target molecule, researchers, sometimes working as a team, set into action a synthetic strategy aimed at developing an efficient assembly of the targeted structure. It is at this point in the research project that researchers develop critical analysis as well as problem solving skills. Due to the complexity of the synthetic problems, we often encounter unforeseen obstacles which require the redesign of the original strategy or the development of a new reaction or modification of an existing process. It is this evolutionary aspect of the synthetic program that leads to new innovations with broader implications in organic synthesis and related areas. Indeed some of the reactions and strategies developed within the context of one natural product have been subsequently applied to other (new) target structures.

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Chemical Physics, Physical Chemistry, and Chemometrics

My research interests span a range of topics, many of which involve the diatomic molecule as a common theme: emission spectra from electrical discharges through gases, computational methods, least-squares analysis of data, simulation of spectra, and derivation of potential energy curves.

My current work on emission spectroscopy emphasizes the capabilities of the CCD array detector in application to high-resolution spectroscopy. By employing state-of-the-art data analysis methods to interpret the abundant and very high quality data obtainable from this detector, I am learning how to squeeze out every last “bit” of information. These studies have applications in spectroscopy and in analytical and environmental chemistry.

A strong component of all my work is the development of computational methods for interpreting and analyzing data. One new focus in this area is the design of more efficient experiments using the method of isothermal titration calorimetry (ITC)—a technique widely used to study the thermodynamics of binding and complexation.

David Wright

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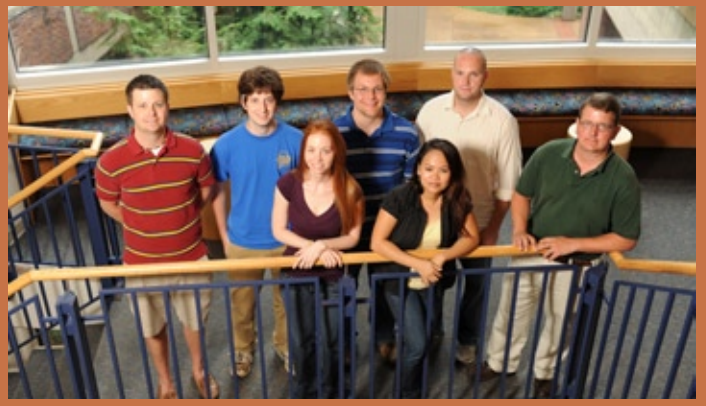
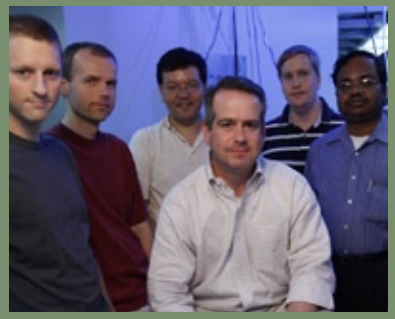


Bioinorganic and Biomaterials Chemistry

Biomineralization results in an expansive array of complex materials ranging from laminate composites and ceramics such as bones, teeth, and shells to magnetic materials such as the forms of magnetite found in magnetobacteria. It also produces non-linear optical materials, such as the unique peptide-coated cadmium sulfide particles which result from heavy metal detoxification mechanisms within some yeast and plants. These natural biominerals often represent unique crystal forms extending over several size domains that are synthesized in aqueous solutions at room temperature and standard pressure. Additionally, many of these crystal forms, and their associated properties, cannot be readily produced in the laboratory! Biomineralization processes also play important roles in the pathologies of a number of diseases including osteoporosis and malaria. Understanding these processes is leading to novel discoveries ranging from new materials to new therapeutic advances for the treatment of disease.

The primary focus of research in our group is the design, synthesis, and characterization of organic templates capable of mediating the growth of biologically important biominerals. Specific studies under way in our labs include:

- Mechanistic and structural studies of the scaffold biopolymers that nucleate the critical detoxification mineral hemozoin within the digestive vacuole of the malaria parasite, Plasmodium falciparum.
- Role of hemozoin in the modulation of host innate immune system response. Reactivity studies between hemozoin and fatty acid substrates indicate a wide distribution of highly immunomodulatory products including hydroxylated fatty acids, isoprostanes, and prostaglandins.
- The use of combinatorial chemistry to understand the role of matrix peptides in the formations of monodisperse biogenic nanocrystals. These studies will yield functionalized building blocks for the construction of novel nanodevices.
- Diatoms form diverse nanopatterned silica structures. In contrast to many current materials approaches to the synthesis of patterned silica, biogenic silica is formed rapidly under mild conditions mediated by a highly post-translationally modified peptide. We are taking a wide variety of approaches in not only understanding the function of such peptides, but also in applying our methods to the design of new functionalized SiO2 materials.



Thank you for taking a few minutes to investigate some of the opportunities of the Graduate Program in Chemistry. We feel we have a lot to offer you – faculty who are renown in their field, state-of-the-art instrumentation and lab facilities, and a wonderful environment in which to live in Nashville.

Hopefully, you found research that you would like to be doing in graduate school. Our faculty is always interested in your ideas, and will find funding for new projects.

There is no cost to apply to the Graduate Program in Chemistry (www.Vanderbilt.edu/AnS/Chemistry/apply/). I hope you will do so in the very near future; the deadline for application is January 15.

We process our applications as soon as they are completed, often resulting in an early decision. Based on the Department of Chemistry recommendation, the Dean of the Graduate School offers admission to well qualified students.

If you have any questions, or if I may be of assistance as you work your way through the application, please do not hesitate to contact me.

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