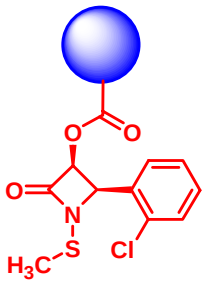
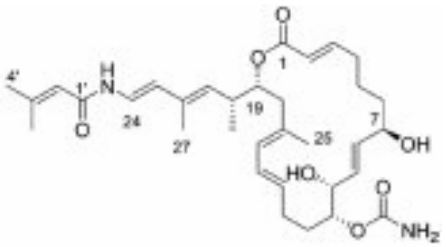
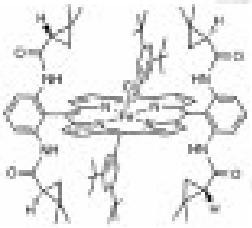
CMD^5: Center for Molecular Diversity in Drug Design, Discovery, and Delivery

Mission: ***To advance science and education in the discovery, design, synthesis and development of structurally diverse biologically-relevant molecules and drug delivery modes for the prevention and cure of human diseases***







CMD^5 Areas of Investigation

Drug synthesis and delivery
Alzheimers/Parkinsons drugs
Synthetic methodologies
Bioanalytical methods
Nanoparticle antibiotics
Protein synthesis
Bioassay development
Antibiotics and anticancer agents
Natural products
Nutraceutical R&D
Biopolymer design and synthesis
Computational drug design
Bio-NMR and mass spectrometry
High-throughput biotesting

Recent CMD^5 Highlights

- **A central component of USF's Florida Center of Excellence proposal for Biomolecular Identification and Therapeutic Therapy (BITT), which has been ranked 1st out of 32 applications submitted**
- **Eight faculty researchers have been hired since 2001 (including one joint with Moffitt) in cognate drug discovery areas such as organic synthesis, medicinal chemistry, molecular modeling, biophysical chemistry and biochemistry**
- **New research labs in Natural and Environmental Sciences (NES) and Chemistry (CHE) buildings are equipped with state-of-the-art mass spectroscopy, nuclear magnetic resonance, and protein synthesis core facilities, which are managed by Ph.D.-level directors**
- **Increase in the number of Ph.D. students studying drug discovery to about 50**
- **Development of a 5-year BS/MS degree in drug discovery**
- **Numerous research publications and patent applications in the past 3 years**
- **$5 million in external funding from National Science Foundation and National Institute for Health in past 3 years**
- **A wide variety of ongoing collaborations with a number of major pharmaceutical companies and outside academic labs**
- **Creation of a spin-out company (Nanopharma Technologies) in the USF small business incubator**



CMD^5 Researchers and Their Interestes

Organic Synthesis

Ed Turos, Ph.D. (Professor of Chemistry, Director of CMD^5)
Our lab focuses on the synthesis and evaluation of new antibacterial and anticancer agents, as well as development of nanoparticle polymers as drug delivery vehicles and biomedical plastics. His research group does both synthetic methods development and microbiological studies on new antibiotics and nanoparticles for drug delivery, collaborating with a number of groups at USF. He is also a co-founder and chief scientific advisor of Nanopharma Technologies, Inc., a research and development spin-out company located in the USF research park.

Mark L. McLaughlin, Ph.D. (Professor of Chemistry and Interdisciplinary Oncology)
Our lab is investigating: short highly helical amphipathic peptides with direct and indirect antimicrobial activity and anticancer activity and constrained dipeptides that enforce an extended conformation for use in the synthesis of stable beta-sheet-like peptide structures with applications to age-related disease such as Alzheimer's and Parkinson's disease. We are developing a new class of HIV protease inhibitors based on easily synthesized constrained dipeptide-like units using a structure-based approach.

Kirpal Bisht, Ph.D. (Associate Professor of Chemistry)
Our group focuses on efficient and environmentally friendly synthetic routes towards synthesis of polymers for biodegradable applications, as well as stereocontrolled synthesis/modification of molecules that serve as precursors to biologically active molecule, i.e., unnatural amino acids, sugars, etc. Another active area of investigation in the Bisht lab is the regio- and stereoselective synthesis of multi-arm dendrimers by chemo/enzymatic routes.

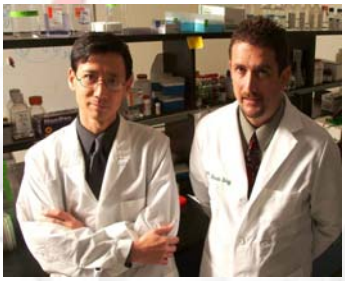
Peter Zhang, Ph.D. (Associate Professor of Chemistry)
Inspired by the extraordinary versatility and capability of heme and related enzymes, we are interested in designing and constructing metalloporphyrin-based artificial enzymes to catalyze selective chemical transformations. Current focuses included the development of efficient catalytic systems for asymmetric atom/group transfer reactions, including epoxidation, aziridination and cyclopropanation of alkenes as well as hydroxylation, animation and carbine insertion of C-H bonds. These catalytic synthetic methods allow us to selectively convert inexpensive and abundant hydrocarbons into value-added functional molecules such as chiral compounds that have potential applications in medicine and materials.

Roman Manetsch, Ph.D. (Assistant Professor of Chemistry)
The research of our laboratory focuses on the development of fragment-based lead discovery and optimization methods using synthesis of small molecules and liquid chromatography with mass spectrometry (LC-MS). We are especially exploring methods using the protein of interests to assemble high-affinity ligands from a pool of complimentary reacting fragments. Currently, we are applying our lead discovery methods for the discovery of therapeutic agents targeting cancer, malaria and infectious diseases. Additionally, our laboratory is developing chemical tools to specifically label proteins and/or to profile entire proteomes.

Jon Antilla, Ph.D. (Assistant Professor of Chemistry)
The Antilla lab has developed numerous synthetically interesting transformations whereby chiral Brønsted acids can act as effective organocatalysts. This new approach to catalysis allows for the general synthesis of various highly desired chiral heterocycles. We have also initiated a project whereby guanidine analogues are prepared by new synthetic methods for subsequent in vitro and in vivo studies for potential as anti-stroke therapeutics by collaborators in the USF College of Medicine.

Natural Products

Bill Baker, Ph.D. (Professor of Chemistry)
The Baker lab investigates various aspects of natural products chemistry, including the biosynthesis of alkaloids in Floridian tunicates, chemical ecology of shallow-water Antarctic marine invertebrates, chemotherapeutic agents from marine invertebrates, natural products from marine microorganisms, as well as the synthesis, semi-synthesis and lead optimization of bioactive marine natural products.



Jun Tan, M.D., Ph.D. and R Douglas Shytle, Ph.D.
Our labs have both preclinical and clinical R&D experience, and we investigate the effects of natural compounds in various cell systems and animal models to determine the feasibility of developing nutraceutical (therapeutic natural compounds) and pharmaceutical (semi-synthetic natural compounds) products for the treatment of neurodegenerative diseases. These investigations have led to submission of several USF provisional patents. In addition, one of our studies on green tea component, EGCG, was recently published in the prestigious *Journal of Neuroscience* and received world-wide press coverage. Our aim is to use Florida-based nutraceutical companies as a conduit for conducting translational research on our intellectual property through the use of private investment (venture capital) and federal funding obtained through NIH SBIR/STTR and/or Florida High Tech Corridor grant mechanisms.

Computational Methods

Alfredo Cardenas, Ph.D. (Assistant Professor of Chemistry)
The Cardenas lab is studying computer simulations of protein molecules to understand their conformational changes and folding processes. Our methods include molecular dynamics (for short-time dynamics) and the stochastic difference algorithm (for longer time dynamics) to compute conformational variations on those systems. Among the proteins that are currently studied in our lab are Cu,Zn Superoxide dismutase that is implicated in familial forms of Amyotrophic Lateral Sclerosis and the RNA binding domain of the non-structural protein 1 from influenza virus.

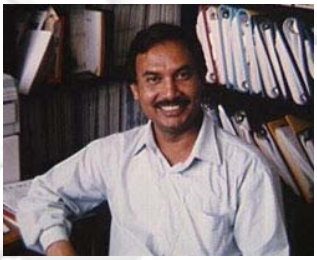
Wayne Guida, Ph.D. (Professor of Chemistry)
The Guida group uses computational chemistry for the structure-based design of novel therapeutic agents primarily directed against cancer. The lab performs *in silico* screening of large chemical databases to identify lead compounds and performs molecular modeling studies in collaboration with medicinal chemists for lead optimization studies that ultimately results in new molecular entities that can be tested in a clinical setting.

Biochemistry

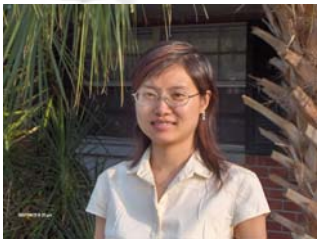
David Merkler, Ph.D. (Professor of Chemistry)
Our lab conducts research on peptidylglycine α-amidating enzyme and other enzymes catalyzing post-translational modifications of proteins and peptides, such as tyrosylprotein sulfotransferase, acyl-CoA:glycine N-acyltransferase, peptidylarginine deiminase, and other oxygenases, such as tyrosinase.

Gloria C. Ferreira, Ph.D. (Professor of Molecular Medicine)
Heme, a ferrous iron-chelating tetrapyrrole, plays multiple roles in vital cellular processes, including aerobic respiration, oxygen transport, signal transduction, regulation of transcription and translation and cellular differentiation. Our research program combines a wide range of experimental approaches (steady-state and transient kinetics, biochemical and molecular biological analyses) to investigate the reaction and regulation mechanisms of the heme biosynthetic pathway enzymes, in particular the enzymes responsible for the first and terminal steps of the pathway. By studying the structural, functional and regulatory aspects associated with heme biosynthesis, knowledge can be gained to help develop therapies for blood disorders and generation of enzymes of relevance in biotechnology.

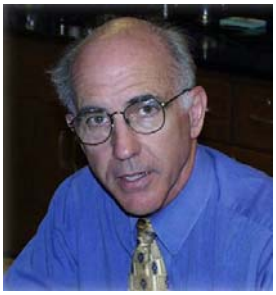
Biophysical and Bioanalytical Methods



Abdul Malik, Ph.D. (Associate Professor of Chemistry)
Our research focus is on analytical separations and sample preparation techniques, as well as the hyphenation of sample preparation and separation techniques. This is a key area of drug discovery that meshes well with numerous other research groups and thus is an integral part of research and drug development.



Xiao Li (Sheryl), Ph.D. (Assistant Professor of Chemistry)
We use cutting-edge confocal Raman microscopy and electrochemical methods (ultramicroelectrodes) to probe important biological processes such as the neuron transmission process, and investigations on the effect of drugs on cancer cells.



Ronald L. Musselman, Ph.D. (Research Professor of Chemistry)
My group employs polarized specular reflectance UV/vis/IR spectroscopy and semi-empirical MO calculations and electronic state-transition modelling to study solid-state materials such as porphyrins, co-crystallized drug components, one-dimensional conductors and photovoltaic cell components. Our porphyrin work, for example, has provided information necessary for *in-vivo* probing of porphyrin geometries. Our polarization capability allows us to determine more details about electronic transitions than those available with solution spectroscopy, making transition assignments more reliable. Finally, our semi-empirical ZINDO calculations allow modeling of the transitions and orbitals to assign transitions with even more accuracy.

Bioassay Development

Dennis Kyle, Ph.D. (Professor of Global Health)
The Kyle laboratory focuses on discovery, lead optimization, and development of drugs for the treatment of malaria and leishmaniasis. Dr. Kyle formerly led the Drug Discovery and Lead Optimization programs at the Walter Reed Army Institute of Research. His new lab at USF is housed in the Interdisciplinary Research Building located in the Research Park, and conducts in vitro and in vivo models for evaluating antiparasitic drugs. In addition, the Kyle lab uses cell, molecular, and chemical biology approaches to understand antimalarial drug resistance mechanisms.

Alberto van Olphen, D.V.M., Ph.D. (Assistant Professor of Global health)
Dr. van Olphen is the Director of the Virology Core of the USF-Center for Biological Defense (CBD) located in the USF research park. Research activities of the van Olphen lab include the development of new molecular and immunological diagnostics, drug screening for antiviral drugs and characterization of drug resistance for viral agents with bioterrorist potential and emerging viral diseases. A. van Olphen has established collaborations with faculty at the USF Chemistry Department working in the identification and characterization of natural products and pure compounds with antiviral capacity. Dr. van Olphen is also a member of the Global Health Infectious Disease Research (GHIDR) program**.**

John Adams, Ph.D. (Professor of Global Health)
The goal of my research is to gain a better understanding of the biology of malaria parasites in order to identify new targets and improve existing targets of therapeutic interventions. The research analyzes functions of essential parasite ligands, including their interactions with host receptors, proteolytic processing, and immune evasion mechanisms. A functional genomics project is using a whole genome, high throughput genetic screen to identify novel targets, define metabolic pathways, and validate drug targets.

Innovation in Drug Development

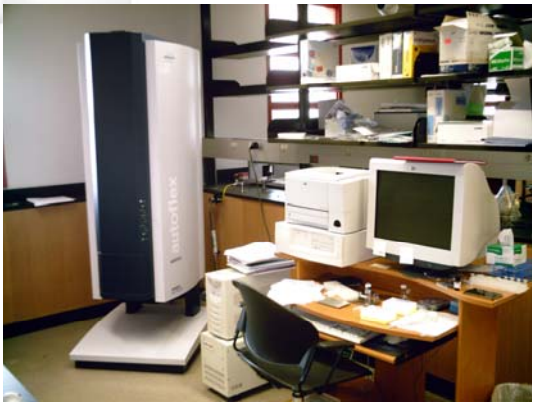
Wil Milhous is small molecule drug developer with 26 years of bench-top to bedside experience. Wil came to USF from the Walter Reed Army Institute of Research (WRAIR) to teach critical path as an academic discipline in the Global Health Infectious Disease Research Program and the CMD5. Wil began his infectious disease chemotherapy training in a combined doctoral (UNC) and training with industry (GSK) program has been more recently involved in evaluating emerging technologies to enhance R&D productivity and accelerate the drug development process. He has served as PI, Co-PI or senior advisor of multiple research grant awards from the National Institutes of Allergy and Infectious Disease (NIAID), Military Infectious Disease Research Program (MIDRP), World Health Organization (WHO), and the Medicines for Malaria Venture (MMV).

Instrumental Core Facilities

Ted Gauthier, Ph.D. (Research Assistant Professor of Chemistry, Director of the Mass Spectrometry and Peptide Synthesis Core Facility). The *USF Peptide and Mass Spectrometry Facility* supports the research efforts of a variety of scientific disciplines from engineering to drug discovery. The facility is supporting the scientific community at USF by providing state-of-the-art instrumentation, training, scientific and technical support, and education. Currently, I am involved in two research areas. The first is the development of a new HIV protease inhibitor with Dr. Mark McLaughlin (Chemistry). The second is an interdisciplinary effort with Drs. Jun (COM) and Shytle (COM) to use mass spectrometry to determine the pharmacokinetics of EGCG in biological systems.

Edwin Rivera-Otero, Ph.D. (Research Assistant Professor of Chemistry, Director of the NMR Core Facility). The *Interdisciplinary NMR Facility* at USF is built on the concept of supporting a variety of scientific disciplines including CMD[5]'s drug discovery program. From small drug-like molecules to large macromolecules, such as proteins and nucleic acids of therapeutic interest, and solid-state NMR, the NMR facility is supports the scientific community at USF by facilitating state-of-the art experiments and instrumentation via training, scientific consultation, technical support and education. My research is an interdisciplinary collaboration with Drs Manetsch (Chemistry) and van Olphen (CBD-Public Health) where we use multidimensional NMR and isotopically labeled proteins to discover drugable sites from viral proteins that may be of therapeutic interest.

NMR instruments operate at 250, 300, 400, and 500 MHz. Additional facilities available for CMD[5] researchers include a solids characterization facility (which includes a Bruker APEX single crystal x-ray diffractometer with 4K CCD detector and Oxford Cryostream low temperature accessory and a Bruker D-8 Advance powder x-ray diffractometer) and more routine instruments such as FT-IR, UV-vis, LC, GC, and GC/MS.



MALDI-TOF mass spectrometer

500 MHz nmr spectrometer