Hayes Investment Fund

2002 Awards

Final Report

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2002 HAYES INVESTMENT FUND AWARDS

FINAL REPORT

INTRODUCTION

A total of fifty-one preliminary proposals were received in response to the RFP issued in May 2001. Each proposal was read by at least three external readers, with the readers evaluating the proposals according to criteria that included the project's potential for national excellence, the capabilities of the project investigators, the potential for leveraging future support from federal and industrial sources, the potential to achieve the delineated research goals, the advancement of basic research and education, and meaningful collaboration among the partners. Based upon the evaluations and rankings of the external readers, all of whom were leaders in their disciplinary areas, a total of twenty-four proposed projects were selected to move to the final proposal phase of the competition in the spring of 2002. A seven person Review Panel was selected to evaluate and rank these proposed projects. The members of the Panel were selected based not only on their research expertise, but also on the experience they had in directing or administering diverse research programs that spanned multiple disciplines.

The Panel members were provided not only the detailed final proposal, but also the reviews from the disciplinary readers for the preliminary proposal. Each full proposal was reviewed by at least three panel members. For this evaluation the Panel was instructed to use not only the evaluation criteria used by the readers of the preliminary proposals, but also to consider the relationship and consistency of the proposal with the goals and objectives of **The Ohio Plan for Technology and Economic Development** in the three focus areas of biotechnology, nanotechnology, and information technology. After careful deliberations the Panel recommended that the nine proposals delineated on the following table be provided a 2002 Hayes Investment Fund award.

SUMMARY OF RESULTS

As indicated on the table, awards totaling $12,020,000 were made to the nine research consortiums, whose members included all doctoral granting research universities in the state in addition to the Air Force Institute of Technology, the Cleveland Clinic Foundation, the Ohio Supercomputer Center, and Wright Patterson Air Force Base. As of the summer of 2006, these Hayes Investment Fund awards have resulted in federal and industry research awards to the consortium members totaling over $150,000,000. In addition, over 540 peered reviewed publications have been published and 102 new research collaborations have been established with other universities (67) and industry partners (35). Six patents have been issued as a result of this research, with 7 inventions now having pending patents. Finally, students using the equipment acquired under these awards for their research projects have received 125 Ph.D. degrees and 74 MS degrees. A brief overview of the results for each project follows, with full reports for each project following the overview section.

Hayes Investment Fund Awards
June 20, 2002

Universities in the Consortium	Program	HIF Award
University of Akron, Cleveland State University, Cleveland Clinic Foundation, Case Western Reserve University, Youngstown State University, Ohio State University, University of Cincinnati, Ohio University, and Kent State University	Mass Spectrometry Consortium for Materials and Medical Research	**$1,870,000**
Bowling Green State University, Case Western Reserve University, Medical College of Ohio, Ohio State University, University of Akron, University of Cincinnati, University of Toledo, and Wright Patterson Air Force Base	Ohio Consortium for Kinetic Spectrometry	**$1,300,000**
Case Western Reserve University, Cleveland State University,Kent State University,Northeast Ohio Universities Collge of Medicine,Ohio State University, and University of Akron	Ohio Cellular and Molecular Imaging Consortium	**$2,000,000**
University of Cincinnati, Ohio State University, and University of Dayton	Center for Nondestructive Characterization and Reliability Assurance of Micro- and Nano-Materials	**$500,000**
University of Cincinnati, and Wright State University	A Genome Research Institute in Ohio	**$1,700,000**
Kent State University, Case Western Reserve University, and Ohio State University	Ohio Organic Semiconductor Consortium	**$900,000**
Ohio State University, Case Western Reserve University, Kent State University, Miami University, Ohio University, University of Akron, University of Cincinnati, University of Toledo, and Wright State University	Ohio NMR Consortium	**$2,000,000**
Wright State University, Ohio State University, and Air Force Institute of Technology	Ohio Research in Advanced Internet Utilization, Simulation, and Telerobotics	**$800,000**
Wright State University, Kent State University, Ohio State University, Miami University, and University of Cincinnati	Consortium for Environmental and Process Technologies	**$950,000**

OVERVIEW OF PROJECT RESULTS

Mass Spectrometry Consortium for Materials and Medical Research

Partners: University of Akron, Cleveland State University, Cleveland Clinic Foundation, Case Western Reserve University, Youngstown State University, Ohio State University, University of Cincinnati, Ohio University, Kent State University

The mass spectrometry (MS) equipment purchased with the funds provided by the Hayes Investment Fund (HIF) has helped to build up Ohio's MS infrastructure with the state-of-the-art technology needed to solve critical analytical problems in materials and biomedical science, which play key roles in the state's economy. The improved instrumentation has enhanced funding from federal agencies, promoted collaborations within the consortium partners and between consortium members and industrial corporations, and provided unique educational opportunities, including hands-on-experience, to Ohio's college and postgraduate students.

The Consortium has instituted a new annual conference, the Ohio Mass Spectrometry Consortium Symposium (OMSCS), where the consortium members, their academic and industrial partners, and the Ohio MS community meet to present and discuss their MS results, learn about new developments in the MS field, and foster new collaborations. Attendance of these conferences has risen dramatically (2004 – 43 attendees, 2005 – 70 attendees, 2006 – 108 attendees), reflecting the increased use of MS in answering research questions as well as a steadily increasing number of collaborations, both brought upon by the improved MS infrastructure created by the HIF grant.

The Mass Spectrometry Consortium has also greatly enhanced the technology transfer, collaborations with industry, and commercialization activities of the participating universities. At the University of Akron, patents issued to Professors Daniel J. Smith (use of electro-spun fibers in wound repair kits) and Wiley J. Youngs (new cancer drugs), and pending patents of professor Jun Hu (glucose sensors) resulted from studies that utilized UA's Mass Spectrometry Center, including the new mass spectrometers funded by the HIF grant. The patents of D. J. Smith have been of particular value to start-up companies. The University of Cincinnati mass spectrometry center has made special efforts to support local industry. Recent examples include Hexion Specialty Chemicals, on eight occasions for analyses involving competitor product identification, impurities in production, and tank samples identified for disposal; and Cornerstone Research Group, Inc. for identification of an unknown material and confirmation of a proposed material. Currently a quote is being prepared for GE aircraft engines involving extensive GC/MS analyses. Finally, at Case Western Reserve University, NEO Proteomics, incorporated in 2006, is a biotech startup based on concepts developed in the Case Proteomics Center.

Ohio Consortium for Kinetic Spectrometry

Partners: Bowling Green State University, Case Western Reserve University, Medical College of Ohio, Ohio State University, University of Akron, University of Cincinnati, University of Toledo, Wright Patterson AFB

The Ohio Laboratory for Kinetic Spectrometry (OLKS) continues to flourish within the Center for Photochemical Sciences at Bowling Green State University. The Laboratory is now the premiere laboratory of its type in the nation and is designed and operated for the free and open use of those in the Ohio scientific community having needs for access to the instrumentation and services it provides. The community of users and collaborators are drawn from Ohio's Universities and Colleges and from a number of Ohio-based industries. The Laboratory has become an integral part of the present and future basic/applied research programs of many of the scientific community in the state of Ohio. Important additional benefits accrue. For example, it serves to stimulate collaborative ventures among individual members of the user group and new research partnerships are thus spawned between scientists from different universities, and between university scientists and those in an industrial setting. Not least in the anticipated outcomes of the Laboratory is the fact that it has become a training ground for graduate students of all disciplines who make up the next generation of leaders in science and technology.

The array of instrumentation in the Laboratory is designed to study of the earliest of events, that is, those occurring in the time window 10^{-3} to 10^{-14} s, wherein a rich harvest of new knowledge is being revealed. Instruments that can measure events on such time scales are expensive, not commercially available and must be constructed and operated by persons trained in their intricacies. As a result, many scientists whose research programs would clearly benefit from dynamic information on such time scales cannot achieve their full research potential. The Laboratory provides a state-of-the-art experimental facility manned by experts that is open and accessible to the Ohio scientific community. Areas of science that are addressable at the Laboratory include photosciences, opto-electronics, materials, nanoscale systems, tumor therapy, and alternative energy research. The common thread connecting the user community is an interest in the fundamental knowledge that can be gained about many of today's pressing scientific and technological questions through the employment of instruments that generate information about the dynamics of transient chemical and biological entities.

In addition to its independent existence, the Laboratory works closely with the personnel of the Wright Photoscience Laboratory (WPL). Employees of WPL carry out research activities at OLKS and are involved in collaborative ventures with OLKS personnel. A major objective of the WPL is to enable technology transfer and opportunities in the private sector. An OLKS collaboration involving 2 photon optical limiting with Spectra Group Ltd. has resulted in a recent SBIR proposal to the Army Office of Research. In addition, a spin-off company, Ultrafast Systems LLC was launched in late 2003. It manufactures time-resolved spectrometers to the global research community.

The Ohio Cellular and Molecular Imaging Consortium

Partners: Case Western Reserve University, Cleveland State University,
Kent State University, NE Ohio University College of Medicine,
Ohio State University, University of Akron

As of October 2005, site construction has been completed with the magnet installed and acceptance testing completed. The ~$2.7 million construction/renovation of the centralized Imaging Research Center began in January 2005. The facility became operational in November 2005. The Imaging Research Center is one of the few in the nation with the multitude of MRI, optical, and nuclear medicine imaging resources all located under one roof and led by a single organizational structure. With the completion of site construction, the Bruker 7T High-Field, In-Vivo Magnetic Resonance Imaging and Spectroscopy System was delivered. This unit is a state-of-the-art magnetic resonance imaging and multi-nuclear MR system. This system is designed specifically to obtain in-vivo images and NMR spectra from various nuclei of animal models of various human diseases (ex. cancer, diabetes, cardiovascular disease). In-vivo imaging of these animals models (primarily mice and rats), require extremely high resolution.

As described in the original proposal, in order to capitalize on the opportunity that imaging brings to Case Western Reserve University and the other consortium members, it was important to recruit several research faculty to help jump start development of a comprehensive imaging research program. Significant progress has been made in this area. Successful recruitments have been made in the fMRI imaging area, for the development of neuroactive PET agents, and in the area of the design of novel imaging tools to image individual and multiple molecular markers of disease. These recruitments, along with existing faculty at the consortium universities, have enabled the consortium to initiate many of the originally proposed research projects. These include early breast cancer detection and therapy monitoring by new methods in MR imaging. The importance of early detection of breast cancer is well accepted. While new imaging methods like MRI have emerging roles in breast cancer diagnosis, sensitivity and specificity with available MR contrast agents need to be improved. In this project, we are creating a novel mechanism to prolong contrast agent circulation time in the body, to increase targeting to tumor cells while also minimizing uptake in healthy cells through a liposomal delivery approach, to watch erbB2 expression during and following therapy, and to monitor biological changes in response using MR imaging. We will then, retrospectively, relate this to the ultimate treatment response as a means of developing tools to predict anticipated efficacy of therapy at the earliest stages. Among the other projects underway two involve prostate cancer and one colon cancer, all looking at better early detection methods.

As initially proposed, several educational lecture/seminar series have been instituted, including one that brings in national and international experts in the emerging roles for imaging in cancer centers. In addition to having a very positive affect on attracting external research funds, the consortium has resulted in twenty new collaborations among the participating universities.

Center for Nondestructive Characterization and Reliability Assurance of Micro- and Nano-Materials

Partners: University of Cincinnati, Ohio State University, University of Dayton

The main objective of this collaborative effort among the University of Cincinnati (UC), The Ohio State University (OSU), and the University of Dayton (UD) was to develop innovative characterization tools to measure micro- and nano-scale physical properties without destructively sectioning the component. The ability to nondestructively characterize a structure and to provide quantitative information at the micro- and nano-scales leads to better understanding of failure mechanisms and has the potential to revolutionize failure prevention methodologies. Our efforts to date have greatly facilitated cooperation among the participating members in sponsored research projects and provide a unique infrastructure for multidisciplinary student training.

The team at the University of Cincinnati focuses on nondestructive materials characterization using high-resolution Scanning Acoustic Microscopy (SAM). This research effort in collaboration with OSU and UD has resulted in a five-year research award received from the Department of the Air Force to study surface-treated materials. Some of these efforts have already been successfully concluded, such as a study of microstructural features in nickel-base superalloys to facilitate the development of better residual stress measurement procedures and a series of projects aimed at the development of nondestructive residual stress management methods for engine rotor life extension. The uniquely high resolution of high-frequency acoustic microscopy is also exploited in a couple of current and proposed collaborative research efforts with Fermi National Accelerator Laboratory and Imperial College London, UK. Of particular interest in most of these research efforts is the complementary use of high-resolution acoustic and electromagnetic methods to characterize microstructural material features. The team at The Ohio State University concentrates on the development of new micro- and nano-scale nondestructive characterization capabilities tailored to measure hardness, elastic modulus, friction, adhesion, wear resistance, and other material properties. The first such study was aimed at characterization of nano-mechanical properties of very thin SiCOH films on Si substrates with samples supplied by IBM. The second project is focused on characterization of cold work and microstructural features in nickel-base superalloys in collaboration with UC, which was sponsored by AFRL. In this project, a new method of scaling functions has been developed to better characterize mechanical properties from nano-indentation measurements. At the University of Dayton facilities to characterize stresses and strains in nano-structured materials through combining a digital correlation technique called microDAC with a variety of image techniques such as AFM, UFM, WLIM, and near field scanning optical microscopy (NSOM) has been developed. As a preliminary test of the system's performance, the microDAC was successfully applied to study local stress fields in front of fatigue cracks of high strength Aluminum alloys and results have been obtained based on AFM/UFM and WLIM images. The AFM function of the Veeco Explorer SPM was also used for the characterization of carbon nanotubes (CNT).

A Genome Research Institute in Ohio

Partners: University of Cincinnati, Wright State University

The objective of the GRIO Program, funded by the Hayes Award, was to establish a comprehensive research infrastructure which would allow the Partner institutions, the University of Cincinnati and Wright State University, to successfully achieve a leadership role in biomedical research. GRIO's core facilities were created to support basic, clinical, and pharmaceutical research which will lead to the creation of proprietary gene and protein expression databases, the development of new therapeutic strategies, new research initiatives, and novel drug targets, all of which will eventually lead to improved health care for the citizens of Ohio and the nation. The initial project focus was the establishment of core facilities for genomics, proteomics, bioinformatics, biological validation, phenotyping, medicinal chemistry and protein production. Funds from HIF were specifically earmarked for essential animal holding and procedure facilities and were to be augmented with University, other State and federal grant funds to establish the complete GRIO infrastructure. This included creation of suitable space, identifying critical personnel, and securing equipment and supplies. Efforts were also to be undertaken to initiate projects utilizing these cores with a wide range of academic, government and industry collaborators.

GRIO has grown in less than four years into a major research enterprise with forty Principal Investigator laboratories and a total staff of more than 350. World-class leaders in cancer, obesity, diabetes, neurobehavioral and cardiovascular research have been recruited from across the U.S., Europe and Australia. GRIO investigators have more than fifty extramurally funded research projects, worth over $15,000,000 per year, in place at the current time, with sources which include the National Institutes of Health, Department of Defense, American Cancer Society, American Heart Association, Diabetes Foundation and many others.

All of the core facilities established by the Hayes award and associated funding are now in place. Additionally, during the last calendar quarter, agreement was reached to purchase high throughput screening equipment using funds provided by the State to the Computation Medicine Center, to initiate the development of drug candidates. We are also working to add additional medicinal chemistry and protein production capabilities to make GRI truly a unique center of excellence in translational medicine. New projects are being added on a regular basis and several are making excellent progress towards commercializable endpoints focusing on diagnostics and drug candidates in the areas of cancer, obesity, diabetes and heart disease. GRIO and its Partners are now competing for sizeable federal grants and contracts which would have been impossible without these resources. GRI is also actively courting existing pharmaceutical and biotechnology companies with the goal of moving projects and on-the-ground activities to Ohio.

Ohio Organic Semiconductor Consortium (OOSC)

Partners: Kent State University, Case Western Reserve University,
Ohio State University

The work at KSU falls into three main categories. First, there is a synthesis category in which candidate organic semiconductor materials are designed, synthesized and purified. Second, there is a characterization category in which the salient physical properties including time of flight charge mobility and charge generation are determined. Third, there is a more theoretical category in which models are developed to describe and interpret the experimental results. In category one the materials themselves may be broken into three different classes by structure: single crystal, liquid crystal and amorphous glass monomers. Efforts in single crystal materials have concentrated on acenes (such as pentacene) and their derivatives and iodoaromatics. A range of simple iodoaromatics have been prepared and amongst them 1,4-diiodobenzene has been studied in substantial detail (synthesis and purification, hole mobility, modeling of transport). This substance has a hole mobility rivaling the other best organic semiconductors which are always much larger conjugated molecules. Studies of liquid crystal organic semiconductors have included both discotic and calamitic thermotropic liquid crystals. In the discotic area studies have concentrated on the known hexaalkoxytriphenylene class, especially HAT-5 and also nitro derivatives of HAT-5. Another ongoing project is to examine the existence of discotic liquid crystal phases in benzofuran containing aromatics. In the calamitic liquid crystal area we have pursued molecules with significant heterocyclic ring content. A very general synthetic method has been developed to introduce a 2,5-pyridine structure into liquid crystals. In the third area of study, a range of triarylimidazoles have been prepared as potential monomer glass forming charge transport agents. The triarylimidazole structure was chosen due to its known propensity for glass formation. Physical measurements to date have not revealed any unusual mobility properties, though the observation of clear Poole-Frenkel behavior has motivated future work on the role of dipolar disorder in hopping conduction.

The instruments purchased by Case Western Reserve University have been used to study the photoluminescence characteristics of conjugated, organic semiconducting materials in solution and the solid state, for the electrochemical synthesis of semiconducting materials, including conducting polymers and organic/inorganic hybrid materials and to investigate new polymeric materials for capacitors with a DuPont processing plant in Circleville, Ohio. Careful imaging and kinetic studies of CuS and Ag_2S solid electrolytic flash memory cells has led to an important discovery about the layered structure of PET and PVDF films under investigation for capacitor applications. We are connecting all of the nano-metrology tools in the laboratory to the Nano-Grid that is being set-up across Ohio to provide remote control access to other institutions and small businesses in the area. This will provide an opportunity for these institutions to use state-of-the-art instrument without having to invest in one. The access through web enables complete control and instantaneous monitoring of images obtained by the AFM in real-time. We are in the process of starting a small company to develop the Nano-Grid across Ohio.

Ohio NMR Consortium

Partners: Ohio State University, Case Western Reserve University, Kent State University, Miami University, Ohio University, University of Akron, University of Cincinnati, University of Toledo, Wright State University

The 2002 Hayes Award allowed the Ohio NMR Consortium to build on an earlier Investment Fund awarded in 1996. This earlier award enabled OSU to purchase an 800 MHz NMR spectrometer and UC to purchase items for an 800 MHz spectrometer previously ordered. The award also provided funding for many other Ohio universities in the consortium allowing them to upgrade their facilities. The 2002 award continued to increase the prominence of Ohio in the NMR community by partially funding the purchase of a Bruker 900 MHz NMR spectrometer for the Cleveland Center for Structural Biology, formed by CWRU, CSU and the Cleveland Clinic Research Foundation. The 900 MHz spectrometer was delivered in December 2005, and by the spring of 2006 it was operational. To date, the major impact of the 900 has been a significant increase in funding for projects which require the use this new spectrometer.

The Campus Chemical Instrument Center (CCIC) at OSU and UC's College of Medicine purchased cryoprobes. These probes provide much greater sensitivity than standard probes by reducing thermal noise in the receiver coil and the preamp. OSU leveraged its Hayes award with enough matching money to purchase two Bruker cryoprobes, one for a 600 MHz spectrometer and another for an 800 MHz spectrometer. UC purchased a Varian cryoprobe for their 500 MHz system. The Cincinnati probe was installed early in 2005 and CCIC installed its 600 probe in February 2005 and its 800 probe in June 2005. Although only in use for a little more than a year, these probes enabled research progress that would have been impossible prior to the upgrades either because of time constraints or because of effects due to concentration such as low signal to noise and solute-solute interactions.

The University of Toledo was able to leverage money it received from this award to purchase a Varian 600 MHz spectrometer. This gave them a more versatile system which is used for biological NMR projects, metabolite studies, and synthetic medicinal chemistry structural analysis. In addition to the Chemistry Department, the spectrometer is available to the College of Pharmacy and with the merger of the University of Toledo and the Medical University of Ohio there will be increased collaboration with the NMR facility. Miami University has used its Bruker 500 MHz spectrometer to conduct studies ranging from the structure and dynamics of membrane proteins, metabolism of short chain fatty acids in plant and microbial systems, and the reaction of organic intermediates called aryloxenium ions. Miami University has created a Center for Industrial Organic Chemistry and this NMR spectrometer has been a pivotal asset in work with an Ohio company and two multinational corporations with large Ohio presences.
WSU and OU each purchased Bruker 300 MHz spectrometers UC's Department of Chemistry purchased a Bruker 400 MHz spectrometer. These state-of-the art spectrometers have greatly expanded access both to universities and industry researchers in Ohio to powerful NMR technologies for examining the properties of small molecules, polymers, and solids

State-of-the-Art Infrastructure to Support Ohio Research in Advanced Internet Utilization, Simulation, and Telerobotics

Partners: Wright State University, Ohio State University, Air Force Institute of Technology

The goal of this project has been to enable existing collaborations in the areas of virtual environments, simulation, telerobotics (robots controlled from a distance), and advanced networking and to promote new and expand existing collaborations. These goals have been implemented through targeted capital expenditures on state-of-the-art infrastructure. High-end virtual environment workstations are installed at WSU (2 stations), the Air Force Research Laboratory (AFRL) (1 station), the AFIT (1 station), and the Ohio Supercomputer Center at OSU (2 stations). In addition, the capabilities of the CAVE® virtual environment system in the WSU Virtual Environment Research, Interactive Technology, and Simulation facility at WPAFB have been upgraded and significantly enhanced. These facilities have greatly strengthened our research capabilities, increased collaborations, helped to attract additional funding to the State of Ohio, and supported improved graduate training.

A collaborative research project on enhanced auditory displays for general aviation, involving WSU, General Dynamics, and the AFRL, to transfer 3-dimensional auditory display technology originally developed for military applications to the civilian sector is now underway. Translated into General Aviation cockpits we envision this technology aiding pilots by having the auditory signal from a Traffic Collision Avoidance Device appear to arise from the direction of the proximal traffic, by providing an auditory "navigation beacon" which allows pilots to maintain a desired course without looking at other instruments (e.g., when map reading), and incorporating an auditory attitude indicator designed to help pilots avoid spatial disorientation in reduced visibility environments. Another ongoing basic research project between WSU and AFRL is examining how sound can improve the visual detection and identification of objects in cluttered environments. Previous research has demonstrated dramatic reductions in search times when a sound is co-located with the visual target. The results are being related to traditional models (i.e., without an auditory component) of visual search and visual attention.

An effort among WSU, OSU, Veridian Inc. and AFRL is developing a simulation environment to evaluate the impact of delay in telerobotic tasks. Researchers at WSU are examining the active regulation of speed during a low-altitude flight task as a function of global optical flow rate, speed, and the presence or absence of a concurrent altitude disturbance. A research project between OSU and the Ohio Supercomputer Center is investigating tactile perception in simulation environments while researchers at the AFIT are examining future reconnaissance systems that are likely to incorporate large numbers ("swarms") of Uninhabited Aerial Vehicles with wide-ranging sensor capability. Another project at OSU among the Departments of Computer Science and Engineering and Biomedical Informatics, and the Ohio Supercomputer Center is developing a computing and networking research test-bed for next generation data driven, interactive applications.

Consortium for Environmental and Process Technologies

Partners: Wright State University, Kent State University, Ohio State University, Miami University, University of Cincinnati

The goal of this Hayes project was to formally establish a Consortium for Environmental and Process Technologies (CEPT), which specifically focuses its research efforts on the development and application of new methodology and techniques for monitoring toxic, persistent, and accumulating contaminates in the environment. Among the more problematic compounds that have been specifically targeted by CEPT scientists are highly chlorinated compounds like dioxins, furans, and PCBs, as well as their bromonated analogs. These compounds are potent mutagens and can result in a number of severe health problems. Other important compounds under investigation during the course of this grant have been polybromonated diphenyl ethers, which are used widely as fire retardants and various agrochemical and pharmaceuticals, especially those that can degrade to form even more highly toxic compounds.

During the last four years, CEPT researchers have been engaged in a variety of projects that have ranged from basic research related to the development and characterization of new materials, methods, and instrumentation to various applied in-field studies of the fate and effects of the targeted compounds. Among the milestones achieved are: 1) the establishment of a statewide program for assaying wastewater sludge for the presence of dioxins, furans, and PCBs; 2) various fundamental and applied in-field studies have been carried out to evaluate the fate and effects of a number of highly toxic organic and inorganic contaminants in the environment including their distribution in land masses and aquatic systems; and, 3) pioneering work has been carried out on the synthesis of various silica and carbon-based nanostructured materials including the development of a novel self-assembly procedure for producing uniformly controlled pore structures.

As part of the environmental research conducted on dioxins, dioxin-like, and related organic compounds, the toxicity and bioaccumulation of a common polycyclic aromatic hydrocarbon (PAH), phenanthrene (PHE), in earthworms was measured. Results of this study can be used in support of ecological risk assessments carried out in support of site-cleanup of areas such as brownfields. The techniques developed in this study for measuring these chemicals have many advantages such as decreased time and expense and increased sensitivity relative to traditional solvent-extraction techniques. Another ongoing phase of the project is to develop new methodologies for sample preparation. Environmental samples are typically comprised of multifaceted matrices with complex mixtures of analytes and potential interferences. Thus, they typically require significant pretreatment but the pretreatment must be carefully designed to minimize perturbation of the sample desired analytic composition. The approach is to investigate the potential of a novel class of materials called ionic liquids for selective sequestration of dioxins. Their ionic character gives rise to a liquid with virtually no vapor pressure. Hence, they are of considerable interest as potentially "green" solvents.

Mass Spectrometry Consortium for Materials and Medical Research

Final Research Progress Report

Partners: University of Akron, Cleveland State University, Cleveland Clinic Foundation, Case Western Reserve University, Youngstown State University, Ohio State University, University of Cincinnati, Ohio University, Kent State University

Introduction

The mass spectrometry (MS) equipment purchased with the funds provided by the Hayes Investment Fund (HIF) has helped to build up Ohio's MS infrastructure with the state-of-the-art technology needed to solve critical analytical problems in materials and biomedical science, which play key roles in the state's economy. The improved instrumentation has enhanced funding from federal agencies, promoted collaborations within the consortium partners and between consortium members and industrial corporations, and provided unique educational opportunities, including hands-on-experience, to Ohio's college and postgraduate students.

The consortium has instituted a new annual conference, the Ohio Mass Spectrometry Consortium Symposium (OMSCS), where the consortium members, their academic and industrial partners, and the Ohio MS community meet to present and discuss their MS results, learn about new developments in the MS field, and foster new collaborations. Attendance of these conferences has risen dramatically (2004 – 43 attendees, 2005 – 70 attendees, 2006 – 108 attendees), reflecting the increased use of MS in answering research questions as well as a steadily increasing number of collaborations, both brought upon by the improved MS infrastructure created by the HIF grant. The following overview outlines the research and educational activities and achievements of the participating institutions.

The University of Akron, UA (C. Wesdemiotis, PI)

The 2001 HIF grant enabled UA to purchase two high resolution tandem mass spectrometers, viz. a Waters AutoSpec-Q magnetic hybrid for the analysis of volatile substances and a Waters Ultima quadrupole / time-of-flight (Q/ToF) tandem mass spectrometer, equipped with MALDI (matrix-assisted laser desorption ionization), for the characterization of synthetic polymers and other macromolecular assemblies. This equipment has provided vital support to its users in the development of new synthetic polymers and new technologies based on these polymers. The instruments' value for materials research projects at UA, its research partners, and the surrounding community is reflected by the steadily increasing use of UA's Mass Spectrometry Center, which analyzed approximately 2,200 samples in 2003, 5300 samples in 2004, and 6,300 samples in 2005.

Leveraging results. The major users of the UA Mass Spectrometry Center are research groups at the Departments of Chemistry, Polymer Science, and Polymer

Engineering. Twenty-five PIs and their students from these departments regularly employ mass spectrometry analyses for the structural characterization of their products. These major users have received $10,000,000 grants from federal agencies and industrial partners since July 2002. The non-state research funding received in the same period by all UA users exceeds $35,000,000.

The new MS equipment has also enabled projects aiming at the development of new and/or better mass spectrometry methods for the characterization of complex synthetic polymers. Two recent grants in this field include: NSF/CHE-0517909, "Tandem Mass Spectrometry and Degradation / Mass Spectrometry Studies of Synthetic Polymers" ($397,600), 8/05-7/08; and NIST-70NANB5H1159, "The Effect of Molecular Structure on the Environmental Stability of Ballistic Materials" ($578,140) 6/05-6/08 (to C. Wesdemiotis).

Graduate students. This grant enabled mass spectrometry studies and analyses that have been incorporated in 6 M.S. theses and 30 Ph.D. dissertations from 2003 until now.

Publications. MS analyses with the equipment purchased through this grant are regularly reported in the publications of the research groups, in which these compounds are synthesized. The following studies relied on this equipment (* indicates collaborative study):

1* Quirk, R. P.; You, F.; Wesdemiotis, C.; Arnould, M. A. Anionic synthesis and characterization of ω-hydroxyl-functionalized poly(1,3-cyclohexadiene), *Macromolecules* **2004**, *37*, 1234-1242.

2* Quirk, R. P.; Guo, M.; Wesdemiotis, C.; Arnould, M. A. Investigation of ethylene oxide oligomerization during functionalization of poly(butadienyl)lithium using MALDI-TOF MS and ^{1}H NMR analyses, *Polymer* **2004**, *45*, 3423-3428.

3* Pingitore, F.; Polce, M. J.; Wang, P.; Wesdemiotis, C.; Paizs, B. Intramolecular condensation reactions in protonated dipeptides: carbon monoxide, water, and ammonia losses in competition, *J. Am. Soc. Mass Spectrom.* **2004**, *15*, 1025-1038.

4* Lee, J. S.; Quirk, R. P.; Foster, M. D.; Wollyung, K. M.; Wesdemiotis, C. A new methodology for the synthesis of star polymers utilizing the reaction of living polymers with alkoxysilyl-functionalized polymers, *Macromolecules* **2004**, *37*, 6385-6394.

5* Quirk, R. P.; Hasegawa, H.; Gomochak, D. L.; Wesdemiotis, C.; Wollyung, K. Functionalization of poly(styryl)lithium with styrene oxide, *Macromolecules* **2004**, *37*, 7146-7155.

6 Wesdemiotis, C. Entropy considerations in kinetic method applications, *J. Mass Spectrom.* **2004**, *39*, 998-1003.

7* Arnould, M. A.; Polce, M. J.; Quirk, R. P.; Wesdemiotis, C. Probing chain-end functionalization reactions in living anionic polymerization via matrix-assisted laser desorption ionization time-of-flight mass spectrometry, *Int. J. Mass Spectrom.* **2004**, *238*, 245-255.

8 Polce, M. J.; Modarelli, J. M.; Wesdemiotis, C. Li^{+}-coordinated polyglycol radicals: ions-molecule reactions with alkenes and ethers, *Eur. J. Mass Spectrom.* **2004**, *10*, 909-920.

9* Wollyung, K.M.; Wesdemiotis, C.; Nagy, A.; Kennedy, J.P. Synthesis and mass spectrometry characterization of centrally and terminally amine-functionalized polyisobutylenes, *J. Polym. Sci. Part A: Polym. Chem.* **2005**, *43*, 946-958.

10 Pingitore, F.; Wesdemiotis, C. Characterization of dipeptide isomers by tandem mass spectrometry of their mono- vs. dilithiated complexes, *Anal. Chem.* **2005**, *77*, 1796-1806.

11* Quirk, R.P.; Kim, H.; Chowdhury, S.R. Anionic syntheses of perfluoroalkyl-substituted polymers, *Polymer Prepr.* **2005**, *46(2)*, 583-584.

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13* Quirk, R.P.; Pickel, J.M.; Arnould, M.A.; Wollyung, K.M.; Wesdemiotis, C. Efficient synthesis of ω-(p-vinylbenzyl)polystyrene by direct functionalization of poly(styryl)lithium with p-vinylbenzyl chloride in hydrocarbon solvent with lithium 2,3-dimethyl-3-pentoxide, *Macromolecules* **2006**, *39*, 1681-1692.

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Technology transfer. Patents issued to Professors Daniel J. Smith (use of electro-spun fibers in wound repair kits) and Wiley J. Youngs (new cancer drugs), and pending patents of professor Jun Hu (glucose sensors) resulted from studied that utilized UA's Mass Spectrometry Center, including the new mass spectrometers funded by the HIF grant. The patents of D. J. Smith have been of particular value to start-up companies.

Collaborations. The UA Mass Spectrometry Center has established collaborations with many PIs within UA, especially with research groups from the Departments of Chemistry, Polymer Science, Polymer Engineering, Chemical Engineering, and Biology, for which MS characterizations have become essential. In addition, close collaborations have been established with the following academic and industrial partners: College of Wooster, Kent State University, Case Western Reserve University, University of Washington (Seattle), Ecole Polytechnique (France), German Cancer Research Center (Heidelberg), Ferro Corporation, Omnova Solutions, Goodyear, Noveon Inc., Lubrizol Inc., Equistar, Caraustar Inc., Millennium Petrochemicals, First Energy Corporation, and Invista.

Cleveland State University, CSU (David J. Anderson, co-PI)

Leveraging results. Cleveland State Mass Spectrometry Facility has made significant strides in securing external funding and in doing and publishing biomedical research using mass spectrometry supported by the Hayes Investment Fund program. The Hayes Investment Fund money has fostered the development of research at Cleveland State that has significant potential for commercialization. This research has led to four pending patents in the area of drug development (safer drug for preventing clot formations, applied to heart disease, strokes and other clotting diseases) and the discovery of new disease markers (non-invasive test for colon cancer). There has been a total four federal external grants totaling over $3 million that have been funded in

the areas of drug development (examining the problem of drug resistance for treating tumors), understanding the mechanisms of kidney disease, and studying stool DNA analysis for detecting cancer. There have been two SBIR grants funded in this latter area, further indicating the economic impact of this work. All this research is directly dependent on the mass spectrometry facility funded by the Hayes Investment program. The funding of the facility has also led to collaborative research between Cleveland State and several outside institutions including Case Western Reserve University (joint grant proposal funded, joint publications), Cleveland Clinic Foundation (collaborative research and joint publication), Veterans Administration Medical Center (collaborative publications), and MetroHealth Medical Center (joint grant proposal funded). Finally, Cleveland State students have received extensive training in mass spectrometry, with the awarding of 2 MS and 3 PhDs having thesis or dissertation work in mass spectrometry, with 8 students currently doing work in mass spectrometry. In summary, the $180K Hayes Investment Fund money received by Cleveland State has been significantly leveraged to obtain the goals stated in the proposal: elevating the biomedical research taking place at CSU, promoting the development of new ideas with potential for commercialization, and fostering significant collaborations between Cleveland State and other institutions, and the training of students in sophisticated mass spectrometry technology.

Publications. *** indicates joint institutional collaboration.

1. X. Sun and B. Guo**, "**Genotyping Single Nucleotide Polymorphism by Matrix-Assisted Laser Desorption/ionization Mass Spectrometry**". *Cardiovascular Diseases,*** edited by Qing Wang, 1 (in press).
2. X. Sun, Y. Liu, J. Lutterbaugh, W.D. Chen, S.D. Markowitz, B. Guo, "Detection of Mononucleotide Repeat Sequence Alterations in a Large Background of Normal DNA for Screening High-frequency Microsatellite Instability Cancers". ***Clinical Cancer Research***. 12, (2006), 454-9.
3. C. Pan, S. Xu, H. Zou, Z. Guo, Y. Zhang, B.C. Guo, "Carbon Nanotubes as Adsorbent of Solid-phase Extraction and Matrix for Laser Desorption/ionization Mass Spectrometry". ***J. Am. Soc. Mass Spectrom,*** 263-270, (2005).
4. C. Pan, S. Xu, L. Hu, X. Su, J. Ou, H. Zou, Z. Guo, Y. Zhang, B. Guo, "Using Oxidized Carbon Nanotubes as Matrix for Analysis of Small Molecules by MALDI-TOF MS". ***J Am Soc Mass Spectrom,*** 16, (2005), 883-92.
5. J.A. Hribar, X. Zhou, D.J. Anderson, "Microbore Gradient Chromatofocusing-Mass Spectrometry in the Analysis of Proteins". ***Proceedings of the 53rd ASMS Conference on Mass Spectrometry and Allied Topics,*** (2005)**.**
6. J. Tang, X. Zhou, B. Guo, D.J. Anderson, "Gradient Chromatofocusing-MALDI-TOF Analysis of Proteins". ***Proceedings of the 53rd ASMS Conference on Mass Spectrometry and Allied Topics,*** (2005)**.**
7. ***D. Sulton, D. Pagan-Rodriguez, X. Zhou, Y. Liu, A.M. Hujer, C.R. Bethel, M.S. Helfand, V.B. Anderson, L.M. Ng, and R.A Bonomo, "Clavulanic Acid Inactivation of Shv-1 and the Inhibitor Resistant Ser130gly Shv-1 Beta-Lactamase: Insights into the Mechanism of Inhibition". ***Journal of Biological Chemistry,*** 280, (2005)**,** 35528-35536.
8. ***D. Pagan-Rodriguez, X. Zhou, C. Bethel, A. Hujer, M. Helfand, Z. Jin, B. Guo, V. Anderson, L. Ng and R. Bonomo, "Tazobactam Inactivation Of Shv-1 and the Inhibitor Resistant Ser130gly Mutant of Shv-1 Beta-Lactamase Studied by Electrospray Mass Spectrometry". ***Journal of Biological Chemistry***, 279, (2004)**,** 19494.

9. D.O. Beck, M.A. Bukys, L.S. Singh, K.A. Szabo, and M. Kalafatis, "The Contribution of Amino Acid Region Asp^{695}-Tyr^{698} of Factor V to Procofactor Activation and Factor Va Function". ***J. Biol. Chem.*** 279, (2004), 3084-3095.
10. S. Yang, X. Zhou, Y. Xu, "Determination of Genistein and Daidzein in Human Plasma by Liquid Chromatography and Tandem Mass Spectrometry". ***Journal of Liquid Chromatography and Related Technologies,*** 27, (2004)**,** 471-489.
11. Y. Xu, B. Keith, J. L. Grem, "Measurement of the Anticancer Agent Gemcitabine and its Deaminated Metabolite at Low Concentrations in Human Plasma by Liquid Chromatography and Mass Spectrometric Detection". ***Journal of Chromatography,*** B 802, (2004)**,** 263-270.
12. ***A.G. Grozav, T.E. Hutson, X. Zhou, R.M. Bukowski, R. Ganapathi, Y. Xu, "Rapid Analysis of Docetaxel in Human Plasma by Tandem Mass Spectrometry With Online Sample Extraction". ***Journal of Pharmaceutical and Biomedical Analysis,*** 36, (2004)**,** 125-131.

External grants.

David Anderson, Co-PI, "Mechanisms of Tubular Atrophy in Kidney Disease", ***National Institute of Health*, (*1R01DK067528-01A2), **$1,687,290** (total), **2005-2010** (Collaboration with MetroHealth Medical Center).

Yan Xu, Co-PI "Modulating Base Excision Repair in Tumor Drug Resistance", ***National Institutes of Health *(2 R01 CA86357-5)*, **$284,613** to Yan Xu, **2004-2009** (Collaboration with Case Western Reserve University).

Baochuan Guo, PI, "Surveying the Status of a Large Number of Mutations by a Single PEPD Assay", ***National Institute of Health*** (SBIR Program, R44CA121932-02), **$1,200,000**, **2006-2008**.

Baochuan Guo, PI, "A Novel Technology for Capturing Fecal Human DNA", ***National Institute of Health*** (SBIR Program, R43CA118340-01), **$145,000**, **2006-2007**.

Pending patents. *** indicates joint institutional collaboration.

1. B. C. Guo and X. Sun, "Detection of Tumor Mutations in the Presence of Excess Amounts of Normal DNA" (pending).
2. B. C. Guo, "A Novel Strategy for the Detection of Mutant DNA in a Large Background of Normal DNA" (pending).
3. B. C. Guo, "Detection of Multiple Mutations in the Presence of Excess Amounts of Normal DNA" (pending).
4. M. Kalafatis, "Exosite-Directed Thrombin Inhibitors" (pending).

Inter-institutional collaborations promoted.

1. Cleveland State University and Case Western Reserve University

Collaboration between Dr. Yan Xu (CSU) and Dr. Stanley Gerson (CWRU) studying the drug resistance of tumor drugs (joint grant from NIH awarded)

Collaboration between Dr. Lily Ng (CSU) and Dr. Vernon Anderson (CWRU) in the study of the mechanism of anti-bacterial drugs (co-authorship on two publications)

2. Cleveland State University and Cleveland Clinic Foundation

Collaboration between Dr. David Anderson (CSU) and Dr. John Crabb (CCF) at the Cleveland Clinic studying proteomics of the eye (presentations at the American Chemical Society meeting)

Collaboration between Dr. Yan Xu (CSU) and Dr. Ram Ganapathi (CCF) in the analysis of anti-tumor drugs (co-authorship on publication)

3. Cleveland State University and MetroHealth Medical Center

Collaboration between Dr. David Anderson (CSU) and Dr. Jeffrey Schelling (MetroHealth Medical Center) (joint grant from NIH awarded)

4. Cleveland State University and Veterans Administration Medical Center

Collaboration between Dr. Lily Ng (CSU) and Dr. R. Bonomo (VAMC) in the study of the mechanism of anti-bacterial drugs (co-authorship on two publications).

Graduate students receiving degrees doing mass spectrometry research. 2 – Masters and 3- Ph.D.s.

Equipment purchased. HPLC-ESI Ion-Trap MS (Bruker-Daltonics HCT-Esquire Mass Spectrometer, Agilent Capillary HPLC), $205,000.

Cleveland Clinic Foundation, CCF (Michael T. Kinter, co-PI)

The instrument system purchased with funding from the Hayes Investment Fund was a Finnigan LTQ system with HPLC and Mascot database search system. The purchase was finalized in December 2003 and has been in constant use since that time in the CCF Proteomics Laboratory (Director Michael Kinter).

Leveraging results. The expanded capabilities of the lab has facilitated its inclusion in a number of new NIH grants since that time, listed below:

Monocyte Pathogenesis: Regulation of NADPH Oxidase. M. Cathcart PI, NIH R01 HL061971 04/1/04-03/30/08; M. Kinter Co-investigator.

Axonal Pathology in Multiple Sclerosis. B. Trapp, PI, NIH P01 NS038667, 12/1/2004-11/30/2009; M. Kinter, Co-Investigator. Synemin is an A-Kinase Anchoring Protein in the Heart . M. Bond PI, NIH R01 HL079134, 12/15/2004-11/30/2008; M. Kinter, Co-Investigator.

B-defensin protection of human oral epithelial cells. A. Weinberg, PI, NIH R01 DE016334, 7/1/2005-6/30/2009, M. Kinter, Co-Investigator.

Publications. Our work has also been included in a number of peer reviewed publications, also listed:

1 J.A. Keightley, L. Shang, and M. Kinter. Proteomic Analysis of Oxidative Stress-Resistant Cells: A Specific Role for Aldose Reductase Overexpression in Cytoprotection. *Mol. Cell. Proteomics.* 3:167-175, 2004.

2 J.K. Morris, B.B. Willard, X. Yin, G. Jeserich, M. Kinter, and B.D. Trapp. The 36K Protein of Zebrafish CNS Myelin is a Short-Chain Dehydrogenase. *Glia.* 45:378-391, 2004.

3 M. Cicek, R.S. Samant, M. Kinter, D.R. Welch, and G. Casey. Identification of Metastasis-Associated Proteins Through Protein Analysis of Metastatic MDA-MB-435 and Metastasis-Suppressed BRMS1 Transfected-MDA-MB-435 Cells. *Clin. Exp. Metastasis.* 21:149-157, 2004.

4 C.I. Ruse, F-L. Tan, M. Kinter, and M. Bond. Integrated Analysis of the Human Cardiac Transcriptome, Proteome, and Phosphoproteome. *Proteomics.* 4:1505-1516, 2004.

5 G.L. Coaker, B.B. Willard, M.T. Kinter, E.J. Stockinger, and D.M. Francis. Proteomic Analysis of Resistance Mediated by Rem 2.0 and Rcm 5.1, Two Loci Controlling Resistance to Bacterial Canker of Tomato. *Molec.Plant-Microbe Interact.* 17:1019-1028, 2004.

6 L L. Zheng, B. Nukuna, M-L. Brennan, M. Sun, M. Goormastic, M. Settle, D. Schmitt, X. Fu, L. Thomson, P.L. Fox, H. Ischiropoulos, J.D. Smith, M. Kinter, and S.L. Hazen. Apolipoprotein A-I is a Selective Target for Myeloperoxidase-Catalyzed Oxidation and Functional Impairment in Subjects with Cardiovascular Disease. *J. Clin. Invest.* 114:529-541, 2004.
7 K.R. Santhamma, R. Sadhukhan, M. Kinter, S. Chattopadhyay, B. McCue, and I. Sen. Role of Tyrosine Phosphorylation in the Regulation of Cleavage-Secretion of Angiotensin-Converting Enzyme. *J. Biol. Chem.* 279:40227-40236, 2004.
8 P. Sampath, B. Mazumder, V. Seshadri, C.A. Gerber, L. Chavatte, M. Kinter, S.M. Ting, J.D. Dignam, S. Kim, D. Driscoll, and P.L. Fox. Non-Canonical Function of Glutamyl-Prolyl-tRNA Synthetase: Gene-Specific Silencing of Translation. *Cell.* 119:195-208, 2004.
9 J. Yuan, M. Kinter, J. McGeehan, G. Perry, G. Kneale, P. Gambetti, W-Q. Zou. Concealment of Epitope by Reduction and Alkylation in Prion Protein. *Biochem. Biophys. Res. Comm.* 326:652-659, 2005.
10 L. Zheng, M. Settle, G. Brubaker, S.L. Hazen, J.D. Smith, and M. Kinter. Myeloperoxidase-mediated Oxidative Modification of Apolipoprotein AI in Human Atheroma: Localization of Nitration and Chlorination Sites and Association with Impaired ABCA1-dependent Cholesterol Efflux from Macrophages. *J. Biol. Chem.* 280:38-47, 2005.
11 N. Terada, G.J. Kidd, M. Kinter, C. Bjartmar, K. Moran-Jones, and B.D. Trapp. Beta(IV) Tubulin is Selectively Expressed by Oligodendrocytes in the Central Nervous System. *Glia*, 50:212-222, 2005.
12 M.G. Rosca, T.G. Mustata, M. Kinter, A.M. Ozdemir, T.S. Kern, L.I. Szweda, M. Brownlee, V.M. Monnier, M.F. Weiss. Glycation of Mitochondrial Proteins from Diabetic Rat Kidney is Associated with Excess Superoxide Formation. *Am. J. Physiol. Renal Physiol.* 289:F420-F430, 2005.
13 F.A. Masri, S.A. Comhair, T. Koeck, D.J. Stuehr, W. Xu, A. Janocha, S. Ghosh, R.A. Dweik, J. Golish, M. Kinter, S.C. Erzurum, K.S. Aulak. Abnormalities in Nitric Oxide and its Derivatives in Lung Cancer. *Am. J. Respir. Crit. Care Med.* 172:597-605, 2005.
14 M. Goel, W. Sinkins, A. Keightley, M. Kinter, W.P. Schilling. Proteomic Analysis of TRPC5- and TRPC6-binding Partners Reveals Interaction with the Plasmalemmal Na+/K+-ATPase. *Pflugers Arch.* 451:87-98, 2005.
15 S. Chattopadhyay, K.R. Santhamma, S. Sengupta, B. McCue, M. Kinter, G.C. Sen, I. Sen. Calmodulin Binds to the Cytoplasmic Domain of Angiotensin-Converting Enzyme and Regulates its Phosphorylation and Cleavage Secretion. *J. Biol. Chem.* 280:33847-33855, 2005.
16 D.Q. Peng, Z. Wu, G. Brubaker, L. Zheng, M. Settle, E. Gross, M. Kinter, S.L. Hazen, J.D. Smith. Tyrosine Modification is Not Required for Myeloperoxidase-Induced Loss of Apolipoprotein A-I Functional Activities. *J. Biol. Chem.* 280:33775-33784, 2005.
17 J.P. Conway and M. Kinter. Proteomic and Transcriptomic Analyses of Macrophages with an Increased Resistance to Oxidized Low Density Lipoprotein (oxLDL)-induced Cytotoxicity Generated by Chronic Exposure to oxLDL. *Mol. Cell. Proteomics.* 4:1522-1540, 2005.
18 S.H. Low; S. Vasanth; N. Sharma; J. Shillingford; J. Widjaja; S. Mukherjee; P. Bhattaram; J. Waern; C. Larson; T. Obara; M. Kinter, and T. Weimbs. Polycystin-1, STAT6 and P100 function in a novel pathway that transduces ciliary

mechanosensation to gene expression and is activated in polycystic kidney disease. *Dev. Cell.* 10:57-69, 2006.
19 S. Ghosh, A.J. Janocha, M.A. Aronica, S. Swaidani, S.A.A. Comhair, W. Xu, L. Zheng, S. Kaveti, M. Kinter, S.L. Hazen, and S.C. Erzurum. Nitrotyrosine proteome survey in asthma identifies oxidative mechanisms of catalase inactivation. *J. Immunol.* In press, 2006.

Graduate students. So far, two students have worked in the lab, Lemin Zheng who received his Ph.D. from Cleveland State in May 2005 and James Conway who is scheduled to defend his dissertation in June 2006. The dissertation work of both students was enhance by the instrument purchased with the Hayes Funding.

Collaborations. A collaboration with Dr. Stanley Hazen has lead to the filing of a patent, Risk Markers for Cardiovascular Disease (application number 20050239136).

Case Western Reserve University, CWRU (Vernon A. Anderson, co-PI)

Two systems were acquired with support obtained from the Hayes Award, as CWRU was able to leverage the Hayes award with funds from both an NIH instrumentation award and with funds from the CWRU Provost opportunity fund. The instruments purchased are a Thermo Finnigan Delta XP(Plus) continuous flow isotope ratio mass spectrometer with gas-chromatography/thermal conversion sample introduction and a Thermo Finnigan LTQ linear ion trap mass spectrometer.

The isotope ratio mass spectrometer system has been used by the Anderson, Previs and Brunengraber laboratories at Case, and collaborations have been established with several outside laboratories to study isotope effects on enzyme reactions. The Previs and Brunengraber laboratories have used the instrument to pursue metabolic studies of labeled compounds. $^{13}CO_2$ has been detected from labeled fatty acids. These studies permit the determination of how perfused organs use fatty acids for energy or lipid synthesis. These studies are important for determining how hearts function during heart attacks, and how livers can vary their metabolism based on different dietary demands. The ability to detect ^{13}C at very low enrichments is important and unique to the isotope ratio mass spectrometer acquired. The Previs laboratory is interested in using D_2O to monitor amino acid and protein metabolism in nutrition and in liver disease. To perform studies in humans, very low D_2O enrichments must be used, making the detection in proteins and amino acids difficult for the standard analytical procedures, but the sensitivity and precision of the GC/TC/IRMS makes these studies possible at very low levels of enrichment. An animal (mice, rats and/or humans) are provided a bolus of D_2O which equilibrates rapidly with all of body water to 0.5-2.0% deuterium. There is a slower incorporation into amino acids that is dependent largely on liver function, and then a slower incorporation into newly synthesized proteins. All of these processes can be monitored precisely using the GC/TC/IRMS system. The Anderson laboratory is interested in measuring isotope effects on enzyme reactions and over the past two years has developed the theory and protocols to use minimally labeled substrates to determine these isotope effects. The GC/TC/IRMS system has functioned quite well and its use in measuring these isotope effects should expand as the necessary proof of principle studies have been completed.

When acquired, the Thermo Finnigan LTQ linear ion trap mass spectrometer instrument was the "top-of-the-line" proteomics system. It was the initial instrument acquired for the Case Mass Spectrometry and Proteomics Center. The Center has become a major contributor to the biomedical research effort at Case. In the summer of 2005, Dr. Mark Chance was hired as director and assumed oversight of the instrument. Prior to that time, the major users of this shared instrument were the Anderson, Hoppel and Chen research laboratories. The Anderson laboratory used this instrument to characterize oxidative modification of proteins result from oxidative species generated during several important disease processes, including diabetes, heart disease and neurodegenerative diseases. The Chen laboratory has used the mass spectrometer to characterize proteins that interact with prion proteins, such as those present in mad cow disease. The Hopple laboratory has used the instrument to examine mitochondrial proteomics and to characterize post-translational modifications of mitochondrial proteins in vivo.

Grants awarded that have included preliminary studies generated by these two instruments:
Metabolomic and Isotopomer Analysis of Xenobiotic Stress NIH 1R01ES013925-01 2006 $1,500,000
Regulation of Liver CPT-I during Diabetic Ketosis NIH 1R01DK066107-01 2005
Biomarkers for exposure to *Stachybotrys* NIH R21 ES014653-01 2006 $415,000
Center for Proteomics Cleveland Foundation 2005 $1,500,000
(and numerous others still pending)

Graduate students who completed thesis/dissertations under this award. 1 Ph.D. (so far).

Publications resulting from this award:
1) Nucleophilic Activation in Enzyme Catalysis. *Chem. Rev.* 2006.
2) 2) 3-Nitropropionic acid is a suicide inhibitor of mitochondrial respiration that, upon oxidation by complex II, forms a covalent adduct with a catalytic-base arginine in the active site of the enzyme. *J Biol Chem* 2006.
3) 3) A strategy for distinguishing modified peptides based on post-digestion 18O labeling and mass spectrometry. *Rapid Communications in Mass Spectrometry* 2005.
4) 4) Phosphorylation of rat liver mitochondrial carnitine palmitoyltransferase-I: effect on the kinetic properties of the enzyme. *J Biol Chem* 2004.

Collaborations established: NEO Proteomics Incorporated 2/5/2006 is a biotech startup based on concepts developed in the Case Proteomics Center.

Details of instruments acquired. The Thermo Finnigan Delta XP(Plus) continuous flow isotope ratio mass spectrometer with gas-chromatography/thermal conversion sample introduction is designed to determine the isotopic composition of molecules separated by GC. The instrument included a high performance GC, a quadrupole mass spectrometer to check peak identification and purity, a thermal conversion furnace and the Delta XP(plus) isotope ratio mass spectrometer. This mass spectrometer is capable of precisely determining isotope ratios of ^{13}C, ^{15}N, ^{18}O and ^{2}H. The Thermo Finnigan LTQ linear ion trap mass spectrometer is highly sensitive and is the workhorse instrument in the Case Proteomics Center.

Youngstown State University, YSU (Jeffrey A. Smiley, co-PI)

The HIF grant was used to purchase a VG Instruments IsoPrime isotope ratio mass spectrometer (IRMS). Using this instrument, the procedures for CO_2 collection and isotope analysis have been refined, and CO_2 samples can now be analyzed with very good precision. CO_2 samples have been generated from decarboxylation reactions (both enzymatic and non-enzymatic) and a few isotope effects have already been measured. Publishable results are expected this year, as two MS students will be finishing their degrees.

Leveraging results. ACS PRF grant from 2003: "Determination of Carbon Isotope Effects for Three Mechanistically Diverse Enzymatic Decarboxylations", $50K for three years.

Graduate students. 3 MS students will have contributions to their degrees from this instrumentation by the end of 2006 (one has already finished).

The Ohio State University, OSU (Michael A. Freitas and Kari-Green Church, co-PIs)

As a result of the investment by the Ohio Board of Regents for the 2001 Hayes Investment Fund, Ohio State University Mass Spectrometry and Proteomics Facility (MS&P) purchased a Micromass LCT (electrospray Time-of-Flight Mass spectrometer for the characterization of small organic molecules, polymer samples, environmental pollutants, and for the development of proteomics analysis. The CCIC MS&P is a service facility providing researchers a resource for mass spectrometry analyses. The mandate of the CCIC Mass Spectrometry and Proteomics Facility is to provide state-of-the-art instrumentation to The Ohio State University and the surrounding research community. The nature of our laboratory allows for both routine analyses for faculty who can not afford nor desire the purchase of their own mass spectrometry instrumentation and yet our Facility also provides researchers the opportunity and access to very sophisticated experiments by working closely in a true collaborative effort between faculty, students and staff. The Mass Spectrometry and Proteomics Facility at CCIC clearly is an interdisciplinary unit. The majority of the users are performing research supported by federal grants.

Leveraging results. Since 2002, CCIC MS&P has supported 215 PI's with a funding total of $365,208,529 between 2002 and 2006. The PI's using the MS&P have benefited directly from the Hayes Award by offering mass spectrometry support to their research. Projects requiring accurate mass analysis, electrospray and LC-MS would not have been possible without the acquisition of the mass spectrometer funded by the Hayes Award.

Graduate students. Since the MS&P is an open access lab, it is unknown exactly how many students have completed their theses/dissertations under this award. Estimate: 2 M.S. and 15 PhD students.

Publications / presentations.

1 Zhang, L.; Freitas, M.A.; Wickham, J.; Parthun, M.R.; Klisovic, M.I.; Marcussi, G.; Byrd, J.C. "Differential Expression of Histone Post-Translational Modifications in Acute Myeloid and Chronic Lymphocytic Leukemia Determined by High-Pressure Liquid Chromatography and Mass Spectrometry", *J. Am. Soc. Mass Spectrom.* **2004**, 15, 77-87.

2 Zhang, L.; Freitas, M.A. "Comparison of Peptide Mass Mapping and Electron Capture Dissociation as Assays for Histone Posttranslational Modifications" *Int. J. Mass Spectrom.* **2004**, 234, 213-225.

3 Ye, J.; Ai, X.; Eugeni, E.E.; Zhang, L.; Carpenter, L.R. ; Jelinek, M.A. ; Freitas, M.A.; Parthun, M.R. "Histone H4 lysine 91 acetylation a core domain modification associated with chromatin assembly" *Mol. Cell.* **2005**, 18, 123-130.

4 Zhang, L.; Freitas, M.A.; Dragon, Y.P.; Kleinholz, N.M.; **Green-Church, K.B.** "Mapping Global Modifications of Core Histones by Mass Spectrometry" *Proc. 50th ASMS Conf. On Mass Spectrom. & Allied Topics,* Orlando, Fl, June, **2002**.

5 Kleinholz, N.M.; **Green-Church, K.B.**; Demers, M.D.; Coleman, R.S. "Identification of DNA Reaction Products with Anti-Tumor Agents Using LC/MS and MS/MS", *Proc. 50th ASMS Conf. On Mass Spectrom. & Allied Topics,* Orlando, Fl, June, **2002**.

6 Freitas, M.A.; Zhang, L.; Kleinholz, N.M.; **Green-Church, K.B**.; Parthun, M.R.; Jacobs, S.; Dragan, Y.P. "Differential Expression of Histone Post-translational Modifications in Tumors Determined by High-pressure Liquid Chromatography and Mass Spectrometry", *Proc. 51st ASMS Conf. On Mass Spectrom. & Allied Topics,* Montreal, Canada, June, **2003**.

7 Zhang, L.; Su, X.; Davis, M.E.; Lucas, D.M.; Byrd, J.C.; Freitas, M.A.; **Green-Church, K.B**. "Quantitative Determination of Histone H4 Post Translational Modification Via USUtable UIUsotopic ULUabeling with UAUmino Acid in UCUell Culture (SILAC)" *The Sixth Annual Comprehensive Cancer Center Scientific Meeting: Control and Prevention of Lung Cancer: Mechanisms and Intervention Strategies,* Columbus, OH, January, **2004**.

8 Nichols, K.K., Ziegler, C., **Green-Church, K.B.**, Nichols, J.J. "Analysis of Meibomian Gland Secretions Using Time-of-Flight Mass Spectrometry", *4th International Conference on the Lacrimal Gland, Tear Film, Ocular Surface and Dry Eye Syndromes: Basic Science and Clinical Relevance*, Fajardo, Puerto Rico, November **2004**.

9 **Green-Church, K.B.**: Ziegler, C.; Nichols, J.J.; Nichols, K.K. "Identification and Analysis of Polar and Non-Polar Lipids from Meibomian Gland Secretions Using Electrospray Ionization Mass Spectrometry", *2005 Association for Research in Vision and Ophthalmology,* Ft. Lauderdale, May **2005**.

10 Nichols, K.K.; Young, L.; **Green-Church, K.B.;** Zeigler, C.; Nichols, J.J. "Assessment of Meibomian Lipids in Postmenopausal Women Using Electrospray Ionization Mass Spectrometry", *2005 Association for Research in Vision and Ophthalmology,* Ft. Lauderdale, May **2005**.

11 Jones, R.B.; Zeigler, C.; Pitsch, R. L.; Nichols, J.J.; Nichols, K.K.; **Green-Church, K.B.** "Analysis and Identification of Meibomian Gland Secretions Using Mass Spectrometry", *Proc. 53rd ASMS Conf. On Mass Spectrom. & Allied Topics,* San Antonio, TX, June **2005**.

12 Ziegler, C.D., **Green-Church, K.B.**, Nichols K.K. "Analysis of Lipid Deposition on Silicone Hydrogel Contact Lenses Using Electrospray Time-of-Flight Mass Spectrometry," *2005 American Academy of Optometry*, San Diego, December **2005**.

Collaborations. In addition to the 215 Ohio State Faculty researchers using the MS&P, we also have collaborations with the following institutions.

Non-OSU Academic Users (28%). Battelle Memorial Institute; Case Western Reserve University; Central Michigan University; Children's Research Institute; Cornell University; Denison University; Kent State University; Miami University; Louisiana State University; Montana State University; NASA Glenn Research Institute; Northern Kentucky University; Ohio University; Optimum Therapeutics, LLC; Portland State University; Queens College of CUNY; Rose-Hulman Institute of Technology; State University of New York at Upstate Medical University; Syracuse University; University of Akron; University of Central Florida; University of Dayton; University of Louisiana at Monroe; University of Louisville; University of Mississippi; University of Missouri at Columbia; University of Notre Dame; University of Rochester; University of Texas Medical Branch; University of Toledo; Wright State University; Youngstown State University.

Industrial Users (0.5%). Abbott Laboratories; Chemsys, Inc.; Lebensmittel Consulting; Middle East Technical University, Ankara, Turkey; Sun Chemical Security Corporation.

University of Cincinnati, UC (Patrick A. Limbach, co-PI)

UC purchased grant a Waters/Micromass GCT (Gas Chromatography Time-of-Flight Mass Spectrometer) with the OBR.

Publications.

1 Interpretation of alkyl diselenide and selenosulfenate mass spectra. Meija, Juris; Beck, Thomas L.; Caruso, Joseph A. *Journal of The American Society for Mass Spectrometry* (2004), 15 (9), 1325-1332.
2 Deconvolution of isobaric interferences in mass spectra. Meija, Juris; Caruso, Joseph. *Journal of The American Society for Mass Spectrometry* (2004), 15 (5), 654-658.
3 Photoenolization of 2-(2-methyl benzoyl) benzoic acid, methyl ester: Effect of E photoenol lifetime on the photochemistry. Armands Konosonoks, P. John Wright, Meng-Lin Tsao, Jana Pika, Kevin Novak, Sarah M. Mandel, Jeanette A. Krause Bauer, Cornelia Bohne, and Anna D. Gudmundsdottir. *J. Org. Chem.* Vol. 70, No. 7, 2005, 2763-2770.
4 Photoenolization as a means to release alcohols. Jana Pika, Armands Konosonoks, Rachel M. Robinson, Pradeep N. D. Singh, and Anna Gudmundsdottir. *J. Org. Chem.* Vol. 68, No. 5, 2003, 1964-1972.
5 Intermolecular triplet-sensitized photolysis of alky azides trapping of triplet alkyl nitrenes. Rodney F. Klima, Anna D. Gudmundsdottir. *Journal of Photochemistry and Photobiology A. Chemistry* 162 (2004) 239-247.

Graduate students. The new equipment was used in the thesis: "Evidence for Metabolism of Scavenged Sterols by the P. *carinii* SAM:SMT Enzyme; Transmethylation of Desmosterol". A thesis submitted to the Division of Research and Advanced Studies of the University of Cincinnati in the Department of Biological Sciences McMicken College of Arts and Sciences (2004) by DeAlma Nicole Worsham, Committee chair Dr. Edna S. Kaneshiro.

Collaborations.

Major Users from the Departments of Chemistry and Biological Sciences. Dr. Edna Kaneshiro, Dr. Joseph Caruso, Dr. Anna Gudmundsdotti, Dr. William Connick
Major users from local industry. The GCT has supported local industry. Recent examples include Hexion Speciality Chemicals for analyses involving competitor product identification (3/10/05, 3/18/05, 4/5/05, 5/10/05, 10/25/05, and 10/26/05), impurities in production (2/3/06), and tank samples identified for disposal (5/18/06); and Cornerstone Research Group, Inc. for identification of an unknown material and confirmation of a proposed material (12/14/05). Currently a quote is being prepared for GE aircraft engines involving extensive GC/MS analyses.
Total users since acquisition. 2001: Chemistry Dept. = 38, Other Dept. = 5, Other Universities = 9 (U of Akron), Industry = 4. **2002**: Chemistry Dept. = 13, Other Dept. = 2, Industry = 2, Other = 1 (NIOSH). **2003**: Chemistry Dept. = 23, Other Dept. = 11, Other Universities = 1 (U of Pittsburg), Industry = 2, Other = 1 (Children's Hospital). **2004**: Chemistry Dept. = 23, Other Dept. = 1, Medical School = 1, Industry = 5. **2005**: Chemistry Dept. = 6, Other Dept. = 3, Industry = 8 (Industry thus far in 2006 is at 8).

Ohio University, OU (Bruce R. McCord and Peter de B. Harrington, co-PIs)

A Waters MALDI-ToF (matrix-assisted laser desorption ionization time-of-fight) *LR* mass spectrometer was purchased with the HIF grant. This instrument has seen increased use by OU's biochemistry faculty.

Graduate students. The MALDI mass spectrometer has been employed in the dissertation of Mariela L. Ochoa, entitled "Forensic and Proteomic Applications Of Thermal Desorption Ion Mobility Spectrometry and Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry" (Ph.D. 2005).

Publications.

1) P.B. Harrington*, N.E. Vieira, P. Chen, J. Espinoza, J.K. Nien, R. Romero, and A.L. Yergey, "Proteomic Analysis of Amniotic Fluids Using Analysis of Variance-Principal Component Analysis and Fuzzy Rule-Building Expert Systems Applied to Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry" *Chemometrics and Intelligent Laboratory Systems,* **82** (2006) 283-293.
2) C. Laurent*, D.F. Levinson, S.A. Schwartz, P.B. Harrington, S.P. Markey, R.M. Caprioli, and P. Levitt, Direct Profiling of the Cerebellum by MALDI MS: A Methodological Study in Postnatal and Adult Mouse. *Journal of Neuroscience Research*, **81:5** (2005) 613-621.
3) M.L. Ochoa and P.B. Harrington*, Immunomagnetic Isolation of Enterohemorrhagic *Escherichia coli* O157:H7 from Ground Beef and Identification by Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry and Database Searches. *Analytical Chemistry,* **77** (2005) 5258-5267.
4) P.B. Harrington*, N.E. Vieira, J. Espinoza, J.K. Nien, R. Romero, and A.L. Yergey, Analysis of Variance-Principal Component Analysis: A Soft Tool for Proteomic Discovery. *Analytica Chimica Acta*, **544** (2005) 118-127.
5) P.B. Harrington*, C. Laurent, D.F. Levinson, R.M. Caprioli, P. Levitt, and S.P. Markey, "Bootstrap Classification and Feature Selection from Age-Staged Mouse

Cerebellum Tissues of Matrix Assisted Laser Desorption/Ionization Mass Spectra using a Fuzzy Rule-Building Expert System" in preparation, *Analytical Chemistry*.

6) Ping Chen and P.B. Harrington*, "Investigation of Reproducibility of Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry of Escherichia Coli Using Analysis of Variance-Principal Component Analysis", in preparation, *Analytical Chemistry.*

Proposals submitted.

Source: National Institutes of Health, Project Title: Proteomics to Diagnose Diabetes and Pre-diabetes, Investigators: John Kopchick, Peter Harrington, Lonnie Welch, Amount Requested: $3,238,011. Submitted 2005 (denied).

Source: National Institutes of Health, Project Title: Proteomics to Diagnose Diabetes and Pre-diabetes, Investigators: John Kopchick, Douglas Kohn, Edward List, Shigeru Okada, Peter Harrington, Amount Requested: $2,124,337, Submitted 2004 (denied).

Kent State University, KSU (Kenneth K. Laali, co-PI)

The Applied Biosystems Voyager MALDI-TOF mass spectrometer could be purchased with the funds available to KSU. The maintenance of this instrument has been rather problematic, mainly due to the robotics arm that holds the sample and inserts it into the instrument.

Collaborations.

Professor Kenneth Laali, postdoctoral fellow Cedric Brule, and graduate student Melati Khaiuddean have examined host-guest complexes with this instrument. The results of these studies were included in one article currently under review (Organic and Biomolecular Chemistry).

Dr. Gangoda (analytical instrumentation facility manager) has provided service to the following faculty:
-Dr. Diane Stroup, biochemistry assistant professor (protein analyses);
-Dr. Scott Bunge, inorganic assistant professor (mass spectral data of polymers).

The instrument was also utilized by Dr. Gangoda for Analytical Instrumentation Facility (AIF) to provide molecular weight and structural information of polymers for following industrial collaborators:
-Frank Danko, Degussa Admixtures, Inc., Cleveland, Ohio;
-Larry Landis, IDI Industrial Dielectrics, Indiana.

Summary of mass spectrometry systems purchased with HIF grant

Institution	Equipment
The University of Akron, UA	1. Waters AutoSpec-Q sector/quadrupole tandem mass spectrometer 2. Waters Ultima Q/ToF MALDI tandem mass spectrometer
Cleveland State University, CSU	3. HPLC-ESI ion trap mass spectrometer
Cleveland Clinic Foundation, CCF	4. Finnigan LTQ ion trap with HPLC and Mascot database search
Case Western Reserve University, CWRU	5. Thermo Finnigan Delta(Plus) continuous flow isotope ratio mass spectrometer with GC/thermal conversion sample introduction 6. Thermo Finnigan LTQ linear ion trap mass spectrometer
Youngstown State University, YSU	7. VG Instruments IsoPrime isotope ratio mass spectrometer
The Ohio State University, OSU	8. Micromass LCT (electrospray/ToF) mass spectrometer
University of Cincinnati, UC	9. Waters GCT (GC/ToF) mass spectrometer
Ohio University, OU	10. Waters MALDI/ToF *LR* mass spectrometer
Kent State University, KSU	11. Applied Biosystems Voyager MALDI/ToF mass spectrometer

OHIO CONSORTIUM FOR KINETIC SPECTROMETRY

FINAL RESEARCH PROGRESS REPORT

Partners: Bowling Green State University, Case Western Reserve University, Medical College of Ohio, Ohio State University, University of Akron, University of Cincinnati, University of Toledo, Wright Patterson AFB

1. Achievement of Goals and Objectives

The Ohio Laboratory for Kinetic Spectrometry continues to flourish within the Department of Chemistry and the Center for Photochemical Sciences at Bowling Green State University. It was established with a grant of $1.3 million from the Hayes Investment Fund for equipment purchase and matching funds from BGSU for scientific staff. The necessary space to house the new instruments was redeployed from the Rodgers' suite of laboratories in the Physical Sciences building on the BGSU main campus. The Laboratory is now the premiere laboratory of its type in the nation and is designed and operated for the free and open use of those in the Ohio scientific community having needs for access to the instrumentation and services it provides. The community of users and collaborators are drawn from Ohio's Universities and Colleges and from a number of Ohio-based industries. The Laboratory has become an integral part of the present and future basic/applied research programs of many of the scientific community in the state of Ohio, and in doing so it significantly enhances research, scholarship, and education in the state. At its most basic level, the Laboratory provides the scientific community in the state with a readily accessible locale for acquiring new information at the cutting edge of physical and photo science. Important additional benefits accrue. For example, it serves to stimulate collaborative ventures among individual members of the user group and new research partnerships are thus spawned between scientists from different universities, and between university scientists and those in an industrial setting. Furthermore, through on-site encounters, members of the user group come to the realization that alternative instrumental approaches to a particular problem could bring unanticipated fruit. Not least in the anticipated outcomes of the Laboratory is the fact that it has become a training ground for graduate students of all disciplines who make up the next generation of leaders in science and technology.

The array of instrumentation in the Laboratory is designed to study of the earliest of events, that is, those occurring in the time window 10^{-3} to 10^{-14} s, wherein a rich harvest of new knowledge is being revealed. Instruments that can measure events on such time scales are expensive, not commercially available and must be constructed and operated by persons trained in their intricacies. As a result, many scientists whose research programs would clearly benefit from dynamic information on such time scales cannot achieve their full research potential. The Laboratory provides a state-of-the-art experimental facility manned by experts that is open and accessible to the Ohio scientific community.

In addition to its independent existence, the Laboratory works closely with the personnel of the Wright Photoscience Laboratory that was recently established on the BGSU campus. Employees of the Wright unit carry out research activities at OLKS and are involved in collaborative ventures with OLKS personnel.
Areas of science that are addressable at the Laboratory include photosciences, opto-electronics, materials, nanoscale systems, tumor therapy, and alternative energy research. The common thread connecting the user community is an interest in the fundamental knowledge that can be gained about many of today's pressing scientific and technological questions through the employment of instruments that generate information about the dynamics of transient chemical and biological entities.

2. Leveraging results

The existence of the Ohio Laboratory for Kinetic Spectrometry on the BGSU campus has significantly impacted the leveraging of Federal and State funds for R and D activities. These are tabulated below, by year.

FY 2003 (July 1, 2002 - June 30, 2003)

Anzenbacher Pavel	A Study of Vectorial Energy Transfer in Conjugated Oligomers--Implications for Multianalyte Sensing	American Chemical Society Research Grant, Type G	$20,000
Neckers Douglas	Photoinitiated Polymerization with Visible Lasers	National Science Foundation	$120,000
Rodgers Michael	Photothermal Sensitization of Biological Systems: Mechanisms of Action	National Institutes of Health	$252,733
Castellano Felix	Molecular-Wire Behavior in Photo-Initiated Energy Transfer	American Chemical Society	$12,500
Castellano Felix	Towards Molecular Optical Data Storage Using Luminescent Inorganic Compounds with Photochromic Quenchers	National Science Foundation	$91,289
Leontis Neocles Deanne Snavely	Undergraduate Research in the Photochemical and Biomolecular Sciences Research Experiences for Undergraduates (REU)	National Science Foundation	$60,000
Neckers Douglas Rodgers Michael	Northwest Ohio Partnership on Alternative Energy Systems	University of Toledo (National Science Foundation Collaboration) Partnerships for Innovation	$25,000
Ogawa Michael	Electron-Transfer Studies of Coiled-Coil	National Institutes of Health	$132,675

	Metalloproteins		
Popik Vladimir	Development of Two-Photon Photoactivatable Enediyne Antibiotics	Ohio Cancer Research Associates	$25,000

FY 2004 (July 1, 2003 - June 30, 2004)

Anzenbacher Pavel	A Study of Vectorial Energy Transfer in Conjugated Oligomers--Implications for Multianalyte Sensing	American Chemical Society Research Grant, Type G	$15,000
Anzenbacher Pavel	High Quantum Efficiency Coordination Polymers and Networks for OLED Application Electronic Materials - Polymers	National Science Foundation	$108,352
Castellano Felix	Towards Molecular Optical Data Storage Using Luminescent Inorganic Compounds with Photochromic Quenchers	National Science Foundation	$93,688
Neckers Douglas	Energy Cure in Remote Locations	US Dept. of Defense	$450,000
Neckers Douglas	Luminescent Materials and Devices for Displays	US Dept. of Defense	$120,000
Neckers Douglas Rodgers Michael	Northwest Ohio Partnership on Alternative Energy Systems	University of Toledo (National Science Foundation Collaboration) Partnerships for Innovation	$25,000
Ogawa Michael	Metal-Peptide Nanoassemblies	American Chemical Society	$40,000
Popik Vladimir Leontis Neocles	Photoactivatable Enediyne Antibiotics	National Institutes of Health	$68,100

FY 2005 (July 1, 2004 - June 30, 2005)

Anzenbacher Pavel	High Quantum Efficiency Coordination Polymers and Networks for OLED Application Electronic Materials - Polymers	Nation al Science Foundation	$100,807
Castellano Felix	Towards Molecular Optical Data Storage Using Luminescent Inorganic Compounds with Photochromic Quenchers	National Science Foundation	$95,000
Castellano Felix	Programmable Triplet Formation and Decay in Metal-Organic Chromophores	US Department of Defense	$75,000
Neckers Douglas	Energy Cure in Remote Locations	US Dept. of Defense	$450,000
Neckers Douglas Rodgers Michael	Northwest Ohio Partnership on Alternative Energy Systems	University of Toledo (National Science Foundation Collaboration) Partnerships for	$15,000

		Innovation	
Ogawa Michael	Metal-Peptide Nanoassemblies	American Chemical Society	$40,000
Popik Vladimir	Towards Space- and Time-Resolved Generation of p-Benzyne Diradical: Development of Photoswitchable Analogs of Natural Enediyne Antibiotics	National Science Foundation	$126,170

FY 2006 (July 1, 2005 - December 31, 2005)

Anzenbacher Pavel	High Quantum Efficiency Coordination Polymers and Networks for OLED Application Electronic Materials - Polymers	Nation al Science Foundation	$88,174
Castellano Felix	Programmable Triplet Formation and Decay in Metal-Organic Chromophores	US Department of Defense	$95,801
Ogawa Michael	Metal-Peptide Nanoassemblies	American Chemical Society	$125,000
Popik Vladimir	Towards Space- and Time-Resolved Generation of p-Benzyne Diradical: Development of Photoswitchable Analogs of Natural Enediyne Antibiotics	National Science Foundation	$19,500

3. Graduate students who completed thesis/dissertations under this award.

From August 2002 – to March 2006:
In this time period 13 M.S. graduates and 33 Ph.D. graduates whose research was related to the studies conducted at OLKS have been awarded their degrees. About 80% of these students were themselves users of the OLKS instrumentation and have thus been trained in the intricacies of time-resolved spectrometry. The other 20% were peripherally involved in that they were doing synthetic/preparation work in support of the majority. There are currently some 3 MS and 15 PhD students who are actively engaged on OLKS-related research projects. These are expected to graduate in the next 2 years.

4. **Publications resulting from this award**

Since the laboratory commenced operation some 60+ papers have been published by the user community in peer-reviewed journals. This process continues unabated. Listed below is the totality of peer-reviewed papers and abstracts for conference proceedings.

1. Urdabayev, N. K.; Poloukhtine, A.; Popik, V. V. "Two-photon induced photodecarbonylation reaction of cyclopropenones" *Chemical Communications (Cambridge, United Kingdom)* **2006**, 454-456.
2. Shikhova, E.; Kinayyigit, S.; Danilov, E. O.; Pomestchenko, I. E.; Castellano, F. N. "Excited state properties of platinum(II) terpyridyl acetylides" *Abstracts of Papers, 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006* **2006**, INOR-170.
3. Rachford, A. A.; Petersen, J. L.; Rack, J. J. "Efficient Energy Conversion in

Photochromic Ruthenium DMSO Complexes" *Inorganic Chemistry* **2006**, ACS ASAP.
4. Polyansky, D. E.; Danilov, E. O.; Voskresensky, S. V.; Rodgers, M. A. J.; Neckers, D. C. "Photodecomposition of Peroxides Containing a 1,4-Bis(phenylethynyl)benzene Chromophore" *Journal of Physical Chemistry A* **2006**, *110*, 4969-4978.
5. Polyansky, D. E.; Danilov, E. O.; Castellano, F. N. "Observation of Triplet Intraligand Excited States through Nanosecond Step-Scan Fourier Transform Infrared Spectroscopy" *Inorganic Chemistry* **2006**, *45*, 2370-2372.
6. Poloukhtine, A.; Popik, V. V. "Mechanism of the Cyclopropenone Decarbonylation Reaction. A Density Functional Theory and Transient Spectroscopy Study" *Journal of Physical Chemistry A* **2006**, *110*, 1749-1757.
7. Kulikov, A.; Popik, V. "Design of a new photoremovable protecting (caging) group" *Abstracts of Papers, 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006* **2006**, ORGN-127.
8. Hua, F.; Kinayyigit, S.; Cable, J. R.; Castellano, F. N. "Green photoluminescence from platinum(II) complexes bearing silylacetylide ligands" *Abstracts of Papers, 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006* **2006**, INOR-171.
9. Hua, F.; Kinayyigit, S.; Castellano, F. N. "Platinum(II) diimine bidentate diacetylides" *Abstracts of Papers, 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006* **2006**, INOR-173.
10. Hua, F.; Kinayyigit, S.; Cable, J. R.; Castellano, F. N. "Platinum(II) Diimine Diacetylides: Metallacyclization Enhances Photophysical Properties" *Inorganic Chemistry* **2006**, *45*, 4304-4306.
11. Hong, J.; Kharenko, O. A.; Ogawa, M. Y. "A miniature Cu(I) metalloprotein undergoes photoinduced electron-transfer in the inverted Marcus regime" *Abstracts of Papers, 231st ACS National Meeting, Atlanta, GA, United States, March 26-30, 2006* **2006**, INOR-137.
12. Castellano, F. N.; Pomestchenko, I. E.; Shikhova, E.; Hua, F.; Muro, M. L.; Rajapakse, N. "Photophysics in bipyridyl and terpyridyl platinum(II) acetylides" *Coordination Chemistry Reviews* **2006**, *250*, 1819-1828.
13. Anula, H. M.; Myshkin, E.; Guliaev, A.; Luman, C.; Danilov, E. O.; Castellano, F. N.; Bullerjahn, G. S.; Rodgers, M. A. J. "Photo Processes on Self-Associated Cationic Porphyrins and Plastocyanin Complexes 1. Ligation of Plastocyanin Tyrosine 83 onto Metalloporphyrins and Electron-Transfer Fluorescence Quenching" *Journal of Physical Chemistry A* **2006**, *110*, 2545-2559.
14. Anula, H. M.; Berlin, J. C.; Wu, H.; Li, Y.-S.; Peng, X.; Kenney, M. E.; Rodgers, M. A. J. "Synthesis and Photophysical Properties of Silicon Phthalocyanines with Axial Siloxy Ligands Bearing Alkylamine Termini" *Journal of Physical Chemistry A* **2006**, *110*, 5215-5223.
15. Velate, S.; Danilov, E. O.; Rodgers, M. A. J. "Ultrafast Dynamics of the Azobenzene-Coumarin Complex: Investigation of Cooling Dynamics Measured by an Integrated Molecular Thermometer" *Journal of Physical Chemistry A* **2005**, *109*, 8969-8975.
16. Urdabayev, N. K.; Danilov, E. O.; Popik, V. V. "Development of photoreactive organic molecules with large two-photon absorption cross sections" *Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005* **2005**, ORGN-580.
17. Sutherland, R. L.; Brant, M. C.; Heinrichs, J.; Rogers, J. E.; Slagle, J. E.; McLean, D. G.; Fleitz, P. A. "Excited-state characterization and effective three-photon

absorption model of two-photon-induced excited-state absorption in organic push-pull charge-transfer chromophores" *Journal of the Optical Society of America B: Optical Physics* **2005**, *22*, 1939-1948.
18. Shah, B. K.; Neckers, D. C. "Polymerization initiation and transient spectrometric studies of water-soluble and -insoluble tert-butyl aroylperbenzoates" *Journal of Photochemistry and Photobiology, A: Chemistry* **2005**, *170*, 195-201.
19. Rosa, A.; Ricciardi, G.; Baerends, E. J.; Zimin, M.; Rodgers, M. A. J.; Matsumoto, S.; Ono, N. "Structural, Optical, and Photophysical Properties of Nickel(II) Alkylthioporphyrins: Insights from Experimental and DFT/TDDFT Studies" *Inorganic Chemistry* **2005**, *44*, 6609-6622.
20. Pomestchenko, I. E.; Polyansky, D. E.; Castellano, F. N. "Influence of a Gold(I)-Acetylide Subunit on the Photophysics of Re(Phen)(CO)3Cl" *Inorganic Chemistry* **2005**, *44*, 3412-3421.
21. Polyansky, D. E.; Danilov, E. O.; Voskresensky, S. V.; Rodgers, M. A. J.; Neckers, D. C. "Delocalization of Free Electron Density through Phenylene-Ethynylene: Structural Changes Studied by Time-Resolved Infrared Spectroscopy" *Journal of the American Chemical Society* **2005**, *127*, 13452-13453.
22. Polyansky, D. E.; Neckers, D. C. "Photodecomposition of Organic Peroxides Containing Coumarin Chromophore: Spectroscopic Studies" *Journal of Physical Chemistry A* **2005**, *109*, 2793-2800.
23. Poloukhtine, A.; Popik, V. V. "Application of Photochemical Decarbonylation of Cyclopropenones for the in Situ Generation of Reactive Enediynes. Construction of a Cyclopropenone-Containing Enediyne Precursor by Using a Cyclopropenone Acetal Building Block" *Journal of Organic Chemistry* **2005**, *70*, 1297-1305.
24. Poloukhtine, A.; Popik, V. V. "Photoswitchable enediynes: use of cyclopropenone as photocleavable masking group for the enediyne triple bond" *Chemical Communications (Cambridge, United Kingdom)* **2005**, 617-619.
25. Okhrimenko, A. N.; Gusev, A. V.; Rodgers, M. A. J. "Excited State Relaxation Dynamics of the Zinc(II) Tetraphenylporphine Cation Radical" *Journal of Physical Chemistry A* **2005**, *109*, 7653-7656.
26. Neckers, D. C.; Wolff, T.; Jenks, W. S.; Editors *Advances in Photochemistry, Volume 28*, 2005.
27. Moiseev, A. G.; Danilov, E. O.; Neckers, D. C. "Photochemistry of 3,5-dimethyl-3,5-diphenyl-3,5-dihydro-4H-pyrazol-4-one" *Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005* **2005**, ORGN-514.
28. McLean, D. G.; Sutherland, R. L.; Rogers, J. E.; Slagle, J. E.; Brant, M. C.; Fleitz, P. A. "Interpretation of two photon absorption driven nonlinear absorption" *Proceedings of SPIE-The International Society for Optical Engineering* **2005**, *5934*, 593401/593401-593401/593415.
29. Hua, F.; Kinayyigit, S.; Cable, J. R.; Castellano, F. N. "Green Photoluminescence from Platinum(II) Complexes Bearing Silylacetylide Ligands" *Inorganic Chemistry* **2005**, *44*, 471-473.
30. Hewavitharanage, P.; Danilov, E. O.; Neckers, D. C. "Pentafluorophenyl Transfer: A New Group-Transfer Reaction in Organoborate Salts" *Journal of Organic Chemistry* **2005**, *70*, 10653-10659.
31. Gunaratne, T. C.; Gusev, A. V.; Peng, X.; Rosa, A.; Ricciardi, G.; Baerends, E. J.; Rizzoli, C.; Kenney, M. E.; Rodgers, M. A. J. "Photophysics of Octabutoxy Phthalocyaninato-Ni(II) in Toluene: Ultrafast Experiments and DFT/TDDFT Studies" *Journal of Physical Chemistry A* **2005**, *109*, 2078-2089.
32. Golovkova, T. A.; Kozlov, D. V.; Neckers, D. C. "Synthesis and Properties of Novel

Fluorescent Switches" *Journal of Organic Chemistry* **2005**, *70*, 5545-5549.
33. Danilov, E.; Polyansky, D.; Neckers, D. C. "Two photon absorption in 1,4-bis([oxycarbonyphenyl]ethynyl)benzene chromophores" *Spectrum (Bowling Green, OH, United States)* **2005**, *18*, 12-17.
34. Danilov, E. O.; Pomestchenko, I. E.; Kinayyigit, S.; Gentili, P. L.; Hissler, M.; Ziessel, R.; Castellano, F. N. "Ultrafast Energy Migration in Platinum(II) Diimine Complexes Bearing Pyrenylacetylide Chromophores" *Journal of Physical Chemistry A* **2005**, *109*, 2465-2471.
35. Castellano, F. N. "Metal-organic approaches to photoluminescence spanning the visible to the near-IR" *Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, 2005* **2005**, INOR-413.
36. Camerin, M.; Rodgers, M. A. J.; Kenney, M. E.; Jori, G. "Photothermal sensitisation: evidence for the lack of oxygen effect on the photosensitising activity" *Photochemical & Photobiological Sciences* **2005**, *4*, 251-253.
37. Camerin, M.; Rello, S.; Villanueva, A.; Ping, X.; Kenney, M. E.; Rodgers, M. A. J.; Jori, G. "Photothermal sensitisation as a novel therapeutic approach for tumours: Studies at the cellular and animal level" *European Journal of Cancer* **2005**, *41*, 1203-1212.
38. Aoudia, M.; Rodgers, M. A. J. "Spectroscopic Investigations of Metalloporphyrin-Oligopeptide Systems: Evidence for Peptide Aggregation" *Langmuir* **2005**, *21*, 10355-10361.
39. Zamyatin, A. V.; Gusev, A. V.; Rodgers, M. A. J. "Two-Pump-One-Probe Femtosecond Studies of Ni(II) Porphyrins Excited States" *Journal of the American Chemical Society* **2004**, *126*, 15934-15935.
40. Vicente, M. G. H.; Gottumukkala, V.; Wickramasinghe, A.; Anikovsky, M.; Rodgers, M. A. J. "Singlet oxygen generation and dark toxicity of a nido- and a closo-carboranylporphyrin" *Proceedings of SPIE-The International Society for Optical Engineering* **2004**, *5315*, 33-40.
41. Urdabayev, N. K.; Popik, V. V. "Wolff Rearrangement of 2-Diazo-1(2H)-Naphthalenone Induced by Nonresonant Two-Photon Absorption of NIR Radiation" *Journal of the American Chemical Society* **2004**, *126*, 4058-4059.
42. Ullrich, B.; Erlacher, A.; Danilov, E. O. "Switch performance and electronic nature of photonic laser digitizing through thin GaAs films on glass" *Semiconductor Science and Technology* **2004**, *19*, L111-L114.
43. Shah, B. K.; Neckers, D. C. "Laser Flash Photolysis of tert-Butyl Aroylperbenzoates: Kinetics of the Singlet and Triplet States and the Aroylphenyl Radicals" *Journal of the American Chemical Society* **2004**, *126*, 1830-1835.
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5. Technology transfer activities (patents, licenses, start-ups, etc.)

5.1 The Wright Photosciences Laboratory

The Wright Photosciences Laboratory (WPL) is a small business support unit run from the Center for Photochemical Sciences. A major objective of the WPL is to enable technology transfer and opportunities in the private sector. Though OLKS is not directly involved in any specific technology that has been transferred to the private sector, an OLKS collaboration involving 2 photon optical limiting with Spectra Group Ltd. has resulted in a recent SBIR proposal to the Army Office of Research. Dr. Oleg Grinevich and Dr. Alexandre' Mejiritski are the PI's on this proposal. Four other former post-doctoral and graduate students from the Center for Photochemical Sciences also work for Spectra Group. WPL has submitted multiple papers and one patent application as a result of its work.

5.2 Ultrafast Systems LLC

In late 2003 a spin-off company, Ultrafast Systems LLC (UFS), was launched. UFS manufactures and purveys time-resolved spectrometers to the global research community. Optical absorption spectrometers for femtosecond and for suprananosecond studies are part of the product catalog, as is a femtosecond fluorescence spectrometer. The managing partner of UFS is Dr. Alexey Gusev, a PhD graduate of the Rodgers' laboratory. Two other graduates from the same laboratory are employed by the company that is currently located in Sarasota, FL (see http://www.ultrafastsystems.com).

6. Collaborations established

6.1. Dr. M.Y. Ogawa

Prof. Michael Maroney UMass, Amherst
Prof. Joshua Telser Roosevelt University
Prof. Brian Gibney Columbia University
Prof. Ron Viola University of Toledo

6.2. Dr. M. A. J. Rodgers

Prof M. E. Kenney, Case Western Reserve University (enhanced long-standing interactions)
Prof. Giulio Jori, University of Padova, It (enhanced long-standing interactions)
Prof. Angela Rosa, University of Basilicata, Potenza, It

6.3 Dr. F.N. Castellano

Profs. Kirk Schanze and John Reynolds, University of Florida
Prof. Raymond Ziessel, Laboratoire de Chimie Moléculaire associé au Centre National de la Recherche Scientifique (CNRS), Ecole de Chimie, polymères, Matériaux (ECPM), 25 rue Becquerel 67087 Strasbourg Cedex, France (enhanced long standing collaboration)

6.4. Dr. D. C. Neckers

The Neckers group collaborates with Arizona State University (electrical engineering) in developing new organic materials for field effect transistors, with Georgia Institute of Technology in theoretical studies of new FET's, with the Army Office of Research (Adelphi, MD), the Office of Naval Research and Naval Research Laboratories (Washington, D.C.) in developing new marine paints, with the Department of Biological Sciences at Bowling Green State University in development of herbicidal paints for marine applications and with Spectra Group Ltd. and Plastics Technologies Inc. in the private sector. OLKS is a supporting laboratory though not specifically involved in these collaborations.

THE OHIO CELLULAR and MOLECULAR IMAGING CONSORTIUM

FINAL RESEARCH PROGRESS REPORT

Partners: Case Western Reserve University, Cleveland State University, Kent State University, NE Ohio University College of Medicine, Ohio State University, University of Akron

The following report contains description of progress during the reporting period:

1. Site construction completion, installation and acceptance testing of the 7T
2. Progress on scientific faculty recruitment
3. Scientific progress
4. Progress on educational outreach
5. Leveraging results

1. Site Construction: As of October 2005, site construction has been completed with the magnet installed and acceptance testing completed. The space, in the basement of Lerner Tower, is approximately 100 feet from the existing MRI research and clinical center. The ~$2.7 million construction/renovation of the centralized Imaging Research Center began in January 2005 with the installation of the reinforced foundation for the 7T system. The facility became operational in November 2005, which included relocation of existing infrastructure previously dispersed throughout the campus to the new centralized state-of-the-art facility. The Imaging Research Center is one of the few in the nation with the multitude of MRI, optical, and nuclear medicine imaging resources all located under one roof and led by a single organizational structure.

With the completion of site construction, the Bruker 7T High-Field, In-Vivo Magnetic Resonance Imaging and Spectroscopy System was delivered. This unit is a state-of-the-art magnetic resonance imaging and multi-nuclear MR system. This system is designed specifically to obtain in-vivo images and NMR spectra from various nuclei of animal models of various human diseases (ex. cancer, diabetes, cardiovascular disease). In-vivo imaging of these animals models (primarily mice and rats), require extremely high resolution. This is made possible by the high magnetic field strength as well as the high performance gradient sets that will provide excellent images with <100um resolution. The 7T MRI system also comes equipped with multinuclear capabilities necessary for the spectroscopic and imaging studies described below.

2. Faculty Recruitment: As described in the original proposal, in order to capitalize on the opportunity that imaging brings to Case Western Reserve University, it was important to recruit several research faculty to help jump start development of a comprehensive imaging research program. A lot of progress has been made in this area.

Dr. Jean Tkach was recruited in December 2005 and has successfully begun establishing the fMRI imaging program. Dr. Tkach is an expert in Functional MR Imaging with many years of experience. Her research expertise and interests make way for numerous interdisciplinary collaborations.

In addition, we were able to complete another successful recruitment. Dr. Yanming Wang, a radiochemist from University of Illinois at Chicago accepted an Associate Professor position in the department. Dr. Wang's vast research background includes development of neuroactive PET agents, which will directly benefit the work performed under this contract. In addition to building his own research program, Dr. Wang will provide radiochemistry service support to the department.

Dr. James Basilion joined our group in September 2005. Dr. Basilion is an expert in development and application of Molecular Imaging technologies. Specifically, he designs novel imaging tools to image individual and multiple molecular markers of disease. Some areas of his research include defining "molecular signatures" of disease, developing paradigms to image multiple markers of disease simultaneously, developing methods to image intracellular disease markers in breast cancer, and developing molecular imaging technologies that allow for intra-operative assessment of disease progression.

3. Scientific Progress: With the successful establishment of the Cellular and Molecular Imaging Consortium, many of the originally proposed as well as related research projects are underway. Summaries of only a few selected small animal imaging projects are provided below.

Early Breast Cancer Detection and Therapy Monitoring by New Methods in MR Imaging Supplement via the Activities to Promote Research Collaborations (APRC) by the NCI Division of Cancer Biology. Supplement to R01- CA90398 erbB2-induced Mammary Gland Cancer. (PI: Ruth Keri, Case)

The importance of early detection of breast cancer is well accepted. While new imaging methods like MRI have emerging roles in breast cancer diagnosis, sensitivity and specificity with available MR contrast agents need to improved In this project, we are creating a novel mechanism to prolong contrast agent circulation time in the body, to increase targeting to tumor cells while also minimizing uptake in healthy cells through a liposomal delivery approach, to watch erbB2 expression during and following therapy, and to monitor biological changes in response using MR imaging. We will then, retrospectively, relate this to the ultimate treatment response as a means of developing tools to predict anticipated efficacy of therapy at the earliest stages.

Molecular Mechanisms of Prostate Cancer Chemoprevention by Apigenin: Funded by NCI RO1 CA 108512 (PI: Sunjay Gupta, Case)

Epidemiological studies and observational data support the notion that high intake of fruits and vegetables may be associated with reduced cancer risk. These studies are consistent with the observations that Asian men who consume a low fat, high-fiber, plant-based diet rich in flavonoids have the lowest prostate cancer incidence in the World. Studies conducted in cell culture have demonstrated that apigenin, a common dietary flavonoid present in fruits and vegetables, affords protection against prostate cancer. Much of the cancer preventive effects of apigenin are attributed due to modulations in signal transduction pathways related to inflammation, proliferation, and apoptosis. Longitudinal in-vivo imaging studies are being conducted on a transgenic mouse model of prostate cancer (TRAMP) to determine the effectiveness of

apigenin to mediate these effects through down regulation of NF-kappaB by analyzing levels and activity of key kinase molecules while simultaneously using high resolution MRI and bioluminescence to monitor the tumor morphology and gene expression that are involved in the NF-kappaB signaling pathway of the murine prostate.

Photodynamic Therapy of Prostate Cancer and Metabolic Imaging: Funded by NCI R01 CA083917 (PI: Nancy Oleinick, Case)

Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of death among US males. A hallmark of human prostate cancer is resistance to apoptosis in response to treatment. Photodynamic Therapy (PDT), which uses a photosensitizer and red light, offers the advantage of potent induction of apoptosis and independence of growth rate, cell cycle, and androgen sensitivity. The proposed research is based on our recent observation that the tyrosine kinase Etk counters apoptosis in human prostate cancer cells. MicroPET and MRI imaging are being used to evaluate the regional tumor viability before, during, and post PDT therapy in implanted prostate tumor models. Specifically, diffusion tensor imaging (DTI) is being evaluated as a potential tool for early-onset therapeutic assessment.

Optical Coherence Tomography and Colon Cancer
Development of the optical coherence tomography (OCT) modality has progressed substantially. Progress has been made towards developing light sources for very-high resolution OCT on two fronts. First, in our laboratory we are developing light sources based on phononic crystal optical fibers pumped with femtosecond lasers to generate supercontinuum spectra. We have developed a light source that provides high power (for high SNR) and broad bandwidth (for high resolution) in the two optical bands of primary interest for OCT imaging simultaneously. With the recent completion of facility construction, the basic OCT system is being constructed in the OCT laboratory. The instrument will be modified and enhanced as technology improves and in response to project needs.

4. Educational Outreach: Several educational lecture/seminar series have been instituted as part of educational outreach activities originally proposed.

- A “Frontiers in Imaging” lecture series in which national and international experts in the emerging roles for imaging in a cancer center are brought to Case to participate in the weekly “Blood Club” lecture series. Some of the guest speakers that were jointly supported by the Imaging Research Core Facility were Dr. Marc Berridge, Dr. Henry Van Brocklin and Dr. Marit Nilsen Hamilton.
- The Cellular and Molecular Imaging Consortium sponsors development and conduction of specific graduate level courses in MRI, cellular, and molecular imaging, image processing, and tissue engineering designed to develop individuals to contribute to the local and world-wide imaging industry.
- Visiting Professors, Resident Scientists- Consistent with the NIH Roadmap vision for interdisciplinary interaction, we have begun and will expand our visiting professor program in imaging of animal models of cancer is initiates to encourage researchers across northeast Ohio to utilize services provided in our Imaging Research Facility. For example, we recruited Gheorghe Matteescu (Case, Chemistry), who is recognized world-wide as a father of O-17 MRI, to the

center to explore aspects of mitochondrial oxygen utilization in normal and cancerous tissue.

5. Leveraging Results: With the funds awarded under this project aiding in the establishment of the Ohio Cellular and Molecular Imaging Consortium as part of the Case Center for Imaging Research, a pronounced effect resulted in the number of collaborative research efforts in the Department of Radiology and throughout the University. Attachments 1 through 3 illustrate some of the results. A selected list of collaborations is shown in attachment 3. These collaborative efforts have resulted in new grant awards and numerous manuscripts.

One of the awards received as a result of the Hayes' investment is worth highlighting: A prestigious NIH R24 – Small Animal Imaging Resource Program (SAIRP) grant (Dr. Jeffrey Duerk – PI) was awarded in 2004. The R24 grant provides an additional ~$500K / year of funding to the consortium to support personnel, new equipment (ex. bioluminescence / OCT), imaging service in MR, contrast agent development, nuclear imaging, optical imaging, quantitative image analysis, as well as, funds to support pilot imaging studies for high impact research projects. Other support, in the form of visiting professorships and lecture series, was also made available and has been utilized. R24 – associated activities and those of the Imaging Consortium are closely integrated to ensure the greatest synergies and cohesive, coordinated goals and objectives. This is achieved by combining internal advisory committee meetings for both entities, and putting in place comprehensive and uniform operational policies.

Selected publications

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Image-guided and -monitored renal artery stenting using only MRI.
J Magn Reson Imaging. 2006 May;23(5):619-27.
2. Moriguchi H, Duerk JL.
Bunched phase encoding (BPE): a new fast data acquisition method in MRI.
Magn Reson Med. 2006 Mar;55(3):633-48.
3. Wacker FK, Vogt S, Khamene A, Jesberger JA, Nour SG, Elgort DR, Sauer F, Duerk JL, Lewin JS.
An augmented reality system for MR image-guided needle biopsy: initial results in a swine model.
Radiology. 2006 Feb;238(2):497-504.
4. Hillenbrand CM, Jesberger JA, Wong EY, Zhang S, Chang DT, Wacker FK, Lewin JS, Duerk JL.
Toward rapid high resolution in vivo intravascular MRI: evaluation of vessel wall conspicuity in a porcine model using multiple imaging protocols.
J Magn Reson Imaging. 2006 Feb;23(2):135-44.
5. Milliken EL, Zhang X, Flask C, Duerk JL, MacDonald PN, Keri RA.
EB1089, a vitamin D receptor agonist, reduces proliferation and decreases tumor growth rate in a mouse model of hormone-induced mammary cancer.
Cancer Lett. 2005 Nov 18;229(2):205-15. Epub 2005 Aug 22.
6.Wacker FK, Hillenbrand C, Elgort DR, Zhang S, Duerk JL, Lewin JS.
MR imaging-guided percutaneous angioplasty and stent placement in a swine model comparison of open- and closed-bore scanners.
Acad Radiol. 2005 Sep;12(9):1085-8.
7. Elgort DR, Duerk JL.

A review of technical advances in interventional magnetic resonance imaging.
Acad Radiol. 2005 Sep;12(9):1089-99. Review.

8. Wacker FK, Hillenbrand CM, Duerk JL, Lewin JS.
MR-guided endovascular interventions: device visualization, tracking, navigation, clinical applications, and safety aspects.
Magn Reson Imaging Clin N Am. 2005 Aug;13(3):431-9. Review.
9.Derakhshan JJ, Duerk JL.
Update to pulse sequences for interventional MR imaging.
Magn Reson Imaging Clin N Am. 2005 Aug;13(3):415-29.
10. Fei B, Duerk JL, Sodee DB, Wilson DL.
Semiautomatic nonrigid registration for the prostate and pelvic MR volumes.
Acad Radiol. 2005 Jul;12(7):815-24.
11. Zhang S, Suri JS, Salvado O, Chen Y, Wacker FK, Wilson DL, Duerk JL, Lewin JS.
Inter- and Intra-Observer Variability Assessment of in Vivo Carotid Plaque Burden Quantification Using Multi-Contrast Dark Blood MR Images.
Stud Health Technol Inform. 2005;113:384-93.
12. Moffitt MA, Dale BM, Duerk JL, Grill WM.
Functional magnetic resonance imaging of the human lumbar spinal cord.
J Magn Reson Imaging. 2005 May;21(5):527-35.
13. Shillingford JM, Murcia NS, Larson CH, Low SH, Hedgepeth R, Brown N, Flask CA, Novick AC, Goldfarb DA, Kramer-Zucker A, Walz G, Piontek KB, Germino GG, Weimbs T. The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease.
Proc Natl Acad Sci U S A. 2006 Apr 4;103(14):5466-71. Epub 2006 Mar 27.
14. Flask CA, Dale B, Lewin JS, Duerk JL.
Radial alternating TE sequence for faster fat suppression.
Magn Reson Med. 2003 Nov;50(5):1095-9.
15. Flask CA, Salem KA, Moriguchi H, Lewin JS, Wilson DL, Duerk JL.
Keyhole Dixon method for faster, perceptually equivalent fat suppression.
J Magn Reson Imaging. 2003 Jul;18(1):103-12.
16. Muzic RF Jr, Christian BT.
Evaluation of objective functions for estimation of kinetic parameters.
Med Phys. 2006 Feb;33(2):342-53.
17. Charnigo R, Sun J, Muzic R Jr.
A semi-local paradigm for wavelet denoising.
IEEE Trans Image Process. 2006 Mar;15(3):666-77.
18. Morris ED, Yoder KK, Wang C, Normandin MD, Zheng QH, Mock B, Muzic RF Jr, Froehlich JC. ntPET: a new application of PET imaging for characterizing the kinetics of endogenous neurotransmitter release.
Mol Imaging. 2005 Oct-Dec;4(4):473-89.
19. Salinas C, Muzic RF Jr, Berridge M, Ernsberger P.
PET imaging of myocardial beta-adrenergic receptors with fluorocarazolol: lack of interference by endogenous catecholamines.
J Cardiovasc Pharmacol. 2005 Aug;46(2):222-31.
20. Yu Kuang, Schomisch SJ, Chandramouli V, Lee Z.
Hexokinase and glucose-6-phosphatase activity in woodchuck model of hepatitis virus-induced hepatocellular carcinoma.
Comp Biochem Physiol C Toxicol Pharmacol. 2006 Mar 6; [Epub ahead of print]
21. Lee Z, Sodee DB, Resnick M, Maclennan GT.

Multimodal and three-dimensional imaging of prostate cancer.
Comput Med Imaging Graph. 2005 Sep;29(6):477-86.

22. Chaturvedi A, Lee Z. Related Articles, Links
Three-dimensional segmentation and skeletonization to build an airway tree data structure for small animals.
Phys Med Biol. 2005 Apr 7;50(7):1405-19. Epub 2005 Mar 16.
23. Breuer FA, Blaimer M, Mueller MF, Seiberlich N, Heidemann RM, Griswold MA, Jakob PM.
Controlled aliasing in volumetric parallel imaging (2D CAIPIRINHA).
Magn Reson Med. 2006 Mar;55(3):549-56.
24. Griswold MA, Blaimer M, Breuer F, Heidemann RM, Mueller M, Jakob PM.
Parallel magnetic resonance imaging using the GRAPPA operator formalism.
Magn Reson Med. 2005 Dec;54(6):1553-6.
25. Stadler A, Jakob PM, Griswold M, Barth M, Bankier AA. s
T1 mapping of the entire lung parenchyma: Influence of the respiratory phase in healthy individuals.
J Magn Reson Imaging. 2005 Jun;21(6):759-64.
26. Breuer FA, Kellman P, Griswold MA, Jakob PM.
Dynamic autocalibrated parallel imaging using temporal GRAPPA (TGRAPPA).
Magn Reson Med. 2005 Apr;53(4):981-5.
27. Breuer FA, Blaimer M, Heidemann RM, Mueller MF, Griswold MA, Jakob PM.
Related Articles, Links
Controlled aliasing in parallel imaging results in higher acceleration (CAIPIRINHA) for multi-slice imaging.
Magn Reson Med. 2005 Mar;53(3):684-91.
28. Haaga JR, Exner AA, Wang Y, Stowe NT, Tarcha PJ.
Combined tumor therapy by using radiofrequency ablation and 5-FU-laden polymer implants: evaluation in rats and rabbits.
Radiology. 2005 Dec;237(3):911-8. Epub 2005 Oct 19.
29. Exner AA, Krupka TM, Scherrer K, Teets JM.
Enhancement of carboplatin toxicity by Pluronic block copolymers.
J Control Release. 2005 Aug 18;106(1-2):188-97.

Leveraging Results (selected awards)

Principal Investigator	*Grant Number/ Agency*	*Grant Description*	*Date*	*Amount Awarded*
Jeffrey Duerk	CA110943-01/ NIH	NCI / Small Animal Imaging Resource Program	9/1/2004	$3,837,581
Jeffrey Duerk	EB004637 NIH	Improvements in Spiral MRI	9/1/2005	$1,735,071
Zhenghong Lee	CA-110224-01/ NIH	Novel Technologies for in vivo Imaging	9/1/2004	$100,980
Zhenghong Lee	CA-095307	Quantitative FDG/PET for Imaging…	7/1/2003	$1,122,087
Agata Exner	CA-118399-01A1/ NIH	Functional Polymer Matrixes for Site-Specific, Image Guided Drug Delivery	7/1/2006	$1,250,000
James Basilion	CA-109620-01A1/NIH	Imaging of Gene Expression in Glioblastoma	7/1/2006	$1,250,000
Baowei Fei	CA120536-01/NIH	Multimodality in vivo Molecular Imaging for Prostate PDT	4/1/2006	$206,070
Raymond Muzic	CA-101073	COMKAT: Tools for Quantitative…	4/1/2004	$587,041

Selected Interdisciplinary Collaborations

Imaging enabling technologies investigator-
Radiology

- SPECT Imaging for In Vivo Tracking of Stem Cells; PI: Lee (Radiology and BME), Gerson (Oncology); DOE $900K
- Magneto-liposomes for early tumor detection; PI: Duerk (Radiology and BME); Bellamkonda (BME), Keri (Pharmacology); NIH R01 supplement
- In vivo measurements of controlled drug release; PI: Gao (BME), Wilson (BME and Radiology), Haaga (Radiology); $300K NIH
- Bioluminescent molecular imaging of clusterin, a potential radiation biodosimeter for space travel; PI: Wilson (BME and Radiology), Rollins (BME); Boothman (Oncology). NASA,

- OCT imaging of GI cancer; PI: Sivak (Gastroenterology), Wilson (BME and Radiology), Rollins (BME); $1.5M NIH
- PET Imaging of Topotecan, an anti-cancer agent. PI: Muzic (Radiology and BME), Dowlati (Oncology). Lee (Radiology and BME). ICMIC funding.
- PET Imaging to Assess Hepatocellular Carcinoma in a Woodchuck Model. PI: Lee (Radiology and BME), Wilson (BME and Radiology), Muzic (Radiology and BME), Haaga (Radiology). NIH R01.
- A Mouse Model for Imaging Liver Cancer *In Vivo*. PI: Luo (Cancer Center), Wilson (BME and Radiology), Lee (Radiology and BME).
- Nanocrystal-Antibody Conjugates for Optical Imaging of HER2 Overexpression in Breast Cancer. PI: Burda (Chemistry), Fitzmaurice (Pathology), Gerson (Oncology). ICMIC funding.
- NIS Gene for In Vivo Imaging of Human MSC Distribution and Engraftment. PI: Koc (Oncology), Lee (Radiology and BME), Gerson (Oncology). ICMIC funding.
- Bioluminescence for In Vivo Stem Cell Tracking. Co-PIs: Gerson (Oncology), Wilson (BME and Radiology); ICMIC funding.
- Long Circulating Time Magneto-liposomes for Early Tumor Detection. Co-PIs: Duerk (Radiology and BME), Bellamkonda (BME), Keri (Pharmacology); NIH R01 supplement.
- Combined CT/PET Imaging Modality for Tumor Efficacy Studies in the Millirod Therapy. PI: Gao (BME), Lee (Radiology and BME), Wilson (BME and Radiology); ICMIC development.
- Improved Targeting and "Smart" Detection of Doxorubicin Delivery to Metastatic Breast Tumors. PI: Pagel (BME and Radiology), Gao (BME), Boothman (Oncology), Apte (BME CCF).
- Development of MRI Agents for Improved Assessment of Tumor Angiogenesis. PI: Pagel (BME and Radiology), Muzic (Radiology and BME), Remick, (Oncology), Cancer Center funding.
- Development of Multi-Modality Molecular Imaging Agents for *in* vivo Assessments of Nitric Oxide in Tumor Angiogenesis and Apoptosis. PI: Pagel (BME and Radiology), Theresa Pretlow (Pathology), Oleinick (Oncology); ICMIC funding
- Assessment of Non-Small Cell Lung Carcinoma (NSCLC) and Chemotherapy with Multimodality Imaging. PI: Lee (Radiology and BME), Gao (BME and Radiology), Boothman (Oncology), NIH.
- In Vivo Molecular Imaging of Sustained Release, Non-Viral Gene Delivery. PI: Wilson (BME and Radiology), Bellamkonda (BME), ICMIC development.
- PET imaging of photodynamic therapy; PI: Oleinick (Radiation Oncology), Muzic (Radiology and BME); ICMIC development
- Determination of OCT features in GI cancerous lesions; PI: Rollins (BME), Sivak (Gastroenterology); ICMIC development

CENTER for NONDESTRUCTIVE CHARACTERIZATION and RELIABILITY ASSURANCE of MICRO- and NANO-MATERIALS

FINAL RESEARCH PROGRESS REPORT

Partners: University of Cincinnati, Ohio State University, University of Dayton

1 General Objectives

The main objective of this collaborative effort among the University of Cincinnati (UC), The Ohio State University (OSU), and the University of Dayton (UD) was to develop innovative characterization tools to measure micro- and nano-scale physical properties without destructively sectioning the component. The ability to nondestructively characterize a structure and to provide quantitative information at the micro- and nano-scales leads to better understanding of failure mechanisms and has the potential to revolutionize failure prevention methodologies. To achieve this objective, our interdisciplinary team established a research center in the area of Nondestructive Characterization of Micro- and Nano-Materials. This center facilitates cooperation among the participating members in sponsored research projects and provides a unique infrastructure for multidisciplinary student training.

2 Scientific and Technological Progress

Developing the foundation for nondestructive life assessment and damage characterization of advanced materials has been a major focus of research and development in the NDE laboratories at UC, OSU, and UD for many years. The development of such methodologies for micro- and nano-materials is the main objective of the present project. As a result of the 2002 Hayes Investment Fund Program Award we have purchased and installed unique research instrumentation and have obtained additional very substantial additional funds to conduct sponsored research in these new facilities.

<u>University of Cincinnati</u>

The team at the University of Cincinnati, led by Professor Peter B. Nagy of the Department of Aerospace Engineering and Engineering Mechanics, focuses on nondestructive materials characterization using high-resolution Scanning Acoustic Microscopy (SAM). SAM is a novel ultrasonic imaging technique that provides exceptionally high spatial resolution. Nevertheless, the significance of acoustic microscopy does not lie in its resolution alone. There are three fundamental advantages of using high-frequency ultrasonic waves for imaging, namely, the ability of such waves to penetrate materials that are opaque to other kinds of radiation, the distinctive origin of the contrast in the microscopic mechanical properties of the specimen, and, most importantly, the ability of SAM to detect and characterize tightly closed cracks with less than 1 nm crack-opening, that are hidden from any other type of inspection. To facilitate advanced research in this area we have purchased and installed a Quantum 350™ Scanning Acoustic Microscope (SAM) from Sonix Inc. In addition, we purchased an academic license for the PZFlex Software from Weidlinger Associates Inc. This software package was purchased in part from Departmental and

College funds, which have been committed for this purpose as required cost-sharing to the OBR grant.

Initial research efforts based on the 2002 Hayes Investment Fund Award include a five-year research award received from the Department of the Air Force to study surface-treated materials and collaborative research efforts with the team members from both OSU and UD. Some of these efforts have already been successfully concluded, such as a study of microstructural features in nickel-base superalloys to facilitate the development of better residual stress measurement procedures in collaboration with Professor Rokhlin of OSU and a series of projects aimed at the development of nondestructive residual stress management methods for engine rotor life extension in collaboration with investigators at UD and Iowa State University (ISU). The uniquely high resolution of high-frequency acoustic microscopy is also exploited in a couple of current and proposed collaborative research efforts with Fermi National Accelerator Laboratory and Imperial College London, UK. Of particular interest in most of these research efforts is the complementary use of high-resolution acoustic and electromagnetic methods to characterize microstructural material features.

The Ohio State University

The team at The Ohio State University, led by Professor Stanislav I. Rokhlin of the Industrial, Welding, and Systems Engineering Department, concentrates on the development of new micro- and nano-scale nondestructive characterization capabilities tailored to measure hardness, elastic modulus, friction, adhesion, wear resistance, and other material properties. To reach as much as possible our original goals from the reduced award, we have purchased a reconditioned MTS instrumented nano-indentation system with a new scanning nano-table and controller and a dedicated finite element software for numerical modeling of nano-indentation experiments. Several research programs have been initiated with use of this equipment. The first such study was aimed at characterization of nano-mechanical properties of very thin SiCOH films on Si substrates with samples supplied by IBM. These films contain nano-size pores of different concentration to reduce the dielectric constant of SiCOH and are being considered for use as low-permittivity materials in the next generations of Ultra Large Scale Integrated circuits (ULSI). The second project is focused on characterization of cold work and microstructural features in nickel-base superalloys in collaboration with UC, which was sponsored by AFRL. In this project, a new method of scaling functions have been developed to better characterize mechanical properties from nano-indentation measurements.

The second capability that has been developed at OSU is based on a Quesant AFM with a Hysitron Interface and the necessary measuring equipment for integration with the Quesant AFM. Research initiatives started in this area include the utilization of the Quesant platform for materials nano-processing for which a project entitled "Photo-Assisted Spark-Plasma Process for Nanoscale Manufacturing," has been funded partly by the NSF Nano-scale Exploratory Research (NER) initiative and partly by the OSU NSF Center of Excellence: NSEC - The Center for Affordable Nanoengineering of Polymer Biomedical Devices.

University of Dayton

The University of Dayton team was led by Professor Norbert G. H. Meyendorf of the Materials Engineering Department. The Center for Materials Diagnostics (CMD) at the University of Dayton developed facilities to characterize stresses and strains in nano-structured materials through combining a digital correlation technique called microDAC with a variety of image techniques such as AFM, UFM, WLIM, and near field scanning optical microscopy (NSOM). A microDAC specimen loading stage and image correlation software have been purchased and tested in conjunction with various imaging techniques available at the CMD. As a preliminary test of the system's performance, the microDAC was successfully applied to study local stress fields in front of fatigue cracks of high strength Aluminum alloys and results have been obtained based on AFM/UFM and WLIM images. In the future, other image sources such as NSOM will also be used. Under the support of this grant, we upgraded the AFM/UFM at the CMD to ensure the compatibility between different image systems and the microDAC. We have also completed the acquisition/development of a NSOM based on a Veeco Explorer Scanning Probe Microscope (SPM) platform. Its collection mode operation has been tested using a grating mask. The NSOM system has been used for the characterization of silicon micro-optic devices (Wright Brothers Project) in the near-infrared spectral region. The AFM function of the Veeco Explorer SPM was also used for the characterization of carbon nanotubes (CNT). The NSOM is an important complimentary tool to strengthen our capabilities in nano-characterization and NDE at UD. It will be used as one of the image sources for the microDAC digital correlation technique.

We are presently upgrading our NSOM into a nano-Raman probe as an additional option for high-resolution stress/strain measurement. To construct such a Raman system, complementary equipments had to be purchased. An MS-257 spectrometer was purchased from Spectra-Physics. Through leveraging with other grants and supports, we were also able to purchase a Perkin Elmer SPCM single photon counting module, a Mad City Labs micro-stage and nano-positioner system and an Andor Technology iDUS cooled CCD camera to be used in the development of such a unique nano-Raman probe. Realization of Raman spectroscopy with nanoscale spatial resolution is both scientifically and technically very challenging and is considered as the "holy grail" in the Raman community. We will continue working on the development and implementation of a nano-Raman probe with the NSOM system for nanoscale stress/strain imaging. The equipments purchased under this Hayes Investment Fund Program Award have been and continue to be very helpful to develop a unique nondestructive characterization capability for the assurance of reliability of micro- and nano-materials and to secure further research support.

3 Leveraging

Externally funded research projects facilitated by the 2002 OBR Hayes Investment Fund Program Award are listed below (academic institution, project title, sponsor agency, date, amount). The total amount of leveraged funds at the participating three academic institutions to date since the purchase and installation of the HIF equipments is $7.92M.

UC, Nondestructive Evaluation of Residual Stress Relaxation in Surface Treated Engine Alloys, Department of the Air Force, 06.03 – 12.08, $231k.

UC, Nondestructive Residual Stress Management Methods for Engine Rotor Life Extension, Iowa State University/Air Force Research Laboratory, 10.03 – 05.06, $400k.

UC/UD, Cold Work and Residual Stress Effects in Nickel-Base Superalloys, Air Force Research Laboratory, 11.04 – 07.07, $152k.

UC/OSU, Microstructural Features in Nickel-Base Superalloys to Facilitate the Development of Better Residual Stress Measurement Procedures, Universal Technology Corporation/Air Force Research Laboratory, 06.04 – 11.05, $533k.

OSU, Nanoscale Solid Freeform Fabrication Process with a Photo-Assisted Spark Plasma Thermal Source, National Science Foundation, 3.05 – 2.08, $350k.

OSU/UD Wright Center for Innovation: Center for Multifunctional Polymer Nanomaterials and Devices, Ohio Department of Development, 06.05 – 06.10, $5M ($22.5M for total program).

UD, Incorporation of Advanced Sensor Technology to Enable Complex Laser Micromachining of Silicon Carbide and Silicon Nitride Devices, Missile Defense Agency, 08.04 –09.07, $88k.

UD, Development and Commercialization of Long-Wavelength Infrared Focal Plane Arrays, Ohio Department of Development, 01.05 – 12.07, $1,093k.

UD, Development of Robust Nondestructive Evaluation Methodology for Aircraft Materials, Ohio Aerospace Institute, 03.03 – 09.04, $75k.

4 Graduated Students

UC, 2 PhD students: Alberto Ruiz "Surface acoustic wave velocity measurements on surface-treated metals by laser-ultrasonic spectroscopy," 2004, Feng Yu "Nondestructive evaluation of near-surface residual stress in shot-peened nickel-base superalloys," 2005

OSU, 1 PhD student: Bahman Zoofan "Quantitative microradiography and its applications to microdamage assessment," PhD, 2004

UD, 2 PhD students and 3 MS students: Weibin Chen (Ph.D. in Electro-Optics), Mr. Deming Cao (Ph.D. in Materials Engineering), Yiyang Tsai (M.S. in Materials Engineering), Alain Tschimwangan (M.S. in Electro-Optics), Sunny Cijy (M.S. in Electro-Optics), these students have not graduated yet

5 Books/Book Chapters/ Refereed Journal Publications

N.G.H. Meyendorf, P.B. Nagy, S.I. Rokhlin (eds.) *Nondestructive Materials Characterization with Applications to Aerospace Materials* (Springer-Verlag, Berlin, 2004).

J. Sakamoto, P. Decuzzi, F. Gentile, S.I. Rokhlin, L. Wang, B. Xie, and M. Ferrari "Nanomechanics and Tissue Pathology, " in *Biological and Biomedical Nanotechnology* Vol. 1, Boston, MA (2006).

L. Wang and S.I. Rokhlin "Universal scaling functions for continuous stiffness nanoindentation with sharp indenters," International Journal of Solids and Structures 42, 3807-3832 (2005).

L. Wang, M. Ganor and S.I. Rokhlin " Inverse scaling functions in nanoindentation with sharp indenters: determination of material properties" Journal of Material Research 20, 987-1001 (2005).

L. Wang, M. Ganor, S.I. Rokhlin and A. Grill "Mechanical properties of ultras-low dielectric constant SiCOH films: nanoindentation measurements," Journal of Material Research 20, 2080-2093 (2005).

J.H. Sakamoto, B.R. Smith, B. Xie, S.I. Rokhlin, S.C. Lee and M. Ferrari "The molecular analysis of breast cancer utilizing targeted nanoparticle ultrasound contrast agents," Technology in Cancer Research and Treatment 4, 627-636 (2005).

D.F. Farson, H.W. Choi and S.I. Rokhlin "Electrical discharges between platinum nanoprobe tips and gold films at nanometer gap lengths," Nanotechnology 17, 132-139 (2006).

L. Wang and S.I. Rokhlin "On determination of materials parameters from loading and unloading responses in nanoindentation with a single sharp indenter," Journal of Material Research 21, 995-1011 (2006).

R. Wang, N. Katsube, R.R. Seghi and S.I. Rokhlin, "Statistical failure analysis of brittle coatings by spherical indentation: theory and experiment," Journal of Material Science (in press).

A. Ruiz and P.B. Nagy, "SAW dispersion measurements for ultrasonic characterization of surface-treated metals," Instrumentation, Measurement and Metrology 3, 59-85 (2003).

A. Ruiz and P.B. Nagy, "Laser-ultrasonic surface wave dispersion measurements on surface-treated metals," Ultrasonics 42, 665-669 (2004).

F. Yu and P.B. Nagy, "Simple analytical approximations for eddy current profiling of the near-surface residual stress in shot-peened metals," Journal of Applied Physics 96, 1257-1266 (2004).

F. Yu and P. B. Nagy, "Dynamic piezoresistivity calibration for eddy current nondestructive residual stress measurements," Journal of Nondestructive Evaluation 24, 143-152 (2005).

N. Meyendorf, S. Sathish, C. Druffner, J. Blackshire, J. Hoffman, Q. Zhan, R. Andrews, "High-resolution nondestructive evaluation at the Center for Materials Diagnostics," Proc. SPIE – Int. Soc. Opt. Eng., Testing, Reliability, and Application of Micro- and Nano-Material Systems, 5392, 256-265 (2004).

A. Cooney, J. Blackshire, K. Hix, L. Dosser, P. Yaney, Q. Zhan, "Nondestructive evaluation of laser machined ceramics," in the Proc. SPIE - Int. Soc. Opt. Eng., Testing, Reliability, and Application of Micro- and Nano-Material Systems, (2005).

Xiaojun Li, Wei Chen, Qiwen Zhan, Liming Dai, Laura Sowards, Mark Pender and Rajesh R Naik, "Direct measurement of interactions between polypeptides and Carbon Nanotubes," submitted for publication, (2006).

6 Technology Transfer

S.I. Rokhlin and D.F. Farson, "Materials processing by discharge from nanoprobes," OSU Invention Disclosure # 0425, October 28, 2002.

S.I. Rokhlin and D.F. Farson, "Heat treating and joining of materials by nanoprobes," OSU Invention Disclosure # 0427, October 28, 2002.

S.I. Rokhlin and D.F. Farson, "Nanoscale piezoelectric actuator," OSU Invention Disclosure # 0426, October 28, 2002.

7 Collaborations Established

UC/OSU, Enhancement of collaboration between the University of Cincinnati and The Ohio State University in studying cold work in nickel-base superalloys by nanoindentation.

UC/UD, Two collaborative research projects in the area of nondestructive residual stress assessment.

UC/Iowa State University, Three collaborative projects in the area of nondestructive residual stress assessment.

UC/Imperial College (UK), Collaboration in microstructural characterization of stainless steel.

UD, 3 Post Docs and visiting faculty: Dr. Xiaojun Li (Post Doc in Materials Engineering), Dr. Bernd Koehler (Visiting Scientist from Fraunhofer Institute, Germany), Prof. Todd Smith (Professor in Physics, University of Dayton)

A Genome Research Institute in Ohio (GRIO)

Final Research Progress Report

Partners: University of Cincinnati, Wright State University

The objective of the GRIO Program, funded by the Hayes Award, was to establish a comprehensive research infrastructure which would allow the Partner institutions, the University of Cincinnati and Wright State University, to successfully achieve a leadership role in biomedical research. GRIO's core facilities were created to support basic, clinical, and pharmaceutical research which will lead to the creation of proprietary gene and protein expression databases, the development of new therapeutic strategies, new research initiatives, and novel drug targets, all of which will eventually lead to improved health care for the citizens of Ohio and the nation. The initial project focus was the establishment of core facilities for genomics, proteomics, bioinformatics, biological validation, phenotyping, medicinal chemistry and protein production. Funds from HIF were specifically earmarked for essential animal holding and procedure facilities and were to be augmented with University, other State and federal grant funds to establish the complete GRIO infrastructure. This included creation of suitable space, identifying critical personnel, and securing equipment and supplies. Efforts were also to be undertaken to initiate projects utilizing these cores with a wide range of academic, government and industry collaborators.

GRIO has grown in less than four years into a major research enterprise with forty Principal Investigator laboratories and a total staff of more than 350. Worldclass leaders in cancer, obesity, diabetes, neurobehavioral and cardiovascular research have been recruited from across the U.S., Europe and Australia. GRIO investigators have more than fifty extramurally funded research projects, worth over $15,000,000 per year, in place at the current time, with sources which include the National Institutes of Health, Department of Defense, American Cancer Society, American Heart Association, Diabetes Foundation and many others.

All of the core facilities established by the Hayes award and associated funding are now in place. Additionally, during the last calendar quarter, agreement was reached to purchase high throughput screening equipment using funds provided by the State to the Computation Medicine Center, to initiate the development of drug candidates. We are also working to add additional medicinal chemistry and protein production capabilities to make GRI truly a unique center of excellence in translational medicine. New projects are being added on a regular basis and several are making excellent progress towards commercializable endpoints focusing on diagnostics and drug candidates in the areas of cancer, obesity, diabetes and heart disease. GRIO and its Partners are now competing for sizeable federal grants and contracts which would have been impossible without these resources. GRI is also actively courting existing pharmaceutical and biotechnology companies with the goal of moving projects and on-the-ground activities to Ohio.

The genomics (both Affymetrix at WSU and SSH at GRI), proteomics, sequencing, bioinformatics, cell, drosophila, zebrafish, rodent, phenotyping, electrophysiology,

virus vector and medicinal chemistry cores are now operational. Protein production efforts are underway using bacterial cells. An important addition to the computing infrastructure is now making excellent progress, with funding from the Third Frontier Network (TFN) and the University of Cincinnati. This new effort, in collaboration with the Ohio Supercomputer, will provide GRI with a significant Structural Modeling capability which will enhance its work to understand the structure of target proteins and to design new diagnostic and drug products. The software product being developed will be made compatible with the user interface being developed by the Computation Medicine Center, also funded by ODOD and OBR. Many other projects are also in progress utilizing the currently available GRIO cores.

GRI is expanding its collaboration with the Air Force Research Lab. We have completed both a Collaborative Development Agreement (CRADA) and Educational Partnership Agreement (EPA) with the AF, which will aid future collaborations and funding proposals. GRI has also received $1,000,000 in funding for a project identified by AFRL's Human Effectiveness Branch as a high priority. This collaborative project, which will focus on the possible increase in ALS among deployed warfighters, will utilize the Department of Defense serum repository which has over a decade of samples from service members and their families and the related patient information. This will allow us to explore the gene and protein changes which may be attributable to warfighter deployments or to use the data as a representation of the population as a whole, splitting groups by diseased versus normals. This is the one of the first uses of the serum repository for detailed molecular biology research.

GRI's Behavioral organization has been awarded a major research grant of $2,000,000 over four years in conjunction with the Air Force Research Lab to study animal models of fatigue and the impact of nutrition and drugs on cognition under stress conditions. This work will utilize core facilities established by Hayes and University funds. It has significant long term potential for commercialization of biomarkers, diagnostics, new nutritional diets/supplements and improved drugs. This research team is also submitting proposals for work on fatigue, cognition, nutrition and longer term obesity effects for funding from the Congressionally Mandated Defense Research Program. Bringing such work to Ohio will take advantage of the growing staff at AFRL and the biomedical research capabilities at GRI. Goals include identification of diagnostics, sensors, biomarkers, drugs and nutritional products which enhance warfighter protection and performance.

The zebrafish laboratory is now involved in a series of disease related projects with extramural funding support:

- NIH/NIEHS – The goal of this study is to determine the effects of secondhand smoke exposure during early development on predisposition for cardiovascular disease as an adult.
- AHA (Ohio Valley Affiliate) – The purpose of this study is to determine the effects of blood flow on the timing of heart valve development. We will use the zebrafish animal model for these experiments. We will induce early regurgitant (backwards) blood flow in the heart and look for changes in the appearance of heart valves in both healthy and mutated embryos. Blood flow characterization will be accomplished using micro-scale flow visualization techniques.

- Kidney Foundation of Greater Cincinnati – The goal of this study is to determine the effects of fluid flow within the developing kidney on both normal and abnormally growing organs. We will map kidney fluid flow using injected tracer particles in both healthy and flow-compromised embryos. Particle motions will be tracked and development monitored using high-speed fluorescent confocal microscopy. Genetic defects will be mimicked by mechanically induced lesions of the kidney via microlaser surgery.

GRI is continuing to develop a collaboration with EvotecOAI, a German/English company specializing in high throughput screening and medicinal chemistry for the development of drug leads. The CMC will purchase Evotec High Throughput Screening equipment and locate these assets at GRI. GRI will supply biological leads for protein targets which have been identified and validated using core facilities. GRI will also use its emerging computational capabilities to identify prospective small molecules as drug leads. Evotec will locate staff at GRI to direct high throughput screening to move these leads towards the market. GRI and Evotec will collaborate in finding pharmaceutical and biotech funding for individual developments. This model, which Evotec has demonstrated works successfully in two Europe based biotechs, can be repeated here. Much work remains before the promise of this opportunity is realized, but we are actively pursuing it. Leads, in the areas of obesity, diabetes, migrane and cancer have already been identified and are in early development.

Evotec will also locate a significant portion of its North American commercial activities at GRI. This includes technical support for the high throughput screening equipment in the U.S., a showroom for such equipment and sales efforts for its services. This modest beginning can be expanded substantially as we find new customers and partners in drug development.

In summary, GRIO has leveraged Hayes and other State of Ohio funding to create a unique biomedical research center with the mission of understanding the basic mechanisms of disease AND translating this understanding into future therapies and cures.

2005-2006
SPONSORED AWARDS

ORGANIZATION: GRIO

Principal Investigator AWARD Grant Agency		FY06 DIRECT FUNDING
Anderson - Chemoprevention of Lung Cancer (NCI)		2,666,292
Anderson - Genetic Epidemiology of Lung Cancer (NCI)		924,329
Anderson - Mechanisms of Mouse Lung Carcinogenisis (NCI)		47,389
Anderson - Wash U Sub (NCI)		80,925
Czyzyk-Krezska – ACS		21,577
Czyzyk-Krezska - NIH HL 58687Gene Experession		185,685
Czyzyk-Krzeska - NIH HL66312 Hypoxia/Apnea		206,000
Dedman - AHA		55,000
Dedman - AHA Ohio Valley (Ji)		55,000
Dept – BRTT		1,681,496
Dept - Hayes Award for Proteomics		229,744
Drew – ACS		27,273
Hove - AHA		55,000
Hove - Kidney Award		27,905
Millhorn - NIH HL 33831 Oxygen Sensing		124,887
Millhorn - NIH HL 59945 Hypoxia		152,000
Millhorn- Army Breast Cancer		108,000

Plas - NIH Young Investigator		147,650
Schmann - ManTech / Alion		110,000
Schumann – ALS Military		50,000
Schumann - Orise Fellowship (Wendy Dominic)		35,000
Seta - Smoking Award		100,000
Thomas - Novartis (Um)		55,000
Thomas - Orise Fellowship (Dann)		40,000
Thomas - Sloan Kettering		86,344
Thomas - Swiss Institute of Cell Biology		173,964
Wortman - Third Frontier Network		615,000
Davidson-Apolipoprotein A-1 (NIH)		175,000
Davidson-Apoliproprtotein Cholesterol (NIH)		175,000
	-	-
Davidson-Ceramide (Pfizer		182,000
Benoit-CNSMelanocortin (NIH)		143,500
Benoit-CNS Behavior (NIH)		143,500
Herman-Stress Adaptation (NIH)		22,000
Herman-Limbic Circuits (NIH)		225,000
Herman-Glucocorticoid (NIH)		225,000
Herman-Brainstem (NIH)		225,000
Herman-Pituitary (NIH)		216,000
Kascow-Schizophrenia (NIH)		225,000
Mueller-Pituitary (NIH)		44,000
Sakai-Stress and Body Weight (NIH)		220,000
Seeley-Gut/Brain Obesity(NIH)		141,000
Seeley-Mouse Diabetes (NIH)		100,000
Seeley-CNS Adiposity (NIH)		191,000
Seeley-Energy Balance (NIH)		172,000
Stern-Angiotensin (NIH)		30,000
Stern-Hypertension (NIH)		330,000
Woods-Obesity (NIH)		150,000
Woods-Homeostasis (NIH)		272,000

Woollett-Sterol Metabolism (NIH)	158,000
Woollett-Bile (NIH)	158,000
Tso- Mouse Phenotyping (NIH)	580,000
Sun-Plasma Triglycerides (NIH)	55,000
Tso-Obesity Signals (NIH)	225,000
Tso-Obesity and Diet (NIH)	205,000
Liu-Food Intake (NIH)	165,000
Hui-Lipogenisis (NIH)	225,000
Hui-Vascular (NIH)	250,000
Hui-Apolipoprotein (NIH)	248,000
Hui-Lipolytic Enzymes (NIH)	230,000
Hui-Lipid Metabolism (NIH)	50,000
Frolov-Lipoprotein (NIH)	59,000
Granholm-Appo (NIH)	275,000
D'Allessio-Diabetes (NIH)	450,000
Anthonelli-Stress, Alcohol (NIH)	300,000
Total	15,301,459

Publications in Peer Reviewed Journals by Leading Faculty:

Dr. Maria Czyzyk-Krzeska
Dr. Jay Hove
Dr. Yong Ji
Dr. John Dedman
Dr. Marcia Kaetzel
Dr. George Thomas
Dr. Sara Kozma
Dr. Mattius Tschoep
Dr. Randy Seeley
Dr. David Hui
Dr. Patrick Tso

A. V. Kuznetsova, J. Meller, P.O. Schnell, J.A. Nash, M.L. Ignacak Y. Sanchez, R.C. Conaway, J.W. Conaway, M. F. Czyzyk-Krzeska (2003) VHL tumor suppressor complex binds hyperphosphorylated large subunit of RNA polymerase II through a proline hydroxylation motif and targets it for ubiquitination. Proc. Natl Acad. Sci. USA 100, 2706-2711.

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hypoxia in neuroendocrine cells and sympathetic neurons. Hypertension, 42, 1130-1136.

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A.L. Bauer, A. S. Hui, J. B. Striet, P.O. Schnell, M.F. Czyzyk-Krzeska (2005) Regulation of HIF 1α protein translation by calcium. (submitted to Mol Cell Biol)

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Hove, J.R., Köster, R.W., Forouhar, A.S., Acevedo-Bolton, G., Fraser, S.E. and Gharib, M. (2003). Intracardiac fluid-forces are an essential epigenetic factor for embryonic cardiogenesis. *Nature* **421**: 172-177.

Hove, J.R. (2004). In vivo biofluid dynamic imaging in the developing zebrafish. *Birth Defects Research C: Embryo Today* **72**: 277-289.

Forouhar, A.S., Hove, J.R., Calvert, C., Flores, J., Jadvar, H., and Gharib, M. (2004). Electrocardiographic characterization of embryonic zebrafish. *Proceedings of the 26th Annual Conference of the IEEE EMBS*, pp. 3615-3617.

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GRIO Collaborations

University and Non-Profits:
Cincinnati Children's Hospital Research Foundation
University of Minnesota
Washington University
Wayne State University
University of Texas Southwestern
M.D. Anderson
Medical University of Ohio
Ohio Supercomputer
University Hospital, Colorado
Louisiana State University
University of Virginia
British Columbia Cancer Center
University of Basel, Switzerland
University of Chicago
California Institute of Technology
University of Washington
Sloan Kettering Cancer Center
Ohio University
Battelle
Swiss Cancer Institute
Novartis Foundation
CSIO (Spanish Biomedical Institute)
Government
Air Force Research Laboratory
Department of the Army
National Institutes of Health
Environmental Protection Agency
Industry
Procter & Gamble Pharmaceuticals
Meridian Bioscience
Girindus America (Solvay)
Novartis
Eli Lilly
Cognis (Johnson& Johnson)
Ethicon
iCAD
Microsoft
Leadscope

Ohio Organic Semiconductor Consortium

Final Research Progress Report

Partners: Kent State University, Case Western Reserve University, Ohio State University

Kent State University

In an earlier report (February 24, 2004) a group of KSU hardware items acquired with Hayes support were documented (Buck Scientific Atomic Absorption Spectrometer, Headway spin-coater, Janus cryostat, Neslab chiller, Bruker-Agilent MS-HPLC). All these items have found continued use since the original report. For example, the cryostat has been employed in the characterization of the crystalline organic semiconductor 1,4-diiodobenzene and the MS-HPLC has been employed for the characterization of many intermediates and final products in the semiconductor project. Notably, the HPLC hardware has found heavy use supporting the work in other projects in the chemistry department as diverse as vitamin B12 chemistry.

Additional hardware purchased at KSU since the earlier report includes an Oxford Cryosystems chiller for X-ray samples. This device cools the crystals while they are irradiated so that the data is collected with less thermal scattering. It is also used to investigate low-temperature structural phase behavior. A BioAnalytical Systems potentiostat was purchased for the electrochemical characterization (oxidation and reduction potentials in solution) of the organic semiconductors. A GC-MS with automated sample injection was purchased from Thermoelectron. This device is also used to analyze reaction mixtures and assay the purity of organic samples. Finally, a Silicon Graphics computer has been purchased to run calculations on the physical properties of the organic semiconductors. This eight-cpu Itanium-II machine has proved of great value in band structure calculations on crystalline organics, as well as accelerating single-molecule calculations on, e.g., liquid crystalline and glassy semiconductors. Substantial funds have also been spent in improving the mobility measurement capabilities at KSU. Our cryogen-free cryostat is essential when characterizing, e.g., crystals such as halobenzene derivatives and for low-T liquid crystal phases such as those displayed by the nitro-HAT5 system. The purchase of a high-performance spectrometer (Ocean Optics) makes possible a variety of experiments, including mobility measurements on free-standing liquid crystalline films. Finally, a high-purity inert-atmosphere glove box (MBraun) will extremely useful in characterizing the *electron* mobility of many organic systems. It will also be used for handling various oxygen- or air-sensitive systems.

The scientific work at KSU supported by the Hayes grant falls into three main categories. First, there is a synthesis category in which candidate organic semiconductor materials are designed, synthesized and purified. Second, there is a characterization category in which the salient physical properties including time of flight charge mobility and charge generation are determined. Third, there is a more theoretical category in which models are developed to describe and interpret the experimental results.

In category one the materials themselves may be broken into three different classes by structure: single crystal, liquid crystal and amorphous glass monomers. Our efforts in single crystal materials have concentrated on acenes (such as pentacene) and their derivatives and iodoaromatics. This latter class of materials is the most unique and interesting. We have prepared a range of simple iodoaromatics and amongst them 1,4-diiodobenzene has been studied in substantial detail (synthesis and purification, hole mobility, modeling of transport). This substance has a hole mobility rivaling the other best organic semiconductors which are always much larger conjugated molecules. We continue to study other materials in this class. Studies of liquid crystal organic semiconductors have included both discotic and calamitic thermotropic liquid crystals. In the discotic area studies have concentrated on the known hexaalkoxytriphenylene class, especially HAT-5 and also nitro derivatives of HAT-5. We also have a project ongoing to examine the existence of discotic liquid crystal phases in benzofuran containing aromatics. In the calamitic liquid crystal area we have pursued molecules with significant heterocyclic ring content. A very general synthetic method has been developed to introduce a 2,5-pyridine structure into liquid crystals and also more recently combinations of pyridine with thiophene. In the third materials area of study we have prepared a range of triarylimidazoles as potential monomer glass forming charge transport agents. The triarylimidazole structure was chosen due to its known propensity for glass formation. Physical measurements to date have not revealed any unusual mobility properties, though the observation of clear Poole-Frenkel behavior has motivated future work on the role of dipolar disorder in hopping conduction.

The availability of world-class hardware for both measurement and computing has led to closely coupled theoretical/experimental work on organics. The 1,4-diiodobenzene paper listed below presents measured dispersion-free photoconductivity transients along with computational results that imply an important role for the halogen in the conduction mechanism. This led to a (submitted) theoretical paper on the band structure of this compound and the role of the iodine in determining bandwidths and mobility. We also have a submitted work (listed below) on the role of ions in charge carrier mobility measurements that depend on both computational and experimental results. The ability to carry out coupled experimental and theoretical investigations was an early aim of the collaboration and has begun to bear fruit.

*** Leveraging results:** A couple of grants were received in close proximity to the Hayes awards (mutually leveraging). Other grant applications were not funded.

07/01/01-06/30/04	Hanna PI Twieg co-PI Bushby co-PI Haarer co-PI	Self Organizing Molecular Semiconductors: Synthesis, Properties and Applications	NEDO Subcontract Tokyo Institute of Technology	$82K

08/08/01- 07/31/04	Twieg PI Ellman co-PI Huang co-PI	Acquisition of an Organic Semiconductor Processing and Characterization Facility for Research and Student Training	NSF	$200K
08/21/02 08/21/05	Twieg PI Ellman co-PI Huang co-PI	Organic Semiconductor Consortium I OOSC	Ohio Board of Regents Hayes	$300K (KSU)
07/17/03- 07/16/06	Twieg PI Ellman co-PI	Organic Semiconductor Consortium II OOSC	Ohio Board of Regents Hayes	$250K (KSU)

*** Graduate students** who completed thesis/dissertations under this award. At KSU, a number of graduate students have been involved in the different projects that use the hardware from the Hayes awards.

Twieg group (Chemistry, 1 Ph. D. completed, 2 Ph.D. underway)
Alexander Semyonov (Ph.D. August 2006). Alexander's thesis covered the synthesis of halogenated crystalline and also liquid crystalline organic semiconductors.
Yulia Getmanenko (Ph. D. anticipated Spring 2007). Yulia's thesis concentrates on calamitic liquid crystal and amorphous glass organic semiconductors.
Na Liu (Ph. D. anticipated Spring 2008). Na's research has involved the synthesis of benzofurans seeking discotic liquid crystal behavior and semiconductor activity

Ellman group (Physics, 1 M.S. Completed, 2 Ph.D. underway)
Shailesh Nene (M.S. December 2004). Shailesh's thesis concentrated on crystalline organic semiconductor purification, crystal growth, and characterization.
Chandra Pohkrel (Ph.D. expected Fall 2008). Chandra is concentrating on new liquid crystalline (LC) semiconductors and on experimental techniques in LC semiconductor research.
Naresh Shakya (Ph.D. expected Fall 2008). Naresh is working on crystalline materials, spatially resolved measurements and freestanding liquid crystalline film measurements.

*** Publications** resulting from this award (title, date, and journal name)

A number of publications have resulted from research performed using hardware obtained from the Hayes grants. The list below is restricted to those papers that concentrate on organic semiconductors. Actually the impact in other areas has been quite substantial as well.

1) K. Hudson, B. Ellman, V. Gettwert, Y. Getmanenko, R. J. Twieg, "Radiation-induced trapping and charge transport in a smectic liquid crystal", Appl. Phys. Lett., 87, Art No 152103 (2005).

2) V. Duzhko, K. D. Singer, A. Semyonov, R. J. Twieg, "Correlated Polaron Transport in Quasi One-dimensional Liquid Crystals", Phys. Rev. B., Art. No. 064201 (2006).

3) Y. A. Getmanenko, R. J. Twieg, B. D. Ellman, "2,5-dibromopyridine as a key building block in the synthesis of 2,5-disubstituted pyridine-based liquid crystals", Liquid Crystals, 33, 267-288 (2006).

Accepted but not published:
1) B. Ellman, S. Nene, A. N. Semyonov, R. J. Twieg, "High Mobility, Low Dispersion Hole Transport in 1,4-diiodobenzene", Adv. Mater., accepted for publication.

Submitted:
1) Volodimyr Duzhko, Hefei Shi, Kenneth D. Singer, Alexander Semyonov, Robert J. Twieg, "Controlled self-assembly of triphenylene-based molecular nanostructures", submitted to Langmuir.

2) Brett Ellman, "Study of the electronic structure of the crystalline high-mobility organic semiconductor 1,4-diiodobenzene", submitted to Journal of Chemical Physics.
3) C. Pokhrel, N. Shakya, Steven Purtee, Brett Ellman, Aexander N. Semyonov and Robert J. Twieg, "The Effect of Mobile Ions on Charge Mobility Measurements", submitted to Journal of Applied Physics.

* **Technology transfer** activities (patents, licenses, start-ups, etc.). At present, there are no entries in this category.

***Collaborations** established (new or enhancement of existing with other universities or industry). The Hayes award has cemented relationships amongst the three partner universities and also internally amongst groups in the three respective universities. Our collaboration at Tokyo Institute of Technology (Hanna group) was augmented by the Hayes award. A new collaboration at Georgia Tech (Marder group) on liquid crystal semiconductors has been initiated.

Case Western Reserve University

The Hayes Investment Fund along with matching funds from a DuPont Aid to Education Award was used to purchase a PTI C-720F state-of-the-art research fluorescence spectrofluorometer, and a Princeton Applied Research Model 263A-2 potentiostat.

The PTI C-720F instrument has and has become a workhorse for the investigation of the photoluminescence characteristics of conjugated, organic semiconducting materials in solution and the solid state. In particular its ability to conduct lifetime

measurements makes the instrument useful study molecular relaxation processes in detail. The instrument has facilitated a number of publications, including a manuscript on materials with self-assessing capabilities, which was highlighted in Chemical and Engineering News and other media.

The 263A-2 potentiostat/galvanostat was also installed in December 2002. This instrument is being used for the electrochemical synthesis of semiconducting materials, including conducting polymers and organic/inorganic hybrid materials. With additional funding, the instrument has been equipped with a frequency response detector, which allows one to determine the ion conductivity of proton exchange membranes.

A nanoscope IV atomic force microscopy unit was purchased and installed. It has provided extensive service to two multi-investigator grants that began in solid-electrolyte memory devices (SRC) and polymer capacitors (NIST) in 2003. Through the NIST grant, in particular, the AFM will be used to investigate new polymeric materials for capacitors with a DuPont processing plant in Circleville, OH. The AFM enables careful imaging and kinetic studies of CuS and Ag_2S solid electrolytic flash memory cells and it has also led to an important discovery about the layered structure of PET and PVDF films under investigation for capacitor applications. Currently other groups at Case in materials research and biology are also using it.

We are connecting the AFM and other nano-metrology tools in the laboratory to the Nano-Grid that is being set-up across Ohio to provide remote control access to other institutions and small businesses in the area. This will provide an opportunity for these institutions to use state-of-the-art instrument without having to invest in one. The access through web enables complete control and instantaneous monitoring of images obtained by the AFM in real-time. We are in the process of starting a small company to develop the Nano-Grid across Ohio.

We have purchased a PicoQuant Time-Harp 200 time-resolved single photon counting module for use in the study of new organic optoelectronic materials. It is presently being installed for molecular-scale optical response measurements in connection with a three-year NSF collaborative grant (Singer-Petschek-Twieg) facilitated by the Ohio Organic Semiconductor Consortium. Its intended use has recently been described in an invited article.

Most recently, we have purchased a regeneratively amplified Ti:Sapphire laser system (Model: CPA2010) from Clark MXR as well as an optical parametric amplifier from Quantronix (Model: Topas). Both comprise a widely tunable laser system for the study of the optical and electronic properties of organic molecular and condensed media. In particular, this laser source has been incorporated into a nonlinear optical scattering measurement of the molecular hyperpolarizability resulting in several publications to date, and several more in preparation. It is currently being extended for use in measuring nonlinear transmission for two new projects involving photonic crystals being funded by NSF. Hayes Investment Funds were also used to purchase components necessary to complete these measurement systems. This system is being used in the NSF collaborative grant mentioned in the previous paragraph as well as two recent NSF awards involving Singer and Weder. This system has been essential to the furtherance of the Hayes collaboration and the award of new grants.

Leveraging results (title, sponsoring agency, date, and amount)

Title	Sponsor	Period	Total Amount ($)
Synthesis of Organic/ Inorganic Hybrid Polymers	Army Research Office	09.03 - 08.06	240,000
Single Molecule Conductors	Case Pres. Res.Ini.	04.04 - 04.07	50,000
Polymers with Integrated Deformation Sensors	NSF-DMI	09.04 - 08.07	352,000
Mechanochromic Polymers	Kimberly-Clark	01.05 - 06.06	100,000
NSF Special Creativity Award	NSF-DMR	09.05 - 08.07	192,000
Synthesis of High-Spin Conducting Polymers	EU Marie Curie Grant GKSS	07.05 - 06.07	48,000
Responsive Polymers for Cortical Electrodes	NIH	12.05 - 11.07	402,200
Multifunctional Metallo-supramolecular Polymers	Army Research Office	09.06 - 08.08	250,000
Dynamic Inorganic/Organic Hybrid Photonic Crystals	NSF-Materials World Network	07.06 - 05.09	582,000
Nonpolar Electro-optic Materials	NSF	07.03-06.07	485,882
Photorefractivity in Liquid Crystals and Their Application for Optical Processing	NATO	01.03-12.04	16,000 Euro
Graduate Assistance in Areas of National Need Fellowship Program: Optical Materials	Dept of Education	8.03-6.07	714,867
Electronic Charge Injection, Photogeneration, and Transport in Smectic and Columnar Liquid Crystals	Petroleum Research Fund	5.04-7.06	80,000
Center for Layered Polymer Systems	NSF-Science and Technology Ctr.	8.06-7.11	18,960,000

Graduate students who completed thesis/dissertations under this award
7 Ph. D., 1 M.S.
2 Postdoctoral scholars

Publications resulting from this award

Crenshaw, B.; Weder, C.; Deformation–Induced Color Changes in Melt-Processed Photoluminescent Polymer Blends; *Chem. Mater.* **2003**, *15*, 4717-4724.

Schroers, M.; Kokil, A.; Weder, C.; Solid Polymer Electrolytes based on Nanocomposites of Ethylene Oxide-Epichlorohydrin Copolymers and Cellulose Whiskers; *J. Appl. Polym. Sci.* **2004**, *93*, 2883-2888.

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Voskerician, G.; Weder, C.; Electronic Properties of Poly(*p*-phenylene ethynylene)s; *Adv. Polym. Sci.* **2005**, *177*, 209-248.

K.D. Singer, R.G. Petschek, V. Ostroverkhov, R.J. Twieg, and L. Sukhomlinova, "Non-Polar Second-Order Nonlinear and Electro-Optic Materials: Axially Ordered Chiral Polymers and Liquid Crystals," *J. Polym. Sci.: Polym. Phys* . **41**, 2744-2754 (2003).

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Jessica Merlin, Mark Winkler, Kenneth D. Singer, Platon Korneychuk, and Yuri Reznikov, "All-optical switching in a nematic liquid crystal twist cell," *Optics Express* **13**, 5024-5029 (2005).

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Massood Tabib-Azar and Yaqiang Wang, "Imaging Embedded Structures using Microfabricated Scanning Near-Field Microwave Probes Compatible with Atomic Force Microscopy." IEEE Transactions on Microwave Theory and Techniques, March 04 Issue.

M. Tabib-Azar and L.You , "XYZ Positioning Microactuator for Local Probe Microscopy." J. MEMS (sub: 10/03).

Massood Tabib-Azar, S. R. LeClair, J. F. Maguire, and W. C. Fitzgerald, Microwave Imaging of Materials and Defects with Super-Resolution, Journal of Nondestructive Evaluation (2002).

Tao Zhang and M. Tabib-Azar, "Calculation and Accurate Measurement Capacitance of Electrically Small Axi symmetric Microstructures near a Probe Tip." IEEE 61st ARFTG Conference, June 13th, 2003, Philadelphia, PA

Weder, C. Organometallic Conjugated Polymer Networks; *J. Inorg. Organomet. Polym. Mat.* Submitted.

Technology transfer activities

Patent application filed: Kinami, M.; Crenshaw, B.R.; Weder, C.; Time-Temperature Indicators; US Provisional Patent Application filed.

Disclosure: Liquid Crystal Device for All-Optical Control, Optical Limiting, and Eye and Optical Sensor Protection

Collaborations established

- Ciba Specialty Chemical
- Kimberly Clark Co.
- Toyobo Co Ltd
- Bayer MaterialScience
- Eugene Collins, Fisk University
- Weijie Lu, Fisk University
- Richard Mu, Fisk University
- Martin Steinhart, Max Planck Institute, Halle, Germany
- Ralf Wehrspohn, U. Paderborn, Germany
- Yuri Reznikov, Institute of Physics, Ukraine
- Victor Reshetnyak, Kiev University, Ukraine
- Joachim Stumpe, Frauenhofer Institute, Potsdam, Germany
- Janusz Parka, Military Institute, Warsaw, Poland
- Alan Levine, Case Western Reserve University
- Steven Eppel, Case Western Reserve University
- Jie Shan, Case Western Reserve University

The Ohio State University

The revised OOSC revised budget supported $224,911 at OSU towards the acquisition of a multilayer organic semiconductor device preparation/handling system. The selected vendor for the integrated system is Vacuum Atmosphere at $565,617.57. The difference between the OOSC budget ($224,911) is made up by (a) $51,089.00 from the Ohio Organic Semiconductor Consortium award received in 2003; (b) an action fund cost share ($72,404.40) on a DARPA program for Spin Driven Electronics Beyond Silicon; (c) OSU cost share ($72,404.40); and (d) funds from the DARPA program for Spin Driven Electronics Beyond Silicon ($144,808.80). Delivery is expected in mid-summer.

Approval by the Ohio Controlling Board to select Vacuum Atmosphers as the vendor was received on February 23. The deposition systems and vacuum pumps will be supplied principally by BOC Edwards. The system will consist of three separate boxes connected by a cross or "X" antechamber 15-17" in diameter. One of the boxes will have a separately purchased user installed equipment including AFM, another will contain a spincoater, a hotplate and a freezer, and the third box will contain both organic and metals/dielectrics thin film deposition systems and a freezer. A fourth independent "wet" box will also be acquired for synthesis of specific precursors. All pumps will be oil free. Oxygen and water level analyzers will be in each box to assure operation at less then 1 ppm O_2 and 1ppm H_2O (except the wet box). Static eliminators and particle filtration systems will be integral in each of the three

interconnected boxes to maintain an environment necessary for multilayer device fabrication.

The Organic Depositions System will have two resistance sources and two organic evaporation sources for controlled deposition, as well as film thickness and rate monitors. The Metals/Dielectrics Deposition System will have two resistance sources, a DC/RF sputtering source, and an e-beam deposition source, with appropriate power supplies, cooling systems, and thickness and rate monitors. Both organic and and metal/dielectric deposition systems will be accessible both from inside and from outside the glove box and both use turbomolecular pumps.

To further support the ongoing exploration of polymer devices for electronics and optoelectronics, equipment below was purchased to facilitate their fabrication and testing. The following items were purchased and is located in the labs of Prof. Paul Berger at OSU. The approximate cost of these items is $75,089.

A Veeco Dektak^3 profilometer (used) was purchased for determining the thicknesses of films at their step edges. Fixtures from GP Distributors were purchased which enable the packaging of polymeric devices for later testing. This is key, because, some polymer materials and/or metal contacts are sensitive to moisture and must be manipulated in a nitrogen-rich glovebox environment. To move these devices into the natural environment, they must undergo encapsulation that prevents making electrical connections to the devices of interest. The fixtures purchased provide a packaged device to be outfitted with leads that overcome this obstacle. A custom designed and built Keithley L-I-V measurement system with an integrated spectroradiometer was purchased. The system is designed around a Keithley 4200-SCS/F semiconductor characterization system with a 12 inch flat panel display. A 400-channel switching system and Quad 110 multiplexer card enables the rapid and semi-automatic testing of 88 arrays of PLEDs, which could consist of up to 8 glass slides and 8 individual PLED pixels per 1 in^2 glass slide. Remote pre-amps that extend the resolution to 100FA to 100 aA and a master power supply complete the hardware system. A large area photodetector collects the emitted light for L-I-V measurements. A fiber optic head collects the emission from just one pixel or substrate and directs it to the spectroradiometer for spectral analysis of the light output.

Ohio NMR Consortium

Final Research Progress Report

Partners: Ohio State University, Case Western Reserve University, Kent State University, Miami University, Ohio University, University of Akron, University of Cincinnati, University of Toledo, Wright State University

Introduction

When the proposal for the Hayes Investment Fund was submitted the following statement was in the abstract: "the Ohio NMR Consortium hoped to enhance the NMR infrastructure through the purchase of a 900 MHz spectrometer for structural biology research, and to upgrade existing facilities. It was anticipated that state-of-the-art facilities would put the consortium in a unique position to compete for Federal Grants, would provide quality graduate and under-graduate training, and would continue to promote collaboration between researchers in Ohio through the sharing of high-field NMR instruments."

The 2002 Hayes Award allowed the Ohio NMR Consortium to build on an earlier Office of the Board of Regents Investment Fund awarded in 1996. This earlier award enabled The Ohio State University to purchase an 800 MHz NMR spectrometer and the University of Cincinnati, College of Medicine to purchase items for an 800 MHz spectrometer that they had on order (in 1996, an 800 MHz spectrometer had the highest field magnet available). The award also provided funding for many other Ohio universities and colleges in the consortium allowing them to upgrade their facilities.

The 2002 award continued to increase the prominence of Ohio in the NMR community by partially funding the purchase of a Bruker 900 MHz NMR spectrometer for the Cleveland Center for Structural Biology, CCSB, formed by Case Western Reserve University, Cleveland State University and the Cleveland Clinic Research Foundation. In addition, funds were provided for the purchase of cryoprobes, as well as for new spectrometers in the laboratories of several of our members to further upgrade and enhance their facilities.

The CCSB purchase of the 900 MHz spectrometer was the major item for the consortium during this round of funding. A new building had to be constructed to house this spectrometer as well as three Varian spectrometers (300, 500 and 600 MHZ) which were relocated from the Cleveland Clinic. Other shared instruments in the CCSB include Bruker 600, 700 and 800 MHz spectrometers that are located in the Case Western Department of Biochemistry. The 900 MHz spectrometer was delivered in December 2005, and by the spring of 2006 the instrument had met its specifications and was operational. To date, the major impact of the 900 has been the increase in funding for projects which require the use this new spectrometer. Now that the spectrometer is operational results should soon follow.

The Ohio State University Campus Chemical Instrument Center (CCIC) and the University of Cincinnati, College of Medicine purchased cryoprobes. These probes

provide much greater sensitivity than standard probes by reducing thermal noise in the receiver coil and the preamp. OSU leveraged its Hayes award with enough matching money to purchase two Bruker cryoprobes, one for a 600 MHz spectrometer and another for an 800 MHz spectrometer. The University of Cincinnati purchased a Varian cryoprobe for their 500 MHz system. The Cincinnati probe was installed early in 2005 and CCIC installed its 600 probe in February 2005 and its 800 probe in June 2005. Although only in use for a little more than a year, these probes enabled research progress that would have been impossible prior to the upgrades either because of time constraints or because of effects due to concentration such as low signal to noise and solute-solute interactions.

The University of Toledo was able to leverage money it received from this award to purchase a Varian 600 MHz spectrometer instead of the 500 MHz spectrometer that they had originally requested. This gave them a more versatile system which is used for biological NMR projects, metabolite studies, and synthetic medicinal chemistry structural analysis. In addition to the Chemistry Department, the spectrometer is available to the College of Pharmacy and with the merger of the University of Toledo and the Medical University of Ohio there will be increased collaboration with the NMR facility.

Miami University has used its Bruker 500 MHz spectrometer to conduct studies ranging from the structure and dynamics of membrane proteins, metabolism of short chain fatty acids in plant and microbial systems, and the reaction of organic intermediates called aryloxenium ions. Miami University has created a Center for Industrial Organic Chemistry and this NMR spectrometer has been a pivotal asset in work with an Ohio company and two multinational corporations with large Ohio presences.

Wright State University and Ohio University purchased Bruker 300 MHz spectrometers. The University of Cincinnati's Department of Chemistry purchased a Bruker 400 MHz spectrometer. All of these departments now have access to spectrometers which are state-of-the-art and can perform the 1- and 2-dimensional NMR experiments that are so vital in structure determination of organic compounds. In addition the availability of the latest generation of NMR spectrometers has facilitated their efforts to obtain grants.

The University of Akron has not made a purchase yet. They have worked on leveraging their Hayes money with other sources of funding to purchase a 500 MHz three channel solids/liquids spectrometer. Starting with the $96,500 from the Hayes Fund they have been able amass $632,000 for the purchase of a spectrometer.

The universities in the Ohio NMR Consortium have graduated 26 Ph.D. students and 16 M.S. students whose work was performed on instruments funded by the 2002 Hayes Award. Since several of the systems were not put into use until 2005 and early this year (2006) an even greater number of degrees should be granted in the next three years.

It is evident that seed money from the Ohio Board of Regents has greatly enhanced the use of NMR for biological structural analysis in the State of Ohio. The awards (1996 and 2002) have helped to increase funding from private as well as governmental

agencies, produced a new cadre of highly trained scientists, and have attracted new faculty to Ohio universities. Just as important as these high-profile achievements, this funding has benefited the infrastructure of the Ohio NMR community by helping to fund the purchase of state-of-the art spectrometers thereby expanding access to powerful NMR technologies for examining the properties of small molecules, polymers, and solids

An additional benefit of the Hayes funding is that there has been an increased usage of shared instrumentation. Just as Ohio State's CCIC had offered usage of its 800 MHz system and other spectrometers to the Ohio NMR community at the same rate as internal users, CCSB has extended a similar offer to the members of the Ohio NMR community for usage of their systems.

Individual Institution Information

Cleveland Center for Structural Biology (CCSB)

In 2003 CWRU committed to build a new structure to house their Bruker 900 MHz NMR spectrometer as well as other NMR instruments. The construction was completed in the summer of 2005 and the spectrometer delivered December 2005. By the spring of 2006 the instrument was operational and meeting specifications. Of note a major celebratory symposium was held May 12-14, 2006. This was attended by about 180 including nearly all the prominent US names in the field and representatives from several local and national companies, plus one Nobel laureate (Wuthrich) from Switzerland. This really put the CCSB and Ohio on the map in the NMR world.

While the instrument has not been operational long enough for a discussion of results and publications, funding received by the following researchers has been buttressed by showing how the arrival of the 900 will affect their research.

Dr Jun Qin

Title: Molecular Basis of ILK Signaling in Cell Adhesion
PI: Jun Qin; Agency: NIH
Type: R01HL58758; Period: 03/01/03 02/28/08 The major goal is to understand the structural basis of ILK kinase localization, activation, and phosphorylation on target proteins.

Title: NMR Structural Elucidation of Integrin Activation and Signaling
PI: Jun Qin; Agency: NIH
Type: R01GM62823; Period: 07/01/02 06/30/06 The major goal is to determine structures of integrin cytoplasmic domains and to understand how they regulate integrin activation.

Title: Structure and function of beta3 integrins on blood cells
PI; Edward Plow (JunQin Co-investigator) Agency: NIH
Type: P01HL073311-01; Period: 04/01/04 03/31/09
The major goal of this proposal is to understand the cellular function of b3 integrins on platelets and endothelial cells. Dr Qin will participate in

examining how talin and skelemin activate the b3 integrins.

Roughly, Dr. Qin's funding is valued at $3.5 M (direct plus indirect)

Dr Kwaku Dayie.

One NSF funded MCB-0316783
Title: Molecular Basis of Group II Intron Domain 5 Catalytic Function
Funding Period: 2003/08-2006/07
PI percent effort: 20%
Total costs/1st yr: $150,000.00
One NIH RO1 submitted
Title: Structural Basis for activating Group II Intron ribozymes
PI percent effort: 20%
Total costs/1st yr: $225,000.00

Dr Matthias Buck

KO-2 Independent Scientist/Career Award National Institutes of Health,
Heart, Lung and Blood Institute
Matthias Buck, PI 4/6/06 - 3/31/11
Project Title: "Molecular Mechanisms of Plexin Signaling in the Heart and Vascular System"
Priority score of 140 at study section meeting on 10/31/05.
total value ~ 500,000
planned for submission in mid-July:
NSF project grant
Matthias Buck, PI
Project Title: Molecular dynamics and binding of small GTPases
total value ~ 800,000

Dr Mike Zagorski
NIH RO1 JUST APPROVED 06-11
Value 1.5 million

Dr Mike Weiss
Presently has high NMR content in two ongoing NIH RO1s
Total value 2.4 million
Plus two new grants have just been submitted which feature the 900.

Dr Frank Sonnichsen
He is out of country but has one ongoing RO1, is co-investigator in a program project and is submitting a new grant Fall 2006.

Souces of funding

Funders for the center are Case Western Reserve University; the Case School of Medicine's Department of Biochemistry; National Institutes of Health; Ohio Biennial Capital Bill, FY2005-2006; Ohio Board of Regents Action Fund; Ohio Board of Regents Hayes Fund; The Cleveland Clinic Foundation; The Cleveland Foundation; The Fred A.

Lennon Charitable Trust; Health Resources and Services, and the Administration of U.S. Department of Health and Human Services.

University of Cincinnati

The major pieces of equipment purchased as a result of the 2002 OBR NMR Consortium Hayes Investment Fund award to the University of Cincinnati were a solution state Bruker Avance 400MHz NMR for the Department of Chemistry and a Varian 500MHz cryoprobe for the College of Medicine. The 400MHz NMR was installed and fully operational by mid-2004 while the cryoprobe was installed by early-2005. The OBR funds represented approximately 48% of the purchase price of the 400 MHz spectrometer and 30% of the purchase and installation price of the 500 MHz cryoprobe. The period used for this progress report for UC based upon these equipment items covers late 2004 until now.

Dept. of Chemistry 400MHz NMR spectrometer:

The overall impact upon the U. of Cincinnati as a result of the funds obtained from the 2002 OBR Hayes Investment Fund award has been considerable, especially with respect to the younger faculty at this University. This equipment has provided numerous Chemistry faculty with better capabilities as far as their NMR research efforts in a wide range of areas including drug delivery design, uptake of cellular agents, green chemistry, photochemistry, vapochromism, carbohydrate chemistry and biosensor research. In terms of research productivity, this equipment has also contributed to data used for a significant number of publications (16). The OBR-funded NMR also helped faculty leverage considerable funding via external grants (>$1.3million in total costs as shown below from agencies such as NIH, NSF, The Beckman Foundation, e.g.). Just as importantly, this equipment helped some investigators to establish collaborations (3) within and outside this University. Technology developments which rely upon access to this equipment have already led to two patent applications. With respect to higher education, the thesis research of seven graduate students (six Ph.D. and one Masters) relied upon data obtained using this particular NMR.

College of Medicine 500 MHz cryoprobe:

Although the 500 MHz cryoprobe has only been in place for a little over one year, it is already having a dramatic impact on the quality of research that is achievable within the structural biology/NMR facility in the College of Medicine. The sensitivity improvement afforded by this probe has greatly facilitated many experiments and permitted new experiments to be done that were otherwise not feasible. Use of this cryoprobe has been critical for a number of research projects in the general field of structural biology, including studies of the structure and dynamics of calcium-binding proteins, studies of dynamics in protein/DNA complexes, structure determinations of proteins involved in the bacterial competence system, structure/dynamics studies of toxins that are used as probes of membrane ion channels, dynamics studies of response regulator proteins, and structural studies of the cardiac troponin complex. These studies are supported by grants from the NIH and the Dept. of Energy. The acquisition of this cryoprobe has allowed the NMR facility to remain state-of-the-art, and has been invaluable for obtaining preliminary data to support several new grant

applications to date. The cryoprobe was part of the facilities that were used by four Ph.D. students who all graduated in 2005, and five papers have recently been published based on their work (contained in Publication List below).

List of Publications:

Department of Chemistry:

H. Jude, J. A. Krause Bauer, W. B. Connick, "Tuning the Electronic Structures of Platinum(II) Complexes with a Cyclometallating Aryldiamine Ligand, *J. Inorg. Chem.*, **2004**, 43, 725-733.

PJ Ball, T. R. Shtoyko, J. A. Krause Bauer, W. J. Oldham, W. B. Connick, "Binuclear Rhenium(I) Complexes with Bridging [2.2]Paracyclophane-Diimine Ligands: Probing Electronic Coupling Through p-p Interactions," *J.Inorg. Chem.*, **2004**, 43,622-632.

L. J. Grove, J. M. Rennekamp, H. Jude, W. B. Connick, "A New Class of Platinum(II) Vapochromic Salts," *J. Am. Chem. Soc.*, **2004**, 126, 1594-1595.

S. A. Willison, H. Jude, R. M. Antonelli, J. M. Rennekamp, N.A. Eckert, J. A. Krause Bauer, W. B. Connick, "A Luminescent Platinum(II) 2,6-bis(N-pyrazolyl)pyridine Complex", *J. Inorg. Chem.*, **2004**, 43, 2548-2555.

H. Jude, J. A. Krause Bauer, W. B. Connick, "Luminescent Platinum(II) Dimers with a Cyclometallating Aryldiamine Ligand", *J. Inorg. Chem.* **2005**, 44, 1211-1220.

T. W. Green, R. Lieberman, N. Mitchell, J. A. Krause Bauer, W. B. Connick, "Intramolecular Metal-Sulfur Interactions of Platinum(II) 1,4,7-Trithiacyclononane Complexes with Bipyridyl Ligands: the Relationship Between Molecular and Electronic Structures", *J. Inorg. Chem.* **2005**, 44, 1955-1965.

S. Tastan, J. A. Krause, W. B. Connick, "Synthesis, Structures and Spectroscopic Properties of Palladium(II) Complexes with Tridentate Piperidyl-Containing Pincer Ligands", *J Inorg. Chim. Acta* **2006**, 359, 1889-1898.

Konosonoks, A., Wright, P.J., Tsao, M.-L., Pika, J., Novak, K., Mandel, S.M., Krause Bauer, J.A., Bohne, C., Gudmundsdóttir, A.D., "Photoenolization of 2-(2-methyl benzoyl) benzoic acid, methyl ester: Effect of e photoenol lifetime on the photochemistry", *J. Organic Chemistry* **2005** 70, 2763-2770.

Singh, P.N.D., Klima, R.F., Muthukrishnan, S., Murthy, R.S., Sankaranarayanan, J., Stahlecker, H.M., Patel, B., Gudmundsdóttir, A.D.,"An efficient one-pot synthesis of pyrrolines and tetrahydropyridines from their chloro-precursors via in situ aza-Wittig reaction", *Tetrahedron Letters* **2005** 46, 4213-4217.

S. Srinivasachari, Y. Liu, G. Zhang, L. Prevette, T. M. Reineke**,** "Trehalose Click Polymers Inhibit Nanoparticle Aggregation and Promote pDNA Delivery in Serum" *J. Am. Chem. Soc.* **2006** Accepted.

Y. Liu, L. Wenning, M. Lynch, T. M. Reineke, "Gene Delivery with Novel Poly(L-tartaraminoamine)s" *Polymeric Drug Delivery Volume I - Particulate Drug Carriers*,

Svenson, S. (Ed.), ACS Symposium Series, Vol. 923, American Chemical Society, Washington, DC, **2006**, 217-227.

C. Gulgas, T. M. Reineke**,** "Synthesis, Characterization, and Luminescence Properties of a New Series of Eu^{3+} - Containing Macrocycles" *Inorg. Chem.* **2005,** *44*, 9829-9836.

Y. Liu, T. M. Reineke**,** "Hydroxyl Stereochemistry and Amine Number within Poly(glycoamidoamine)s Affect Intracellular DNA Delivery" *J. Am. Chem. Soc.* **2005**, *127*, 3004-3015.

Y. Liu, L. Wenning, M. Lynch, and T. M. Reineke, "New Poly(D-glucaramidoamine)s Induce DNA Nanoparticle Formation and Efficient Gene Delivery into Mammalian Cells" *J. Am. Chem. Soc.* **2004** 126, 7422-7423.

J. Fotins, D.B. Smithrud "Creation and investigation of protein-core mimetics with parallel and antiparallel aligned amino acids", *J.Organic Chemistry* **2005** 70, 4452-4459.

P. R. Ettireddy, M. Orchin "[(CO)3(dppe)Mn(OH2)]BF4 (1). A synthetically versatile compound and its use as a probe for determining the preferred site of coordination on ambident ligands", *Polyhedron* **2006** 25, 1147-1156.

College of Medicine:

Introduction of Negative Charge Mimicking Protein Kinase C Phosphorylation of Cardiac Troponin I: EFFECTS ON CARDIAC TROPONIN C. Natosha L. Finley and Paul R. Rosevear (2004) J. Biol. Chem. 279, 54833 – 54840.

In Vivo and *in Vitro* Analysis of Cardiac Troponin I Phosphorylation. Sadayappan Sakthivel, Natosha L. Finley, Paul R. Rosevear, John N. Lorenz, James Gulick, Scott Kim, Peter VanBuren, Lisa A. Martin, and Jeffrey Robbins (2005) J. Biol. Chem. 280, 703 – 714.

Solution structure of the K50 class homeodomain PITX2 bound to DNA and implications for mutations that cause Rieger syndrome. Beth A. Chaney, Kimber Clark-Baldwin, Vrushank Dave, Jun Ma and Mark Rance (2005) Biochemistry 44, 7497-7511.

The Solution Structure of the Native K50 Bicoid Homeodomain Bound to the Consensus TAATCC DNA-binding Site. Jamie M. Baird-Titus, Kimber Clark-Baldwin, Vrushank Dave, Carol A. Caperelli, Jun Ma, and Mark Rance (2006) J. Mol. Biol. 356, 1137-1151.

Effects of Calcium Binding on the Side-Chain Methyl Dynamics of Calbindin D_{9k}: A ^2H NMR Relaxation Study. Eric Johnson, Walter J. Chazin, and Mark Rance (2006) J. Mol. Biol. 357, 1237-1252.

List of Funded Proposals:

"CAREER: Synthetic Design and Biological Study of Novel Polymeric DNA Delivery Vehicles" NSF **$535,804** (direct plus indirect costs) 4/05-3/10. *T.M. Reineke, PI*

"New Polymer-DNA Nanomedicines for Treatment of Heart-Related Ailments" UC Institute for Nanoscale Scale Science and Technology Grant **$25,000** (direct costs) 1/05-12/05. *T.M. Reineke, PI.*

"Development of Novel Synthetic Carriers for NF-kB Blockade in the Myocardium" Arnold and Mabel Beckman Foundation, Beckman Young Investigator Award **$264,000** (direct costs) 9/05-8/08. *T.M. Reineke, PI*

"CAREER: Utilization of Mechanochemistry for solvent waste reduction" NSF, **$550,000** (total costs) 4/06-3/11. *J. Mack, PI*

Ohio State University Campus Chemical Instrument Center

As a result of the Hayes award of $348,000, the Campus Chemical Instrument Center, CCIC, at Ohio State University was able to purchase two cryoprobes from Bruker Bio-Spin costing $547,100. A cryoprobe for our Bruker 600 MHz NMR spectrometer was installed February 2005 and the 800 cryoprobe was installed June 2005. It should be pointed out that the 800 MHz NMR spectrometer was partially funded with an earlier OBR Investment Fund award in 1996.

Results, publications and funding of some major users follow and in addition the CCIC staff have collaborated and worked with the Ohio Department of Agriculture, Battelle as well as some of its subsidiaries and on an on going basis with other Consortium members.

Mark Foster

Impact of 2002 Hayes Award – NMR Cryoprobes

The primary focus of Prof. Foster's laboratory is to study the structure and function of proteins and their interactions with nucleic acids (RNA and DNA). These molecular complexes can be quite large, pushing the limits of available technology for NMR spectroscopy of macromolecules. The PI has made extensive use of the NMR facilities at the Ohio State University CCIC NMR facility. Acquisition of two cryogenically cooled NMR probes (cryoprobes), in which the signal-to-noise ratio is increased by reducing the operating temperature of the coil and the pre-amplifier, has been crucial for advancing several research projects.

Although acquisition of the cryoprobes has significantly impacted the progress of all projects in the laboratory, impact has been particularly noteworthy in three research areas. Each of these projects involves NMR spectroscopic analysis of large biomolecules. The need for high concentrations of biomolecules for NMR analysis is often a complicating factor for NMR studies, but is even more acute for large molecular

weight systems because high molar concentrations result in undesirable features due to solute-solute interactions in concentrated solutions. Thus, the cryoprobes, with their enhanced sensitivity, enable study of macromolecular systems at sufficiently low concentrations that solute-solute interactions do not degrade the quality of the observed signal.

1. Structure and Function in Catalytic RNP Assembl*y*

This proposal seeks to reveal how protein and nucleic acid molecules (RNA) cooperate to enable biological function. Many important processes in cells are carried out by molecular particles (RNPs) containing both RNA and protein components. The molecule that is the target of this project is the catalytic ribozyme, ribonuclease P (RNase P). RNase P is an enzyme that is essential in all domains of life and is responsible for performing a conserved chemical reaction: maturation of precursor tRNA molecules. One of the most significant scientific discoveries of the past 50 years is that the RNA subunit of the enzyme is responsible for catalyzing the chemical reaction – a role previously thought to be restricted to proteins. This finding has revolutionized the way scientists approach a number of questions, and has lead to new ways of treating disease.

Although decades of work have revealed much about the enzyme, how the protein and RNA components cooperate to form the functional enzyme remains poorly understood. This uncertainty is exacerbated in the case of the human enzyme, which has been studied much less than the bacterial enzyme, and contains many more protein subunits (1 in bacteria, 10 in humans). We have been working to understand the protein-RNA interplay in a model system of intermediate complexity: RNase P from archaebacteria (4 proteins). In many important ways, archaebacteria are much closer to eukaryotes than are bacteria, and studies focused on molecules from archaebacteria are more easily extrapolated to humans.

We have been using NMR spectroscopy to study the structures of the protein subunits and their interactions with the other subunits of the enzyme. Although the archaebacterial enzyme is less complicated than the human one, its study remains very difficult by conventional methods because the enzyme is large from the standpoint of solution NMR methods. Nevertheless, availability of the cryoprobes has allowed us to make significant progress on this challenging system.

2. Structure and Dynamics in Allosteric Gene Regulation

TRAP, *T*rp *R*NA-Binding *A*ttenuation *P*rotein, regulates expression of certain genes by binding single-stranded mRNA in the 5' leader regions the genes. TRAP directly senses the intracellular levels of tryptophan and binds in an allosteric fashion to the RNA only when intracellular concentrations are high. TRAP is an 91,000 Dalton 'donut'-shaped oligomer containing 11 monomers exhibiting perfect 11-fold symmetry. Using the available cryoprobe technology has enabled us to understand how ligand binding activates TRAP for binding to RNA (and turning off the gene).

3. Lambda Integrase

Lambda integrase is a viral enzyme responsible for integrating viral DNA into its host's genome. The Foster group has been working to determine the mechanism by which the enzyme recognizes the sites on the host DNA that are the targets of integration, as well as the mechanism by which the viral DNA is inserted. High quality NMR spectra can be obtained on the enzyme at relatively low concentrations of protein; above this it tends to precipitate. The sensitivity provided by cryoprobes enables data collection at lower concentrations, allowing progress on these questions.

The research made possible by the cryoprobes has resulted in the following tangibles:

External Funding:

NIH/NIGMS R01 GM 067807 4/1/04-3/31/2009 $962,500 (direct)

Co-PI: Venkat Gopalan

Structure and function in catalytic RNP assembly

This project aims to use biochemical and biophysical methods to probe the structure and function of RNA-protein complexes, with a particular emphasis on RNase P from higher organisms.

Pennsylvania State Univ (22000030) 7/1/2005-6/30/2008

Subcontract from NIH/NIAID AI053531-03 $188,177 (direct)

PI: Craig Cameron

Picornavirus genome replication

This project seeks to use NMR spectroscopy to map RNA protein interactions in the PV 3C protease.

Pending Funding

NIH/NIGMS R01 GM077234-01A1 04/01/2006 - 03/31/2011; Pending $1,556,250 (direct)

Structure and dynamics in allosteric gene regulation

The proposal seeks to provide fundamental insights into the mechanism of ligand-mediated gene regulation through NMR, biophysical and biochemical studies of the TRAP protein.

Graduate students supported by the instrumentation:

3 PhD students, June 2005.

Publications:

McElroy, C. A.; Manfredo, A.; Gollnick, P.; Foster, M. P. Thermodynamics of Tryptophan-Mediated Activation of the trp RNA-Binding Attenuation Protein. *Biochemistry*; 2006; ASAP Article; DOI: 10.1021/bi0526074

Wilson RC, Bohlen CJ, Foster MP, Bell CE, Structure of Pfu Pop5, an archaeal RNase P protein. *Proc Natl Acad Sci U S A*. 2006 Jan 24;103(4):873-8.

Subramaniam S, Tewari AK, Nunes-Duby SE, Foster MP. Dynamics and DNA substrate recognition by the catalytic domain of lambda integrase. *J Mol Biol.* 2003 Jun 6;329(3):423-39.

Boomershine WP, McElroy CA, Tsai HY, Wilson RC, Gopalan V, Foster MP. Structure of Mth11/Mth Rpp29, an essential protein subunit of archaeal and eukaryotic RNase P. *Proc Natl Acad Sci U S A.* 2003 Dec 23;100(26):15398-403.

McElroy C, Manfredo A, Wendt A, Gollnick P, Foster M. TROSY-NMR studies of the 91kDa TRAP protein reveal allosteric control of a gene regulatory protein by ligand-altered flexibility.

J Mol Biol. 2002 Oct 25;323(3):463-73.

Boomershine WP, Raj ML, Gopalan V, Foster MP. Preparation of uniformly labeled NMR samples in Escherichia coli under the tight control of the araBAD promoter: expression of an archaeal homolog of the RNase P Rpp29 protein. *Protein Expr Purif.* 2003 Apr;28(2):246-51.

Collaborations established/enhanced

Venkat Gopalan, OSU, Department of Biochemistry
Structure and function in catalytic RNP assembly

Paul Gollnick, University at Buffalo, Department of Biological Sciences
Structure and dynamics in allosteric gene regulation

Craig E. Cameron, Penn State University, Department of Chemistry
Picornavirus genome replication

Justin Wu

Research in the laboratory of Justin Wu is focused on understanding key protein-protein and protein-nucleic acid interactions by elucidation of their three-dimensional structures using NMR spectroscopy. Cryoprobe technology greatly facilitates our research in the following two ways: first, most proteins we are working with are either hard to produce in large quantities or have low solubility; as a consequence, we have to work with concentrations that otherwise would not be possible using standard room temperature probes. For instance, HIV-1 Viral Infectious Factor is soluble up to 200 M. Concentrations above this threshold result in aggregation and precipitation. With the cryoprobe, high quality NMR data can now be obtained within a reasonable period of time.

Second, high resolution molecular structures can be obtained by NMR by a combination of conventional NOE-based experiments and modern dipolar coupling methods. Under weak alignment conditions induced by anisotropic environment such as liquid crystals formed by phospholipid bicelles, filamentous phage, polyethylene glycol analogs, or strained hydro-gel, residual dipolar couplings no longer average to

zero as in isotropic solution. A wealth of structural information can be then derived from these couplings, and significantly increase the accuracy of NMR structures. However, measurements of these couplings can sometimes be problematic, given the fact that weak alignment concurrently introduces homonuclear dipolar couplings, which inevitably increases the signal linewidth and reduces the sensitivity. Consequently, the very high signal to noise ratio provided by the cryoprobe, allows precise measurements of these dipolar couplings high resolution structure determination.

Ming-Daw Tsai

The director of the Campus Chemical Instrument Center has research projects that involve the mechanism of calcium-dependent phospholipase C, structure-function relationships of DNA polymerase beta, and structure-function relationships of tumor suppressors. Each of these projects involves NMR studies of interactions between proteins and large and small molecule ligands. The enhanced sensitivity provided by the Hayes-sponsored cryoprobe technology has had significant impact on the progress of each of these research areas.

Recent Publications

"Dissection of CDK4-binding and Transactivation Activities of $p34^{SEI-1}$ and Comparison between Functions of $p34^{SEI-1}$ and $p16^{INK4}$". Junan Li, Peter Muscarella, Sang Hoon Joo, Thomas, J. Knobloch, W. Scott Melvin, Christopher, M. Weghorst, and Ming-Daw Tsai, *Biochemistry*, in press (2005).

"Sequential Phosphorylation and Multisite Interactions Characterize Specific Target Recognition by the FHA Domain of Ki-67", by In-Ja L. Byeon, Hongyuan Li, Haiyan Song, Angela M. Gronenborn, and Ming-Daw Tsai, *Nature Structural and Molecular Biology*, in press (2005).

"FHA Domain-Ligand Interactions: Importance of Integrating Chemical and Biological Approaches". A. Mahajan, C. Yuan, B. L. Pike, J. Heierhorst, C.-F. Chang, and M.-D. Tsai, *J. Am. Chem. Soc.* In press.

Ongoing Research Support

RO1 CA69472-09 (Tsai PI) 4/1/05 – 3/31/10
NIH/NCI
Structure-Function Relationship of Tumor Suppressors
The major goal of this project is to understand the structure-function relationship of newly discovered tumor suppressors, particularly the INK4 family and ankyrin-repeat proteins (e.g., p16, p15, p18, gankyrin, and IkBa), and to study their binding to CDK4. A recently discovered oncoprotein SEI-1 is also a focus.
Role: PI Value $2.6 million

RO1 GM43268-12 (Tsai PI) 7/1/02 - 6/30/07
NIH/NIGMS
Mechanism of DNA Polymerases

The major goal of this project is to study the structure-function relationship of DNA polymerase beta from rat brain and DNA polymerase X from ASFV. The current main thrust is to understand the mechanism of fidelity. The knowledge should be useful for other polymerases.
Role: PI Value $1.38 million

University of Miami Department of Chemistry and Biochemistry

The Lorigan research group uses the 500 MHz NMR spectrometer acquired through the Hayes Investment Fund to study the structural and dynamic properties of integral membrane proteins. Currently, three graduate students have received training from this instrument (Junxia Lu, Shadi Abu-Baker, and Shidong Chu). We have published one paper from the funding of this proposal (J. Magn. Reson.) In this project, Membrane topology changes introduced by the association of biologically pertinent molecules with membranes were analyzed utilizing the 1H-13C heteronuclear dipolar solid-state NMR spectroscopy technique (SAMMY) on magnetically aligned phospholipid bilayers (bicelles). The phospholipids 1H-13C dipolar coupling profiles lipid motions at the headgroup, glycerol backbone, and the acyl chain region. The transmembrane segment of phospholamban, the antimicrobial peptide (KIGAKI)3 and cholesterol were incorporated into the bicelles, respectively. The lipids 1H-13C dipolar coupling profiles exhibit different shifts in the dipolar coupling contour positions upon the addition of these molecules, demonstrating a variety of interaction mechanisms exist between the biological molecules and the membranes. The membrane topology changes revealed by the SAMMY pulse sequence provide a complete screening method for analyzing how these biologically active molecules interact with the membrane.

The Crowder group has been using the solution 500 MHz NMR spectrometer for two different purposes. First, my group is currently working on 6 different metalloenzymes, and we are structurally and mechanistically characterizing these enzymes to obtain information that will be used to rationally design inhibitors. We have used the 500 MHz NMR spectrometer to characterize Co(II)-substituted, Zn(II)-metalloenzymes. Specifically, we can determine the number of histidines (and often the number of aspartic or glutamic acid) bound to the metal ion(s). We have also used NMR to probe whether cysteine groups are bound to the metal ion. The NMR experiments that we conduct can also inform us of the type of metal center that we have in several of our iron containing metalloenzymes. For example, the presence of paramagnetically-shifted, proton resonances in samples containing iron metalloenzymes indicates that either the iron is Fe(II) or part of an antiferromagnetically-coupled Fe(III)Fe(II) center. Second, we routinely use the 500 MHz NMR to characterize the inhibitors that we synthesize in the lab. To date, we have synthesized 40 novel inhibitors towards metallo-b-lactamases (involved in antibiotic resistance), glyoxalase 2 (a potential antitumor target), and VanX (involved in antibiotic resistance).

Since the NMR grant was approved, the Novak research group has initiated a new project on the reactions of a group of organic reactive intermediates called aryloxenium ions. The 500 MHz NMR spectrometer was instrumental in obtaining initial data for a successful grant application listed below, and several publications that resulted from that project have also acknowledged data from the new NMR spectrometer.

Briefly, we have utilized the NMR facility to help identify reaction products of trapping experiments that are meant to provide evidence for the existence of the aryloxenium ions, and to provide isotopic labeling data that has allowed a mechanistic picture of the generation of oxenium ions from their precursors to be developed. The labeling experiments allowed for the indirect detection of ^{18}O by the $^{18}O/^{16}O$ dependent chemical shift of ^{13}C nuclei directly bonded to an isotopically labeled O atom. These data allowed us to distinguish between O atoms that came for the H_2O solvent and those that were already present on the purported oxenium ion precursors. Incorporation of ^{18}O into reaction products provided evidence for solvent trapping of an oxenium ion, while the lack of incorporation of ^{18}O provided evidence for alternative mechanisms not involving oxenium ions. Our data showed that oxenium ions were generated in some specific cases, but in other cases with slightly different structures other reaction mechanisms were occurring.

The 500 MHz NMR spectrometer has also been instrumental in our continuing investigation of the reactions of carcinogens derived from heterocyclic amines produced in the cooking of protein-containing foods. The NMR data has been used predominately to identify reaction products produced by decomposition reactions of these carcinogens.

The Hawes group is using proton, 13C, and 15N NMR to study metabolism of short chain fatty acids and branched-chain acids in plant and microbial systems. In one project we are correlating the metabolism of short-chain acids with their induction of acid resistance in Salmonella typhimurium. These experiments have led to development of a novel metabolic mechanism that explains the induction of acid resistance by short chain acids like propionate and butyrate. In another project we are investigating the metabolism of propionate and propionate derivatives in plants. Plants do not metabolize propionate by the same pathways as other organisms. Our data show that plants metabolize propionate primarily through the production of beta-hydroxypropionate. We are using 15N NMR to investigate the synthesis of beta-aminopropionate (beta-alanine) in plants. These projects have involved one PhD student, one MS student, and 3 undergraduate students.

Leveraging results (title, sponsoring agency, date, and amount of each external award received as a result of this Hayes award)

"Search for Zn(II) metallochaperones in E. coli" National Institutes of Health, 6/1/06-5/31/08, $490,000

Graduate students who completed thesis/dissertations under this award
(number of each degree awarded, e.g. 2 M.S., 3 Ph.D., etc.)

3 M.S.
4 Ph.D.

Publications resulting from this award (title, date, and journal name)

J.X. Lu, K. Damodaran, G.A. Lorigan**, "**Probing membrane topology by high-resolution H-1-C-13 heteronuclear dipolar solid-state NMR spectroscopy", Journal of Magnetic Resonance 178 (2): 283-287 Feb. 2006

"The Hydrolysis of 4-Acyloxy-4-substituted-2,5-cyclohexadienones: Limitations of Aryloxenium Ion Chemistry", M. Novak and S. A. Glover, *Journal of the American Chemical Society* **2005**, *127*, 8090-8097.

"Computational Study of the Properties of Phenyloxenium Ions: A Comparison with Phenylnitrenium and Phenylcarbenium Ions", S. A. Glover and M. Novak, *Canadian Journal of Chemistry* **2005**, *83*, 1372-1381.

"4´-Substituted-4-biphenylyloxenium Ions: Reactivity and Selectivity In Aqueous Solution ", Michael Novak, Matthew J. Poturalski*, Whitney L. Johnson*, Matthew P. Jones*, Yueting Wang, and Stephen A. Glover, *Journal of Organic Chemistry* **2006***, 71,* 3778-3785.

G.R. Periyannan, A.L. Costello, D.L. Tierney, B. Bennett, K.W. Yang, and M.W. Crowder, "Sequential Binding of Co(II) to Metallo-b-Lactamase CcrA" Biochemistry (2006) 45 1313-1320.

G.P.K. Marasinghe, I.M. Sander, Brian Bennett, Ke-Wu Yang, Gopalraj Periyannan, C.A. Makaroff, and M.W. Crowder, "Structural Studies on a Mitochondrial Glyoxalase II" J. Biol. Chem. (2005) 280 40668-40675.
Ke-Wu Yang, F.C. Golich, T.K. Sigdel, and M.W. Crowder, "Phosphinate, Sulfonate, and Sulfonamidate Dipeptides as Potential Inhibitors of E. coli Aminopeptidase N" Bioorg. Med. Chem. Lett. (2005) 15 5150 - 5153.

P.A. Crawford, K.W. Yang, N. Sharma, B. Bennett, and M.W. Crowder "Spectroscopic Studies on Co(II)-Substituted Metallo-b-Lactamase ImiS from Aeromonas veronii bv. sobria" Biochemistry (2005) 44 5168 - 5176.

R.M. Breece, A. Costello, B. Bennett, T.K. Sigdel, M.L. Matthews, D.L. Tierney, and M.W. Crowder, "A five-coordinate metal center in Co(II)-substituted VanX" J. Biol. Chem. (2005) 280 11074-11081.
K.W. Yang and M.W. Crowder, "A Method for Removing EDTA from Apo-proteins" Anal. Biochem. (2004) 329 342-344.

K.W. Yang, D.N. Sobieski, A.L. Carenbauer, P.A. Crawford, C.A. Makaroff, and M.W. Crowder, "Explaining the Inhibition of Glyoxalase II by FMOC-Protected Glutathione Derivatives" Arch. Biochem. Biophys. (2003) 414 271-278.

Technology transfer activities (patents, licenses, start-ups, etc.)

None

Collaborations established (new or enhancement of existing ones with other universities or industry)

The 500MHz NMR spectrometer is a key component in the design of a Center for Industrial Organic Chemistry. The Center has been organized with seed money from the Research Office and is actively seeking partners for technology transfer and contract research. To date, demonstration projects with three companies have been

undertaken (an Ohio small business and two multinational corporations with a large Ohio presence). Of these potential clients, the NMR is a pivotal asset in the work with two and we are confident that funding commitments have been made with one of them. In the upcoming year, as the Center becomes an official university entity, a more aggressive marketing campaign will be undertaken.

Type and number of equipment items acquired, using the attached table with the generic category listing.

500 MHz instrument with broadband and inverse probes.

University of Toledo

In order to enhance our organic chemistry division it was essential to have the modern instrumentation that is necessary for the characterization of synthesized compounds. The acquisition of our new high field 600 MHz NMR spectrometer with the capacity to carry out all of the latest experiments was essential in the recruitment of 4 outstanding scientists to join our chemistry faculty at the University of Toledo (UT). Dr. Xuefei Huang was hired in 2002 from Scripps Research Institute, Dr. Yun-Ming Lin in 2003 from Stanford University, Dr. Steve Sucheck in 2005 from Scripps Research Institute and Optimer Pharmaceuticals, and Dr. Jared Anderson from Iowa State University. Dr. Huang's research is currently focused on the development of novel methods for syntheses of biologically active oligosaccharides. The multidimensional NMR capabilities and resolution of the 600 MHz spectrometer provides critical structural information for his research and was very important for his receipt of an NSF Career Award.

Since the acquisition of 600 MHz NMR spectrometer, the researchers in the Medicinal and Biological Chemistry department (including Drs. Erhardt, Hudson, Peseckis, Messer and Slama) have come to rely solely on the chemistry NMR Facility for their NMR needs. The University of Toledo (UT) College of Pharmacy's Center for Drug Design and Development (CD3) relies heavily upon the NMR Facility at UT. In particular, the 600 MHz instrument is utilized in synthetic medicinal chemistry research involving small molecule structures derived from complex natural products. Dr. Erhardt said that "the 600 MHz spectra (at UT) is often the only way to confirm the structural integrity of our complex organic molecules on route to becoming potential diagnostic and therapeutic agents primarily directed toward the treatment of cancer".

The merger of the University of Toledo and the Medical University of Ohio, their research facilities together with its enhanced capabilities will create more demand for the NMR facility and would be critical for attracting research funding to UT and northwest Ohio

Equipment acquired:

Although the funding was approved for a 500MHz NMR spectrometer, by purchasing the console and superconducting magnet separately, we successfully installed a 600 MHz Varian Inova NMR spectrometer. The system has 3 pulse field gradients, 4 rf

channels and 5 probes. Its capabilities far exceed those of the proposed 500MHz spectrometer.

Grants:

National Institute of General Medical Sciences, NIH
Title: "*Development of New Carbohydrate Synthesis Methodologies*"
PI: Xuefei Huang, 3/1/2005 – 2/28/2010. Award amount: $1,194,834 (R01 GM72667)

National Science Foundation
Title:"*CAREER Syntheses of Hyaluronan Oligosaccharides as Biological Probes*"
PI: Xuefei Huang, 6/1/2006 – 5/31/2011. Award amount: $525,000 (CHE 0547504).

Funding agency: the American Chemical Society Petroleum Research Fund (ACS PRF)
Title: "Asymmetric Morita-Baylis-Hillman Reaction: A Novel Tethered Bifunctional Lewis Acid-Lewis Base Catalysis Strategy"
Pi: Yun-Ming Lin, Award amount: $35,000.00 (04/01/2005 - 008/31/2007).

NIH grant AI068758
Title: "Structure and Dynamics of MHC Bound Peptides",
PI: Herman Von Grafenstein , Award amount: $150,000 05/01/2006 – 06/31/2008

National Institutes of Health, NS 31173,
Title: Muscarinic agonists for neurological disorders.
PI: William S. Messer, Jr. 07/01/04-06/30/08, Award amount $919,452.

US Army;
Title: "*PAM Inhibitors* (for the treatment of prostate cancer)"; 4/1/02 – 4/1/05;
PI: Paul W. Erhardt, Award amount $ 533 K.

USDA;
Title: "*Phytoestrogens in Development of Natural Products* (for treatment of various cancers but primarily breast cancer)";
PI: Paul W. Erhardt, Award amount $ 533 K. 4/1/03 – ongoing for an estimated total of 10 years; ca. $ 500 K per year.

NIH SBIR (with Cognitive Pharmaceuticals);
Title: "*Development of CDD-0102* (agent to potentially treat Alzheimer's disease)"; PI: Paul W. Erhardt, 6/1/04 – 6/1/06; Award amount: $ 150 K (CD3 portion).

SRA (from Pfizer, Inc.);
Title: *Prodrugs* (for various therapeutic indications);
PI: Paul W. Erhardt, 6/1/05 – 6/1/07; Award amount: $600 K.

Patent:

Xuefei Huang, Xin-shan Ye (co-inventor, Peking Univ., China) "Iterative One-pot Oligosaccharide Synthesis", US patent filed, 2004

William S. Messer, Jr. and Tejada, application submitted "Muscarinic agonists"
Technology licensed to Cognitive Pharmaceuticals Ltd., Toledo, OH

P. Erhardt, "*Aralkyl Ester Soft Drugs* (Divisional I: Clonidine Indication)"; US Patent, **6,750,238 B1** (2004).
P. Erhardt and M. Aouthmany, "*Method and Compositions for Treating Persistent Pulmonary Hypertension* (Aralkyl Ester Soft Drugs CIP I)"; US Patent, **6,756,047 B2** (2004).

W. Klis, J. Sarver and P. Erhardt; "*Method for Selective Removal of Acyl-functionality Attached to the 2'-Hydroxy-group of Pacletaxel-related Derivatives*"; US Patent, **6,846,937 B2** (2005).

P. Erhardt; "*Method and Compositions for Temporarily Incapacitating Subjects* (Aralkyl Ester Soft Drugs CIP II)"; US Patent Application, Allowed (2005).
P. Erhardt, W. Klis and J. Sarver; "*Paclitaxel Hybrid Derivatives*"; US Patent Application, **Filed** (2003) [Publication **WO 2004/080412 A2** (2005)].

Students who have graduated (had used the new spectrometer)

PhD. Students: 10
MS Students: 7

Publications:

Jing, Y.; Huang, X. "Fluorous Thiols in Oligosaccharide Synthesis" *Tetrahedron Lett.* **2004**, *45*, 4615-4618

Huang, L.; Wang, Z.; Huang, X. "One-pot Oligosaccharide Synthesis: Reactivity Tuning by Post-synthetic Modification of Aglycon" *Chem. Commun.* **2004**, 1960-1961.

Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. "Iterative One-Pot Oligosaccharide Synthesis" *Angew. Chem. Int. Ed.* **2004**, *43*, 5221-5224.

Wang, Y.; Huang, X.; Zhang, L.-H.; Ye, X.-S. "A Four-Component One-Pot Synthesis of a-Gal Pentasaccharide" *Org. Lett.* 2004, *6*, 4415-4417.

Huang, L.; Wang, Z.; Li, X.; Huang, X. "Iterative One-pot Synthesis of Chitotetrose", *Carbohydr. Res.* **2006**, *341*, 1669-1679.

Huang, L.; Teumelsan, N.; Huang, X. "A Facile Method for Oxidation of Primary Alcohols to Carboxylic Acids and Its Application in Glycosaminoglycan Syntheses" *Chem. Eur. J.* **2006**, in press.

Liu, Q; Tillekeratne, L.M.V.; Kim, Y-W; Kirchhoff, J.R.; Hudson, R.A. "*Evaluation of the Chiral Discrimination of Highly Negatively Charged Enantiomers by Quaternary Ammonium β-Cyclodextrin using ^{1}H NMR.*" *Chirality* **2005**, *17*, 570-576

S. Han, R. A. Moore, and R. E. Viola, A Facile Synthesis of a Difluoromethylene Analog of β-Aspartyl Phosphate as an Inhibitor of L-Aspartate-β-Semialdehyde Dehydrogenases, *SynLett.*, 845-846 (2003).

S. Han and R. E. Viola, Splicing of Unnatural Amino Acids into Proteins: A Peptide Model Study, *Prot. Pept. Lett.* **11**, 107-114 (2004).

E. Cama, S. Pethe, J.-L. Boucher, S. Han, F. A. Emig, D. E. Ash, R. E. Viola, D. Mansuy, and D. W. Christianson, Inhibitor Coordination Interactions in the Binuclear Manganese Cluster of Arginase, *Biochemistry* **43**, 8987-8999 (2004).

D. M. Colleluori, R. S. Reczknwski, F. A. Emig, E. Cama, J. D. Cox, L. R. Scolnick, K. Compher, K. Jude, S. Han, R. E. Viola, D. W. Christianson, and D. E. Ash, Probing the Role of the Hyper-Reactive Histidine Residue of Arginase, *Arch. Biochem. Biophys.* **444**, 15-26 (2005).

Cao, Y., M. Zhang, C. Wu, S. Lee, M.E. Wroblewski, T. Whipple, P.I. Nagy, K. Takács-Novák, A. Balázs, S. Tőrös and William S. Messer, Jr."Synthesis and biological characterization of 1-methyl-1,2,5,6-tetrahydropyridyl-1,2,5-thiadiazole derivatives as muscarinic agonists for the treatment of neurological disorders". J. Med. Chem. 46: 4273-4286, 2003.

Nagy, P.I., F. Tejada, J.G. Sarver and W.S. Messer, Jr."Conformational analysis and derivation of molecular mechanics parameters for esters and thioesters". J. Phys. Chem. A. 108(46): 10173-10185, 2004.

Nagy, P. I., F.R. Tejada, W.S. Messer, Jr."Theoretical studies of the tautomeric equilibria for five-member N-heterocycles in the gas phase and in solution". J. Phys. Chem. B. 109(47): 22588-22602, 2005.

Tejada, F., P.I. Nagy, M. Xu, T. Katz, J. Dorsey, M. Rieman, E. Lawlor and W.S. Messer, Jr., "Design and synthesis of novel derivatives of the muscarinic agonist tetra(ethylene glycol) (3-methoxy-1,2,5-thiadiazol-4-yl)[3-(1-methyl-1,2,5,6-tetrahydropyrid-3-yl)-1,2,5-thiadiazol-4-l]ether (CDD-0304): effects of varying the spacer on the binding and activity at muscarinic receptor subtypes". (submitted for publication).

V. Mauro, L. Mauro, J. Kleshinski, S. Khuder, Y. Wang and P. Erhardt; "*Impact of Ginkgo Biloba on the Pharmacokinetics of Digoxin*"; Am. J. Therapeutics, **10**, 247-51 (2003).

M. Dhanajeyan, P. Erhardt and C. Corbit; "*Simultaneous Determination of Vinclozolin and Detection of its Degradation Products in Mouse Bio-fluids by High Performance Liquid Chromatography*", J. Chromatography A, **Accepted**.

M. Dhanajeyan, C. Bykowski, J. Trendel, J. Sarver, K. Bachmann, H. Ando and P. Erhardt; "*A Rapid LC-MS/MS Assay for the Simultaneous Determination of Procaine and PABA*"; J. Chromatography A, **Submitted**.

Ruel Nacario, Shailaja Kotakonda, David M. D. Fouchard, L. M. Viranga Tillekeratne,and Richard A. Hudson, "Reductive Monoalkylation of Aromatic and Aliphatic Nitro Compounds and the Corresponding Amines with Nitriles", *Organic Letters.* **2005**, *7*, 471-474.

Mamoun M. Alhamadsheh, Richard A. Hudson, and L. M. Viranga Tillekeratne, "Design, Total Synthesis, and Evaluation of Novel Open-Chain Epothilone Analogues", *Organic Letters.* **2005**, *8*, 685-688.

Ohio University, Department of Chemistry & Biochemistry

Due to a critical need to update an archaic routine NMR we received permission to use the Hayes money to purchase a state-of-the-art Bruker 300 MHz NMR. The NMR was installed the summer of 2005. The NMR is utilized by the entire department (faculty, graduate students, undergraduates and postdoctoral students). Accomplishments and research of the major users that directly resulted from having the instrument this past year are summarized below.

Accomplishments since installation of NMR in summer 2005:

Research group of Dr. Stephen C. Bergmeier, associate professor
Design and synthesis of complex organic molecules with interesting biological activity.

Publications
Structure Activity Studies of Oxazolidinone Analogs as RNA-Binding Agents. J. Means, S. J. Katz, R. Anupam, A. Nayek, J.C. Hines, & S.C. Bergmeier, *Bioorg. Med. Chem. Lett.* **2006**, In Press.

Structure Activity Studies Of Quinuclidinone Analogs As Anti-Proliferative Agents In Lung Cancer Cell Lines. A. Malki, A. Pulipaka, S. C. Evans, S. C. Bergmeier, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1156-1159

Grants
National Institutes of Health
Fermentation Initiated Antibiotic Synthesis
$55,480 - direct costs, September 2005 - August 2006, PI

Collaborations
University of Leipzig, Germany (Prof. Ralf Hoffmann)

Research group of Dr. Jeffrey Rack, assistant professor
Synthesis of transition metal complexes to investigate photon-to-potential energy conversion.

Publications
"Efficient Energy Conversion in Photochromic Ruthenium DMSO Complexes." Rachford, A. A.; Petersen, J. L.; Rack, J. J. *Inorg. Chem.* **2006**, *in press.*
"Subnanosecond Isomerization in an Osmium-Dimethylsulfoxide Complex." Mockus, N. V.; Petersen, J. L.; Rack, J. J. *Inorg. Chem.* **2006**, *45*, 8-10.

"Designing Molecular Bistabilityin Ruthenium Dimethylsulfoxide Complexes." Rachford, A. A.; Petersen, J. L.; Rack, J. J. *Inorg. Chem.* **2005**, *44*, 8065-8075.

Collaborations
Argonne National Laboratory (Drs. Lin X. Chen and Erik Wasinger), Ohio State University (Profs. Claudia Turro and Christopher Hadad) and Virginia Tech (Prof. Gordon Yee).

Degrees awarded
1 Ph.D. student graduated

Research group of Dr. Michael Jensen, assistant professor
Characterization of primary phosphine complexation by 31P NMR spectroscopy.

Publications
"Spectroscopic Characterization of Primary and Secondary Phosphine Ligation on Ruthenium(II) Complexes." SIM Paris, JL Petersen, E Hey-Hawkins, MP Jensen, Inorganic Chemistry 2006, in press

Collaborations
University of Leipzig, Germany (Prof. E. Hey-Hawkins)

Wright State University

A Bruker Avance 300 NMR spectrometer was purchased and installed at Wright State in July 2003. Research projects that have employed the spectrometer include phosphine oxide dendrimer synthesis and characterization (Fossum), fuel cell membrane synthesis (Feld), hyperbranched poly(benoxazole) synthesis (Feld), combinatorial synthesis product characterization (Ketcha), syndone synthesis (Turnbull and ruthenium complex synthesis (Higgins).

Papers Published – Since NMR Acquisition
1. Kaiti, S.[g]; Fossum, E. "Effect of Reaction Conditions on the Molecular Weight and Polydispersity of Linear Poly(arylene ether phosphine oxide)s Prepared from an AB Monomer" *J. Poly. Sci., Part A: Polym. Chem.*, **2006**, *44,* 2099 – 2106.
2. Himmelberg, P.; Fossum, E. "Development of an Efficient Route to Hyperbranched Poly(arylene ether sulfone)s" *J. Poly. Sci., Part A: Polym. Chem*, **2005**, *43(13)*, 3178 – 3187.

3. Fossum, E.; Tan, L.-S. "Geometrical Influence of AB_n Monomer Structure on the Thermal Properties of Linear-Hyperbranched Ether-Ketone Copolymers Prepared via an AB + AB_n Route" *Polymer* **2005**, *46*, 9686 – 9693.
4. Czupik, M.[u]; Bankey, N.[u]; Fossum, E. "A Study of the Aryl-Aryl Coupling Reactions of $(4\text{-X-}C_6H_4)Ph_2P{=}O$" *Synthetic Communications*, **2004**, *34 (4)*, 705 – 714.

Graduate Students
5 M.S. Students have completed a thesis utilizing the new instrument.

Funding Received - Since NMR Acquisition

"Synthesis and Application of Water Solube, UV Curable Oligomers, Phase II" Scitex Digital Printing, Dayton, OH $22,612. Awarded Dec. 2003, expired Dec. 2004

"Synthesis of Intermediates for AFX Chromophores" Air Force Office of Scientific Research, awarded Dec. 2003, expired Nov. 2004 ($44,992)

"Synthesis of Intermediates for AFX Chromophores" Air Force Office of Scientific Research, supplement – October 2004 ($20,000)

"Copolymers with Defined Morphologies via Kinetically Controlled Polycondensation Reactions" Dayton Area Graduate Studies Institute - June 2005 – June 2006 ($55,000)

"Water Soluble/Waterfast Ink Systems" Kodak Versamark, Inc. June 2005 – August 2006 ($58,000)

"AFX Chromophore Synthesis"-, AT&T Government Solutions – AFOSR ($10,000)

Daychem Laboratories "Molecular Weight Studies on a Variety of Modified Linear Polymers" ($6,440 and up)

"Custom Synthesis of AFX Chromophore Intermediates" – Universal Technology Corporation Awarded March 2006 – 3- years ($241,000)

Collaborations - New

Professor Pat Mather – Case Western Reserve University
"Blending Studies of Hyperbranched Poly(arylene ether sulfone)s with Linear Systems"

University of Akron

The funds have not been spent yet. We expect to place an order during this summer for a 500 MHz 3 channel solids/liquids instrument.

We used Hayes funds to leverage additional funding from UA and NSF as follows:

$366,200	NSF-CHE-0341701	5-32083
$96,500	OBR Hayes	NA
$96,500	UA Match to Hayes Grant	5-33024
$73,215	UA Match to NSF	5-33959
$632,415	Total	

STATE-OF-THE-ART INFRASTRUCTURE TO SUPPORT OHIO RESEARCH IN ADVANCED INTERNET UTILIZATION, SIMULATION, AND TELEROBOTICS

FINAL RESEARCH PROGRESS REPORT

Partners: Wright State University, Ohio State University, Air Force Institute of Technology

Introduction

The goal of this project has been to enable existing collaborations in the areas of virtual environments, simulation, telerobotics, and advanced networking and to promote new collaborations and expand existing collaborations. We have implemented these goals through targeted capital expenditures on state-of-the-art infrastructure. We have purchased 6 high-end virtual environment (VE) workstations, which are installed at the Air Force Research Laboratory (1 workstation), the Air Force Institute of Technology (1 workstation), the Ohio Supercomputer Center (2 workstations), and Wright State University (2 workstations). In addition, we have upgraded and significantly enhanced the capabilities of the CAVE® virtual environment system in the Wright State University Virtual Environment Research, Interactive Technology, And Simulation (VERITAS) facility at Wright-Patterson Air Force Base. These facilities have significantly enhanced our research, promoted collaborations, helped us to attract significant funding to the State of Ohio, and supported graduate training.

Research

Enhanced Auditory Displays for General Aviation. This collaborative project, involving Wright State University (WSU), General Dynamics, and the Air Force Research Laboratory (AFRL), aimed to transfer 3-dimensional auditory display technology originally developed for military applications to the civilian sector. These 3D displays allow sounds to be presented through headphones such that they *appear* to arise, not from the headphones, but from specific locations in the environment around the listener. Identified military applications for this technology include directing visual attention to potential threats and targets, and aiding navigation. Translated into General Aviation cockpits we envision this technology aiding pilots by having the auditory signal from a Traffic Collision Avoidance Device appear to arise from the direction of the proximal traffic, by providing an auditory "navigation beacon" which allows pilots to maintain a desired course without looking at other instruments (e.g., when map reading), and incorporating an auditory attitude indicator designed to help pilots avoid spatial disorientation in reduced visibility environments. Initial development and evaluation of these devices was performed in VERITAS and subsequent flight tests were performed at the Air Force Test Pilot School, Edwards AFB, and at NASA Langley Research Center.

Auditory-Aided Visual Search. This ongoing basic research project is a collaborative effort between WSU and AFRL. It is examining how sound can improve the visual detection and identification of objects in cluttered environments. Previous research

has demonstrated dramatic reductions in search times when a sound is co-located with the visual target. This project is examining how the parameters of the cuing sound, the visual target, and the visual distracters interact to determine target acquisition speed. The results are being related to traditional models (i.e., without an auditory component) of visual search and visual attention.

"Wearable" Auditory Displays to Aid in Combat Search and Rescue. This ongoing applied research project is a collaborative effort between WSU and AFRL. The goal is to design and evaluate wearable interfaces for Pararescue Jumpers (PJs) (responsible for locating and rescuing downed pilots). The focus is on auditory displays similar to those that we have been investigating in cockpits. To evaluate these displays we have developed both urban and jungle simulation environments in the VERITAS CAVE®, which can be deterministically or randomly altered to meet the requirements of the experiment. The simulation allows 2 users to work together. The "ground-user" represents the PJ and the "aerial-user" represents a reconnaissance observer, either in a helicopter or via a UAV, above the environment. The aerial-user is able to provide real-time information about threats, targets, and waypoints to the ground-user, through visual and 3-D audio displays. New audio communications capabilities are being added between the two users; this will include spatialized live-speech cueing. Initial results indicate that providing subjects with a navigation display significantly speeds locating the pilot. Auditory displays are as or more effective than visual displays providing similar information, but auditory displays allow the subject to operate in a "heads-up" mode, which should provide better situation awareness and enhanced ability to address unexpected threats. These questions will be addressed in future studies.

The Impact of Delays in a Simulated Telerobotic Manipulation Task. This ongoing basic research project is a collaborative effort between WSU, the Ohio State University (OSU), Veridian Inc. (now General Dynamics) and AFRL. We have developed a simulation environment to evaluate the impact of delay in telerobotic (robots controlled from a distance) tasks. The 1-m cubic workspace is viewed through a high-resolution, stereoscopic, head-mounted display. The subject's task is to use a 3-dimentional joystic to position a cursor in small spherical targets as they appear in the workspace. As anticipated, the findings indicate that positioning times are substantially increased as delay is increased from 32 to 800 ms. However, more surprisingly, variable delays had little more impact than fixed delay. Initial attempts to offset the effects of delays using "real-time" spatialized auditory cuing have not been successful.

Active regulation of speed during a simulated low-altitude flight task. Researchers at WSU are examining the active regulation of speed during a low-altitude flight task as a function of global optical flow rate, speed, and the presence or absence of a concurrent altitude disturbance. The results showed that altitude clearly had an impact on speed control. Control of speed was much more difficult when altitude disturbances were present. Even in the no altitude disturbance conditions performance tended to be best at lower altitudes. Consistent with previous research, the results suggest that speed and altitude changes have additive effects on speed judgments. This is inconsistent with the simple global optical flow rate hypothesis that had suggested multiplicative effects. However, it is consistent with the general notion

that judgments of self motion are based on properties of optical flow fields (i.e., angles and angular rates) that depend on distance and motion relative to textured surfaces.

Multisensory roughness perception of virtual surfaces. This collaborative research project between OSU and the Ohio Supercomputer Center is investigating tactile perception in simulation environments. Our own previous studies of haptic/visual interactions in virtual sensing support the notion that multisensory input can actually improve perceptual acuity. We investigated the ability to discriminate the roughness of two haptic simulated gratings that differed in grating spatial period (i.e., the thickness of the bars on the grating). These gratings were presented haptically using a 6-degree-of-freedom PHANToM haptic interface provided from Hayes Investment funding, and visually using a stereoscopic visual display. Their findings indicated that for some values of grating spatial period, performance in the multimodal haptic+visual presentation condition was superior to that for either haptic-only or visual-only presentation, suggesting a facilitatory interaction of the two modalities. In follow-up work, Weisenberger and Poling (2004) investigated the addition of auditory feedback to the virtual grating discrimination task, and found that in some cases, performance in the three-modality haptic+visual+auditory condition was superior to that for any two-modality combination, again supporting the idea that multisensory presentation can provide additional information that can be used by the observer to improve performance beyond unisensory limits. The results of these studies help to provide the basic science base for designing applications in virtual environments.

Modeling Information Quality Expectation in Unmanned Aerial Vehicle Swarm Sensor Databases High-End. Researchers at the Air Force Institute of Technology (AFIT) are examining future reconnaissance systems that are likely to incorporate large numbers ("swarms") of Uninhabited Aerial Vehicles (UAVs) with wide-ranging sensor capability. Because the volume of data involved is likely to overwhelm telecommunication systems, it is anticipated that these data will be stored locally (i.e., in the UAVs) and downloaded only when queried. This project developed models and tools to help operators visualize the behavior of the swarm, and thereby better predict if the swarm has obtained relevant information and if so where in the swarm the information can be found.

Computing and Networking Research Test-bed for Next generation Data Driven, Interactive Applications. This infrastructure project involves collaboration among the Ohio State University Departments of Computer Science and Engineering and Biomedical Informatics, and the Ohio Supercomputer Center to establish a networked cluster test-bed consisting of a compute cluster, a storage cluster, an SMP system, inter-cluster networking, and visualization including haptic devices. This dedicated test-bed will support multiple research directions in data-intensive computing and visualization.

Evaluating Elicited Anxiety in a Simulation Environment. This applied research project at OSC aims to harness emerging technologies to simulate a common agricultural setting that provides the potential for acute injuries. The investigators are adapting current technologies to simulate an environment with a power take off (PTO), an indispensable tool found on farms that transfers power from a common tractor to be redirected to drive various implements. The PTO has continuously proven to be problematic in providing acute injuries through entrapment or entanglement. The

experimental design is exploratory and will be used to characterize the sample sizes for future controlled studies and the possible extension of the simulation for use as a supplemental training tool in agricultural safety (additional proposals are planned in FY07).

Grants and Contracts

Enhanced Auditory Displays for General Aviation. Air Force Research Laboratory to General Dynamics Inc. $2,600,000, 2003-2005. Subcontract to WSU - Use of auditory displays for general aviation. $225,094, 2004-2005. (Gilkey, PI.)

Target Detection in Virtual. Environments. Veridian Engineering, $20,200, 2003 - 2004. (Gilkey, PI)
Auditory-Aided Visual Target Acquisition. Air Force Office of Scientific Research, Funding to WSU: $50,000, 2003-2004. (R. H. Gilkey, PI)

Multisource sound localization. Subcontract from General Dynamics Inc., $12,311, 2004-2005. (Gilkey, PI.)

Collaborative research on multisensory interaction. Air Force Research Laboratory, $179,548, 2005-2008. (Gilkey, PI.)

Robotic Systems for On-Orbit Servicing. DAGSI, $200,000. 2001-2004 (Weisenberger, PI)
Support for Ohio Research in Advanced Internet Utilization, Simulation, and Telerobotic Ohio Board of Regents Research Challenge, $52,000. (R. H. Gilkey, PI)

High-End Computing and Networking Research Test-bed for Next generation Data Driven, Interactive Applications. National Science Foundation, $1,530,000, 2004-2009. (Panda, PI)
Evaluating Elicited Anxiety in a Simulation Environment. Great Lakes Center for Agricultural Safety and Health (GLCASH)/National Institute for Occupational Safety and Health, $15,000, 2005 – 2006. (Stredney, PI)

Publications

Bennett, A.M., Flach, J.M., McEwen, T.R., Russell, S.M. (2006). Active regulation of speed during a simulated low-altitude flight task. *Proceedings of the Human Factors and Ergonomics Society.* San Francisco, Oct. 2006.

Mateo, J. C., Manning, J. T., Cowgill, J. L., Simpson, B. D., Moore, T. J., Weisenberger, J. M., & Gilkey, R. H. (2005). Evaluation of a collaborative movement task in a distributed three-dimensional virtual environment. *Proceedings of the HFES 49th Annual Meeting, 49,* 1578-1582.

Poling, G.L., Weisenberger, J.M., and Kerwin, T. (2003). The role of multisensory feedback in haptic surface perception. *Proceedings of IEEE-VR 2003*, 742-748

Repperger, D.W., Gilkey, R.H., Green, R., LaFleuer, T.C., and Haas, M.W. (2003). The effects of haptic feedback and turbulence on landing performance in an immersive Cave automatic virtual environment (CAVE). *Perceptual and Motor Skills, 97,* 820-832.

Saltz, J.H., Çatalyürek, U.V., Kurç, T.M., Gray, M. Hastings, S., Langella, S., Narayanan, S., Martino, S., Bryant, S., Peszynka, M., Wheeler, M., Sussman, A., Beynon, M., Hansen, C., Stredney, D., Sessanna, D.: Driving Scientific Applications by Data in Distributed Environments. *International Conference on Computational Science 2003*: 355-364

Simpson, B.D., Brungart, D.S., Dallman, R.C., Joffrion, J., Presnar, M., and Gilkey, R.H. (2005). Spatial audio as a navigation aid and attitude indicator. *Proceedings of the HFES 49th Annual Meeting*, *49,* 1602-1606.

Simpson, B.D., Brungart, D.S., Gilkey. R.H., Cowgill, R.l., Dallman, R.C., Green, R.F., Youngblood, K.L., and Moore. T.J. (2004). 3D audio cueing for target identification in a simulated flight task. *Proceedings of the Human Factors and Ergonomics Society 48th Meeting, 48,* 1686-1690.

Simpson, B.D., Brungart, D.S., McKinley, R.L., and Gilkey, R.H. (2005). Spatial audio displays for improving safety and enhancing situation awareness in general aviation environments. *Proceedings of the NATO HFM Symposium on New Directions for Improving Audio Effectiveness, P26-1 - P26-15.*

Stredney D., Bryan, J., Sessanna D., and Kerwin, T. (2003) Facilitating Real-Time Volume Interaction, Proc. MMVR 2003, Westwood (Eds). IOS Press, Amsterdam, 329-335

Stredney D., Sessanna D., Hittle B., and Guthikonda,S., Evaluating Elicited Anxiety in a Simulated Environment, Proc. MMVR15, submitted.

Weisenberger, J.W., and Poling, G.L. (2004). Multisensory roughness perception of virtual surfaces: Effects of correlated cues. *Proceedings of IEEE-VR 2004*, 161-168.

Other Talks

Bennett, A.M., Flach, J.M., McEwen, T.R., Russell, S.M. (2006). Detecting changes in speed during an active control task: Are we effective controllers? *International Society for Ecological Psychology, North American Meeting, University of Cincinnati*, Cincinnati, OH (June 22-24).

Theses

Baldwin, P. D. (2005) Modeling Information Quality Expectation in Unmanned Aerial Vehicle Swarm Sensor Databases, MS Thesis, Air Force Institute of Technology.

Bennett, A.M. (anticipated Sept 2006). Active regulation of speed during a simulated low-altitude flight task. Masters Thesis, Wright State University.

Joffrion, J.M. (2004). Inertial Head Tracking for 3D Audio (Project "Sound Advice"), MS Thesis, Air Force Institute of Technology.

Lee, W C. (2004) Swarm Based Implementation of a Virtual Distributed Database System in a Sensor Network, MS Thesis, Air Force Institute of Technology.

Manning, J.T. (anticipated Summer, 2006). Real time auditory feedback in three-dimensional environments with delayed auditory feedback. Senior Honors Thesis, Wright State University.

Mateo, J. (anticipated Fall, 2006). Effect of Variable Transmission Delay on Target-Acquisition Performance: A Parametric Study. Masters Thesis, Wright State University

Poling, G. L. (2002). The Role of Multisensory Feedback in Haptic Surface Perception. Senior Honors Thesis, Department of Speech and Hearing Science, Ohio State University.

Patents

A patent application describing the auditory attitude indicator discussed in the section on “Enhanced Auditory Displays for General Aviation” is being prepared by Douglas Brungart and Brian Simpson of AFRL.

Collaborations

Most of the research involved extensions of existing collaborations. The institutions involved are indicated in the descriptions of the research projects. In particular, the collaborations between WSU researchers and AFRL researchers have expanded considerably and changed qualitatively. We now work together much more as a research team, rather than simply in a granteer-grantor relationship.

Consortium for Enviromental and Process Technology

Final Research Progress Report

Partners: Wright State University, Kent State University, Ohio State University, Miami University, University of Cincinnati

Summary Report: The goal of this Hayes project was to formally establish a Consortium for Environmental and Process Technologies (CEPT), which specifically focuses its research efforts on the development and application of new methodology and techniques for monitoring toxic, persistant, and accumulating contaminates in the enviroment. Among the more problematic compounds that have been specifically targeted by CEPT scientists are highly chlorinated compounds like dioxins, furans, and PCBs, as well as their bromonated analogs. These compounts are potent mutigens and can result in a number of severe health problems. Other important compounds under investigation during the course of this grant have been polybromonated diphenyl ethers, which are used widely as fire retardants and various agrochemical and pharmaceuticals, especially those that can degrade to form even more highly toxic compounds.

Wright State University serves as the host for CEPT, which is madeup of additional members from Kent State University, Miami University, Ohio State University and the University of Cincinnati. During the last four years, CEPT researchers have been engaged in a variety of projects that have ranged from basic research related to the development and characterization of new materials, methods, and instrumentation to various applied in-field studies of the fate and effects of the targeted compounds. Likewise, during this same time, the Hayes funds were used to purchase various types of equipment for sample collection and workup, as well as equipment for carrying out state-of-the-art measurments, including various chromatographic and mass spectrometric instruments. Three mass spectrometers were purchased, two smaller GC-ion trap units, one each at OSU and UC, and a larger Bruker BioTOF III high resolution spectrometer equipped with both conventional and microsample introduction accessories as well as on-line HPLC and capillary electrophoresis units at WSU. Other major equipment purchased were 1) a pressure-adsorption characterization unit and a flow-cyctometer at KSU, 2) an atomic absorption spectrometer at Miami, and 3) an ultra centrifuge, a parallel processing chromatograph, and a high pressure accelerated extraction unit at WSU.
During the course of the current Hayes grant a number of important milestones have been made towards accomplishing CEPT's general goals as summarized above. Among these have been:

1) The establishment of a statewide program for assaying wastewater sludge for the presence of dioxins, furans, and PCBs. This program was a direct result of Ohio EPA mandated testing for these compounds and utilizes Hayes instrumentation. Currently Brehm Research Laboratory, host for CEPT, carries out assays yearly for about 40 to 45% of all municipalities within Ohio affected by mandated testing program and hopes to increase the number of Ohio users by 25 to 30% over the next three to five years.
2) Various fundamental and applied in-field studies have been carried out to evaluate the fate and effects of a number of highly toxic organic and inorganic contaminants in

the environment including their distribution in land masses and aquatic systems. This work has resulted in numerous publications and presentations (i.e., those listed below) as well as the involvement of many undergraduate and graduate students in carrying out this work.
3) During the course of the Hayes grant, a number of important contract projects continued, including work on the U.S. EPA's Superfund Project, testing for various State Agencies like Alabama, New York, Texas, etc., and varous national and international companies. In one instance, the development of a novel procedure for measuring nitrosoglyphosate in commerical agricultural products has resulted in a two-step procedure that has potential for comericalization.
4) Pioneering work has been carried out on the synthesis of various silica and carbon-based nanostructured materials including the development of a novel self-assembly procedure for producing uniformly controlled pore structures. This work has resulted in numerious publications as well as one patent application. With the potential of additional patents related to their application as novel adsorbents for sesquestering targeted compounds (e.g., metal chelated surfaces).
In addition, to the above research and development efforts by CEPT members, over twenty graduate students and numerous undergraduates have been trained using instrumentation purchased by the Hayes money. The number of scientific publications by CEPT members have exceeded 130 and the number of presentations given scientific meeetings over 120. Likewise, the amount of funding generated directly related to CEPT goals has been about 1.5 million dollars during the course of the grant.

Recently, WSU has reloacated Brehm Environmental Laboratory, to a new state-of-the-art Laboratory Faciltiy with nearly 9,000 sq.ft. of laboratory and office space. This internally funded project demonstrates the importance Wright State Universiy places on the research and development efforts of the Laboratory including its close affiliation with CEPT. The new facility will be an important investment in helping to attract additional funding and in the commericalization of new technology that results from the current on-going research and development efforts.

As part of the environmental research conducted on dioxins, dioxin-like, and related organic compounds, CEPT researchers specifically examined the toxicity and bioaccumulation of a common polycyclic aromatic hydrocarbon (PAH), phenanthrene (PHE), in earthworms. Results of this study can be used in support of ecological risk assessments carried out in support of site-cleanup of areas such as brownfields. One portion of the study focused on measuring PHE in earthworm tissues during toxicity and bioaccumulation tests in soils differing in physical/chemical characteristics and another portion examined the applicability of solid-phase extraction techniques (solid phase-microextraction fibers (SPMEs) and C18 disks) as surrogates for modeling the uptake of PHE by earthworms. SPMEs and C18 disks are technologies that have received increased attention over the last decade as a unique tool for measuring chemicals in aquatic systems, but their application to sediments and soils has been limited. Their application for measuring chemicals has many advantages such as decreased time and expense and increased sensitivity relative to traditional solvent-extraction techniques. Since they are solid phases, they also can be used to estimate the rates of chemical uptake, similar to what is done with organisms during bioaccumulation studies. In this way, they can be "biomimetic" or mimic an organism

in the way they take up organic chemicals. If there is a strong correlation between chemical uptake by SPME or C18 disks and chemical uptake by the organism, then bioaccumulation testing with organisms can be reduced or even eliminated from screening-level assessments during the ecological risk assessment process, resulting in significant cost reductions.

The development of Ecological Soil Screening Levels (EcoSSLs) for PAHs by the US Environmental Protection Agency (US EPA) is based upon total chemical levels in the soil. EcoSSLs are soil chemical concentrations intended for use during screening level risk calculations. However, the physical and chemical characteristics of soil may drastically affect chemical bioavailability by binding chemicals and influencing uptake, bioaccumulation, and toxicity, resulting in siginificant overestimation of the bioavailability and toxicity of a chemical in a soil. Chemical measurements using SPMEs or C18 disks have the added benefit of measuring the potentially bioavailable fraction of PAHs in soil and may provide a more accurate measure of chemical exposure, resulting in more realistic clean-up guidelines and reduced clean-up costs.

In the present study, the bioaccumulation of PHE and its chronic toxicity to the earthworm (*Eisenia andrei*) in five different soils was examined. The soils used (Kirkland clay loam, Perkins sandy loam, Richfield clay loam, Sassafras sandy loam and Webster clay loam) exhibited a wide range of physico-chemical characteristics (pH - 4.0-7.3; organic carbon content - 0.4-2.4 g/kg; clay content - 12-36%). The toxicity of PHE was estimated by monitoring reproduction (cocoon production). PHE bioaccumulation tests were also conducted in the five different soils to examine the effect of soil type on the uptake kinetics of PHE by the earthworm. The bioavailability of PHE in toxicity and bioaccumulation tests was studied by measuring PHE body burdens in earthworm tissues and C18 disk soil extractions over time. SPME measurements are currently being conducted.

The highest reproductive toxicity and accumulation was observed in soils with the lowest content of organic carbon (Perkins sandy loam) and, thus, highest levels of bioavailable PHE. Body residues measured in day 28 for this study did not correlate well with toxicity. Highest body residues were found in earthworms from soils with lower organic matter content. Concentrations of PHE extracted by C18 disks correlated well with PHE body residues and, thus, this biomimetic technique can potentially be used to estimate PHE body residues in *E. andrei* and predict toxicity.

In addition to the research with earthworms, we are currently embarking on a similar project examining the correlation between the uptake of polychlorinated biphenyls (PCBs) by zebra mussels and SPMEs. Zebra mussels will be exposed to a mixture of 21 PCBs in solution and the uptake of PCBs by the mussels and the SPMEs will be monitored over time to establish a correlation in uptake.

Additionally, we have also established research collaborations with Dr. David Culver (Department of Evolution, Ecology, and Organismal Biology, Ohio State University) and his PhD student, Annie Jacob. As part of a larger project entitled “Impacts of the use of fertilizers, herbicides and algaecides in aquaculture”. This project examines the effects of various management practices used for controlling algae and aquatic vascular plants in Ohio Department of Natural Resources (ODNR) fish culture

facilities. Control of algae is achieved using copper sulphate, while aquatic vascular plants are controlled by applying fluridone, an aquatic herbicide. Differences in fish production have been observed in different culture facilities and the question is whether reduced production is a result of chemical applications. Therefore, the fluridone and copper content of water samples taken from aquaculture ponds at ODNR fish culture facilities in Hebron and Senecaville has been monitored and its relationship to fish production assessed.

An exponential decline in fluridone concentrations was observed in ponds after treatment, with a half-life of fluridone of approximately 21days. Application of fluridone and copper together reduced the macrophyte biomass by 86% while fluridone alone reduced the macrophyte biomass only by 28%. This is because Chara was the dominant macrophyte in many ponds and fluridone was ineffective in controlling Chara while copper sulfate has been reported to control Chara from previous studies. These results have allowed us to focus on copper as the more likely source of reduced fish production in these facilities.

The HPLC purchased with financial assistance from the Hayes Investment Fund was used for some of the chemical analysis conducted in these studies and will continue to be a valuable addition to OSU's laboratory chemical analysis capabilities in future studies.

Another phase of the project was to develop new methodologies for sample preparation. Environmental samples are typically comprised of multifaceted matrices with complex mixtures of analytes and potential interferences. Thus, they typically require significant pretreatment but the pretreatment must be carefully designed to minimize perturbation of the sample desired analyte composition. Her approach was to investigate the potential of a novel class of materials called ionic liquids for selective sequestration of dioxins. Ionic liquids, sometimes referred to as molten salts, are ionic substances which are liquids at or near room temperature. Their ionic character gives rise to a liquid with virtually no vapor pressure. Hence, they are of considerable interest as potentially "green" solvents. Prior work by Professor Stalcup at the University of Cincinnati revealed that these ionic liquids have a particular affinity for oxygen-containing aromatic substances related to dioxins. Much of the effort expended during the funding cycle was directed towards better characterization of the interactions between ionic liquids and aromatics. The work has resulted in the award of a grant to UC from the National Institutes of Health.

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Solch, J. G., Gilpin, R. K., and Wagel. D.J.: "Web-Based Simulation for Chemistry Classrooms, Labs, and Distance Learning," Pittcon2003, Orlando, FL, March 2003.

VanNess, G. F., Rukunda, F. L., Gilpin, R. K., and Solch, J. G.: "Improved Sample Preparation Strategies for Dioxins, Furans, and PCBs," Pittcon2003, Orlando, FL, March 2003.

Gilpin, R. K., Solch, J. G., Garrett, J. H., VanNess, G. F., Rukunda, F. L., and Wagel, D. J.: "Assessment of Polybrominated Diphenyl Ethers in Sewage Sludge," Pittcon2003, Orlando, FL, March 2003.

Gilpin, R. K. and W. Zhou: "A Simple Infrared Method for Characterizing the Polymorphic States of Mefenamic Acid," Pittcon2004, Chicago, IL, March 2004.

Gilpin, R. K. and W. Zhou: "HPLC and ESI-MS Studies of the Thermal Degradation of Mefenamic Acid by Alternate Mechanisms," Pittcon2004, Chicago, IL, March 2004.

Gilpin, R. K. , Zhou, W., and Gilpin, C. S.: "Infrared Studies of the Thermal Conversion of Flufenamic Acid Between Polymorphic States," Pittcon2004, Chicago, IL, March 2004.

Gilpin, C. S., Zhou, W., and Solch, J. G.: "Studies of the Thermal Fragmentation of Fenamates under ESI-MS Conditions," Pittcon2004, Chicago, IL, March 2004.

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Zhou, W. and Gilpin, R. K.: "Reversed-Phase HPLC Method for the Determination of Nitrosoglyphosate in Commercial and Envirnomental Samples," Pittcon2005, Orlando, FL, March, 2005.

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Oksana Olkhovyk, Mietek Jaroniec: Synthesis and Adsorption Properties of Periodic Mesoporous Organosilicas with Large Heterocyclic Bridging Groups Abstracts of the International Symposium on Nanoporous Materials IV, Niagara Falls, Ontario, Canada, June 7-10, 2005.

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Burton, GA. 2005. Field assessment of benthic invertebrate community to sediment nickel toxicity. Nickel Environmental Risk Assessment Panel. Ghent, Belgium.

Custer KW, Burton GA. 2005. Macroinvertebrate community responses in streams using the benthic in situ Toxicity Identification Evaluation (BiTIE) chamber. Abstr. Annu. Meeting North American Benthological Society. New Orleans, LA.

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Jacob, A.P., Conroy, J.D, Voigt, A., Lanno, R.P., Hosack, M., Tew, K.S., Culver, D.A. An evaluation of the effects and effectiveness of herbicides in aquaculture ponds. 45th

Annual Meeting, Aquatic Plant Management Society, San Antonio, TX, Jul. 10-13, 2005.

Graduate Students by University:

Wright State University – 12
Kent State University – 9* (1 of these student was co-directed by Dr. Jaroniec and Dr. Gilpin)
Miami University (of Ohio) – 1
University of Cincinnati – 2
Ohio State University – 1

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Wright State University:

R. K. Gilpin $911,959

G. A. Burton – none reported

Kent State University:

M. Jaroniec - $416,693

J. Blank – no information provided

Miami University (of Ohio):

J. T. Oris – none reported

University of Cincinnati:

A.M. Stalcup - $788,434

Ohio State University:

R.P. Lanno - $47,756