IUCRG Recipients and project titles are:

"A Plant Biology Informatics Partnership to Compete in the Emerging Field of Epigenetics," Craig Pikaard (College of Arts and Sciences) and Haixu Tang (School of Informatics and Computing)

Epigenomics is a new field that combines genomics - the high-throughput analysis of DNA and RNA sequences representing entire genomes - with epigenetics, the analysis of alternative gene activity states. Chemical and structural modifications of chromosomes that influence gene expression are key to epigenetic regulation, affecting such processes as development, gene dosage control, defense against invading viruses or transposable elements and responses to the environment, including diet. Epigenetic gene silencing poses obstacles to genetic engineering and gene therapy in agriculture and medicine and contributes to disease states such as cancer by inactivating genes that keep cell proliferation in check. For all of these reasons, epigenetic research is among the most active sub-fields in biology.

To compete for funding in the emerging field of epigenomics, expertise in several key methodologies is needed, including genome-wide DNA methylation analyses, genome-wide analyses of small RNAs that program epigenetic modifications, and genome-wide analyses of chromosomal sequences to which key regulatory proteins bind. In this collaborative study by the Pikaard and Tang groups, we will establish these capabilities at IUB while examining the inter-relationships between HISTONE DEACETYLASE 6 (HDA6), the plant-specific DNA-dependent RNA Polymerase, Pol V and the biogenesis of short-interfering RNAs (siRNAs) responsible for the epigenetic process of RNA-directed DNA methylation.

"All-atom Theory of Virus Behavior: Applications to Vaccine Discovery," Peter Ortoleva (College of Arts & Sciences) and Darren Brown (School of Medicine)

The overall objective of this project is to use basic principles of physics to understand the behaviors of viruses and use this knowledge to design antiviral vaccines. Using basic laws of physics we are seeking to develop nanoscale constructs that emulate a virus and thereby trigger an immune response. Through computer simulation using our unique software, we design optimized vaccines which are thermally and chemically stable, with cross-protectiveness against a spectrum of viral types. Existing vaccines usually require an expensive infrastructure usually not available in developing countries. The physics used to achieve these goals has been implemented as a computer code. This code simulates the motions of all the

atoms constituting the virus or virus-like vaccine particle. Using this software, we are demonstrating a procedure for achieving the computer-aided design of vaccines. Our demonstration system is human papillomavirus, the causative agent of a number of cancers that is responsible for the deaths of several hundred thousand women annually. Demonstrating our methods on HPV will open the door to applications to a variety of other threats to global health.
This project is a collaboration between Prof. D. Brown, M.D. (IUSoM, Indianapolis) and Distinguished Prof. P. Ortoleva (Department of Chemistry, IUB). Our team of graduate and postdoctoral researchers will use the Indiana University Collaborative Research Grant funds to carry out demonstration simulations on HPV vaccine design. We hope to discover a more stable and cross-protective HPV vaccine and perfect our methodology for use with other viral threats to global health.

"Citizen Participation in Environmental Science Studies: Addressing Air Quality Issues in NW Indiana," Julia Peller, Erin Argyilan, and Ellen Szarleta (IU Northwest)

Of the many environmental and health concerns in Northwest Indiana, substandard air quality ranks at the top. Northwest Indiana has a history of being designated by the EPA as a nonattainment area for criteria air pollutants. Science based data on high levels of air pollutants overlap with issues of environmental justice and public health, which have largely focused on the heavily urban communities in Lake County. Often neglected are the weather patterns that alter the distribution of air pollutants, necessitating air quality investigations in communities located near the point sources of pollution and in communities located downwind from the major sources.

This project brings together faculty from the School of Public and Environmental Affairs (SPEA), Chemistry and Geosciences to address critical public health and science issues and existing perceptions related to air quality. It will be the first step in bridging the gap between the technical science of air quality assurance and the concerned citizens in northern Indiana communities. Methods for scientific data collection of specific air pollutants from vehicular and industrial emissions will be established with the involvement of concerned citizens. The project will empower citizens with new knowledge and strengthen existing knowledge of public health issues related to air quality, enabling the community to actively engage in policy discussions and decisions. Moreover, the project will initiate an understanding of the impacts of various sources of air pollutants, the communities most affected and the influences of

prominent weather patterns, along with their implications on climate change.

"Coupling Atmospheric Chemistry with Human Health: A Novel Approach to Investigating the Source of Chronic Childhood Lead Poisoning," Gabriel Filippelli (School of Science) and Sara Pryor (College of Arts and Sciences)

One in six U.S. children under 7 years of age have lead poisoning. How this many children are still being exposed to harmful lead is a mystery. The core of this research project is to develop novel techniques and experiments bridging the health and physical sciences to understand how children are exposed to the harmful element lead, and thus gain information on how to reduce this exposure. Based on our previous work, we hypothesize that lead-saturated soils and the resuspension of fine materials from these soils during dry seasons play a major role in lead exposure to urban children, with inhalation being the missing link between exposure and human uptake. This might be an important answer to the puzzle of why 30% of children with clinically-defined lead poisoning do not have a clear lead paint source for exposure. This apparent link between ambient particle concentrations (droplets or solids suspended in the atmosphere) and lead exposure is the core thesis of our proposed project.

We will combine atmospheric particulate sampling and novel geochemical techniques designed to simulate human pulmonary fluids to explore the spatial and temporal patterns in lead bioavailability in Indianapolis. The particulate sampling will be based on several techniques using stationary and model detectors. We will combine the particulate chemistry and simulated human uptake results with extant blood lead records for Indianapolis children, thus providing an initial test of our hypothesis and providing adequate preliminary data to compile a competitive larger research proposal for external funding.

"Drug-Drug Interaction Prediction from Large-scale Mining of Literature and Patient Records," Lang Li (School of Medicine), Luis Rocha (School of Informatics and Computing), and Jonathan Duke (School of Medicine)

Drug interactions are a significant cause of adverse drug events and have been associated with increased patient morbidity and mortality. Drug interactions result in considerable cost to the public health system and may limit the utility of newly developed drugs. Large repositories of clinical data have become increasingly valuable tools for drug safety surveillance. With longitudinal data on millions of patients, we now have the ability to perform large-scale analyses on these resources, which can uncover even rare adverse drug events. Over the past 18 months, the *Regenstrief Institute* has taken a leading role in a national project known as the *Observational Medical Outcomes Project*. This effort has resulted in the generation of a large-scale (~2.5 million patient) database designed specifically for the efficient performance of drug safety research. *Biomedical literature mining* is an important informatics methodology for large scale information extraction from repositories of textual documents, ultimately leading to knowledge discovery.

In this project, we will develop new literature mining methods to predict drug interactions, and correlate our predicted drug interactions with actual adverse events seen in the large patient database. Our approach is significant for:

(1) Large-scale mining and analysis of drug interactions among FDA approved drugs.
(2) Assessing the clinical importance of discovered interactions based on the analysis of a large-scale patient repository.

"Establishment of a Human *in vitro* Model System for Studies of Usher Syndrome," Jason Meyer (School of Science) and Eri Hashino (School of Medicine)

Usher Syndrome is a disease characterized by the combination of blindness and hearing impairment. However, due to the complexity of the genetic basis for this disease, little evidence has been collected to explain how this disease leads to the loss of sensory receptor cells in the retina and inner ear. Additionally, no treatment option is available to treat this progressive degenerative disorder. With combined expertise in the development of both the retina and the inner ear, along with extensive experience working to specify a neural fate from stem cells, the investigators in this proposal are uniquely suited to address important questions about this complex disorder. In this application, we aim to improve our understanding of Usher syndrome by generating induced pluripotent stem cells (iPSCs) from a patient afflicted with this disease. A well-defined protocol exists for the derivation of iPSCs from skin cells, which reprograms them to a stem cell fate using a specific set of genes. These iPSCs possess the ability to generate all cell types of the body, including the nervous system. We predict that reprogrammed iPSCs from a patient with Usher Syndrome will provide a novel model system using human cells wherein unique studies of disease progression can be undertaken. These newly established Usher-iPSCs can be directed by standard protocols to develop into affected cell types of the nervous system, exhibiting key symptoms associated with Usher Syndrome. Furthermore, it will also be possible to screen new drugs for their ability to halt disease-related symptoms.

"Functional Analysis of Protein Phosphatases in Tumorgenesis and Metastasis," Zhong-Yin Zhang and Weinian Shou (School of Medicine)

Reversible protein phosphorylation, regulated by the coordinated actions of protein kinases and protein phosphatases, is of critical importance to signaling events that underlie all essential cellular processes. Not surprisingly, aberrant protein phosphorylation has been linked to many human diseases, including cancer. Unlike protein kinases whose role in cancer is well established,

the involvement of protein phosphatases in cancer progression and development is less well defined. The focus of this proposal is on the Prl (phosphatase of regenerating liver) phosphatses and protein phosphatase 5 (PP5), both of which are implicated in tumorigenesis and metastasis. Prls are overexpressed in a variety of tumors and high levels of Prl expression are associated with tumor metastasis. PP5 is up-regulated in human cancers, and PP5 may also represent a novel target for cancer therapy. The proposed study combines the complementary expertise of two highly productive laboratories to generate mutant mice lacking Prl phosphatases to define the in vivo function of prls and to identify small molecule inhibitors of PP5 for therapeutic development. This collaborative endeavor will enable Dr. Zhang to gain experience in mouse genetics and its application to address the in vivo function of protein phosphatases involved in cancer. The collaboration will also help Dr. Shou to move into the realm of small molecule therapeutics targeting novel cancer promoting pathways. Successful completion of this 1-year pilot project will produce sufficient preliminary data for two joint RO1 applications, one aimed at in vivo functional studies of the Prl phosphatases in cancer biology, and one aimed at targeting PP5 for novel anticancer agents.

"Injection of Endothelial Colony Forming Cells to Enhance Fracture Repair and Bone Regeneration," Jiliang Li (School of Science) and Mervin Yoder (School of Medicine)

Bone injuries are common and costly to the public through high health care expenditures. Although bone has the capacity to self-heal, this is limited to a relatively minor fracture, and additional treatments are required for bone healing of large defects. The long-term goal of this project is to develop a novel cell therapy strategy using endothelial colony forming cells (ECFCs) to accelerate healing of bone fractures and repair of bone defects. ECFCs are circulating progenitor cells that take part in new blood vessel formation and it is known that new vessel formation is required for new bone formation. Further, endothelial cells have been shown to undergo an endothelial to mesenchymal cell transition to become mesenchymal stem cells (MSCs). MSCs may differentiate into osteoblasts; a critical cell required to form new bone. The potential capacity of ECFC to be directed to form new vessels and bone tissues simultaneously makes ECFCs an excellent candidate cell population to be tested to enhance fracture repair and regenerate new bone tissue. In the current study, we will inject a collagen matrix containing ECFCs into fracture or defective bone healing sites that are surgically produced in animal models. We will investigate whether ECFCs can enhance new blood vessel formation at the site of damaged bone and subsequently

induce bone regeneration. Repair of bone damage will be assessed using state-of-the-art technology, such as micro-Computed Tomography and Fluorescent microscopic imaging. Successful accomplishment of this project would make it possible to translate this pre-clinical study to human clinical trials.

"Mathematical Modeling of Ocular Blood Flow and Its Relations to Glaucoma," Giovana Guidoboni (School of Science) and Alon Harris (School of Medicine)

Glaucoma is a disease in which the optic nerve is damaged, leading to progressive, irreversible loss of vision. Glaucoma is the second leading cause of blindness worldwide, and yet the mechanisms underlying its occurrence remain elusive. Elevated intraocular pressure (IOP) remains the current focus of therapy, but unfortunately many glaucoma patients continue to experience disease progression despite lowered IOP, even to target levels. Clinical observations show that alterations in ocular blood flow play a very important role in the progression of glaucoma. Significant correlations have been found between impaired vascular function and optic nerve damage, but the mechanisms giving rise to these correlations are still unknown.

The goal of this project is to investigate the bio-mechanical connections between vascular function and optic nerve damage, in order to gain a better understanding of the risk factors that may be responsible for glaucoma onset and progression. To reach this goal, a variety of mathematical models will be used to describe the different ocular anatomical components, including humors, retina, choroid and sclera. From the mathematical viewpoint, the project involves multiscale problems and fluid-structure interactions, which are still active areas of research in the mathematical field. From the medical viewpoint, our analysis will provide valuable insights on glaucoma disease, hopefully leading to the design of novel more comprehensive therapies for glaucoma patients. The project will then have a significant impact on both the mathematical and medical communities and, ultimately, on the whole society improving the quality of life of many individuals.

"Microbial Interactions Within Pathogen Vectors and Human Disease Risk," Keith Clay (College of Arts and Sciences), Clay Fuqua (College of Arts and Sciences) and Frank Yang (School of Medicine)

The goal of this project is to investigate how microbial interactions within the black-legged deer tick (*Ixodes scapularis*) affect transmission of the agent of Lyme disease and infection of vertebrate hosts. The pathogen, *Borrelia burgdorferi* is transmitted by bites of infected deer ticks. Lyme disease is the most common vector-borne disease in the US with nearly 30,000 new cases reported in 2009. Recent research has revealed high

levels of microbial diversity within ticks and other arthropods which may contribute to their nutrition and defense against parasites and pathogens. Recent research by the Clay and Fuqua labs, in collaboration with colleagues at Ball State University, has documented the diversity and distribution of microbes in black-legged deer ticks. Recent results from the Yang lab have shown that *B. burgdorferi* dramatically alters its gene expression profile during tick feeding and that these changes are essential for successful colonization of the tick and transmission to the mammalian host. Here we specifically propose to: 1) experimentally manipulate and quantify microbial communities of black-legged deer ticks, 2) evaluate transmission of *B. burgdorferi* in relation to other microbes present within ticks, and 3) quantify gene expression of the tick microbial community in response to colonization by *B. burgdorferi*. Our results will provide basic knowledge of how microbial interactions within ticks affect the acquisition, transmission and virulence of human pathogens, and they will have potential applications for reducing disease burden. Further, our results will have direct application to other arthropod vectors such as mosquitoes, lice and fleas.

"Perioperative System Reengineering Program," Bradley Doebbeling (School of Medicine), Jason Saleem (School of Engineering & Technology), Matthew Burton (School of Medicine), Hamid Ekbia (School of Library & Information Sciences), and Mikyoung Lee (School of Nursing)

"Pilot Initiative to Improve Transfers of Care between Nursing Homes & Emergency Departments," Kevin Terrell (School of Medicine) and Susan Hickman (School of Nursing)

Emergency departments (EDs) are major providers of nursing home residents. Regrettably, many care settings, such as nursing homes and EDs, operate in isolation, providing care without complete information about the patient's condition, medical history, or expectations of the other site of care. The objectives of this research pilot are (1) to develop a new collaborative research partnership that includes the School of Medicine and the School of Nursing and (2) to take our research in new directions by (a) implementing and testing a promising intervention to improve the quality and safety of transfers of care between nursing homes and EDs and (b) carrying out the pilot in a community-based (i.e., non-academic) setting, giving it real-world applicability. The intervention includes three key parts: more useful transfer documents, better verbal communication across sites of care, and close partnership with participating care sites. The participating sites will include the only ED in Lebanon, Indiana (i.e., Witham Health Services), the only emergency medical services (EMS) system in Lebanon (i.e., Boone County EMS),

and the four nursing facilities in Lebanon (i.e., Hickory Creek, Homewood, Essex, and Parkwood). We will collect information about all transfers of care between the nursing facilities and the ED over a 10-month period. We will collect important outcomes in preparation for a future grant submission to a federal funder, such as the Agency for Healthcare Research and Quality (AHRQ).

"Provider Decision-Making For The Management Of Comorbid Pain And Depression: A Novel Virtual Human Technology Investigation," Adam Hirsh (School of Science), Kurt Kroenke (School of Medicine), Matthew Bair (School of Medicine) and Marianne Matthias (School of Liberal Arts)

Over 75 million Americans experience pain annually, and 50 million are disabled by pain. Chronic pain has emotional consequences as well. Depression is present in up to 85% of patients with a coexisting pain condition. Not only do these conditions exert a considerable toll on patients, families, and society, they also present a significant challenge to health care providers. Chronic pain providers face competing demands and make difficult treatment decisions daily without clear research evidence guiding their choices. Consequently, all patients with chronic pain and depression are at risk for receiving suboptimal care, and research suggests that certain patient groups (e.g., racial and ethnic minorities) may be at particular risk. The objective of this research is to better understand how providers make assessment and treatment decisions for patients with chronic pain and depression. A combination of research methods will be used in this study. We will create computer simulations of patients using virtual human technology. This technology will allow us to control key patient demographic and clinical variables under investigation. We will also use interview methodology to examine providers' reasons and motivations for electing particular treatment options for pain and depression. These interviews will allow us to capture a richer, more complete picture of why providers make particular decisions. This project addresses a critical public health issue and will contribute to the long-term objectives of improving chronic pain care and reducing health care disparities. The results of this study will inform future research, practice, and health care education.

"Real-Time Multi-Channel Neural Signal Processor System," Ken Yoshida (School of Engineering & Technology), Jonathan Mills (School of Informatics & Computing) and Richard Eberhart (School of Engineering & Technology)

Almost all interactions between the brain, the body and the environment are generated, conveyed to, relayed through information flowing through the nervous system. The ability to intercept information from, or artificially place the information

into the nervous system can revolutionize the way the brain interacts with the body and the environment. Such an method can, for example, help those who are paralyzed or have lost the ability to control or have lost sensations in part of their body through injury or disease to regain some of what was lost. Recent advancements in micro-scaled neuroprosthetic electrodes now offer the tantalizing possibilities of accessing or introducing information in the nervous system at the micro scale, leading to the possibility of bridging the communication gap left by the injury through the use of neuroprosthetic devices implanted above and below the injury. Although access to the information stream is achieved through these multichannel devices, tracking, decoding, and understanding the information contained within remains a considerable challenge. To meet this challenge, we aim to apply a revolutionary data processing device, the Extended Analog Computer, to this problem and develop a real-time neural signal processor.

"Role of Kalirin in the Local and Central Control of Bone Mass," Angela Bruzzaniti (School of Dentistry), Teresita Bellido (School of Medicine), Ruben Vidal (School of Medicine) and Matthew Allen (School of Medicine)

Osteoporosis is a common disease that affects millions of people, and is major concern for women after menopause. Osteoporosis leads to thinning of bones which break easily and is associated with pain, immobility, long hospital stays and other medical problems that reduce quality of life. Bone loss is also a complicating factor of arthritis, periodontal disease and bone cancers. The most common drugs to treat osteoporosis work by blocking the actions of the bone-degrading cells, called osteoclasts. These drugs, called antiresorptives, slow bone loss but do not increase the growth of new bone. In addition, these drugs are not appropriate for everyone with bone loss, and can lead to serious clinical complications if taken for long periods of time. Therefore there is a need to develop new approaches to prevent bone loss and increase bone mass. We have identified a new enzyme called kalirin that is important in controlling bone mass in mice. Mice lacking kalirin have a dramatic decrease in bone mass and we found that kalirin is important in the actions of the osteoclasts that degrade bone as well as the cells that make new bone (osteoblasts). In this study, we will use several mouse models to examine the actions of kalirin in the different bone cells and the role of kalirin in controlling bone loss associated with menopause. By studying the actions of Kalirin, we hope to one day identify new drug treatments that can prevent bone loss and increase bone mass in patients with osteoporosis.

"Semiautonomous Decision-Making in Vehicle Emergency Safety Decisions," Kris Hauser (School of Informatics & Computing), Sarah Koskie (School of Engineering & Technology), and Michael Justiss (School of Health & Rehabilitation Sciences)

This project studies advanced driver assistance systems that detect emergency situations using sensors and react automatically without human input. Active safety systems have the promise to make driving safer by reducing the frequency and severity of collisions, and auto makers are beginning to adopt these emerging technologies into trucks and passenger cars. Unlike other active safety technologies like lane departure warnings that use sensors to enhance driver awareness, autonomous emergency handling systems must be ready to take control away from the human driver by considering the car's surroundings, the mental state of the driver, and other drivers on the road. The researchers will use robust probabilistic algorithms from robotics in order to enable a car to better understand the rapidly changing driving environment and decide when and how to take autonomous action. Using a commercial driving simulator at the Transportation Active Safety Institute at IUPUI, the researchers will study drivers of all ages to evaluate whether autonomous safety systems are effective in reducing rear-end collisions and collisions during unprotected left hand turns, which are the top two causes of crashes for elderly drivers. The results of this research will be used to inform engineers, policymakers, and society about advanced vehicle safety technologies, and will make progress toward the ultimate goal make driving safer.

"Towards Effectively Quantifying Programming Language Abstraction," Andrew Lumsdaine (School of Informatics & Computing) and Rob Goldstone (College of Arts and Sciences)

"Understanding Sspc-DNA Interaction Via Chemical, Biochemical, And Structural Biology Studies," Millie Georgiadis (School of Science) and Lei Li (School of Science)

Spore-forming bacterial strains are responsible for a number of serious human diseases including botulism and anthrax. Moreover, *B. anthracis* spore was used in the 2001 bioterrorist attack, representing a realistic threat to the United States. These spores are extremely resistant to harsh environment owing to the fact that their genomic DNA is saturated by a group of proteins named SASPs and thus well-protected against externally added reagents. The SASP-DNA interaction also changes the outcome of DNA photochemistry, generating a unique product named spore photoproduct (SP) as such a complex is only found in bacterial spores in Nature.

All SASP proteins function similarly in associating with DNA; we thus choose a protein named SspC as a model system to help understand the SASP-DNA interaction. A combinatorial approach using chemical,

biochemical and structural biology means will be adopted in our investigation as a joint effort between the Li laboratory in the Chemistry Department at IUPUI and the Georgiadis laboratory in the Department of Biochemistry at IUSM. The proposed studies will help reveal how the spore genomic DNA is protected by the SASPs; they can shed light on the mechanism of the unique spore SP photochemistry as well. Elucidation of these key biochemical processes in spores may eventually enable us to selectively target these spore-forming bacterial strains and design better strategies to battle the related deadly diseases, improving human health as well as national security.