WV-INBRE NEWSLETTER

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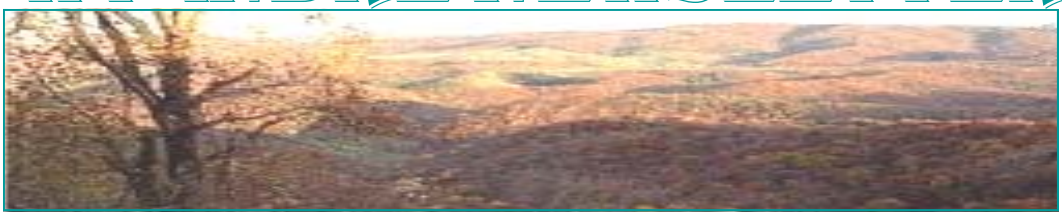

ACoRN Supports Stroke Research at WVU

ACoRN supports research projects that seek to discover the causes of cardiovascular disease especially those projects that rely on genomic and bioinformatic approaches. Dr. Taura Barr in the WVU School of Nursing and Center for Neuroscience is the recipient of an ACoRN pilot grant. Her proposal, entitled "Monitoring gene expression post-stroke to predict stroke outcome", is designed to identify a blood gene profile associated with stroke outcome. This will help to identify molecular pathways involved in brain recovery and novel targets for stroke therapeutics.

Principal Investigator: *Taura Barr PhD RN Nursing, Emergency Medicine and Center for Neuroscience*
Co-Investigators: *Laurie Gutmann MD, Neurology; Todd Crocco MD Emergency Medicine; Stephen Davis MS Emergency Medicine; Reyna VanGilder PhD Nursing and Center for Neuroscience; Jason Huber PhD Basic Pharmaceutical Sciences; Charles Rosen MD PhD Neurosurgery; James Denvir PhD Biostatistics.*

Stroke is the third leading cause of death in the United States and accounts for 10% of deaths worldwide. Approximately 780,000 people experience a stroke each year in the US, contributing to an overall financial burden of $65.5 billion. Ischemic stroke occurs when there is a decrease or loss of bloodflow to an area of the brain resulting in tissue damage or destruction. It is the largest subtype of stroke pathologies and therefore accounts for the majority of the death and disability associated with stroke.

Taura L. Barr, Ph.D., RN

One of the goals of the Appalachian Cardiovascular Research Network (ACoRN) is to discover the molecular, genetic and environmental causes of cardiovascular disease. Cardiovascular Disease (CVD) includes dysfunctional conditions of the heart, arteries, and/or veins that supply oxygen to life sustaining organs, such as the heart and the brain. Currently, 1 in 3 Americans has some form of CVD, and this rate is higher in West Virginia.

(see Monitoring Gene Expression, p. 3)

Inside this issue:

Institutions of the WV-INBRE

Lead Universities

Marshall University
West Virginia University

Partner Institutions

Alderson-Broaddus College
Bethany College
Bluefield State College
Concord University
Davis & Elkins College
Fairmont State University
Glenville State College
Mountain State University
Salem International University
Shepherd University
University of Charleston
West Liberty University
West Virginia State University
West Virginia Wesleyan College
Wheeling Jesuit University

Message from the WV-INBRE Principal Investigator Gary O. Rankin, Ph.D

With a new funding year fast approaching, we are preparing for new activities, as well as waiting to see the impact of significant changes at the National Institutes of Health (NIH) that could affect WV-INBRE.

First, I am pleased to announce that Dr. Tesfaye Belay, Department of Biology at Bluefield State College, is the newest Project Investigator for a major WV-INBRE partner institution research award. His project is entitled "Effect of stress on pathogenesis and immunity during *Chlamydia* genital infection" and will be funded beginning on May 1, 2011. Dr. Belay's research has been supported by a Faculty Research Development Award (FRDA), and his application was the only major research award funded following the most recent competition. He joins Dr. Charlie Chen (Alderson-Broaddus College), Drs. Gerald Hankins and Robert Harris (West Virginia State University), Dr. Robert Shurina (Wheeling Jesuit University) and Drs. Jarrett Aguilar and Robert Kreisberg (West Liberty University) as the current major Project Investigators.

Perhaps one of the biggest news items from the National Institutes of Health has been the planned dissolution of the National Center for Research Resources (NCRR), the NIH center that funds the INBRE program. This action will result in the redistribution of NCRR programs and staff within NIH. One of the initial steps in this plan happened on December 7, 2010, when the Scientific Management Review Board voted to create a new center for translational research to be called the National Center for Advancing Translational Science (NCATS).

This new center would receive a number of programs that currently reside in various centers and institutes at NIH. For NCRR, creation of this new center would mean the transfer to NCATS of the Clinical Translational Science Award (CTSA) program, which constitutes a significant portion of NCRR funding. The Review Board felt that the remaining programs did not constitute sufficient funding and staff for NCRR to remain a viable center.

An NCRR Task Force Straw Model was subsequently developed that relocated the remaining NCRR programs within other NIH institutes/centers and placed the IDeA programs (INBRE and COBRE) into an interim infrastructure unit in the Office of the NIH Director, Dr. Francis Collins. After comments posted on an NIH website, several phone conferences and meetings between NIH officials and representatives of the affected parties (including input from the National Association of IDeA Principal Investigators (NAIPI)) and letters from concerned organizations (including the EPSCoR/IDeA Foundation and the WV Higher Education Policy Commission) and U.S. Senators (spearheaded by Senator Rockefeller and several of his colleagues), the model was changed to place the IDeA programs in the National Institute of General Medical Sciences (NIGMS).

Whether the NIGMS is the final new location for IDeA or not will be determined over the next few weeks. The tentative NIH plan is that staff and funding for the various NCRR programs will move with the programs once NCRR is dissolved. It is anticipated that these changes will take place on October 1, 2011 when the new fiscal year begins for the U.S. Government.

The impact of these NCRR program relocations on our interactions with SEPA programs (i.e. the Health Sciences and Technology Academy in WV) remains to be determined, since SEPA was placed in the interim infrastructure unit and remains there at this time. Unfortunately, the consequences of these moves for the IDeA program and WV-INBRE are presently unclear. I will try to keep everyone updated as I learn more. So, stay tuned!

Monitoring Gene Expression Post-stroke To Predict Stroke Outcome

(continued from page 1)

The importance of this study is paramount, because there are presently no rapid, accurate diagnostic procedures or methods that can be used to determine whether a patient has suffered an acute ischemic stroke (AIS). Current technologies for diagnosis of AIS are limited by speed and resources as well as inaccuracy and generally require a high level of training to interpret the results. Our team has recently discovered that expression levels of a set of nine genes may be used as biomarkers for diagnosis of AIS[1]. Many of these genes are involved in innate and adaptive immune responses related to stroke outcome. Given the fact that roughly 5-8% of stroke patients receive the only FDA approved drug for ischemic stroke (tissue plasminogen activator (tPA), there remains a demand for alternative acute stroke therapies in clinical practice. Animal studies have been helpful in guiding human stroke trials; however the nature of the human response to ischemic stroke is extremely complex and is dependent upon how severe the injury is, the patient's environmental exposures and CVD risk factors, how long blood flow has been stopped to brain, and mediators of immunity. Limited knowledge exists regarding the implications of genomic variability and biological interactions on individual recovery from ischemic stroke.

Gene expression profiling simultaneously assesses the approximately 25,000 genes of the human genome. It has proven to be a powerful and effective approach to identify genes, pathways and interactions correlated with a phenotype (e.g. leukemia disease classification); the technology has also been used to identify genes and gene interactions for the prediction of a phenotype (e.g. positive versus negative response to chemotherapeutics). Given these advancements it is logical that gene expression profiling can be used to diagnosis stroke from stroke mimic or predict the occurrence of good versus bad outcome for many forms of CVD. Gene expression profiling also has the potential to identify biomarkers to stratify risk for patients with common asymptomatic neurological diseases, such as asymptomatic aneurysm and carotid stenosis. A stratification of risk for these patients based on a blood gene profile would aid in difficult decision making to treat or not to treat, dramatically improving current practice.

In this study, we will use gene expression profiling to identify pathways associated with stroke recovery. We will enroll a total of 35 male and female subjects from West Virginia University (WVU) Ruby Memorial Hospital, Morgantown, West Virginia. Patients must have symptoms of acute neurologic dysfunction consistent with focal brain ischemia and imaging (MRI or CT) and present to the emergency room (ER) within 24 hours from known onset of symptoms. Stroke patients will be assessed as soon as possible following presentation to the ER (day 0, 0-24 hours from symptom onset), at 24 hours (day 2, 24-48 hours from symptom onset), at 5 days after admission and at day 90. A variety of clinical, imaging, and laboratory data that are part of routine standard of care will be collected (e.g. National Institutes of Health Stroke Scale score (NIHSS), infarct volume, modified Rankin scale (MRS), blood markers of inflammation and coagulation); and patient relevant outcomes will be determined using functional, neurological and psychological measures.

The biomarkers we identify in this study may be rapidly identified using peripheral whole blood and may form the basis of a rapid and accurate clinical point of care diagnostic test. This invention may lead to the development of a rapid and accurate clinical diagnostic kit that would require very little training for proper use and could be used in the field or the emergency room setting for differential diagnosis and outcome prediction. It is anticipated that this project will result in the development of a genomic-based prediction model for ischemic stroke and identify novel avenues to target stroke therapeutics.

Reyna VanGilder, Ph.D.
Post Doctoral Research Fellow

Barr TL, Conley Y, Ding J, Dillman A, Warach S, Singleton A, Matarin M. Genomic biomarkers and cellular pathways of ischemic stroke by RNA gene expression profiling. Neurology 2010 Sep 14;75(11):1009-1014. [PubMed: 20837969]

US Patent, Application No. 61/307,233 filed 23 Feb 2010

Former Summer Interns Complete Ph.D. Training

Two former WV-BRIN/ INBRE Summer Interns completed studies for their Ph.D. degrees this year.

Melinda Varney, a 2004 summer intern, received her Ph.D. from the Biomedical Sciences Graduate Program at the John C. Edwards School of Medicine, Marshall University. Dr. Varney's research consisted of investigating the roles of both genetic and environmental factors in regulating hematopoiesis. Her research suggests that dietary fatty acid content, lipid metabolism, and bone properties are key regulators of hematopoiesis. The medical relevance of understanding how the process of hematopoiesis is controlled lies in the attempt to understand why this process goes awry in acute myelogenous leukemia and its precursors. Her research has appeared in the journals *Lipids; Pigment Cell & Melanoma Research;* and *Lipids in Health and Disease.* In recognition of her research, Dr. Varney was awarded the West Virginia Graduate Researcher of the Year by the West Virginia Higher Education Policy Commission. She has taken a postdoctoral training position with Dr. Dan Starczynowski's stem cell research group at Children's Hospital Medical Center in Cincinnati. Dr. Varney is conducting research on myeloplastic syndromes.

Cara (Henry) Halldin, Ph.D.

Cara (Henry) Halldin, a 2005 summer intern, conducted her Ph.D.research at the Center for Global Health and Diseases in the Case Western University School of Medicine. The title of her dissertation was ""Disease vectors of Papua New Guinea, members of the *Anopheles punctulatus* species complex (Diptera:Culicidae)- Molecular diversity, species identification and implications for integrated vector management." Dr. Halldin's research focused on gaining a better understanding of the diversity, differentiation, and ancestral relationships of the five most prominent members of the *Anopheles* mosquito species. Her work was part of an international collaboration with the Papua New Guinea Institute of Medical Research where she traveled to conduct field work on her project. In the process of exploring genetic species definitions, she was able to develop molecular methods for reliable species identification as well as methods to monitor for the development of point mutations associated with increased resistance to insecticides used for vector/disease control purposes. Her research appears in a number of publications including the *Proceedings of the National Academy of Sciences, USA*; *American Journal of Tropical Medicine and Hygiene;*, *Infection, Genetics and Evolution*; and *Pharmacogenetics.* In July, Dr. Halldin will begin a postdoctoral fellowship in the program of Epidemic Intelligence Service at the Centers for Disease Control and Prevention in Atlanta.

Melinda Varney, Ph.D.

The WV-INBRE family congratulates Drs. Varney and Halldin on their accomplishments!

INBRE/HSTA Program

The WV-INBRE has partnered with the Health Science Technology Academy (HSTA) program which is funded by the NCRR and headquartered at WVU. The partnership is designed to encourage undergraduate students who have demonstrated an interest in biomedical research through their participation in the HSTA program while in high school in West Virginia to participate in biomedical research once they enroll in one of the PUIs.

During the second year of this partnership, 8 HSTA students are participating in this program: at Bluefield State College, Christina Sargent and Sasha Richmond are working with Dr. Tesfaye Belay; at Concord University, Jeremy Lloyd is working with Dr. Darrell Crick; at West Virginia State University, Anthony Johnson is working with Dr. Robert Harris; at West Liberty University, Amber Wilson is working with Dr. Jarrett Aguilar and Kyle McGill is working with Dr. Robert Kreisberg; at West Virginia Wesleyan College, Jacob Wagoner is working with Dr. Timothy Troyer and Morgan Miller is working with Dr. Luke Huggins. All interns will present their research at the 10th Annual WV-INBRE Summer Research Symposium in Hungtington WV on July 28, 2011.

Another component of this joint program is to provide opportunities for high school science educators to participate in biomedical research for up to nine weeks during the summer with a mentor at either West Virginia University, Marshall University, or one of the funded mentors at a PUI. Participation is open to high school science educators who teach in the state of West Virginia during the previous academic school year. The goal of this part of the program is to provide research opportunities to interested science teachers with the expectation they will take their research experience back into their classrooms and inspire their students to pursue biomedical research opportunities once they enter college. Additionally, it is anticipated that the techniques they learn from the research will enhance the scientific teaching experience in the classroom. For summer 2011 there were 11 applicants and the WV-INBRE program was able to fund 7 positions.

Johnathan Baldwin from Scott High School, Madison WV will work with Dr. Gerald Hankins at West Virginia State University; Denise Gipson from Jefferson High School , Shenandoah Junction WV and Wendy Lee from Musselman High School, Inwood WV will work with Dr. Seung-yum Kim at Shepherd University; Tiffani Smith from Huntington High School and Timothy Clifton from Herbert Hoover High School, Clendenin WV will work with Dr. Robert Harris at West Virginia State University; Brian McNeel from Cabell Midland High School, Ona WV will work with Dr. Richard Egleton at Marshall University; and Rene Normal from Sissonville High School, Charleston WV will work with Dr. Dean Reardon at the University of Charleston. All research interns will present their research at the 10th Annual WV-INBRE Summer Research Symposium in Huntington, WV on July 28, 2011.

WV-INBRE Faculty Development Awards

A significant component of WV-INBRE has been the Faculty Research Development Award (FRDA) program, which are smaller grants that are awarded annually to faculty at the predominantly undergraduate institutions to conduct biomedical research at their home institution. FRDA grants are awarded on a competitive basis through an application procedure using standard NIH forms, followed by review of the applications by faculty at WVU and Marshall. Grants must involve undergraduates in the research plan and be clearly biomedical in nature. Incentive funds for the current fiscal year allowed us to make more, and larger, awards than has normally been the case. The following grants, totaling $221,081 were awarded last Spring for the current 2010-2011 fiscal year: Dr. Kenneth Cushman, West Liberty University, "Regulation of human endothelial cell genes by USF1", $48,000; Dr. Gagan Kaushal, University of Charleston, "D-Cycloserine transdermal gel formulation development", $48,000; Dr. Sueng-yun Kim, Shepherd University, "Modeling, verification. & simulation. of molecular biology system processes-Petri Nets", $24,695; Dr. Rebecca Linger, University of Charleston, "Investigating the allosteric signaling in guanosine monophosphate *5*synthase", $20,000; Dr. Haitao Luo, Alderson-Broaddus College, "Kaempferol inhibits angiogenesis in prostate cancer cells", $50,000; and Dr. Melanie Sal, WV Wesleyan College, "Allelic exchange mutagenesis in Borrelia burgdorferi", $30,386. Several of

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WV-INBRE Faculty Development Awards

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these projects have been quite successful, resulting in papers presented at national meetings in the relevant fields.

Unfortunately, this year has been an anomaly in terms of the amount of funding we were able to offer. The funds anticipated to be available for FRDA grants in the next fiscal year, 2011-2012 is only $90,000, direct plus indirect costs, so the number and size of awards had to be cut. The most recent FRDA grant application cycle resulted in the following direct cost awards for our next fiscal year: Dr. Gagan Kaushal, University of Charleston, "D-Cycloserine transdermal formulation development based on an enhanced treatment", $13,200; Dr. Sueng-yun Kim, Shepherd University, "Petri Nets-based modeling of human systems: towards drug trial modeling & simulation", $20,000; Dr. Rebecca Linger, University of Charleston, "Investigating the allosteric signaling in guanosine monophosphate synthetase", $8,000; Dr. Haitoao Luo, Alderson-Broaddus College, "Chaetoglobosin K and Angiopreventioin in Ovarian Cancer Cells", $40,000.

Interns and Fellows Selected for 2011 Summer Research Program

Twenty-two undergraduate student interns and two faculty fellows have been selected to participate in the 2011 WV-INBRE Summer Research Program at West Virginia University and Marshall University. The selection process for the internships was highly competitive. Sixty-eight applications were reviewed to fill the twenty-two positions. The applicant pool was the largest in the history of the program. The Summer Research Program will run from May 31 – July 29. **Summer Research Program Participants at West Virginia University:**

Student Interns	Mentor
Arielle Baker – West Virginia Wesleyan College	Dr. James O'Donnell
Rachel Brown – Concord University	Dr. Patrick Callery
Carissa Dunn – Davis & Elkins College	Dr. Peter Stoilov
Ryan Johnson – Bethany College	Dr. Hunter Zhang
Sara Kurian – Shepherd University	Dr. Bingyun Li
Gabrielle LaFata - West Virginia Wesleyan College	Dr. John Hollander
Kyle Oney – Alderson-Broaddus College	Dr. Michael Schaller
Kathleen Roberts - West Virginia Wesleyan College	Dr. Mark Olfert
Emily Sechrest – Bethany College	Dr. Rosana Schafer
Anthony Thorpe – Alderson-Broaddus College	Dr. Robert Brock
Kiril Tuntevski – University of Charleston	Dr. Slawomir Lukomski
Faculty Fellow	
Dr. Kimberly Fisher – Bethany College	Dr. William Wonderlin

Summer Research Program Participants at Marshall University:

Student Interns	Mentor
Hannah Cavender – West Virginia State University	Dr. Larry Grover
Joshua Kim – West Virginia State University	Dr. Gary Rankin
Benjamin Kordusky - West Virginia Wesleyan College	Dr. Elaine Hardman
Andre Lamyaithong – Wheeling Jesuit University	Dr. Monica Valentovic
Emma Levin-Nielson - West Virginia Wesleyan College	Dr. Richard Egleton
Daniel Mai – University of Charleston	Dr. Jung Han Kim
Sarah Monsheimer – University of Charleston	Dr. Simon Collier
Niraj Nepal – West Virginia State University	Dr. Eric Blough
Rebekah Sine – Alderson-Broadus College	Dr. Maria Serrat
Megan Smith – Alderson-Broaddus College	Dr. Hongwei Yu
Richard Thomas - West Virginia Wesleyan College	Dr. Philippe Georgel
Faculty Fellow	
Dr. Gary Morris – Glenville State College	Dr. Travis Salisbury

Next Generation Sequencing Arrives in West Virginia

Next Generation Sequencing (NGS) proceeds by massively parallel sequencing reactions. This enables rapid and relatively inexpensive sequencing of large amounts of DNA or RNA, such as entire genomes or transcriptomes,

The Marshall University Genomics Core has installed an Illumina HiSeq1000 Next Gen sequence analyzer, and instrumentation for preparation of the target to be sequenced (purification, shearing, amplification and quality assessment). This Illumina System offers a short-insert paired-end capability for high-resolution sequencing as well as long-insert paired-end reads that can be used in many applications:

(1) Genetic variant discovery by whole genome re-sequencing;

(2) De novo sequencing and assembly of bacterial and lower eukaryote genomes;

(3) whole transcriptome analysis or expression profiling (e.g. RNA Seq);

(4) small RNA discovery and analysis;

(5) genome wide profiling of epigenetic modifications and chromatin structure (Methyl-Seq, ChIP-Seq etc), and

(6) novel species discovery and classification through metagenomic methods.

The large amount of sequence data generated creates large data analysis needs. WV-INBRE is acquiring all the hardware and software necessary to perform NGS data analysis.

The Partek Genomics Suite has tools for analysis of the NGS applications described above and more. With visualization-intense statistical and discovery tools, Partek Genomics Suite can be used for microarray data analysis as well as NGS. Integrated analysis of microarray and NGS data is supported, for example using ChIP-Seq and expression microarray to identify regulatory binding sites and assess change of mRNA expression.

Investigators wanting to use NGS should contact the Genomics and Bioinformatics Cores to discuss experimental design and cost prior to initiating the experiment. Please contact Don Primerano in the MU Genomics Core at 304-696-7338 for additional guidance.

WV-INBRE-supported NGS projects include whole exome sequencing of patients with Familial Combined Hyperlipidemia (FCHL) and the following NGS pilot grant projects:

Christopher Cuff will use NGS of subgingival plaque samples from an elderly population to identify bacteria phylotype. Differences in the microbiome and cognitive function will be analyzed to asses which phylotypes contribute to the known relationship between poor oral health and cognitive degeneration.

Philippe Georgel and Elaine Hardman will use ChIP-Seq methods to establish the genes bound by MeCP2 and to map genome-wide methylation. By comparing omega-3 fatty acid exposed offspring to controls, epigenetic influences associated with decreased cancer risk will be assessed.

Alexey Ivanov will use ChIP-Seq to identify genomic binding sites for the transcriptional repressor Snail in epithelial cells undergoing epithelial-mesenchymal transition as part of the metastatic process.

Travis Salisbury will use ChIP-seq to discover where in the genome the AH receptor binds DNA. AH receptor antagonists inhibit adipocyte-stimulated breast cancer cell growth; this project will identify candidate genes or miRNAs that regulate growth.

Wei-ping Zeng will use NGS to perform analysis of DNase I hypersensitivity sites in the genome of regulatory T Cells and identify candidate cis gene regulatory elements involved in the activation of regulatory T cells.

Supported by:

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