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WV-BRIN Researchers Study Mechanisms of Breast Cancer Development



The WV-BRIN participants, Drs. Albert Magro of Fairmont State College (right) and Michael Miller of West Virginia University (left), are currently investigating the role of arachidonate lipoxigenase in the induction of apoptosis in human breast cancer cells (MCF-7). Experiments tested the hypothesis that the blocking of cellular lipoxigenases in MCF-7 cells inhibits growth, induces

apoptosis, and modulates the transcriptional expression of the pro-apoptotic gene Bax- α and the anti-apoptotic gene Bcl-2. They have demonstrated that inhibition of arachidonate 5, 8, and 12 lipoxigenases induces massive apoptosis as measured by nuclear fragmentation DNA laddering, which are classical manifestations of apoptosis. The detection of soluble cytoplasmic DNA histone complexes resulting from apoptotic nucleosomes, that are tightly bound with core histones and appear in the cytosol before the plasma membrane disintegrates, also indicates that the inhibition of lipoxigenases induces apoptosis in MCF-7 cells. Preliminary RT-PCR data indicate that the induction of apoptosis is accompanied by a decrease in the steady-state expression of Bcl-2 with an increase in the expression of Bax- α . An interesting aspect of this study is that MCF-7 cells, which are deficient in caspase 3, still manifest classical apoptosis that is believed to be caspase-dependent. Furthermore, the broad caspase inhibitor, Z-VAD FMK, prevents apoptosis induced by lipoxigenase inhibition in these cells. This was unexpected and the investigators are currently pursuing the interesting question of which effector caspases are activated during the apoptotic process. These molecular studies between arachidonic acid metabolism and apoptosis in breast cancer cells raise the possibility for identification of novel molecular targets for cancer, chemoprevention, and treatment. Dr. Magro presented the results of this research at the Cold Spring Harbor Laboratory Meeting entitled "Programmed Cell Death", September 17-23, 2003.

In addition to their research on breast cancer, Drs. Magro and Miller were recently awarded a \$20,000 grant from the NASA WV-EPSCoR College-University Collaboration Program, for a study entitled "Analysis of Human Epithelial Cells and Cortical Neurons for Susceptibility to Apoptosis Induced by Hypoxia".

Institutions of the WV-BRIN

Lead Universities

Marshall University
West Virginia University

Predominantly Undergraduate Institutions (PUIs)

Alderson-Broaddus College
Bluefield State College
Fairmont State College
Salem International University
Shepherd College
West Liberty State College
West Virginia State College
Wheeling Jesuit University

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Summer Research Program

The 2003 WV-BRIN Summer Research Program began on June 9 and concluded on August 7 with the Summer Research Symposium held in Huntington at Marshall University. Twenty two interns and seven faculty members from the PUIs participated in the program. The following poster presentations were made by interns and fellows and also by recipients of Pilot Research Grant Awards

<u>2003 Interns and Fellows</u>	<u>Mentor</u>	<u>Project Title</u>
Dr. Jarrett Aguilar West Liberty State College	Dr. Peter Gannett	-Molecular Dynamics Studies of Flurbiprofen and Dapsone Docking in the Active Site of Cytochrome P450 2C9 and the Correlation Of Modeled Flurbiprofen Docking to T1 NMR Data
Malathi Banda Salem International University	Dr. Quentin Li	-Effect and Mechanism of Elemene and Cisplatin in Human Prostate Cancer Cells
Bernard Boswell Shepherd College	Dr. Robert Haining	-Characterization of CYP2D mRNA in CYP2D6 Humanized Mouse
Ruthanne Cain Alderson-Broaddus College	Dr. Tim Norman	-Torsion Testing of Tibias from Skeletally Mature Ovariectomized/Residronate-Treated New Zealand White Rabbits
Dr. Yi Charlie Chen Alderson-Broaddus College	Dr. Bing-Hua Jiang	-Inhibition of Hypoxia-Inducible Factor 1a and Vascular Endothelial Growth Factor by Anti-Cancer Drugs in Human Ovarian Cells
Monica Chroussis Alderson-Broaddus College	Dr. Rosana Schafer	-The Effect of Herbicides on the Thymus and Bone Marrow after Inhalation Exposure
Christy Clark Wheeling Jesuit University	Dr. Janine Mendola	-Cortical Morphologic Changes Characterize Amblyopia: Both the Strabismic and Anisometric Types
Samuel Clark Bluefield State College	Dr. Frank Reilly	-Insulin 1-A Stretch-Responsive Gene-Specific Protein in the Skin
Nicole Dent West Virginia State College	Dr. Todd Green	-12-Lipoxygenase Protein Expression in a Rat Model of Obesity-Associated Hypertension
Dr. Mark Flood Fairmont State College	Pilot Grant Recipient	-Genotype Frequency for Three Apolipoprotein B Polymorphisms in a West Virginia Sample -Analysis of the Factor V Leiden (FVL) Polymorphism in Two West Virginia Groups -Obesity-Associated Cardiovascular Disease (OCARD) Collaboration -Genotype Frequency for C-Reactive Protein And Paraxonase Polymorphisms in a West Virginia Sample -Genotype Frequency for Apolipoproteins A1 and E Polymorphisms in a West Virginia Sample
Kari Habursky Wheeling Jesuit University	Dr. Brad Hillgartner	-The Effects of the Liver X Receptor (LXR) Signaling Pathway on Genes Involved In Fatty Synthesis and Cholesterol Export
Lauren Klug West Liberty State College	Dr. James Sheil	-The Effects of Atrazine Exposure on Proliferation and Function of Alloreactive Cytotoxic T Lymphocytes
Dr. Patrick Lai	Pilot Grant Recipient	-Relocation of Functional Epitope from Borna Disease Virus p40 to a Carrier Protein Reduces the Cytotoxic Response when Administered as a DNA Vaccine -Humoral Immune Response Elicited by a BDV-P10X DNA Vaccine are Dose-Dependent -Sub-cloning, Expression, and Partial Purification Of Borna Disease Virus p40 as a Recombinant Fusion Protein in Prokaryotes
Danielle Large Alderson-Broaddus College	Dr. Laura Gibson	-Effects of High Dose Chemotherapy on Matrix Metalloproteinase Expression In Leukemia

Summer Research Program continued:

Aaron Lee Shepherd College	Dr. Drew Shiemke	-DPI Inhibition in Methanotrophic Bacteria
Joshua Lewis Fairmont State College	Dr. Kathleen Brundage	-The Effect of Propanil on JNK Activity in Jurkat Cells
Dr. Albert Magro Fairmont State College	Dr. Michael Miller	-Gene Expression in MCF-7 Cells and CR-2610 Upon Induction of Apoptosis
Nicole McEwan West Liberty State College	Dr. Peter Gannett	-Formaldehyde Fixation Effects on DNA Fingerprinting
Antoinette Moran Wheeling Jesuit University	Dr. Will McCumbee	-Obese Zucker Rats are Normotensive with or without Increased Fat Intake
Cindy Morris West Liberty state College	Dr. Mike Gunther	-Synthesis of Fluorescent Spin Traps
Aaron Parry Wheeling Jesuit University	Dr. Robert Haining	-Preparation of Monospecific Polyclonal Antibodies for Detection of CYP2D6 in Mice
Joy Parsons Alderson-Broaddus College	Dr. Christine Baylis	-Do High Levels of Aldosterone Trigger Kidney Fibrosis?
Justin Sanders Salem International University	Dr. Patrick Callery	-Computer-Aided Drug Design of Novel Antibiotic Staphylococcal Protein A Inhibitors
Dr. Roger Seeber, Jr. West Liberty State College	Dr. Patrick Callery	-Extraction and Isolation of Hypericin and Hyperforin from Various Sources of St. Johns Wort
Dr. Robert Shurina Wheeling Jesuit University	Dr. Daniel Flynn	-Creating a Recombinant AFAP Fusion Protein to Monitor the Role of AFAP-110 in Cell Division
Jeremy Smith Salem International University	Dr. Chris Cuff	-Cytotoxic T-Lymphocyte Epitope Mapping of T3D Reovirus Proteins
Kimberly Snodgrass West Virginia State College	Dr. Elsa Mangiarua	-Role of 12-Lipoxygenase in Obese Hypertensive Rats
Krystal Thompson Alderson-Broaddus College	Dr. Nilay Mukherjee	-TGF- β Expression in an ATDC5 Cell Line
Kristina Whiting West Virginia State College	Dr. Gary Wright	-Remodeling of the Actin Cytoskeleton in Smooth Muscle Cells in Response to Mechanical Stretch

Achievements of the 2002 and 2003 Summer Interns

The results of the 2002 summer research project in which **Ruthanne Cain**, Alderson-Broaddus College, was involved were presented at the 2003 Annual Meeting of the Society of Toxicology in Salt Lake City, Utah on March 12, 2003. The title of the presentation was "Alterations in the Immune System After Exposure to the Triazine Herbicide Atrazine". In addition to Miss Cain, authors of the presentation were Drs. Kathleen Brundage, John Barnett and Rosana Schafer.

Lela Taylor (2002), Fairmont State College, has been accepted into the 2003 medical class at Marshall University School of Medicine.

Anita Sayre (2002) and **Natasha Pillay** (2002), Salem International University, have been accepted into the 2003 medical class at the West Virginia School of Osteopathic Medicine.

Cortney Taylor (2002), Alderson-Broaddus College, has been accepted into Physical Therapy School at Wheeling Jesuit University.

Jessica Francisco (2002), West Virginia State College, has been accepted into the Physician's Assistant program at Mountain State University.

Achievements of the 2002 and 2003 Summer Interns continued:

Danielle Large (2003), Alderson-Broaddus College, has been awarded a scholarship from the National Institutes of Health (NIH) Undergraduate Scholarship Program for Individuals from Disadvantaged Backgrounds. This prestigious scholarship is only awarded to fifteen individuals nationwide each year.

This NIH Undergraduate Scholarship is awarded for 1-year periods (renewable up to 4 years) and covers tuition and reasonable educational and living expenses up to \$20,000 for each academic year. In return, Danielle has committed to two types of service obligation for each year of scholarship: 1) 10-week summer service as a paid employee in an NIH research laboratory and 2) after graduation, 1 year of full-time paid employment in an NIH research laboratory. **Congratulations, Danni!**

Ruthanne Cain (2002 &2003), Alderson Broaddus College, has been accepted into the Physician's Assistant program at that institution

The following interns presented research results at the West Virginia State College's Ninth Annual Research Symposium, April 25, 2003:

Lynnette May (2002) – "Immunofluorescent Visualization of α -Actin in A7r5 Cells Cultured on Flexible Membranes". Dr. Robert Harris was co-author.

Kristina Whiting (2003) – "Remodeling of the Actin Cytoskeleton in Smooth Muscle Cells in Response to Mechanical Stretch". Dr. Robert Harris was co-author. She was also a co-author on the presentation "Stretch-Induced Changes in the Shape and Orientation of Smooth Muscle Cells".

Training Awards

The following individuals have received training awards from the WV-BRIN:

Dr. Huey Miin Lee, Salem International University to attend the course "Genetic Analysis of Complex Human Diseases" at Duke University, April 26-30, 2003.

Dr. Alain Blanchetot, Marshall University, to attend two workshops, "Techniques in Bioinformatics and Comparative Genomics", August 4-8, 2003, and "Computational Approaches to Analyzing Gene Expression Data", August 11-15, 2003. Both workshops are sponsored by: National Center for Genome Resources and Promega Corporation and are being held at BTCi in Madison, Wisconsin.

Travel Grants

The WV-BRIN has awarded the following travel grants:

Dr. Albert Magro, Fairmont State College to attend the Cold Spring Harbor Laboratory Meeting, September 17-23, 2003, where he presented research sponsored by the WV-BRIN. Dr. Magro received support to present this research at the West Virginia Academy of Sciences Annual Meeting on April 5, 2003. His coauthors were Jessica Hammond of Fairmont State College, and Dr. Michael Miller of West Virginia University.

Dr. Roger Seeber, Jr., West Liberty State College, to attend the West Virginia Academy of Sciences Annual Meeting on April 5, 2003, where he presented research supported by the WV-BRIN. The title of his presentation was "The Development of a Rapid Assay for Hypericin and Hyperformin in St. John's Wort Using HPLC and Mass Spec".

Dr. Robert Warburton, Shepherd College, to attend the Experimental Biology Meeting in San Diego, CA, April 11 – 15, 2003.

Dr. Suzanne Rogers and **Li Chen**, Salem International University, to attend the 2003 Congress on In Vitro Biology in Portland, Oregon, May 31-June 4, 2003. The title of their presentation was "Transformation and Regeneration of the Wetland Monocot *Juncus accuminatus* using Different Binary Vectors. Additional coauthors were Drs. R. Nadakumar and Patrick Lai.

The *West Virginia Biomedical Research Infrastructure Network (WV-BRIN)* has completed a successful second year of operations in the midst of significant focused growth and hopes for continued funding from the National Center for Research Resources (NCRR) of the National Institutes of Health (NIH) for phase II of the program. During the past year, one of the real highlights of our program was the annual Summer Research Program as we completed a second year of summer research activity with participants from across the state at mentor laboratories at both Marshall University School of Medicine and West Virginia University Health Sciences Center. In addition to WV-BRIN Summer Research Program opportunities, a significant number of partner institution faculty, in collaboration with established investigators at WVUHSC and MUSOM as mentors, have initiated or continued with research projects funded by pilot research grants from the WV-BRIN.

As discussed during the WV-BRIN Steering Committee meeting last summer, through the direction provided by the National Center for Research Resources (NCRR), significant changes and refinements of the WV-BRIN Program are being instituted to focus the network on measurable research objectives. The Request for Applications for phase II of the network-building program, issued this past summer, directs all BRIN networks to make the transition from their research-planning phase under the Biomedical Research Infrastructure Networks (BRIN) program to the research-intensive phase II **IDeA Networks of Biomedical Research Excellence (INBRE)** program. We have just submitted our research proposal for establishing the WV-INBRE program over the next five years. If funded, this project will result in the development of a stronger network of research activity in West Virginia's institutions of higher education that will become well integrated into the efforts at the state level to support scientific research through the programs of WV-EPSCoR.

The WV-INBRE proposal focuses on six well-designed and planned biomedical research initiatives supported by the WV-BRIN and associated with the research programs of established investigators at WVU and MU as mentors. These projects are being conducted at four institutions: Fairmont State College (two projects - Dr. Mark Flood and Dr. Albert Magro; project investigators); West Liberty State College (two projects - Dr. Jarrett Aguilar and Dr. Robert Kreisberg; project investigators); West Virginia State College - (Dr. Robert Harris, project investigator) and Wheeling Jesuit University - (Dr. Robert Shurina; project investigator). Together these six research projects will spearhead the overall WV-INBRE research program with cellular and molecular biology as its scientific thematic approach. In addition, the proposed WV-INBRE will develop a strong outreach program to encourage other institutions in the state to increase their biomedical research capacity.

The direction of biomedical research program development of the WV-INBRE is to build a particular strength in cardiovascular research, in conjunction with the evolving impact of the WV-BRIN- established and supported *Appalachian Cardiovascular Research Network (ACoRN)*. By the end of the five-year phase II WV-INBRE program period, we hope to develop a Cardiovascular Research Center of national prominence in the State of West Virginia. A change in leadership for the network has been proposed for the phase II WV-INBRE, since Dr. L. Howard Aulick, Executive Director of WV-BRIN has announced his planned retirement in a couple years. We are fortunate that Dr. Gary Rankin, an established investigator and Chair of the Department of Pharmacology at MUSOM, has agreed to direct the proposed phase II WV-INBRE program. Dr. James M. Sheil, WV-BRIN Program Director, will serve as the Program Coordinator for the proposed WV-INBRE and will direct liaison activities and coordinate program initiatives with all network research and outreach institutions.

With all these changes in the making, there is much excitement about future directions and opportunities for biomedical research in West Virginia. It is hoped that the proposed WV-INBRE program will serve as an impetus for institutions of higher education across the state to consider seriously their commitment to biomedical research, both in developing their own academic programs and in fostering a stronger commitment to biomedical research and training in the state.



Summer Research Program: The 2004 Summer Research Program will be held from June 7 to August 6 with the Research Symposium scheduled for August 5. Students and faculty from the PUIs will have the opportunity to conduct biomedical research at either Marshall University or West Virginia University under the direction of a faculty mentor. Beginning January 5, 2004, applications will be available on the WV-BRIN web site (www.wv-brin.org) or can be obtained from the WV-BRIN office. Applications are due February 27, 2004, and applicants will be notified of their status by March 17, 2004. The Mentors Directory, in which mentors are listed and available projects are described, will be available on the web site by January 5, 2004. Copies will also be available from the WV-BRIN Resource Teams at each institution. Members of the Training and Mentoring Core will be visiting the PUIs in January and February to promote the program and will have application forms and Mentors Directories available at that time.

Travel Grants: Funds are available for faculty and students to attend local and national scientific meetings. Preference will be given to those presenting research conducted at their home institutions or in the summer research program. There is no application deadline; applications are accepted at any time. The guidelines and application form can be found on the WV-BRIN web site, or contact Dr. Mark Reasor at (304) 293-2418 or at mreasor@hsc.wvu.edu.

Workshop and Short-Course Training Awards: PUI faculty who are interested in attending a workshop or mini-course that would benefit their research or further the goals of the WV-BRIN are encouraged to contact Dr. Reasor for information on how to apply for support.

**Working in the Labs
During the 2003 Summer Research Program**



Jeremy Smith - Salem International University



Aaron Lee - Shepherd College



Josh Lewis - Fairmont State College



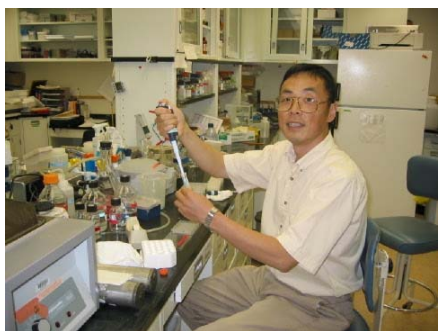
Christy Clark - Wheeling Jesuit University



Burt Clark - Bluefield State College



Danni Large - Alderson-Broaddus College



Dr. Charlie Chen - Alderson-Broaddus College



Monica Chroussis - Alderson-Broaddus College



Ruthanne Cain - Alderson-Broaddus College

Working in the labs continued:



Kari Habursky - Wheeling Jesuit University



Malathi Banda - Salem International University



Lauren Klug - West Liberty State College



Nicole MacEwan - West Liberty State College

Social Activities



Summer interns playing Bocce Ball at Dr. Sheil's farm.



Summer interns enjoying the orientation day picnic at Krepps Park

Publication

Dr. Patrick Lai, Salem International University, has published research supported by a WV-BRIN Pilot Research Grant. The citation is: Yoshio Hashimoto, Horng-Shen Chen, Cynthia Cunningham, Tahir H. Malik, and Patrick K. Lai, "Two Major Histocompatibility Complex class I-Restricted Epitopes of the Borna Disease Virus p10 Protein Identified by Cytotoxic T Lymphocytes Induced by DNA-Based Immunization", *Journal of Virology*, 77 (10), 6076-6081, 2003.

Marshall University DNA Core Facility Offer

The Marshall University DNA Core Facility will allocate \$1,000 to each of the WV-BRIN member institutions for purchase of synthetic oligos (primers), DNA sequencing, or DNA microarray analysis. Requests for the DNA synthesis and sequencing should be placed on the online order forms at <http://www.musom.marshall.edu/oligos/>. On the PO# line on the order form, please enter "WV-BRIN" Inquiries about any of the services should be directed to Dr. Don Primerano (304-696-7338) or Liping Wei (304-696-7358). The offer is extended to the Resource Team at each institution who should inform all biomedical researchers of this opportunity. Questions about your account balance should be directed to Kristen Webb at 304-696-7312.

Bioinformatics Workshop

GCG 101, a three day workshop on using the GCG/Wisconsin software was held at West Virginia University June 4-6 and was attended by 23 WV-BRIN faculty and students. The instructor was Pei-Li Li, from Accelrys, the vendor for the software.

The WVU GCG server supports both the SeqLab and SeqWeb interfaces. The GCG/Wisconsin Package runs using Unix command line language. SeqLab provides access to the full GCG/Wisconsin package using an X-Windows interface that is somewhat like Windows but less user friendly. SeqLab was the focus of the workshop. The SeqWeb interface uses a web browser interface; links give SeqWeb an interactive quality that is user friendly. Not all of the sub-programs are available via SeqWeb.

The workshop included both lecture-format material and hands-on instruction and focused on using SeqLab. Participants were provided with a notebook of slides of the lecture materials, additional lecture notes, and lab exercises (which includes "how to" details). Exercises included primer design, pairwise comparison of sequences, database searching using BLAST and FastA, multiple sequence analysis, pattern and motif finding, and Hidden Markov Models.

WV-BRIN hosted another GCG101 workshop at Marshall University September 25 – 27, 2003.



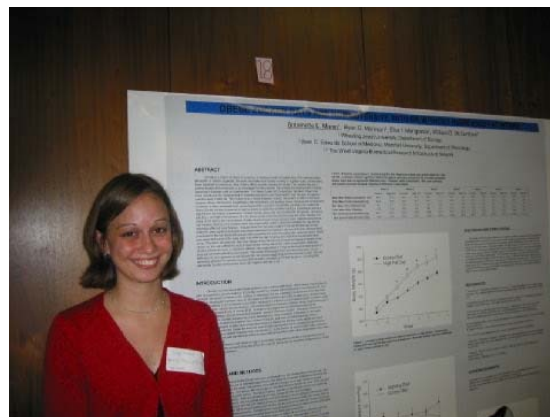
Pei-Li Li from Accelrys provides instruction on the GCG/Wisconsin package.



Nicole Dent, from West Virginia State College, participates in the workshop.



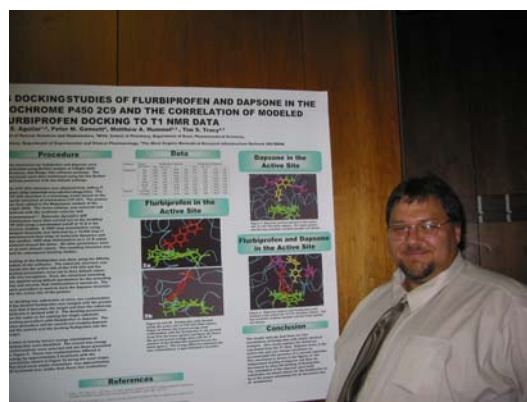
One of the guest speakers, Dr. Robert Elston, from Case Western University, discusses the analysis of multifactorial genetic traits.



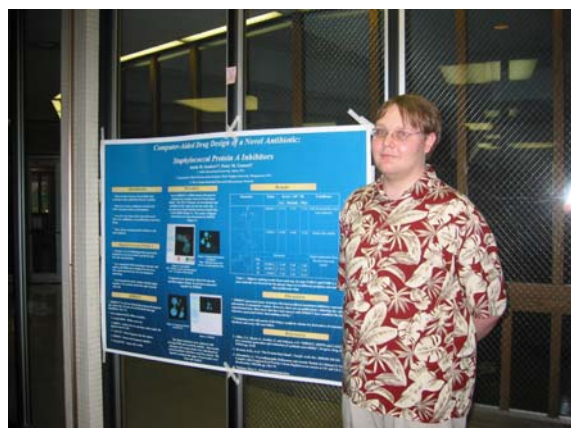
Toni Moran, from Wheeling Jesuit University, displays her poster "Obese Zucker Rats are Normotensive with or without Increased Fat Intake".



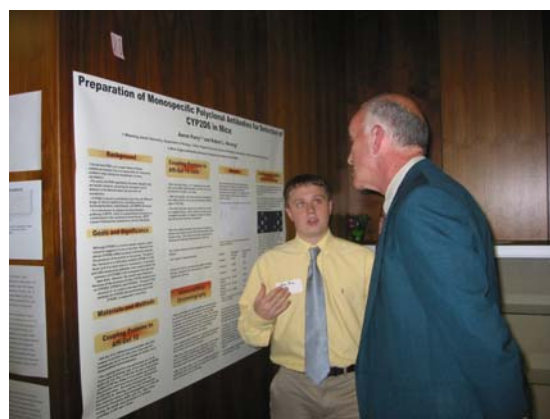
Kristina Whiting, from West Virginia State College, explains her summer research, "Remodeling of the Actin Cytoskeleton in Smooth Muscle Cells in Response to Mechanical Stretch" to Dr. Todd Green.



Dr. Jarrett Aguilar, from West Liberty State College, displays his summer research project entitled "Molecular Dynamics Studies of Flurbiprofen and Dapsone Docking in the Active Site of Cytochrome P450 2C9 and the Correlation Of Modeled Flurbiprofen Docking to T1 NMR Data".



Justin Sanders, from Salem International University, displays his summer research project entitled "Computer-Aided Drug Design of Novel Antibiotic Staphylococcal Protein A Inhibitors".



Dr. Jim Sheil of the WV-BRIN, and Aaron Parry, from Wheeling Jesuit University, discuss the results of Aaron's research entitled "Preparation of Monospecific Polyclonal Antibodies for Detection of CYP2D6 in Mice".

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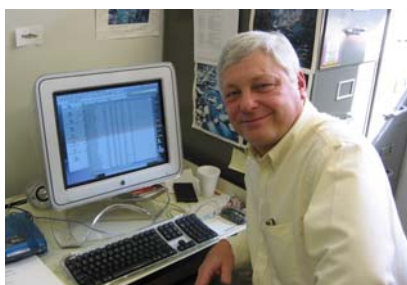
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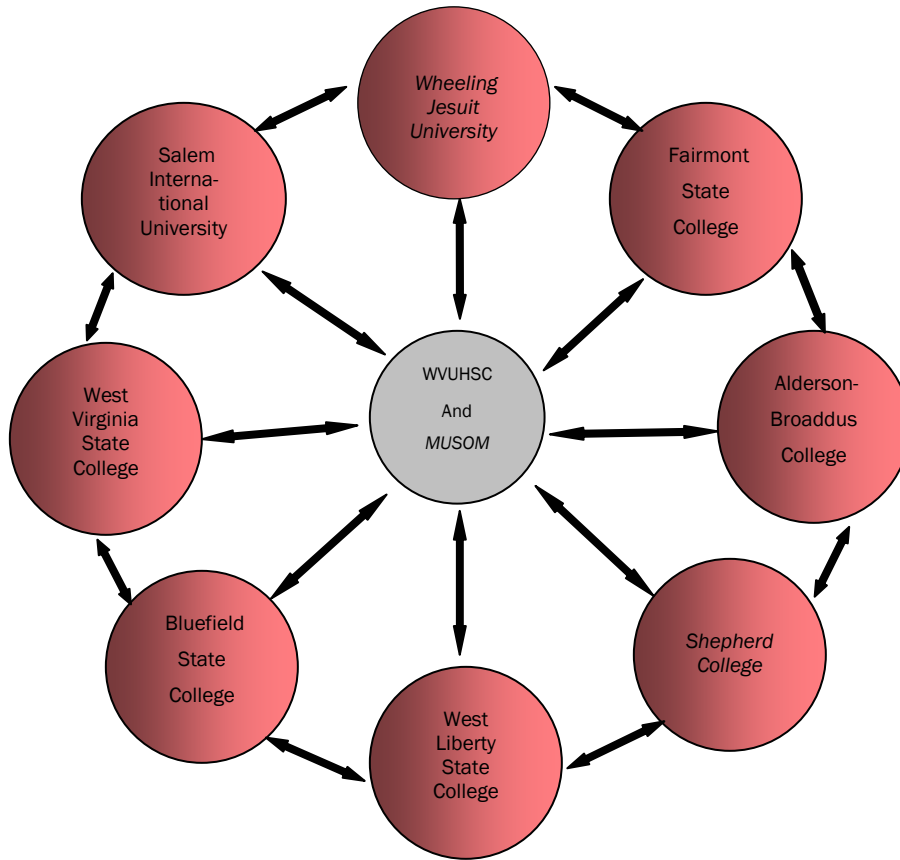


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Administrative Associate



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(WV-BRIN)



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