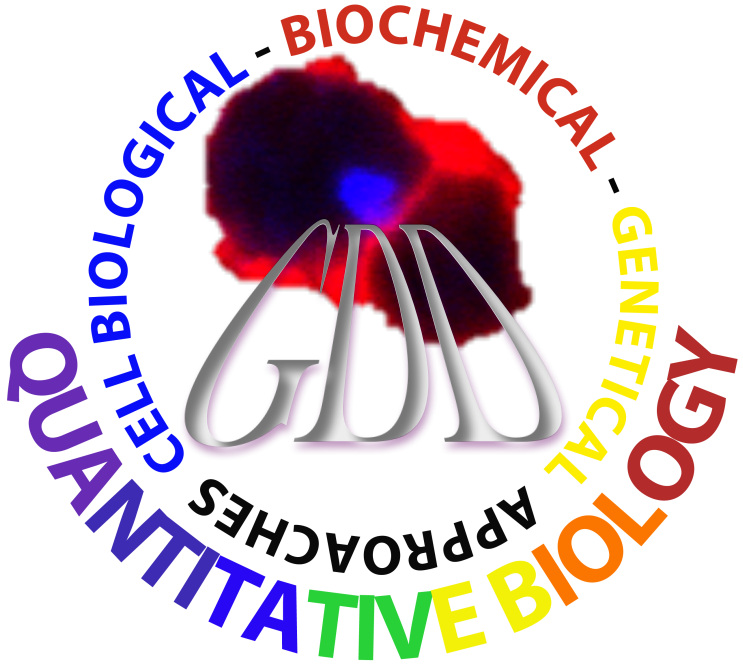
2018 PROGRESS REPORT



GERMS, DEFENSES, & DISEASES

UNDERGRADUATE RESEARCH PROGRAM

LEARNING QUANTITATIVE BIOLOGY FROM HANDS-ON CELL BIOLOGICAL, BIOCHEMICAL, AND GENETICAL APPROACHES TO DISEASES THAT AIL HUMANKIND

PROGRAM DESCRIPTION IN BRIEF

GERMS, DEFENSES, & DISEASES research program provides opportunities for undergraduates to learn quantitative biology through hands-on bench research. Research areas include infection biology and immunology, and cell and molecular bases of diseases that ail mankind. This research program is supported by the Vanderbilt Institute for Infection, Immunology, & Inflammation (VI4) and the Department of Pathology, Microbiology, and Immunology (PMI). Germs, Defenses, & Diseases research program was launched in the summer of 2017. In 2017, the program hosted SEVEN VI4 Scholars, one of whom was supported by a VI4 summer research scholarship.

Germs, Defenses, & Diseases research program has grown in the past year. It provides two opportunities for hands on research experience within a VI4 or PMI Faculty laboratory:

- One opportunity is full-time and runs during the summer months. This opportunity is available to all rising sophomores, juniors, seniors, as well as seniors graduating in the fall following the summer.
- The second opportunity is part-time that runs through the school year. This is a great opportunity for sophomores, juniors and seniors attending Vanderbilt or a college/university in the Nashville area.

2018 SUMMER RESEARCH REPORT

Recruitment into the 2018 summer research program was made through the Vanderbilt Summer Science Academy by nation-wide search for young talents. Thirteen VI4 Summer Scholars were recruited and joined the program. The 13 VI4 Summer Scholars came from a variety of different colleges and universities in the US (Table 1). They ranged from rising sophomore to rising senior in their undergraduate education (Table 1).

TABLE 1: Names, undergraduate background and origins of the V14 Summer Scholars

Supported by Short-Term Training Program for Minority Students

Name	Year in College/University, 2018	Undergraduate College/University
Meagan Branch	rising senior	Elon University
Karyssa Yvonne Clark	rising junior	Illinois Wesleyan University
Noyna Francheska Fabre	rising senior	Hunter College
Rachel Alicia Francis	rising senior	Sewanee: The University of the South
Jordan Galbraith	rising junior	Vanderbilt University
Micah Harris	rising senior	Wright State University
Chanelle Hunter	senior, graduating Dec'18	University of Central Florida

TABLE 1 *continued ...*		
Supported by Short-Term Training Program for Minority Students		
Name	**Year in College/University, 2018**	**Undergraduate College/University**
Caroline McLaughlin	rising junior	Emory University
Leah S. Rowe	rising junior	University of Arkansas at Pine Bluff
Supported by VI4 Summer Scholarship		
Sydney Lindsay Castellanos	rising sophomore	Indiana University, Bloomington
Eliot TC Forster-Benson	rising junior	Vanderbilt University
Myriam Shehata	rising sophomore	Vanderbilt University
Lorrayya Louise Williams	rising senior	Calvin College

Four Summer Scholars were supported by the VI4 Summer Scholarship. The remaining nine Summer Scholars were supported through an R25 grant entitled "Short-Term Training Program (STTP) for Minority Students for research in Vascular Biology" awarded by the NHLBI/NIH. The 13 VI4 Summer Scholars trained in 12 different laboratories (Table 2). Research in the 12 host laboratories covered a wide range of topics (Table 2).

TABLE 2: Names, host laboratory and research title		
Supported by Short-Term Training Program for Minority Students		
Name	**Host laboratory**	**Research title**
Meagan Branch	Michells Southard-Smith, Ph.D.	The role of Pax3 in the development and differentiation of Pelvic Ganglia
Karyssa Yvonne Clark	Julie Sterling, Ph.D.	Regulation of integrin expression and signaling by Gli2 in tumor-induced bone disease
Noyna Francheska Fabre	Donald Alcendor, Ph.D. Meharry	Assessment of BK Virus replication in cellular components of the human glomerular vascular unit: implications for BK virus associated nephropathy
Rachel Alicia Francis	Kevin Niswender, M.D., Ph.D.	A glucagon-like peptide-1 receptor variant contributes to cardioprotection

TABLE 2 *continued ...*		
Supported by Short-Term Training Program for Minority Students		
Name	**Host Laboratory**	**Research Title**
Jordan Galbraith	Jeffrey Conn, Ph. D.	Dopamine regulation via allosteric modulation of the M1 receptor: implications for the negative symptoms of schizophrenia
Micah Harris	Jeff Reese, M.D.	Determining the presence of and functional significance of dopamine receptors in the ductus arteriosus (DA) during development
Chanelle Hunter	Julie Sterling, Ph.D.	Characterization of receptor expression and aberrant Gli2 signaling in osteosarcoma cells
Caroline McLaughlin	Eric Delpire, Ph.D.	Mechanism of KS-WNK1 activation of sodium transport in oocytes
Leah S. Rowe	Sean Davies, Ph.D.	Effects of isolevuglandin, a highly reactive lipid dicarbonyl, on modifying apolipoprotein A-1 and phosphatidylethanolamine in synthetic high-density lipoprotein
Supported by VI4 Summer Scholarship		
Sydney Lindsay Castellanos	Carlos Henrique Serezani, Ph.D.	Examination of the effects of hyperglycemia on inflammasome activation
Eliot TC Forster-Benson	Charles Sanders, Ph.D. Christopher Aiken, Ph.D.	Characterizing the Native Structure of the HIV-1 gp41 Cytoplasmic Tail and Its Interactions with the Gag Matrix Protein
Myriam Shehata	John Karijolich, Ph.D.	Probing novel mechanisms of nucleic acid sensing in innate immunity
Lorrayya Louise Williams	Michael Noto, Ph.D., M.D.	Pilus-expressing *acinetobacter baumannii*, mediated enhanced bacterial clearance involving inflammasomes signaling

The VSSA-sponsored 16th Annual Student Research Symposium, held on the 2nd day of August, 2018, was the grand finale of the summer undergraduate research program. All thirteen VI4 Summer Scholars presented a poster describing their summer research work. This event was attended by a large Vanderbilt community of undergraduate and graduate students, postdoctoral fellows and faculty. The ensuing pages contain a brief description of summer research activities of each student and their poster presentation.

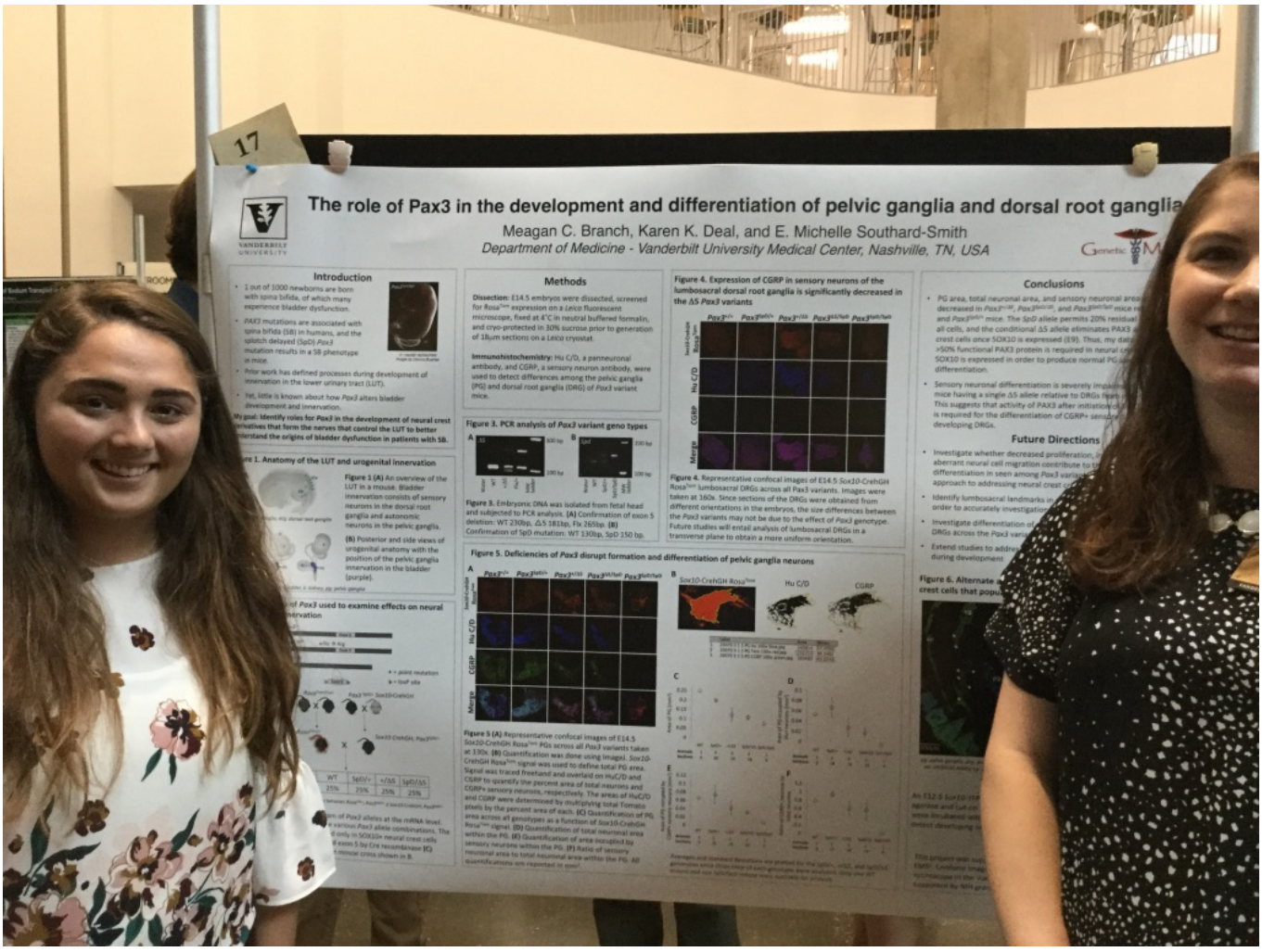
THE ROLE OF PAX3 IN THE DEVELOPMENT AND DIFFERENTIATION OF PELVIC GANGLIA

Meagan Branch
Elon University
Vascular Biology-Short Term Training Program for Minority Students

Michells Southard-Smith, Ph.D.
Department of Medicine

Summary

- The hypothesis that spina bifida (SB) mouse exhibit alterations in bladder innervation due to developmental deficits in pelvic ganglia.
- SB mouse exhibited significant changes in composition of pelvic ganglia neuronal subtypes, particularly those marked by CGRP.
- This finding suggests that changes in bladder innervation of SB mice are due in part to alterations within pelvic ganglia.



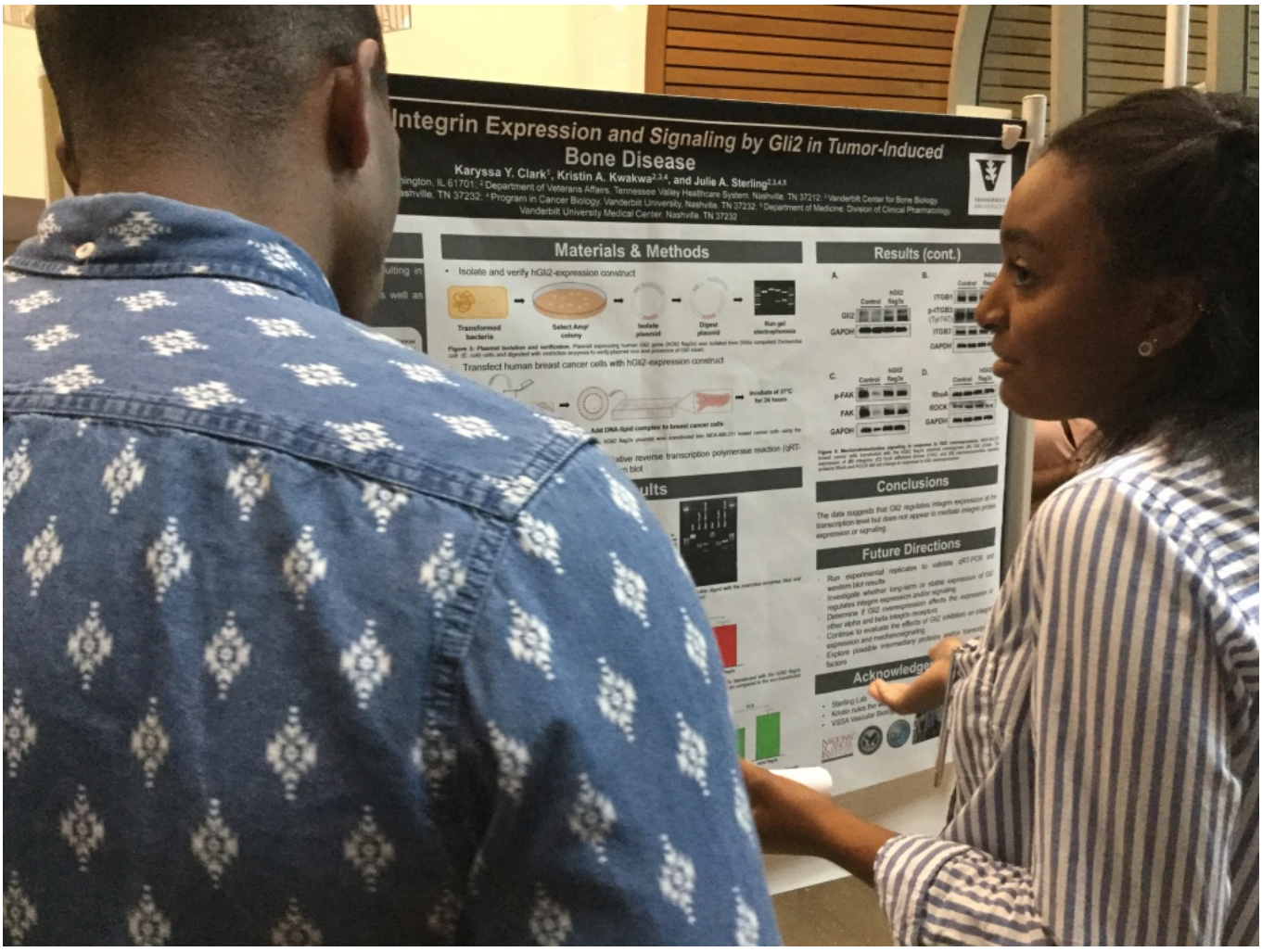
REGULATION OF INTEGRIN EXPRESSION AND SIGNALING BY GLI2 IN TUMOR-INDUCED BONE DISEASE

Karyssa Yvonne Clark
Illinois Wesleyan University
Vascular Biology-Short Term Training Program for Minority Students

Julie Sterling, Ph.D.
Department of Bone Biology

Summary

- The transcription factor Gli2 contros integrin expression and signaling in metastatic breast cancer cells to promote tumor-induced bone disease.
- Gene expression of integrin beta 1 and 5 decreased with Gli2 overexpression while beta 3 increased. No changes were observed at the protein level.
- Gli2 controls integrin expression at the transcription level but does not appear to impact integrin protein expression or signaling.



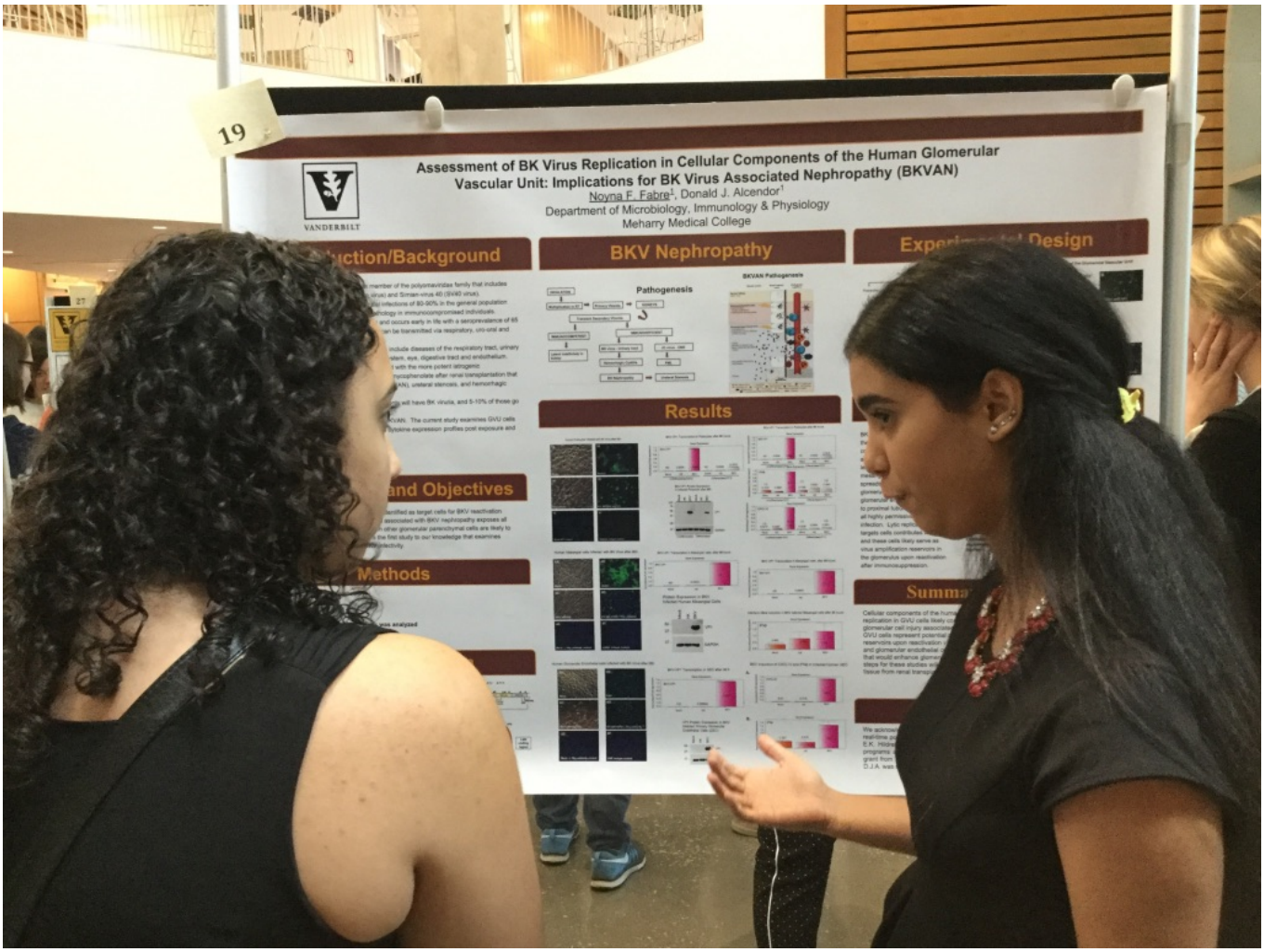
ASSESSMENT OF BK VIRUS REPLICATION IN CELLULAR COMPONENTS OF THE HUMAN GLOMERULAR VASCULAR UNIT: IMPLICATIONS FOR BK VIRUS ASSOCIATED NEPHROPATHY

Noyna Francheska Fabre
Hunter college
Vascular Biology-Short Term Training Program for Minority Students

Donald Alcendor, Ph.D.
Department of Microbiology, Immunology, and Physiology

Summary

- Latent BK polyomavirus reactivates in immunosuppressed transplant patients yet the effect of BKV infection of glomerular vascular unit remains unexplored.
- Infection induced IFN- and CXCL10 in the glomerular vascular unit but cytopathology only in podocytes and glomerular endothelial cells and not mesangium.
- BKV infection may contribute to glomerular inflammation and cytopathology observed in BKV-associated nephropathy amongst renal transplant patients.



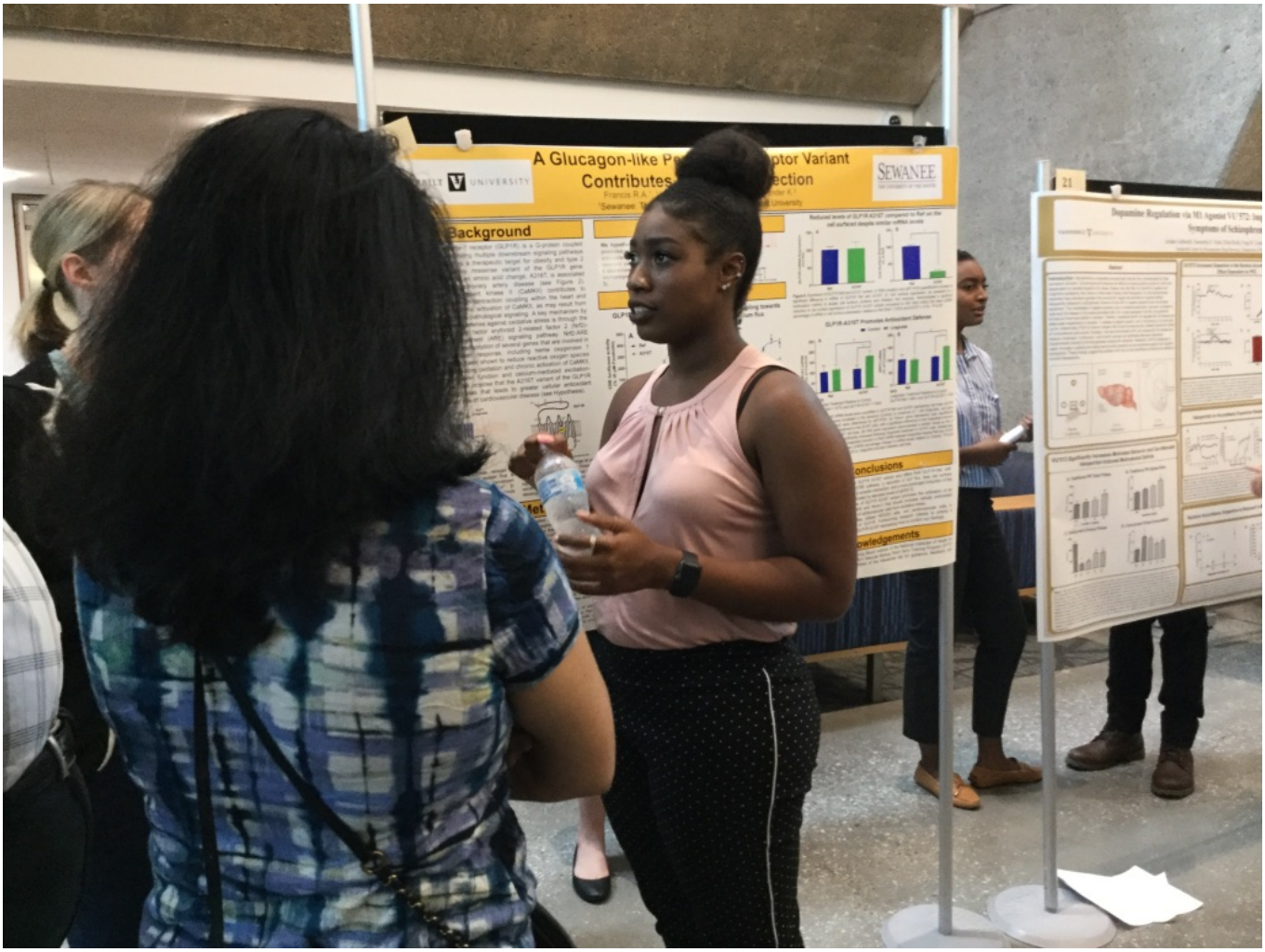
A GLUCAGON-LIKE PEPTIDE-1 RECEPTOR VARIANT CONTRIBUTES TO CARDIOPROTECTION

Rachel Alicia Francis
Sewanee: The University of the South
Vascular Biology-Short Term Training Program for Minority Students

Kevin Niswender, M.D., Ph.D
Department of Diabetes, Endocrinology, & Metabolism

Summary

- Identify if signaling bias occurs with a missense variant (A316T) of the GLP1R gene that is associated with reduced risk of coronary artery disease.
- The signaling of the GLP1R A316T variant promotes greater antioxidant capacity than the reference GLP1R.
- The unique signaling properties of the cardio-protective GLP1R A316T variant promotes an antioxidant defense.



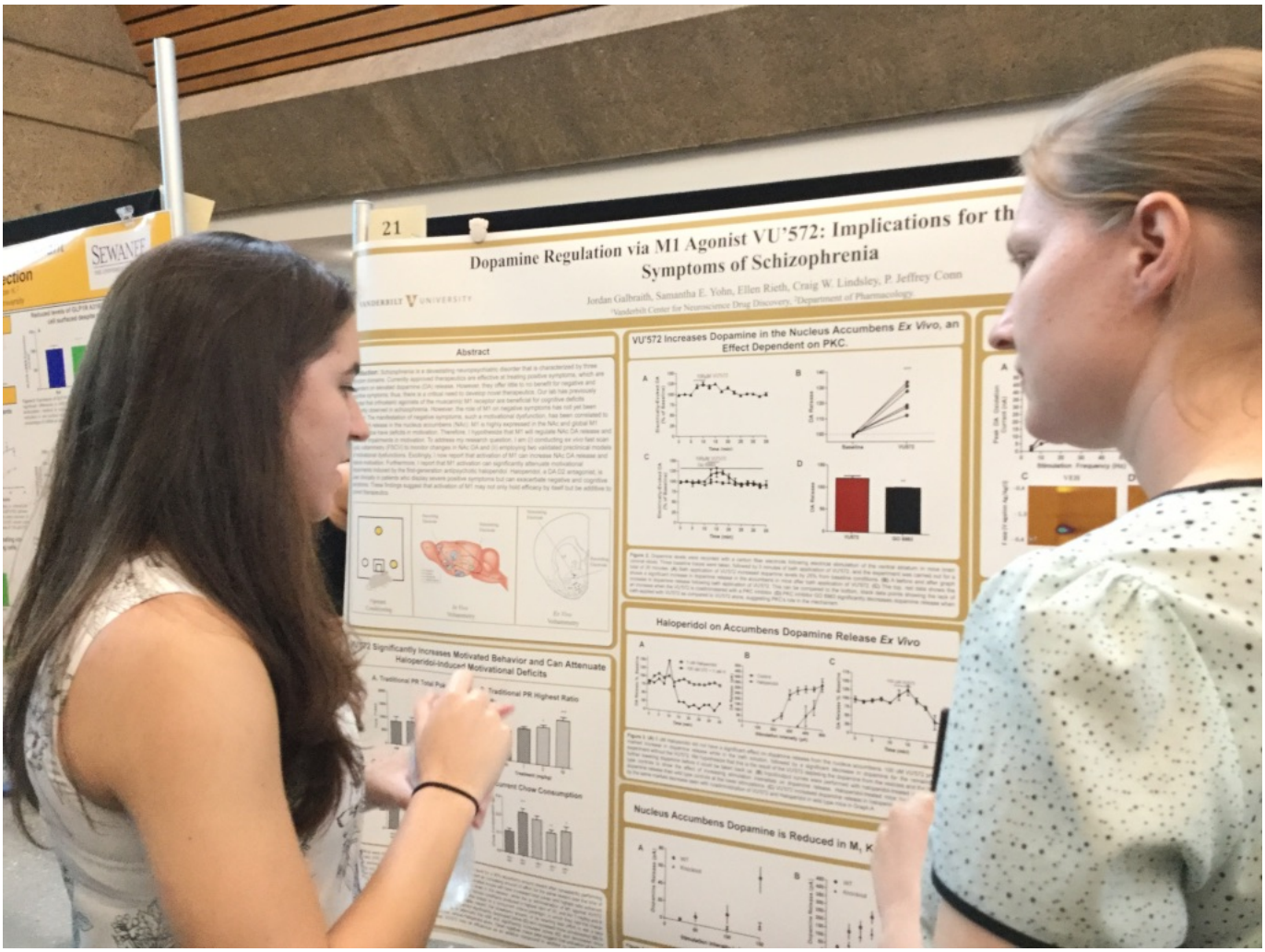
DOPAMINE REGULATION VIA ALLOSTERIC MODULATION OF THE M1 RECEPTOR: IMPLICATIONS FOR THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Jordan Galbraith
Vanderbilt University
Vascular Biology-Short Term Training Program for Minority Students

Jeffrey Conn, Ph. D.
Department of Pharmacology

Summary

- My project addressed how activation of the M1 receptor controls dopamine neurotransmission and subsequent motivated behavior.
- I discovered that activation of the M1 receptor by the an allosteric modulator agonist increases dopamine (DA) release through activation of protein kinase C.
- These findings suggest that the M1 receptor may be efficacious for the treatment of motivational.



DETERMINING THE PRESENCE OF AND FUNCTIONAL SIGNIFICANCE OF DOPAMINE RECEPTORS IN THE DUCTUS ARTERIOSUS DURING DEVELOPMENT

Micah Harris
Wright State University
Vascular Biology-Short Term Training Program for Minority Students

Jeff Reese, M.D.
Department of Pediatrics

Summary

- The hypothesis that Fenoldopam, a selective D1 dopamine receptor agonist, inhibits ductus arteriosus tone and prevents its postnatal closure, was tested.
- I found that Fenoldopam delivered in vivo did not prevent natural closure of the DA after birth.
- Hence, studies to evaluate Fenoldopam treatment of preterm newborns who are about to receive NSAID treatment for a patent ductus arteriosus are warranted.

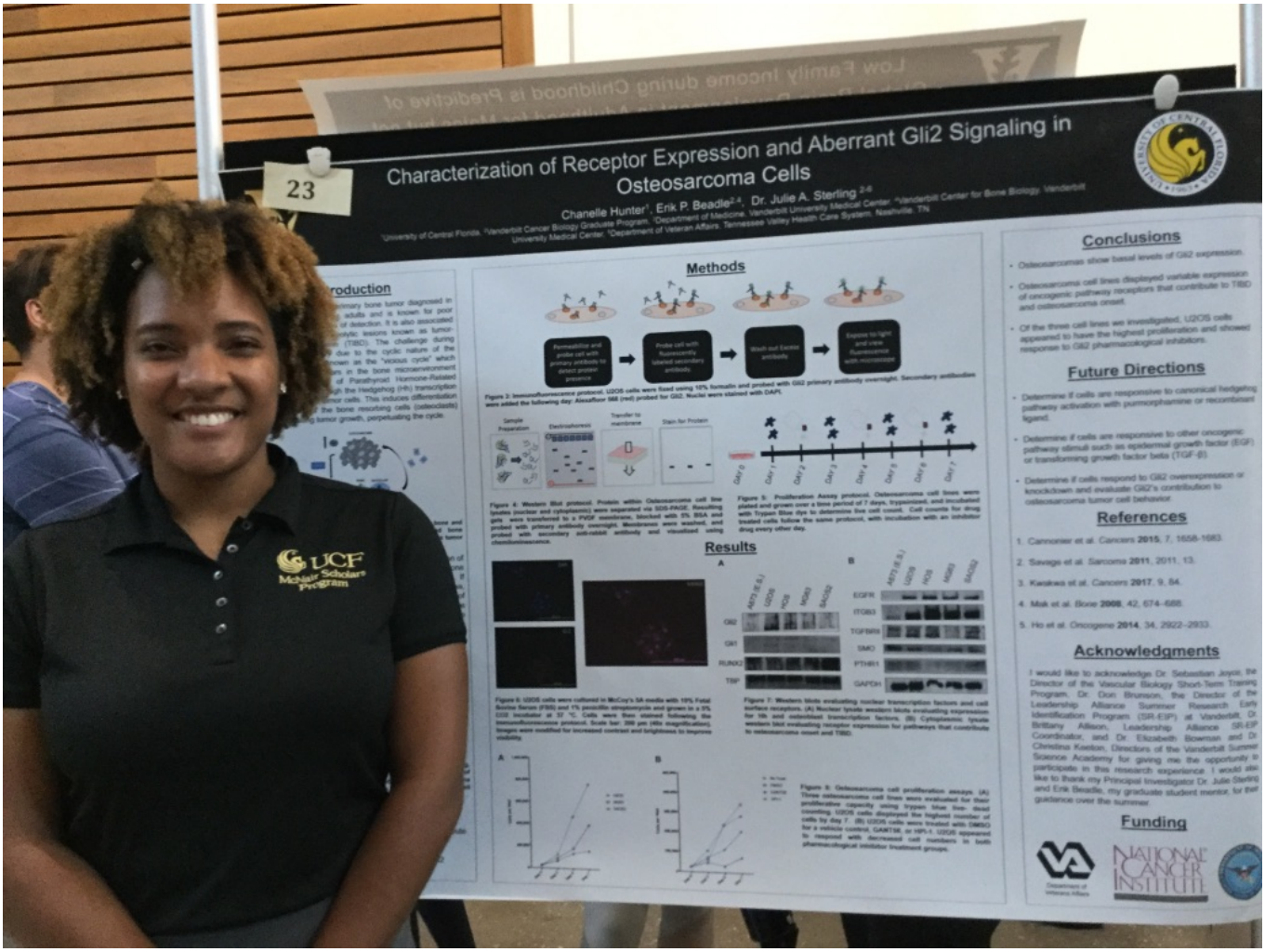
CHARACTERIZATION OF RECEPTOR EXPRESSION AND ABERRANT GLI2 SIGNALING IN OSTEOSARCOMA CELLS

Chanelle Hunter
University of Central Florida
Vascular Biology-Short Term Training Program for Minority Students

Julie Sterling, Ph.D.
Vanderbilt Center for Bone Biology (Department of Medicine and Division of Clinical Pharmacology)

Summary

- Exploring signaling regulation in osteosarcomas to find common targets within a variety of tumor samples (varying activating mutations, etc).
- The transcription factor Gli2 was overexpressed in all of the bone sarcoma cells investigated regardless of other mutations present.
- Hence, Gli2 is a potential therapeutic target for osteosarcoma patients with a wide variability in genomic mutations.



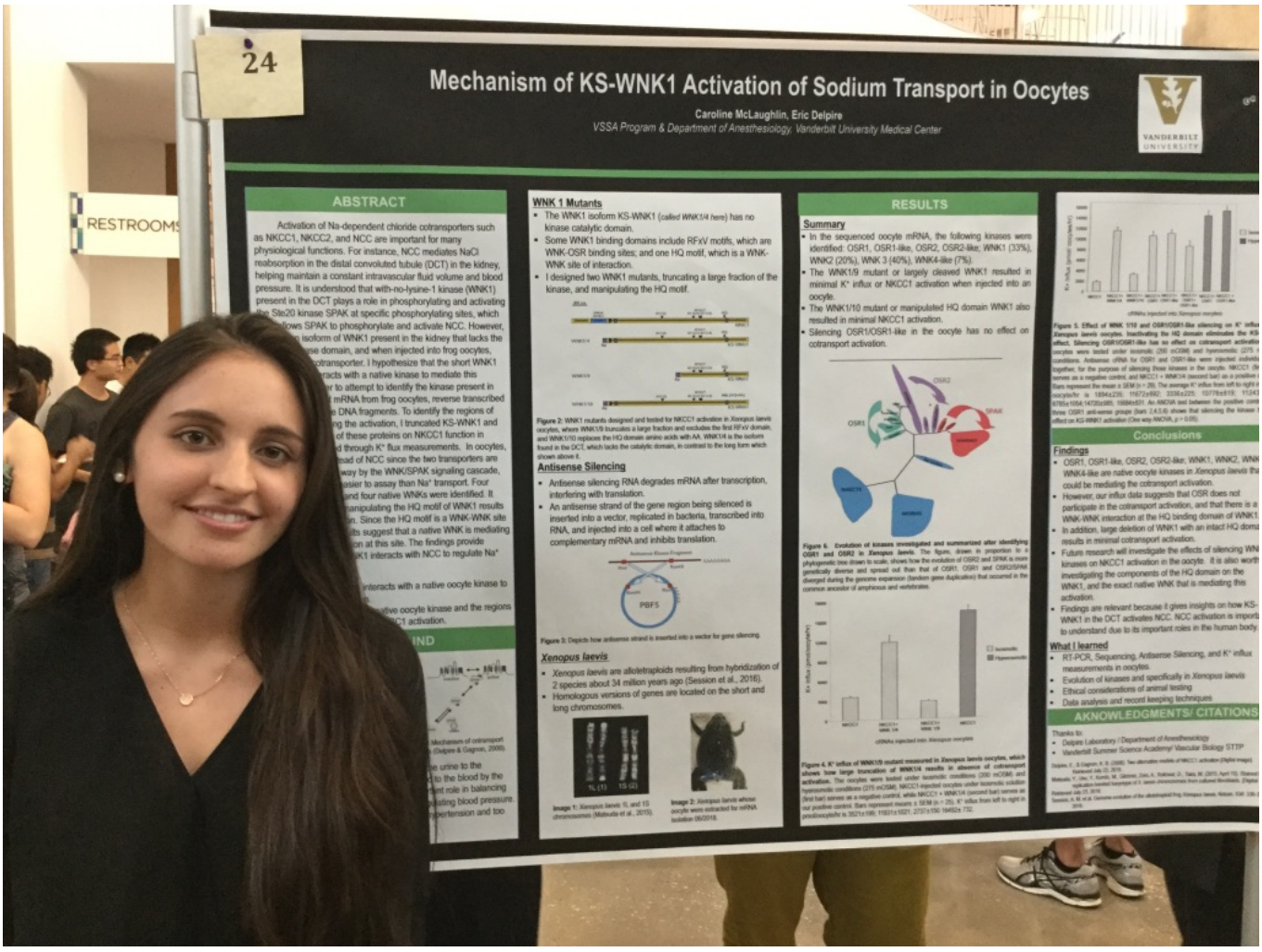
MECHANISM OF KS-WNK1 ACTIVATION OF SODIUM TRANSPORT IN OOCYTES

Caroline McLaughlin
Emory University
Vascular Biology-Short Term Training Program for Minority Students

Eric Delpire, Ph.D
Department of Anesthesiology

Summary

- Despite lacking kinase activity, the kidney-specific isoform With-No-Lysine Kinase-1 (KS-WNK1) activates Na+ transporters in *Xenopus laevis* oocytes.
- All 4 WNK as well as OSR1 and SPAK kinases are expressed in oocytes; and mutations in SPAK-WNK binding or WNK interaction motif affects activation.
- The physiological role of KS-WNK in the distal convoluted tubule is unknown, but it may play a role in Na+ transport function by acting on other kinases.



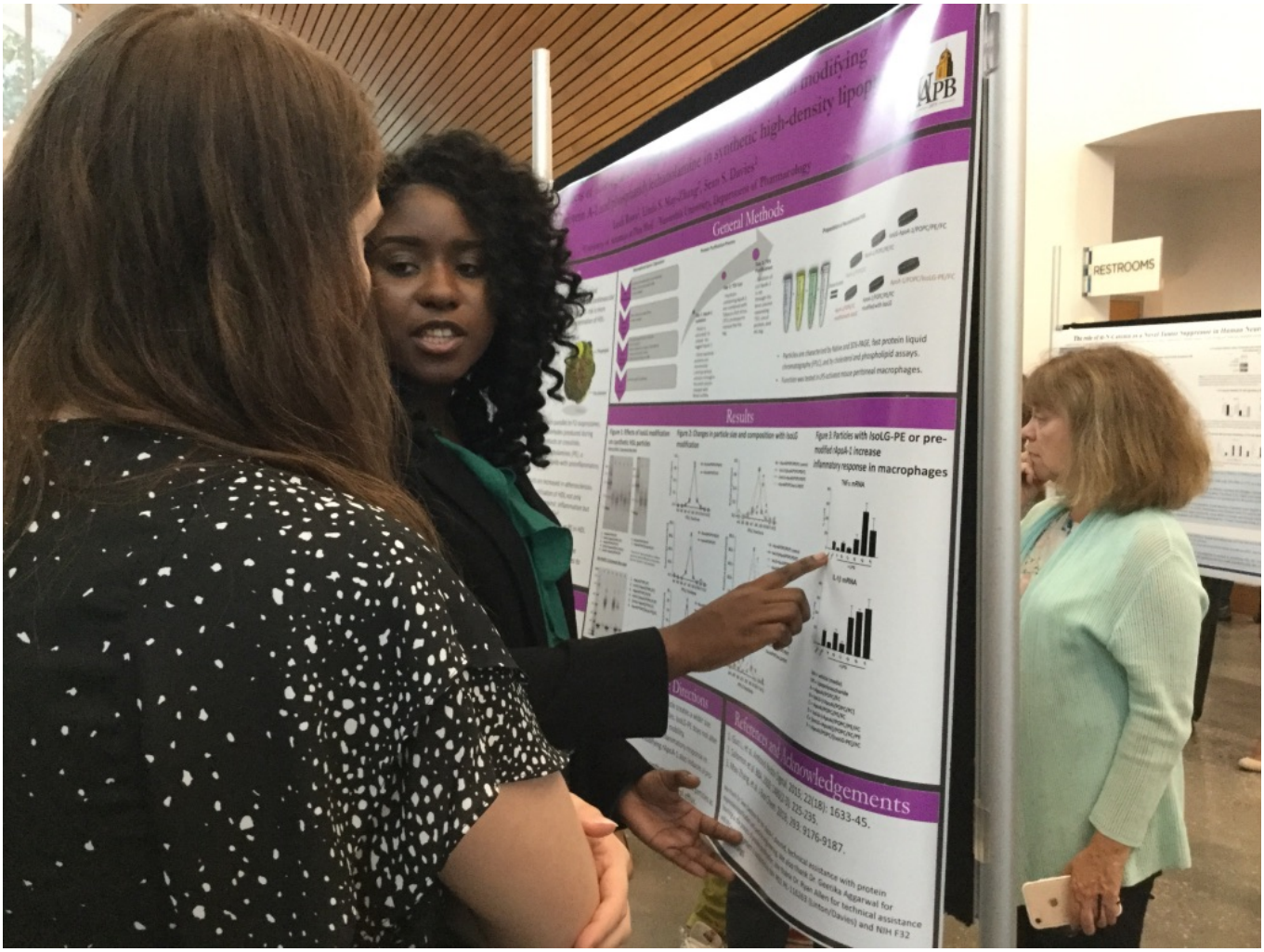
EFFECTS OF ISOLEVUGLANDIN, A HIGHLY REACTIVE LIPID DICARBONYL, ON MODIFYING APOLIPOPROTEIN A-1 AND PHOSPHATIDYLETHANOLAMINE IN SYNTHETIC HIGH-DENSITY LIPOPROTEIN

Leah S. Rowe
University of Arkansas at Pine Bluff
Vascular Biology-Short Term Training Program for Minority Students

Sean Davies, Ph.D.
Department of Pharmacology

Summary

- Modification of HDL by isolevuglandins (IsoLG) induces pro-inflammatory phenotype in macrophages, but the mechanism remains unknown.
- Recombinant HDL prepared with IsoLG-PE (phosphatidylethanolamine) induced a proinflammatory phenotype but HDL containing ApoAI was dysfunctional.
- These results suggest that IsoLG-modified PE is pro-inflammatory and, thereby, may underlie the atherogenicity of modified HDL.



EXAMINATION OF THE EFFECTS OF HYPERGLYCEMIA ON INFLAMMASOME ACTIVATION

Sydney Lindsay Castellanos
Indiana University - Bloomington
Vanderbilt Institute of Infection, Immunology and Inflammation

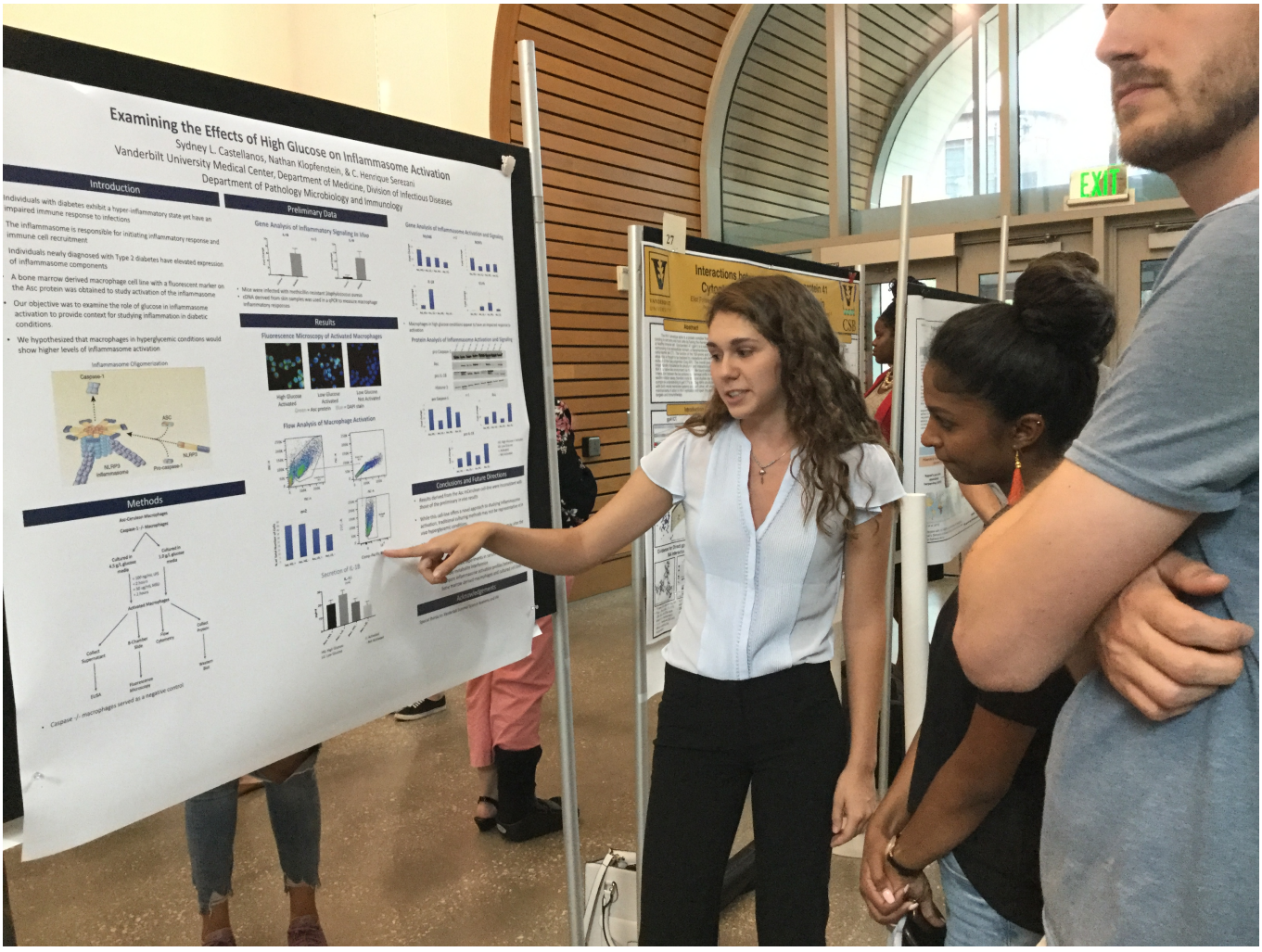
Carlos Henrique Serezani, Ph.D.
Department of Medicine

Summary

- To understand how the immune system works under diabetic conditions, we asked whether glucose threshold impacts inflammasome activation in macrophages.

- We observed that high glucose enhances the expression of inflammasome components, yet did not enhance inflammasome assembly and activation.

- From this observation, we predict that inflammasome activation has very little role in inflammation that is induced by high glucose in diabetic patients.

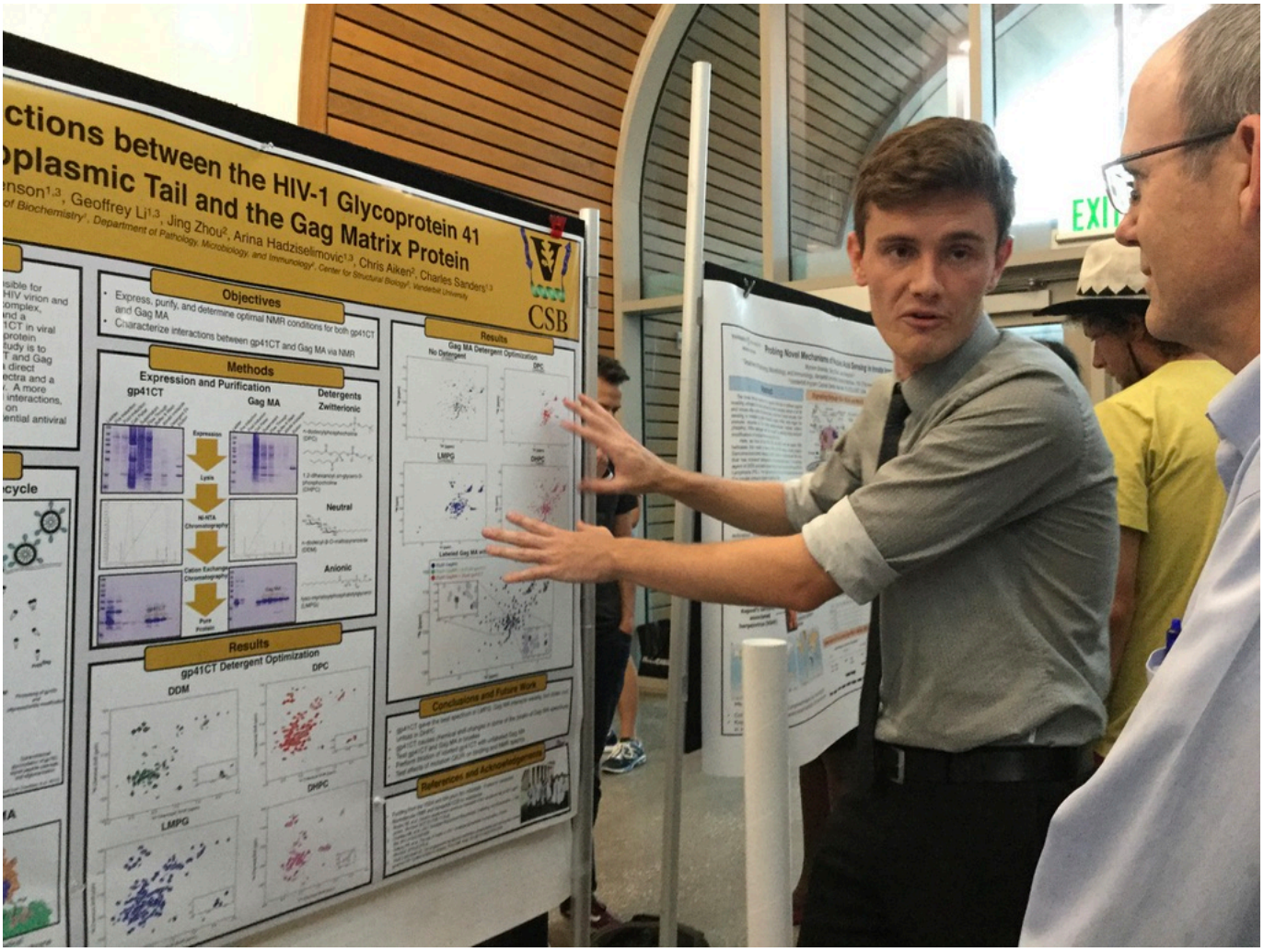


CHARACTERIZING THE NATIVE STRUCTURE OF THE HIV-1 GP41 CYTOPLASMIC TAIL AND ITS INTERACTIONS WITH THE GAG MATRIX PROTEIN

Eliot TC Forster-Benson
Vanderbilt University
Vanderbilt Institute of Infection, Immunology and Inflammation

Charles Sanders, Ph.D.
Department of Biochemistry

- The biochemical and structural bases for HIV matrix (MA) and viral gp41 interactions are not known.
- NMR spectroscopy experiments revealed that the cytosolic tail of gp41 is largely unstructured whose tail appears to bind directly to MA.
- Our findings unveil a new target for the design of new anti-HIV agents.



PROBING NOVEL MECHANISMS OF NUCLEIC ACID SENSING IN INNATE IMMUNITY

Myriam Shehata
Vanderbilt University
Vanderbilt Institute of Infection, Immunology and Inflammation

John Karijolich, Ph.D.
Department of Pathology, Microbiology, and Immunology

Summary

- The goal was to determine whether MDA5 activates STAT1 indirectly even in the absence of interferon B (IFNb) production.
- In the absence of an activating ligand, MDA5 induces very little, if any, IFNb production, yet STAT1 activation remains unabated.
- Hence, MDA5 does not activate STAT1 indirectly of IFN production.

PILUS-EXPRESSING *ACINETOBACTER BAUMANNII*, MEDIATED ENHANCED BACTERIAL CLEARANCE INVOLVING INFLAMMASOMES SIGNALING

Lorrayya Louise Williams
Calvin College
Vanderbilt Institute of Infection, Immunology and Inflammation

Michael Noto, Ph.D. M.D.
Department of Pathology, Microbiology, and Immunology

Summary .

- Pilus-expressing *A. baumannii* differentially activates innate immune system but the differentially activated pathway is not known.
- Bone-marrow derived macrophages and dendritic cells infected with pilus-expressing *A. baumannii* exhibit a caspase-1-dependent increase in IL-1 .
- Increased production of IL-1 by cells infected with pilus-expressing *A. baumannii* suggests a role for inflammasome activation.