

RESULTS AND DISCUSSION

BRET Newsletter
Issue 2, Fall 2015

Photo Credit: Vanderbilt University

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Letter from the Deans

Welcome to the second issue of "Results and Discussion," a newsletter sponsored by the Biomedical Research Education and Training (BRET) office, which is devoted to highlighting the research accomplishments and activities of our Ph.D. graduate students and postdoctoral fellows.

In September, we welcomed 97 new Ph.D. students to Vanderbilt University's School of Medicine and celebrated the start of their scientific training with the sixth annual Simple Beginnings Ceremony. During the ceremony, each student was presented with a monogrammed white lab coat as a classic symbol of their scientific training. We now watch with anticipation to see the impact they will have on biomedical discovery in the coming years.

The goal of publishing Results and Discussion is twofold. First, we want to inform alumni, current trainees, and their families and friends about the important work Vanderbilt's young scientists are doing and the discoveries they are making. Second, the newsletter provides an opportunity for trainees to develop their writing and editing skills for potential careers in science communication. Indeed, this newsletter was designed, written, and edited in its entirety by our current trainees!

If you are inspired by the stories you read here and would like to become

more involved with our students, postdoctoral fellows, or our programs, please let us know. There are many ways that you can become engaged in our efforts to support and prepare the next generation of scientists.

For more information, please visit our website or feel free to reach out to either of us directly. We would love to hear from you.

Sincerely,



Roger G. Chalkley, D. Phil.
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Kathy L. Gould, Ph.D.
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Visit us at our website for more information:

<https://medschool.vanderbilt.edu/bret/>

Shining Light on Cellular Handshakes

By **Sanjay Mishra, Graduate Student**

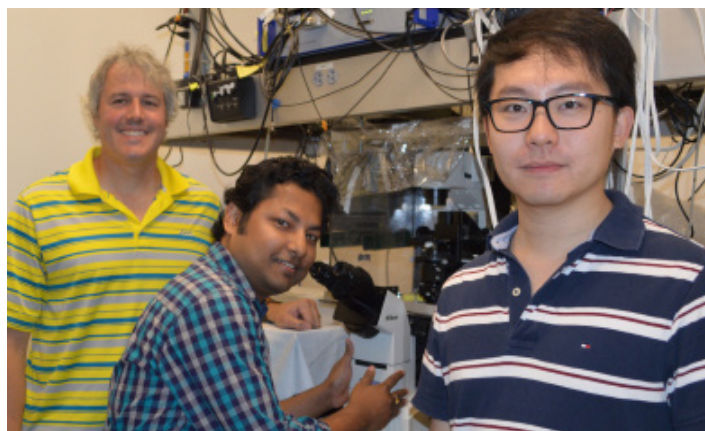
When you meet Dibyendu Kumar Das, Ph.D., in the basement of Olin Hall, rearranging guides of laser beams, like Lego blocks, he seems very unassuming. But as he begins to describe the use of lasers to grab particles and measure subtle forces involved at the biological scale, you realize why he does not notice the loneliness of the small, cramped room. When asked what motivates him to spend long hours in the dark lab, Dr. Das smiles, “Joy of discovery! You are the only one to know something. That joy is enormous. It is thrilling.”

Dr. Das grew up in the agrarian Midnapore in eastern India. His home town was once the center of the Indian renaissance. Growing up in an academic family, Dr. Das always wanted to discover things. He credits his father for instilling in him the expectations and the rigor of science at an early age.

Dr. Das received his bachelor’s degree from the University of Burdwan with honors in Chemistry. After earning a Master of Science in Chemistry from the Indian Institute of Technology, he earned a Ph.D. in Lasers and Spectroscopy from the Indian Association for the Cultivation of Science (IACS). IACS is India’s oldest research institute, shaped by the likes of Sir C.V. Raman, the Nobel laureate who discovered the eponymous Raman Effect.

Dr. Das joined Vanderbilt University in the winter of 2013 as a George Russell Chambers postdoctoral fellow in the lab of Matthew Lang, Ph.D. Dr. Lang is a Professor of Chemical and Biomolecular Engineering and has advanced techniques to measure small biological forces.

The Lang lab uses **laser beams as optical tweezers to grab beads smaller than a billionth of an inch**. The beads are anchored to a surface by a tether that contains a protein of interest and its binding partner. By manipulating the laser, the optical tweezer pulls the bead, which stretches the tether as they increase the tension. When the tether cannot stretch any farther, the link between the protein of interest and its binding partner snaps and the strength of the interaction can



be determined. Dr. Lang’s lab measures these miniature breaking forces to study biological motors and the body’s natural defense system. Under the supervision of Dr. Lang, Dr. Das led a team of researchers to discover how the $\alpha\beta$ T-cell receptor (TCR) on mammalian T cells recognizes pathogens to afford protective immunity. This study was recently published in the Proceedings of the National Academy of Sciences. T cells are a type of white blood cell that keep watch for foreign cells to guard the body against invaders. Cells of all kinds present T cells with a hundred thousand different antigens (peptide IDs), like a handshake with the TCRs, to determine if the cells are friends or foes.

Prior to this study, scientists knew that TCRs can sense forces, and that T cells can be triggered by small forces on the TCRs. They also knew that the triggering depended on the substrate stiffness. What was not clear was how, in the chemically and physically “noisy” environment of the cell, TCRs seek out and bind to rare foreign antigens among countless irrelevant interactions.

Dr. Das and his coworkers at Vanderbilt and Ellis Reinherz and colleagues at the Dana-Farber Cancer Institute in Boston showed that **T cells discriminate “self” from “non-self” by feeling the right amount of tugging force on the TCR during fleeting handshakes**.

Dr. Das used optical tweezers to measure the strength of the interaction made by the TCR latched to a viral protein. He found that TCRs progressively stiffen as they encounter pathogens. His labmate Yinnian Feng recapitulated similar single molecule measurements on single cells.

A unique loop in the receptor “feels” for the force of the handshake and loosens the grip when the force is too weak (self) but strengthens the handshake when the force is just right (non-self). When T cells spot an alien, they mechanically engage a biochemical trigger that releases a chemical alarm that plays a key role in activating the immune system. This mechanism is potentially a powerful weapon against cancer because getting this physical handshake correct may make T cells more likely to recognize and attack cancer cells.

Dr. Das is firmly entrenched in academics. He likes to develop new techniques to visualize microscopic interactions. He quips, “Great techniques are critical for great science.” He wants to study the unique specificity of TCR using a blend of optical tweezers with optogenetics, an emerging technology that makes individual cells photosensitive and then activates those specific cells using flashes of light.

“If we can control the TCR response with light, it can allow for manipulating and programming cells. If someone can do it, it will be revolutionary.”

In the Lab with Lasers

Left to Right: Matthew Lang, Ph.D., Dibyendu Das, Ph.D., and Yinnian Feng. Photo Credit: Meagan Quinlan

Learn More:

Das et al., Force-dependent transition in the T-cell receptor β -subunit allosterically regulates peptide discrimination and pMHC bond Lifetime. PNAS (2015)



Left: Denise Bottiglieri, Ph.D., CEO of Healthcare Consultancy Group speaks to students after her keynote lecture. **Center:** Meghana Rao, Ph.D., gives advice to students interested in a career in consulting. **Right:** Katie Moisse, Ph.D., giving a plenary lecture on her life as an editor.

Photo Credit: Anne Rayner

Career Symposium Emphasizes Importance of Effective Communication

"I wish I had this when I was here"

By **Henry H. Ong, Ph.D., Postdoctoral Fellow**

That sentiment was expressed by Vanderbilt postdoctoral fellow alumna Denise Bottiglieri, Ph.D., CEO of the Healthcare Consultancy Group, as she spoke at the 2015 Annual BRET Career Symposium on "science careers that put your communication skills to work."

Dr. Bottiglieri remarked that when she was completing her postdoctoral training in Clinical Pharmacology at Vanderbilt the only major career options available were academia or industry. Many other careers now exist and a career symposium like this one would have been invaluable for her as she transitioned to a non-academic career.

The day long event was sponsored by the BRET Office of Career Development and the Vanderbilt Medical Alumni Association and was supported by biomedical science training grants. About **300 graduate students and postdoctoral fellows** attended this year's symposium, which featured 16 speakers, 12 of whom were Vanderbilt University alumni and whose careers included consulting, science policy, journalism, outreach, and the nonprofit sector.

"From academia to industry and to government, communication skills are a necessary component of any career," said Kathy Gould, Ph.D., Associate Dean for Biomedical Sciences, in her opening remarks.

A common theme was the power of networking. While networking could potentially lead to a job, connecting with people

in the field can provide valuable information about what a specific career actually entails and how best to make a transition.

It can be difficult to approach a stranger, but **"you only need 20 seconds of courage.** They can only say no and you will be no worse off," said Dr. Bottiglieri.

Volunteering is another good way to gain experience, demonstrate initiative, and learn new skills. At the beginning of her career, Katie Moisse, Ph.D., news editor for the Simons Foundation Autism Research Initiative (SFARI) and former digital health editor at ABC News, volunteered at Scientific American and the ALS (amyotrophic lateral sclerosis) Society, the professional society related to her graduate research.

These opportunities allowed her to write regularly and to build her writing portfolio. Eventually, both organizations hired Moisse as a freelance writer. "If you produce a good product," she said, "someone will pay you for it for fear of losing you."

Breaking into a non-academic career can be daunting. However, a Ph.D. graduate will have many skills that will benefit different companies.

"It's not what you're trained to do, but how you're trained to think," said Vanderbilt Pharmacology graduate program alumnus Steve Roberds, Ph.D., chief scientific officer at the Tuberous Sclerosis Alliance. "A Ph.D. is a doctorate in philosophy. It is really about the thinking process."

Important Dates | 2015-2016

Aug 17

1st Day of Fall Semester

Sep 4

Simple Beginnings

Sep 24

Postdoc Family Picnic

Dec 11

End of Semester Celebration

Dec 11

Open Lab Poster Session

Jan 4

1st Day of Spring Semester

Feb 26

3 Minute Thesis Competition

March 14

ASPIRE to Connect

April 20

1st Year Lab Selection

June 2

Annual Career Symposium

From Neuroscientist to Strategic Consultant

By **Courtney Bricker-Anthony, Graduate Student**

Anuraag Sarangi is the quintessential alumni success story. After Dr. Sarangi earned his Ph.D. in neuroscience from Vanderbilt University in 2009, he completed a brief stint as a postdoctoral fellow at the University of North Carolina at Chapel Hill. From there, he transitioned into his current role of strategic consultant for ETHOS Health Communications. Dr. Sarangi recently returned to Vanderbilt as an invited speaker for the 2015 BRET career symposium. Prior to the symposium, Dr. Sarangi sat down with me to **discuss his journey from academia to industry**, his work at ETHOS, and advice on how to flourish in your post-graduate career.

Before Dr. Sarangi joined the Neuroscience Graduate Program at Vanderbilt, he acquired two degrees in computer science. During that time, he enjoyed building and creating tools for scientists and researchers, but found something lacking. “I noticed that I was getting a superficial understanding of the science involved because I was really concentrating more on the tools,” he said. “I really wanted to get a deeper understanding of the science.”

Ultimately, Dr. Sarangi decided to pursue a Ph.D. in neuroscience under the mentorship of Michael Cooper, M.D. “Now, I feel like I have a greater understanding of the science and I also appreciate how the tools I was developing in computer science were helping scientists do their research.”

During his time in graduate school, Dr. Sarangi co-founded and served as co-director of the academic chapter of the Tennessee Biotechnology Association (TBA) (now Life Science Tennessee). His involvement with the TBA and other professional organizations during his training fostered the development of his networking and leadership skills. His interactions with these organizations also eventually informed his transition from academia to industry. “Developing relationships through the networking opportunities provided by these professional organizations was invaluable.”

Throughout our chat, Dr. Sarangi frequently stressed the importance of networking. **“Networking is essential. It’s an important skill that one needs to continue to develop, even after you’ve chosen a particular career path.”** In my case, networking was essential in opening up not just industry contacts, but also the job opportunities I eventually secured.”

As a strategic consultant for ETHOS, Dr. Sarangi’s job consists of two primary roles: strategic advisor to pharmaceutical clients and team-lead within ETHOS. His dual role within the company

provides him with numerous responsibilities and requires constant communication with clients and members of his team. “The bulk of my work at ETHOS stems from interfacing with pharmaceutical marketing clients. I continue to explore and talk to them about strategies that are relevant to their product or brand within the market place. The other role that I have is to lead my internal team at ETHOS. My team is a relatively large cross-functional team consisting of about 15 people.

Together, we deliver on important client projects, whether they’re strategic projects to gain insights from the marketplace or education and communication projects to compliantly provide information to the medical community about a product. I am providing oversight across different groups within my team. I’m also involved in managing resources within the company and securing new business opportunities for ETHOS.”

As we wrapped up our conversation, Dr. Sarangi offered some valuable insights on the challenges involved in establishing work-life balance. “My weekdays tend to be worse now, but my weekends tend to be better. During weekdays, I am constantly in communication-mode with clients and my team, and there are instances where things can be somewhat unpredictable. However, most weekends tend to be free, where you really disconnect and recharge yourself. **The key is flexibility and a supportive professional and personal environment.”**



Dr. Sarangi talks to students at the career symposium

Learn More:

For the full interview, including what a typical day is like for Dr. Sarangi, visit the BRET Career Development Website, Alumni Spotlight: <https://medschool.vanderbilt.edu/career-development/alumni-spotlight-anuraag-sarangi>

Illuminating the Brain: Can Optogenetics Improve Learning & Memory?

By **Fatima Nawaz, Ph.D., Postdoctoral Fellow**

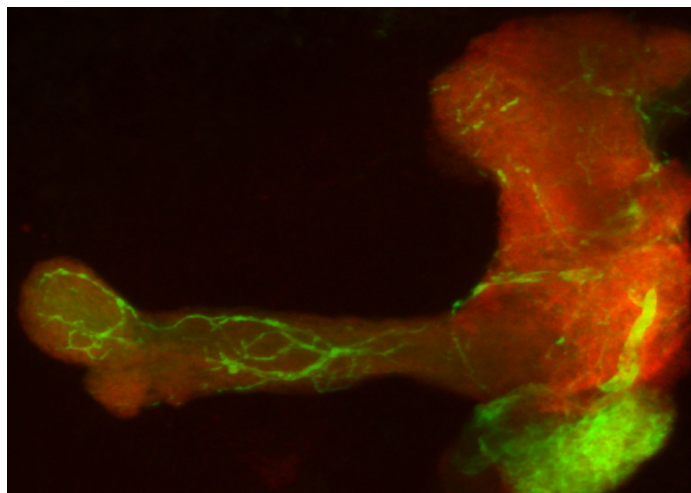
Have you ever stopped to appreciate that the learning and memory functions of your brain arose from critical developmental processes dating back to early childhood? The process termed, “activity-dependent neuronal maturation,” occurs gradually throughout childhood through stimulation of neurons by sensory input from all modalities, including visual, olfactory, gustatory, tactile, and auditory cues.

Sensory input causes neurons to activate a series of genes involved in pruning and reorganization of synapses, including the dendrites that provide input to neuronal cells. This pruning and reorganization leads to the formation of circuits that underlie learning and memory. **Fragile X syndrome (FXS), the leading heritable cause of intellectual disability worldwide**, appears to involve insufficient pruning and maturation of neurons during the critical stages of early development. Caleb Doll, Ph.D., a postdoctoral fellow in the department of Biological Sciences, is the first author of a paper on FXS that was recently published in the journal *Development*. A native Kansan, Dr. Doll moved to Nashville to join the Interdisciplinary Graduate Program at Vanderbilt University. During his graduate studies, he researched neurogenesis under the supervision of Josh Gamse, Ph.D.

“The expansiveness of the unknown,” Dr. Doll says, inspired him to pursue this line of work. “We know so little about the healthy function of the human brain. While some might find this overwhelming, for me it was motivating.” After graduate school, his commitment to research in neuroscience led him to the laboratory of Kendal Broadie, Ph.D., where Dr. Doll now focuses his research on synapse formation and function during development.

Together, Dr. Doll and Dr. Broadie utilized a *Drosophila* model system of FXS to report that activity-dependent synapse formation depends on the presence of Fragile X Mental Retardation Protein (FMRP), the protein missing in FXS. To mimic activity-dependent maturation in flies, they manipulated specific neurons of the learning and memory circuit through expression of optogenetic channels. This technology uses light to stimulate neurons and interestingly results in the pruning of dendrites in a manner analogous to the activity-dependent neuronal maturation.

By illuminating these neurons with hyperpolarizing and depolarizing light during a critical period of development, Dr. Doll successfully stimulated or suppressed dendritic reorganization in neurons in a manner that may mimic the natural ac-



Functional interaction between learning and memory; mushroom body axons (red) and a mushroom body output neuron (green) in *Drosophila melanogaster*. Photo Credit: Caleb Doll, Ph.D.

tivity-dependent maturation and reorganization that occurs in childhood and adolescence. Importantly, this activity-dependent developmental pruning was absent in flies lacking FMRP, suggesting the FXS phenotype may be directly linked to the absence of this protein. “Before optogenetics, the field of neuroscience relied on pharmacological agents and electrophysiology to manipulate neurons, but now we can study and **noninvasively influence the development of individual cells in healthy rodents or flies**, which has entirely re-energized our research landscape,” said Dr. Doll.

Though the precise mechanism of FMRP-mediated neuronal maturation remains elusive, it seems to be acting as a master activity regulator by controlling the translation of a number of important neuronal genes and by directly binding and regulating voltage-gated ion channel function, described Dr. Doll. It is not yet known if other autism spectrum disorders (ASDs) stem from a lack of additional “activity sensors,” but many ASDs are characterized by an imbalance of excitatory and inhibitory signaling in the brain. Optogenetic control of excitation and inhibition therefore represents an intriguing application for studying these neurological disorders.

The findings from Dr. Doll and Dr. Broadie raise a number of exciting questions. What does this mean for the treatment of FXS and related pathologies? Can we promote activity-dependent maturation in FXS children through alternative therapies? Optogenetics has already proven useful in rodent models of epilepsy; can these techniques also provide solutions to memory and learning related developmental disorders? Might other sensory stimulants promote activity-dependent maturation, such as targeted olfactory or audio therapies? For now, optogenetics as a potential human therapy is “decades away from having such a direct clinical application,” Dr. Doll cautions, “however the possibility is certainly very exciting.”

Learn More:

Doll & Broadie. Activity-dependent FMRP requirements in development of the neural circuitry of learning and memory. *Development* (2015)



Photo Credit: Meagan Quinlan

Clint Smith, Ph.D., is a postdoc in the Denison lab studying a potential new target to disrupt the inner working of deadly pathogens

Chemistry Gone Viral

By **Marilyn Holt**, Graduate Student

Coronaviruses passed under the public radar until 2002, when the severe acute respiratory syndrome-associated coronavirus (SARS-CoV) jumped from bats to humans and caused a frightening epidemic that spread to 32 countries and caused 916 deaths. A similar jump occurred in 2012, when the Middle East respiratory syndrome coronavirus (MERS-CoV) began infecting individuals in Saudi Arabia. As of this writing, 473 MERS-related deaths have occurred there since 2012, and the country is currently fighting to contain an outbreak in Riyadh that has already killed four people.

Clint Smith, Ph.D., a postdoctoral fellow in the lab of Mark Denison, M.D., is the lead author of a study recently published in the *Journal of Virology* that has **revealed a potential new target for scientists trying to disrupt the inner workings of these deadly pathogens.**

"I was definitely a convert to virology," said Dr. Smith, who earned his B.S. in Chemistry at the University of Central Arkansas before transitioning to the University of Kentucky for his Ph.D. in Biochemistry. There, he studied the structural biology of how viruses fuse to cells. This inspired him to further delve into the fundamental biology of RNA viruses, and he decided that "maybe it was time to do some real virology."

While Dr. Smith was primarily drawn to the Denison lab by the mentorship and the people, he was also fascinated by the puzzle posed by viral proofreading. In all living organisms—from bacteria to humans—multiple proofreading mechanisms are used to ensure that cells do not make mistakes when copying their genome, the blueprint for the cell. However, viruses, such as coronaviruses, were traditionally thought to be incapable of proofreading.

This idea was turned on its head in 2006, when a proofreading enzyme, nsp14, was discovered in SARS-CoV. **This discovery "breaks the paradigm that RNA viruses**

can't proofread," said Dr. Smith, who "saw that this could be a game changer in the RNA virus world." In 2012, nsp10, a protein with no prior known function, was found to promote the proofreading activity of nsp14. This led to a key question: how does nsp10 stimulate proofreading by nsp14 in SARS-CoV?

Because of its potential to pose a threat to public health and safety, the Center for Disease Control (CDC) added SARS-CoV to the list of "select agents" in 2012, where SARS-CoV joined agents like the Ebola virus. This means use of SARS-CoV is highly regulated, and labs doing research on the virus must take extreme security precautions to ensure that SARS-CoV does not reach the general population. This is good for public health, but it adds an extra layer of difficulty to research on SARS-CoV.

To avoid these issues, Dr. Smith used the murine hepatitis virus (MHV), a coronavirus very similar to SARS-CoV and MERS-CoV, as a model system for investigating coronavirus proofreading. In mice, MHV causes inflammation of the liver and is often fatal. However, MHV is harmless to humans and is not on the CDC's select agents list, which vastly simplifies the process of working with the virus.

Since the structure of a protein often dictates the function of the protein, Dr. Smith developed a model of MHV nsp10 based on the known protein structure of SARS-CoV nsp10. Dr. Smith then used this model to predict mutations that would disrupt the interaction between MHV nsp10 and nsp14. After introducing these mutations into MHV, he tested if the mutated virus was more sensitive to mutagens—chemicals which would cause damaging mutations and decrease viral replication in the absence of proofreading.

Dr. Smith found that the nsp10 mutations resulted in less viral replication, suggestive of a decreased proofreading ability by nsp14. A subsequent experiment in which the mutated virus was grown at different temperatures in the presence of a mutagen supports the idea that the mutations in nsp10 affect the physical interaction between nsp10 and nsp14 and that this interaction is key to promoting proofreading by nsp14.

The inability to proofread is believed to have a negative effect on a virus's ability to cause disease, as well as its ability to generate more copies of itself. According to Dr. Smith, the dream for this project is to purify the entire RNA synthesis machinery, including nsp10 and nsp14, so scientists can ask specific biochemical questions about this complex without the confounding factors present in the intact virus. **Understanding the coronaviruses' ability to proofread their genomes may reveal new targets for antiviral therapies, which could be used to treat patients in the case of another coronavirus outbreak.**

Dr. Smith is currently applying for faculty positions at liberal arts colleges that are supportive of active research programs. Dr. Smith said, "I really enjoy teaching and working with undergraduates, so it is a great fit. I'll still study coronaviruses, just on a smaller scale with a heavier teaching component."

Learn More:

Smith et al., Mutations in coronavirus nonstructural protein 10 decrease virus replication fidelity. *Journal of Virology* (2015)

Giving to the Biomedical Scientists of Tomorrow



Kathy Gould, Ph.D., high fives incoming IGP class members. Photo Credit: Anne Rayner

The research activities and educational training of our Ph.D. students is highly dependent on support received from the US Government, via the National Institutes of Health (NIH). Through a variety of NIH-granting mechanisms, graduate students are financially supported while they receive sophisticated training and contribute to biomedical discovery. Certainly this model for graduate education has been hugely successful, as can be seen in the incredible advances now being made in the understanding and treatment of heart disease, diabetes, cancer, and brain disorders such as Alzheimer's disease. However, the national economic climate makes it challenging to continue with this model, relying so heavily on federal support.

For this reason we want to highlight an opportunity for you to join us in supporting, encouraging, and rewarding our grad-

uate students. Consider giving online to the **Young Biomedical Research Scholar Fund** (<http://vu.edu/biomedscholar>). With your help, we can ensure that our Ph.D. students have access to the best research and training opportunities available.

Your generous philanthropic support can make a tremendous impact on the education afforded our Ph.D. students by providing critical training enhancement opportunities such as participating in trans-institutional collaborations and short courses to learn new techniques and technologies and traveling to national and international scientific conferences.

There are many ways you may wish to help our students. Specific gifts may be designated to support a student pursuing studies in a particular area of research, named endowed scholarships can be established in honor of a particular individual, and bequests are a meaningful way to leave a legacy for future generations. Please let us know if you would like to discuss these options further.

We are committed to helping our graduate students attain the support needed to make valuable contributions in their research. **We welcome your gifts, large and small, and thank you for your support.**

Thank you,

Kathy Gould

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Associate Dean for Biomedical Sciences
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We Will Not Give Up

Student-Initiated Campaign Highlights Perseverance of Young Scientists

By **Courtney Bricker-Anthony**,
Graduate Student

Victoria Cavener is a person with many roles. After 9 years of service in the Navy, she is a veteran who is passionate about eliminating PTSD. Victoria is also a neuroscience graduate student at Vanderbilt University.

Her latest endeavors as founder and creative director of We Will Not Give Up allow Victoria to channel her passion for advocacy and biomedical research into a singular message of hope and determination. We Will Not Give Up is an organization with the goals of changing the public perception of scientists and influencing science policy and funding.

Victoria and her team at Vanderbilt aim to achieve their goals by featuring biomedical trainees and their stories of why they are devoted to their research. While We Will Not Give Up began with Vanderbilt students, the site now highlights trainees from eight universities and research institutes. The site has amassed an audience of 570,000 people worldwide since its launch in March 2015 and continues to grow.



Victoria Cavener starts WWNGU campaign
Photo Credit: Wes Duenkel

To see pictures from more student scientists involved in the campaign and to read their stories or submit your own, visit www.wewillnotgiveup.org

Learn More about Giving Back:

Details about the Young Biomedical Research Scholar Fund can be found at:
<https://medschool.vanderbilt.edu/bret/giving-biomedical-trainees-0>



Photo Credit: Anne Rayner

Simple Beginnings

Vanderbilt University's School of Medicine welcomed 97 new Ph.D. students at the 6th annual Simple Beginnings ceremony on September 4, 2015. Students received a monogrammed white lab coat as a classic symbol of their scientific training, while friends and family were on hand to help celebrate. **Ying Ji**, a first year graduate student in the Interdisciplinary Graduate Program (IGP) as part of the Vanderbilt International Scholars Program (VISP) shakes hands with **Larry Marnett, Ph.D.**, Associate Vice Chancellor for Research and Sr. Associate Dean for Biomedical Sciences, and **Kathy Gould, Ph.D.**, Associate Dean for Biomedical Sciences. **Roger Chalkley, D. Phil.**, Sr. Associate Dean for Biomedical Research, Education and Training is at the podium announcing names of all first year students.

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