

Editors-in-Chief: Marilyn E. Holt, Kendra Oliver, Ph.D. & Tyne Miller-Fleming **Faculty Advisor:** Ashley E. Brady, Ph.D.

Letter from the Deans

Welcome to the fourth 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 PhD graduate students and postdoctoral fellows.

This fall, 71 new biomedical doctoral students arrived on campus to embark on their scientific training. Vanderbilt University's School of Medicine welcomed them by hosting their families at the seventh annual Simple Beginnings Ceremony, where each new student received a monogrammed white lab coat. These lab coats serve as a classic symbol of scientific training and were generously provided through donations from Vanderbilt faculty and staff who are eager to see the discoveries these new scientists will make in the years to come.

We are also excited to share with you that this spring, the BRET office will be hosting its inaugural reunion event marking the 25th anniversary of the Interdisciplinary Graduate Program (IGP) on June 1-2, 2017. We are looking forward to welcoming former trainees back to campus who graduated from our PhD programs. This will be a wonderful opportunity for our alumni to reconnect with former classmates, learn about new discoveries happening in the labs, visit with former mentors and colleagues, and meet and inspire current trainees who

are continuing the BRET tradition. We will hold the reunion in conjunction with the 2017 Annual Career Symposium, hosted by the BRET Office of Career Development, which will feature our alumni and highlight their varied career paths since leaving Vanderbilt.

Please let us know if you would like to learn about ways you can support us in our efforts to 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,

8 chief.

Roger G. Chalkley, D. Phil. Sr. Associate Dean for Biomedical Research Education and Training roger.g.chalkley@vanderbilt.edu

Kathy L. Gould, Ph.D.

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Visit us at our website for more information:

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

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Neandertals: Humans Can Relate

By Barbara O'Brien, Graduate Student

Roughly 50,000 years ago, humans shared the world with Neandertals. a closely related hominin species. Recently, it was discovered that Neandertals left their mark in the modern human genome from interbreeding that occurred between these two groups. Could ancient Neandertal DNA impact people that inherited it from their ancestors? A group of researchers, led by graduate student Corinne Simonti, has shown just that. Their findings, published earlier this year in Science, suggest that **Neandertal** genetic variants are linked to risk for skin disorders, mood disorders, depression, obesity, and even tobacco addiction. This is the most comprehensive study to date that links ancient DNA with modern genotypes and phenotypes to examine the impact of evolution on modern health.

Simonti joined the laboratory of Tony Capra after entering the Vanderbilt Interdisciplinary Graduate Program (IGP) in 2012. The Capra group uses compu-

tational tools and approaches to study evolutionary genetics. One event that impacted human evolution was the interbreeding between humans and Neandertals. In fact, 1-4% of the genome for modern humans of European ancestry is thought to be from Neandertals. While some reports suggested Neandertal DNA could impact modern human health, those studies were unable to provide direct evidence linking Neandertal DNA variants to specific medical conditions.

Simonti and her colleagues thought they could provide this link by showing a correlation between Neandertal DNA variants to medical conditions in patients with those variants. To do this, Simonti turned to the Electronic Medical Records and Genomics (eMERGE) Network, a group of medical center databases across the country, including Vanderbilt's BioVU. BioVU is a database of anonymized Vanderbilt Medical Center patient genomes linked with their medical histories, connecting genetic variants

with specific medical conditions.

In collaboration with Joshua Akey, Ph.D., professor of Genome Sciences at the University of Washington, Simonti and her colleagues searched these databases for known variants Neandertal in more than 28.000 genomes of American adults of European ancestry, hoping to whether determine



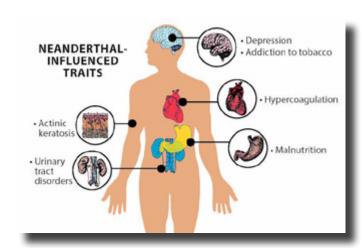
Graduate student Corinne Simonti

Photo credit: Joe Howell.

these variants could be linked with specific medical conditions. Results from their analysis showed that Neandertal variants were in fact linked to medical conditions.

"We didn't even know that interbreeding between humans and Neandertals occurred until very recently," Simonti stated when commenting on the impact of this research. "This study gives us an idea of the lasting effect of this event on human health today."

Simonti, who has always loved science, developed her desire to study evolutionary genetics while earning a bachelor's degree in genetics at the University of Georgia. When asked about her future plans, she said, "I have a pretty wide array of interests, so I have a few projects in the works that examine other genetic variants with interesting evolutionary histories." Simonti says she hopes to continue researching evolutionary genetics.



Simonti et al. provide a link between genetic variants from Neandertals and disorders affecting humans today. **Figure provided by:** Deborah Brewington.

Biosciences Career Symposium Offers Industry Overview

By Lorena Infante Lara, Graduate Student

Don't worry, there is life — and a good job — at the end of graduate and postdoctoral training. But it won't drop in your lap. You have to reach out and talk to people.

That was the message delivered by Dave Jensen during a career symposium recently hosted by the BRET Office of Career Development, which helps graduate students and postdoctoral fellows in the biosciences at Vanderbilt University Medical Center make informed career decisions.

Jensen, a nationally known executive recruiter and biotech industry columnist, was one of several speakers who participated in the daylong event. The three speakers and seven panelists all came from diverse backgrounds, and had a variety of experiences to share.

Attendees learned how to look for industry jobs and the details of the hiring pro-

CESS, which qualities attract employers, how to get their feet wet by applying for postdoctoral positions in industry, and why it's important to have strong communication skills.



Left: Dale Edgar, Ph.D., discusses postdoctoral opportunities in industry with students during a breakout session. **Right:** Dave Jensen, an executive recruiter, shares advice for students considering careers in industry. **Photo credit:** Anne Rayner.



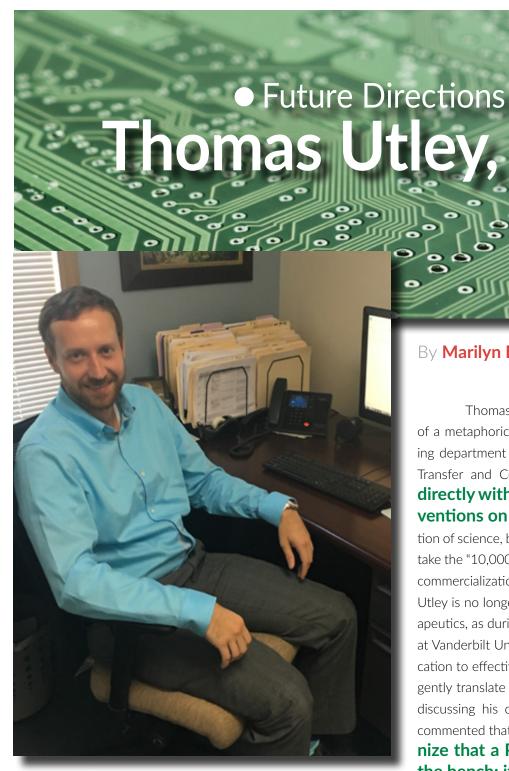
David Tellers, Ph.D., discusses his experiences at Merck and provides tips for success when applying for careers in industry. **Photo credit:** Anne Rayner.

"After attending, I have a much better idea of what careers are available in industry and how to go about applying for those jobs," said Amber Beckett, a third-year Ph.D. student. "I especially appreciated getting a glimpse of the day-to-day activities of people in these careers."

A popular feature of the symposium was Networking Huddles, speed dating-style interactions between attendees and the speakers and panelists, as well as several representatives of local companies and research institutes.

At the end of the day, students and postdoctoral fellows also had the opportunity to network with speakers, panelists and company representatives in a more traditional networking reception setting.

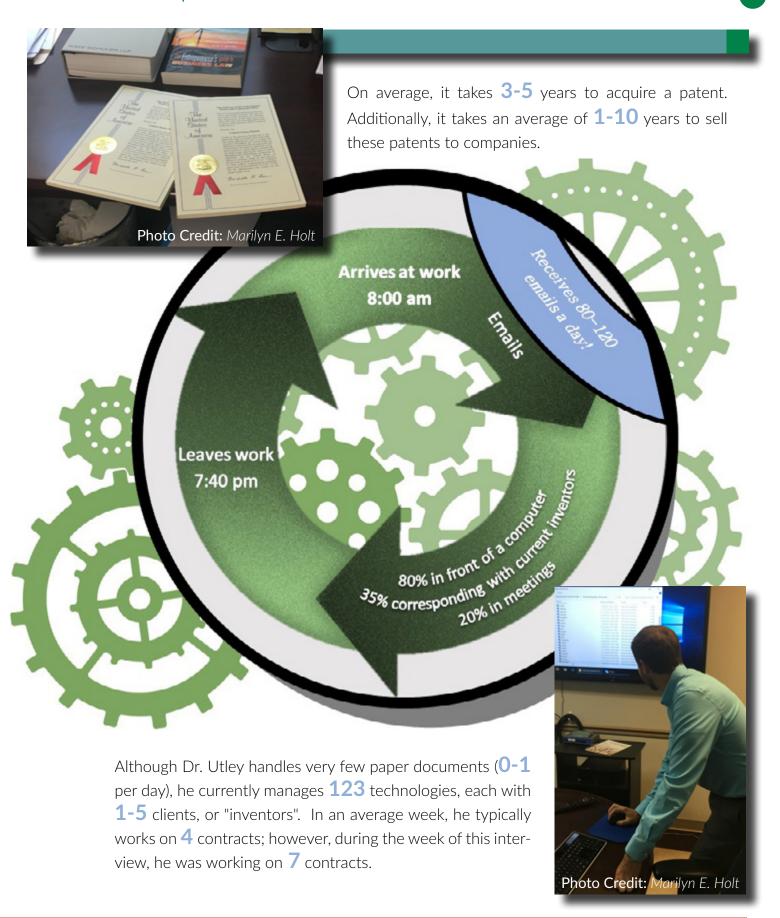


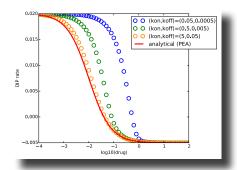


Thomas Utley, Ph.D. (above) has been at Vanderbilt University for 13 years. In his current position at the Center for Technology Transfer and Commercialization, he works directly with inventors to patent their ideas. **Photo Credit:** Marilyn E. Holt.

By Marilyn E. Holt, Graduate Student

Thomas Utley, Ph.D., views science from the top of a metaphorical mountain. As a member of the licensing department at the Vanderbilt Center for Technology Transfer and Commercialization, Dr. Utley works directly with inventors to get Vanderbilt inventions on the market. Working at the intersection of science, business, and law in this way allows him to take the "10.000 foot view" of science as he facilitates the commercialization of emerging technologies. While Dr. Utley is no longer personally investigating potential therapeutics, as during his graduate and postdoctoral training at Vanderbilt University, he still utilizes his scientific education to effectively communicate with scientists and cogently translate scientific concepts for companies. When discussing his career beyond the laboratory, Dr. Utley commented that, "People are starting to recognize that a Ph.D. is not just for working at the bench; it can be applied in a number of different ways." Here, we take a peek into a day in the life at the technology transfer office.





Sample dose response curves. Figure provided by: Leonard Harris, Ph.D.

Postdoctoral research fellow Leonard Harris, Ph.D., may be a chemical engineer by training, but his skills in mathematical modeling and analyses have earned him and his collaborators a publication in *Nature Methods*

After completing his Ph.D. degree in chemical engineering at Cornell University, Dr. Harris began postdoctoral studies in computational systems biology with James Faeder, Ph.D. at the University of Pittsburgh. Now, he is co-mentored by Carlos F. Lopez, Ph.D., and Vito Quaranta, M.D., in the department of Cancer Biology at Vanderbilt University.

"I feel very fortunate to work with Carlos and Vito-it is a unique opportunity to

apply my computational and mathematical background to disease problems," said Dr. Harris.

In fact, Dr. Quaranta, Dr. Lopez, and senior author, Darren Tyson, Ph.D., had been contemplating new methods to measure how well anti-cancer drugs kill cancer cells for some time. Traditionally, cell proliferation is measured at a single time point after drug administration, usually 72 hours (three days). The problem with this, they argue, is that the 72-hour measurement is static and does not account

When I DIP, you DIP, we DIP:

A new method to measure drug effects on cancer cell proliferation

By Katie Hutchinson, Ph.D., Postdoctoral Fellow

for the inherently dynamic processes of cell proliferation and drug activity.

"Anti-cancer compounds work at different rates and behave differently in different cell lines, and cancer cells grow and divide at different rates, so **measuring compound effect at only one time point can be very misleading,"** explained Dr. Harris.

Therefore, they proposed the DIP rate, or drug-induced proliferation rate, which is defined as "the steady-state rate of proliferation of a cell population in the presence of a given concentration of drug." Using mathematical modeling and experimentation, they showed that the DIP rate consolidates drug effects on cell proliferation into a single quantity that allows more statistically sound interpretations.

Dr. Harris and his co-authors ultimate-

ly hope to change the way biomarker and anti-cancer drug discovery efforts are conducted and reported. For example, cancer biologists frequently rely on publicly available data sets, such as the Cancer Cell Line Encyclopedia (CCLE) and Genomics of Drug Sensitivity in Cancer (GDSC) database, for hypothesis generation. Both databases use the 72-hour metric for reporting drug sensitivity. As a result, millions of dollars may be wasted pushing drugs through to cancer clinical trials that ultimately don't work. "In time, we hope to add the DIP rate to the CCLE and GDSC databases to improve drug sensitivity reporting and save taxpayer dollars."

Dr. Harris also stresses that implementing the DIP rate into everyday experimentation will not be difficult. "You just need

a way to measure the number of cells in real time." With advances in robotics and microscopy, this approach is becoming easier and easier.

Later this year, Dr. Harris will apply for a research career development award in hopes of running his own laboratory soon. "My lab will definitely be computationally based, but I plan on collaborating with biological experimentalists—as I have been—to facilitate the best science."



Leonard Harris, Ph.D., and colleagues published a study in *Nature Methods* describing a new approach to measure cancer cell proliferation. **Photo credit:** Tyne Miller-Fleming.

KLF2: The Key to Getting Natural Killer Cells Just Right

By Heather McCartney, Graduate Student

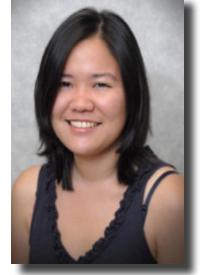
While the transfer of natural killer cells into leukemia patients can lead to remission, this treatment is only successful if the transplanted cells survive and proliferate. **Natural killer cells are lymphocytes that readily kill virally infected cells or tumor cells** without assistance from B or T cells, making them extremely powerful—and potentially dangerous. In research recently published in *PNAS*, Whitney Rabacal, Ph.D. and colleagues discovered that **transcription factor KLF2** is required for natural killer cells to survive and grow. Ultimately, this study outlines a potentially ground-breaking change in how we think about treatment of leukemia with natural killer cell transplantation.

After graduating with a B.A. in Biology from Bowdoin College, Dr. Rabacal was determined to go wherever the most exciting and innovative immunology research was being conducted. Before deciding to pursue a Ph.D., Dr. Rabacal developed her technical skills and research experience by taking a position as a research assistant, studying lupus for four years in an autoimmunity laboratory at Brigham and Women's Hospital in Boston. Drawn to the strong immunology program at Vanderbilt, **Dr. Rabacal was excited to explore more independence in research during graduate school.**

Upon joining the laboratory of Eric Sebzda, Ph.D., Assistant Professor of Pathology, Microbiology, and Immunology, Dr. Rabacal began exploring the project that would define her graduate work. After her first immunology class at Bowdoin College and her research at Brigham and Women's Hospital, Dr. Rabacal was intrigued by research on natural killer cells and immune tolerance. This interest led her to a project involving the complicated relationship between natural killer cells and KLF2.

In natural killer cells, KLF2 intrinsically suppresses immature cell proliferation and mature cell migration. KLF2-directed migration patterns allow natural killer cells to access the essential cytokine, IL-

15, necessary for their "killer" functions and survival. In gene targeted models of KLF2, there are increased numbers of immature NK cells and mature "killer" cells are absent. Dr. Rabacal and colleagues have now shown that **KLF2 may be a potential therapeutic target** which may be manipulated to increase the number and persistence of transferred NK cells in leukemic patents.



Former graduate student Whitney Rabacal, Ph.D. Photo credit: Vanderbilt University.

While this project has been the main focus of Dr. Rabacal's graduate career, she is quick to credit

each author from the article on his or her critical contribution to the study. In addition to feeling supported by her lab and mentor, Dr. Rabacal speaks very highly of the support she received from Dr. Jacek Hawiger's IVBST and Dr. James Thomas's Rheumatology training grants. She also found that the "collegial and collaborative environment" between faculty, students and postdocs within the Immunology community at Vanderbilt provided her a solid foundation to pursue areas of her project that were more challenging experimentally.

While Dr. Rabacal admits that immunology research has not always led her down the simplest or most direct career path, she feels very optimistic about where her Vanderbilt training will take her scientific career. After defending her thesis, Dr. Rabacal plans to pursue a postdoctoral position. She is excited about the possibility of a faculty position, saying "I really love the mix of independence and excitement that academic research provides".

Faculty Spotlight: Craig Lindsley, Ph.D.

By Lorena Infante Lara, Graduate Student

Where did you get your PhD? Where did you do your postdoctoral training?

I went to UC Santa Barbara. I was in a traditional, classic synthetic chemistry program. I then did my post-doc at Harvard. It was one of the first post-docs in the Institute of Chemistry and Cell Biology, which was sort of the preamble to the Broad Institute. It was kind of the first stab

at doing more of the chemical biology and translational science.

Why did you decide to leave academia for a job in industry?

When I finished my post-doc, the idea of doing drug discovery and the ability to use chemistry to solve problems in biology and medicine was just really attractive. When I joined Merck in the early 2000s, they were known for their dedication to basic science. However, the leadership changed constantly and the paradigm switched to trying to reduce discovery to manufacturing principles, shorter timelines, and turning the crank, and the science element was just lost. About two years before I left. Jeff Conn. who was head of neuroscience there. left to come to Vanderbilt to set up a drug discovery program. He kept pinging me, saying, "You should just come look, come look and think about it." I waited awhile until he had the infrastructure on the pharmacology side and the screening side and all



that was missing was chemistry, and then I really fit in and was able to do the medicinal chemistry and DMPK. The ability to go somewhere where we can focus just really deeply on the science, and let science - not business - drive all the decisions about our program was really attractive.

If you could change something about each (academia and industry), what would it be?

If you think back to the golden age of drug discovery, scientists ran the companies; they were the ones in the leadership positions. Now, it's business people. If I could change anything, I would make the leadership of drug companies drug hunters. They think differently.

On the academic side, if I could change anything, I would say there needs to be more support for the enterprise, and an understanding that the big payoffs only come with continued levels of support. Soft money

is always cyclic, it's just... it's erratic.

Do you think that the transition from industry to academia is feasible for everyone?

When I first started, when you finished your post-doc, you either did Path A or Path B, and they were two roads that separate in a wood. Now, you see people going back and forth both ways, multiple times. Uni-

versities are starting drug discovery centers all across the board, not just in the U.S., and they're staffing them with former industrial scientists. The thing that is really important is that drug discovery- medicinal chemistry, drug discovery pharmacology, or drug discovery DMPK -that's something you can only learn at a company. You live it, breathe it, work with the people who know everything about everything, and learn the big team science approach. If you take that and bring it into an academic environment, it's wonderful. Spending five, ten years in industry and then going into academics is really ideal if you want to be able to have a much broader program. [industrial postdocs] would be a good path forward. I've had a couple of students go on to do industrial post-docs and actually end up getting jobs at the company, but in talking to them, it seems that everything that they were exposed to has given them a much broader program, and has given them competencies to compete for translational grants.



"It happened entirely by accident," reflected postdoctoral fellow Elwood Mullins, Ph.D., the first author on a recent *Nature* paper presenting a new mechanism for DNA damage repair. Dr. Mullins and colleagues had suspected the existence of this mechanism for some time, but the direct observation of glycosylase action *in crystallo* was a singular development.

DNA is comprised of bases that are constantly undergoing damage. This can lead to mismatched bases and cell death. DNA glycosylases, a group of enzymes that identify and remove damaged bases, are key players in DNA damage repair. In humans, DNA glycosylases must scan approximately three billion base pairs to identify damaged bases. Exactly how DNA glycosylases recognize these damaged bases in a sea of undamaged DNA is a key question in the DNA damage repair field. The accepted model is that DNA glycosylases directly interact with damaged bases to "flip them out" prior to base removal. However, Dr. Mullins' x-ray crystallography data show that a different mechanism is also possible.

After recieving his Ph.D. in chemistry from Washington University, where he studied the structure of coenzyme A transferases, Dr. Mullins was eager to continue unraveling enzyme function. He joined the group of Brandt Eichmann, Ph.D., Professor of Biological Sciences at Vanderbilt. "I was able to take what I knew about chemistry and apply that to enzymology—working on small molecules as a graduate student, and then DNA as the substrate in Brandt's lab."

To better understand the chemistry underlying interactions between DNA glycosylases and DNA, Dr. Mullins grew a crystal of the DNA glycosylase AlkD in complex with a DNA

substrate containing a damaged base. Surprisingly, Dr. Mullins found that he had captured an intermediate state in the base removal process, suggesting that this process was occurring in the crystal. Building on this unexpected development, he grew a series of crystals that were harvested at various points in time. Ultimately, this allowed him to generate a series of "snapshots" of AlkD as it recognized the damaged base and catalyzed its removal *in crystallo*. "Seeing that first crystal was a breakthrough moment. You try to do everything right to give yourself a chance to be lucky. It was entirely unexpected."

After analyzing the structural data, Dr. Mullins was pleased. Instead of directly flipping out the damaged base, as in the canonical mechanism, Dr. Mullins and colleagues observed that **AlkD recognized the damaged base through hydrogen bond interactions with the phosphoribose backbone of DNA.** This resulted in a new model for recognition and removal of damaged DNA by DNA glycosylases.

Dr. Mullins was quick to credit *in vivo* studies and computational modeling conducted by other lab members as essential to this paper. He **attributes the high impact of the paper to its interdisciplinary nature and expertise from fellow lab members and collaborators** from UC Davis and Japan.

In the short term, Dr. Mullins is directly following up on this publication by examining how AlkD removes larger types of DNA damage. He is also studying another DNA glycosylase that possesses a completely different structure and biological mechanism. Looking ahead, Dr. Mullins ultimately plans to establish his own research group, which will use hybrid structural techniques to better understand enzymes involved in DNA replication.

Symposium highlights research contributions of postdoctoral fellows

By Sarah Baum, Ph.D., Postdoctoral Fellow

It is widely assumed that individuals with autism spectrum disorder (ASD) are insensitive to pain due to the wide prevalence of self-injurious behaviors. A new study at Vanderbilt University Medical Center suggests that this may not be true. The postdoctoral fellow that led this study-Michelle Failla, Ph.D.—was one of the speakers on April 29 at the **10th** Annual Postdoctoral Research and Shared Resources Symposium in Light Hall. The daylong event featured postdoctoral research in both clinical and basic science departments and highlighted the distinctive contributions that postdoctoral fellows make to Vanderbilt University's research enterprise. Award recipients included Boone Prentice, Ph.D., Postdoc of the Year, and Danielle Dean, Ph.D., Best Use of Shared Resources.

In addition to research presentations, the symposium featured a number of talks that spoke to the unique career position of postdoctoral fellows. Peter Fiske, Ph.D. gave a dynamic keynote address on "putting your science to work". According to Fisk, earning a Ph.D. means you possess both technical expertise and a range of transferrable skills. The "soft" skills required to complete a Ph.D.-including excellent problem-solving skills, the ability to work in various environments, and honed technical communication skills—are highly valued by employers and should not be ignored by postdoctoral fellows when assessing their skill set. Perhaps most poignant was a piece of advice offered by one of his clients: "Graduate school gave me the ability and courage to start something even if you don't know how yet."



Ann Price, M.D., awards postdoctoral fellow Boone Prentice. Ph.D., (Caprioli lab) the Postdoc of the Year award. **Photo credit:** John Russell.



Some members of the PDA Symposium organizing committee are pictured above. From left to right: Mohit Chadha, Ph.D., Boone Prentice, Ph.D., Sarah Baum, Ph.D., Huzaifah Salat, Ph.D., Daniel O'Brien, Ph.D., Loren LaPointe, Ph.D., and Janani Varadarajan, Ph.D. Photo credit: John Russell.

The symposium represented a celebration of the accomplishments of postdoctoral fellows at Vanderbilt. In addition to the annual symposium, the Vanderbilt Postdoctoral Association sponsors a number of networking and social events throughout the year. The symposium was co-sponsored by the Vanderbilt Medical Alumni Association and the offices of Biomedical Research, Education and Training (BRET), Postdoctoral Affairs and Research.



Finding the Path to an Ebola Vaccine

By Suneethi Sivakumaran, Ph.D., Postdoctoral Fellow

The Ebola virus grabbed news headlines in early 2014 when, according to the World Health Organization, it caused the worst Ebola epidemic since its discovery in 1976. The infection eventually spread to Liberia, Guinea, Sierra Leone, Nigeria, Mali, and the US, causing over eleven thousand deaths. While there are no approved vaccines to prevent infection, several experimental therapeutics have been investigated, including antibody cocktails that target the surface of the virus. Unfortunately, current cocktails only neutralize one species at a time from the Ebolavirus genus—a major drawback for researchers seeking a broad-spectrum solution.

Three species of *Ebolavirus* are known to have caused large outbreaks in Africa: *Zaire ebolavirus*, *Sudan ebolavirus*, and *Bundibugyo ebolavirus*. The **wide genetic diversity of these virus types has inhibited the development of a single effective vaccine against ebolaviruses.** In a study recently published in Cell, Vanderbilt researchers in the lab of James Crowe, M.D., Director of the Vanderbilt Vaccine Center, in collaboration with researchers at the

University of Texas Medical Branch, provide a road map for developing a single vaccine for these species.

In this study, led by former graduate student Andrew Flyak, Ph.D., the team asked whether people who survive infection from a specific species of Ebolavirus develop antibodies against other Ebolavirus species. To investigate this possibility, they isolated and characterized antibodies from B cells donated by survivors of the Bundibugyo virus outbreak in Uganda. From these samples, they were able to identify cross-reactive monoclonal antibodies that neutralized multiple species of *Ebolavirus*. After identifying and isolating these antibodies, the team was able to show that these antibodies protected mice and guinea pigs from a different *Ebolavirus* infection.

Ultimately, this study suggests that **cross-neutralizing antibodies can be used for treatment against multiple ebolaviruses.** This provides the next step towards identifying monoclonal antibodies that could protect against future related viruses. When discussing this work, Dr. Flyak emphasized the role of the survivors that donated the samples used in this study, saying "I thank all the volunteers for their specimens. This study would not have been possible without them".

Since defending his dissertation, Dr. Flyak has taken a position as a postdoctoral fellow at the California Institute of Technology under the guidance of Dr. Pamela Bjorkman. He has received the Cancer Research Institute Irvington Postdoctoral Fellowship to study the structure of antibodies produced during infection by the Hepatitis C virus. Ultimately, Dr. Flyak plans to continue working on antibodies and gain a broader technical and scientific expertise within this area.



Former graduate student Andrew Flyak, Ph.D. (left) and mentor James Crowe, M.D. (right) found that antibodies from Ebola survivors can be used to battle the virus in infected mice and guinea pigs. **Photo credit:** Anne Rayner.

Learn More:

Flyak et al., Cross-Reactive and Potent Neutralizing Antibody Responses in Human Survivors of Natural Ebolavirus Infection. *Cell* (2016).

ANT DATES

Aug 24

First Day of Fall Semester

Jan 9

First Day of Spring Semester

Sept 2

Simple Beginnings

March 3

ASPIRE to Connect

Sept 20

Postdoc Family Picnic

March 31

3 Minute Thesis Competition

Dec 16

End of Semester Celebration

April 21

First Year Lab Selection

Dec 16

Mid-Year Poster Session

June 1&2

BRET 25th Reunion & Career Symposium

Photo credit: Vanderbilt University

RESULTS AND DISCUSSION

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