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

Refresh. Even though the bacteria never stop multiplying and the mice always need tending, there was a quiet hum of excitement as the new academic year rolled around, and we started anew here in the BRET Office. We welcomed a new class of fresh-eyed graduate students. Departmental seminars began again after a summer break. Our Ph.D. Career Connection series kicked off with a full year of interesting alumni and Ph.D. graduates discussing their path since leaving Vanderbilt.

Now in its 9th year, the Simple Beginnings ceremony welcomed 101 young scientists, eager to start their training programs in biomedical sciences. This event, held each year in September, marks an exciting catapult to not only their entrance to the Vanderbilt community but also their career as young discoverers.

On our horizon is the launch of a new short course, “Data Science Essentials: Transitioning Biomedical Scientists from the Bench to the Cloud.” Made possible through support from the Burroughs Wellcome Fund and executed by the BRET Office of Career Development, this unique opportunity will train future data scientists in a program divided in three parts: a didactic eight-week introduction to data science in partnership with the Nashville Software School, a nine-week module to build communication and networking skills, and 8-10 career case sessions with current data scientists. This course is a perfect fit for many trainees who are life scientists but are hearing about careers in data science and want to explore a possible transition to this career trajectory. This professional development activity will allow trainees to gain a real-world perspective on careers blending computer programming, science, and healthcare with a one-of-a-kind team by their side.

We continue this newsletter, now in its 8th issue, to keep you abreast of the exciting discoveries our trainees are making and to highlight some of their impressive next career steps. An emerging technology, a new discovery, an important mentoring moment provided by our faculty... this is what happens every day for our graduate students and postdocs. We love sharing about a group that refreshes us daily.

Sincerely,

Roger G. Chalkley, D. Phil.
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What’s Inside

Trainee Research Highlights
Chloe Snider by Natalya Ortolano, page 2
Reid Bolus by Lauren Scarfe, Ph.D., page 3
Alexandria Oviatt by Maria Agostini, page 5
Oliver Vranjkovic by Christopher Smith, Ph.D., page 8

Facility Spotlight:
Lauren Jackson, Ph.D.
by Allyson Mally, page 4

Exploring the Most Innovative Square Mile on the Planet
ASPIRE on the Road: Boston
by Ralph Hazlewood, Ph.D. and Jessica Overstreet, Ph.D., page 6

Annual Career Symposium Highlights
by Jessamyn Perlmutter, pages 10-11

Future Directions:
Molly Seale, Ph.D.
by Justine Sinnaeve, page 9

Visit us at our website for more information:
https://medschool.vanderbilt.edu/bret/
To Slide or Not to Slide: How Membrane Lipids Promote Cell Division

By Natalya Ortolano, Graduate Student

Cytokinesis is the last step of cell division, where two daughter cells are ultimately produced. Proper control of cytokinesis is critical for tissue maintenance, and loss of control can lead to diseases such as cancer. A recent article published in Molecular Biology of the Cell by Vanderbilt University graduate student Chloe Snider, postdoctoral fellow Alaina Willet, Ph.D., and colleagues implicates the phosphoinositide (PIP) family of lipids in cytokinesis, providing critical insight into the underlying mechanisms promoting the normal progression of cell division.

Snider’s passion for cell division research was ignited as an undergraduate student at the University of North Carolina at Chapel Hill. Snider pursued her interests in graduate school, entering the Interdisciplinary Graduate Program (IGP) in 2014 and eventually joining the laboratory of Kathy Gould, Ph.D., Professor of Cell and Developmental Biology. There, Snider joined forces with Willet, a passionate scientist with whom she has worked closely since joining the lab. The Gould group focuses on identifying the molecular mechanisms regulating cytokinesis in the fission yeast Schizosaccharomyces pombe. S. pombe is an advantageous model for cell division studies due to its easily visualized division plane. Results in this model organism can be readily extrapolated to more complicated eukaryotes like humans.

A key player in cytokinesis is the cytokinetic ring (CR), which pinches the center of a mother cell and eventually produces two daughter cells. The CR is a giant, protein-rich structure in the cell, but because it is somehow linked to the plasma membrane (which is made up of lipids), it is less rigid than one might expect for a protein-based structure. The question we are trying to answer is how the anchorage between these two very different structures is mediated, explained Snider.

Although several PIPs, a major type of lipid in the cell membrane, have been previously associated with cytokinesis, the underlying mechanistic link has remained elusive. Snider and Willet’s article determined that two essential PIP kinases, a type of enzyme that adds a phosphate group to its substrate, play critical roles in CR anchoring: the activity of both kinases promotes the enrichment of a PIP called PIP(4,5)P2 in the plasma membrane. Functional disruption of either kinase promotes CR sliding from the center of a dividing yeast cell, resulting in incomplete cell division and death. Conversely, the depletion of kinases regulating other PIP species does not result in CR sliding, indicating that PIP(4,5)P2 may be the primary PIP involved in CR anchoring even in human cells. Snider speculates that the disruption of its regulatory kinases could contribute to diseases involving dysregulated cell growth like cancer.

Future studies in the Gould laboratory will focus on how PIP-modifying enzymes themselves are regulated and on their role in CR anchoring. Snider’s work so far has only strengthened her passion for studying cytokinesis, and she plans on applying for postdoctoral positions to keep investigating the subject after she graduates. With her tenacity, Snider will surely excel in her future research endeavors.

Learn More:
Snider, C.E. and Willet, A.H., et al., Analysis of the contribution of phosphoinositides to medial septation in fission yeast highlights the importance of PIP(4,5)P2 for medial contractile ring anchoring, Molecular Biology of the Cell (2018).

The Complex Role of White Blood Cells in Regulating Obesity

By Lauren Scarfe, Ph.D., Postdoctoral Fellow

Obesity is a serious health problem worldwide that leads to an increased risk for various other diseases, such as diabetes and cardiovascular disease. It is perhaps less well known, however, that eosinophils, a type of white blood cell, may be involved in the regulation of metabolic fitness, a term that describes how well the body responds to and processes energy substrates. Recent publications have suggested that increasing the number of eosinophils in adipose (fat) tissue increases metabolic fitness and reduces obesity; however, a new study published in Molecular Metabolism by Reid Bolus, Ph.D., a postdoctoral fellow at Vanderbilt University, suggests that the situation is a lot more complicated than that.

Bolus is a Tennessee native who has always felt a natural pull toward science. “Everyone goes through the ‘why?’ phase when they are a child, and I don’t think I ever really grew out of it,” shared Bolus.

He has always enjoyed asking questions about nature and biology; however, his specific interest in immuno-metabolism began during his first year in the Interdisciplinary Graduate Program (IGP) at Vanderbilt. Bolus was immediately drawn to the research carried out in the lab of Alyssa Hasty, Ph.D., Professor of Molecular Physiology and Biophysics, who studies adipose tissue inflammation in the context of obesity and how inflammation may drive diseases such as type 2 diabetes.

Previous research has found that eosinophil-deficient mice are more susceptible to weight gain and poorer metabolic health compared to mice with normal levels of eosinophils. Elevating the eosinophil levels in these mice led to better adipose tissue health, and thus better metabolic health. However, these previous studies elevated eosinophils by indirect methods or to non-physiological levels. As obese mice have lower levels of adipose eosinophils compared to healthy mice, Bolus set out to determine whether restoring the eosinophils of obese mice to the physiological levels seen in lean mice would improve metabolic health. He accomplished this by injecting mice with IL-5, a cytokine (a small protein) known to regulate eosinophil accumulation and activation. Bolus carried out a comprehensive battery of metabolic fitness tests that revealed that restoring eosinophil levels to normal physiological levels was not sufficient to improve metabolic fitness in the obese mice.

To illustrate this, Bolus notes that the white blood cell, eosinophils, are involved in the body’s immune response, and thus, inflammation, which is the body’s reaction to injury or illness, could be involved in the obesity phenomenon. Such an inflammatory response is not always healthy and can lead to additional health problems, such as diabetes and obesity. In order to determine the role of eosinophils in regulating obesity, Bolus studied the number of eosinophils in adipose tissue and analyzed their impact on metabolic fitness.

Bolus, W.P., et al., Elevating adipose eosinophils in obese mice to physiologically normal levels does not rescue metabolic impairments, Molecular Metabolism (2017).

This study therefore suggests that the role of eosinophils in regulating adipose tissue function could be more complex and dynamic than originally thought, and that simply increasing eosinophil numbers alone is not sufficient to drive metabolic changes.

This project comprised a large portion of Bolus’s Ph.D. thesis, which he successfully defended last year. He is now completing a short postdoctoral fellowship in the Hasty lab to wrap up his projects and soon will start working as a postdoctoral scholar at the University of California, San Francisco in the lab of Suneil Koliwad, Ph.D., Molecular Metabolism.

Bolus is looking forward to the challenges associated with working in a new environment but will miss working with the investigators who do diabetes and obesity research at Vanderbilt, as well as the impressive Nashville music scene!

Learn More:
Bolus, W.P., et al., Elevating adipose eosinophils in obese mice to physiologically normal levels does not rescue metabolic impairments, Molecular Metabolism (2017).
Faculty Spotlight: Lauren Jackson, Ph.D
From Structural Biology to BCG and Back Again

By Allyson P. Mallya, Graduate Student

Lauren Parker Jackson, Ph.D., Assistant Professor of Biological Sciences at Vanderbilt University, likes to keep it local. She grew up in nearby Rutherford County and graduated from Vanderbilt 15 years ago with a B.S. in chemistry and a minor in classical studies. While at Vanderbilt, she worked in the lab of Gerald Stubbs, Ph.D., where she first developed an interest in structural biology. With Stubbs’ encouragement, Jackson pursued a doctoral degree at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, to learn X-ray crystallography, a technique that is used to determine the structure of proteins. She then served as a junior consultant with the Boston Consulting Group (BCG) in London, working on cases within the television, insurance, and healthcare industries before returning to academia and completing her postdoctoral training at the Cambridge Institute for Medical Research. In 2014, she returned to her Vanderbilt roots as a faculty member.

What drove you to initially pursue a career outside of academia as a management consultant?

I was curious what other jobs were like, and the healthcare industry seemed like a natural fit for someone with my life sciences background. It was an exciting time in consulting; prior to the financial crash, there were many cool strategic projects available in a global financial capital like London. Once the crash happened, everything changed. There were fewer strategic projects, and more projects focused on cost cutting.

What led you back to academia?

I didn’t have much control over which projects I worked on, and I really missed my academic colleagues. Academia is a very high-risk, high-reward environment, but those sorts of challenges appealed to me more than proposing different organizational charts to a company. I also found that my academic colleagues were more willing to band together during stressful projects and tough times.

We often hear about the bad things of academia, but at the end of the day I chose to come back because there are also many positives. You shouldn’t discount it because it seems too hard. Let your mentorship help you fend off that if that’s what you’re really committed to doing. To me, the only reason to do it is if you love it.

Tell us about your research.

My lab looks at the detailed mechanisms of how the “FedEx system” of our cells works. Just like FedEx needs to sort packages into destinations, our cells have to transport molecules between different compartments. Breakdowns in the system are linked to horrible neurological diseases like Parkinson’s, Alzheimer’s, and others. When it goes wrong, it goes really wrong.

What most excites you about your work?

I’m a structural biology nerd. I love to see electron densities. In a sense, those are real data you’re seeing; a manifestation on a computer of a real physical thing. I like understanding how things work at a molecular, detailed, and mechanistic level. To this day, I’m still excited about making fundamental discoveries or having fundamental insights based on the chemistry and the physics of molecules.

What do you enjoy doing in your free time?

I have a 2-year-old so I don’t have much free time. When I do, I really like exercising, being outdoors, and eating out. I love wine -- that could be my other career path. Maybe when I retire I’ll try becoming a winemaker. It’s really a difficult qualification to get.

What advice would you give to new faculty just starting their labs?

Stay in the lab as much as you can. Don’t rush to hire people. It’s better to have a few great people than to open the floodgates, because doing so pulls you in different directions. Find and really invest in one or two key people at the beginning to work with you.

Learn More:
Visit the Jackson Lab site: www.jackson-lab.com.

Pick Your (Topoisomerase) Poison

By Maria Agostini, Graduate Student

Can we make cancer therapies with fewer side effects? Alexandra Oviatt, a graduate student in the laboratory of Neil Osheroff, Ph.D., Professor of Biochemistry and Medicine, has started tackling this question for one group of anticancer drugs known as topoisomerase II poisons. These enzymes perform a number of important functions in cells, as they remove knots, tangles, and tension from DNA by cleaving it and ultimately joining it back together, leaving it unscathed. Etoposide, one of the most highly prescribed anticancer drugs, is classified as a type II topoisomerase poison; it stabilizes topoisomerase II-induced DNA breaks, killing cancer cells by overwhelming them with DNA damage.

Like many anticancer drugs, however, etoposide can have severe side effects, including the generation of therapy-related leukemias. In an attempt to minimize such side effects, researchers modified etoposide to interact preferentially with polyanamine transporters, which are more common on cancer cells, and one of these polyamine-containing etoposide derivatives has even made it into clinical trials. But non-selective entry into cancer cells is not the only factor to consider when developing new drugs. For instance, evidence suggests that drug interaction with topoisomerase Iα, one of the two topoisomerase isoforms in humans, may be important for killing cancer cells. Interaction with the other isoform, topoisomerase Iβ, may be the culprit behind etoposide’s side effects.

Oviatt’s recent study, published in Bioorganic and Medicinal Chemistry Letters, describes how changes in the drugs affect their interaction with both enzyme isoforms. Utilizing a series of polyanamine-containing etoposide derivatives, she first observed that each compound was better at inducing DNA cleavage by topoisomerase Iβ than by topoisomerase Iα. Oviatt noted that it was surprising to see such a difference in the patterns of cleavage between α and β because they have such high sequence similarity. Using computational models, Oviatt’s study identified the amino acid on the α isoform that is responsible for stabilizing the enzyme-drug interaction and leading to more DNA cleavage. The study also found that the corresponding amino acid on the α isoform lacks this stabilizing capability.

“Finding that the polyanamine derivatives targeted the β isoform better than the α isoform was interesting, but not ideal,” she said.

Given that specifically targeting compounds to the α isoform may aid in minimizing the side effects of etoposide and other topoisomerase II poisons, Oviatt’s work has laid an important framework for the improved targeting of these anticancer therapeutics.

Passionate and supportive mentors have played an important role in Oviatt’s scientific trajectory thus far. She is quick to thank her current mentor for his support, and an undergraduate research advisor for inspiring her to pursue a career in science. Outside of the lab, Oviatt’s passions lead her to the kitchen to bake and to nature areas near Nashville to hike. Oviatt is eager to continue her studies on the interactions between etoposide derivatives and topoisomerase II isoforms, hopefully leading the way to improved anticancer therapeutics.

Learn More:
Scientific Director of Preclinical Research, and other scientists, was evident in the presentations by Dean Hickman, Ph.D., the computers, rooms, and lab benches. The impact of this design on the free exchange of information by removing assigned desks, in an “open lab” layout designed to facilitate collaboration and workforce through outreach.

Our group of six graduate students and five postdoctoral fellows arrived in Boston on May 2nd and set off to explore the Cambridge area on foot through a walking tour led by the Massachusetts Biotechnology Education Foundation, a local non-profit organization dedicated to increasing the life sciences workforce through outreach.

On the first full day of our trip, we visited Amgen, hosted by Vanderbilt alumnus Charlie Knutson, Ph.D. Amgen participates in an “open lab” layout designed to facilitate collaboration and the free exchange of information by removing assigned desks, computers, rooms, and lab benches. The impact of this design was evident in the presentations by Dean Hickman, Ph.D., the Scientific Director of Preclinical Research, and other scientists, which showcased how teamwork across different departments is leading to new treatments that improve patients’ lives.

The group’s second visit was to Merck Research Laboratories, which is located just outside Kendall Square. We immediately sensed the buzz of excitement stemming from the recent FDA approval of a first-in-class cancer immunotherapy drug. There, we met by Vanderbilt alumnus Chris Tan, Ph.D., Director of Business Development and Licensing, whose role is to establish bold and meaningful collaborations with start-ups and biotech companies, academic centers, and even other big Pharma companies by leveraging the expertise of each organization to drive innovation and collectively tackle complex diseases.

To round out our first day, we helped welcome over 60 Vanderbilt Ph.D. alumni for a networking happy hour at a restaurant in the heart of downtown Boston. Unsurprisingly, this event was a favorite amongst our group because we had the opportunity to meet and talk to numerous scientists who are now in many different professional roles in the Boston area.

Graduate student and program participant Francis Prael, III, was “impressed with the diversity of careers of the Vanderbilt alumni and how excited they were to talk about their work.”

Megan Vogel, Ph.D., a postdoctoral fellow on the trip, shared our sentiments that “the alumni were very willing and eager to provide support and guidance to us as we attempt to transition from academia into industry.”

The happy hour was also beneficial for the alumni who used the time to reconnect with each other. After the happy hour, a small group of participants and alumni wrapped up the night by dining at a quaint French restaurant in downtown Boston.

We visited Pfizer and Kymera Therapeutics on the second day of our trip. A few of us were specifically looking forward to visiting Pfizer because of the great rapport we had developed with our host, Ghazal Hariri, Ph.D., and with other alumni the previous night. At Pfizer, we learned about the research areas of focus, hiring practices, and the postdoc program through a series of seminars held during breakfast. Next, we toured the lab spaces and cores, which, as expected, were state-of-the-art and exceptionally clean. The Pfizer Innovation Research (PfIR, pronounced “fire”) Lab tour was a real treat, as we learned how their scientists are exploring ways to use wearable technology to diagnose neurological diseases. We wrapped up the visit with a Q&A session with Pfizer scientists and postdocs who were very open about what it is like to work in an industry lab and about how to transition into industry positions. The key takeaways? Network, network, network... and to really hone those soft, transferrable skills.

Our final visit was to Kymera Therapeutics, a start-up which is housed at an innovation hub called Lab Central with about 60 other biotech start-ups. As we toured Lab Central, it was easy to be inspired and to understand how the shared laboratory spaces and resources, which include expensive lab equipment that would normally be beyond the reach of individual companies, help to...
Ketamine’s Antidepressant Properties May Be a Treatment for Drug Addiction

By Christopher Smith, Ph.D., Postdoctoral Fellow

Addiction arises from a variety of factors, including dealing with persistent feelings of depression and anxiety. Oliver Vranjkovic, Ph.D., is interested in understanding the brain mechanisms behind drug use and addiction that are driven by negative reinforcement (e.g., drinking to alleviate unpleasant anxiety and depression).

Vranjkovic indicated that some drug companies are conducting clinical trials focused on ketamine as a treatment for depression. “Our work suggests an expanded application for ketamine in potentially preventing alcohol abuse in specific patients, particularly those who drink in order to self-medicate their anxiety and depression,” he says.

His findings also offer a potential brain target and administration timing to maximize ketamine’s effects, which could ultimately lead to the development more effective treatments for alcohol addiction.

Vranjkovic is focused on why the antidepressant and anti-anxiety effects of the anesthetic drug ketamine last so long. Earlier work in the Winder lab showed that an acute injection of ketamine 30 minutes before behavioral testing can reduce depression-like behaviors in rodent models of alcohol withdrawal. Although it shows promise as a potential treatment, ketamine itself is subject to abuse and addiction, and thus its possible efficacy must be tempered by the need to limit its use. Thankfully, a single dose of ketamine during a critical period after forced ethanol abstinence inhibits the development of alcohol dependence.

During the alcohol exposure phase of Vranjkovic’s study, mice are given the choice to consume 10% alcohol or water in their home cage. Image credit: Katie Holleran.

Learn More:
Vranjkovic, O. et. al., Ketamine administration during a critical period after forced ethanol abstinence inhibits the development of time-dependent, Neuropsychopharmacology (2018).
Career Symposium Features the Significance of Mentorship and Networking

By Jessamyn Perlmutter, Graduate Student

Each year, the BRET Office holds its Annual Career Symposium for hundreds of graduate students and postdoctoral fellows looking for advice on how to take the next steps in their careers. Held on June 1, this year’s event -- "R3: Research and Research-Related Careers in Academia, Government, and Nonprofits" -- featured a keynote address by Lynn Matrisian, Ph.D., former Chair of Cancer Biology at Vanderbilt University and current Chief Scientific Officer of the Pancreatic Cancer Action Network, along with small group sessions led by a team of ten alumni with expertise in teaching, research, and research-related roles.

Despite such a diverse set of topics, there were common threads across all of the panels. One recurring theme was the importance of mentorship. No matter the career path, all speakers spoke to the critical role of mentors in their own success. Mentors encouraged and supported the speakers in developing the skills they needed to succeed in their fields, and were essential to getting them ready to transition to a new job.

Finally, another shared aspect of all careers was the need to find funding for salaries, research, company expenses, educational materials, and other job-related costs. The support can come from government grants, independent contracts, donations, student tuition, or investors (depending on the field you are in), but regardless of its purpose or source, finding funding for people and projects is an unavoidable aspect of research and research-related positions.

Although the alumni represented a broad range of experiences and expertise, their input at this year’s symposium can be invaluable to anyone looking to build up their own career. So for all the current trainees reading this: the sooner you reach out to mentors and build a presence in your professional community, the better off you will be when it is time for you to apply for jobs.

Advice for Teaching Careers
1. Get teaching experience early, since teaching takes practice.
2. Enhance your verbal and written communication skills.
3. Learn when to say no, as your time is a valuable asset.
4. Consider gaining extra experience as a postdoc.
5. Engage your network to get a position.

Advice for Government Careers
1. Expect a months-long timeline to get a position.
2. Tailor your application well to the job description.
3. Consider a fellowship or contractor job to get started.
4. Expect less flexibility in promotions and salary negotiation.
5. Talk to insiders; reach out to your network.

Advice for Research Careers
1. Experience diverse research topics and take note of other mentorship styles.
2. Learn business management skills to help you run a lab.
3. Be opportunistic; apply to many positions.
4. Learn about research and management from your mentors.
5. Network! It is critical.

Advice for Clinical Research Careers
1. Be willing to learn new skills from the ground up.
2. Work on your people skills; interactions are critical.
3. Start with entry-level positions or transitional fellowships.
4. Expect an experience that is not quite like bench research.
5. Develop teamwork skills; clinical research is not a solo job.
6. Leverage your network to find positions.

Advice for Entrepreneurs
1. Learn from as many mentors and advisors as you can.
2. Get experience making pitches and seeking investor funding.
3. Start as soon as you can; there is never a good time.
4. Develop teamwork and collaboration skills.
5. Build your network early; expand it beyond the university.

Advice for Postdocs and Graduates
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2018 Career Symposium Quick Takes...

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Congratulations to our Recent Graduates!
March-August 2018

Alex Andrews
Sandhya Bangaru
Amber Beckett
Kamakoti Bhat
Michael Bray
Judith Brown
Denise Buenrostro
James Case
Alex Cheng
Lucy D’Agostino McGowan
Heng Dai
Claire DelBove
Deon Doxie
Amanda Duran
David Earl
Haley Eidem
Zachary Elmore
Meredith Frazier
Chelsea Gibson
Juan Gnecco
Raajaram Gowrishankar
Allison Greenplate
Katie Hebron
Charles Herring
Francis Hickman
Merla Hubler
Jonathan Knowlton
Sandya Lakkur
Nalin Leelatian
Britney Lizama
Roxana Loperena Cortes
Katarzyna Ludwik
Annabelle Manalo
Jea Young Min
Sanjay Mishra
Monica Murphy
Shan Parikh
Matthew Puccetti
Christina Saunders
Diane Saunders
Rongxin Shi
Megan Shuey-Henthorn
Leah Sigle
David Simon
Diana Tafoya
Brandon Turner
Jennifer Vega
Meredith Weck
Eric Wilkey
Yan Xia
Paula Zamora