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IN THIS ISSUE

RESEARCH SPOTLIGHT

Stromal Virions Add Another Dimension to the Tumor Microenvironment

Kanika Jain

Cancer research has seen a steady shift towards'tumor microenvironment' driven hypotheses. Tumor cells exploit their environment to fuel their own growth and metastases. Thus, targeting the crosstalk between the tumor cells, stromal cells and the immune microenvironment has gained new appreciation for cancer therapeutics.

Paracrine or juxtacrine signaling via soluble chemokines and cytokines are the major known drivers of the crosstalk between the heterotypic cells in a tumor. However, the role of exosomes (extracellular vesicles) as dynamic modulators of intercellular communication has only recently been highlighted. A study published in *Cell* in July 2017 beautifully unveiled the role of stromal exosomal RNA (exoRNA) as viral mimics driving the tumor-stromal crosstalk in triple negative breast cancer (TNBC). It was co-authored by Cancer Biology student Barzin Nabet from Dr. Andy J. Minn's lab.

Exosomes are 40-150 nanometer vesicles released by all cell types. They are composed of a lipid bilayer and contain all major cellular constituents proteins, DNA and RNA. At any given time, the contents of exosomes reflect the phenotypic state of the cell that generates them. The ability of exosomes to shuttle the constituents of one cell to another has added an additional dimension to the complexity of cellular interactions in a tumor microenvironment. In October 2014, another study published by Dr. Minn's group in *Cell* highlighted that upon stimulation by tumor cells, stromal cells release exosomes with RNA molecules that have a close sequence similarity to viral RNAs. Inevitably, these RNA molecules are then recognized as damage associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs) in the tumor cells, thus initiating a cascade of anti-viral responses. In general, upon interaction with specific PRRs, viral RNAs direct transcriptional activation of interferon stimulated genes (ISGs). Ironically, across many common human cancers, various tumors have been reported to express high levels of ISGs even in the absence of any prior viral infection. Further, studies have shown that patients with tumors expressing high levels of ISGs are more prone to relapse after radiation or chemotherapy. These observations strongly suggest the presence of a viral mimic in the tumor microenvironment.

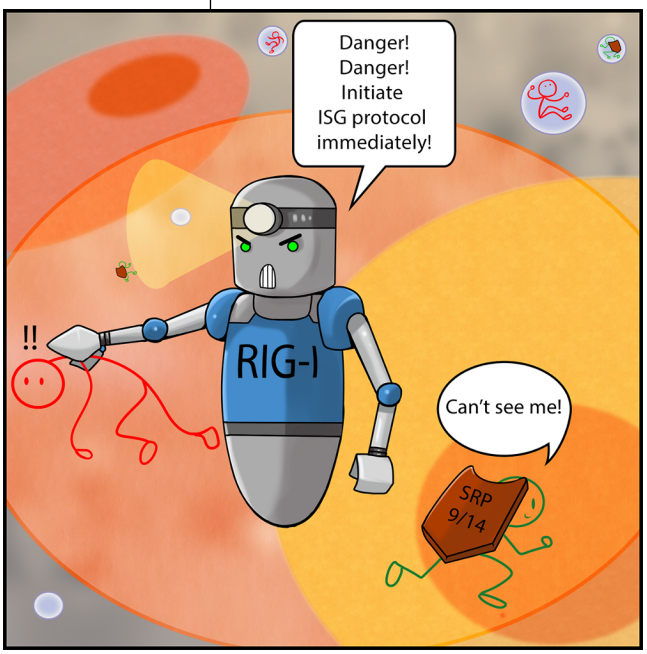


Illustration by Arun Abbas

Endogenous RNAs can be extruded into the tumor microenvironment as exosomes. **Healthy stromal fibroblasts generate RNAs (green) that are normally shielded by the RNA binding proteins SRP9 and SRP14. However, cancerous fibroblasts increase their expression of a specific endogenous RNA RN7SL (red). Notably, this RNA is not shielded and thus acts as a danger associated molecular pattern (DAMP) similar to viral RNA. The presence of this DAMP can be detected by the intracellular pattern recognition receptor RIG-I. Stimulating RIG-I in tumor cells induces interferon stimulated genes (ISGs), which ultimately promotes cell growth and metastasis.**

In the current study, Barzin and colleagues connected the dots to draw out the intricate mechanism by which stromal exoRNAs drive growth and inflammation in the tumor microenvironment. Co-culture experiments between MRC5 human fibroblast and 1833 ISG-responding (ISG-R) breast cancer cell lines as well as RNA sequencing data confirmed the presence of non-coding RNA (ncRNA) transcripts in stromal exosomes. By definition, these ncRNAs do not translate into proteins but function to regulate gene expression at transcriptional and post-transcriptional level. RN7SL1 stood out as the only ncRNA with elevated levels in the exosomes upon co-culture in comparison to the monocultures. Tandem pull-down assays confirmed specific binding of RN7SL1 to RIG-I receptors (PRR) in the tumor cells. This interaction induced ISG expression in both stromal and ISG-R breast cancer cells in a RIG-I dependent manner. Intricate secondary structure at the 5'end of the RNA stood out as a prerequisite for RIG-I - RN7SL1 binding.

5'-triphosphate (5'-ppp) RN7SL1 is highly abundant in the cell at physiological conditions and thus can bind RIG-I in the cytoplasm at all times. Hence one would wonder why our cells fail to initiate a danger response signal at all times? "This posed a conceptual glitch to the proposed mechanism," Barzin shared. Variable

levels of RNA 'shielding' by RNA binding proteins (RBPs) were found in cells and exosomes. Normalized minimum free energy calculations revealed markedly shielded RN7SL1 in cells in comparison to highly unshielded RN7SL1 in co- culture exosomes. The extensive shielding by RBPs at physiological conditions prevents RN7SL1's recognition by RIG- I. However, upon stimulation by tumor cells, stromal cells selectively deploy unshielded RN7SL1 in the exosomes. qRT- PCR and immunoblot analyses after co- culture experiments confirmed the role of signal recognition particle proteins – SRP9 and SRP14 in shielding RN7SL1 from inappropriate recognition by RIG- I in the cytoplasm.

Barzin Nabet, CB

Transcriptional profiling of stromal and tumor cells upon co- culture revealed the activation of NOTCH juxtacrine signaling pathway. This fits well with the requirement of physical cell- cell interaction for ISG induction. Transcription factor MYC being downstream of NOTCH signaling, was also upregulated and its overexpression drove RNA Polymerase (POL 3) and RN7SL levels in the stromal cells. Exosomes derived from MYC- activated stromal cells were injected in athymic nude mice carrying flank tumors. A substantial increase in myeloid cell infiltration with cells displaying high levels of activation markers like CD40, CD86, PDL1 and MHC-II was seen. The impact on T cell infiltration levels, however, is yet to be studied.

Barzin and colleagues demonstrated increased tumorigenic and metastatic potential of tumors expressing high RIG-I signaling and ISG levels through RIG-I KO studies in mice. Finally, they collected serum samples from two cohorts of cancer patients and performed exoRNA-sequencing analysis. The results of these studies confirmed an expected increase in unshielded RN7SL1 and POL3 transcripts levels in serum samples from the cancer patients compared to healthy controls.

Horizontal transfer of DAMPs is a shared feature between viral infections and tumor- stromal cell interactions. Hence, the current study presents a classic case of viral mimicry where the stromal virions crosstalk with tumor cells thus activating anti- viral signaling in the microenvironment. This has provided new insights for directing research towards exosomal crosstalk as a potential target for cancer therapeutics.

Nabet, B.Y., Qiu, Y., Shabason, J.E., Wu, T.J., Yoon, T., Kim, B.C., Benci, J.L., DeMichele, A.M., Tchou, J., Marcotrigiano, J., Minn, A.J. Exosome RNA Unshielding Couples Stromal Activation to Pattern Recognition Receptor Signaling in Cancer.*Cell*2017; 170(2):352-366.e13.

Uncovering the *Leishmania*-cal Plot of Dysbiosis and Inflammation

Clarissa Rous

In a run-down shanty town, a fly drinks from a standing pool of water and unknowingly ingests unicellular protozoans of the genus *Leishmania*. As the sand fly takes its blood meal from an unsuspecting human, the parasites deploy into the fly's saliva and enter the human's bloodstream. There, they infect host macrophages and multiply until the cells fill and burst, which further spreads the parasite to more macrophages. In a short amount of time, the *Leishmania* parasite can induce painful, open lesions of the skin in what is known as cutaneous leishmaniasis. This disease is most prevalent in the poorest areas of the world and is due to a lack of quality housing, sanitation, and proper nutrition. And although the WHO and CDC report a global annual prevalence of approximately a million cases, the treatment options are surprisingly scarce; no vaccine is available and most drugs are ineffective against the parasite. Recent work from Ciara Gimblet, a CAMB- MVP student in the lab of Dr. Philip Scott, has unearthed a new aspect of the pathology of leishmaniasis that could be exploited to combat the disease.

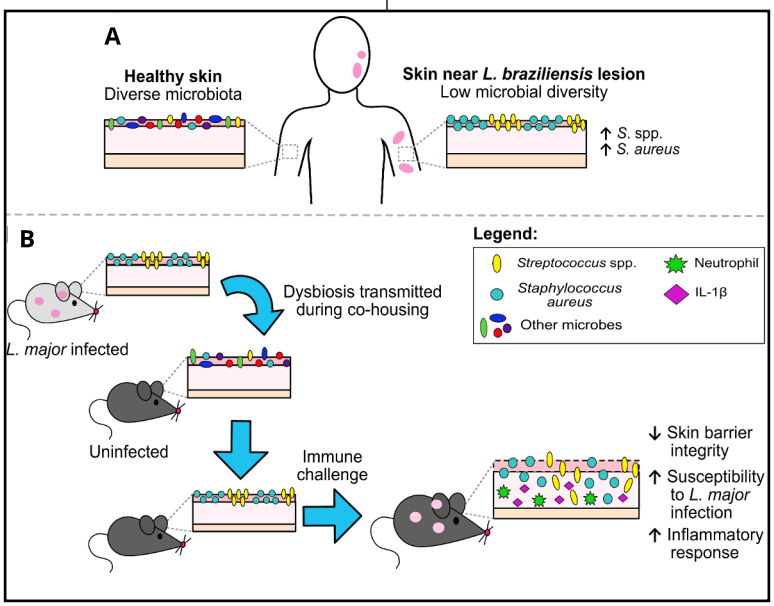


Illustration by Ewa Stypulkowski

Skin near leishmania-infected lesions exhibits low microbial diversity (dominated by *Streptococcus* spp. and/or *Staphylococcus aureus*) when compared to healthy, contralateral skin. This phenomenon was observed in human patients and mouse models (A). Uninfected mice co-housed with Leishmania-infected mice develop dysbiosis. When challenged with pharmacologic irritants or *L. major*, the dysbiotic mice experience more tissue damage (B).

Cutaneous leishmaniasis cases differ in severity of clinical outcomes. Earlier studies have found that the worst manifestation of this disease is a result of a heightened immune response and inflammation. Gimblet previously found that the cytokine Interleukin-22 (Il-22) mitigates cutaneous damage in leishmaniasis. Since Il-22 increases the production of antimicrobial compounds in the skin during infection, she hypothesized that the pathogenesis of cutaneous leishmaniasis is driven by alterations to the skin microbiome and induction of an inflammatory response.

To investigate how leishmaniasis impacts the skin microbiome, Gimblet et. al. first examined human patients with cutaneous *Leishmania* lesions. Taking swabs at the lesion, near the lesion, and contralateral to the lesion from each patient, the group found the lesions had lower microbial diversity than healthy skin and exhibited an unusually high percentage of *Staphylococcus aureus* or *Streptococcus* spp. While an increase in *Staphylococcus* and *Streptococcus* abundance is not unusual among skin inflammatory diseases, the patients in this study displayed a dramatic decrease in skin microbiome diversity. Furthermore, the microbiomes at and near the lesion were similar in diversity, consistent with the involvement of a local immune response.

Since it's impossible to test human skin microbiome at the site prior to infection, the group used mouse models to elucidate the connection between cutaneous leishmaniasis and abnormal skin microbiome (also known as dysbiosis). C57BL/6 mice, a common strain used to study disease development and progression, were first swabbed on both ears before one ear was infected with *Leishmania major*. Swabs were then taken when lesion was fully developed at 6 weeks and when the lesion resolved at 12 weeks. Over the first 6 weeks, the microbiome at the infection site became less diverse and more dominated by

Staphylococcus but returned to normal by 12 weeks.

If dysbiosis is a factor in leishmaniasis progression, then a high degree of dysbiosis would correlate with severe disease. To determine whether this was the case, Gimblet compared L. major pathogenesis in two mouse strains: C57BL/6 mice whose lesions heal by 12 weeks and BALB/c mice that develop chronic lesions. After 6 weeks, the BALB/c mice had lower microbial diversity and greater *Streptococcus* colonization than the C57BL/6 mice, thus strengthening Gimblet's hypothesis. The group also

Ciara Gimblet, MVP

created a mouse model of severe cutaneous leishmaniasis using C57BL/6 mice. They depleted Interleukin-12 (Il-12) because it was previously implicated separately in disease severity and in antimicrobial compound production. The IL-12-depleted mice phenocopied the BALB/c mice, again linking inflammation and dysbiosis to disease severity.

Gimblet et. al. identified a specific *Staphylococcus* species, *S. xylosus*, that is present on healthy mouse skin, but increases in abundance during cutaneous leishmaniasis in bacterial isolates taken from L. major infected mice. Previous studies had demonstrated that a change in even one species in skin microbiome can amplify inflammation. The group asked whether inoculating mice with S. xylosus could increase inflammatory response in the absence of L. major. Inflammation was seen only in mice infected intradermally with S. xylosus, as assessed by increased neutrophil recruitment and IL-1β expression. These results indicate S. xylosus contributes to inflammatory responses, but only in the presence of tissue damage.

What's more, Gimblet et. al. also found that skin bacteria can be transmitted from L. major infected mice to co-housed, uninfected mice without inducing an inflammatory response. This allowed the group to make a healthy mouse that has a skin microbiome similar to that induced by L. major infection. Using the dysbiotic model, they asked whether dysbiosis prior to infection causes more severe lesions and greater immune response. Prior to infection, dysbiotic mice had a heightened inflammatory response compared to mice with healthy skin. Moreover, dysbiotic mice infected with L. major developed more severe lesions and inflammation. Thus, an altered skin microbiome contributes to the severity of cutaneous leishmaniasis, in part due to an injury-induced inflammatory response. Whether dysbiosis of cutaneous leishmaniasis is transmitted between humans remains unknown and is a question that Gimblet hopes can be answered by sampling the skin of friends and family of affected individuals.

So how does leishmaniasis alter the proportions of different bacteria on skin? Gimblet postulates that the body attempts to fight L. major infection by expressing antimicrobial peptides (AMPs), which kill certain species of bacteria more effectively than others. Staphylococcus and Streptococcus are particularly resistant to AMPs and may dominate the microbiome while other bacteria are killed.

Since cutaneous leishmaniasis is exacerbated by Staphylococcus and Streptococcus, Gimblet hypothesized that antibiotics could be an effective treatment. Unfortunately, treating L. major-infected mice with sulfatrim and mupirocin, two antibiotics reported to treat cutaneous Staphylococcus infection, did not significantly change the microbiome or improve clinical outcome. The jury's still out, given that antibiotics can also cause greater harm by disturbing the microbiome. Restoring the microbiome could be another promising treatment, so further studies might shed light on this hypothesis. Importantly, the study from Gimblet et. al. provides key insights into the mechanisms of leishmaniasis-induced dysbiosis, and opens doors for future research into the discovery of new therapeutic targets or treatment strategies to stop this insidious, microscopic parasite.

Ciara Gimblet, meanwhile, has set her sights on another family of tropical diseases, this time viral instead of protozoan. In her postdoc at the University of North Carolina, Chapel Hill, she is working on characterizing the immune response in adults and in fetuses during the course of infection with flaviviruses, including the infamous Zika virus.

Gimblet, C., Meisel, J.S., Loesche, M.A., Cole, S.D., Horwinski, J., Novais, F.O., Misic, A.M., Bradley, C.W., Beiting, D.P., Rankin, S.C., Carvalho, L.P., Carvalho, E.M., Scott, P., Grice, E.A. Cutaneous Leishmaniasis Induces a Transmissible Dysbiotic Skin Microbiota that Promotes Skin Inflammation. Cell Host Microbe 2017; 22(1):13-24.e4.

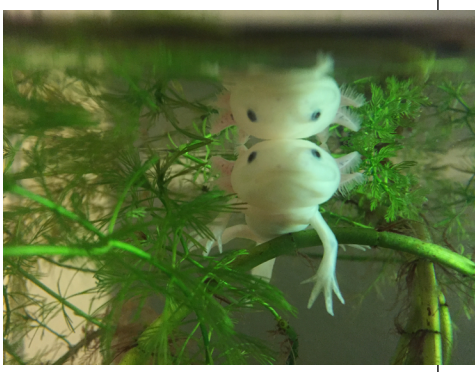
SPECIAL INTEREST

Lots and Lots of Axolotls

Camille Syrett

With its captivating wide-mouthed smile and prominent feathery headdress of gills, it is easy to adore the axolotl (*Ambystoma mexicanum)*. Both salamander enthusiasts and scientists acknowledge the utility of these unique aquatic creatures. Axolotls are wizards of regeneration, a trait that is recognized by biomedical researchers across the globe. A PubMed query for 'axolotl' returns more than 3400 results, with recent publications in high impact journals such as *Cell* and *Nature*. As axolotls are picking up steam as model organisms, they're also becoming quite popular in the homes of several CAMB graduate students who share a love for these unique creatures.

The axolotl's name is deeply rooted in Aztec mythology and according to legend, Xolotl, the god of death and lightning, morphed into an axolotl to avoid being killed by other gods. Axolotls can live up to 15 years in the wild and can grow up to an impressive 12 inches in length. Interestingly, axolotls retain larval features, like their feathery external gills and tadpole-like tails, well into adulthood, and are solely aquatic even at sexual maturity. These one-of-a-kind salamanders really are just that; found exclusively in lake Xochimilco in southern Mexico City, axolotls are currently listed as a critically endangered species, as their population continues to decline. Wild axolotls face many threats to their habitat including widespread water pollution and lake drainage. Lake Xochimilco has also recently become the site of large-fish farming, which comes at the expense of axolotls. These large tilapia and carp compete with axolotls for resources and eat axolotl eggs.



Glompner, one of Ben Tajer's axolotls

Another lesser-known reason for their population decline is that axolotls are considered a delicacy when roasted and are rumored to taste like a cross between a fish and a chicken.

Although axolotls face significant challenges in the wild, they are thriving in captivity. Possessing prodigal regenerative abilities, axolotls are no strangers to the laboratory as they have been used in research since 1864. Compared to other salamanders, axolotls are easy to breed and their large embryos are easily manipulated. Perhaps the biggest draw of using axolotls as a model organism is that they can recover from an incredible amount of injury. Axolotls faithfully regenerate entire limbs, and can do so without scarring, even after repeated removal of the same limb. Researchers can crush or remove a segment of the spinal cord and it will still regenerate. The list of regenerative body parts is virtually endless and includes limbs, tail, jaw, and parts of many vital organs such as the brain and heart. Intriguingly, an axolotl can also accept transplanted organs without rejection, and future studies may uncover insights for preventing graft rejection in transplant recipients.

Blumpus and Glompner

Not all axolotl science is so Frankensteinian in nature. Researchers these days are also engaged in experiments using the latest cutting-edge technologies to better understand regeneration. In a manuscript published in *Cell Reports* in early 2017, scientists at Harvard assembled 88% of the axolotl genome and used this assembly to perform RNA-Seq to identify conserved genes involved in limb outgrowth. Researchers in Germany created transgenic brainbow-labeled axolotls to perform live-imaging based lineage tracing in a *Developmental Cell* paper from 2016. This powerful tool was used to examine the dynamics of cellular recruitment and migration during limb regeneration. These and other recent studies demonstrate the power of the axolotl as a model organism, and researchers hope that these seminal discoveries will advance the field of mammalian regeneration to recreate the phenomenon in humans.

It's no wonder that axolotls are also popular pets in the homes of several CAMB-DSRB students. These always smiley and ever-regenerating creatures are easy to care for in captivity and are quite happy as long as the water flow, temperature, and quality are well controlled. As carnivores, axolotls most commonly consume frozen cubes of bloodworms, but they also enjoy pieces of cooked shrimp and other meats as special treats. Axolotls are quite voracious and, if left hungry, will not hesitate to resort to cannibalism. Most axolotls are also perfectly happy living alone so, to avoid undue stress and epic fish carnage, some prefer to house their axolotls in separate tanks. Unfortunately these little guys aren't always the smartest and may try to eat anything smaller than their own head. For this reason, avoid pebbles in axolotl tanks and use sand instead. Finally, as their hearty appetite predicts, axolotls are excretory machines and keeping up with waste removal and water cleaning is a must for a stress-free animal.

Graduate student Ben Tajer (DSRB), the reigning axolotl expert of CAMB, is no stranger to raising salamanders. After fortuitously stumbling upon an abandoned 40-gallon aquarium in Clark Park, he ordered axolotl eggs for both himself and to share with friends, plus extras (50 to be exact). Ben currently hosts an impressive cast of axolotl characters named Glompner, Blumpus, Flumpus, TeeneeMeenee, Cousin Melvis, and Chompner. But don't be fooled by their smiling faces. Ben says, "I look into my axolotls' eyes and I see pure murder. They are relaxed most of the time, but when they notice me near the aquarium they will come to the side and start attacking each other in anticipation of food. They eat the blood worm cubes before they melt, and I have had to isolate the particularly violent ones." In particular, Chompner has perfected a technique for twisting arms off the other axolotls and is now in solitary confinement.

Sparkles

Not all axolotls are bloodthirsty, and they can be great friends, too. Robyn Allen (VMD/DSRB) owns Lancelotl (Lance) and Camelotl (Cam) that tend to hang out next to each other and have even burrowed a nest into the sand together. Some CAMB-ers prefer to own a single axolotl. Will Towler (DSRB) describes Morty's (aka Baby Mort-Mort) personality as "similar to a rock, but timid." Morty is still getting the hang of the whole eating thing. During feeding he "swims to the surface of his tank, attacks the air, realizes the empty atmosphere itself wasn't the brick of food he thought it was, and gives up, only to finally eat once food is falling directly on his face" says Will. Ernest Monahan (DSRB) shares that his axolotl Poseidon, who also happens to be a polydactyl, will "usually ignore my existence unless it becomes too hungry."

The endearing perma-smile, Pokémon-esque looks, and occasional lapse of intelligence have clearly won over the hearts of CAMB students, and axolotls have become wonderful companions for some. Ben says that the best part about being an axolotl owner is "watching them grow and change".

Want more axolotls? You can head over to our blog site for this article's sources. If you really want more axolotls and are interested in adopting a *wild type* axolotl of your own, contact Ben Tajer at tajer@pennmedicine.upenn.edu for more information. **Note: Axolotls will only be given to those with proper knowledge of axolotl care and housing

A Discussion on Mental Health: Pursuing Higher Education with Higher Support

Jessica Phan

It is no mystery that the path of higher education is a difficult task. For graduate students in the Biomedical Graduate Studies program, the experience can be particularly onerous due to the unpredictable nature of scientific research -- students often work on projects in ambiguity for weeks or months with limited foresight on the end result. In addition, students working in competitive research fields may feel added pressure to publish quickly before getting scooped. With deadlines to meet, pressure to collect data, and an urgency for publication, the task of being a graduate student can be overwhelming. When does it all become too much?

In 2014, a Graduate Student Happiness and Well-Being Report conducted by the University of California, Berkeley showed that 43-46% of Biological Sciences, Physical Sciences, Engineering PhD graduate students exhibited signs of depression. The study indicated that the top predictors of depression include inadequate sleep, decline in physical health, and academic

disengagement. Similarly, another study conducted at multiple universities in Flanders, Belgium showed that graduate students were 2.5 times more likely to develop a mental health disease compared to other non-graduate students at the university.

Dr. William Alexander, from Penn's Counseling and Psychological Services (CAPS), states that many students "feel the weight to produce," but that they "don't recognize early on that they're slipping. "The transition to graduate school from a previous job or undergraduate school experience can be difficult because academic and personal support may be hard to establish quickly. Thus, Dr. Alexander stresses the importance for students to find support from advisors within their graduate department who are likely familiar with unique academic pressures attributed by their particular field of study. In addition, Dr. Alexander advises for students to actively engage in their academic community and network of peers to build individualized support group to help share experiences and alleviate the pressures of graduate school.

Early this year, the chair of the Cellular and Molecular Biology graduate group, Dr. Dan Kessler, began holding office hours for students who needed additional guidance and support. Dan says "there's no guarantee of success in this kind of creative work" and thus, "it's unlike other academic pursuits." He stresses that it is a partnership between the program and students and states that the program "makes a commitment to provide the best training experience that [they] can to support [students]," but also notes the "need [for] students to speak up on their own behalf, especially for those who are struggling."

Mental health is an important topic of discussion throughout all stages of education; however, graduate students in sciences face unique challenges due to the unpredictability of research. Thus, it is important for students to reach out if they are having a difficult time, and to express these concerns early on. Fortunately, the resources on Penn's campus are abundant and pressures can be reduced by strong support groups from surrounding peers, mentors, and program chairs. In addition, the Counseling and Psychological Services (CAPS) at Penn offers free services for undergraduate, graduate, and professional students for those who are facing difficult points during their academic pursuits. **For more information, students can visit https://www.vpul.upenn.edu/caps/ or contact CAPS at 215-898-7021.**

Letters from an Editor

Arwa Abbas and Camille Syrett

Researchers range from indifferent to disparaging in their impressions of journal editors. These stereotypes may stem from social media memes such as "Reviewer Number 3" or from grumpy lab gossip. Though editors review the products of our blood, sweat, tears, and cell culture media, most of us are unfamiliar with their own respective travails. This was the impetus for Dr. Brett Benedetti, a senior editor from *Nature Medicine*, to visit Penn. His visit shined a light on how editors orchestrate the peer-review process. He also encouraged trainees who love to think critically and be abreast of current scientific events to consider a career as a scientific editor.

Brett had not entered graduate school intending to be a scientific editor. After completing his doctoral degree at Carnegie Mellon University, he began a post-doctoral position at the NYU Neuroscience Institute with Gordon Fishell. Brett had originally intended to pursue a faculty position until an unexpected and unprecedented event in 2012, Hurricane Sandy, severely rained on his parade. Rather than face the frustrations of continuing his slow-moving research after their animal colony was wiped out and moved a subway ride across town, Brett reached out to his advisor to discuss potential alternatives. Dr. Fishell pointed out that Brett had a talent for communicating new research findings and giving constructive criticism. His mentor connected him with an editor of the journal *Neuron*. Although Brett didn't land that position, his increased awareness of this career field led him to find and apply for a position at *Nature Medicine*, where he has worked since 2014.

Brett describes editing research manuscripts as akin to preparing for a journal club presentation with some added difficulties unique to the editorial position. The goals of an editor are to identify the papers' strengths and problem areas, to evaluate whether the data support the main arguments, and to distill out key points. Additionally, editors must determine if the subject matter is appropriate for the journal's target audience. Since editors receive submissions from broad range of topic areas, they must remain privy to technological advances in multiple fields and interact with the ground force of bench scientists to do so. Next, they must be familiar with and reach out to other qualified researchers to review submissions. Finally, they have to synthesize reviewer comments and suggestions into a clear and actionable response, delivered in a timely manner to the anxiously waiting research group.

Brett's recount of his daily schedule unveils how editors tackle these eclectic responsibilities. At *Nature Medicine*, each editor is responsible for approximately 500 articles per year from a pool of over 3,000 yearly submissions. To keep up with this formidable quantity, Brett reads and takes notes on two articles daily and stresses that he reads every single submission in his queue in its entirety, which can take up to four hours per manuscript.

To help identify manuscripts that will be sent out for review, Brett attends three editorial meetings weekly. As senior editor, Brett spends a lot of time reviewing referee comments and rebuttal letters, which culminates in a final decision that often involves meeting with the editor-in-chief. While *Nature Medicine* doesn't have a quota, around 5% of all yearly submissions are published.

When not actively reading and taking notes, Brett searches for referees, reviews critiques, or talks to the authors themselves. While the routine can be quite flexible, there are still time-sensitive workflows to adhere to, especially once a paper is accepted. He reconvenes monthly with editors and other journal staff to discuss broader topics including policy changes and strategies. As a senior editor, Brett also travels to national and international meetings and performs outreach events such as his public lecture and interview at Penn. Based on his personal experience, he believes the median time as an editor is 5 years, although there are members on his team that have been there longer. Upward movement is swift but limited; most entry-level associate editors quickly transition to senior editors, but becoming a chief editor or team leader is more difficult. When editors do leave, they migrate to a variety of positions. Brett's former colleagues are scattered amongst universities, non-profit organizations, government, and industry where they often continue being liaisons between data generators and disseminators.

For those interested in pursuing editorial positions, Brett describes the application process. Strong candidates are those who are excited about science and thus, are up-to-date on the latest breakthroughs. Rather than having a CV replete with high impact journal publications, a critical component of the application is crafting a "News and Views" article appropriate for the journal. This piece demonstrates the applicant's ability to choose a relevant and important recent publication, summarize the main points, fairly state the limitations, and speculate on the future directions the research could take. The in-person interview takes this a step further, where interviewees are given multiple articles, and after a short time must present them to the editorial staff with a final recommendation and editorial suggestions. This tests the candidates' ability to quickly glean and evaluate the paper's essence under pressure.

To encourage young scientists to consider this career and dispel the notion that editors are elusive and operate in enigmatic ways, Brett shared his feelings on his position. For example, he admits that he struggles when presented with a manuscript that is obviously a significant time investment by multiple people but doesn't align with the journal's scope. Brett's detailed and candid discussion of the ethos and logistics of his work allowed the audience to gain a better understanding and appreciation for scientific editors.