CAMB Student Newsletter

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Letter from the Editors

Dear CAMB Students, Faculty, and Alumni,

We are excited to share with you the March 2024 installment of the CAMB student Newsletter! In this month's issue, we speak with Assistant Professor of Radiation Oncology Dr. Crystal Conn about her research on dynamic mRNA regulation in health and disease, as well as her mentoring philosophy and career journey. Additionally, we surveyed the CAMB student community for a detailed conversation about switching thesis labs. This can obviously be a stressful decision, so read on if you are interested in advice from colleagues who have been there and done (or not!) that. This issue also highlights the fascinating work of CAMB MVP MD/PhD student Clayton Otter, recapping his latest findings on determinants of disease severity in mild and lethal human coronaviruses.Finally, we show some love to the more senior graduate students in our community with a special interest article with tips on preparing a dissertation.

For additional articles, past publications, and to learn more about the CAMB Student Newsletter team, visit our blog at cambnewsletter.wix.com/blog or follow us on Twitter at @CambNewsletter. Current students interested in contributing to the CAMB Student Newsletter can reach out to jamesges@pennmedicine.upenn.edu and/or klabella@pennmedicine.upenn.edu. Our next meeting is March 13 in BRB 1403 at 1pm.

Sincerely,
Kay Labella and James Gesualdi
Editors-in-Chief

Faculty Spotlight
Dr. Crystal Conn

Mara Davis

Peer Edited by Nivitha Murali

Today we are interviewing Dr. Crystal Conn, an assistant professor in Radiation Oncology here at UPenn! Dr. Conn, a member of the Trainee Advocacy Alliance and founding member of the Radiation Oncology Committee for Diversity, Equity and Inclusion, started their lab in 2020. Since then, the Conn lab has grown and their molecular and cell biology research has developed around the goal of understanding how dynamic mRNA regulation influences disease progression. Read on to learn more about the questions the Conn lab aims to answer, to hear what it's like to be a professor at Penn, and to get advice on thriving during your PhD!

What are the overarching questions your lab hopes to answer, and how do you aim to go about answering these questions?

We are looking to understand the role of mRNA regulation in the contexts of disease progression and cell adaptation. Focusing on protein synthesis under intrinsic and extrinsic stress allows us to study dynamic cellular processes that orchestrate cell survival. We typically focus on cancer progression and resistance to drug therapy with a focus on RNA localization, modifications, and non-canonical factors that navigate these responses. We use polysomes and ribosome profiling to directly observe RNAs selected for translation and compare those to total mRNA abundance to highlight translation specificity. Our aim is to take our findings back to *in vivo* models and/or human samples to study the factors and effects we identify in physiological contexts of disease.

Dr. Crystal Conn

What do you find most interesting about the questions your lab aims to answer?

The ability to change where and when translation happens can alter the cellular phenotype faster than transcriptional responses and, based on where the ribosome starts, can alter the proteome altogether leading to enhanced diversity independent of all pre-translational regulation. This is an area of my interest over the past 12 years and only in the past few years are others starting to see the complexity of this and the magnitude of downstream outcomes. Looking far from the textbooks to see how little we know about a subject... is what I always find the most interesting.

Are you looking for rotation students? What would you like interested CAMB students to know about your lab environment and research?

Always open to rotation students, though we typically only take ~4/year due to space and time. My favorite thing to do for rotations is have the students build their rotation project alongside me. It is critical that you are interested in what you do and driven by the project you are working on, so what better way than to build it based on your own ideas. I aim to assist projects along, but want to give creative freedom. The focus should be learning new techniques, expanding scientific knowledge, and if the project works well – it can be a great starting point for PhD work. As a new lab, it is also important for me to see student's ability to be rather independent in driving their research, as there are no direct mentors to work side by side with in the lab. The lab mates all can aid for different aspects of the project and that helps to determine if the environment is a good fit as well. I feel very fortunate to have an amazing lab of unique personalities that vibe well and luckily are witty for entertainment too.

What advice would you like most to impart on Ph.D. students, both those who are just starting out and those farther along?

Perspective- you might not realize this in the moment, but you are going to do great. It might not seem that way day to day -or- when things are failing, but each step you are learning something new… so you are already winning. Honestly, no matter where you are in your scientific career or what lab you join, you can do great things and are the one in control to guide your research success. Mindset is everything and your perspective is critical to reflect on this. Look back and think about where you were at the start of the journey- 1st year of undergrad or 1st year of grad school and celebrate the success you have already made to be where you are in the current moment. Research life can get difficult, so think of the bigger picture of everything, celebrate all the little wins, and keep going!

Any suggestions on how to complete a Ph.D.? Do you have tips on battling burnout and finding out what you want your career path to look like?

Your "why" needs to drive you. You need to love your research question and be beyond driven by curiosity. When things don't work out or if/when you hit a wall for endless weeks on something, it helps when the question and the experiments are your ideas (not placed on you)... because then you are invested! Always recommend small side-projects too to stay motivated in other areas or to try new things out. What kept me sane during grad school –I picked up running when I was stressed out (which became often during the last 2yrs) and doing outreach with local afterschool programs. I did not let these side things distract me, but they aided my 'why'. Teaching middle schoolers the background between a hypothesis and seeing them excited helped to re-motivate myself as well. Going to scientific conferences, once my science was ready to present, was also exciting to see others really curious about my findings and to hear all the fascinating work ongoing by our field. It let me see my work in a different light and re-motivate me to ask the next questions.

What factors influenced your decision to become a professor? When did you know it was the right path for you?

I did not intend to stay in academia. I worked at two industrial/pharmaceutical jobs in and after undergrad and realized I needed a PhD in order to one-day drive teams to make career moves. However, during grad school I learned the freedom of academia that I didn't see in industry jobs; I could start and follow many side projects and be the first to make discoveries. I decided to do a traditional postdoc and turned down a few high paying industry jobs for it because I knew I wanted to learn more scientific fields/ techniques before 'settling' into a career. Towards the end of my postdoc- I realized I had wrote and funded my research, trained my technicians, and presented my findings internationally… so I should at least try for an academic position to answer a few burning curiosities I have. In academia, no one tells me 'no' or 'drop this project, our funding is elsewhere'… literally the lab is a rather limitless place for discovery. I have learned the joy of also having those new discoveries shared with me from the researchers in the lab and getting excited for their next experiments.

What's your favorite part about being a PI at Penn? How did you decide where to start your lab?

I used to always say my favorite and my least favorite thing about Penn is the same thing "numerous resources" - it can be overwhelming to focus in when you are starting and trying to determine where to use what services. The people here have really become my favorite singular thing though. I have met outgoing, no-ego, phenomenal scientists that want to do great work together and I am genuinely so happy that I found these individuals to surround myself with in seminars, committee meetings, and late night dinners. When starting up the lab and applying for positions – one big thing for me was location. Location can be key for your happiness and your happiness is key for your success. I only applied to a select number of places I'd want to do science in and live. Penn offered many things- a university overflowing with resources (as noted above), top-notch scientists, and neighboring institutes, while also being in a city filled of history that has great cuisine, music, and art (while not being over-bearing). Luckily, it also has a major airport for conference travel and the area brought me home to the East Coast. In many ways Philly was the only location where I would have wanted to start my lab and Penn was my top choice.

To learn more about the team and/or the research ongoing in the Conn lab, visit the lab website at https://www.csconnlab.com/team. Dr. Conn is currently looking for interested graduate students!

The Conn Lab

Special Interest

Switching it up: Thoughts and Statistics on Switching Labs

Ariana Majer

Peer Edited by James Gesualdi and Kay Labella

Have you ever thought about changing thesis labs? You are not alone. Changing labs may seem scary or impossible, but that's because we hardly ever talk about it. The fact is, switching labs is more common than you think. In this article, we answer questions you may have about changing labs and share the perspectives of CAMB students who have switched labs to demystify the process. If you are unhappy in your current lab, it is possible to change labs and have a more positive and rewarding grad school experience.

Why have CAMB students switched labs?

There are many reasons why a student may change thesis labs. In the past, CAMB students have switched labs because:

- Their PI was moving to a different university
- The lab environment was hostile and/or toxic
- Their PI was unsupportive, had unrealistic expectations, and/or ignored their ideas
- There were significant issues with communication, a misalignment of goals for the student's training, and/or a misalignment in how they approached the student's project and science in general
- The PI misrepresented themselves during the student's rotation

Students have also switched labs because their PI asked them to leave, though it is far more common for the student to initiate the change in labs. However, not all students in those kinds of situations choose to change labs.

Students who choose to stay in their current lab have done so because:

- They were able to work through their issues with their PI with the help of a third party
- They found people other than their PI, such as committee members or senior labmates, who were able to provide them with the guidance and mentorship they need
- The timing did not work out
- They did not think things would be any better in a different lab

What are the benefits of switching labs?

Many CAMB students who switch labs are happy with their decision. In switching labs, many students have found they have a better idea of what they are looking for in a mentor and lab, so they were able to find an environment that suited them better. Along those lines, students have also found that they obtained a better mentor-mentee relationship and a better support system as a result of changing labs. On a more personal level, many students feel that changing labs significantly improved their mental, emotional, and physical health and also improved their confidence in their abilities to make big decisions and to advocate for themselves. Being in an unsupportive or toxic environment can be emotionally draining, and it can change the way you feel about science, your abilities as a scientist, and your future in academia or science in general. It's easy to blame yourself when there are problems, and you may even be receiving the message that

you are to blame because you're not working hard enough or you're not smart enough, when the truth is that you are not being provided with the tools, support, and training you need to progress. Fortunately, many students who switch labs find they eventually regain their confidence and rediscover their passion for science, though some students found that their experiences permanently soured them on science.

While most students who switch labs consider their decision to be overall beneficial, they have also faced challenges. For example, some students have faced judgment from colleagues, friends, or family members for not sticking it out in their first lab or have been treated like they alone were responsible for the problems they faced in their previous lab. Additionally, even if the new lab is a better environment, it can still be difficult starting over again in a new lab emotionally and in terms of having to learn the workings of a new lab, in addition to potentially extending the duration of your PhD.

How does switching labs work?

Switching labs can take different forms depending on your situation. While there is no one-size-fits-all protocol for switching labs, there is a general path that many students follow. A common first step is to determine whether switching labs is the best course of action for you. This includes talking to your fellow CAMB students about their lab experiences and talking to trusted faculty to determine if your situation is more severe than the typical lows of grad school, as well as taking time to think about your goals and whether your current environment will help you achieve those goals. Once you have decided you would like to change labs, you first have to inform the CAMB chair (Dan Kessler) of your decision.

With Dan's approval, the next step is to inform your current mentor of your decision to leave their lab. This can take multiple forms depending on your situation, and Dan and Craig Bassing are able to assist you with informing your PI. After informing your PI, you should officially finish up your work in your current lab and start reaching out to potential new PIs. Prior to joining a new lab, you are required to do an ~6-week transitional rotation in the lab. The transitional rotation will be coordinated by Dan, and it basically functions to help determine that this new lab and mentor are a good fit for you before you fully commit. Dan will check in with you and your new PI throughout the rotation to see how things are going. If either you or the PI feels things are not working out at any point, then the rotation can be terminated early and you will do a second transitional rotation with a different PI. (It helps to have a backup PI in mind in case the first rotation does not work out.) At the end of your transitional rotation, if you both feel positively about how things are going, then you will become an official thesis student in that lab.

How will switching labs affect my time to graduation?

Some current CAMB students who switched labs feel that switching labs ultimately has not affected their PhD timeline, while other students feel their change in labs has set them back somewhat. However, of the students who feel switching labs has prolonged their time to graduation, most agree that extending the duration of their PhD for a healthier, more positive environment was worth it. In choosing a new lab, many students have found that whether you have to completely start over on a brand new project or whether you pick up a project that has already been started by someone can make a big difference, so if you are worried about your timeline, it is important to be open with potential new PIs about your ideal timeline/goals and ask them about projects they have available for you to pick up and run with. The timing of when you switch labs can also influence how big of an impact your change in labs has on the duration of your PhD, but what matters most is that you are in a supportive environment.

How do I know if leaving my current lab is the right decision?

If you've tried communicating your concerns to your PI and they did not listen, or if you've involved a third party such as your program chair or thesis committee to work through issues and nothing has changed, then changing labs is probably a good decision. It's also probably the right decision to change labs if you are unhappy and your current lab situation is starting to negatively affect your mental, emotional, or physical well-being. In deciding whether to leave your current lab, the most important thing is to trust yourself and what you're feeling. If you feel like you need to switch labs, then you probably do.

How will changing labs affect my funding?

BGS has a fund set aside specifically for students switching labs, so you will continue to be funded through the process of finding a new lab. Once you've informed your current PI of your decision to leave and set an approximate last day in their lab, Dan will petition BGS for funding on your behalf. BGS will support you through the process of finding a new lab, including a 6-week transitional rotation prior to officially joining a lab. If you have an F31, you may be able to keep your funding depending on how similar your new project is to your previous project and how lenient your program officer is. The official NIH policy is that your new project should fall within the scope of the project you proposed in your grant application. To determine this, your program officer may ask you for a written summary of your new project, and they may also ask you for an explanation of why you switched mentors and how your new mentor/resources compare to your previous mentor/resources, among other things. If possible, you should wait to inform your program officer of your change in labs until you are settled in a new lab and know what you will be studying.

How does switching labs affect the prelim process?

Students who switch after passing their prelim do not have to repeat the prelim process in their new lab. For students who are looking to switch in their second year before their prelims, the situation is a bit more complex. Barring extreme exceptions, PhD students need to pass their prelim before the start of their third year, and combined degree students need to pass their prelim before the start of their fourth year. This means that your prelim can be delayed a few weeks if necessary. While everyone's situation is different, students switching labs in the fall semester of their second year or early in the spring semester have typically taken their prelim on their new project in their new lab, and students who have switched later in the spring semester closer to the prelim have typically taken the prelim based on their work in the lab they are leaving. In the latter situation, Dan and Craig will ask your former mentor to remain actively involved in your prelim prep.

How should I go about finding a new thesis advisor?

A good first step is to think about what you want in a mentor and lab, and what you want to get out of your graduate school experience. Once you have a concrete idea of what you are looking for, you can narrow down labs that might be a good fit for you. If you had a positive experience in any of your other rotation labs and think they would be a good environment for you, then reaching out to that PI and seeing if they have the space and the funding for you is a good place to start. If you're really passionate about the work you were doing in your previous lab, you can reach out to any PIs whose labs you collaborated with in your previous lab, your committee members, or other labs that do similar work and see if any of those PIs are taking new students. If you're not sure where to start, it can be helpful to talk to multiple people, including your fellow CAMB students, CAMB leadership, your program chair, your committee members, and trusted faculty members.

Once you've identified some potential new PIs, it is important to thoroughly look into those PIs and their labs. Hopefully your time in your first lab has taught you a bit more about what you do and don't like in a mentor, what you need from a mentor, the type of lab environment and culture you need, etc. that will allow you to better focus your questions in talking to prospective new mentors and their trainees. It is important to ask prospective new mentors about their

expectations for grad students, their mentorship style, their funding, whether they have any available projects where the groundwork has already been laid out, and any other questions that are important to you. You should also talk to multiple lab members, and not just the lab members the PI recommends, about their experience in the lab and the PI's mentorship from their point of view.

Dan and Craig want you to know that switching labs is possible and that the outcomes are often positive, so if you feel your needs are not being met in your current lab you shouldn't hesitate to talk to them about what you are experiencing. Changing thesis labs is not uncommon.

Did you know?

- 26 CAMB students have switched labs in the last 5 years.
- 6 switched before their prelims
- 9 switched shortly after prelims
- 2 switched ~1 year after prelims
- 8 switched >1 year after prelims
- 1 student's mentor left Penn

The average time to degree for these students who have already graduated is 5.59 years, which is comparable to the overall CAMB time to degree.

Acknowledgments: *A massive thank you to the CAMB students who answered our surveys. Your insight was invaluable to this article, and we greatly appreciate you sharing your experiences with us. We would also like to thank Dan, Craig, and Meagan for their support of and help with this article. And to all CAMB students who are currently thinking about switching labs, please know that you are not alone and that you can always reach out to CAMB leadership and your fellow CAMB students for help.*

If you are thinking about switching labs there are resources available to you and plenty of people ready and willing to help you, including:

- Your fellow CAMB students
- Your thesis committee
- Your program chair and vice chair
- Faculty and students affiliated with the Trainee Advocacy Alliance (TAA)
- Dan Kessler and Craig Bassing
- Kelly Jordan-Sciutto

CAMB Student Perspectives

"As I talk to more graduate students, I realized I am not the only one switching labs so I wear that as a badge of honor. Some students have even dropped out of PhD and/or MD programs entirely because of the toxic PI/lab...I think graduate students should speak up more and be honest about their lab experience, and you will realize many students are quite miserable because of the imbalanced power dynamics and the lack of resources to navigate through this difficult situation."

"Everyone is on their own path, the most important part of your graduate training is that you get what you need out of it, which is training and experience for your next step in your career. If you feel that you are not getting the training you need and deserve, which you often find out from discussing the opportunities you are receiving from your lab with your peers, then seriously consider moving on to another lab."

"I forgot who I was and what I stood for in my old thesis lab. I became a shell of myself over the years of torture I endured…If you are in a bad situation, get out…You deserve to be treated with respect, kindness, and compassion. My feelings about myself 100% changed after I switched labs…I became myself again and also grew into the professional I am today."

Interview with a PI

"…when the student joined my lab I wouldn't say I had reservations about the student, but I had reservations about what I was personally capable of for mentoring them…Shortly after getting through the prelim, I took paternity leave, and it was hard for the student to continue to work and show productivity, so I initiated conversation with them that I did not think the environment was the best for them anymore…[I] thought it would be better if they found another lab, and I informed them of who else I thought would be a good mentor, I wrote them a letter of recommendation, and I helped transfer their F31 to their new thesis lab. We kept a professional and civil relationship after they left my lab."

"One of the critical things with [taking] each [new] student was making sure that they were a good fit with others in the lab, so that mini rotation is important…it was critical that they also got along well with everyone in the lab, which they each did."

"It is, I find, stressful taking any student in the lab because you want to treat them like your kids, you want to support them and help them grow. You feel responsible for them, and I feel it's an even greater responsibility when someone switches into your lab because you don't have that real rotation experience and…you don't want them to have to start from the beginning. So, for anyone moving into my lab, I wanted to make sure there was a solid thesis project or projects that they could pursue. I would never have someone switch into my lab and say oh well figure out what you want to do."

If you're interested in reading more about current CAMB students' experiences with changing labs, please see our blog for additional student testimonials!

Research Spotlight
Clayton Otter

James Gesualdi
Peer Edited by Kay Labella

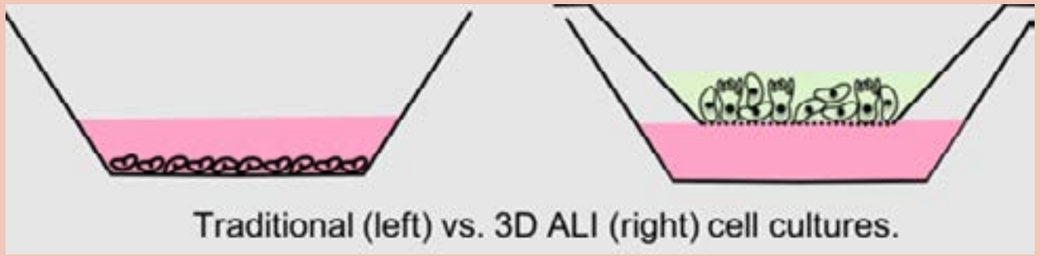
We are all familiar with SARS-CoV-2, the virus responsible for COVID-19 and the ongoing pandemic that has now seen nearly 800 million cases worldwide according to the World Health Organization. Most have also probably heard of SARS-CoV-2's relatives, particularly SARS-CoV, which caused a smaller pandemic in 2003, and MERS-CoV, a rarer but more severe virus that continues to circulate mainly in western Asia and the Arabian Peninsula. However, these headline grabbers are also related to many other human coronaviruses (HCoVs) that cause more mild disease and are responsible for 15-30% of common cold cases worldwide (1). This range of disease severity caused by various HCoVs is an important area of study for virologists because it represents a sort of natural experiment; differences in pathogenesis between mild and severe HCoVs can yield insights about protective host immune responses and key virulence factors. However, determinants of disease severity in HCoVs remain poorly understood. Luckily, recent work by CAMB-MVP MD/PhD candidate Clayton Otter and colleagues in Susan Weiss' lab has elucidated shared characteristics of common cold-associated HCoVs that may be predictive of infection outcomes and symptom severity in both mild and severe HCoV infections.

Subsets of HCoVs have been known to cause common colds for decades, but research of their infection dynamics was somewhat overlooked due to their mild nature. Interest in studying these non-lethal respiratory viruses has, of course, greatly increased since the onset of the SARS-CoV-2 pandemic. Clayton's work in this study focuses on examining virulence factors, replication kinetics, and induced host immune responses in both mild and severe HCoVs to understand the marked differences in disease severity associated with these viruses.

To investigate the behavior of different HCoVs, the authors used a primary cell culture system with patient-derived nasal epithelial cells differentiated at an air-liquid interface. Cells were cultured on transwell supports with specialized air-liquid interface (ALI) media on the basal face of the transwell and no media on the apical face. This unique approach allowed the authors to effectively model the environment of the nasal epithelium and upper airway, where primary infection and replication of HCoVs occurs.

Additionally, this system allowed for equilibration of nasal epithelial cultures at either 33°C or 37°C to further model the microenvironment of the upper and lower respiratory tract, respectively. Patient-derived ALI cultures were used to study replication dynamics and host immune response in the nasal epithelium following challenge with two common cold-associated HCoVs (HCoV-NL63 and HCoV-229E) and two severe HCoVs (SARS-CoV-2 and MERS-CoV).

Infection of ALI nasal epithelial cells showed that common-cold HCoVs are quickly cleared by the innate immune response after a rapid peak of initial replication. On the other hand, severe HCoVs replicate more slowly in initial time points, but eventually replicate strongly and reach a plateau; in other words, these viruses cannot be cleared by the immune response of nasal epithelial cells. Based on this difference in replication kinetics, Clayton hypothesized that common-cold HCoVs induce a robust host immune response in nasal epithelial cells, while severe HCoVs are capable of blunting or evading the host immune response. Indeed, bulk RNA-sequencing of infected nasal epithelial cultures showed that common-cold HCoVs induce strong interferon responses, a typical innate immune antiviral pathway. Interferons (IFNs) are cytokines that are produced after cytosolic pattern recognition receptors sense viral nucleic acids. Their production leads to the upregulation of a host of antiviral effectors called interferon stimulated genes (ISGs) capable of antagonizing viral life cycles at multiple stages. This suggests that the rapid



Cells were cultured on transwell supports with specialized air-liquid interface (ALI) media on the basal face of the transwell and no media on the apical face.

clearance of common-cold HCoVs by nasal epithelial cells may depend on this antiviral pathway.

In contrast, SARS-CoV-2 only mildly induces the interferon response, whereas MERS-CoV infection does not trigger interferon production at all. This comparative lack of interferon response and ISG induction by these more severe HCoVs is likely what prevents nasal epithelial cells from resolving these infections. To test this more directly, Clayton performed another round of infection with HCoVs in ALI nasal epithelial cells, this time in conjunction with ruxolitinib treatment. Ruxolitinib is a small molecular inhibitor of JAK1/2 signaling that prevents transcription of ISGs downstream of interferon sensing at the cell surface, effectively blocking antiviral interferon responses. Ruxolitinib treatment led to increased replication of common-cold HCoVs in ALI cultures and prevented viral clearance, validating that restriction of these viruses by nasal epithelial cells depends on interferon signaling. Interestingly, ruxolitinib treatment had a minimal effect on viral kinetics of MERS-CoV and SARS-CoV-2 in ALI cultures. The authors expected this due to the inability of nasal epithelial cells to clear these severe HCoVs under normal infection conditions and the lack of strong interferon responses induced in these infections. Conversely, pre-treatment of ALI cultures with either IFNβ or IFNλ strikingly attenuated replication of both severe and common-cold HCoVs. This suggests that under normal conditions, severe HCoVs somehow antagonize the interferon response, facilitating increased replication.

Both SARS-CoV-2 and MERS-CoV encode accessory proteins that counteract the activity of cytosolic pattern recognition receptors that sense viral nucleic acids and mount IFN production. These virulence factors consist of the conserved non-structural protein nsp15 and an additional MERS-CoV accessory protein called NS4a. These proteins antagonize the interferon response by digesting or sequestering viral nucleic acids, respectively, thereby preventing receptors such as MDA5 from triggering IFN pathways. To test whether these virulence factors are necessary for SARS-CoV-2 and MERS-CoV replication in nasal epithelial cells, Clayton performed another round of infections with mutant versions of these viruses in which the relevant accessory proteins were deleted. Infection of ALI cultures with these mutant severe HCoVs led to robust induction of the interferon response and attenuated replication compared to wild type viruses. These data show that inactivation of the interferon response by severe HCoV accessory proteins is critical for their robust replication in the nasal epithelium.

Previous work by the Weiss group has shown that all assayed HCoVs except MERS-CoV preferentially replicate at 33°C - a temperature associated with the nasal cavity and upper airway - compared to 37°C, the typical temperature of the lungs or lower airway. In accordance with this, mild HCoVs tend to replicate only in the colder upper airway without ever penetrating into the lungs, leading to less severe disease in vivo. Based on the importance of interferon responses demonstrated in this manuscript, Clayton and colleagues hypothesized that nasal ep-

ithelial cells produce more robust IFN induction and ISG upregulation at 37°C. Indeed, interferon responses as measured by STAT phosphorylation and ISG protein levels are significantly upregulated when ALI cultures are infected at 37°C compared to 33°C. This stronger interferon response at warmer temperatures led to faster viral clearance of common-cold HCoVs, but again failed to clear SARS-CoV-2 infection, likely due to this virus' ability to antagonize ISG induction. This also mirrors the in vivo situation, in which severe HCoVs maintain the ability to replicate in the warmer microenvironment of the lower airway and lung, leading to more extreme symptoms.

Of course, at this stage of the COVID-19 pandemic, there is no single SARS-CoV-2 virus, as innumerable variants have emerged due to the large number of total cases. Only a small subset of these variants are thoroughly characterized: typically those that become the most prevalent or "dominant" strain during a given surge in cases. The omicron variants are some of the most well studied novel strains of SARS-CoV-2 due to their extreme prevalence during the major wave of infections in the winter of 2021-2022, when the CDC abruptly and unscientifically reduced the recommended quarantine time for COVID patients (2). One of the defining characteristics of the various omicron strains was a penchant for replication in the upper respiratory tract, not unlike common-cold associated HCoVs. Given this clinical context, Clayton hypothesized that these SARS-CoV-2 variants would also replicate faster at 33°C rather than 37°C and induce a robust IFN response comparable to what was observed with common cold HCoVs. However, despite triggering a strong induction of ISGs and IFN secretion like common cold HCoVs, BA.1 replicated at comparable rates at each temperature and was not cleared by nasal epithelial cells at later time points. This suggests that BA.1 is less susceptible to IFN-mediated restriction than common cold HCoVs. Furthermore, even pre-treatment with IFNβ or IFNλ did not restrict replication of BA.1 or lead to viral clearance, suggesting that the BA.1 variant of SARS-CoV-2 is substantially less interferon-sensitive than ancestral strains overall. These data could potentially have important epidemiological implications, as novel SARS-CoV-2 variants may be growing more resistant to protective interferon responses that help to mitigate respiratory infections.

Clayton's data show that interferon responses restrict the replication of common cold HCoVs. These viruses preferentially replicate in colder environments reminiscent of the nasal epithelium and upper airway. All of these phenotypes of mild HCoVs are similar to those observed in other common cold viruses such as human rhinovirus 16. This suggests that these shared characteristics are what drives the mild disease caused by these common cold viruses. On the other hand, severe HCoVs are not controlled by interferon responses in the nasal epithelium. Potentially lethal HCoVs encode accessory proteins that evade canonical interferon induction, and these virulence factors are indispensable for viral replication in epithelial cells throughout the airway. However, some severe HCoVs remain interferon sensitive, as pre-treatment with IFNβ or IFNλ showed. Additionally, recent clinical studies have shown that a stronger IFN response in the nasal epithelium is highly correlated with a more mild course of COVID-19 disease (3). Therefore, administration of these cytokines could potentially be therapeutically or prophylactically useful for treatment of the now omnipresent severe HCoVs. That said, Clayton's analysis of the SARS-CoV-2 variant BA.1 suggests that more novel strains may be evolving their way out of this interferon sensitivity. These data highlight the importance of continuing to monitor and study SARS-CoV-2 variants of concern and the many insights that are available through research of more "mundane" common-cold associated HCoVs.

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Special Interest: So what is a thesis, actually?

Kay Labella

Peer Edited by James Gesualdi

Congratulations, CAMBer! Your prelim is passed, your paper is published, and your box has been checked on that Permission to Write form. You've been approved to defend your thesis – but where to start? Never fear! The CAMB Newsletter Crew is here to cover the basics.

So, what is a dissertation, anyways?

According to the CAMB website, a dissertation "represents a definitive contribution to scientific knowledge and that demonstrates the student's ability to perform independent research." In short, it will serve as a summary of all the hard work you have done throughout your time as a thesis candidate. Much like a paper, a thesis walks the reader through a project – or projects – from hypothesis to data. Unlike a publication, though, your dissertation may include avenues of investigation that didn't end up getting pursued, data from a rotation project, or even experiments that didn't quite work. In fact, 'negative' data can be quite important to include in a dissertation as a resource for others in your field.

What makes up a thesis?

Title, Abstract, and Other Openers:

According to the PhD Formatting Guide published by the Office of Graduate Studies, a dissertation requires a title page, an abstract, a table of contents, and lists of tables and illustrations. Optional to include are a copyright notice, a dedication and/or acknowledgement, and a short preface as to the topics you'll be covering. All of these will appear before the main body of your work.

Thesis Body:

The CAMB website outlines five sections for a dissertation:

As one might expect, the **general introduction** consists of a more in-depth background segment in which you will discuss previous literature relevant to your project or projects. As such, it will bear some similarity to a long review or a textbook chapter, and will be cited accordingly. You will also include your hypothesis in this section.

The **material and methods** are comprised of a comprehensive and detailed description of each experiment included in your results section. Antibodies, primers, and other reagents are presented as a large table, with notes on the vendor and catalog number.

The bulk of the thesis will be the **results**, which will likely span several chapters. Each chapter will cover about a paper's worth of experiments, the resulting data, and, of course, your interpretation of those data. If needed, additional background information or a short discussion can also be included in each part of this section.

Finally, the **conclusions and future directions** will serve as a summary of all your results – a discussion of all your previous chapter-specific discussions. It will also be a chance to draw broader conclusions about your data's relevance and importance to your field of research. Take time to speculate on the future – elaborating on where your project can go next and why is a must!

And, of course, you'll need to cite your sources with your **references!** Per your preference, the reference section can be broken up by chapter, or put all together after the main text.

Formatting

A thesis is required to have one-inch margins. It is recommended that your thesis be double-spaced, and written in one of the following fonts: Arial (10pt), Calibri (11pt), Georgia (11pt), or Times New Roman (12 pt). There are additional formatting rules around how to number the preliminary pages versus the main body of the text versus the bibliography, so when polishing your draft, make sure to give that some particular attention.

Resources:

If you're about to start writing, we recommend checking out the CAMB website's section on Permission to Write and Defend, as well as the PhD Formatting Guide, Dissertation Formatting Checklist, and Dissertation Templates provided by the Office of Graduate Studies.

Thank you for reading.

For any questions, comments, concerns, or if you're interested in joining our team, please feel free to contact us at:
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