Vulnerable Cancer Cells Are Stressed Out by Vitamin C

By Shana R. Spindler, PhD

Researchers at NICHD and partnering institutes are investigating if vitamin C can slow the progression of metastatic pheochromocytomas and paragangliomas (PCPGs), aggressive hormone secreting tumors associated with poor survival rates. The initial studies are promising. In a subtype of PCPG cancer cells, vitamin C acts as an oxidant that causes excessive DNA damage and cell death, according to their recent publication in Clinical Cancer Research.

PCPGs arise in cells of the neuroendocrine system. Many cases are benign, but treatment becomes difficult when PCPG cells metastasize to other parts of the body. “We are working to clarify cellular changes and make targeted therapies, as these patients usually carry specific genetic backgrounds,” said Dr. Ying Pang, NICHD postdoctoral fellow in Dr. Karel Pacak’s laboratory (Section on Medical Neuroendocrinology) and co-lead author of the study.

The team focuses on succinate dehydrogenase B (SDHB) gene mutations, commonly found in metastatic PCPG. Under normal conditions, the SDHB protein is part of a mitochondrial complex that helps process oxygen. But when this reaction is disrupted, the cell enters a condition of oxidative stress, which results in cellular damage.

Pang and colleagues found that PCPG cells increase signals to indicate a lack of oxygen—a state called pseudohypoxia—when they lack SDHB protein. These pseudohypoxic cells respond by increasing iron levels. The combination of oxidative stress and iron overload (which exacerbates oxidative stress) makes these cells vulnerable to additional insult—a condition that Pang aims to exploit with vitamin C.

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Letter from the Editor

I'm a planner. I like to look ahead, organize tasks, and focus on a goal until it's complete. During normal times, this can be an advantageous trait. During the coronavirus, however, being a planner lends to frustration when schedules are upended by unforeseen challenges—cue screaming five-year-old running through the living room office. This feels like a similar experience to benchwork. We've all encountered experiments not going as expected, forcing a stop and redo before moving forward with the next step. In honor of the inability to really know what's happening next, we're focusing this issue on research.

To kick off our research edition, we share work out of the Pacak lab in our “Hot Off the Press” column. Their research into vitamin C therapy for an aggressive type of pheochromocytoma reveals intriguing vulnerabilities in these cancer cells. A new clinical trial may be on the horizon.

Next up in our “Former Fellow Follow-Up” Q&A, former postdoctoral fellow Dr. Eric Horstick talks about his experience forming his own research group at West Virginia University. He describes how his academic environment influences his research and the trials and tribulations of setting up a new basic science lab. And for our clinically-minded trainees, in this month's “Clinical Corner” column, current fellow Dr. Crystal Kamilaris shares why she entered endocrinology-centered research.

As the NIH re-opens campus slowly, we will likely feel the effects—and potential stress—from the coronavirus for months to come. In our next installment of the COPING series, the NICHD Office of Education offers evidence-based methods to mitigate stress. You can find additional “virtual” support from the NICHD and NIH in the June announcements and events.

Over the next few months, let's plan to re-plan when needed. Research will pick up in due time, and your scientific careers will continue to progress. After all, it's the research that's going to make all those plans happen.

Your Editor in Chief,
Shana R. Spindler, PhD

Questions, comments, or ideas? Please contact our editor at shana.spindler@nih.gov.
Vulnerable Cancer Cells Are Stressed Out by Vitamin C
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High concentrations of vitamin C create cell-damaging hydrogen peroxide in cancer cells but are well tolerated by healthy tissue. Pang and colleagues hypothesized that pharmacological doses of vitamin C, combined with the oxidative stress and iron overload in SDHB-deficient PCPGs, would selectively affect the PCPG cells.

The idea was a success. The team found vitamin C induced markers for cell death and decreased colony growth in human PCPG-like cells that have decreased SDHB. To study this in a living animal, they injected pharmacological doses of vitamin C into mice with SDHB-deficient metastatic PCPG tumors. The team observed delayed metastasis and suppression of tumor growth in the mice—supporting a potential for therapeutic uses.

“This is a team effort among several institutes at NIH,” Pang emphasized. Based on their preclinical results and clinical observations from colleagues at NIDDK, Pang foresees a phase I clinical trial for metastatic PCPG using pharmacological levels of vitamin C, which has the advantage of a pre-established safety profile, as part of a novel treatment regimen.

REFERENCES
Former Fellow Follow-up with Dr. Eric Horstick

Eric Horstick, PhD, is an assistant professor in the Department of Biology at West Virginia University (WVU). He completed his postdoctoral training in the lab of Dr. Harold Burgess from 2013–2019. Initially, Dr. Horstick aimed to study sensorimotor processing. But over time, his studies evolved into exploring the circuits and molecular pathways that establish and maintain asymmetric function in the brain, which Dr. Horstick continues to study in his own lab.

Check out our Q&A with Dr. Horstick to learn more about beginning a career in academic research:

Q: Did you always know you wanted to run your own lab?
A: I hoped I would run my own lab. Since high school, I was interested in biology, and as such pursued a biology degree in college. My advisor at the Bloomsburg University of Pennsylvania got me working in his wife’s lab (the Robishaw lab) at the Weis Center for Research. There I used zebrafish to investigate G-protein signaling. The topics have changed over time, yet the fish stuck. I feel like science, and research in particular, has a current: you start, get caught in the current, and then find yourself moving along through the steps (i.e. grad school, postdoc). Before you know it, you’re looking for a faculty position.

Q: What’s your typical day like as an assistant professor at your institution?
A: I’m still very new. Only five to six months in my position. Therefore, I spend a lot of time in lab getting equipment set up and experiments moving. Otherwise, life is emails and grant writing.

Q: How does your academic environment influence your research?
A: Recently, WVU was promoted to a Research 1 institution, so rigorous, quality research is central to success and promotion. The biology department composition covers a broad spectrum of fields. One major area of growth is neuroscience and the department has recently expanded their imaging core which significantly expands research opportunities.

Q: On average, how many hours per week do you spend teaching/mentoring, writing grants, and managing the lab?
A: At WVU, I have one year of teaching exemption, which is very generous and helpful in getting a lab setup. After my exemption period, I will teach one course a semester. I try to get five to six hours per week in the lab doing experiments or directly working with my lab members. Otherwise, I’m writing grants or taking care of administrative responsibilities.

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Q: **How did you define the scope of your research? Did you find it hard to find a balance between broad questions versus a narrow focus?**
A: Honestly the approach is to be all encompassing. With the difficulty of funding, you cannot limit your scope. You need to approach your research from every angle—and submit a grant on it.

Q: **What are your funding sources for your research and how did you secure them?**
A: Currently, I am working on startup funds. I am also developing grants for both NIH and National Science Foundation mechanisms.

Q: **What trials and tribulations did you encounter while setting up your lab and forming your group?**
A: The most difficult adjustment is timing. You quickly learn everything, literally everything, takes much longer than anticipated. This spans from hiring, training, lab set up, to experiments. As a postdoc, you know the experimental logistics and your own capabilities that allow for rapid data collection. Working with new people, you will need to adjust those expectations—and more importantly, learn to not get too frustrated.

Q: **How did you find lab personnel, and do you have recommendations for how to structure your lab at the beginning?**
A: Recruitment is difficult, especially as a new person. Contacting your friends, using university job sites, and self-promoting at conferences are some of the best ways to start. As for composition, this is really a personal preference. Each level of personnel comes with different expectations that are important to keep in mind.

Q: **Where do you seek out mentorship?**
A: My previous mentors are immensely helpful. Also, WVU Biology supports both an internal and external mentor program. This helps to semi-officially establish a support system both inside and outside the department. Systems like this are immensely valuable to junior faculty.

Q: **Do you have any final tips for fellows who are thinking about running their own labs?**
A: There is no guidebook or one set of expectations—so really, no point looking. That is why asking for input and advice is necessary. It can be intimidating to do so because you don't want to look foolish or unprepared, yet everyone was new at some point, and there wasn't a guidebook then either. However, a skill you need to develop is the ability to distinguish the advice that is, or is not, good for your research program.
Let’s Talk About Stress

A DISCUSSION ABOUT EVIDENCE-BASED TOOLS TO COMBAT THE NEGATIVE EFFECTS OF STRESS

By Triesta Fowler, MD

Stress is now more than ever a part of our everyday lives. Stress is created when the balance between the demands that a person may have on them and the resources that they use to respond to them are unequal. But what is stress? And how can we keep it from harming us?

The body’s response to stress is thought to be in three stages. In the first stage, the body is put on alert and its reaction is one of alarm. The second stage is resistance as the body prepares to deal with the stress by triggering autonomic activity commonly known as the flight or fight response. The final stage of exhaustion occurs when the body is no longer able to deal with the stress, so the system becomes damaged. Each individual goes through the second stage differently, and some manage to escape the final stage. However, if any stress persists long enough, it will be inevitable that someone will enter the third stage.

Life for us drastically changed almost overnight with the COVID-19 pandemic. We are experiencing an unprecedented set of demands that challenge us in every way and thus has made this time very stressful. This stress has triggered an alarm in our bodies that has caused both mental and physical reactions. We are now left to figure out how to handle this stress, adapt to a new normal, and avoid any negative sequelae. These tasks are becoming increasingly more difficult as this stressful period persists. So, coping strategies have become very important parts of our lives. Coping is a way to control the imbalance that is created by stress. Here are some evidenced-based ways to cope with stress in a healthy way:

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★ Try to remove or decrease the source of the stress — Each individual will have a unique response to a stressor based on how it is perceived. Not all stressful situations can be completely avoided or removed. However, it can be helpful to find small ways to decrease the level or intensity of the situation.

★ Change how you think about the situation — Thoughts are influenced by emotions which impact behavior. So, adjusting thoughts or a mindset to a stressful situation is the first step in altering the body’s response. Be aware that this can be difficult to put into practice, so it is important to set realistic goals in this area. Also, at times it is helpful to accept the fact that some situations cannot be controlled. In these cases, the focus can be on learning how to adapt.

★ Keep moving and get rest — Physical activity can reduce the impact of stress on the body even at a low or moderate level. Start simple and be mindful of any physical limitations or health conditions. Being active can also help improve sleep. Develop a consistent sleep routine that limits the amount of screen time around bedtime.

★ Meditation — Mindful meditation has shown great success in reducing stress and anxiety. Finding a small amount of time to sit quietly and control your breathing is all it takes. This may even be able to help with sleeping difficulties.

★ Muscle Relaxation — Stress can cause muscle tension that can lead to tension headaches and back aches. Stretching, massages, and warm baths can help.

Stress will always be a part of life. Recently, the level of stress has markedly increased. Unfortunately, this level of stress may persist for some time. Accepting its presence is the first step in implementing ways to combat it. It is always good to start small and set attainable goals as you begin to practice these methods. Once there is some improvement, explore other techniques and build on that success. Remember to reach out for help from your family, friends or healthcare professionals at any time that you feel overwhelmed.
Clinical Corner: Meet Dr. Crystal Kamilaris

Crystal Kamilaris, MD, is a clinical fellow in adult endocrinology, diabetes, and metabolism in NIH’s Inter-Institute Endocrinology Training Program (IETP). Her research interests include endocrine hypertension, adrenocortical tumors, pituitary disease, and multiple endocrine neoplasia. As a senior clinical fellow, she supervises and teaches other fellows, medical students, and staff. She also has served as fellows’ representative and as the representative for adult endocrinology on NIH’s Clinical Fellows Committee.

We asked Dr. Kamilaris a few questions about herself to get to know the person behind the degree. Introducing Dr. Kamilaris:

What influenced you to go into medicine/research?
Having grown up in Long Island, New York, and as the daughter of two physicians, I was able to observe first-hand the gratification of contributing to science and one’s community through medicine and research. This propelled me to pursue a career in this field.

After receiving my high school degree, I completed my medical school training at the University of Patras School of Health Sciences in Patras, Greece and then my internal medicine residency training at the University of Connecticut in Farmington, Connecticut. Throughout my medical training, I developed a passion for scientific inquiry that was further strengthened after completing a rotation as an internal medicine resident at the NIH IETP. While in this program, I was able to observe how the study of rare diseases has helped elucidate the pathophysiology of many endocrine conditions, allowing for advances in diagnostics and therapeutics that can have a broad effect. This fueled my interest for clinical and translational research.

Why did you choose this line of research?
Since I was a medical student, I have been fascinated with the intricacy of human physiology. Small changes at the molecular level can lead to a significant pathology in the human body. Endocrinology, in my opinion, best embodies this wide spectrum of pathophysiology. Endocrinology involves multiple organ systems and processes. Understanding this pathophysiology from the molecular to the clinical level allows for specific disease detection through history, physical examination, and precise diagnostics, as well as the development of therapeutics that target specific disease processes—with ample opportunities for research to further the field.

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I became enamored with the field of adrenocortical disease, endocrine hypertension, and multiple endocrine neoplasia syndromes after observing the significant effects that excess cortisol and/or aldosterone can have on metabolic, cardiovascular, and bone health—amongst other systems. I’ve observed how specific genetic defects and alterations in certain key intracellular pathways can lead to disease and/or tumorigenesis in the adrenal gland and in other endocrine organs. I became interested in diseases of the pituitary gland and neuroendocrine disorders, as the pituitary is intricately involved in multiple endocrine/hormonal axes.

What brought you to NIH?
NIH fosters a culture of excellence and offers unparalleled opportunities to build a strong foundation for a career as a physician-scientist. I chose to pursue my fellowship in endocrinology, diabetes, and metabolism at NIH as this fellowship program provides unique opportunities to develop clinical and research expertise as well as teaching experience. The IETP, through collaborations with other local institutions, allows for fellows to have a broad clinical experience while developing clinical and research expertise while seeing patients at the NIH. Importantly, NIH is a referral center for many rare endocrine disorders, supporting clinical trials involving most of the major areas of endocrinology. NIH also promotes the development of basic, translational, and clinical research skills, with advantages provided by the Clinical Research Center, NIH facilities, and mentorship from leaders in the field.

What is your most memorable experience so far at NICHD?
I have been lucky to have many memorable experiences while at NICHD. Most recently, we had a patient that was diagnosed with primary aldosteronism at a young age due to bilateral adrenal hyperplasia.* He required surgical treatment with bilateral adrenalectomy in the third decade of his life due to progressive disease. His phenotype was more severe than that of a patient with sporadic primary aldosteronism due to somatic mutations, but less severe than that of patients with familial hyperaldosteronism due to germline mutations.

Focused exome sequencing in multiple nodules from both of his adrenal glands revealed a hot-spot pathogenic mutation as the cause of his primary aldosteronism, but Sanger sequencing did not detect DNA defects in peripheral blood and other tissues. Whole exome “deep” sequencing revealed that 0.23% of the copies of his germline DNA carried the hotspot mutation present in the adrenocortical nodules, suggesting low level germline mosaicism as the cause of his primary aldosteronism—which had not been previously reported.

This is a great example of how a specific molecular process resulted in a unique clinical phenotype, with implications for the patient’s prognosis and genetic counseling.

*Editor’s Note: Bilateral adrenal hyperplasia is the enlargement of hormone-producing glands (called adrenal glands) on both kidneys. Primary aldosteronism is a disorder that occurs when the adrenal glands produce too much of the hormone aldosterone, which leads to high blood pressure.
The Rep Report
By Anshika Jain, PhD

As the current NICHD Basic Sciences Institutes and Centers (IC) Representative, I represent NICHD postdoctoral fellows at the Fellows Committee (FelCom) meeting every month and share the latest news with you here. Do you have a concern or question that you want brought up at the next meeting? Contact me at anshika.jain@nih.gov!

Stay well, everyone!

FelCom announced two new open positions in the committee: the FAES Liaison and FelCom Co-chair. Elections for these positions will be held in June and August 2020, respectively. Please email Kathy Reding (katherine.reding@nih.gov) if you are interested in applying for these positions.

The Office of Intramural Training and Education announced that the first virtual NIH Career Symposium, held on May 8, 2020, was a huge success and was attended by postdocs and students both in and outside NIH. Career panelists’ biosketches and recordings of discussions are now available at the OITE YouTube page. The clinical panel was postponed until summer 2020.

The Office of Intramural Research announced that an increase in the stipend for fellows came into effect May 1, 2020, and NIH leadership now has a plan for phased-re-opening of NIH.

The National Postdoc Association is collecting stories on postdocs during quarantine. They also announced that IRTA/CRTA fellows are now eligible to contribute to an Individual Retirement Account (IRA).

The FAES announced that all Summer and Fall 2020 courses through FAES will be online.

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The Medical Executive Committee announced a plan to roll out a formal telemedicine platform to help navigate patient appointments during the COVID-19 crisis. The Clinical Center (CC) plans to increase both their inpatient and outpatient census and resume some surgical procedures. This will involve aggressive screening measures, with the potential for routine testing of asymptomatic staff members for coronavirus.

The Outreach Committee invites ideas for the “I am Intramural” blog. Please send your ideas to Craig Myrum (craig.myrum@nih.gov) if you or someone you know recently published an interesting study that others might want to know about. This is a great platform to draw attention to your research! Be sure to join the LinkedIn page for more updates (Fellows at the NIH-FelCom).

Recreation and Welfare/Health and Wellness Committees liaisons Rosario B. Jaime-Lara (rosario.jaime-lara@nih.gov) and Surangi Perera (sarangi.perera@nih.gov) invite you to contact them if you would like the opportunity to present your work in the Prokaryotic Pathogens Seminar Series. Each virtual seminar features two 15-minute talks from early career researchers, such as technicians, trainees, and new investigators. The event takes place on Fridays at 3 p.m. To sign-up for the mailing list or submit an abstract, please visit https://forms.gle/UkyU3LaSE7XED7N97.
June Announcements

CONGRATS TO THE 2020 VIRTUAL POSTBAC POSTER DAY WINNERS!

Congratulations to the following NICHD postbacs (and their mentors) for scoring among the top 20% of NIH postbacs in the 2020 Virtual Postbac Poster Day competition on April 28-30, 2020:

» Fountane Chan (Dr. Judith Kassis)
» Alexandra Fister (Dr. Brant Weinstein)
» Sydney Hertafeld (Dr. Ryan Dale)
» Michael Hilzendeger (Dr. Ajay Chitnis)
» Anisa Holloman (Dr. Cuilin Zhang)
» Anna Horacek (Dr. Judith Kassis)
» Nicholas Johnson (Dr. Ryan Dale)
» Katherine Maultsby (Dr. Denise Haynie)
» John Millerhagen (Dr. Amir Gandjbakche)
» Risha Sheni (Dr. Jack Yanovski)
» Avery Swearer (Dr. Brant Weinstein)
» Ndeah Terry (Dr. Rajeshwari Sundaram)
» Jessica Tung (Dr. Matthias Machner)
» Claire Weinstein (Dr. Matthias Machner)

To score posters, teams composed of graduate students, postdocs, and NIH scientific staff reviewed poster content, poster appearance, and student presentation for all postbac participants. A total of 69 NICHD postbacs participated in the day!

POSTPONED: ANNUAL NICHD FELLOWS MEETING

The 16th Annual Meeting for Postdoctoral, Clinical, and Visiting Fellows and Graduate Students has been postponed until Friday, October 23, 2020. This year’s retreat will be held at The National Museum of the American Indian.

This meeting will allow you to step away from the lab for a day to network with your NICHD colleagues, participate in a career exploration session, and learn more about the recent developments in our intramural research programs. More details to follow!

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GAIN PROGRAMMING SKILLS WHILE TELEWORKING FROM HOME
During this time of extended telework, the NICHD’s Bioinformatics and Scientific Programming Core (BSPC) is offering to help fellows gain valuable programming and data analysis skills. BSPC can provide several resources for learning the R programming language as well as develop custom learning plans using online resources to meet specific learning goals.

You can start learning the R programming language directly in a web browser at https://rstudio.cloud/learn/primers. If you want to progress further, you can use the free online book https://r4ds.had.co.nz as a guide.

If you are interested in programming and data analysis, please contact Dr. Ryan Dale at ryan.dale@nih.gov. He can work with you directly or coordinate with others in BSPC to schedule “virtual office hours” to help you understand how these skills fit into your research or to help with installation issues and coordination with IT.

MENTOR OF THE YEAR AWARDS: ACCEPTING NOMINATIONS NOW!
Do you have an outstanding mentor?
The time has come for you to nominate your fellow or PI for the 2020 NICHD Mentor of the Year Awards. This is your chance to recognize an individual in the Division of Intramural Research (DIR) or Division of Intramural Population Health Research (DIPHR) whose mentoring has made a difference in your life at the NIH!

Below is the link to obtain information about the NICHD’s two annual intramural Mentor of the Year Awards, one for a fellow and one for an investigator. Please submit your nomination form and a 500-word (maximum) narrative electronically to Ms. Monica Cooper (cooperm@mail.nih.gov). The submission deadline is Friday, June 26, 2020.

Please contact the Office of Education if you have any questions about the nomination instructions or selection process. Information available at: Mentor of the Year Awards

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NCATS AND FAES PARTNER FOR VIRTUAL TRANSLATIONAL SCIENCE COURSE
MEDI 501: Principles of Preclinical Translational Science
A CASE STUDY FROM CANCER DRUG DISCOVERY AND DEVELOPMENT

Enhance your translational science skills this summer with a seven-week online course designed by the National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health (NIH). The course will run from June 15–July 3.

This course—MEDI 501: Principles of Preclinical Translational Science—is offered by NCATS in partnership with the Foundation for Advanced Education in the Sciences (FAES).

In this course, students will learn preclinical translational science principles. Faculty will teach these principles through a case study of a highly successful translational research partnership involving NCATS, the National Cancer Institute, Northwestern University and the University of Kansas. The partnership produced a promising potential drug shown to inhibit cancer metastasis in animal models and that is being examined in a first-in-human clinical trial in 2020.

This one-credit course requires a time commitment of about one hour per week to listen to course lectures, plus time to complete course readings and other short assignments.

For more information, go to https://faes.org/courses.

ONGOING VIRTUAL TRAINING EVENTS AT NIH
NIH-Wide Office of Intramural Training and Education (OITE) Events
For more information and registration, please visit Upcoming OITE Events.

NIH Library Training and Events
For more information and registration, please visit the NIH Library Calendar.

FAES CONTINUES VIRTUAL SUMMER OFFERINGS
All of the Foundation for the Advanced Education in the Science (FAES) June and July courses are being held online. You can view upcoming FAES online courses and workshops at https://faes.org/workshops-conferences.

If you are interested in registering for one of the courses and there is a cost associated with the registration, please reach out to the Office of Education for sponsorship (yvette.pittman@nih.gov).
June Events

WEDNESDAY, JUNE 10, 10–11 AM
Virtual “Coffee Fix” session on self-advocacy—via Zoom

Come get your fix as we talk about various areas of concern facing fellows. Every other month, we’ll brew up unfiltered conversation on tough topics. During the upcoming session, we will discuss issues related to self-advocacy. Zoom connection details will be circulated soon!

WEDNESDAY, JUNE 17, 1–3 PM
Virtual Grant Writing Session for IRF Applicants

In 2018, DIR launched the Intramural Research Fellowship (IRF), a competitive research funding opportunity for NICHD postdoctoral, visiting, and clinical fellows. Its main objective is to promote grant writing among our intramural trainees, while enhancing awareness of the various components of an NIH grant application. For all prospective applicants, the Office of Education will offer a training session to cover various components of an NIH grant, details about the application and review processes, and tips on preparing an IRF application.

The IRF submission date is Monday, September 14, 2020. Attendance at this virtual training session is a requirement for submission. For more information on the IRF, please visit NICHD Intramural Research Fellowship.

Please email Dr. Erin Walsh (erin.walsh@nih.gov) if you are planning to attend the training session.