Issue 35 MARCH 2019

THE DOSSIER

The Digest On CCR Staff Scientists and Staff Clinicians: Information, Employment and Research

From the Editor

Anu and I looking over the March issue

In April 2010, Anu Budhu, the Editor-in-Chief of the newly launched Dossier, shared her ambitions for this new publication by highlighting its key role in helping, "enhance our research, employment opportunities and knowledge, and to make us aware of resources and events pertinent to our group". From that first issue onwards, the Dossier has flourished with Anu attentively shaping the publication in her role as Editor-in-Chief. The Dossier has grown to become an important source of information for NCI Staff Scientists and Staff Clinicians. I joined as a section editor in 2011, soon after I became a Staff Scientist, and I always looked forward to reading the other sections in the Dossier. It made me feel like part of a community, even on weeks when my schedule prohibited me from partaking in the activities listed in the newsletter. I thank Anu for her excellent stewardship of the Dossier, and am glad she is staying on as Senior Editor. I am greatly excited and honored to take on the reins as Editor-in-Chief. Putting together this issue has been deeply satisfying thanks to the support of the excellent team of section editors, the Office of the Director, Staff Scientists and PIs, all of whom make the time to write insightful and informative articles for this newsletter. My aim is that the Dossier continues to evolve in ways that benefit us, highlighting information that helps us succeed and providing us with a community that supports each other's success.

Lakshmi Balagopalan, Ph.D. (SS)
Editor-in-Chief
Laboratory of Cellular and Molecular Biology

In This Issue

Mark your calendars

The 15th Annual SSSC Retreat April 26, 2019

"Tumor Initiation: Microenvironment and Metastasis"

Registration with Abstract deadline: Feb 22

Registration without Abstract deadline: March 3

Career Development

- **SSSC Technical Enrichment Program (STEP) OPEN** Details about the program and application process can be found here
- **SSSC Career Enrichment** Program launched, agenda listed here
- Visit the **SSSC WEBSITE** for more information

The Office of The Director: Guest Editorial*

NCI-Frederick's Contract Operations: A Valuable Resource

We all know that there are many characteristics of the NCI intramural program that make the scientific environment here unique. The funding flexibility, intellectual freedom, and inherent opportunities for crossover between basic and clinical research, all play key roles in our ability to attract and retain some of the best scientific minds in the world. To support this unique scientific environment, we have a large and flexible operational infrastructure. A great deal of that flexibility comes from the close collaboration between a dedicated federal workforce and an extensive contract presence. This synergy provides the infrastructure needed for the rapid expansion and/or redirection of specific scientific priorities, permitting CCR investigators to effectively adapt to the rapidly evolving scientific landscape. Many of our daily activities are impacted by contract activities. This is particularly apparent in our Frederick operations, where virtually every aspect of scientific life involves contractor personnel and activities. This includes everything from building maintenance and operations, environmental health and safety, purchasing and travel support, to the operation and oversight of state-of-the-art animal facilities. On the Bethesda campus, activities as diverse as clinical nursing support, animal facility operations, and bioinformatics are supported via contract agreements.

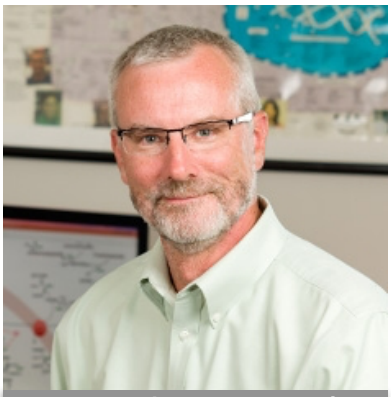
"Contract operations are a major part of how we do science in the CCR. Your input into how we use contract activities is important to us."

Managing the myriad of contract activities is a complex undertaking. We are pleased to have recently recruited Robin Winkler-Pickett (winklerr@mail.nih.gov) to work as CCR's Frederick contract activities liaison. She will be working closely with CCR leadership, the Administrative Resource Centers, CCR staff using Leidos Biomedical Research (LBR) services, and components of the NCI Office of Scientific Operations (OSO), to identify and mitigate any contract issues, and to do our best to assure that future contract operations are well suited to meet your future needs and objectives.

We also want to urge you to consider taking advantage of an exciting new program recently launched by the CCR that is made possible by the state-of-the-art core facilities operated under the NCI contract. The Staff Scientist/Staff Clinician Technology Enrichment Program (STEP) is a career enrichment program for Staff Scientists and Staff Clinicians. Based on feedback from the Staff Scientist/Staff Clinician (SS/SC) community regarding the desire for expanded avenues for career development, this program supports the placement of SS or SC into CCR technical core facilities, so they can gain hands-on experience in the rapidly evolving technologies that push our science forward. In the STEP program, SS or SC will work closely with core managers/directors to learn firsthand the application of a core technology from experimental design, sample preparation, data collection, through to data analysis. The experience will be part of an ongoing project in the SS or SC research program. By spending significant continuous periods of time with the core, a SS or SC will not only benefit her/his specific research but will return to their Lab/Branch with invaluable expertise and insight into the operation and application of a given core technology. The core costs incurred during a STEP deployment will be covered centrally by CCR, so STEP proposals will be solicited via a call for letters of intent (LOI), followed by applications going into the STARS process for evaluation and award. The STEP program is really a win-win-win, with SS and SC gaining valuable experience, their research receiving central core funding, and expertise returning to the Lab/Branch that will enhance the utility of CCR cores in meeting CCR mission goals. Expect the STEP LOI call soon and stay tuned to the SS/SC websites for further information. In the meantime, consider how direct experience with high end sequencing, mass spectroscopy, high resolution imaging, advanced protein chemistry approaches, or other services supplied by our CCR cores could catapult your projects and your careers forward.

**The CCR Director regularly invites senior staff members as guest columnists to expertly inform the SSSC community on diverse aspects of the CCR*

Contract operations are a major part of how we do science in the CCR. Your input into how we use contract activities is important to us. We will be happy to work with you, your Lab/Branch Chief, and/or your CCR Deputy Director to help resolve any problems and, where possible, consider changes to the contract operational requirements that might improve our science, enhance our efficacy, and/or alleviate any concerns going forward.



Daniel W. McVicar, Ph.D.
Deputy Director, CCR

Tom Misteli, Ph.D.
Director, CCR

The 15th Annual SSSC Retreat

The theme for this year's retreat is

"Tumor Initiation:
Microenvironment and Metastasis"

Please mark your calendars

April 26, 2019

The annual Staff Scientist and Staff Clinician retreat of the National Cancer Institute's Center for Cancer Research (CCR), Division of Cancer Epidemiology and Genetics (DCEG) and Frederick National Laboratory for Cancer Research (FNLCR) will be held on April 26th, 2019. The theme for this year's retreat is "*Tumor Initiation: Microenvironment and Metastasis*". This retreat is marked by two keynote presentations from both basic research and clinical scientists. The retreat will start with the keynote presentation of Stuart H. Yuspa, M.D., Co-Chief of the Laboratory of Cancer Biology and Genetics, CCR. Dr. Yuspa is a pioneer scientist on cancer pathogenesis and tumor microenvironment. The keynote speaker for afternoon session is the distinguished scientist, Rosandra Kaplan, M.D., Investigator of Pediatric Oncology Branch and Head of the Tumor Microenvironment Section, CCR. Dr Kaplan is a pediatric oncologist and developed the concept that the growing tumor creates an environment that is conducive for metastasis.

In the morning session, the Keynote talk by Dr Yuspa will be followed by the presentations from top experts on cancer biology: Patricia S. Steeg, Ph.D., Deputy Chief of Women's Malignancies Branch, CCR; Roberto Weigert, Ph.D., Senior Investigator, Laboratory of Cellular and Molecular Biology, CCR; and Gretchen L. Gierach, Ph.D., M.P.H., Deputy Chief and Senior Investigator, DCEG. A highly interactive and informative panel discussion will follow the talks to explore the challenges and ideas about different aspects of tumor development and progression.

The poster session is divided into two parts (a morning and afternoon session), to provide opportunities to spend more time on interesting posters, having discussions, and building network and collaborations among SSSC colleagues. Each abstract and poster submission will be judged by multiple NCI principal investigators and the four highest scored abstracts will be selected for oral presentations. There are travel awards for the best-reviewed posters and the best oral presented abstract. In the afternoon session, Dr Kaplan's presentation will be followed by the selected oral presentations of Staff Scientists and Staff Clinicians (SSSC).

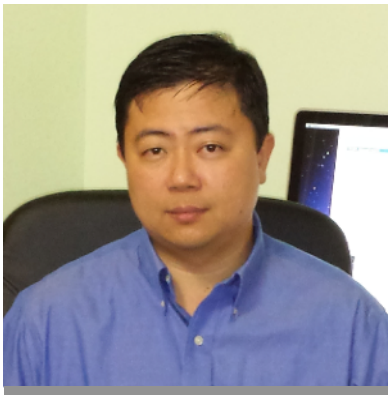
Please note that the abstracts are not limited to Tumor initiation or metastasis. Any subject belonging to one the three categories are welcome: Basic Research; Translational, Clinical and Epidemiological Research;

Technologies and Methodological Development. SSSCs can bring one NCI colleague to the retreat, so bring along your lab mates/post doc/ post bac/student.

Please mark the date on your calendar: April 26, 2019. For details, please visit the website https://events.cancer.gov/cct/sssc-retreat

Kajal Biswas, Ph.D. (SS)
Co-chair, SSSC Retreat 2019

Patricia Day, Ph.D. (AS)
Co-chair, SSSC Retreat 2019



Yien Che Tsai, Ph.D. (SS)
Co-chair, SSSC Retreat 2019

The Professional Development Corner

A Report on the 2018 Annual NCI SSSC Professional Development Day

The SS/SC Professional Development Committee held its Annual NCI SS/SC Professional Development Day 2018 on November 16, 2018. This year the SS/SC Professional Development Committee tried a new format for the meeting. The meeting was shortened to a half day session, followed by a pizza lunch. Due to inclement weather, delays and closures, attendance was down from previous years. To accommodate as many SS/SC as possible, a WebEx was set up for virtual attendance. The Chair of the SS/SC Professional Development Committee, Swati Choksi, Ph.D., opened the meeting with a brief overview of the activities and accomplishments of the committee for 2018. The first session with Dr. Hannah Valantine, *Implicit Bias Education: NIH's Scientific Approach to Inclusive Excellence,* was unfortunately cancelled.

The next session was the introduction of the much awaited *Enrichment Program*. Many of us had heard bits and pieces of this new program being developed specifically for the SS/SC community, so we had Dr. Cynthia Masison, Program Specialist, Office of Scientific Programs, Office of the Director, NCI and Margaret Randol, Program Manager, Office of Workforce Planning and Development, on hand to brief us and answer all our questions. Dr. Choksi, in a TED-Talk style, asked detailed questions of the panel. The Enrichment Program is a program developed by the Center for Cancer Training, in collaboration with the NCI OD and is intended to provide the participants with strategies to network, develop mentoring partnerships and increase efficiency at work. With the guidance of coaching experts, the SS/SCs will be empowered to create a productive and fulfilling environment. Of note, Dr. Masison informed us that participation in this program was encouraged by the NCI leadership. We learned that while informing your PI of your intent to enroll in the program is recommended, it is not necessary to get a formal approval. Ms. Randol told us that a cohort of 8 people had been selected from the applicant pool,

Professional Day 2018 Highlights

- Enrichment program launched in January
- Understanding the Quad Review
- Pitching your Science

Swati Choksi , Ph.D. (6th from left) with other Staff Scientists at the 2018 Professional Development Day.

and would go through the year long program to gain important career development training. Many in the audience were very interested in signing up, as some did on the spot! In January the Enrichment Program had its first session. More information can be found at SS/SC Enrichment Program.

Dr. Masison was then joined by Rena Rodriguez, Deputy Director, Office of Management, NCI for the next session - *Understanding the Quadrennial Review Process*. They did an excellent job in covering the details of the Quadrennial Review Process from start to finish. Dr. Masison reminded us that a similar information session on Quadrennial Review is offered every September to PIs and supervisors to help the SS submit a strong review package. Both Ms. Rodriguez and Dr. Masison stressed the importance of a well written PI letter that covers all the points in the Quad Review Checklist.

Our last session was a workshop conducted by Scott Morgan, of The Morgan Group, on *The Elevator Speech or Pitching Your Science*. This workshop was very interactive and Scott made participation by the audience fun and informative. Participants were shown how to explain their work to a variety of audiences with a wide range of backgrounds. These oral skills can be put to immediate use at conferences and during recruitments. Scott Morgan has made his slides on topics such as: identifying common ground, explaining the work of the lab, adding personal connection, verbalizing the rationale, and framing one's work within the larger scientific picture, available on our website. The workshop was a big hit and we look forward to having Scott at our next Professional Development Day.

We ended the meeting with a pizza lunch graciously provided by the Professional Development Committee. Thank you for attending this meeting and with your continued support we will bring you programs that promote professional development.

Swati Choksi, Ph.D. (SS)
Chair, Professional Development Committee

The Core Corner

Section Editor: Anne Gegonne, Ph.D. (SS)

High-throughput Imaging to Systematically Study GR Transcriptional Regulation Dynamics in Live Single Cells

Understanding transcriptional dynamics using quantitative imaging techniques has been a major research focus in the Hormone Action and Ontogenesis (HAO) Group led by Gordon Hager, Ph.D. Previous work in our lab demonstrated that glucocorticoid receptor (GR) and many other transcription factors (TFs) involved in transcription regulation are transiently associated with genomic targets, promoters and/or enhancers, proximal to GR-regulated genes[1-3]. It is however unclear how these transient protein-DNA interactions regulate RNA synthesis in a living cell.

To address this question, our laboratory has recently developed a semi-automated, high-throughput imaging assay to measure the dynamics of RNA production in

real time in hundreds of live cells per experimental condition. This assay is based on cell lines where constructs encoding tandem arrays of multiple bacteriophage MS2 or PP7 RNA hairpins are positioned under the control of a GR-responsive promoter. Once these cell lines are stimulated with a GR ligand, the MS2 or PP7 RNA hairpins are transcribed, and they are recognized by their respective MS2 and PP7 coat proteins (MCP and PCP, respectively) labeled with fluorescent proteins such as GFP or mCherry. The accumulation of fluorescently labelled mRNA molecules at the site of active transcription leads to the formation of a fluorescent spot-like signal that can be identified and measured over time. Using this system, Dr. Dan Larson's laboratory in CCR previously demonstrated that transcription is not a continuous process, but is rather composed of short bursts of RNA production. However, it is still currently unclear how transient binding of TFs and chromatin modifying factors regulates mRNA bursting. As an added layer of complexity for the study of GR-regulated transcription, many physiological signals, including glucocorticoid hormones, are pulsatile and subjected to circadian fluctuations, and the effects of these hormone patterns on RNA bursting are unknown. Our aim was to correlate changes in GR dynamics, as measured by a single molecule tracking method, with the changes of the RNA bursting kinetics to better understand glucocorticoid signaling.

"These studies allowed us to reconstruct the real time GR signaling on timescales ranging from days to milliseconds and to relate single cell transcriptional dynamics to glucocorticoid physiology."

To obtain robust statistical estimates of the kinetics of RNA transcription in living cells using the assay described above, we needed to collect and analyze hundreds of RNA intensity traces per experimental conditions, which was simply unfeasible by regular confocal microscopy and generic image processing. For this reason, we teamed-up with Gianluca Pegoraro, Ph.D. and Prabhakar R. Gudla, Ph.D. of the High-Throughput Imaging Facility (HiTIF) at NCI. This fruitful collaboration led to the development and implementation of an automated pipeline for image acquisition and analysis of bursting data using the Yokogawa CV7000 high-throughput microscope and the open-source KNIME software. This integrated image acquisition and analysis platform allowed us to collect hundreds of RNA intensity traces per treatment condition and to acquire data of a quality and quantity which is unmatched by the currently published bursting measurements.

Ultimately, these studies allowed us to reconstruct the real-time GR signaling on timescales ranging from days to seconds and milliseconds and to relate single cell transcriptional dynamics to glucocorticoid physiology. These experiments could not have been possible without the inventiveness and the dedication of our collaborators from the High-Throughput Imaging Facility!

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Gianluca Pegoraro, Ph.D. (SS)
Lab of Receptor Biology and Gene Expression; Head, HiTIF

Diana Stavrera, Ph.D. (SS)
Lab of Receptor Biology and Gene Expression

The PI Corner

Section Editor: Liu-ya Tang, Ph.D. (SS)

Alexander Wlodawer, Ph.D. (center) with (from L to R) Jacek Lubkowski, Ph.D., Alla Gustchina, Ph.D., Maria Miller, Ph.D. and Mi Li, Ph.D.

It has been over 30 years since I first established the Macromolecular Structure Laboratory (MSL) in the former Advanced Bioscience Laboratories (ABL) contract program. The MSL has undergone a number of changes throughout the years, expanding and contracting, but its primary interest has never changed. We have been working on structural studies of a wide range of macromolecules, both proteins and nucleic acids. Some examples include retroviral proteases (including determining the first correct structure of the enzyme from HIV), a number of cytokines and their complexes with receptors, antiviral lectins, proteins involved in ribosome biogenesis, and many others. The aim has always been to combine structural and biochemical information in order to explain how the target macromolecules work and how to use this information for creating better drugs.

The organizational transfer of MSL into the direct intramural NCI program resulted in the change of its name to Macromolecular Crystallography Laboratory (MCL), and in the change of official job titles for some of my close associates. The only Staff Scientist in my research group is Alla Gustchina, Ph.D. (who is also my spouse). Dr. Gustchina is an expert in the interpretation of protein structural data, always finding important new properties hidden in the details that are sometimes not easy to notice. Her principal interest lies in structural studies of proteases, particularly retropepsins such as HIV PR. Maria Miller, Ph.D. who collaborated with me even before my arrival at the NCI, is officially a Biologist (due to some peculiarities of the process of transferring to the government), but in practice functions very independently and is leading a project that involves collaborative studies of the transcription factor C/EBPβ and its interacting proteins.

Three other close collaborators are assigned to the MCL Office of the Chief, but I rely very much on interacting with them very closely. Jacek Lubkowski, Ph.D. is an Associate Scientist who directs our long-term study of the cytokine signaling pathways, as well as trying to figure out the mechanism of action of L-asparaginase, an enzyme that is used very successfully as a drug against leukemia. Mi Li, Ph.D. is a Leidos Associate Scientist in charge of our X-ray diffraction facility who, in his spare time, has solved a large number of macromolecular structures. Finally George Lountos, Ph.D., a Leidos Scientist I, has been working for a number of years on fragment-based screening for new drugs (as a member of the MCL Section headed by David Waugh), but has recently transitioned to the new and exciting field of cryo-EM.

Thus, from my point of view, the independence, intellectual curiosity, and technical ability possessed by my co-workers have been the key factors in making our laboratory successful. I have been privileged to work with colleagues who function very independently and that do not mind telling me to stay out and not interfere with their experimental work in the laboratory. Thankfully they still let me look at, interpret, and discuss the results, of which there are always plenty. One cannot be more lucky.

Alexander Wlodawer, Ph.D.
Chief, Macromolecular Crystallography Laboratory
Senior Investigator

The Author's Corner

Section Editor: Cristina Bergamaschi, Ph.D. (SS)

ONC201 kills breast cancer cells in vitro by targeting mitochondria

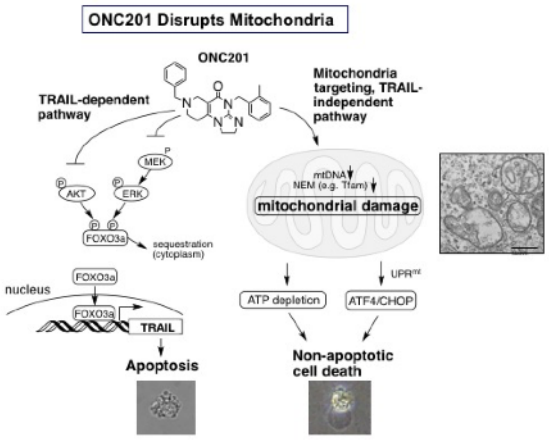
Yoshimi Endo Greer, Natalie Porat-Shliom, Kunio Nagashima, Christina Stuelten, Dan Crooks, Vishal N. Koparde, Samuel F. Gilbert, Celia Islam, Ashley Ubaldini, Yun Ji, Luca Gattinoni, Ferri Soheilian, Xiantao Wang, Markus Hafner, Jyoti Shetty, Bao Tran, Parthav Jailwala, Maggie Cam, Martin Lang, Donna Voeller, William C. Reinhold, Vinodh Rajapakse, Yves Pommier, Roberto Weigert, W. Marston Linehan and Stanley Lipkowitz. Oncotarget, 2018 Apr 6;9(26):18454-18479

ONC201 was originally identified as a small molecule that transcriptionally induces TRAIL gene expression[3]. The mechanism involves inhibition of Akt and ERK, dephosphorylation and stabilization of Foxo3a, leading to TRAIL transcription[3]. Later, two groups reported that ONC201 induces TRAIL-independent cell death via stress mechanisms, involving Activating Transcription Factor 4 (ATF4) and C/EBP-homologous protein (CHOP), although the mechanism remained unclear. Given the interest in TRAIL-induced apoptosis, we obtained ONC201 and started to test the effect in breast cancer cells.

Soon, we faced an unexpected observation. ONC201 effectively killed all types of breast cancer cell lines tested in our lab, however, the mode of cell death appeared to be different from TRAIL-mediated apoptosis. Apoptotic cell death is characterized with a specific morphology called "apoptotic body"; cells shrink, and cell membrane forms budding. Cancer cells treated with ONC201 showed completely distinct phenotype; cell membrane ballooned and eventually ruptured (see Figure). We also did not see any biochemical data that supports caspase-mediated apoptosis. We did, however, observe that ATF4 and CHOP were induced by ONC201.

One day, I wondered if cells are facing "energy deficit" by ONC201. Western blot of AMP-activated protein kinase (AMPK), an ATP sensor, was a game changer. AMPK was significantly induced by ONC201, indicating that cellular ATP level is decreased. There are two sources for cellular ATP; one is glycolysis, the other is oxidative phosphorylation (OxPhos) in mitochondria. When cells were treated with ONC201 in the presence or absence of glucose, cells became extremely sensitive to ONC201 in non-glucose media. This suggested that the drug is targeting mitochondrial respiration.

Next, we confirmed that ONC201 inhibits mitochondrial respiration by Seahorse XF analyzer, although it took 4-6h to see the inhibitory effect, distinct from direct mitochondria-targeting drugs, such as oligomycin or rotenone. Imaging analysis using electron and confocal microscopy demonstrated that ONC201 induces mitochondrial structural and functional damage. Interestingly, time-course analysis with EM suggested that ONC201-induced mitochondrial damage is



detectable as early as 3h (see Figure), and other intracellular organelles, such as Golgi, ER remained intact until much later times (48-72 h). This made us think that ONC201 may specifically target mitochondria, and mitochondrial DNA (mtDNA) is affected. Quantitative PCR confirmed ONC201 depletes mtDNA copy number as early as 3-6 h, while other mitochondria-targeting drugs did not affect mtDNA. Moreover, cells dependent on glycolysis, such as fumarate hydratase deficient cancer cells and mtDNA-

depleted cancer cell lines were all resistant to ONC201. We also found that induction of ATF4 and CHOP was partially due to mitochondrial unfolded protein response. In conclusion, we report that ONC201 has a novel mechanism whereby it disrupts mitochondrial function and results in cell death in breast cancer cells (see Figure).

The exact mechanism how ONC201 depletes mtDNA and leads to cell death is still unknown. The earliest detectable event of this drug is mtDNA depletion and Tfam (mitochondrial transcriptional factor A) protein degradation at 3-6 h, implying that drug has specific effect on mtDNA metabolism.

Our results establish that ONC201 targets mitochondria, and challenge the "Warburg effect", a concept that cancer cells are dependent on glycolysis (reviewed in[4]). Recent studies have led to a new model for understanding the Warburg effect as it applies to tumor metabolism including breast cancer[5]. According to this revised hypothesis, epithelial cancer cells induce the Warburg effect (aerobic glycolysis) in neighboring stromal fibroblasts. The cancer-associated fibroblasts secrete lactate and pyruvate (energy metabolites resulting from aerobic glycolysis) that are taken up by epithelial cancer cells and used as fuel in the mitochondrial TCA cycle, thereby promoting efficient energy production (ATP generation via OxPhos), which enables a higher proliferative capacity. In essence, fibroblastic tumor stroma would directly feed the epithelial cancer cells, in a type of host-parasite relationship (so-called "Reverse Warburg Effect"). This model is still consistent with Warburg's original observation that tumors show a metabolic shift towards aerobic glycolysis. This concept also supports our findings that breast cancer cell lines are dependent on mitochondrial respiration. Our results also predict that the ONC201 sensitivity or resistance may depend on the relative dependence of their tumors on OxPhos or glycolysis, respectively. Mitochondria targeting might extend to other cancers.

ONC201 is currently tested in multiple phase 2 clinical trials, including Women's Malignancies Branch, NCI (NCT03394027). Our aim is to evaluate if ONC201 affects mitochondrial function in breast and endometrial cancer patients and improves clinical outcome.

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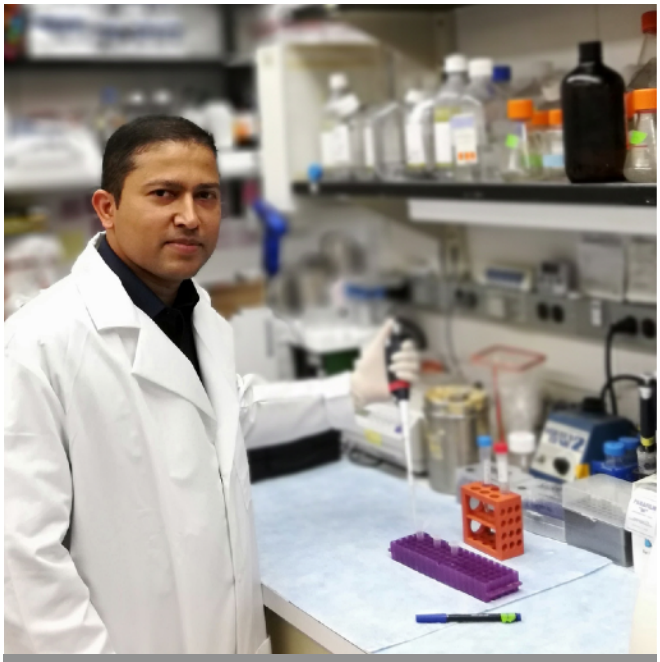
Yoshimi E. Greer M.D., Ph.D. (SS)
Women's Malignancies Branch

Yoshimi E. Greer, M.D., Ph.D., is a Staff Scientist in the Women's Malignancies Branch, NCI. She leads a few core projects in the lab, providing both scientific and technical support to fellows and students. She is actively seeking collaboration opportunities within other NIH or extramural labs. She is interested in supporting the SSSC community, and currently serves as a Bethesda Co-Chair of SSSC organization. She is also involved with the SSSC brown bag seminar series and the SSSC retreat committee.

The SSSC Corner

Section Editor: Takashi Furusawa, Ph.D. (SS)



Devaiah Ballachanda, Ph.D. in the laboratory at the Experimental Immunology Branch

My path to the NIH was a little unconventional since I came with a background in plant sciences and a Ph.D. in plant molecular biology. Soon after completing my graduate work at Purdue University, I started my postdoctoral fellowship in the laboratory of Dinah Singer, Ph.D. at the Molecular Regulation Section of the Experimental Immunology Branch at NCI. Dr Singer's lab studies components of the transcriptional machinery and transcriptional programs that they control. I found her work very exciting as I am fascinated by the complex but elegant transcriptional gene regulatory mechanisms that are often biological equivalents of Rube Goldberg machines. Since my graduate work was on plant transcription factors and I had worked to develop an edible recombinant Rabies vaccine while gaining a MS degree in Biotechnology, my transition to mammalian molecular biology and immunology was fortunately not as intimidating as I had expected.

"The incredibly deep pool of expertise, skills and resources that are available here at the NIH....makes me believe that I am truly privileged to work here."

It is hard to believe that it has been eleven years since I joined Dr Singer's lab, but I still love the work that I do here and the degree of support and intellectual stimulation that Dr Singer offers is key. I became a Staff Scientist in 2014 and continued working here largely due to Dr Singer's amazing mentorship and support. Her unique management style that allows her to be fully engaged in my work while letting me think independently has helped me become a critical thinker and skilled troubleshooter. She has also gave me the opportunity to mentor several younger trainees and postdocs in the lab, helping me develop my management skills. Her encouragement and my work have allowed me to establish numerous collaborations both within NIH as well as across the world. The incredibly deep pool of expertise, skills and resources that are available here at the NIH was the bedrock for establishing these collaborations and makes me believe that I am truly privileged to work here.

Overall, my time in NIH thus far has been a tremendously rewarding and amazing learning experience. My initial work here helped to improve our understanding of the functions of basal transcription factors, demonstrating that these factors played critical, active roles in gene regulation contrary to prevailing dogma. More recently, my work has focused on an important transcription factor called BRD4 that has been identified as a therapeutic target in over a dozen different types of cancers ranging from colon cancer to AML. Working with Dr. Singer, I was able to demonstrate that BRD4 is both a novel kinase as well as a histone acetyltransferase which controls transcription and chromatin architecture. My current work continues to explore this fascinating, multifunctional protein.

Outside the lab, my favorite hobbies include gardening and traveling. Although my work veered away from plants, I continue to nurse a 'green thumb' at home and spend my weekends experimenting with interesting fruit and berry plant varieties in my backyard orchard. My wife, who is an architect, and I also enjoying traveling whenever we get a chance. The diversity and beauty of the places we visit helps keep our creative juices flowing!

Devaiah N. Ballachanda, Ph.D. (SS)
Molecular Regulation Section
Experimental Immunology Branch

Dr. Ballachanda with his wife on a recent trip to Iceland

The Personal Development Corner

Section Editor: Brunilde Gil, Ph.D., M.P.S. (SS)

When Western Science Meets Eastern Philosophy

On March 7th, 2014, more than 3,000 NIH employees were glued to the NIH videocasting website, mesmerized by an inspiring dialogue between His Holiness the 14th Dalai Lama and Francis Collins, M.D. Ph.D., director of the NIH. Witnessing and celebrating the merge of two different cultures, we all partook in this symbolic and heartwarming conversation. We need Eastern wisdom and contemplative practices to permeate our western world to counterbalance our fast-paced, self-centered, goal-oriented culture.

Contemplative traditions, such as Buddhism, emphasize the importance of training the mind through meditation. "***If you want to change the quality of your conscious experiences, change the quality of your mind.***"- Segyu Choepel Rinpoche, internationally renowned Tibetan Buddhist master. These meditative practices are grounded on specific values such as compassion and acceptance and on keen observation of our reality; understanding the everchanging nature of our experiences and the interdependence of every phenomenon. Training the mind and integrating those principles provide an inexhaustible fountain of healing properties.

Eastern philosophy and meditative practices have colored our western culture through self-help books, pop culture, wellness centers and clinical interventions. From managing daily pressure to treating mental health disorders, meditative practices have been the underpinnings of the most successful psychological interventions[1]. One of the first and most successful adaptions of eastern meditation is the mindfulness-based stress reduction (MBSR) program, an 8–10-week course, developed by Jon Kabat-Zinn Ph.D., and colleagues[2]. Dr. Kabat-Zinn defines mindfulness as "***the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment***"[2]. We often go through our day accumulating tasks and running

from one place to another while being barely aware of what we are doing. We forget to be present, to just be. Mindfulness meditation trains us to observe the stream of a conscious moment after conscious moment. It is the antidote to the autopilot and to our incessant digressive thoughts.

The benefits of mindfulness meditation have been evaluated and highlighted in different contexts: anxiety, depression, stress, chronic pain, high blood pressure, substance and alcohol abuse[1-4]. More interventions are under investigation. I was fortunate to be one of the therapists in a study using Breathing-Based Mindfulness Therapy (BBMT), a 9-week program delivered to college students to help them adjust to the competitive academic world. The BBMT was developed by and has been delivered at The Center for Addictions, Personality, and Emotion Research (CAPER), University of Maryland, College Park, MD. I could see firsthand the excitement of undergraduates learning about mindfulness and breathing techniques giving them concrete tools to manage their stress and emotions. Hopefully, this study will lead to an effective program for college students.

Biological correlatives supporting the efficacy of mindfulness meditation have been investigated. In 2016, Richard J. Davidson, Ph.D., Professor of Psychology and Psychiatry, at the University of Wisconsin Madison, was invited at NIH to present the 7th annual Stephen E. Straus Distinguished Lecture in the Science of Complementary Therapies. Dr. Davidson presented his work entitled "Change Your Brain by Transforming Your Mind", in front of a captivated crowd in the Masur auditorium. Interestingly, he showed that individuals randomized to the 8 weeks mindfulness-based stress reduction (MBSR) program presented a stronger immune response when challenged by flu vaccine[5].

Mindfulness training at the NIH

- Mindfulness sessions through OITE
- Mindfulnesss Based Self Care program (MBSC) through FAES

Meditative practices aim at training attention. The ability to focus sharply in the present is a key aspect to improve cognitive function[6] and emotional balance. A famous illustration of meditative practices was developed by George Lucas and is called Use the Force! No misleading, though. You won't become Buddha or Yoda in a few weeks, not even years. This is a lifetime practice. *Realistically*, an achievable goal would be using your concentration to lift your spaceship out of the mud.

In addition to those cognitive abilities illustrated by George Lucas, Mindfulness Meditation (MM) stabilizes your emotions. MM teaches us how to stop being a slave of our emotional triggers and conditioned experiences. This is to me the most important benefit of MM (with the ability to lift your spaceship, of course!). This faculty is best summarized in a quote from Viktor E. Frankl, M.D. Ph.D. (yes, Dr. Frankl again, for those of you who read the June 2018 issue) "***Between the stimulus and the response there is space. In that space is our power to choose our response. In our response lies our growth and our freedom***." Just a small comment can trigger anger and we react violently, damaging our relationships by losing trust and credibility. Our culture has normalized aggressive behaviors (drive on the beltway and you will feel it). For most of us, the space between the trigger and the response is infinitesimal and imperceptible. The purpose of mindfulness meditation is to increase that space, to create the mental and temporal space to choose our response to challenging situations. We distance ourselves from our own impulses and from the emotional reaction of our interlocutor. Doing what pleases us and following our impulses is the least form of freedom. It is just repeating behaviors bypassing consciousness. Freedom is about breaking the habits of these conditioned experiences. "***Through discipline comes freedom***" - Aristotle. Again, this ability requires time and discipline. I have been a meditation practitioner for several years and I still find myself falling into the traps of emotional triggers. Sadly, behaving ungracefully, it can take me weeks to claw my way out to the surface and regain a sense of decency. But, I do it less frequently…hopefully. Interestingly, or scarily, as we become more mindful about our behaviors, we start seeing the depth of our toxic

impulses and self-embarrassing patterns; it is overwhelming. If it happens to you too, do not despair, you are on the right track! Because even if we are just discovering it now, I can assure you that everyone else has been seeing it for a while. So, we might as well be aware of it to start working on it .

As I always emphasize, the resources offered by the NIH are countless and we are fortunate to have dedicated and skilled health providers offering mindfulness training to the NIH community: Rezvan Ameli, Ph.D., from the NIH Pain and Palliative Care Services, and Michael Sheridan, Ph.D. and Julia Jarvis, MDiv. from the NIH Office of Intramural Training & Education (OITE). Dr. Sheridan and Mrs. Jarvis provide mindfulness sessions through OITE twice a week. Dr. Ameli offers a Mindfulness Based Self Care (MBSC) program[7] through the Foundation for Advanced Education in the Sciences (FAES) and has recently developed an abbreviated version of the program to adapt to our busy schedule.

In his dialogue with Dr. Collins, the Dalia Lama emphasized the importance of a communication between science and religion and appreciated the "immense benefit of learning from science." I am returning the sentiment by highlighting the immense benefits of learning from eastern philosophy.

Chose freedom, train your attention!

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