THE DOSSIER

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

March 2018 Issue 31

From the Editor

Welcome to the March issue of The Dossier, a newsletter dedicated to the Staff Scientists and Staff Clinicians (SSSC) of CCR!

This issue contains information from Tom Misteli, Ph.D., Director, CCR, along with Douglas Figg, Pharm.D., and Patricia Steeg, Ph.D., Co-Associate Directors of CCR's Office of Translational Research, and an overview of the upcoming Annual SSSC Retreat by the 2018 Co-Chairs Abdul Waheed, Ph.D., and Yoshimi Greer, M.D., Ph.D. In our Quad Corner, Cynthia Masison, Ph.D., provides updates on the nomination process for Associate Scientist and Senior Associate Scientist positions, while in our PI Corner, Joost J. Oppenheim, M.D., discusses the important roles of his Staff Scientist, De Yang, M.D., Ph.D. We also highlight the published work of H. Diego Folco, Ph.D., in our Author's Corner. Meanwhile, in our Clinical Corner, we obtain the viewpoints of Fatima Karzai, M.D., on several aspects of the Staff Clinician position and in our Core Corner, Raj Chari, Ph.D. describes the newly launched Genome Modification Core. We are also pleased to introduce our new Section Editor, Brunilde Gril, Ph.D., M.P.S., who will focus on articles covering personal development in relation to workplace potential. We hope to continue to provide pertinent information to aid in the success of SSSCs. Please send your contributions, suggestions and comments to budhua@mail.nih.gov.

Anuradha Budhu, Ph.D. (SAS)
Editor-in-Chief
Laboratory of Human Carcinogenesis

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The Office of the Director: Guest Editorial*

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

CCR's Office of Translational Resources

The translation of basic research into clinical applications is a high priority for the CCR. While we have a long history of creating important clinical advances from the laboratory, it is often a long and challenging path that requires diverse expertise. In October 2017, the CCR Office of Translational Resources (OTR) was created to provide support for CCR scientists navigating this process. The mission of the OTR is to facilitate the rapid translation of advances in laboratory and clinical research into successful therapeutics and treatments for cancer.

An important goal of the OTR is to provide advice and assistance to CCR scientists to facilitate translation of promising basic research into preclinical models and ideally into the clinic. Key to this objective is the Drug Development Consortium (DDC), which serves as a scientific advisory group for the OTR. The DDC is comprised of 18 scientists with diverse areas of expertise spanning basic, translational and clinical research. Topics addressed by the DDC include genetics, pharmacology, immunotherapy, antibody engineering, drug formulation, dose and schedule, preclinical animal modeling, molecular targets, peptide design, as well as medical and radiation oncology. Scientists seeking guidance in moving basic discoveries towards preclinical and clinical studies present their data to the DDC for discussion. The group then offers specific recommendations on both practical and strategic aspects of the project, including experimental design, sources of technical and financial assistance, as well as advice on "Go-No Go" decision points. The DDC can also provide limited discretionary funding for projects of promise, as well as access to some laboratory or contract resources for work significantly beyond the capabilities of the PI and his/her collaborators. In addition, the DDC reviews and guides more advanced projects with well-developed preclinical data for potential clinical testing. These projects are then presented to the CCR Director for discussion of possible future directions and potential funding options.

A major challenge for scientists seeking to expand their work into the clinic is identification of academic and commercial partners to expedite the process. To help PIs clear this hurdle, the OTR is working with the NCI and NIH Technology Transfer Centers (TTC) to facilitate commercial partnerships. Sabarni Chatterjee, Ph.D., serves within the OTR as the CCR liason with the TTC to work on issues of over riding importance, such as patent licensing, and monitoring licensee progress.

Another key goal of the OTR is providing CCR scientists with information on translational resources within the CCR, the NCI, the NIH and/or the extramural community. The OTR will sponsor seminars and workshops on technologies important to drug development and translational studies. The OTR will also serve as a hub for diverse translational programs within and outside NIH, including at the National Center for Advancing Translational Sciences (NCATS), the NCI Division of Cancer Treatment and Diagnosis (DCTD), the NIH Foundation, the CCR Center for Advanced Preclinical Research (CAPR) and others. An expanded webpage for the OTR, that will offer information to CCR PIs on translational resources, is currently in development.

In summary, the OTR is envisioned as a one-stop resource for CCR drug development and translational initiatives that will offer PIs project-by-project advice

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The Office of the Director: Guest Editorial Con't

and practical help. More information can be found at the OTR webpage. Please contact Diana Linnekin for information on the OTR, or if you are interested in making a presentation to the DDC for input on a project and/or consideration for resources.

Douglas Figg, Pharm.D.
Co-Associate Director, OTR

Patricia Steeg, Ph.D.
Co-Associate Director, OTR

Tom Misteli, Ph.D.
Director, CCR

The Quad Review Corner

Nominating Associate and Senior Associate Scientists

Starting this year, the Office of the Director has implemented a new nomination process for Associate Scientist (AS) and Senior Associate Scientist (SAS) positions.

The AS and SAS positions were created in 2006 to provide professional recognition of Staff Scientists who function at a senior level. NIH mandates that each of these titles are no more than 10% of the total number of Staff Scientists in the IC. AS/SAS are Staff Scientists who play a variety of critical roles within the CCR. To be considered for an AS/SAS position, the Staff Scientist should demonstrate a substantial record of achievement, play a major role within their research program, have made major contributions to peer-reviewed publications in journals generally acknowledged to be of high quality, and be highly regarded by peers. For example, AS/SASs are frequently called upon as experts by outside institutions, are invited to give seminars at research institutions and national meetings, and/or serve on grant study sections. In addition, the candidate should have received an "Outstanding" rating by the CCR Quadrennial Review Panel. For SAS, in addition to fulfilling the requirements for an AS, a candidate must have made contributions that significantly promote the mission of the NCI or other IC's, participate in the work of NCI or NIH committees, made significant methodological or other contributions to the scientific literature, may be required to supervise doctoral-level

The Quad Review Corner Con't

staff, and received an "Outstanding" rating by the CCR Quadrennial (Quad) Review Panel in consecutive reviews.

While AS and SAS will be expected to engage in active research, they will also be expected to devote upwards of 10% of their time to service to NCI/CCR, bringing their scientific expertise to a number of different areas. These activities may include committee membership and participation (e.g. animal care, IRB, ad hoc committees), teaching/lecturing in CCR-sponsored courses, hosting speakers in the CCR seminar series, attending and participating in the PI retreat, participating in Centers of Excellence, Working Groups, and Faculty activities, representing CCR at on- and off- campus meetings as necessary, and performing any other activities at the request of the Director.

In the past, Staff Scientists were nominated by their Lab/Branch Chief at any time during the year. The nomination package was submitted to the CCR ARC and then presented by the assigned CCR Deputy Director to CCR Senior Leadership who then made the final decision on the promotion.

The new process is designed to reduce the administrative burden and streamline the process while staying fully compliant with the NIH title limits. In this new process, AS/SAS nominations will only be reviewed in March in conjunction with the Staff Scientist Quadrennial Review. For nominations outside the Staff Scientist Quad Review, nomination packages need to be submitted to the CCR ARC before March 1st. The Promotion Review Panel will make recommendations for titling of the Staff Scientists being evaluated during the regular quadrennial review. The Panel will notify the Lab/Branch Chief before the recommendations are returned to the CCR ARC to ensure the Lab/Branch Chief is supportive. The CCR ARC will determine how many slots are available to fill. All applications will be evaluated together by CCR Deputy Directors and Scientific Directors and final title determinations made. This new process will ensure a fairer, streamlined review of nominations and will allow CCR to more efficiently recognize and appoint deserving Staff Scientists to AS or SAS positions.

Cynthia Masison, Ph.D.
Scientific Program Officer,
Office of the Director

The 14th Annual SSSC Retreat

The National Cancer Institute's Center for Cancer Research (CCR), Division of Cancer Epidemiology and Genetics (DCEG), and the Frederick National Laboratory for Cancer Research (FNLCR) will hold the annual Staff Scientist and Staff Clinician retreat on April 6, 2018 at NCI Shady Grove. The theme of this year's retreat is "Cutting Edge in Cancer Research: Cancer Immunotherapy" a rapidly advancing field in the treatment of cancer. We invite all SSSCs to submit abstracts and participate in poster sessions.

The morning session will start with a keynote presentation by Steven Rosenberg, M.D., Ph.D., Chief of Surgery Branch and Head of the Tumor Immunology Section, CCR. Dr. Rosenberg's pioneering work in the development of the first effective immunotherapies for patients with advanced cancers. Dr. Rosenberg's presentation will be followed by short visionary

The 14th Annual SSSC Retreat Con't

talks by top experts in the field of cancer immunotherapy: Nicholas P. Restifo, M.D., Senior Investigator, Surgery Branch, CCR; Ira Pastan, M.D., Head, Molecular Biology Section, CCR; James Hodge, Ph.D., Senior Investigator, Laboratory of Tumor Immunology and Biology, CCR; and Louis Weiner, M.D., Director, Georgetown Lombardi Comprehensive Cancer Center, Georgetown University. The panel discussion will be moderated by Claudia Palena, Ph.D., Senior Investigator, Laboratory of Tumor Immunology and Biology, CCR. The panel discussion will be highly interactive, informative, and explore the kinds of challenges facing immunotherapy development for different types of cancer. So, to make the retreat exciting, please bring your burning questions.

In the afternoon, there will be two poster sessions. This year, the time for poster sessions has been extended to provide more opportunities to interact and build networks with SSSC colleagues. Each poster will be judged by poster judges, and the top three posters will win travel awards. Following the poster sessions, there will be oral presentations from SSSCs. All submitted abstracts will be judged by Principle Investigators at NCI, and the top five abstracts will be selected for oral presentations. The best oral presentation will be awarded a travel award. In addition, there will be outstanding mentor awards to SSSCs selected from submitted nominations.

Please note that abstracts are not limited to *Cancer Immunotherapy*. Any subject belonging to one of the following three categories are welcome: Basic Research; Translational, Clinical & Epidemiological Research; Technologies & Methodological Development. SSSCs can bring one NCI colleague to the retreat, so, bring along your lab mates/postdoc/postbac/student.

Please mark the date on your calendars: April 6, 2018. For details please, visit the website: https://ncifrederick.cancer.gov/events/SSSCRetreat2018/default.asp

We look forward to seeing you at the retreat!

Abdul Waheed, Ph.D. (SS)
& Yoshimi Greer, M.D., Ph.D. (SS)
Co-Chairs, SSSC Retreat 2018

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The PI Corner

Section Editor: Lakshmi Balagopalan, Ph.D. (*SS*)

De Yang, M.D., Ph.D., is currently the Staff Scientist in my laboratory. Dr. De Yang left China after the events at Tiananmen Square and obtained his Ph.D. training in Japan. He joined my lab in Frederick in 1998 and already in 1999 published the pivotal observation in *Science* showing that human defensins utilize the CCR6 chemokine receptor. This provided the most convincing evidence for our hypothesis that antimicrobial peptides (AMP's) had a second major function of activating immune cells by interacting with receptors on host dendritic cells (DCs).

Dr. Yang progressed from the rank of Visiting Scientist to becoming an SAIC contract scientist from 2002 – 2015 and subsequently a Staff Scientist. During this period, Dr. Yang showed that a variety of neutrophil granule-derived proteins participated in enhancing both innate and adaptive immune reactions. This included proteins such as cathelicidin (LL37), which activated FPRL1 receptors on inflammatory neutrophils and monocytes, but also on immune T cells. Ironically, in 2003, Dr. Yang even documented that many chemokines also showed antimicrobial activities. By 2004, Dr. Yang and I realized that a number of constitutively available cellular proteins that were rapidly released in response to infectious insults or cellular injuries not only chemoattracted, but also activated immune cells, and we termed these first responders, alarmins. This concept was also of great interest to surgeons since it suggested that immune responses to cell injuries emulated the responses to invasive organisms.

The most recent phase of Dr. Yang's research began with the observation that HMGB1, even though it is a chromatin binding gene activating protein, acts as an extracellular alarmin activator of DCs. This led us to test another chromatin binding protein, HMGN1, kindly provided by Michael Bustin, Ph.D., of the NCI. Dr. Yang observed that it also had alarmin activity and that like many of the alarmins, HMGN1 activated one of the Toll-like-Receptors (TLR4). Since HMGN1 resulted in potent activation of DCs, we chose to determine whether its immunoadjuvant effects resulted in potent antitumor activities.

Dr. Yang was encouraged to find that mice engineered to have defective HMGN1 genes were immuno-deficient and supported more rapid tumor growth than normal control mice. Conversely, tumor cells transfected to overexpress HMGN1 were more rapidly rejected than untransfected tumor cells. In addition, Dr. Yang found that immunizing mice with

Joost J. Oppenheim, M.D., is pictured alongside Staff Scientist, De Yang, M.D., Ph.D.

HMGN1 linked to a tumor antigen prophylactically protected them against tumor challenge. However, therapeutic intratumor injections of HMGN1 only slowed tumor growth a little bit, which was very disappointing. Consequently, Dr. Yang decided that a cocktail of immunological reagents would be needed to cure cancer in mice. Dr. Yang therefore screened various combinations of TLR stimulating ligands and determined that a ligand of TLR7/8 known as R848 (Resiquimod) together with the TLR4 ligand, HMGN1, had the most synergistic immunostimulating effect. Intra-tumoral injection of this combination together with a checkpoint inhibitor, such as anti-PD-L1 or anti -CTLA4 or suppression of T regulatory cells by Cytoxan, cured mice bearing large (1cm. Diameter) tumors of the colon (CT26), thymomas (EG7), kidney (RENCA), liver (Hepal-6) and lung (LL). The cured mice were immune and selectively resisted challenges with injections of the same tumor several months later.

I have summarized Dr. Yang's remarkable achievements at the NCI over the past 20 years. He continues to fine-tune our results in an effort to justify our hope that our treatment regimen will be tried on cancer patients and that they will respond as well as the mice. His career beautifully illustrates how basic and translational research are inextricably intertwined, just as Principal Investigators and their Staff Scientists.

Joost J. Oppenheim, M.D.
Senior Investigator and Head,
Cell Immunology Section
Cancer and Inflammation Program

Untimely Expression of Gametogenic Genes in Vegetative Cells Causes Uniparental Disomy

Folco H.D., Chalamcharla V.R., Sugiyama T., Thillainadesan G., Zofall M., Balachandran V., Dhakshnamoorthy J., Mizuguchi T. & Grewal S.I. *Nature* 543, 126-130.

Somatic cells in our bodies contain one set of chromosomes from the father and one set from the mother. Uniparental disomy (UPD) occurs when a cell has two copies of a given chromosome from one parent and none from the other parent. First proposed by Eric Engel in 1980, this frequent phenomenon occurs in approximately 1 of every 3,500 live births and is receiving increasing attention because of its association with numerous recessive disorders and with cancer[1]. Indeed, UPD may lead to the duplication of recessive or imprinted genes and it is a main cause of loss of heterozygosity (LOH), one of the hallmarks of cancer cells. UPD is believed to result mostly from pre- or post-zygotic chromosome missegregation events, however, the molecular factors (e.g. mutations, aberrant gene expression) that trigger UPD have remained largely unknown. In a recent paper, H. Diego Folco, Ph.D., Staff Scientist in the Laboratory of Biochemistry and Molecular Biology headed by Shiv Grewal, Ph.D., and collegues describe the establishment of various genetic and imaging assays for detecting UPD in the highly tractable fission yeast *Schizosaccharomyces pombe*, which resulted in the first identification of causative factors (i.e. untimely expression of gametogenic genes) for this chromosomal anomaly (*Figure 1*).

The genetic tractability and small karyotype of fission yeast, which contains only three chromosomes, provide an outstanding model for studying chromosome

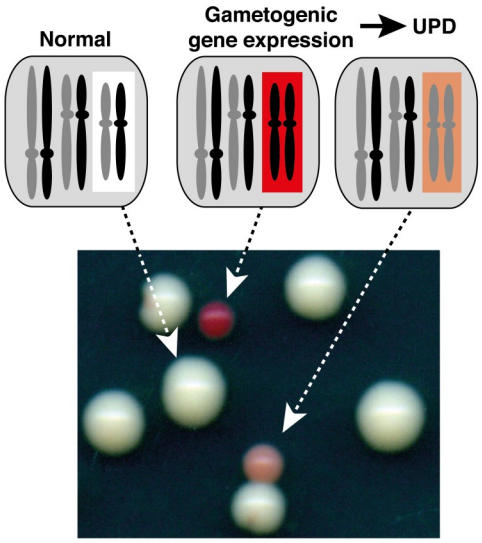

Figure 1. Normal diploid eukaryotic cells contain two copies of each chromosome - one from each parent. UPD occurs when cells contain two copies of a given chromosome from one parent and none from the other parent (e.g. chromosomes highlighted in "red" or "pink"). Using this genetic assay, UPD in fission yeast is indicated by colony color (white: normal; red or pink: UPD), and is triggered by aberrant expression of gametogenic genes in cells lacking RNA processing factors.

segregation. The centromeres are coated in heterochromatin targeted by the RNA interference (RNAi) machinery, and resemble the typical repetitive arrays of higher eukaryotic centromeres[2]. Once gametogenic commitment occurs, normal gametogenesis in the fission yeast requires the induction of a number of tightly regulated genes. During mitotic proliferation, these genes are suppressed at the transcriptional and posttranscriptional levels through a RNAi- and exosome-dependent pathway controlled by the YTHDF protein Mmi[3].

Recently, we noticed that RNAi-deficient mitotic cells (with aberrant levels of gametogenic mRNAs) exhibited chromosome mis-segregation events, including high levels of UPD. Because RNA1 also plays a role in assembling centromeric heterochromatin to allow

proper chromosome segregation, we wondered which one of those two processes (i.e. gametogenic genes or heterochromatin assembly) was linked to the UPD phenotype. We examined Mmi1-deficient cells that are defective in silencing gametogenic genes but display normal heterochromatin assembly. Remarkably, those yeast cells still developed UPD, indicating that abnormal expression of gametogenic genes triggers the chromosomal anomaly. This result was unexpected because it is logical to assume that problems with heterochromatin assembly were likely causing UPD.

Next, we identified the gene responsible for UPD by genome wide transcriptional and genetic analyses. Deletion of the upregulated gene encoding the meiotic cohesin Rec8 suppressed the UPD phenotype in both RNAi and *mmi1* mutants. We also discovered that when Rec8 was overexpressed in otherwise normal somatic cells, UPD occurred at high frequency. We found that Rec8 expressed in those cells localizes to centromeres where it is required for localization of the cohesin subunit Psc3. In meiosis I, Rec8 is required for centromere mono-orientation. Thus, the untimely localization of meiotic cohesins Rec8 and Psc3 at mitotic centromeres may promote mono-orientation of sister kinetochores resulting in reductional segregations and subsequent UPD.

Our findings open up the possibility that the activation of only a single gametogenic factor (i.e. REC8) can potentiate an oncogenic transformation, and might lead to the development of drugs that disrupt REC8 function in humans. In this regard, it was proposed that REC8 may drive therapeutic resistance in tumors by inducing "pseudomeiotic" chromosome segregation events that enable endopolyploid tumors to survive genotoxic treatment[4]. Finally, this study may advance the application of UPD as a "chromosome therapy" tool for the correction of chromosomal aberrations[5]. In this futuristic scenario, UPD would be induced in patients to eliminate chromosomes with erroneous genetic information and replace them with normal counterparts.

H. Diego Folco, Ph.D. (SS)
Chromosome Biology Section
Laboratory of Biochemistry and Molecular Biology

H. Diego Folco, Ph.D., is a Staff Scientist in the Chromosome Biology Section of the Laboratory of Biochemistry and Molecular Biology, Center for Cancer Research. His role as a Staff Scientist includes leading studies on chromosome segregation, the results of which are highlighted in the aforementioned study, and developing genetic screens to open up more avenues of research within the lab. Additionally, he supervises students and actively contributes to the mentoring of Postdoctoral Fellows by providing both scientific and technical training.

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The Clinical Corner

Section Editor: Alexandra Zimmer, M.D. (*SC*)

Getting to Know our Staff Clinicians

The main goal of this section is to increase the participation of Staff Clinicians, and make their work better known at NIH. In this issue, we interview our Staff Clinician, Fatima Karzai, M.D., to hear perspectives about her work and collaborations at NIH.

An Interview with Fatima Karzai , M.D.

What is your general role as Staff Clinician?
I am a Staff Clinician in the Genitourinary Malignancies Branch, where I began my clinical research career at the NCI as a fellow in the Medical Oncology Service under the mentorship of William Dahut, M.D. and James Gulley, M.D., Ph.D. I was fortunate to be able to stay to continue my research projects as a Staff Clinician. I have an active role in patient care, which encompasses a wide variety of responsibilities including overseeing patient safety on our studies, managing clinical complications and adverse events, and supervising our weekly clinic as the Clinic Chief. I also am involved in clinical protocol development and implementation from conception to active clinical trial. As a Staff Clinician, I also attend meetings, both national and international, to present data and publish manuscripts. My role also involves working closely with our team's research nurses, patient care coordinators, and other clinicians/mid-level providers, who are all integral to our commitment to our patients.

Could you point out steps and difficulties to implement a clinical trial?
Clinical trial implementation is a unique and mostly rewarding process. The NIH affords the intramural research program the opportunity to be able to pursue novel therapeutic approaches that may not be easily implemented in the outside world. Difficulties include moving ideas from bench to bedside quickly. Once a clinical trial has been approved through the appropriate regulatory and administrative bodies, patient accrual and retention can be problematic for some studies. Collaborations need to be fostered in the academic community to accrue and complete trials in order to potentially achieve and/or enhance scientific breakthroughs.

What is your contact with Staff Scientists? Any report of cooperation from bench to bedside?
Our team works closely with Staff Scientists both in the Molecular Pharmacology Section and with the Laboratory of Tumor Immunology and Biology. Many of our clinical studies have a foundation in pre-clinical research or have been enhanced by the work of Staff Scientists.

How do you see patient care at NIH? Can you give examples of benefits and limitations?
Patient care at the NIH is incredibly rewarding to me as a clinician. Our patients are given specialized care for their disease. The benefits include utilizing a team approach to take care of patients and utilizing the resources we have available here at the Clinical Center to ensure that we provide the best and most comprehensive care possible. As an oncologist, one of the main limitations I encounter is not having an appropriate clinical trial available for a patient who is in need of treatment and has exhausted standard of care options.

What is the career path of a Staff Clinician? Where do they go from here?
The career path of a Staff Clinician is as varied as Staff Clinicians themselves. Staff Clinicians are afforded the opportunity to develop and enhance their careers here at the NIH by expanding their leadership roles and responsibilities within their areas of expertise. It is important to have career goals for yourself to be able to flourish in your role. Whatever you determine your career trajectory is, you can develop the necessary skills as a Staff Clinician to help achieve it.

The Clinical Corner Con't

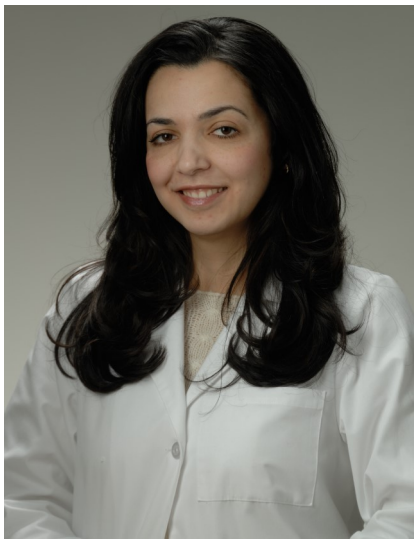
Section Editor: Alexandra Zimmer, M.D. (*SC*)

Any final advice for new Staff Clinicians or about collaboration between Staff Clinicians and Staff Scientists?

It is important to determine what you want from your time as a Staff Clinician and not be afraid to pursue your ideas. This is especially important when considering collaborations. Collaborations are beneficial to all parties involved and should not be limited. Explore all that is available to you and don't be hesitant to ask for help.

Have you identified any differences or challenges in being a woman scientist? Any specific advice to other young women starting in that path?

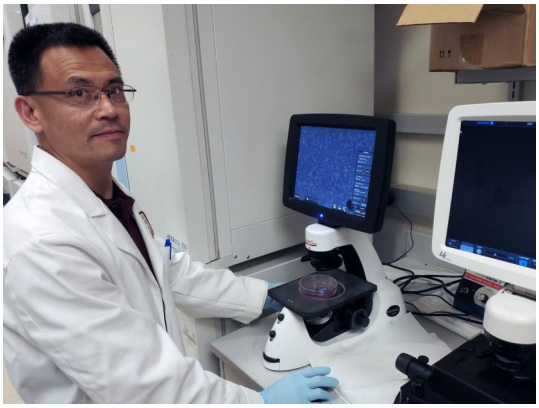
There are both differences and challenges in being a female in science. While women have made great strides in science, it is imperative for all to realize that there is still more that can be done to foster opportunities and recognition for women. As women scientists, we must be proactive and make our voices heard. I think it is very important that those who are starting out identify junior and senior female mentors that can help guide them.



Fatima Karzai, M.D. (SC)
Director, Prostate Cancer Clinic
Genitourinary Malignancies Branch

The SSSC Corner

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



Cutting edge science is being done at NCI; and that is exactly the case in the laboratory of Len Neckers, Ph.D. In the mid-1990s, Dr. Neckers and his colleagues found that geldanamycin, an antibiotic, inhibited the growth of cancer cells by binding to the molecular chaperone Hsp90, instead of kinases, as it was thought at the time. Their work started a totally new avenue for cancer chemotherapy.

I joined Dr. Neckers' lab as a Postdoctoral Fellow after obtaining a Ph.D. from the University of Maryland, Baltimore, and took on the question of how client kinases are degraded upon Hsp90 inhibition by geldanamycin. As a molecular chaperone, Hsp90 was known to interact with proteins, so called clients and many of them are cancerous protein kinases. It was postulated that this interaction protects the clients from degradation. Interestingly, not all the proteins depend on Hsp90 for their stability; and in some cases, highly homologous proteins show divergent dependence, exemplified by Epidermal Growth Factor Receptor (EGFR) and its closely related family member HER2. While HER2 is very sensitive to Hsp90 inhibition, mature EGFR protein is resistant to geldanamycin-induced protein degradation. Using my techniques and knowledge in molecular biology, I

pinpointed the molecular details that determine the distinct dependence of HER2 on Hsp90, revealing the mechanism, on the molecular level, of why a client kinase relies on the chaperoning function of the Hsp90 machinery while others do not. I further discovered that upon inhibition by geldanamycin, Hsp90 disassociates from HER2 protein. Along with the disassociation of Hsp90, HER2 binds another chaperone, Hsp70, which brings along CHIP, a ubiquitin ligase. CHIP then mediates the ubiquitination of the HER2 protein, leading to its targeting to the proteasome where it is degraded. These findings unraveled a paradigm that was later proved to be true for many other client proteins of Hsp90, and provided therapeutic targets for cancer treatment.

In recent years, I have shifted my research focus to Hsp90, more specifically, to the post-translational modification (PTM) of Hsp90 and how PTMs modulate the chaperone function. Hsp90 assists its clients by going through an ATP-driven conformational cycle, which is further tuned by co-chaperones that either modulate the ATPase activity or the formation of the complex. We postulated that PTMs may regulate Hsp90 function by affecting these aspects. Indeed, my work showed that Hsp90 undergoes phosphorylation, and phosphorylation on one tyrosine residue facilitates the interaction of the co-chaperone Aha1, which stimulates the ATPase activity, while phosphorylation on another tyrosine promotes the dissociation of Aha1 as well as the client protein. Together, these phosphorylation events help to drive the progress of the Hsp90 conformational cycle, thus the chaperoning function. Besides phosphorylation, Hsp90 also undergoes acetylation, sumoylation, nitrosylation, and ubiquitination. I am actively involved in pursuing the significance of these PTMs in our lab.

Wangping is pictured above with his family

Back at home, I enjoy music of different genres; classic, pop, and folk songs. Cooking is my newly found hobby. It's satisfying to see my children enjoying my work, and my wife having something other than her own preparations. Maybe, someday I will bring my experimental edge from the lab to the kitchen; it would be interesting to see what will come out from the oven or pan.

Wanping Xu, M.D., Ph.D. (SS)
Urologic Oncology Branch

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The Genome Modification Core (GMC) at the Frederick National Lab for Cancer Research

CRISPR/Cas9 technology has allowed for the unprecedented ability to edit the endogenous genome of many different organisms (Figure 1) [1]. Moreover, the technology is rapidly developing; from simply knocking out an individual gene to making targeting replacements and to now, editing RNA transcripts in a highly specific manner [2,3]. Thus, it can be incredibly overwhelming for any investigator to keep up with this technology while keeping up with their own research area. The Genome Modification Core (GMC) aims to provide advice, reagents, and services to all investigators within the CCR. Since the core is new and recently launched, this has been formatted into a more Q and A type format.

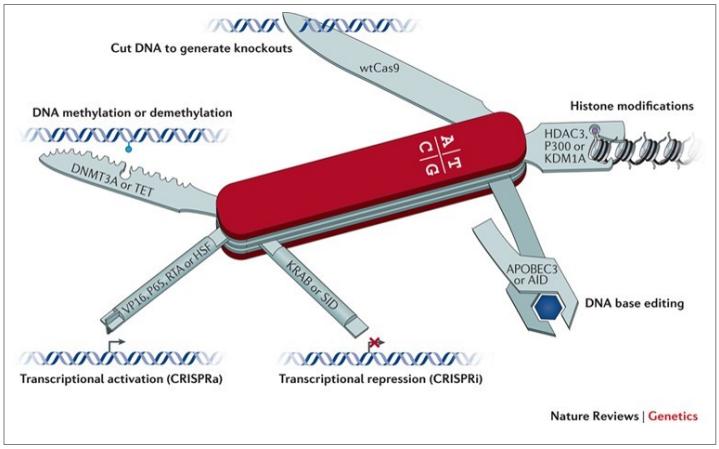

Figure 1. The wide variety of functionalities emanating from CRISPR/Cas. Adapted from Doench,8, Nature Reviews Genetics [4].

Who are we?

We are one of a number of cores within the Laboratory Animal Sciences Program (LASP) at the Frederick National Lab for Cancer Research (Figure 2). Our cores work closely together, allowing our investigators to have a smooth, seamless experience. The GMC, specifically, works closely with the Mouse Modeling and Cryopreservation Core (MMC) and Animal Diagnostics Laboratory and Genotyping Core (ADL) to produce validated mouse models.

How are we staying current?

To remain at the forefront of this field, the GMC utilizes a three-pronged approach. First, we attend the main meetings and conferences for the field as well as stay up-to-date with published literature. Second, we have forged collaborations with other labs, in industry and academia, to gain early access to technologies. Finally, we are heavily focused on technology development where we are developing new tools and approaches which will be useful to the CCR investigator community.

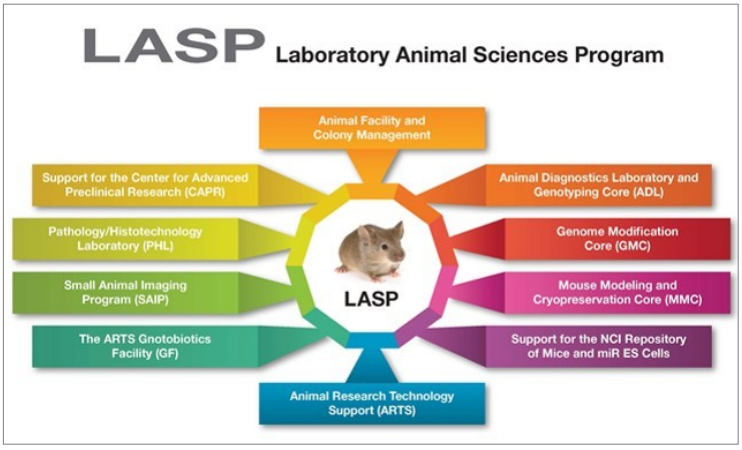

Figure 2. Cores within the Laboratory Animal Sciences Program at the Frederick National Lab for Cancer Research

What services are we currently providing?

We were first established in the middle of August and have been fully functional since the middle of December 2017. We currently offer the following services:

Consulting (no charge) - New to CRISPR? Want to know how to design these experiments? Which approach to use? We are here to help! Feel free to email or call (see contact information below) to set up a time to meet. Meetings can be held at either the Bethesda campus, Ft. Detrick or at the ATRF in Frederick.

Single locus editing - The most basic service we provide is the ability to knockout a single locus. For CRISPR-based editing, we will experimentally test up to 6 different guide RNAs and provide the investigator with the two or three of the top performing guides from our experimental testing. We also support homology directed repair (HDR) to insert specific changes. Procurement of donor DNA will be extra charge. We can also help with epigenetic editing using either CRISPRa or CRISPRi.

The Core Corner Con't

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

Pooled library screens - There are many instances where the gene or genes of interest are not known *a priori***.** We have procured many of the commonly used genome wide libraries from Addgene for whole genome knockout, activation and repression. We are happy to provide these resources to investigators**.** There also may be cases where a whole genome screen is not needed. To this end, we also can build custom libraries which have guides targeting small subsets of genes such as signaling pathways**.** Please inquire further on pricing as this will depend on the source and scale of the desired library.

Where are we located?
Currently, we are located at the ATRF in Frederick. Dr. Chari's office is Rm. C2029 and his lab is in Rm. C2036. We will be moving back to Building 549 at Ft. Detrick after refurbishment.

How do I contact the GMC?
Please email Raj Chari (Director) at raj.chari@nih.gov. He can also be reached by phone at 301-846-7199. More information and requests for services can be made at our website: https://ncifrederick.cancer.gov/Lasp/GMC.aspx

References:

[1] Chari et al Nature Review Genetics (PMID: 28852223)
[2] Komor et al Cell (PMID: 28431253)
[3] Abudayyeh et al Nature (PMID: 28976959)
[4] Doench Nature Reviews Genetics (PMID: 29199283)

Raj Chari, Ph.D.
Director, Genome Modification Core
Laboratory Animal Sciences Program

The Personal Development Corner

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

This new section will provide a space to present ideas and strategies on how to unfold our potential and feel fulfilled in the workplace. Well-being is a crucial component of work productivity. The tasks performed by Staff Scientists and Staff Clinicians are very heterogeneous and dynamic. We all have different strategies to express our scientific skills in a framework coherent with our values. How do you feel energized and motivated in your job?

If you would like to express your experience and perspectives on how to thrive in your work environment, please contact Brunilde Gril, Ph.D., M.P.S., (grilbrun@mail.nih.gov). We welcome any articles that can contribute to the fulfillment and growth of our SSSC community.

The Personal Development Corner Con't

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

Productivity and Happiness at Your Workplace

Are you excited to get up in the morning and go to work? How much do you enjoy your job and daily tasks? If you think it is utopian to jump out of your bed in the morning out of excitement for your work, I challenge you to embark on the journey of soul searching and professional development, following the programs offered by our institute. I came to realize that very few of us are aware of the professional development programs offered by our institute. The NCI is devoted to the fulfillment and success of its employees as illustrated by the important resources allocated to training, professional development, and inclusion and diversity programs (Office of Workforce Planning and Development (OWPD) and Center for Cancer Training (CTC)). Through an official structure, those programs create the time and space for you to explore and develop your potential.

I was appointed Staff Scientist in 2013. I initially found this position very challenging because of the diversity of the tasks. During our Postdoctoral Fellowship, we can focus mainly on our research project. We live for these occasional moments of euphoria when we find a new interaction between two proteins or identify a new function for a cell type, which helps us to tolerate the dreadful vagaries of scientific research. But as a Staff Scientist, we are also dealing with lots of administration and management of people, projects, and materials. Feeling overwhelmed, I followed a colleague/friend's advice (Christophe Marchand, Ph.D., Health Scientist Administrator, Center for Research Strategy, former Staff Scientist) and registered for training programs offered by OWPD. It was four years ago, and new exciting perspectives had unfolded in front of my eyes, while still being in the same position.

I can personally attest to the high quality and the benefits gained from two of those programs: the NCI Executive Leadership Coaching Program and the NCI Career Mentoring Advantage Program (CMAP). Through introspection and professional guidance, you define your values, vision, and strengths, as well as learn skills for management and dealing with conflicts, and you will expand your network. Here, I am sharing some highlights of these programs, hoping some of you will find them inspiring.

Reflecting upon my deepest values was a revelation. Why define your core values? As opposed to external goals (e.g., money, power, title…), core values have intrinsic worth, i.e., they cannot be taken away from you. The list is endless, but here are some examples: honesty, compassion, generosity, health, ethic, humor. Values are the foundation of your self-confidence and well-being. They influence your daily choices. They are guides and sources of meaning when facing stressful situations at work. You may lose an argument, you may encounter aggressive people, but if you stick to your values, none of those will affect you. Defining your values will take time. In the book "The power of full engagement" from Loehr and Schwartz, the following questions can help you define your deepest values: "*what are the three most important lessons you have learned and why? Think of someone you deeply respect, describe three qualities you most admire*?"

One of the most empowering tools, I thought, was the assessment to identify your top five strengths. We are often told to work on our shortcomings and deficiencies. This assessment takes a different perspective by focusing instead on our talents to enhance them. The StrengthsFinder test was developed by Gallup®. It is available online, and you can buy an access code with the book "StengthsFinder 2.0" or "Strengths-based leadership" by Tom Rath and Barry Conchie. Gallup® studied human strengths for 40 years and identified 34 common talents. They subsequently analyzed the skills and strengths of numerous leaders. Interestingly, they could not identify a single pattern of strengths re-occurring in all the leaders. What the successful leaders shared was their awareness of their strengths; they could build upon those aptitudes and knew how to surround themselves with the right persons to complement their skills.

In their article, "*Social intelligence and the Biology of Leadership,*" Goleman and Boyatzis emphasize the role of mood contagion and how our behaviors affect our co-workers. This mood contagion is more prominent if it comes from a position of supervisors. Staff Scientists and Staff Clinicians are often the second-in-command in the lab, below the PI. Because of this position in relation to students and Postdoctoral Fellows, we hold responsibilities for the culture of the lab and the atmosphere. Do we want a competitive atmosphere or a place of trust, honesty, and openness? We play a crucial role in determining the tone of the lab and creating a flourishing environment.

The Personal Development Corner Con't

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

An important aspect of the aforementioned programs is the opportunity to build your network. Through CMAP, you will be able to develop a mentoring relationship with a person of your choice at NIH. This includes learning a new technique, a new field, or wanting to explore other encouraging mentoring or reaching out to people for informational interviews. When you learn these skills, you realize that most people are more than happy to discuss their science and expertise with you.

These programs require a fair amount of time commitment which might be an intimidating factor. If you feel you don't have the time, but still want to try, I would recommend starting with the Executive Leadership Coaching program. Through this program, you have the luxury to have individual sessions with a coach who will guide you on any issues you may encounter, for 12 weeks. You will learn new skills to implement in your daily work. In my experience, the benefits gained from programs of this type give you more energy, and you discover that you are accomplishing more in the same amount of time. You experience the relativity of the concept of time!

Most likely, we will all find different ways to express and implement what we have learned through professional development training. To give some concrete examples, I will share a couple of examples from my experience. I presented professional development aspects in lab meeting and took the initiative to offer the StrengthsFinder book to everyone in the lab. I went back to school at night to follow a side passion, still maintaining my full-time position as a Staff Scientist. I just graduated with a Master's degree in Clinical Psychological Science, from the University of Maryland. I had managed to merge my cell biology background with my side passion for psychology, and I received an NCI Director's Intramural Innovation Award for my proposal investigating the role of psychological stress on metastasis progression.

Finally, I would like to highlight the work of Ofelia Olivero, Ph.D., who was a Staff Scientist and is now the Chief of the Intramural Diversity Workforce Branch (IDWB). Dr. Olivero is dedicated to the professional development and fulfillment of Postdoctoral Fellows and Staff Scientists. She is running a professional development program for Postdoctoral Fellows and is now working on an enrichment program for Staff Scientists to expand our expertise and develop our potential!

Keep in mind that all these programs will not make your external issues disappear. You will still face conflicts and challenges at work, *c'est la vie*. But it will teach you how to change your thoughts and perspectives about those challenges, which will hopefully change your experiences in a positive and empowering way.

I am grateful for the fantastic resources our institute offers us and hope some of you will embark on this exciting journey of self-discovery and empowerment. Find your passion, values and strengths, and use your work environment to embody and express them. Enjoy!

Brunilde Gril, Ph.D., M.P.S. (SS)
Women's Malignancies Branch

References:

Goleman, D., & Boyatzis, R. (2008). *Social Intelligence and the Biology of Leadership.* [Article]. Harvard Business Review, 86(9), 74-81.

Loehr, J.E., & Tony Schwartz, T. (2005) *The Power of full engagement: Managing energy, not time, is the key to high performance and personal renewal*. New York: Free Press.

Rath, T., & Conchie, B. (2008). *Strengths based leadership: Great leaders, teams, and why people follow*. New York: Gallup Press.

The Personal Development Corner Con't

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Links to career development programs :

Office of Workforce Planning and Development (OWPD) on NCiConnect:

The OWPD Training and Development Opportunity Catalog

The Career Mentoring Advantage Program (CMAP) - formerly known as the Knowledge Management Program

Center for Cancer Training (CCT) : https://www.cancer.gov/grants-training/training/about

Diversity Career Development Program (DCDP) offered by the Intramural Diversity Workforce Branch (IDWB): https://www.cancer.gov/grants-training/training/idwb/dcd-program

Brunilde Gril, Ph.D., M.P.S., is a Staff Scientist in the Women's Malignancies Branch. She joined the laboratory of Patricia Steeg, Ph.D., in 2006, as a Visiting Fellow, and was appointed Staff Scientist in 2013. Her studies focus on brain metastases of breast cancer. The overarching theme of her research involves characterizing the blood-tumor barrier, identifying molecular targets, deciphering signaling pathways, and preclinical testing of developmental therapeutics in mouse models. In parallel, Dr. Gril developed an interest in psychoneuroimmunology and established a mentoring relationship with Paige Green, Ph.D., M.P.H., F.A.B.M.R., Chief of the Basic Biobehavioral and Psychological Sciences Branch, in the Division of Cancer Control and Population Sciences. Dr. Gril recently received a Master's degree in Clinical Psychological Science, from the University of Maryland. A key aspect of her work focuses on mentoring and encouraging people to develop their potential. She is a member of the CCR Staff Scientist/Staff Clinician Professional Development Committee and a mentor in the Sallie Rosen Kaplan (SRK) Postdoctoral Fellowship Program.

Announcements

Congratulations!

2018 Director's Innovation Award Winners

David Sturgill, Ph.D. (SS) Laboratory of Receptor Biology and Gene Expression

Scott Walsh, Ph.D. (SS) Chemical Biology Laboratory

Attend!

The 2018 SSSC Retreat

Friday, April 6, 2018, NCI Shady Grove

https://ncifrederick.cancer.gov/events/SSSCRetreat2018/default.asp

A Call for Content

We need your input! Send your articles or suggestions with subject title "The Dossier" to budhua@mail.nih.gov.

This newsletter is an avenue for you to express your ideas and thoughts on being a Staff Scientist or Staff Clinician at CCR and to make pertinent announcements.

Your contribution is very important to the success of The Dossier. Please send us your commentary, announcements and suggestions for topics/subject matter, and we will do our utmost to include your material in upcoming issues.

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