THE DOSSIER

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

December 2018 Issue 34

From the Editor

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

This issue contains important messages from the Office of the Director regarding CCR research, by Glenn Merlino, Ph.D and Tom Misteli, Ph.D. In our PI Corner, Shalini Oberdoerrfer, Ph.D., discusses her research and the important role of her Staff Scientist, David Sturgill, Ph.D., while we learn about Kazutoshi Yamamoto, Ph.D., in our SSSC Corner. In our Author's Corner, we highlight the published work of Sophia R. Gameiro, Pharm. D., Ph.D., while in our Core Corner, Cynthia Masison, Ph.D., describes the SSSC Technology Enrichment Program. Meanwhile, in our Clinical Corner, we obtain the viewpoints of Jaydira del Rivero, M.D., Ph.D., on several aspects of the Staff Clinician position and in our Quad Corner, Cynthia Masison, Ph.D., discusses the importance of participation in the scientific community by SSSCs. 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. (SS)
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In This Issue

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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.

Cancer Research Like Nobody Else

I'm sure most of you have seen the brand we have come to be known by: "At the CCR, we do cancer research like nobody else!" Of course, there are many institutions across our country and the rest of the world that conduct outstanding science and many that are fully committed to improving the care of cancer patients. Yet the truth is that the CCR *does* in fact do cancer research like nobody else. So how is this possible? CCR offers many advantages to its investigators at all levels, including access to the highest quality technical cores, a full range of quality training, opportunities for supplemental funding, and a genuinely collegial and an unparalleled collaborative environment in which to work. But to me, there are two things that make CCR a truly special place to do cancer research: secure funding and our Staff Scientists and Staff Clinicians (SSSC).

NIH scientists are evaluated every four years through a Site Visit review conducted solely by extramural academic peers. This is a rigorous process that CCR leadership relies on to help make decisions about funding, promotions and tenure. The entire research program of each Principal Investigator (PI) is reviewed, usually with the rest of their Lab or Branch, through written and oral presentations, and the progress they have made over the last four years is critiqued. Although future plans are carefully scrutinized, much of this review is viewed from a retrospective vantage point – the idea being if a PI did very well for the last four years, he/she would very likely do well for the next four years. A huge benefit of our Site Visit review process is that – when successfully navigated -- our PIs have scientific freedom for the next four years to pursue important research questions. CCR investigators have the freedom to choose to tackle a high risk/high reward project, turn in a new direction, or try to answer that burning question that has evaded the scientific community. In CCR, grant study sections do not determine what research a PI can do. In addition, what is sometimes not as fully appreciated is that our funding structure also allows CCR investigators to pursue long-term projects that take more than one review cycle to complete. Extramurally such projects -- even if initially funded by a grant -- would likely not survive a competitive renewal, and therefore often may never be brought to fruition.

SSSC scientists contribute in so many ways to the mission of the CCR, including performing outstanding basic/translational/clinical science, managing laboratories, running cores, taking care of patients, and providing computational expertise. But an aspect of the role of the SSSC that is the absolute envy of extramural investigators is the overall stability each of you brings to the laboratory or clinical team. All of you, who make up CCR's outstanding cadre of SSSC scientists, are the linchpins, providing the historical memory, distinct expertise, intimate knowledge of how the lab works, and ongoing effective mentoring and training. It is the SSSC that makes long-term, high risk/high reward projects feasible and fuels the best and most creative CCR research. So valuable is the role of this position that extramural NCI leadership has devised a grant mechanism (the Research Specialist, R50 mechanism) to try to fund this very type of position at universities across the country.

A great illustration of this is from work in my own lab. My Staff Scientist, Chi-Ping Day, Ph.D., arrived in my lab 13 years ago to spearhead an effort to develop genetically-engineered preclinical mouse models that would allow us to inform clinical trials for melanoma patients. After many challenging years of building new models, testing their relevance and designing reporters, we now possess a group of mouse models that may help improve the outcome of melanoma patients being treated with immune checkpoint inhibitors such as anti-CTLA-4 and anti-PD-1/PD-L1. We were heavily aided in this regard by the Center for Advanced Preclinical Research (CAPR), a CCR-unique core consisting of professional preclinical scientists built just for this purpose.

As a scientist performing basic biomedical research, my dream, like many in CCR, is to contribute in a meaningful way to improving the care of cancer patients. This dream is very much alive today thanks to the Staff Scientists and other outstanding colleagues in my own lab, and because of the unique environment CCR offers. This is just one example of the tremendous value of the SSSC position in the CCR, and how it allows us to do cancer research like nobody else. Thank you SSSC investigators for all that you do, and for making our dreams a reality.

The Office of the Director: Guest Editorial Con't

Glenn Merlino, Ph.D.
Scientific Director for Basic Research
CCR

Tom Misteli, Ph.D.
Director
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The Quad Review Corner

Getting Involved

The next Staff Scientist and Staff Clinician Quadrennial Review will be held in March 2019. This year the Quadrennial Review panels will be evaluating 37 Staff Scientists and 7 Staff Clinicians. This past September, I sent emails to all the Staff Scientists and Staff Clinicians who are up for review along with templates and website links. In addition, I held a PI/Supervisor information session on the Quadrennial Review process on September 24, 2018; as well as a session for Staff Scientists and Staff Clinicians at their Professional Development Day on November 16, 2018.

When Staff Scientists hear they are up for Quadrennial Review, many immediately start counting the number of papers they have published within the last review period. Indeed, scientific productivity, as gauged by publications, is an important review criterion, but only one of several measures of a Staff Scientist's performance. In their evaluation of Staff Scientists, the Quadrennial Review panel also looks for 1) how visible a Staff Scientist is by contributions in collaborations, poster and oral presentations, invited talks and awards received; 2) the role a Staff Scientist plays in mentoring other lab members, Lab/Branch members and collaborators or teaching courses; 3) whether a Staff Scientist is expanding their skills through continuing education and training; 4) whether a Staff Scientist participates in the larger scientific community.

The participation of Staff Scientists in the larger scientific community is an important component that is often underappreciated by many Staff Scientists and their PIs. Participation in the broader scientific community allows a Staff Scientist not only the opportunity to give back to the community, but also to gain a tremendous amount from the experience. Activities such as organizing conferences, workshops or scientific retreats, actively participating in Special Interest Groups and Centers of Excellence and judging abstracts for poster days can enable scientists to acquire new skills and expand their network of interactions. Taking on leadership roles in societies or organizations can increase a Staff Scientist's visibility within the community which often leads to more

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possibilities for getting involved. It is clear that the responsibilities of Staff Scientists can vary tremendously, so it is important to find a balance. Identify activities you will enjoy that allow you to serve the community and receive the benefits without hampering your research activities. Among the many opportunities both intramurally and extramurally, one place to start is in the CCR Staff Scientist and Staff Clinician Organization which has several committees and positions.

So consider getting involved before hitting delete on an email coming from an organization or society asking for volunteers or recruiting members.

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

The PI Corner

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

Dr. Shalini Oberdoerffer (left) is pictured with her Staff Scientist, Dr. David Sturgill (right).

My experience with a Staff Scientist associated with my lab can be summed as "symbiotic". David Sturgill joined the Laboratory of Receptor Biology and Gene Expression (LRBGE) in 2013, after successfully completing his Ph.D. in computational biology at the University of Maryland. David was recruited to the LRBGE to provide computational support for three groups, including my own. By way of background, David came to us with expertise in pre-mRNA splicing analysis. This was a natural fit for my group, as our research focuses on mRNA processing and function, including the regulation of alternative pre-mRNA splicing. However, David was also tasked with providing support on topics ranging from epigenetics, chromatin biology and DNA damage. Needless to say, this required that David rapidly familiarize himself with a range of topics and computational techniques. I'm sure he would describe that part of his training as "intense"! Somehow, David prevailed and is now a *de facto* Jack-of-all-computational trades.

For my part, David has developed into a respected colleague who supports all aspects of our work. David does not simply crunch data, but rather researches emerging techniques and analytical pipelines so that we stay ahead of the curve. Most relevantly, David supervises fellows in my laboratory as they gain critical computational skills. As a result, we have been able to extend our studies into unexpected directions. If you had asked me about our arrangement five years ago, I probably would have complained that a shared Staff Scientist won't be able to dig in deep enough to any particular topic. My experiences over the past five years have truly changed my mind. As science continues to rely on high throughput datasets, I can confidently state that the model of a

The PI Corner Con't

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

a shared Staff Scientist works. As David transfers more and more of his knowledge to fellows in my group, he is not merely providing computational support, but is rather arming the next generation of scientists with essential skills. So how is our arrangement symbiotic? When David joined the LRBGE, he was not interested in pursuing the Principal Investigator route. The Staff Scientist position allows him to do what he loves best (computational analysis), without worrying over the big biological picture. It's a true win-win for us all!

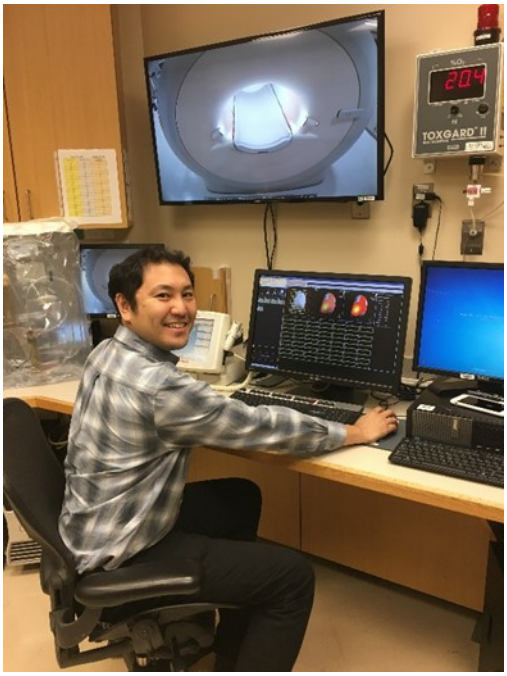
Shalini Oberdoerffer, Ph.D.
Investigator, Laboratory of Receptor Biology and Gene Expression
Head, RNA Processing in Cellular Development Section

The SSSC Corner

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

I remember as a little boy when I first heard of the "National Institutes of Health." I understood it to be a wonderful place where the world's most intricate and important research was conducted; a place where scientists gathered to solve the world's problems; a place where anything was possible. So naturally, growing up in the age of the Ninja Turtles, this meant that the NIH was a place where one particular important issue was discussed: the issue of water, sewage safety, and *radiation* (and mutants!). This misunderstanding was solved very quickly by an older cousin, who is a scientist. However, looking back, I can't help but laugh at the limited confines I had set to describe the expansive work conducted at the NIH.

Now, some years later, I find myself at the very same institution conducting research as a Staff Scientist in the Radiation Biology Branch of the NCI under the lead of Murali K. Cherukuri, Ph.D. My path here began some years prior at the University of Michigan as a Ph.D. student, working on the development of Magnetic Resonance (MR) methodology and its application to biological systems. Using this experience, I entered the NCI and undertook the task of development and application of MR methodologies to molecular imaging in cancer research. We are currently focusing on developing various approaches in metabolic imaging to characterize tumor microenvironments in preclinical and clinical settings, profiling metabolic and physiologic phenotypes of tumors in



Dr. Yamamoto is shown above setting up clinical studies of hyperpolarized MRI on the Philips Achieva 3T MRI machine at the Molecular Imaging Program. This is a highly collaborative project with UOB, MIP, ROB, IPDC, NOB, and RBB in NCI.

treatment planning and earlier response monitoring in cancer treatment. In particular, my recent research topics include multimodal molecular imaging of real-time metabolic imaging of sensitivity-enhanced hyperpolarized ^{13}C MRI, ^{18}F FDG-PET, and EPR imaging oximetry to characterize microenvironments of

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pancreatic tumors, ^{13}C labeled probe developments for ^{13}C MRI, and setting-up clinical translation of hyperpolarized metabolic ^{13}C MRI. I was fortunate to receive training on cGMP related to the clinical trials of the hyperpolarized MRI study. Any of these unique projects cannot be done without NIH's exceptional research environment, including long-term funding and resources, and our wide range of excellent collaborators in UOB, MIP, ROB, LGCP, IPDC, U of Tokyo, ETIB and NOB. Dr. Cherukuri gives me the freedom to work on something that interested me which has led to the development of a long-term project working on hyperpolarized multinuclear probe development, which includes ^{15}N probes, which have extremely long lifetimes of MR hyperpolarization, and which can potentially image the medically relevant metabolic activities of cancer for over an hour.

In my free time, I enjoy spending time with my family and friends, traveling, and playing pick-up soccer games. I have a 9-month-old son and it has been amazing watching him grow so quickly and seeing just what we as human beings are capable of in such a short amount of time. I look forward to the days when I can bring him with me to NIH. I can only imagine what sort of a world he will decide is possible at the NIH.

Dr. Yamamoto is pictured with his son (baby-zilla) after an invited talk at an international conference in Paris, France, in early summer, 2018.

Kazu (Kazutoshi) Yamamoto, Ph.D. (SS)
Radiation Biology Branch

The Author's Corner

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

M7824, a novel bifunctional anti-PD-L1/TGFβ Trap fusion protein, promotes anti-tumor efficacy as monotherapy and in combination with vaccine.

Knudson KM, Hicks KC, Luo X, Chen JQ, Schlom J, Gameiro SR. Oncoimmunology. 2018 Feb 14;7 (5):e1426519. doi: 10.1080/2162402X.2018.1426519. eCollection 2018.

The successful establishment and growth of tumors in humans and mice relies on multiple mechanisms that collectively allow the tumor to escape immune surveillance by both the innate and the adaptive immune system. These immune evasion mechanisms orchestrated by the tumor include the expression of immune checkpoint proteins by cancer cells that inhibit the killing capacity of tumor-specific cytotoxic T cells (CTLs). In addition, tumors also secrete cytokines, such as TGF-β that hampers the effector killer capacity of both CTLs as well as Natural Killer (NK) cells.

Secretion of TGFβ and upregulation of immune checkpoint programmed cell death ligand-1 (PD-L1) are thus two main contributors to tumor immune evasion and progression. PD-L1 blockade has been shown to improve survival for subsets of patients with diverse malignancies, including Merkel cell carcinoma, bladder carcinoma, non-small-cell lung cancer,

and melanoma, among others. This has led to the approval of Atezolizumab (Tecentriq®), Avelumab (Bavencio®), and Durvalumab (Imfinzi®), monoclonal antibodies targeting PD-L1. However, most patients (50-80%) with solid carcinomas do not respond to this type of therapy. Hence, there is an urgent need to improve clinical benefit for these patients. Therapies effectively blocking the immunosuppression caused by TGF-β have yet to be approved by the Food and Drug Administration (FDA). Blocking PD-L1 and TGF-β simultaneously represents a rational therapeutic strategy as these key immunosuppressive pathways have independent and complementary functions.

Sofia R. Gameiro, Pharm.D., Ph.D., Staff Scientist and Head of the Immunomodulation Group in The Laboratory of Tumor Immunology and Biology, and her group examined the immune effects and antitumor efficacy of a first-in-class bifunctional checkpoint inhibitor, the fusion protein M7824, comprising the extracellular domain of human TGFβRII (TGFβ Trap) linked to the C-terminus of human anti-PD-L1 heavy chain (αPD-L1). Using naïve female Balb/c mice, they demonstrated that M7824 increased the number and activation of NK and CD8+ T cells in the lymph nodes. The effect of this agent was also tested in mice orthotopically implanted with EMT6 tumor cells, a murine model of breast carcinoma. In these mice, M7824 significantly reduces plasma TGFβ1, effectively binds to PD-L1 to tumor cells *in vivo*, and decreases TGFβ-induced signaling in the tumor microenvironment. Using two distinct murine models of solid carcinomas, i.e., breast (EMT6) and colon (MC38), we were able to demonstrate that treatment with M7824 promoted a significant level of tumor control, by decreasing tumor size and increasing overall survival. These effects were superior as compared to targeting TGFβ alone.

M7824 treatment promoted $CD8^+$ T cell and NK cell activation in the tumor and/or the tumor periphery, and both of these immune populations were required for optimal M7824-mediated tumor control. In addition, the bifunctional molecule was superior to TGFβ- or αPD-L1-targeted therapies when in combination with a therapeutic cancer vaccine targeting the transcription factor TWIST. These findings demonstrate the value of using a bifunctional molecule to simultaneously target TGFβ and PD-L1/PD-1 immunosuppressive pathways to promote anti-tumor responses and efficacy.

These studies support the potential clinical use of M7824 as a monotherapy or in combination with other immunotherapies, such as therapeutic cancer vaccines, including for patients who have progressed on αPD-L1/αPD-1 checkpoint blockade therapies. In this context, a phase I trial of M7824 in patients with advanced solid tumors (NCT02517398) was conducted here, at the NIH Clinical Center. M7824 was shown to have a manageable safety profile in patients with heavily pretreated advanced solid tumors. Early signs of efficacy were encouraging, leading to the expansion of the trial to multiple patient cohorts, now ongoing in a range of tumors[1].

Sofia R. Gameiro is a Staff Scientist and Head of the Immunomodulation Group in the Laboratory of Tumor Immunology and Biology, CCR/NCI, with expertise in immune modulation, tumor microenvironment and tumor immunology. Her group examines how emerging therapeutics can modulate the immune system to exert potent antitumor activity against solid carcinomas, with particular emphasis on how the mechanisms involved can be exploited to maximize antitumor activity in combination regimens with novel immunotherapies and other anticancer modalities.

References:

1. Strauss, J., *et al.* Phase I Trial of M7824 (MSB0011359C), a Bifunctional Fusion Protein Targeting PD-L1 and TGFbeta, in Advanced Solid Tumors. *Clin Cancer Res* **24**, 1287-1295 (2018).

Sofia R. Gameiro, Pharm.D., Ph.D. (SS
Head, Immunomodulation Group
Laboratory of Tumor Immunology and Biology

Opportunity for Staff Scientists and Staff Clinicians to Expand Their Skill Base

CCR scientists have access to innovative research technologies and specialized expertise through their core laboratories and lab-based facilities. In many cases, these centralized labs are overseen by Staff Scientists or individuals in equivalent positions, who are innovators and leaders in their fields of expertise. While Staff Scientists and Clinicians embedded in research labs greatly benefit from these specialized technologists, there is no formal avenue for them to gain more experience in the application of these innovative technologies.

The Staff Scientist/Staff Clinician Technology Enrichment Program (STEP) was established to provide Staff Scientists and Clinicians an opportunity to compete for project-based funding to gain access to comprehensive training in state-of-the-art techniques available through CCR Cores and Facilities. The goal is for the SSSC to work closely with Core managers/heads to learn a technology application from experimental design, through sample preparation and data analysis. Most of the newer innovative technologies generate big data, creating an acute need for training on data management and interpretation. Thus, a central focus of this program will be connecting participants with relevant opportunities, including developing individual bioinformatics training plans through the CCR Bioinformatics Training and Education Program (BTEP). At the conclusion of their training, this work will not only advance the SSSC's current research projects resulting in publication, but also provide advanced expertise that can benefit future research of the Lab/Branch. In addition, by broadening the Staff Scientist's technical skills and knowledge base, he/she is more transferrable among Labs/Branches/Cores within CCR in the event of PI retirement, closure, or resource reduction. The process begins by sending a letter of intent (LOI) describing the project and technologies proposed, how it contributes to ongoing research, and the approval of the SSSC's Supervisor. From there, CCR Office of Science and Technology Resources (OSTR) will advise the SSSC of the available Cores/Facilities to contact to begin discussions on submitting a full proposal. Proposals that include a more formal write up of the research project, budget justifications, a time table, along with letters of commitment between the SSSC and Core/Facility head(s), will be submitted through the STARS funding mechanism for review. The SS/SC and Cores/Facilities will be notified if the proposal has been approved.

We hope Staff Scientists and Staff Clinicians will take full advantage of this unique opportunity to enhance their research and advance their careers. The program is scheduled to launch in January 2019.

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

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.

An Interview with Jaydira del Rivero, M.D.

What is your general role as Staff Clinician?
My role is to provide clinical care of patients and also support clinical trials in endocrine malignancies where non-oncologists are the PI on the studies.

Could you point out steps and difficulties to implement a clinical trial?
I do believe at the NIH we have an excellent infrastructure for clinical trial implementation and we have an excellent protocol support office.

What is your contact with Staff Scientists? Any report of cooperation from bench to bedside?
In the Pediatric Oncology Branch (POB), we have a good relationship with our Staff Scientists, with many opportunities to share ideas and collaborate.

How do you see patient care at NIH? Can you give examples of benefits and limitations?
I do believe we give excellent patient care. Coming as a physician who practiced outside NIH for some time, I can definitely emphasize that the care that we give is excellent and unique. We dedicate time of our patients and we address their concerns. I personally feel there is no other place like NIH.

What is the career path of a Staff Clinician? Where do they go from here?
To pursue a career in clinical or translational research in cancer care.

Any final advice for new Staff Clinicians or about collaboration between Staff Clinicians and Staff Scientists?
I think communication and exploring what other Staff Scientists are doing within the Clinical Center could open opportunities of collaboration.

Have you identified any differences or challenges in being a woman scientist? Any specific advice to other young women starting in that path?
The NIH is well recognized, and the institution is working hard to help in every way. As of now, I personally don't feel any differences on challenges of being a woman scientist at the NIH. If we work hard, amazing things can happen!

Jaydira del Rivero, M.D. (SC)
Assistant Research Clinician
Pediatric Oncology Branch

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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