THE DOSSIER

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

December 2015 Issue 22

From the Editor

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

This issue contains important messages from the Director's Office, including Genomic Data Sharing Resources at CCR, and a special article by Daniel H. Fowler, M.D. In our SSSC Corner, we feature Yoshimi E. Greer, M.D., Ph.D. The published work of Lisa Ridnour Ph.D., is highlighted in our Author's Corner, while Ana I. Robles, Ph.D., and Daniel C. Edelman, Ph.D., describe their collaborative efforts at the Clinical Molecular Profiling Core.

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)
Editor-in-Chief
Laboratory of Human Carcinogenesis

In This Issue

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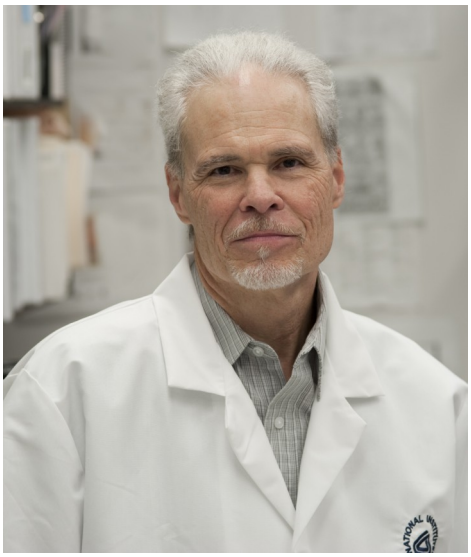
From the Office of the Director

I am pleased to provide my inaugural "Director's Corner" as the CCR Acting Scientific Director for Basic Research. Since Dr. Wiltrout's official retirement in early July, it has been quite a whirlwind, and I continue to be astounded by how much there is to learn about this complex, multilayered organization. I am humbled to be asked to help lead this outstanding scientific enterprise. I believe that the most important role for a Scientific Director is to recruit the highest caliber staff at all levels and give each an equal chance to take full advantage of our organization's many resources, including cutting-edge technology, and training and collaborative opportunities. The hopes and dreams of each of our researchers constitute the hopes and dreams of CCR and our success depends upon our scientists realizing their potential. We are committed to keeping our research at the highest level, which includes hiring exceptional young scientists, emphasizing the enhancement of diversity within CCR.

CCR priorities will in part align with the Long-Term Planning process that was initiated by the NIH Director last year. These include a significant role in the Precision Medicine Initiative, and enhanced efforts in RNA biology, structural biology, natural products, the microbiome, and immune- and cell-based therapies, among others. We anticipate that the CCR research portfolio will consist of a dynamic blend between the most basic questions and the most effective clinical treatments, tethered by highly creative translational efforts.

Staff Scientists and Staff Clinicians have been and will continue to be essential contributors to the success of CCR playing critical, multifaceted roles, including lab managers and core directors, as well as outstanding basic, clinical, and team scientists. My own research program is greatly enhanced by the incredible impact of two outstanding Staff Scientists, who contribute at the basic and translational levels. In CCR we are committed to nurturing this important position, which is so vital to all of our research efforts moving forward.



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

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From the Office of the Director Con't

Genomic Data Sharing-Principles, Policy and Plan

The progress of science has always depended on scientists sharing data with their peers, to verify results, and to develop a common body of knowledge. The National Institutes of Health (NIH) has long valued open access as a way to maximize the use of resources and data. There are several positive drivers for data sharing:

- The scale of data production in the life sciences has grown dramatically in the last decade; these data are generated, processed, and analyzed at a significant cost.
- Open access to data allows outside researchers to verify published claims.
- Large-scale data can be used to address scientific issues distinct from the original research problem.
- The current state of information technology allows data to be transferred, stored, analyzed, and disseminated at a scale that was heretofore impossible.

In August 2014, the NIH expanded the Genome Wide Association Policy by establishing the Genomic Data Sharing (GDS) Policy to promote the sharing of NIH-funded research that generates large-scale human and non-human genomic data, irrespective of funding level or funding mechanism.

Large-scale data include data from genome-wide association studies and single nucleotide polymorphism arrays, as well as genome sequence, transcriptomic, metagenomic, epigenomic, and gene expression data. Metadata around the study and annotations that are necessary to reproduce any published table or analysis must be included with genomic data submissions. In particular, data pertinent to the interpretation of genomic data—such as associated phenotype data (e.g., clinical information), exposure data, and descriptive information (e.g., protocols or methodologies used)—is expected to be shared.

The Trans-NCI Genomic Data Sharing Policy Implementation Working Group (WG) was created to guide NCI in implementing the NIH data sharing policies. The WG is developing a framework that guides the implementation of GDS policy across the extramural and intramural programs. The framework includes guidance for NCI staff as well as the extramural scientific community regarding the expectations the GDS policy (scope, timeline, data standards, sharing or consent exceptions to the policy). In addition, the WG is responsible for the education and outreach to the NCI research community to ensure its robust participation in the genomic data sharing process.

CCR scientific leadership is actively working with the WG to implement GDS policy across its 50 programs, branches and labs. Within CCR, GDS implementation will be in phases. Human studies will be the first to implement the GDS policy effective **December 1, 2015.** Non-human studies will follow with the date to be determined. The CCR Genomic Program Administrator (GPA) Kathy Calzone, Ph.D., R.N., A.P.N.G., F.A.A.N., along with the Genomic Program Administrator Assistant, Anjan Purkayastha, Ph.D., will serve as your point of contact for the implementation of GDS policy within CCR (see *Table #1* for contact details). The GPA: functions as a central point of coordination and information about NCI data sharing activities and implementation of NIH and NCI polices; serves as the point of contact for all CCR investigators regarding the implementation of data sharing expectations; works in concert with CCR and the WG on questions regarding implementation of the policy. The GPA Assistant: collates information in support of the GDS policy; provides training and education regarding implementation of the GDS policy; and provides direct support to assist and train researchers to submit data to dbGaP or other repositories.

To support the implementation of the GDS Policy, CCR has created the following website (see *Table #1*) for CCR with specific guidance on reporting requirements and resources. Detailed SOPs (RPS-21, RPS-22, and RPS-23) have been developed to assist investigators in establishing a Genomic Data Sharing Plan, registering your study, and applying for an exception (access to SOPs detailed in *Table 1*). A training program on the GDS Policy is also available. To request a training session for your Branch or Laboratory, please contact Dr. Purkayastha, the GPA administrator. Other GDS policy resources include: the NCI GDS Policy Website and the NIH GDS Policy Website (see *Table #1* for links).

From the Office of the Director Con't

In summary, CCR will implement the GDS policy to fully support NIH's mission to improve human health by translating biomedical data to knowledge, products, and procedures. Please let Drs. Calzone or Purkayastha know if CCR can provide additional support as you strive to adhere to the GDS Policy.

Kathleen Calzone, Ph.D., R.N., A.P.N.G., F.A.A.N.
Genomic Program Administrator

Anjan Purkayastha, Ph.D.
Genomic Program Administrator Assistant

Table 1: GDS Resources

Points of Contact			
Position	**Name**	**Contact information**	**Role**
Genomic Program Administrator (GPA)	Kathleen Calzone	calzonek@mail.nih.gov, 301-435-0538	• central point of coordination and information about NCI data sharing activities and implementation of NIH and NCI polices; • point of contact for all CCR investigators regarding the implementation of data sharing expectations; • works in concert with CCR and the WG on questions regarding implementation of the policy
Genomic Program Administrator Assistant	Anjan Purkayastha	anjan.purkayastha@nih.gov, 301-594-1395	• collates information in support of the GDS policy; • provides training and education regarding implementation of the GDS policy; • provides direct support to assist and train researchers to submit data to dbGaP or other repositories

Website Resources	
CCR GDS Website	http://bit.ly/CCR_GDS
CCR SOPs	https://ccrod.cancer.gov/confluence/display/CCRCRO/CCR+Standard+Operating+Procedures
NCI GDS Policy	http://www.cancer.gov/grants-training/grants-management/nci-policies/genomic-data#policy
NIH GDS Policy	http://www.cancer.gov/grants-training/grants-management/nci-policies/genomic-data#policy

NOS Inhibition Targets Immune Polarization for Improved Radiation Tumor Response

Ridnour LA, Cheng RY, Weiss JM, Kaur S, Soto-Pantoja DR, Basudhar D, Heinecke JL, Stewart CA, DeGraff W, Sowers AL, Thetford A, Kesarwala AH, Roberts DD, Young HA, Mitchell JB, Trinchieri G, Wiltrout RH, Wink DA., Cancer Research 75(14): 2788-99, 2015.

Radiation therapy remains a primary mode of treatment for more than 50% of cancer patients in North America (1). Sub-lethally irradiated tumors give rise to radio-resistant and invasive phenotypes (2). Therefore, the identification of novel targets for improved tumor response to radiation is warranted. While classical radiobiology has focused mostly on radiation-induced effects on tumor cells, other components of the tumor microenvironment, including host immune cells, also respond to radiation and can be exploited for improved therapeutic efficacy (3, 4). Recent advances in our current understanding of tumor response to radiation has shown improved therapeutic response by targeting T cell receptors before or concurrent with tumor irradiation. This approach increased number and survival of cytolytic $CD8^+$ T cells in order to favor a pro-inflammatory microenvironment while limiting immunosuppression (5, 6). To extend these findings, Lisa A. Ridnour, Ph.D., Staff Scientist in the Molecular Mechanism Section headed by David A. Wink Jr., Ph.D., in the Cancer and Inflammation Program (CIP) at NCI has recently employed a novel approach involving nitric oxide synthase (NOS) inhibition following tumor irradiation. This study aimed to improve radiation efficacy by enhancing $CD8^+$ T cell polarization and pro-inflammatory IL-2, IL-12, and IFN-g cytokine signaling, while limiting immunosuppressive mediators, including IL-10 (7).

Nitric oxide (NO) generated by the NOS enzymes is classically known to mediate neural, vascular, immune, and wound responses in both cGMP-dependent and -independent manners (8, 9). Cancer behaves as a non-healing wound and exploits NO signaling to maintain survival and growth advantages (9-11). Radiation tumor response is oxygen-dependent. To minimize vascular constriction and maintain tumor pO_2 prior to and during tumor irradiation (10 Gy), the NOS inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) was administered to mice in drinking water after tumor irradiation (post-IR)., Post-IR NOS inhibition extended the radiation-induced squamous cell carcinoma (SCC) tumor growth delay, in comparison to tumors that received irradiation alone. The delay was observed in C3H immunocompetent mice, but not nude mice, suggesting that T cells are responsible for this mechanism. Importantly, tumor cytokine profiles revealed that post-IR NOS inhibition favored an overall Th1 pro-inflammatory phenotype as defined by the elevated levels of IL-2, IL-12, and IFN-g. Increased number and activation of cytolytic $CD8^+$ T cells in the NOS inhibited tumors further supported these results (*Figure 1*). In contrast, tumors receiving radiation alone exhibited a Th2 immunosuppressive phenotype as defined by increased IL-3, IL-4, and IL-5 levels, as well as a dramatic early induction of IL-10 24-hr following tumor irradiation, which was abolished by NOS inhibition. In addition, the role of NO in the radiation-induced IL-10 up-regulation was found to be cGMP-dependent in cell culture experiments using Jurkat T cells and ANA-1 macrophages, and targeted suppression of IL-10 enhanced radiation-induced growth delay in tumor-bearing mice in a manner similar to that of NOS inhibition by L-NAME.

The role of NO within the tumor microenvironment is spatially-, temporally-, and flux-dependent. In the case of radiation therapy, an unpaired electron in the outer π orbital of NO exhibits high affinity for other radicals, including radiation-induced DNA damage product carbon radicals. In this context, the direct interaction of NO with carbon radicals improves radiation sensitivity by fixing DNA damage in a manner similar to that of molecular O_2 (12). Another mechanism involves modulation of NO flux, which normalizes tumor vasculature and improves radiation sensitivity through elevated tumor pO_2 (13). These mechanisms involve the modulation of NO flux prior to and/or during radiation treatment for improved tumor response. Our recent study has extended previous knowledge on NOS-derived NO effects by demonstrating that targeted NOS inhibition following therapeutic radiation improves tumor response by a

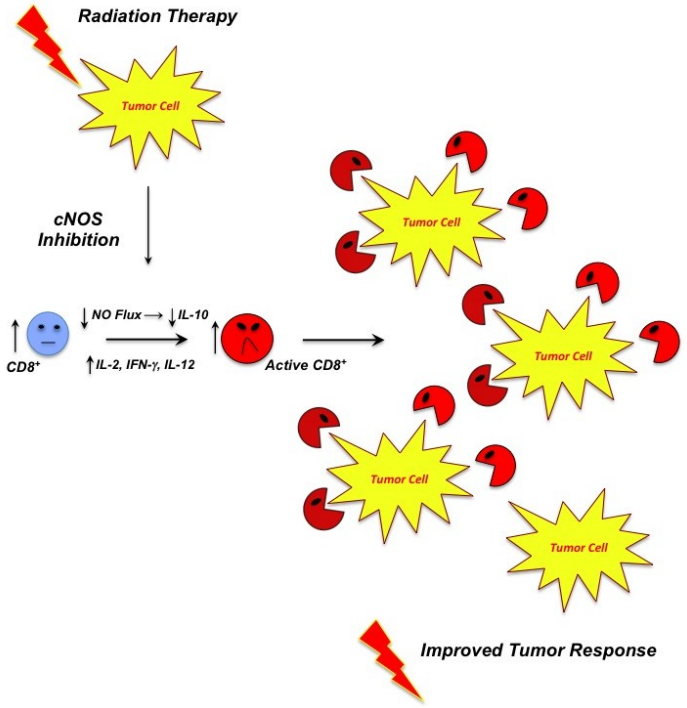

Figure 1. NOS inhibition improves tumor response to radiation by modulation of Th1 pro-inflammatory vs Th2 immunosuppressive cytokine signaling (L-2, IFN-gamma, IL-12p40 vs. IL-10), which results in an increase in the number and activation of cytotoxic T cells.

mechanism involving Th1 immune polarization at the tumor site (7). These results implicate a key role for NO flux in the regulation of IFN-g and cytolytic T cell activation. Importantly, radiation therapeutic efficacy is reduced by blockade of $CD8^+$ T cells or IFN-g inhibition (14, 15). In contrast, tumors receiving radiation alone exhibited rapid Th2 immunosuppressive signaling as defined by accelerated IL-10 production followed by increased IL-3, IL-4, and IL-5 protein levels. Moreover, abated IL-10 also extended radiation-induced tumor growth delay (7). This immunosuppressive cytokine signature is consistent with accelerated wound response and resolution of tissue damage (16, 17). Indeed, immune mediators express both eNOS and iNOS during wound response and abated wound closure has been reported in iNOS knockout mice (18-20). The potentiation of radiation treatment efficacy by NOS inhibition in our model was cGMP-dependent and radiation-induced tumor growth delay was dramatically enhanced in eNOS knockout xenografts (7). Moreover, NO signaling promoted radiation-induced angiogenesis and subsequent tumor recovery following radiation injury (21, 22).

Together, these observations describe a novel mechanism involving low-flux NO in Th1-Th2 transition and accelerated wound recovery of the sublethally irradiated tumor (7). $CD8^+$ T cell regulation and IFN-g induction are determined by NO flux-dependent IL-10 versus IL-2/IL-12 signaling cascades, which can be modulated pharmacologically by NOS inhibitors and provides a novel approach for improved efficacy of therapeutic radiation.

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The Author's Corner Con't

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

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Dr. Lisa Ridnour is a Staff Scientist in Dr. David Wink's laboratory in the Cancer and Inflammation Program at NCI-Frederick. Her research interests include regulatory roles of nitric oxide and extracellular matrix in cancer progression and treatment. In addition to her research projects, she provides training and support for students, post-docs, and visiting fellows. Dr. Ridnour is also involved in various collaborations within and outside of NCI.

Lisa Ridnour, Ph.D. ***(SS)***
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Cancer and Inflammation Program

The PI Corner

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

As a Principal Investigator in the Experimental Transplantation and Immunology Branch (ETIB), I can speak to the substantial merits of the Staff Scientist Program. As head of the ETIB cytokine biology section, I have had the privilege of working with Shoba Amarnath, Ph.D., who served as Staff Scientist in the ETIB. Dr. Amarnath's efforts have greatly accelerated our translational research, which focuses on the role of functional T cell subsets in transplantation therapy.

Dr. Amarnath worked in my lab first as a post-doctoral fellow, and then for several years in the Staff Scientist position. Recently, Shoba left the NIH to pursue a generous offer to initiate an independent research career in the UK at the Institute of Cellular Medicine, Newcastle University. During her time in the ETIB, Shoba and I initiated long-term projects to better characterize the immune regulatory crosstalk that occurs in T cells during graft-versus-host disease (GVHD), including development of a new model of human-into-mouse xenogeneic GVHD. Some of the high-risk/high-reward projects that we developed included: understanding human regulatory T cell (Treg) function; defining mechanisms for the induction or reduction of T cells of Treg phenotype during GVHD; and characterizing the role of mTOR signaling in the development of next generation T cell products for clinical use.

This research progress led to several publications (1-4) and has propelled Shoba into her current trajectory as an independent researcher; importantly, these advances have also provided a wealth of information that will guide our translational efforts for years to come. Let me elaborate on three such examples. First, in the allogeneic stem cell transplantation setting, we are continuing our clinical trials of Th2-polarized, rapamycin-resistant T cells, which we have identified as an anti-apoptotic T cell population that allows alloengraftment with greatly reduced reliance upon toxic host conditioning regimens and mediates a beneficial balance between graft-versus-tumor and GVHD effects (clinical trial #NCT 00077480). Second, prior to our studies, the general consensus in the field was that rapamycin skewed T cell differentiation towards immune suppressive phenotypes such as the Th2 or T-Reg populations. However, due to the convincing studies pioneered in our lab by our Staff Scientist, we demonstrated that it was possible to manufacture rapamycin-resistant human T cells of Th1 phenotype with enhanced in vivo engraftment potential and heightened in vivo effector function. These findings led to our current clinical trial of Th1-polarized, rapamycin-resistant T cells for the autologous T cell therapy of high-risk or refractory multiple myeloma (clinical trial #NCT 01239368). And finally, Shoba's final project in the lab relating to the pathogenesis of chronic GVHD is potentially paradigm changing in that our description of a Th1-based pathogenesis of experimental auto-immune chronic GVHD runs counter to established dogma that chronic GVHD is a process largely driven by a Th2-type mechanism. These data are consistent with ongoing research in the ETIB that associates human clinical chronic GVHD with Th1-type pro-inflammatory molecules (studies led by Fran Hakim, Ph.D., Head of ETIB Preclinical Development and Clinical Monitoring Facility). When combined, these experimental murine studies and clinical disease characterizations will help in the design and implementation of clinical trials of novel therapies for chronic GVHD (under the direction of Steven Pavletic, M.D., ETIB).

Daniel H. Fowler, M.D.
Senior Investigator, Experimental Transplantation and Immunology Branch

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The PI Corner Con't

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

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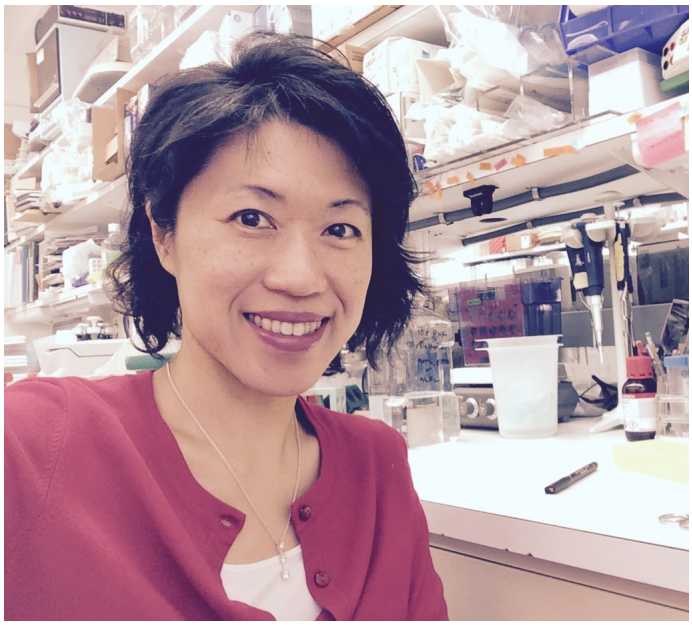
The SSSC Corner

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



At the lab: Yoshimi is pictured at her bench in Building 10 at the NIH Bethesda campus.

I am a Staff Scientist in CCR's Women's Malignancies Branch (WMB). My PI is Stan Lipkowitz, M.D., Ph.D., Chief of WMB. I transferred to WMB in 2014 from the Laboratory of Cellular and Molecular Biology, where I worked for more than 10 years. There my PI was Jeff Rubin, M.D., Ph.D., and we studied Wnt signaling and explored its extended fields. We identified that casein kinase 1 delta (CK1δ), a serine/threonine kinase that mediates Wnt signal, localizes to the centrosome and contributes to Wnt-induced neurite outgrowth. Subsequently, we found CK1δ promotes primary ciliogenesis by multiple mechanisms involving its centrosomal function and another mechanism at the Golgi, where it is important for maintaining Golgi organization and polarized trafficking that is required for ciliary transport. When Dr. Rubin retired, I transferred to Dr. Lipkowitz's laboratory, which was literally right next door. This move was timely and perfect, because I had started to think about getting back into a more clinical side of research. Having had clinical experience early in my career and the basic science knowledge that I gained in LCMB, I hope to make major contributions to breast cancer research. Recently, our laboratory moved from Bldg. 37 to Bldg. 10, and we are actively interacting with others in WMB who are conducting basic and translational research and clinical trials in breast and ovarian cancers.

Our laboratory is conducting breast cancer research with two major focus areas; one is to investigate the functions of Cbl family proteins, a family of E3 ubiquitin ligases that regulate signaling through many tyrosine kinase-dependent pathways. We found all mammalian Cbl proteins mediate ubiquitination and degradation of the activated Epidermal Growth Factor Receptor (EGFR) as well as other components of the signaling complex. Our current work is focused on understanding the biochemical and physiologic

functions of the three mammalian Cbl proteins in epithelial cells and elucidating the differences in their specificity and/or function. Another focus is translational research using TRAIL (tumor necrosis factor-related apoptosis inducing ligand) receptor agonists. We found that subsets of breast cancer cells are particularly sensitive to TRAIL, and we are testing potential TRAIL receptor agonists in cell lines and animal xenograft models through various and active collaborations. We are also trying to identify bio-marker(s) that determine TRAIL sensitivity in breast cancer. Every member in our branch is hardworking, team-oriented, and supportive, I feel very fortunate to be a part of our group and WMB.

Outside of work: Yoshimi is pictured after crossing the finish line of the Marine Corps Marathon on Oct. 25, 2015, Arlington, VA.

Outside of work, my passion is running in recent years. I started to run 5 years ago as a common activity with my husband, and quickly found it so much fun. We both gradually extended the distance, and we've run many 5k, 10k, and half marathon races. We enjoy runcations "running + vacation" in which we visit new place and run a race, explore the town; for example, we ran in Portland, OR, Seattle, WA, and at Walt Disney World in FL. Earlier this year, I decided to try running a full marathon and joined a marathon training program of local running club. As a bench scientist, often it is not easy to stop experiments and go long distance running for hours. However, I feel that running is always helpful to clear my mind and to keep me energetic, both mentally and physically. I also enjoy camaraderie with fellow runners who share pains, stories and goals. This fall, I completed the Marine Corps Marathon in Washington, DC, as my first marathon. It was very challenging but an unforgettable experience. Winter season is a tough time for me because I have to balance my spare time between running and skiing, another life-long activity that defines me.

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

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The Core Corner

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

Genomic Characterization of Early Stage Lung Cancer

Our group at the Laboratory of Human Carcinogenesis studies the molecular characteristics of early stage lung cancer with the overall goal of identifying genetic and biological factors that modulate lung cancer risk and prognosis. Our analysis relies on a knowledgebase that we have built through the acquisition of multiple levels of genomic data from well-characterized patients and controls using biospecimens derived from case-control studies. The Clinical Molecular Profiling Core (CMPC), managed by Dan Edelman, Ph.D., is a collaborative core with extensive expertise in many molecular technologies for the analysis of DNA and RNA from human specimens. Its main function is to support clinical trials at the NCI, but they are open to other collaborative projects within CCR. One example is our "Lung OMICS" project, which encompasses the integrative analysis of DNA methylation, mRNA, and miRNA expression, and tissue metabolites, and was recently extended to include DNA sequencing and the microbiome. This project was started before "precision medicine" became a buzzword, but in essence reflects the tenets of a precision medicine approach: advance the precise diagnosis and treatment of disease in individual patients, lead to a clearer molecular taxonomy of cancer, better inform clinical trials and laboratory research, and all through the integrative analysis of "omic" data. Throughout this project the CMPC worked closely with us to make the best use of our invaluable resources, run the assays with stringent quality control and adherence to standard procedures, and provide bioinformatics support. Our transcriptomic and epigenomic analyses led to the identification of HOXA9 promoter methylation as a biomarker that stratifies resected Stage I lung adenocarcinoma patients based on risk of recurrence (1). Adjuvant therapy is currently only recommended for patients with pathologically high-risk, margin-negative Stage IB tumors, and its benefit for other Stage I patients is controversial. This could be, in part, due to the lack of biomarkers that can molecularly stratify patients. In order to validate our finding from the genome-wide screen in a larger set of samples and additional patient cohorts, we again worked with the CMPC to analyze the specific methylation site by pyrosequencing. Over 200 DNA samples were analyzed by David Petersen at the CMPC. This sample size allowed us to evaluate not only the prognostic value of HOXA9 promoter methylation alone, but also in combination with mRNA and miRNA biomarkers, and build a classifier that comprises these three types of data. Our work was recently featured in the *NCI Cancer Currents blog* and *NIH I am Intramural blog*, and we are hopeful that further clinical development may lead to a test that helps guide the postoperative management of Stage I lung cancer patients at high risk of recurrence.

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Molecular Genetics and Carcinogenesis Section, Laboratory of Human Carcinogenesis

Announcements

Attend!

The 2016 NCI Intramural Scientific Investigators Retreat
Tuesday, January 12, 2016
Ronald Reagan Building and International Trade Center

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For those located in Bethesda, contact Aubrey Wachter (wachteran@mail.nih.gov); Frederick, contact Sue Fox (foxs@mail.nih.gov) or Ave Cline (clineav@mail.nih.gov).

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CCR has a growing presence on Twitter. Please follow us.

@NCIResearchCtr – CCR Office of the Director
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@NCICompOnc – Comparative Oncology Program
@NCICCR_Lymphoma – Lymphoid Malignancies Branch

NCI Guidelines for social media are available here. If your Lab/Branch or Program is interested in starting an official NCI Twitter account, contact Kimberly Martin to get the process started.

CCR Monthly Publications Report

Wonder what researchers in other CCR Labs and Branches are doing? View a list of recently published papers by CCR authors here. A new list will be posted each month. Archived reports are available here.

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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