THE DOSSIER

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

June 2014 Issue 16

From the Editor

Welcome to the June 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 and a special article by Yves Pommier, M.D., Ph.D. A summary of our 2014 SSSC Retreat is provided by our Retreat Co-Chairs, Rimas Orentas, Ph.D. and Anu Puri, Ph.D. The program topics of the upcoming 3rd Biennial SSSC Professional Development Day are presented by Christophe Marchand, Ph.D.

Chi-Ping Day, Ph.D., describes his collaboration with the Laboratory Animal Science Program in our Core Corner, while the published work of Romina S. Goldszmid, Ph.D., is highlighted in our Author's Corner. We also feature Julio Cesar Valencia, M.D., in our SSSC Corner.

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

Utilizing the Bounty of Resources Available to CCR Researchers

Staff Scientists and Staff Clinicians have important scientific and technical expertise that plays an essential role in helping CCR achieve its mission and enabling our labs to accomplish their goals. Many of you have a wide range of duties and responsibilities in individual labs that keep our labs and clinical research running efficiently, whereas some of you head cores and programs that provide vital research resources to our scientists. These shared resources and expertise, available through over 70 Cores and Facilities, contribute to making CCR one of the best environments in the world to conduct basic, translational, and clinical research.

CCR Cores and Facilities fall into nine basic disciplines ranging from genomics and proteomics, to bioinformatics and clinical research support. Whereas Cores are open to all CCR investigators, technologies and expertise offered through Facilities, which often have a more limited or specific mission, are at the discretion of the Facility Head or Lab/Branch Chief. A comprehensive listing of all capabilities available through these internal resources can be found in the CCR Research Exchange (CREx: https://nci.assaydepot.com), an online marketplace for research services developed by the CCR Office of Science and Technology Resources (OSTR). CREx is a versatile resource—detailed in the March 2014 issue of *The Dossier*—that allows CCR researchers to search and request information for services, technologies, or products offered by NCI cores and over 8,000 commercial vendors.

CCR has set up a number of dedicated cores as part of the Cancer Research Technology Program (CRTP) in Frederick. Whereas the major emphasis of CRTP labs are dedicated to the Ras Initiative, these new cores will continue to provide valuable services, including protein characterization, protein expression and purification, electron and optical microscopy. The Sequencing Facility and the Laboratory of Molecular Technology will continue to provide genomic services that are openly available to CCR investigators.

An additional resource is the Tissue Array Research Program (TARP). The TARP develops and distributes multi-tissue microarrays and works with researchers requiring custom microarrays. The Program also performs antibody validation, troubleshoots biospecimen handling, and develops instrumentation.

Several genomic and bioinformatics data mining software packages are available through the Genomics and Bioinformatics Group, Developmental Therapeutics Branch. Among these tools is CellMiner—a suite of web-based tools that provides an improved capacity to compare data derived from large collections of genomic information and against thousands for drugs. The software provides rapid access to data from more than 22,000 genes catalogued in the NCI-60 and from over 20,000 previously analyzed chemical compounds.

A variety of technologies, tools, and research services are available to the CCR community through OSTR (ostr.cancer.gov). OSTR has developed partnerships with a number of biotechnology companies to provide CCR researchers access to a broad range of bioinformatics software and biotechnology products and services in the areas of proteomics, geno-

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From the Office of the Director Con't

-mics, metabolomics, and imaging. The costs of many of these resources are subsidized through the OSTR Technology Subsidy Program. In addition, OSTR has established the Bioinformatics Training and Education Program to increase awareness and understanding of bioinformatics techniques and processes, which will empower CCR scientists to perform a basic, informed set of analyses themselves.

A goal of CCR is the discovery and translation of scientific advances into interventions that help our patients. We strive to offer resources that will assist you in accelerating the process of moving scientific breakthroughs from the bench to the clinic. Thank you for the hard work that all of you do whether it be supporting the research agenda of a Principal Investigator or managing a Core or program that assists the broader CCR community.

Robert H. Wiltrout, Ph.D.
Director, Center for Research

The Professional Development Corner

The Third Biennial NCI SSSC Professional Development Day
September 2014, NCI Shady Grove (Date to be determined)

The SSSC Professional Development Committee is happy to announce the Third Biennial NCI SSSC Professional Development Day to be held at NCI Shady Grove in September 2014. The first Professional Development Day was organized in 2010 and was a great success with over 100 participants. This year's program will be centered around four topics (program is not yet definitive):

1 – New CCR Grant Policy (DOs and DON'Ts)

2 – Panel Discussion with CCR Staff Clinicians

3 – Leadership at any level and/or networking

4 – Panel Discussion about displaced Staff Scientists/Staff Clinicians

Please join us for this unique professional development opportunity. Additional detailed information will be provided in the forthcoming months.

Christophe Marchand, Ph.D. (SS)
Laboratory of Molecular Pharmacology
Developmental Therapeutics Branch

The SSSC Retreat

"Kicking Cancer in the Ras"

April 25, 2014, NCI Shady Grove

The CCR and DCEG SSSC Annual Retreat was held on April, 25th, 2014 at an exciting new location, the NCI campus at Shady Grove. Our theme this year was a bit provocative, titled, "Kicking Cancer in the Ras." The large meeting facility was perfect for our needs and over 150 attendants shared their science, networked, and were inspired by an impressive slate of speakers. Given the renewed focus on RAS driven cancers, especially at the NCI, it was valuable to hear cutting-edge research directly from experts in the field.

Warm opening remarks by the new head of the DCEG, Stephen Chanock, M.D., welcomed us to the retreat. Dr. Chanock shared that we were the first scientific meeting held in the newly named "Dr. Joseph F. Fraumeni, Jr. Conference Room," at the NCI Shady Grove campus.

Our keynote speaker, Frank McCormick, Ph.D., FRS, kicked off the retreat's scientific session with an in-depth overview of RAS in cancer biology. Dr. McCormick's leadership in the field was on full display as his talk related cutting-edge scientific details and also a reflection on his personal journey to scale the obstacles of bringing ras-driven cancers under control. Following his address, four other leaders in the field shared short talks. Ruth Nussinov, Ph.D., gave us a detailed structural view of Ras signaling networks, as did Nadya Tarasova, Ph.D. Their molecular models and detailed description of why this "undruggable target" may be druggable made the issues at hand quite clear. Stuart Yuspa, M.D., a pioneer and leader in the field, highlighted the biological modeling of ras carcinogensis in skin cancer models, while Deborah Morrison, Ph.D., presented a detailed view of Ras and Raf signaling cascades. David Heimbrook, Ph.D., President of Leidos Biomedical Research Inc., brought a challenging view of drug discovery both from his personal experience and from the current efforts at the Frederick National Lab. It was impressive to see this broad range of issues presented, from structural biology to signaling, to management of focused biomedical research programs. A spirited question and answer session among the panel and with the audience followed immediately after these presentations. It seemed like we could have extended these discussions to last the whole day.

During the afternoon session we viewed 73 posters divided among three categories (see below). The submitted abstracts were judged prior to the retreat and those who scored the highest (Drs. Yu, Gril, and Ye) became part of our program, each presenting a short talk just before lunch. During the retreat, we were joined by another set of judges, who looked at the posters, evaluating presentation as well as content. The top posters judged at the retreat received travel awards. The winners of the travel award were: Emily Tai, M.S. (Technologies and Methods Development), Brunilde Gril, Ph.D. (Translational, Clinical, and Epidemiology Research), Yanlin Yu, Ph.D. (Basic Research) and Melissa Rotunno (DCEG award). We are thankful again this year to Jonathan Wiest, Ph.D., CCR Director of the Center for Cancer Training, for his support of the retreat (including emergency AV assistance!) and from his office, LaTasha Beasley and Kathy Augustin. We could not have had the retreat without them! Also, we are indebted to Doug Nichols who sets up the retreat website up for us.

Our closing remarks this year were by the NCI CCR Director, Robert Wiltrout, Ph.D. Dr. Wiltrout shared a realistic message about cancer funding in the current fiscal environment and the steps the NIH in general, and CCR, specifically, have taken. He congratulated us on our determination to keep moving forward, even in this infamous "year of the shutdown." In spite of these challenges, we agree with Dr. Wiltrout that there has never been a better time to be doing cancer research because of the rapid pace at which our understanding of cancer biology, genomics, and new technologies keep developing.

We thank all the attendants and especially the judges who made the trip to Shady Grove from Bethesda, Frederick, or wherever their workplace may be. We also would like to take this opportunity to invite new Staff Scientists and Staff Clinicians to join the retreat committee and help get the ball rolling for next year. Please e-mail us directly.

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The SSSC Retreat, Con't.

We present below the top scored abstracts. We are doing so because this is the first time we had abstract judged ahead of time, and secondly, because the competition was so close! Thanks to all who submitted.

BR (Basic Research)

Oral Abstract (1st place): Yanlin Yu, Ph.D. (PTEN phosphatase inhibits metastasis through negatively affecting Entpd5/IGF1R pathway)

2nd Place: Hanqiao Feng, Ph.D. (Structural investigation of the chromatosome in complex with HMG proteins)

3rd Place: Sven Bilke, Ph.D. (A chromatin structure based model accurately predicts replication timing program in human cells)

TCER (Translational, Clinical and Epidemiology Research)

Oral Abstract (1st place): Brunilde Gril, Ph.D. (Investigation of the molecular underpinnings of altered blood brain barrier permeability in brain metastases model)

2nd Place: Adam Metwalli, M.D. (A Predictive nomogram for urine leak in complex partial nephrectomy)

3rd Place: Anuradha Budhu, Ph.D. (Integrated metabolite and gene expression profiles identify lipid biomarkers associated with progression of hepatocellular carcinoma and patient outcomes)

TMD (Technologies and Methodologies Development)

Oral Abstract (1st place): Xiaoying, Ye, Ph.D. (In-depth mapping of the cell surface glycoproteome of cancer cells expressing specific alleles of K-Ras)

2nd Place: Chi-Ping Day, Ph.D. (Glowing Head Mice: A genetic tool enabling reliable preclinical image-based evaluation of cancers in immunocompetent mice)

3rd Place: Tai,Emily, M.S. (B cell epitope hot spot prediction by accessible surface area)

Rimas Orentas, Ph.D. (AS)
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2014 SSSC Retreat Co-Chair

Anu Puri, Ph.D. (SS)
Basic Research Laboratory
2014 SSSC Retreat Co-Chair

The PI Corner

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

NIH laboratories now have Staff Scientists integrated in their research programs. It is a change from the way NIH was operating initially with a few Postdoctoral Fellows and a technician assigned to each Senior Investigator. Today, the research environment has changed. To find a job after their NIH fellowship, Postdoctoral Fellows are under intense pressure to publish as many papers as possible in journals with the highest impact factor, which is reflected in their concern and reservation to engage in long-term and high-risk projects. In the area of drug discovery, Postdoctoral Fellows tend to favor molecular mechanisms and molecular biology approaches rather than drug screening and biomarker development. It is also likely that the scientific growth set up with the doubling of the NIH Budget will not happen in the near future and that the number of laboratory researchers will continue to exceed the number of faculty positions in academic departments. Yet, NIH laboratories must retain highly qualified and motivated research staff, especially because they do not have the critical mass of graduate students present in extramural laboratories.

Staff Scientists fulfill an important mission of the Developmental Therapeutics Branch (DTB), as they produce a critical mass of work over extended periods of time, thereby contributing to the scientific output and operational backbone of our research. Moreover, contrary to Postdoctoral Fellows, Staff Scientists are one of the pillars of our institutional memory. The DTB has the privilege to have several Staff Scientists across its different sections. They contribute to our mission in several critical ways that complement our Postdoctoral Fellows. They are key players for our long-term projects, and for retaining knowledge, unique techniques, and “savoir faire” in our Branch, such as generation of knockout mice, high throughput screens, development of biomarkers, bioinformatics and genomics analyses in cancer cell lines and TCGA databases, and specific methodologies used in collaboration with intra- and extra-mural investigators, such as DNA combing, radiation biodosimetry, and drug screens. In addition, Staff Scientists from the DTB have contributed to several bench-to-bedside programs aimed at speeding progress toward finding new therapeutics and/or improve diagnostic procedures for patients. In our experience, such projects cannot be successfully set up and maintained over extended periods of time solely by Postdoctoral Fellows with their 5-year term-limited fellowship. The duties and commitment of Staff Scientists are also deeply rooted in the success of the Branch rather than their own. By working with both the Postdoctoral Fellows and the Principal Investigators who supervise them, Staff Scientists act as bridges between Post-doctoral Fellows and Principal Investigators, thereby contributing to the fulfillment of our mentoring mission. They also assure day-to-day operations, enforcing lab safety, attending instruments, maintenance contracts, and helping Senior Investigators in the growing number of regulatory requirements.

As the DTB grew from the Laboratory of Molecular Pharmacology, I now have the privilege to work with a Staff Clinician. As the Branch is being structured for growth, with the establishment of a clinical pipeline focused on genomic approaches to cancer chemotherapy, I have requested another Staff Clinician to join our efforts. Indeed, Staff Clinicians are critically important to develop, submit, and primarily run clinical protocols, where they are involved in the day-to-day clinical management of patients on research protocols, both in the hospital and outpatients. Their work complements Senior Investigators who have the additional task to run a basic research program that prioritizes clinical applications.

To conclude, I believe that Staff Scientists and Staff Clinicians fulfill a unique part of our research mission, and that increasing their number, and in some cases, alternating positions with Postdoctoral Fellows, might allow some laboratories and branches to adapt to the ongoing changes in our biomedical research environment.

Yves Pommier, M.D., Ph.D.
Head, Molecular Pharmacology Group,
Chief, Developmental Therapeutics Branch

The SSSC Corner

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

I developed an interest in science during my time in medical school in Lima, Peru. After graduation, I joined the NIH scientific community as a Postdoctoral Fellow in the Pathology Section at NHLBI headed by Victor Ferrans, M.D., Ph.D. His group was studying a rare, but deathly, disease called Lymphangioleiomyomatosis (LAM). My work focused on understanding how smooth muscle-like cells, called LAM cells, form melanosomes, which are specialized organelles assembled to deposit melanin in melanocytes. After the passing of Dr. Victor Ferrans, I joined the laboratory of Vincent Hearing, Ph.D., at NCI as a Research Fellow. There, I had the opportunity to study the biology of melanosomes again, but this time in their physiological environment, the human skin. As a member of the Hearing lab, we uncovered the complete melanosome proteome and revealed their complex assembly mechanisms during maturation. This study led us to identify novel melanosome-related proteins and their alternate roles in tumor cell biology, such as in drug resistance. After becoming a Staff Scientist, Dr. Hearing gave me the opportunity and confidence to elucidate the complex biology behind melanocyte differentiation markers and the impact of losing their expression on advanced metastatic melanoma. The relative independence of being a Staff Scientist allowed me to explore several options and consult with world experts about the feasibility of every approach. Such advantages combined with the talent and knowledge of several experts accessible on campus enriched not only my research experience but also shaped my character to overcome the many challenges needed to successfully complete those projects. Fostering collaborations between pigment cell and melanoma researchers was one of the reasons I joined and led the Pigment Cell and Melanoma Research Interest group at NIH. Joining any of the NIH Special Interest Groups (SIGs) opens immense scientific and networking opportunities to meet with fellow scientists sharing your field of interest. Taking a moment to reflect, being a Staff Scientist allowed me to pursue complex approaches that otherwise one Postdoctoral Fellow might not be able to undertake fully during their time at NIH. Because of that, the Staff Scientist position represents continuity and stability between the scientists new to the lab and those that preceded them. Such a level of continuity is essential for the group and the program to achieve their scientific goals in an efficient and timely manner.

Julio is pictured above on a break for lunch with his two sons, Javier and Alvaro, at Great Seneca Park, MD.

Outside the lab, I enjoy all kinds of outdoor activities with my family, such as camping and hiking in the nearby Blue Ridge Mountains year round. Every trip teaches us something new and lets us appreciate the beauty of every season. Of course, such appreciation focuses on the vivid colors of nature, the pigments. Besides enjoying time with my family, I play and practice tennis with friends from around the DC metropolitan area.

Julio Cesar Valencia, M.D. (SS)
Pigment Cell Biology Section
Laboratory of Cell Biology

The Author's Corner

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

Commensal Bacteria Control Cancer Response to Therapy by Modulating the Tumor Microenvironment

Noriho Iida*, Amiran Dzutsev*, C. Andrew Stewart*, Loretta Smith, Nicolas Bouladoux, Rebecca A. Weingarten, Daniel A. Molina, Rosalba Salcedo, Timothy Back, Sarah Cramer, Ren-Ming Dai, Hiu Kiu, Marco Cardone, Shruti Naik, Anil K. Patri, Ena Wang, Francesco M. Marincola, Karen M. Frank, Yasmine Belkaid, Giorgio Trinchieri†, Romina S. Goldszmid† .***Science*** 22 November 2013.

Humans have coevolved with microbial partners and are indeed a composite of species, including human, bacterial, archaeal, fungi and viruses. Both in and on the human body, the microbial cells outnumber human cells by 10 fold, and in the gut in particular the microbial genome (microbiome) exceeds the human genome by at least two orders of magnitude. The past 10 years have seen an explosion of studies of the host-microbiome interaction in health and diseases due to the advent of new molecular and computational technologies that allows for the identification of the different species of an individual's microbiome. A large body of evidence has emerged indicating that the commensal microbiota plays a pivotal role in maintaining host homeostasis. For instance, intestinal microbes have a major protective role in displacing pathogens and enhancing barrier fortification. The microbiota also has systemic effects regulating inflammation, immunity, metabolic, cardiovascular and neurological functions. However, in some instances, the gut microbiota itself can become a liability. Recent evidence linked the microbiota to severe disorders ranging from autoimmune conditions, metabolic syndromes as well as autoimmune or inflammatory diseases. The microbiota is closely linked to cancer development both locally (e.g., colorectal carcinoma) and at distant sites (mammary carcinoma, hepatocellular carcinoma and lymphoma), and it is also involved in the establishment of metabolic pathologies favoring cancer (e.g., obesity). It is now well defined that inflammation and immunity affect tumor initiation, progression, dissemination and response to therapy. Emerging experimental and clinical evidence is strongly supporting the concept that the microbiota, via its local or systemic effects on inflammation, immunity, and metabolism, significantly affect all stages of tumor development. This led us to ask whether commensal bacteria could also affect the response to cancer treatment by modulating inflammation in the sterile tumor microenvironment.

To address this question, we selected three mouse transplantable tumors (EL4 lymphoma, MC38 colon carcinoma and B16 melanoma), based on their susceptibility to immunotherapy and chemotherapy. To investigate the role of the microbiota, we treated mice with an antibiotic cocktail (Abx) in drinking water starting 3 weeks prior to tumor injection or we utilized germ-free (GF) animals. Both tumor-bearing Abx-treated and tumor-bearing GF mice were significantly impaired in their ability to respond to a combination immunotherapy regime consisting of intratumoral injection of GpG-oligonucleotide (a TLR9 ligand) and systemic anti-IL-10 receptor antibodies (CpG/αIL-10R), or to platinum-based chemotherapy (e.g., oxaliplatin)[1] (Figure 1). The inability to respond to CpG/αIL-10R therapy was due to a defect in the tumor-infiltrating myeloid-derived cells to produce pro-inflammatory cytokines (e.g., tumor necrosis factor, TNF) and the subsequent induction of TNF-dependent tumor necrosis, both indispensable for tumor regression. The response to CpG/αIL-10R treatment was dependent on the host expression of TLR4, and oral administration of LPS could restore TNF production in Abx-treated mice. After cessation of Abx treatment the number of bacteria recovered to pretreatment levels within a week; however, *tnf* expression levels were not restored until 4 weeks post-Abx. Further, microbiome analysis revealed that several Gram+ and Gram- bacterial spp. positively correlated with the TNF response, whereas certain commensal *Lactobacillus* spp. were found to negatively correlate with the response. This correlation analysis was corroborated when oral administration of cultured *Alistipes shahii* to Abx-treated mice reconstituted the ability of tumor-associated myeloid cells to produce TNF, whereas, administration of *L. fermentum* to intact mice decreased the TNF response. Tumor-bearing Abx-treated and GF mice also failed to respond to chemotherapy with platinum compounds (e.g. oxaliptalin). Gene expression analysis revealed that Abx treatment attenuated most gene expression changes observed in tumors 18 hours post-chemotherapy. Abx treatment was found to impair oxaliplatin-induced expression of inflammatory med-

-diators and to block the induction of Cybb (encoding ROS-generating NADPH oxidase (NOX2)) in myeloid -derived cells (e.g., neutrophils and macrophages). Indeed, in vivo bioluminiscence studies and ex vivo analysis showed that Abx-treated mice were impaired in their ability to produce ROS in response to oxaliplatin. Furthermore, pharmacological inhibition of ROS, genetic ablation of *Cybb* expression and depletion of myeloid-derived cell populations led to impaired response to oxaliplatin treatment. These results indicated that the reduced efficacy of oxaliplatin treatment in Abx (or GF) mice could be due, at least in part, to reduced ROS production by tumor-infiltrating myeloid cells.

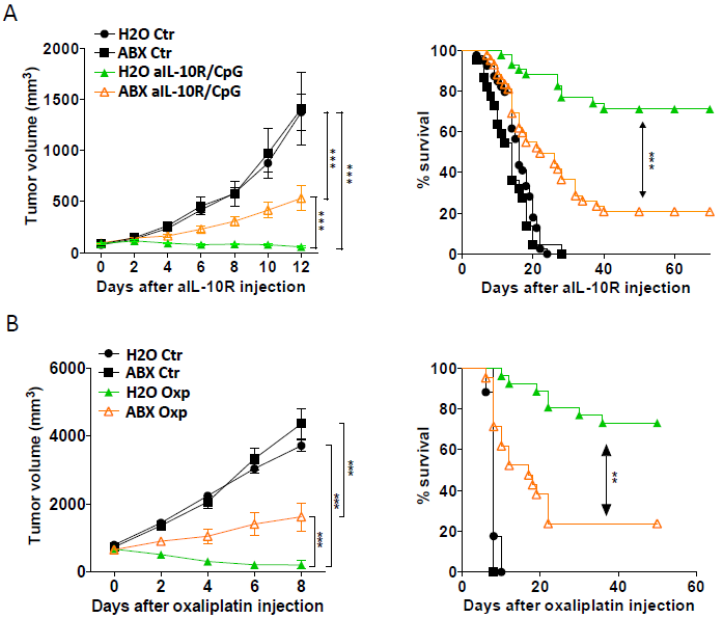


Figure 1. *Oral administration of antibiotics impairs CpG-ODN based immunotherapy and platinum chemotherapy. Tumor volume (left panel; means ±SEM) and corresponding survival data of H_2O-drinking or ABX-treated animals treated (A) with intratumoral injection of CpG-ODN in combination with anti-IL-10R antibody injected i.p. a day earlier (αIL10R/CpG-ODN), (B) with oxaliplatin injected i.p. (Oxp; 10 mg/kg) or left untreated (Ctr).*

In a parallel study, Viaud et al. showed that, in mice, cyclophosphamide (CTX)-induced mucositis (inflammation of the mucous membranes) was associated with altered composition of the intestinal flora and translocation of Gram+ bacteria into the draining lymph nodes. Such bacteria translocation was required for the proper induction of anti-tumor Th17 and Th1 immune responses. Accordingly, CTX chemotherapy was less effective in Abx-treated or GF tumor -bearing mice compared to controls, unless adoptively transferred with pathogenic Th17 cells.[2]

Altogether, these findings underscore the importance of the microbiota in the outcome of cancer treatment. Our study, together with that of Viaud and colleagues, showed that bacteria species can differentially modulate myeloid cell function to either promote or dampen the efficacy of immunotherapy and chemotherapy in several mouse subcutaneous tumor models (Figure 2). It is still unclear how these results translate into humans, but it is tempting to speculate that manipulation of the microbiota composition could lead to improved cancer treatments. Thus, we plan to continue our work in mice to fully understand the underlying mechanism of host-microbiome interactions, to gain a strong foundation of knowledge of how the microbiota communicates with the immune system and tumors at distant sites, and how the microbiota composition and functions change in response to various perturbations. An important future direction will be the study of the role of the microbiome (and the use of antibiotics) in the inflammatory response and outcome of cancer therapy in humans.

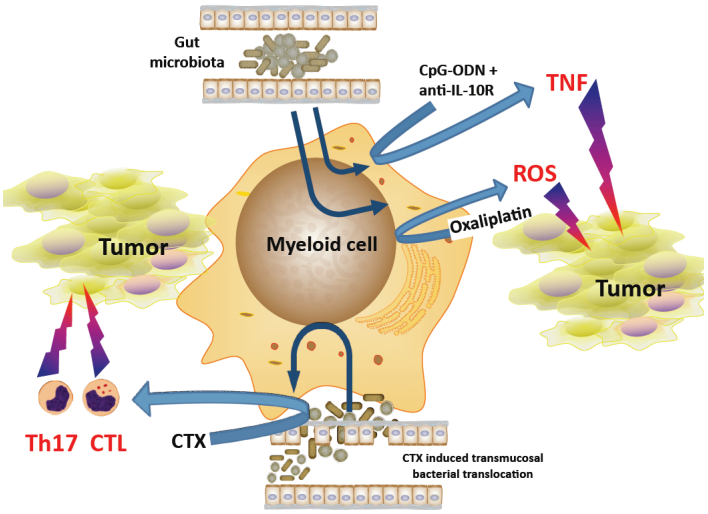
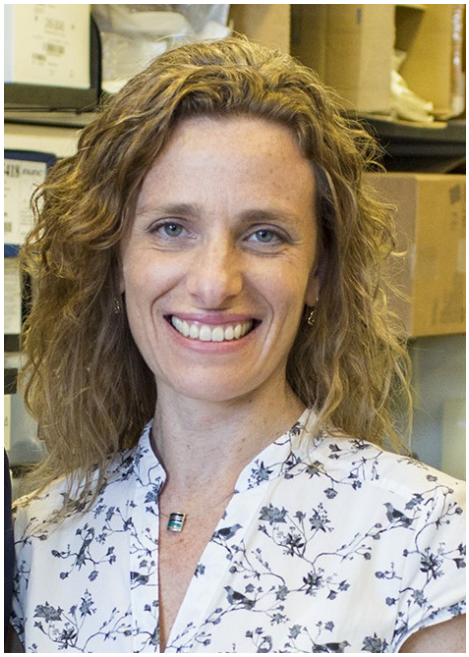


Figure 2. *Contribution of the commensal microbiota to the effectiveness of cancer therapy. The gut microbiota controls the efficacy of CpG-oligonucleotide (ODN) therapy combined with anti-IL-10R antibody treatment by enabling myeloid cells to produce TNF and the early genotoxic effect of oxaliplatin by enabling them to release ROS. Transmucosal translocation of bacteria induced by cyclophosphamide (CTX) treatment is required for the induction of adaptive immunity following CTX-induced immunogenic cell death.*

The Author's Corner Con't

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

Romina S. Goldszmid is a Staff Scientist in the Cancer Immunobiology Section of the Laboratory of Experimental Immunology, Cancer and Inflammation Program, NCI. Her role as a Staff Scientist includes supervising ongoing projects in the lab, by providing both scientific and technical training to Postdoctoral Fellows and students. She also has developed her own line of research and is actively involved in seeking, establishing and maintaining collaborations within other NIH or extramural labs.



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References:

1. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA *et al.* Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. ***Science*** 2013; **342:** 967-970.

2. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillere R, Hannani D *et al.* The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. ***Science*** 2013; **342:** 971-976.

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The Core Corner

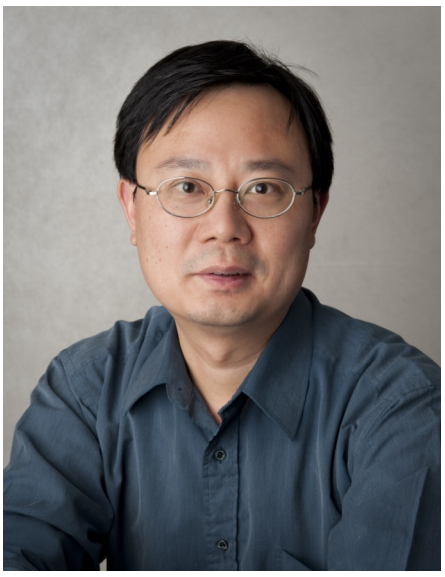
Section Editor: Anne Gegonne, Ph.D. (*SS*)

My collaboration with LASP: Turning red eyes to black in albino mice

In 2005, I started my postdoctoral training in NCI, under the mentorship of Glenn Merlino, Ph.D. Glenn's research focuses on the development of melanocyte and on melanoma mouse models. Specifically, his studies have made critical contributions to our understanding of the mechanism of UV-induced melanocytic transformation and of melanoma metastasis. When I joined his laboratory, we decided to generate a novel mouse model, which would carry a tetracycline-inducible transgene directing melanocyte-specific expression of Microphthalmia-associated transcription factor (MITF), a 'master regulator' of melanocyte differentiation. Our goal was to express this transgene on a background deficient of endogenous MITF (called vga9 and resulting from a heterologous transgene insertion in the MITF locus). The objective was simple: turning on or off the master regulator (MITF) of melanocytes in different developmental stages should allow us to identify melanocytic stem cells.

At that time I had very little experience with generating and breeding transgenic mice, but Glenn assured me that scientists in the NCI Laboratory Animal Science Program (LASP) would provide the necessary assistance. Little did I realize at the time how prescient he had been. We started 'by the book', generating our transgenic mice and hoping to breed them on the Vga9 background. Our LASP team leader, Cari Graff-Cherry figured out the experimental strategy and got the project started quickly. Despite her efforts, progress was slow. We did obtain transgenic mice, but bringing them on the correct background was difficult because of the low fertility of the MITF-null Vga9 strain. This is where LASP assistance became critical. First, Cari and her team tracked the breeding in detail, and found that the MITF-deficient mice would stop breeding after three to four rounds, which made it virtually impossible to assemble all three alleles (MITF-deficiency, the tet-inducible transgene and the tet activator) together. After discussing and trying out possible alternative strategies, we decided on a breeding strategy to generate homozygous mice carrying two of the alleles as the first step, and then add the third allele by microinjection. This sounds easy, but required generating a large enough colony of homozygous mice to perform microinjections. This is again where LASP became crucially involved. Lionel Feigenbaum, Ph.D., Director of LASP (now VP of a biotech in Boston), helped us design this strategy and generated the breeder colony to allow for microinjections. Later we also got help from Simone Difilippantonio, Ph.D., Senior Scientist at LASP, for detailed experiment design. At long last, we obtained mice with all three alleles. The last steps involved a tremendous logistical effort to generate enough mice for microinjections, and I realize how fortunate we were to collaborate with LASP on this project. Without their assistance, we would have given up a long time ago and guess what, we even managed to turn the red eyes of the mice into black.

During this process, I realized how important interactions and communication are for such long-term collaborative projects. Even though LASP scientists and technician are very professional and experienced, they need to understand the science and rationale behind the project, so that they can identify problems and make proper decisions. My experience emphasizes the importance of communication, whether by email, teleconference or actual meetings at the facility. Such visits and discussions, as well as my questions, even if they were naïve, allowed LASP staff to quickly respond to the reported problems. In the end, I had a great and pleasant experience working with LASP and I feel very fortunate to have worked with this great team.



Chi-Ping Day, Ph.D. (SS)
Cancer Modeling Section
Laboratory of Cancer Biology and Genetics

Announcements

Congratulations!

Join us in congratulating this year's travel award winners at our SSSC Retreat!

Emily Tai, M.S., Laboratory of Molecular Biology
Brunilde Gril, Ph.D., Women's Malignancies Branch
Yanlin Yu, Ph.D., Laboratory of Cancer Biology and Genetics
Melissa Rotunno, Ph.D., Genetic Epidemiology Branch

Attend!

Third Biennial NCI SSSC Professional Development Day
September, 2014 (Date TBD)
NCI Shady Grove Campus

Attend!

SSSC Social
June 10, 2014, 3-4 p.m.
Bldg. 37 North Entrance (park benches)
In case of inclement weather: 4-5 p.m., Bldg. 37, Rm. 2107/2014

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A Call for Content

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

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