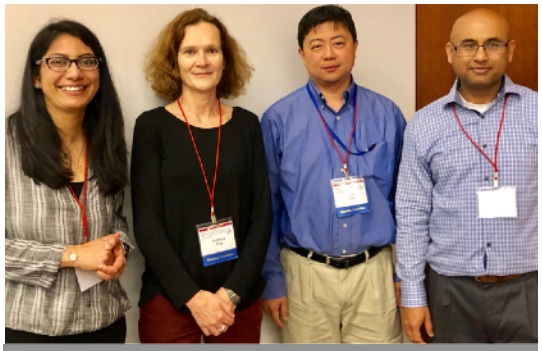
Issue 36 JUNE 2019

THE DOSSIER

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

From the Editor



SSSC retreat co-chairs (Lto R) Patricia, Yien and Kajal, and I (far left) at the recent SSSC Retreat

As SSSCs, we all work hard every day in our labs, in our varied positions, towards our own project goals and to enable the success of others in the lab. To step away from our daily responsibilities and get a vision of how our work fits into the goals of our institute can be deeply motivating. The SSSC Retreat is such an opportunity when we get to see our work through a wider lens, to be informed about the inspiring science taking place at the NCI and also interact with each other away from the lab. A lot of behind-the-scenes planning makes for a successful retreat. Several months before the SSSC Retreat, committees are formed, agendas drawn out, invitations sent and venues booked. I would like to thank all the members of the retreat committee for their hard work in ironing out all the details and organizing a smooth, productive and exciting retreat for all of us. The SSSC retreat in the Spring means summer interns will be here soon. We have a timely article in this issue about why being a mentor can be a rewarding experience for all involved and lists the many mentoring resources available through the Office of Intramural Training and Education. I hope the exciting science we heard about and the conversations we had at the recent SSSC retreat, as well as awareness about the valuable resources available to us, will further boost our supportive network and create momentum in the important work we all do.

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

In This Issue

Congratulations

15th Annual SSSC Retreat

Travel Awards (best posters)
Sohyoung Kim, Ph.D.
Qun Jiang, Ph.D.
Clara Bodelon, Ph.D.

Best Oral Presentation
Hidetaka Ohnuki, Ph.D.

Outstanding Mentor Award
Gwen Murphy, Ph.D.

Career Development

- **SSSC Technical Enrichment Program (STEP)** launched.
- **SSSC Career Enrichment Program** launched. While the program is limited to eight participants at a time, many activities are open to the SSSC community. Agenda listed here.
- Visit the **SSSC WEBSITE** for more information

The NCI Technology Transfer Center: Guest Editorial*

Innovation through Collaboration

NCI research is often translated into products, such as therapeutics, vaccines, diagnostics, or tools that enhance research activities. The primary mechanism that drives this transition from the lab to the market is "technology transfer." Because the NIH is a Federal government entity, it cannot commercialize or manufacture its own discoveries. However, the NCI Technology Transfer Center (TTC) bridges that gap by proactively facilitating partnerships between NCI researchers and outside organizations so that these discoveries can reach the public.

The TTC can be a strong resource and partner to help advance your clinical research. For example, TTC can recommend and facilitate a path to help investigators gain access to investigational drugs and collaborations with industry. Recently, TTC negotiated a Clinical Trial Agreement (CTA) between NCI and Bristol-Myers Squibb (BMS). CTAs allow NCI researchers to access external resources, like investigational drugs, not otherwise available at the NCI or NIH, for use in clinical trials. Through this particular CTA, Jing Wu M.D., Ph.D. from CCR's Neuro-Oncology Branch, obtained BMS' proprietary immune checkpoint inhibitor, nivolumab, and is now leading a clinical trial to test the effects of nivolumab in patients with gliomas. On average, CTAs typically can take anywhere from 3-4 months to complete. For this case, by using a previously negotiated CTA for a different project with BMS, as a starting point for Dr. Wu's CTA, the TTC was able to quickly complete the agreement in 1 month, allowing for a quick trial launch.

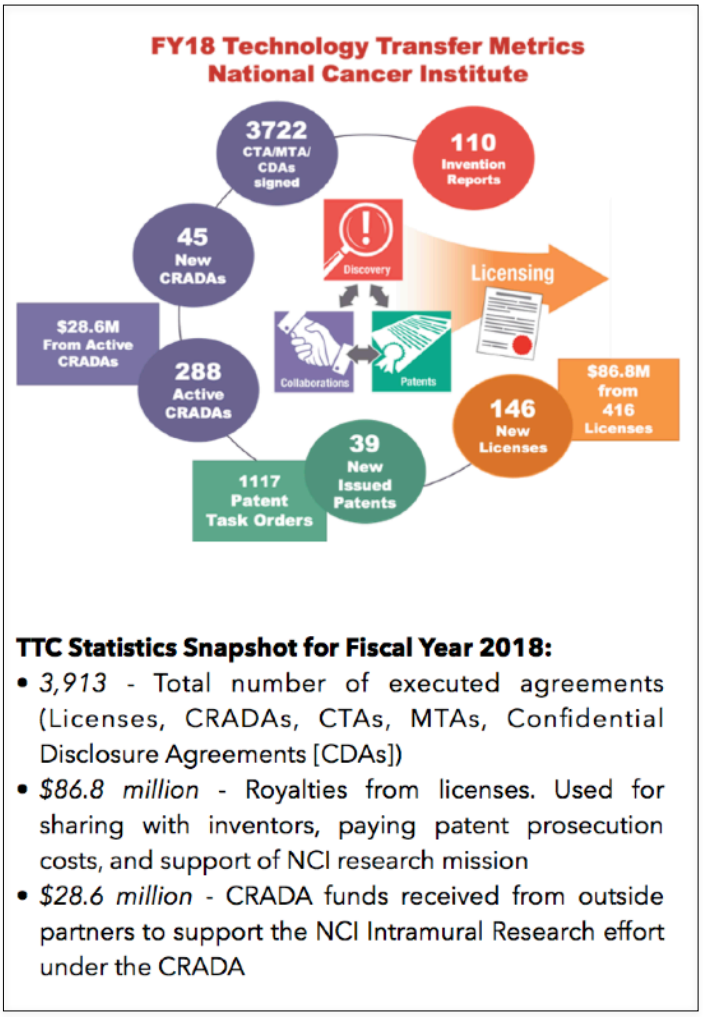
"The TTC can be a strong resource and partner to help advance your research"

The TTC can also facilitate more extensive collaborations. Through a Cooperative Research and Development Agreement (CRADA) and Material Transfer Agreements (MTAs), TTC facilitated a collaboration between EMD Serono and the NCI to further develop avelumab, an antibody that inhibits PD-L1 on the cell surface of tumor cells resulting in immune checkpoint inhibition. These agreements allowed NCI researchers, Jeffrey Schlom, Ph.D. (Chief of CCR's Laboratory for Tumor Immunology and Biology) and James Gulley, M.D., Ph.D. (Chief of CCR's Genitourinary Malignancies Branch) to begin studies of avelumab while it was in the earliest stages of development. Successful preclinical work led the team to explore multiple indications for the drug. Because these experiments were not included in the original agreement, TTC added an amendment to the original CRADA versus generating an entirely new one. Amendments to agreements typically take much less time to negotiate and offer TTC the flexibility to progress quickly with your scientific research needs. Avelumab has since received FDA approval for two indications: The FDA granted avelumab Biologics License Application (BLA) priority reviews for metastatic MCC (November 2016) and urothelial carcinoma (February 2017).

These examples and others, like those highlighted in *The NIH Catalyst's* May article, "Matching Researchers with Industry to Help Get NIH Inventions to Patients," strongly align with TTC's Vision: "*Engaged partnerships benefitting research, innovation, and public health.*" To accomplish this vision, the TTC actively partners CCR Staff Scientists, Staff Clinicians, and post-doctoral scientists with external stakeholders in academia, federal laboratories, non-profit organizations, and industry. By helping to establish these initial partnerships, TTC can further support the development of your collaborative research, help you gain access to external materials, and begin patenting & out-licensing technologies from your lab or from these partnerships.

Overall, the TTC is a part of your team supporting NCI's mission and strives to be flexible in considering the different mechanisms available to NCI to help advance your research and develop your discoveries, so they can be of benefit to patients in need. Through the TTC, there are a variety of services that can facilitate your research

**The CCR Director regularly invites guest columnists to inform the SSSC community on diverse aspects of the CCR and NCI*



TTC Statistics Snapshot for Fiscal Year 2018:

- *3,913* - Total number of executed agreements (Licenses, CRADAs, CTAs, MTAs, Confidential Disclosure Agreements [CDAs])
- *$86.8 million* - Royalties from licenses. Used for sharing with inventors, paying patent prosecution costs, and support of NCI research mission
- *$28.6 million* - CRADA funds received from outside partners to support the NCI Intramural Research effort under the CRADA

and collaborations to: 1) obtain lab-to-market gap funding for intramural research [TTC's Invention Development Program (IDP)], 2) share materials and information (confidential or non-confidential), 3) evaluate new discoveries from your lab for patent protection & business development partnerships (licensing), 4) develop partnerships and collaborations with academia and industry to advance your scientific research, and 5) partner with state and local economic development organizations to assist in commercialization of your discoveries.

Learn more about working with the NCI TTC through the CCR intranet, TTC website, or from your TTC Technology Transfer Manager (TTM). TTMs work with designated CCR labs/ branches to support your translational research efforts. Find out who your TTM is by clicking this link.

Thomas Stackhouse, Ph.D.
Director, TTC, NCI

The 15th Annual SSSC Retreat

A Report on the 15th Annual SSSC Retreat held on April 26th, 2019

"The retreat was attended by more than 90 participants from CCR, DCEG and Leidos, who shared their research, networked and were motivated by the inspiring science presented by the speakers"

The NCI 15th Annual Staff Scientists and Staff Clinicians (SSSC) retreat was held on 26th April 2019, at the Shady Grove campus. The retreat was sponsored by CCR, the Division of Cancer Epidemiology and Genetics (DCEG) and the Frederick National Laboratory for Cancer Research (FNLCR). The topic of this year's retreat was "*Tumor Initiation: Tumor Microenvironment and Metastasis*". Focusing on the development of cancer in complex tissue environments, it was an outstanding opportunity to hear about cutting-edge research from experts of basic, clinical and epidemiological cancer research. The retreat was attended by more than 90 participants who shared their research, networked, and were motivated by the inspiring science presented by the speakers.

The retreat began with welcome remarks from Kathleen Kelly, Ph.D, Deputy Director, CCR. The morning session started with a keynote talk from Stuart Yuspa, M.D., Co-Chief, Laboratory of Cancer Biology and Genetics, CCR.

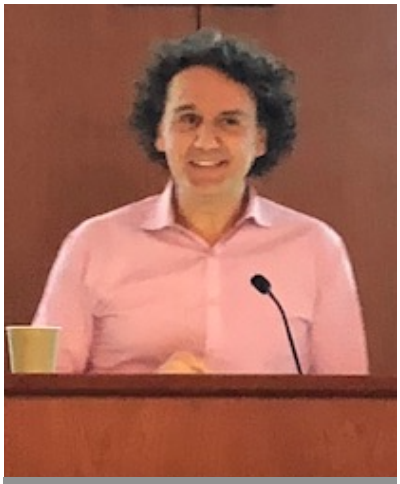
Panel discussion at the 2019 SSSC Retreat

Dr. Yuspa's outstanding talk focused on understanding cancer progression and pathogenesis using a melanoma model and was followed by presentations from three panelists, Patricia Steeg, Ph.D., Deputy Chief, Women's Malignancies Branch, CCR; Roberto Weigert, Ph.D., Senior Investigator, Laboratory of Cellular and Molecular Biology, CCR; and Gretchen Gierach, Ph.D., M.P.H., Deputy Chief, DCEG. These talks were followed by a panel discussion with the invited speakers and the audience. The lectures and discussions covered cancer research from different perspectives: basic science, clinical applications, development of new technologies and epidemiological cancer research. The morning session was moderated by Giovanna Tosato, M.D., Senior Investigator, Laboratory of Cellular Oncology, CCR. After the panel discussions, there were two poster sessions that featured presentations from 55 participants.

The afternoon session was highlighted by a second keynote talk, from the physician scientist Rosandra Kaplan, M.D., Pediatric Oncology Branch, CCR. The outstanding talk from Dr. Kaplan focused on the mechanisms needed for the formation of the pre-metastatic niche. Following this presentation were five oral presentations, which had been selected from the submitted abstracts by the judging committee. The oral presenters this year were Zhihui Liu, Ph.D., Pediatric Oncology Branch, CCR; Xinguo Chen, Ph.D., RNA Biology Laboratory, CCR; Hidetaka Ohnuki, Ph.D., Laboratory of Cellular Oncology, CCR; Noriko Sato, Ph.D., Molecular Imaging Program, CCR; and Lukas Bialkowski, Ph.D., Laboratory of Cellular Oncology, CCR. After the oral presentations from selected abstracts, information about various SSSC sub-committees was provided by Yoshimi Greer, Ph.D., Bethesda SS Co-Chair; Lakshmi Balagopalan, Ph.D., Co-Chair of communication sub-committee and Editor-in-Chief of "*The Dossier*"; and Jason Stagno, Ph.D., Frederick SS Co-Chair. This year's travel award winners were Sohyoung Kim, Ph.D., Qun Jiang, Ph.D., Clara Bodelon, Ph.D. for best posters and Hidetaka Ohnuki, Ph.D. for best oral presentation. Additionally, the SSSC outstanding mentor award winner was Gwen Murphy, Ph.D. To be nominated for a mentor award is in itself an honor. Balamurugan Kuppusamy, Ph.D., Sabrina Lusvarghi, Ph.D., Olusegun Onabajo, Ph.D. and Jason Rausch, Ph.D. were all nominated for this award.

Tom Misteli, Ph.D., Director CCR, delivered the closing remarks. He called the SSSCs an invaluable asset to the NCI research community. He also discussed the recent Women Scientist Advisors' SSSC survey, especially with regards to SS concerns about job stability and career

Group picture of attendees at the 2019 SSSC Retreat



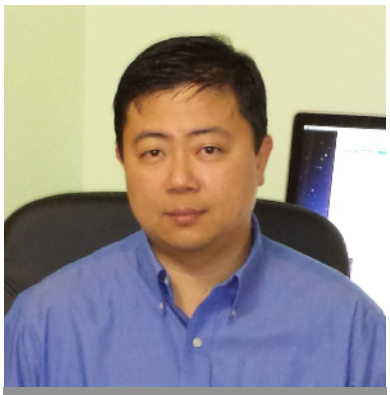
Tom Misteli, Ph.D. Director CCR, delivered the closing remarks

progression. He said he welcomed receiving SS input about ways to improve these aspects of the SS position.

We are thankful to Jonathan Wiest, Ph.D., as always, for his support and advice and Nicole Garner and Angela Jones for assistance in organizing this retreat. We thank all the judges for evaluating abstracts and especially to those who made a trip to Shady Grove to judge posters and oral presentations. We thank all the members of the organizing committee for their hard work and dedication in organizing this retreat. They include Paul Boyer, Ph.D., Ravindra Chalamalasetty, Ph.D., Nicolas Cuburu, Ph.D., David Danforth, Ph.D., Siddhartha Datta, Ph.D., Shannon Doyle, Ph.D., Yoshimi Greer, Ph.D., Duane Hamilton, Ph.D., Michael Kruhlak, Ph.D, Balamurugan Kuppusamy, Ph.D., Zhihui Liu, Ph.D., Ruibai Luo, Ph.D., Vladimir Majerciak, Ph.D., Prashant Mishra, Ph.D., Anu Puri, Ph.D., Arthur Shaffer, Ph.D., Shree Ram Singh, Ph.D., Jason Stagno, Ph.D., Abdul Waheel, Ph.D., and Wanping Xu, Ph.D. We thank all the participants for sharing their research and making it a successful day. See you next year!

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

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



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

Why be a mentor?

Working as a mentor can be an invaluable experience for both parties. Mentors and mentees will likely learn new things about themselves and each other that will help them move toward their individual career goals. Mentors act as advisors and coaches, providing guidance and feedback. You can help mentees step out of their comfort zone and navigate the ups and downs of scientific research. Be enthusiastic and maintain a positive outlook to promote an environment where team work thrives. Encourage your mentees to engage in the larger scientific community by attending lectures and meetings, joining interest groups and taking courses. Help your mentees gain experience and confidence in communicating their work by drafting papers and giving talks in a variety of settings (lab meetings, conferences, journal clubs).

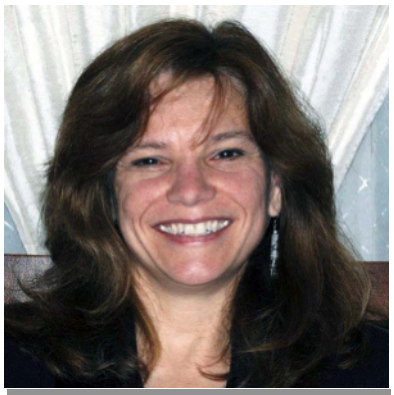
CCR, NCI and NIH all have *training the next cadre of interdisciplinary researchers* as an important component of their mission. The significance placed on mentoring is highlighted by its inclusion as part of the review criteria in both site visits and quadrennial reviews. SS/SC are encouraged to take advantage of opportunities to be actively involved in one or more mentoring roles. The return on your investment can be enormous.

SS/SC often serve as guides and role models for others in the lab. As individuals with sophisticated skills and knowledge essential to the work of the lab, SS/SC often have the opportunity to share their experience and expertise and act as a sounding board for ideas and research plans of biologists, postdoctoral and post baccalaureate fellows in the lab/branch. In addition to the summer student slot for each lab provided by CCR, NCI (Cancer Research Interns, CRI; iCURE) and NIH (Office of Intramural Training and Education, OITE,) also sponsors several summer internship programs that allow SS/SC to mentor summer students; OITE provides a one-day training session for potential mentors and has relevant information about teaching and mentoring opportunities at and outside the NIH on its website (see links in the box). SS/SC can also explore teaching courses through FAES and/or local community colleges. Some SS/SC participate on graduate student thesis committees or arrange training workshops on campus around their particular expertise.

Being a mentor not only provides an opportunity for the mentee to gain professional skills needed to advance their careers, but also provides the SS/SC an opportunity to advance their own career goals. Learning how to work with people who need guidance and support, and helping them figure out the best path forward are traits of a good leader and skills honed through mentoring. In a study by Sun Microsystems which followed the career progress of over 1000 employees, individuals who had acted as mentors were six times more likely to be promoted than counterparts who didn't and 20% more likely to get a raise. Encouraging the growth and development of new researchers, can also provide you with a new perspective on your research and lead to new ideas and projects. So, get involved and become a mentor.

Mentoring Resources through OITE

- OITE website lists teaching and mentoring opportunities at and outside the NIH
- Research Excellence Mentorship Program runs workshops periodically
- OITE summer research mentor training workshops in the spring
- Since summer students will be here soon, read this useful blog on mentoring tips for summer students.



Cynthia Masison, Ph.D. (AS)
Scientific Program Specialist
Office of the Director

The Core Corner

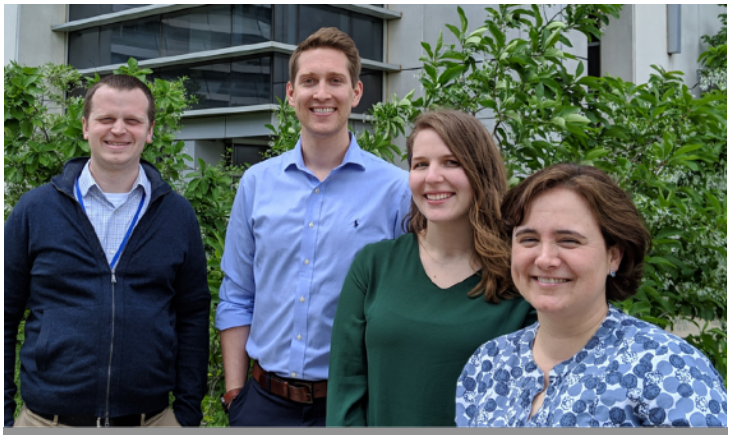
Section Editor: Anne Gegonne, Ph.D. (SS)

The CCR Single Cell Analysis Facility

The single cell is the biological unit that we are often interested in examining in health and disease. Advancements over the past several years have made it possible to interrogate the transcriptome and genome at single cell resolution, and results have provided incredible insights across many biological research disciplines. Within the fields of cancer biology and immunology, the benefits of this technology can be applied to a wide variety of applications, from understanding cell heterogeneity in the tumor environment, characterizing the immune system development and response, comparing differences between treatment responsive and unresponsive cell populations, to mapping cell lineages and clonality of tumor and immune cells.

Building upon existing support for single cell sequencing within CCR, the Single Cell Analysis Facility (SCAF) was established in 2018 to provide expanded and integrated support for the single cell sequencing technologies. The Facility is located on the NIH Bethesda campus in Building 37 for timely processing of samples from Bethesda labs and the clinical center. Support includes consultation on experimental design, methods advise and selection, single cell capture and library preparation, coordination of sequencing, primary data analysis, and coordination and advice on downstream analysis. Current technologies available as part of the SCAF portfolio, include single cell solutions from 10x Genomics (including droplet-based single cell RNA-Seq, ATAC-Seq, and CNV), BD Genomics Rhapsody, Menarini DEPArray, and plate-based single cell solutions. Single cell gene expression profiling on the 10x Genomics platform also allows B-cell and/or T-cell receptor sequence determination along with gene expression profile. More recently, the facility also supports the use of a technique known as antibody feature barcoding, to allow cell surface protein expression detection along with mRNA expression profiling.

The Single Cell Analysis Facility is operated by the Cancer Research Technology Program (Frederick National Laboratory, FNL), and is managed by Mike Kelly, PhD. Staff includes Maria Hernandez, PhD (Scientist), Zach Rae (Research Associate), Allison Ruchinskas (Research Associate), and Ezzat Dadkhah (Scientist, joining the facility this summer). SCAF works closely with the other CCR-dedicated cores within the Cancer Research Technology Program, including the Genomic Technology Lab and the Sequencing Facility, to provide cutting-edge genomics support to the CCR community. SCAF also works in close collaboration with



From L to R: Dr. Mike Kelly, Zach Rae, Allison Ruchinskas and Dr. Maria Hernandez outside Bldg. 37 where the SCAF facility is located.

other CCR cores, including the CCR Genomics Core (Building 37), CCR Collaborative Bioinformatics Resource (CCBR), the LGI Flow Cytometry Core (Building 37), the Genome Analysis Unit (GAU), the Bioinformatics Training and Education Program (BTEP), and the Collaborative Protein Technology Resource (CPTR NanoScale Protein Analysis Unit).

To learn more about SCAF, please visit the CCR Office of Science and Technology (OSTR) website. To submit a project, visit the NCI-Frederick Accessing System: You can also contact Mike Kelly at michael.kelly3@nih.gov with any questions or requests for project consultations.

Single cell support to NCI-CCR Investigators located in Frederick continue to be supported by the CCR Sequencing Facility and CCR Sequencing Facility Informatics groups.

Michael Kelly, Ph.D.
Manager
Single Cell Analysis Facility

The PI Corner

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

Research in my group focuses on understanding how TGF-ß through various signaling conduits mounts a diverse array of cellular responses. We are using a combination of mouse genetic, genomic and proteomic approaches to dissect cell-context dependent roles of TGF-ß during development, adult tissue homeostasis and tumorigenesis. During the past decade, we also carried out detailed studies of Smurf1 and Smurf2-

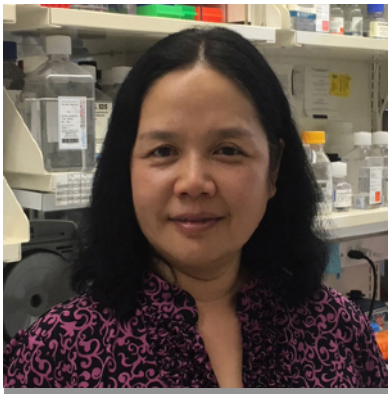
deficient mice and uncovered several unexpected functions of Smurfs in regulating osteogenic differentiation, fat metabolism and genomic stability. In attaining these goals, I'm fortunate in my position as a Senior Investigator to have two Staff Scientists, Liuya Tang, Ph.D. and Christina Stuelten, M.D., Ph.D., working with me.

Dr. Tang received her Ph.D. degree from the Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences in 2008. Her Ph.D. thesis work centered on phosphoproteomic analysis of Wnt signaling, and in the process she became well versed in the areas of biochemistry and proteomics. She joined my group in the Laboratory of Cellular and Molecular Biology (LCMB) first as a Visiting Fellow, progressed to a Research Fellow, and finally became a Staff Scientist in 2017. Liuya was instrumental in characterizing the molecular mechanism underlying the inhibitory role of Smurf2 in TGF-ß/Smad signaling. She found that Smurf2 induces mono-ubiquitination of Smad3 *in vivo* instead of promoting polyubiquitination and degradation. This modification prevents Smad3 from forming a complex with Smad4, thereby attenuating TGF-ß signaling responses. Liuya has also successfully completed a proteomics project in which she systematically examined the protein interaction network in TGF-ß type I receptor (TGFßR1) signaling by employing methods of stable isotope labeling of amino acids in cell culture (SILAC) and mass-spectra analysis. She obtained high quality mass-spectra data generated from this project, which not only provided a comprehensive understanding of protein interaction networks regulated by TGFßR1 signaling, but also identified JAK1 as a TGFßR1 interaction protein. She further showed that JAK1 activates STAT3 in both Smad-independent and dependent manners in response to TGF-ß in hepatic cells. She further demonstrated that STAT3 is required to cooperate with Smad3 to induce fibrotic response in hepatic stellate cells.

"CCR Staff Scientists are essential in maintaining productivity and keeping scientific group stability. The success of the intramural program is highly dependent on them."

Dr. Christina Stuelten joined the CCR in 2003 as a postdoctoral fellow in the lab of Anita Roberts, Ph.D., where she studied the role of TGF-ß signaling in breast cancer. Following the untimely death of Dr. Roberts in 2006, Christina was recruited by John Niederhuber, M.D. to establish his cancer stem cell program and was promoted to Staff Scientist in 2010. When Dr. Niederhuber left NCI in 2011, Christina was transferred to the lab of Carole Parent, Ph.D. in LCMB. In the fall of 2017, Christina joined my group following the departure of Dr. Parent. During her time in Dr. Parent's group, Christina helped Dr. Parent in translating basic knowledge of directed cell migration gained from studies of Dictyostelium and mammalian neutrophils to the study of metastasis. I have known Christina since her time in Dr. Anita Roberts's group. We both served as co-authors of a paper published in Cancer Research in 2004, which characterized the role of a TGFßR1 mutant that my group generated in breast cancer metastasis. So, she is a no stranger to our field. During the past year and a half since she joined my group, she quickly learned mouse models we used in the lab and set up new animal protocols to study TGF-ß signaling in metastasis and wound healing. I am impressed by her knowledge of cancer metastasis, clinical perspective, and skills in imaging technology and quantitative analysis. I believe that she will be a key player in my research program with the potential for high-risk and high-impact research.

From my experience, I believe that CCR Staff Scientists are essential in maintaining productivity and keeping scientific group stability. The success of the intramural program is highly dependent on them.



Ying E. Zhang, Ph.D.
Senior Investigator
Laboratory of Cellular and Molecular Biology

The Author's Corner

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

C/EBPδ links IL-6 and HIF-1 signaling to promote breast cancer stem cell-associated phenotypes

Kuppusamy Balamurugan, Daniel Mendoza-Villanueva, Shikha Sharan, Glenn H. Summers, Lacey E. Dobrolecki, Michael T. Lewis and Esta Sterneck. Oncogene, 2018, doi.org/10.1038/s41388-018-0516-5.

Metastasis and treatment resistance are the primary causes of death for most cancer patients, and cancer cells with stem cell-like characteristics (cancer stem cells, CSCs) have been implicated in these processes. For the development of novel, targeted therapies, there is an immediate need to better understand the mechanisms that lead to the development and maintenance of CSCs. Hypoxia and inflammation are established hallmarks of cancer and many studies have shown that these microenvironmental conditions play an important role in the generation and maintenance of CSCs, and operate in part through induction of NOTCH1, a critical CSC regulator (Balamurugan, 2016). Hypoxia/HIF-1 and IL-6/STAT3 also induce the transcription factor CCAAT/enhancer binding protein delta (C/EBP, CEBPD). In turn, C/EBP promotes HIF-1 expression by transcriptional and post-transcriptional mechanism and directly activates IL-6 gene expression (Balamurugan and Sterneck, 2013; Yamaguchi et al., 2015). In the present study, Kuppusamy Balamurugan, Ph.D., Staff Scientist in the Laboratory of Cell and Developmental Signaling headed by Esta Sterneck, Ph.D, and his colleagues investigate whether C/EBP supports hypoxia- or IL-6-induced cancer cell stemness using genetic mouse models and human breast cancer cell lines.

At first, the authors looked at the role of C/EBPδ in CSC-associated features in mouse and human breast cancer cells using surrogate assays such as mammosphere formation efficiency, self-renewal capacity, and CSC surface markers analysis as well as the circulating tumor cell (CTCs) in MMTV-Neu tumor mouse model. Indeed, C/EBPδ promotes CSC-associated features in mouse and human breast cancer cells. To extend these findings to functional in vivo assays, the role of C/EBPδ was assessed in tumor growth by orthotopic injection of breast tumor cells and stable or inducible gene silencing approaches. The study demonstrated that C/EBPδ promotes tumor growth, lung colonization, and stemness gene expression in vivo. Silencing of C/EBPδ, after the establishment of lung colonies by Dox-induced silencing, significantly reduced the growth of experimental lung metastases indicating that C/EBPδ promotes tumor growth also at a common site of metastasis. Accordingly, C/EBPδ is expressed in a significant number of metastatic patient-derived xenografts. Mechanistically, the author found that C/EBPδ was enriched in CD44+CD24− cells and CSCs defined by the expression of two different experimental reporter genes compared to non-CSC populations, along with the known stemness factors Nanog, Sox2, Klf4, Myc, and also pSTAT3. In particular, C/EBPδ promotes IL-6/STAT3 signaling by regulating the expression of both IL-6 and IL-6R directly. Importantly, this study led to the discovery that C/EBP supports cancer stemness pathways by integrating and amplifying hypoxia- and IL-6-induced signaling including Notch1 activity, in addition to directly targeting the promoters of several genes that encode markers and drivers of stemness (Figure 1).

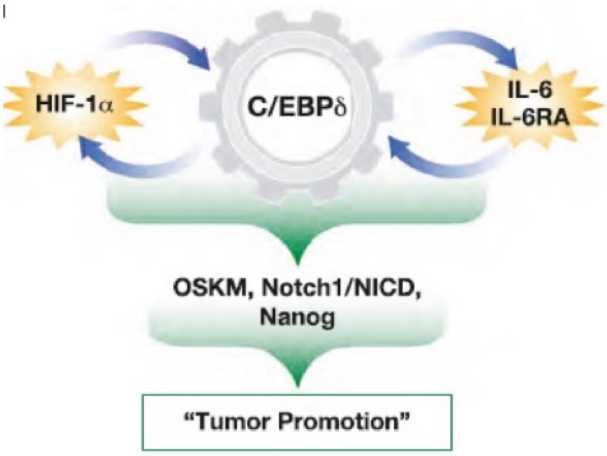


Figure 1. Model illustrating how C/EBPδ integrates two positive feed back loops of HIF-1 and IL-6 signaling, which - together with C/EBPδ's direct targeting of stemness genes - culminates in tumor promotion by conditions commonly found in the tumor microenvironment.

One could ask what is unique about C/EBPδ in promoting CSC pathways? The answer is that it is not a "bystander", rather, by linking several signaling pathways, C/EBPδ serves as an amplifier of pro-metastatic pathways and could represent a unique point of cancer cell vulnerability. Although targeting of transcription factors is challenging, Dr. Balamurugan and the Laboratory of Cell and Developmental Signaling are currently exploring several strategies toward this aim. This study also underscores the important role of tumor microenvironmental conditions and their potential to synergize in promoting the malignancy of cancer cells and provides proof of principle that targeting of C/EBPδ may attenuate the growth of tumors and metastases.

REFERENCES:

1. Balamurugan K, HIF-1 at the cross roads of hypoxia, inflammation and cancer, Int. J. Cancer, 2016, 138, 1058-1066.
2. Balamurugan K, Sterneck E, The many faces of CEBPD and their implications in inflammation and cancer, Int. J. Biol. Sci. 2013, 9, 917-933.
3. Brower V, Cancer stem cells hypothesis evolves with emerging research, J. Natl. Can. Inst. 2016, 108, 2-4.
4. Yamaguchi J, Tanaka T, Eto N, Nangaku M, Inflammation and hypoxia linked to renal injury by CCAAT/Enhancer binding protein delta, Kidney Int. 2015, 88, 262-275.

Balamurugan Kuppusamy, Ph.D. (SS), Laboratory of Cell Development and Signaling

Dr. Balamurugan Kuppusamy, is a Staff Scientist in the Laboratory of Cell and Developmental Signaling, NCI. He leads a few core projects in the lab, providing both scientific and technical support to fellows and students. He supports the SSSC community by serving as a Frederick Vice Co-Chair of SSSC organization. He is also involved with the annual SSSC retreat committee. His areas of expertise include Hypoxia, Signal Transduction, Cancer Stem Cells, Mouse Models, Breast Cancer, CEBPD transcription factor, FBXW7, and Inflammation. He is actively seeking collaboration opportunities within other NIH or extramural labs.

The Clinical Corner

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

An interview with Christopher J. Melani, M.D. (SC, ARP) Lymphoid Malignancies Branch

What is your general role as a Staff Clinician?

As a staff clinician, I am responsible for carrying out the clinical duties and clinical research of our lymphoma group in the Lymphoid Malignancies Branch (LYMB). I currently serve as the Inpatient Service Chief and oversee the care of the LYMB patients admitted to the clinical center. I also participate in the care of the consultations and outpatient screens we see in our lymphoma clinic. Additionally, I serve as either principal or associate investigator on all the clinical protocols lead by our research group. This entails managing the clinical care of these trial patients but also includes the regulatory aspects of the trials, including adverse event assessment, reporting to the trial sponsor/ pharmaceutical collaborators/FDA, and oversight of data collection and analysis.

Could you point out steps and difficulties to implement a clinical trial?

The process of navigating a clinical trial from concept design to study activation is often a long and arduous one. After countless hours authoring the protocol document, including background information, study design, statistical analysis, and more, the protocol needs to then be approved by the scientific review committees of the branch and CCR as well as the pharmaceutical collaborators, FDA and the IRB. This entire process can take on average 6-12 months depending on the complexity of the trial and number of entities involved.

Christopher J. Melani M.D.
(SC, ARP)
Lymphoid Malignancies Branch

Fortunately, there are multiple other people and departments that can help support this process including the CCR Protocol Support Office (PSO) and the NCI Technology Transfer Center (TTC).

What is your contact with the staff scientists? Any report of bench-to-bedside cooperation?

The correlatives that complement our clinical trials are performed by the staff scientists of the laboratory of our branch co-chief, Louis M. Staudt, MD, PhD. At our monthly branch meetings, we plan future molecular analyses and discuss the results of previously performed testing. Collaboration with these staff scientists helps to gain insight into the mechanisms of response/resistance to the therapies we use in our clinical studies. All of our trials are based on strong pre-clinical science from these scientists and we've also started a "bedside-to-bench" conference where interesting findings and cases seen in the clinic are presented and can generate further research questions in order to better understand the underlying biology of these interesting lymphoma cases.

How do you see patient care at NIH? Can you give examples of benefits and limitations?

We are frequently told by our patients that the care they receive at NIH is unlike any other institution they've encountered. This is likely a result of the vast amount of expertise of the clinical investigators as well as the immense time and dedication spent on each individual who is enrolled on a clinical trial. This attention to detail and clinical expertise is a clear benefit to patients cared for at the NIH. Given that we are a federally funded agency, we cannot assume care for every patient we see at NIH and are only able to treat those who fit eligibility criteria for a clinical trial. This can sometimes lead to patient frustration and is a limitation to our institution.

What is the career path of a staff clinician? Where do they go from here?

The staff clinician position provides a great opportunity to build your clinical skills as well as further develop your knowledge and abilities as a clinical investigator. Your position and work, however, depend heavily on your principal investigator (PI), which means that if your PI leaves the institution, you may need to look for another position or job. Some investigators use the staff clinician position to further build their skills and publications and apply for one of the many tenure-track positions offered through the NIH. The staff clinician position also prepares individuals for other professions outside the NIH including careers in industry, regulatory agencies such as the FDA, and other academic institutions.

Any final advice for new staff clinicians or about collaborations between staff clinician & staff scientist?

The staff clinician position provides a unique protected opportunity to learn a tremendous amount of clinical knowledge and research skills. Individuals who are eager to learn and have a solid work ethic can be extremely successful during their time in this role. A reputable, supportive mentor is key to your growth and development and is integral in facilitating the transition from a staff clinician to a more permanent position. Networking and collaborating with other staff clinicians and staff scientists can lead to many important projects and discoveries and can open other opportunities for your future career.

"Streamlining efficiency and time management skills and taking time to reflect on your advancement and accomplishments often helps to keep you motivated and protects you from being engulfed by the never ending list of "to-do's.""

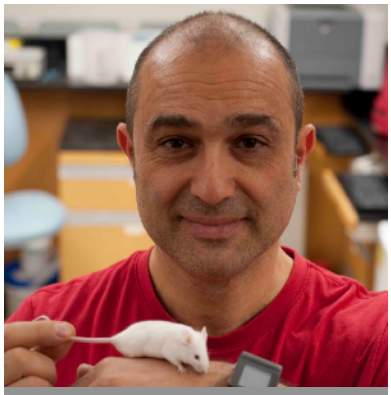
Have you identified any personal issues or challenges in being a medical scientist? Any specific advice to others starting in that path?

Seeing the direct clinical benefit of a novel treatment regimen you designed for the patients you treat is an extremely gratifying experience for a clinical investigator. These positive experiences need to be kept in mind when the burdens of being both a clinician and clinical investigator are encountered. Often, one

feels as if they are performing two simultaneous jobs when they are attempting to manage a busy clinic and inpatient service while also authoring/running clinical protocols, writing manuscripts and presenting at academic conferences. Streamlining efficiency and time management skills and taking time to reflect on your advancement and accomplishments often helps to keep you motivated and protect you from being engulfed by the never ending list of "to-do's." Good relationships with your fellow staff clinician/staff scientist collaborators, nurses, and fellows can also help to offload some of the patient care duties and complete multiple research projects simultaneously.

The SSSC Corner

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



Gianluca Fulgenzi, Ph.D. in the laboratory with topolino (small mouse in Italian)

After my degree in Biology a long, long time ago (1990) I started traveling around for research. I tarveled first to Birmingham, UK, then to Cambridge, UK, then to Munich, Germany, and then again to UK, this time to London. Finally, in 2003, I got tenured at the university of Ancona (my birthplace) as Assistant Professor of Pathology. I thought then that the time for travelling around was over and it was time to settle down. It didn't last very long. Indeed in 2004 I traveled to Naples and then in 2006, during a trip to USA for tourism, I came to visit an old friend who at that time was working at the NCI, Frederick, Vincenzo Coppola, M.D. He introduced me to Lino Tessarollo, Ph.D. I liked the place and we started collaborating. I really settled down (research-wise). After endless short and long research expeditions and 2 sabbaticals from Ancona where I was still teaching in the medical school, in 2017 I began as a staff scientist at the NCI. Working at the NCI in the MCGP program is wonderful, both scientifically and socially. I am experienced to say so!

My research focus is the Brain Derived Neurotrophic Factor receptor TrkB, and in particular Truncated 1, one of its isoforms. My technical expertise: electrophysiology and electron microscopy, are employed and integrated in the research group and allow me to tackle the problems from different points of view. The resources available at the NCI-Frederick are amazing, and the research challenges stimulate me to do better and more. Working with Dr. Tessarollo is easy and very enjoyable. He helps me in finding the right questions and helping me keep focus on a few projects at a time.

Dr. Fulgenzi skiing with his family

Outside the lab my life is mainly devoted to keeping pace with my two daughters Greta and Elettra (6 and 9 years old). My leftover free time is dedicated to sailing in the summer and skiing in the winter, fixing my motorbike, that is constantly broken, and possibly riding it is my supreme pleasure. Lastly, I want to thank my wife for loving and supporting me in my erratic path.

Gianluca Fulgenzi, Ph.D. (SS)
Mouse Cancer Genetics Program
Neural Development Section

SSSC Co-chairs

Bethesda Co-Chair:
Yoshimi E. Greer, M.D., Ph.D. (SS)
Women's Malignancies Branch

Frederick Co-Chair:
Jason Stagno, Ph.D. (AS)
Structural Biophysiscs Laboratory

Clinical Co-Chair:
Lindsey Rowe, M.D. (SC)
Radiation Oncology Branch

Join an SSSC Committee

PROFESSIONAL DEVELOPMENT
Swati Choksi

COMMUNICATIONS
SSSC WEBSITE
Aleksandra Michalowski

DOSSIER
Lakshmi Balagopalan

SSSC RETREAT
Kajal Biswas

Patricia Day

Yien Che Tsai

NETWORKING
SOCIAL
Even Walseng

BROWN BAG SEMINARS
Yoshimi Greer
Christina Stuelten
Emily Tai

We Need Your Input
Send your feedback to
balagopl@mail.nih.gov

VISIT THE
SSSC WEBSITE
FOR INFORMATION ABOUT
THE QUAD REVIEW
SSSC ENRICHMENT PROGRAMS
BROWN BAG SEMINARS
SSSC HANDBOOK
AND MORE