THE DOSSIER

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

September 2017 Issue 29

From the Editor

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

This issue contains information from CCR Director, Tom Misteli, Ph.D., regarding his recent Town Hall meeting with the CCR SSSC community. The Town Hall meeting is also reviewed by our Bethesda SSSC Co-Chair and Vice-Co-Chair, Emily Tai and Lakshmi Balagopalan, Ph.D., along with the Head of our Professional Development Committee, Swati Choksi, Ph.D. We also have a special article by Jay A. Berzofsky, M.D., Ph.D., and highlight the published work of Zhongyu Zhu, Ph.D., in our Author's Corner and feature Xue Zhi Zhao, Ph.D., in our SSSC Corner. Our Core Corner describes the work of Nirali N. Shah, M.D., MHSc., and her collaboration with the Department of Transfusion Medicine, the Laboratory of Pathology-Flow Cytometry Lab, and the Cell Processing Facility. Meanwhile, in our new Clinical Corner, we obtain the viewpoints of Ravi A. Madan, M.D., on several aspects of the Staff Clinician position.

We hope to continue to provide pertinent information to aid in the success of SSSCs. Please send your contributions, suggestions and comments to budhua@mail.nih.gov.

Anuradha Budhu, Ph.D. (SS)
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In This Issue

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The Office of the Director

A few weeks ago, I had the opportunity to meet for two productive hours with CCR Staff Scientists and Staff Clinicians (SSSCs) at a town hall-style meeting hosted by the NCI SSSC Association. I very much appreciated the opportunity to hear your opinions and concerns about some career and workplace-related issues of relevance to SSSC. What left an even more lasting impression was the enthusiasm, commitment and dedication made evident by the comments and questions of those present. Several points to build upon emerged during the conversation.

Many topics discussed related, not surprisingly, in one way or another to career development opportunities for SSSC. The NIH Intramural program has been a pioneer in establishing the concept of SSSC positions, and we are the envy of many academic institutions. Given the community's demand for stable non-tenure track career paths, these institutions are increasingly emulating us by creating similar types of positions.

On the other hand, the SSSCs career trajectory and evolution is not without challenges. Because of the vast heterogeneity in the type of work performed by SSSCs, there is no standard career path with clearly defined milestones that automatically leads to promotions, professional growth and training opportunities. The career evolution of each SSSC is somewhat unique. On the clinical side, SCs often shoulder some responsibilities comparable to those of a PI, but are limited in their independence. To create an attractive career path and a productive work environment for SSSCs and to ensure that the NIH IRP can retain our best SSSCs, it is imperative to continuously evaluate what works and what does not work in the SSSC career structure.

An important aspect of SSSC career development is for SSSCs to be engaged with and to visible in the community. CCR now reserves several speaking slots for SSSCs in the weekly Grand Rounds lecture. A call for nominations for the 2017/18 seminar series has just gone out to PIs and Chiefs. We also encourage CCR committee chairs to include SSSCs on various committees, including search committees and review panels. As we find that SSSCs are particularly well-positioned to help shape CCR technology platforms by participating on committees that advise our facilities and cores, we strongly encourage the participation of SSSCs in these bodies.

CCR led the NIH with the creation of a professional titling model for staff clinicians, to better recognize their career responsibilities and progression and to align them with the extramural track. We remain committed to leading NIH and as outlined at the town hall meeting by Ofelia Olivero, Ph.D., from NCI's Center for Cancer Training, efforts are also underway to create further career development opportunities for SSSCs. It is also important to keep in mind that SSSC are fully eligible to apply for tenure track or senior scientist positions, and CCR has made several such appointments of SSSCs over the past several years.

Finally, one of the many valuable ideas that emerged during the town hall discussion was the suggestion for SSSCs to participate in time-limited details to other laboratories or parts of the CCR to receive training in new technology or to explore areas of the scientific enterprise different from their normal tour of duty. We are certainly supportive in concept of such activities.

The town hall meeting made it clear to me that there is work for us to do in addressing some of the challenges SSSCs face in their career development as well as to ensure that the NIH remains at the forefront of defining successful SSSCs career paths. Given that this model originated here in the IRP and has been such an important component of our success, I very much look forward to working with the SSSC community to do precisely that.

Tom Misteli, Ph.D.
Director, Center for Cancer Research

The PI Corner

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

The Vaccine Branch mission is to elucidate basic mechanisms of immune response and molecular virology and then translate those discoveries to develop vaccines and immunotherapies for cancer, HIV, and viruses that cause cancer. The ultimate goal is to translate these into clinical trials in patients. The branch already has several clinical trials testing discoveries and inventions made by branch scientists. Cancer and chronic viral infections like HIV and SIV share many features in common, including evasion of the immune system, often by exploiting the immune system's own regulatory mechanisms, and escape from the immune responses induced. Both have need for therapeutic as well as prophylactic vaccines. Yet there is generally little communication between HIV researchers and cancer researchers. The Vaccine Branch aims to promote cross-fertilization between these fields. In these endeavors, the Vaccine Branch staff scientists play a central and essential role, leading projects and mentoring postdoctoral and post-baccalaureate fellows. In my own lab, Masaki Terabe, Ph.D., leads the tumor immunology team and mentors several postdocs working on cancer vaccines, immune regulation, and, in particular, regulatory NKT cells, and Yongjun Sui, Ph.D., leads the HIV and mucosal immunology team, also mentoring postdocs and postbacs, and leading studies of SIV vaccines in rhesus macaques. A Staff Clinician, Jennifer Jones, M.D., Ph.D., leads studies on immune abscopal effects induced by radiotherapy, and on use of a novel nanoFACS technology she has developed to visualize and sort subsets of exosomes from patients as possible biomarkers to facilitate course corrections during personalized therapy. Monica Vaccari, Ph.D., a Staff Scientist in the lab of Genoveffa Franchini, M.D., leads studies of novel poxviral SIV vaccines in macaques and studies mechanisms of protection. Thorsten Demberg, Ph.D., a Staff Scientist in the lab of Marjorie Robert-Guroff, Ph.D., pioneered studies of B cell development and function in macaques receiving adenoviral vector SIV vaccines. Cristina Bergamaschi, Ph.D., a Staff Scientist working with Barbara Felber, Ph.D., and George Pavlakis, M.D., Ph.D., has pioneered the development of hetIL-15, a heterodimer of IL-15 and the IL-15Ra chain, which is believed to be the natural stable circulating form of the cytokine. Antonio Valentin, Ph.D., a Staff Scientist working with Dr. Pavlakis and Dr. Felber leads studies of novel DNA therapeutic and prophylactic SIV vaccines in macaques. All of these also mentor postdocs and other fellows in the lab. In addition, a Staff Clinician, Lauren Wood, M.D., has served as Clinical Director for the branch, leading the Vaccine Branch Clinical Trials team that is translating discoveries from the branch scientists into clinical trials. On Lauren's retirement Aug 1, 2017, this role has been taken over by Hoyoung Maeng, M.D., a Staff Clinician who is now heading the Vaccine Branch Clinical Trials Team. Without all of these dedicated Staff Scientists and Staff Clinicians, the Vaccine Branch laboratories and clinical research programs could not function.

Jay A. Berzofsky, M.D., Ph.D.
Chief, Vaccine Branch

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The Professional Development Corner

The NCI SSSC Association was delighted to host CCR Director, Tom Misteli, Ph.D., for a Town Hall meeting on June 6, 2017 in Building 31 at the NIH Bethesda campus. It was also videocast to two Frederick sites, Bldg 549 A and ATRF E-1201, to maximize participation. The meeting was a wonderful opportunity for the SSSC community to hear Dr. Misteli's vision of CCR and his views of the roles and importance of SSSC. It also provided a platform to the SSSC community to voice their opinions and concerns on a variety of topics. Questions from the SSSC community were collected prior to the meeting and consolidated for the meeting. They fell into 5 categories: Visibility and Recognition; Quad Review Policy transparency and awareness; Career Advancement; Job Security and Displacement Policy; and Budget.

Dr. Misteli began the Town Hall by commending the contribution of the SSSC to CCR. Dr. Misteli went on to say that he considers SSSC an integral part of the CCR and that our varied scientific research, expertise and technologies provide a great resource to Principal Investigators (PIs). Yet, it is this same heterogeneity and wide spectrum of roles that SSSC hold, that has led to challenges. It was heartening to hear that Dr. Misteli understands that the long-term career paths of SSSC are of great concern. In that moment, looking around the room, you could see many heads nodding in agreement.

Tom Misteli, Ph.D., is pictured above discussing issues brought up by staff scientists and staff clinicians at the June 2017 Town Hall Meeting.

The floor was then open to the audience for questions. The first set of questions posed to Dr. Misteli concerned visibility, specifically addressing how CCR leadership views SSSC participation in committees or activities outside the lab. Dr. Misteli was clear that SSSC are encouraged to actively contribute their expertise outside the lab through involvement in various committees, research interest groups, Centers for Excellence, advisory committees to cores, etc.

The conversation then turned to the Quadrennial (Quad) Review process which is always foremost in the minds of all SSSC. The Quad Review is a NIH-wide mandate and the purpose of the Quad review process is to compare SSSC across the spectrum to ensure that there are consistent criteria across the population, while taking many factors into consideration. When asked if both PIs and the SSSC can be informed of changes in the Quad Review policy, scoring rubric etc., Dr. Misteli said that every effort is being made to more effectively communicate these changes. The information is available on the SSSC website (sssc.nci.nih.gov). Another vital matter of concern was the lack of a formal appeal process to the outcome of the Quad Review. Dr. Misteli assured us that individuals who feel that their report does not accurately reflect their accomplishments can submit a response letter for their final Quad Review package. This response letter is taken into full consideration for future actions for the individual, but will not impact the Quad Review decision.

The next set of questions dealt with career advancement. The questions that many of us in the SSSC community have wrestled with was: what mechanism exists to establish a career path for SSSC with promotions and what are the requirements to be promoted to Associate Scientist? As to career advancement, Dr. Misteli pointed out that there is no institutional policy against SSSC becoming tenure track investigators through various mechanisms, including the Stadtman Tenure Track Investigator Program, whereby some SSSCs have successfully transitioned to a Stadtman position. Dr. Misteli is of the opinion, that due to the heterogeneity of SSSC responsibilities and expertise, there is no single career path that fits all. Dr. Misteli emphasized that he is a strong supporter of career advancement. Opportunities for detailing, learning new techniques in a collaborator's lab and in general "trying new things" to expand expertise, are welcome upon the PI's agreement and should be further explored and formalized. Ofelia Olivero, Ph.D.,

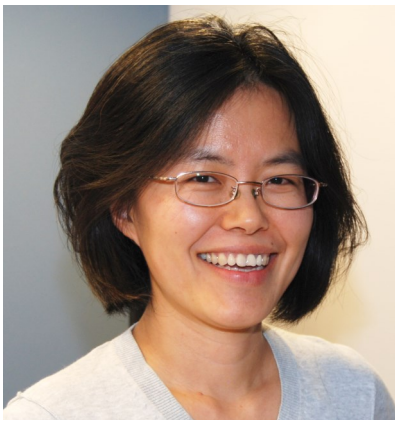
The Professional Development Corner Con't

Pictured from left to right at the table are Emily Tai, Ph.D., Tom Misteli, Ph.D. and Art Shaffer, Ph.D. Pictured above on the screen from left to right are Nadya Tarasova, Ph.D. Jason Stagno, Ph.D. and Sergei Tarasov, Ph.D.

Chief, Intramural Diversity Workforce Branch (IDWB), is developing a program to create opportunities for the advancement of SSSC. We will stay tuned to hear more about this exciting and promising program.

The last section of the Town Hall covered job security and displacement policy where we were heartened to learn that CCR plays a very active role in efforts to place displaced SSSC. Dr. Misteli provided numbers that support this: in the past 3 years 20 SSSC were displaced; 13 were placed within CCR; 4 to other ICs; and 3 left for other reasons. The last questioned concerned potential effects of proposed budget constraints on the SSSC community. Dr. Misteli shared his optimism about our current and upcoming budget and was positive concerning the future need and retention of the SSSC community at CCR.

In summary, the Town Hall was a very promising start to a conversation between the SSSC community and CCR leadership. Dr. Misteli's interest to engage with SSSCs and his support of the community was very evident and much appreciated. There were several excellent questions posed by the SSSC community which were followed by good discussions and suggestions for promising paths forward. The SSSC organization looks forward to working together with CCR leadership to enhance SSSC career opportunities.



Emily Tai (SS)
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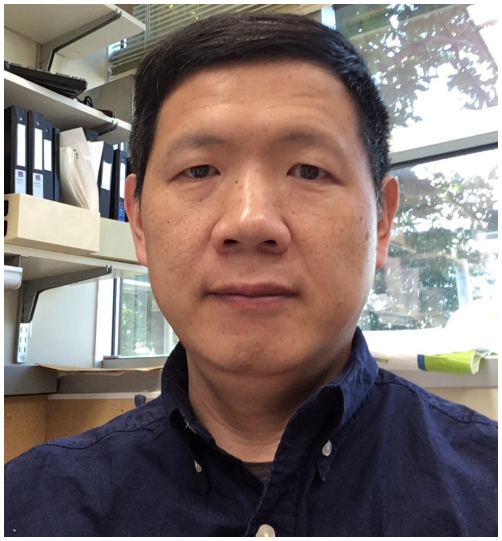
Swati Choksi, Ph.D. (SS)
Head, Professional Development Committee

The Author's Corner

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

Eradication of Tumors Through Simultaneous Ablation of CD276/B7-H3-Positive Tumor Cells and Tumor Vasculature

Steven Seaman*, Zhongyu Zhu*, Saurabh Saha*, Xiaoyan M. Zhang*, Mi Young Yang, Mary Beth Hilton, Karen Morris, Christopher Szot, Holly Morris, Deborah A. Swing, Lino Tessarollo, Sean W. Smith, Sylvia Degrado, Dmitry Borkin, Nareshkumar Jain, Julia Scheiermann, Yang Feng, Yanping Wang, Jinyu Li, Dean Welsch, Gary DeCrescenzo, Amit Chaudhary, Enrique Zudaire, Kimberly D. Klarmann, Jonathan R. Keller, Dimiter S. Dimitrov, and Brad St. Croix. Cancer Cell 31(4): 501-515, 2017. (* Co-first author)



CD276, also known as B7 homolog 3 (B7-H3), shares up to 30% amino acid identity with other B7 family members, which include the immune checkpoint molecules PD-L1 (B7-H1) and PD-L2 (B7-DC) and the co-stimulatory molecules CD80 (B7-1) and CD86 (B7-2). While the physiological functions of CD276 remain unclear, whether CD276 plays a co-stimulatory or co-inhibitory role in the context of the immune system is currently under debate.

The Tumor Angiogenesis Unit in the Mouse Cancer Genetics Program headed by Brad St. Croix, Ph.D., previously identified CD276 as a cell-surface Tumor Endothelial Marker (TEM) that could distinguish pathological and physiological angiogenesis in mice and humans, and demonstrated that CD276 protein is highly expressed in tumor vessels of human lung, breast, colon, endometrial, renal, and ovarian cancer, but not in the angiogenic vessels of normal ovary[1]. Moreover, many studies have confirmed that CD276 protein is strongly overexpressed in a wide variety of cancers and correlates with poor prognosis.

Zhongyu Zhu, Ph.D., a Staff Scientist in the Protein Interactions Section in the Cancer and Inflammation Program (CIP) headed by Dimiter S. Dimitrov, Ph.D., have been working on therapeutic antibody development using various technologies such as phage display and yeast display. Recently, the lab also developed a site-specific Antibody-Drug Conjugate (ADC) methodology in collaboration with Dr. Boopathy Ramakrishnan of Dr. Pradman's group (retired from CCR Nanobiology Program)[2]. The NCI retreat was the occasion to meet and establish a long-term collaboration with Dr. St. Croix, that ultimately led to the development of therapeutic antibodies targeting TEMs[3]. CD276 overexpression by tumor cells and, interestingly, tumor endothelium, made it an appealing target for the development of therapeutic agents that could simultaneously destroy both cancer cells and the associated infiltrating vasculature that supports the tumors growth. Therefore, a CD276-specific ADC could be an ideal weapon to achieve that goal.

Using a naïve yeast display human antibody library and a sequential panning strategy developed in our laboratory, Dr. Zhu and the authors generated a panel of fully human antibodies which are cross-reactive to both human and mouse CD276. Later they also demonstrated the lead antibody (m276) can also bind similarly to rat and monkey CD276. The antibodies cross-reactivity toward CD276 from different species was essential for evaluating the ADCs' efficacy and toxicity in animal models, especially because the CD276 expressed on tumor endothelial cells in animal models is host-derived.

Starting from an m276 IgG1, and collaborating with BioMed Valley Discoveries, a CD276-targeted ADC was produced using a conventional approach and MMAE (microtubule inhibitor) as the payload. Also, using the site-specific ADC methodology developed in-house, a different ADC was prepared using the same antibody, but with pyrrolobenzodiazepine dimers (PBD) as the payload. The two ADCs were then compared using a series of in vitro and in vivo models to evaluate their efficacy.

Using CD276 knockout mice and CRISPR/Cas9 knockout cancer cell lines to evaluate CD276 function in host cells and tumor cells respectively, the authors

demonstrated that CD276 is dispensable for tumor growth, despite its widespread overexpression in both tumor cells and tumor vasculature (Figure 1). The CD276-targeted ADCs potently and specifically killed various cancer cells both in vitro and in vivo. Interestingly, tumor endothelium was found to be resistant to the m276-MMAE ADC, but sensitive to the m276-PBD ADC. Further studies revealed that the drug efflux pump known as P-glycoprotein (P-gp) is highly expressed on tumor endothelium, giving this stromal cell population a high level of resistance to MMAE but not PBD free drug. Because many of the payloads used on modern ADCs in the clinic (including MMAE) are substrates of P-gp, these results could help explain the limited clinical success of current ADCs. Comparing the two different ADCs in vivo, the authors demonstrated that the PBD-ADC was the most efficacious as it could kill both the CD276 positive tumor endothelial cells and cancer cells. Although CD276 is overexpressed in tumors, the fact that CD276 can be detected in normal tissues raises concerns for toxicity. However, no weight loss with either ADC, no alterations in wound healing, no changes in hematopoietic cell populations in *Cd276* wildtype versus knockout mice, and no other overt signs of toxicity were observed.

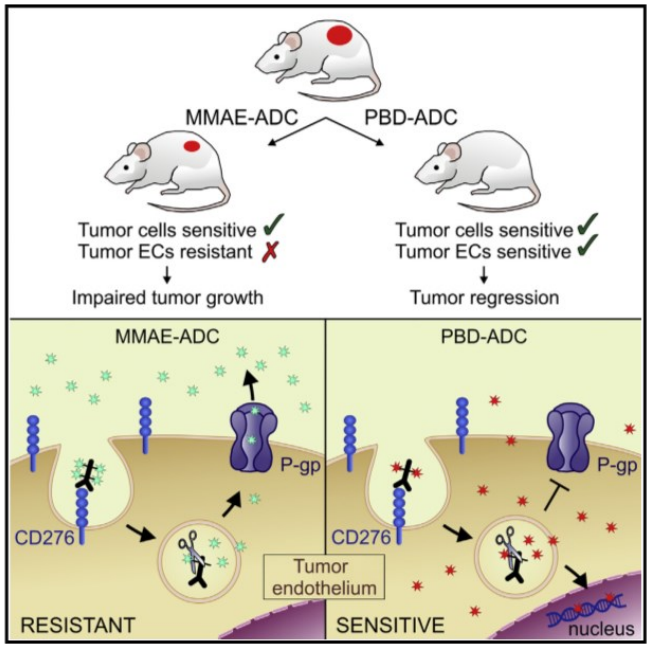


Figure 1. m276-PBD can potently eradicate tumor by simultaneously destroying both the tumor cells and the tumor vasculature, while the tumor endothelium is resistant to m276-MMAE due to its high-level expression of P-Glycoprotein.

Although tumor angiogenesis and metastasis are both hallmarks of cancer, ultimately it is the metastases (often already present at diagnosis) that makes cancer so lethal. Using the HCT-116 liver metastasis model and an experimental 4T1 breast cancer lung metastasis model, the authors demonstrated that the m276-PBD can block the growth of established metastases by destroying both tumor cells and tumor vasculature. These data suggest that CD276 may be a useful ADC target for treatment of late-stage metastatic disease.

It will be important to determine whether selective delivery of m276-ADC into tumor cells and the tumor microenvironment can induce immunogenic death, which might in turn stimulate the immune response toward cancer cells and hopefully enhance immunotherapeutic activity when used in combination with immune checkpoint inhibitors. Whether such combinations will result in synergistic anti-tumor activity in animal models is currently under investigation.

It is worth noting that these studies, starting from target identification, method development to therapeutic antibody isolation and characterizations, were collaboratively performed by different groups within the CCR. This example demonstrates how "The CCR is a unique place of science where we combine diverse expertise with the freedom to thoroughly pursue the most pressing questions in cancer biology and treatment", as recently highlighted by the CCR Director, Tom Misteli, Ph.D. (https://ccr.cancer.gov/about).

Dr. Zhu and colleagues are very encouraged by the preclinical data generated so far and are currently working closely with collaborators at NCI to further develop this technology clinically. The hope is to fulfill the NCI mission: "improve the lives of cancer patients".

Zhongyu Zhu, Ph.D. (SS)
Protein Interactions Section
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The Author's Corner Con't

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

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Zhongyu Zhu, Ph.D., is a Staff Scientist in the Protein Interaction Group, Cancer and Inflammation Program in the Center for Cancer Research. His major role as a Staff Scientist includes establishing and maintaining antibody engineering technology platforms and leading antibody based therapeutics development, such as Antibody Drug Conjugate (ADC), CAR-T and Bi-specific antibody etc. Additionally, he mentors postbacs and helps to train postdoctoral fellows and technical staff on various aspects of antibody engineering techniques, such as phage display and yeast display. He also serves as leading scientist working on various grant-supported projects with collaborators within and outside of NIH. He also leads various research projects under CRADAs sponsored by industry partners.

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The Core Corner

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

CAR Therapies at the NIH: It Takes a Village

Relapsed and refractory acute leukemia in pediatrics has been difficult to treat with conventional therapy due to dose-limiting toxicities. New therapies are being tried utilizing the patients' native t cells, called chimeric antigen receptor (CAR) T cell therapy, to target tumor-specific antigens. In the Pediatric Oncology Branch, scientists and physicians have developed multiple targeted immunotherapeutic options for patients with refractory disease states. Our goal is to provide safe and effective therapy to patients for whom no standard treatment choices remain.

CARs are customized receptors that are composed of an extracellular antigen-binding domain targeting antigens expressed on the malignant cells (such as CD19 expressed on B cell malignancies) combined with the intracellular signaling domains of the T cell. T cells utilizing this genetically modified CAR are independent of MHC restriction. Ideally, an antigen target is one that has high expression on the malignant cell surface, and is not detected on normal tissues (or at least limited), therefore maximizing selectivity and minimizing off-tumor toxicity. To deliver this targeted CAR T cell therapy, multiple steps must be taken to create the product.

This research has been supported by CCR, with major contributions from scientists and physicians in the Clinical Center's Department of Transfusion Medicine (DoTM), CCR's Laboratory of Pathology-Flow Cytometry Lab, and the Cell Processing Facility. Specifically, from the moment a patient is undergoing evaluation for eligibility, under the expertise of Maryalice Stetler-Stevenson M.D., Ph.D. and Constance Yuan, M.D,. Ph.D., the flow core lab utilizes state of the art flow cytometry to evaluate the patient's signature on their leukemia cells. This laboratory has created specialized panels that are not available commercially for multiple clinical protocols. Once eligible, patients undergo an apheresis to collect lymphocytes which are need for CAR production, and returns blood and platelets back to the patient.

With the guidance of David Stroncek, M.D., the Chief of the Cell Processing Section of DoTM, along with our colleagues in the Cell Processing Core Facility purify the lymphapheresis product and utilize either lentiviral or retroviral vectors to introduce this specialized receptor into the t cell. Production of cells takes between 7-10 days, with highly skilled personnel testing and performing rigorous analysis of the cells. Once the cells are produced, and prior to infusing the cells, strict guidelines and parameters need to be met, which include multiple tests for viability, purity, and infection. Once the product has met regulatory standards, patients receive the CAR T cell infusion after a standard lymphodepleting preparative regimen, and re-staging is performed at 1 month to evaluate for response.

It truly takes a village to care for these patients. Overall, the results that we and our collaborators achieved have been quite rewarding, demonstrating the need for a partnership between the scientists and physicians. Multiple times throughout one patients' cycle, we encounter a bench to bedside approach, utilizing effective team communication to discuss suggestions, ideas, and changes that could improve upon our product that is delivered to patients. We hope that we can continue to develop more sophisticated methods and strategies with our core facilities colleagues, that drives the field of immunotherapy forward.

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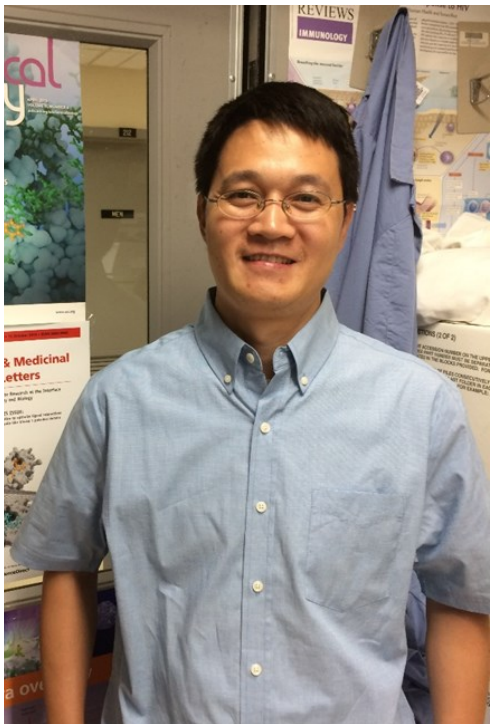
The SSSC Corner

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



After receiving my Ph.D. in organic chemistry from Lanzou University, China, I joined the NCI laboratory of Terrence Burke, Ph.D., as a Visiting Fellow in 2005. I was subsequently promoted to Research Fellow and then to Staff Scientist. When I joined the Burke laboratory, I became part of a decade-long collaboration with Yves Pommier, M.D., Ph.D., to develop novel inhibitors of HIV integrase (IN), with the long-term goal of creating new anti-HIV drugs. Since HIV can develop resistance to all of the available anti-HIV drugs, we are particularly interested in developing compounds that are broadly effective against the known drug-resistant mutants. The integration of HIV DNA into the host genome, which is carried out by the viral enzyme IN, is an essential step in the viral life cycle. Compounds that block integration will block viral replication. My part of the project was to design and synthesize novel IN inhibitors. Dikeoacid-containing compounds had been shown to selectively inhibit the "strand transfer" step of the integration reaction. Agents that block this step are called "integrase strand transfer inhibitors" (INSTIs). Although there were no structures of complexes of IN with a bound inhibitor when I began working on the project, it was believed that two Mg^{2+} ions at the IN active site are critical to the strand transfer reaction and that INSTIs block the reaction by chelating the Mg^{2+}.

My initial efforts explored the development of novel metal chelating compounds that were based on various 2,3-dihydroxybenzoylhydrazides. I used conformational constraints to hold key heteroatoms in a coplanar orientation that would facilitate chelation of the Mg^{2+}. This work resulted in the discovery and development of compounds which inhibited the strand transfer reaction at low nanomolar concentrations and displayed good antiviral potencies in HIV-1 infected cells. However, the first set of inhibitors showed substantial toxicity to cultured cells. At this time, Stephen Hughes, Ph.D., joined the collaboration. His laboratory gave us access to single round viral replication assays that employ a panel of viral constructs having INSTI-resistant mutant forms of IN. We also began a collaboration with Peter Cherepanov, Ph.D., (The Francis Crick Institute, London) who solved X-ray structures of our INSTIs bound to the IN of prototype foamy virus (PFV). PFV IN is structurally similar to HIV IN, and the PFV IN structures revealed the binding mode of our compounds and suggested ways we could modify the compounds to improve their binding affinities. I began to explore a new metal-chelating nucleus that had previously been used in attempts to develop inhibitors of another HIV enzyme, RNase H. After extensive effort, I was able to synthesize compounds that show single-digit nanomolar antiviral potencies against cells infected with a vector that uses wild-type IN, and the best compounds retain their potency against the broad panel of drug-resistant mutants. Importantly, these compounds have extremely low cytotoxicity, which in some cases lead to selectivity indices (EC_{50}/CC_{50}) of greater than 100,000.

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The SSSC Corner Con't

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

The NCI Technology Transfer Office is currently helping us move the best compounds into preclinical testing in animals. Our current inhibitors offer potential leads for further structural variation that may ultimately yield drugs that are broadly effective against the known resistant HIV mutants. Polo-like kinase 1 is an important anti-cancer target. In a separate project, our lab is developing potent Plk1 polo-box domain (PBD)-binding inhibitors based on a 5-mer peptide lead. I am using oxime-diversification to optimize ligand interactions of the peptide within a cryptic pocket of the Plk1 PBD. My current interests also include developing molecular target-directed peptides and small molecules using state-of-the-art biochemical, pharmacological, molecular biological methodologies.

Outside the lab, I enjoy reading, listening to music and watching movies. I also like to play with my two sons, Yidi and Yida. I particularly enjoy watching their soccer games as well as their painting and piano playing. My family likes to travel and we have recently camped at the Assateague State Park.

Xue Zhi Zhao, Ph.D. (SS)
Chemical Biology Laboratory

Xue Zhi Zhao is pictured with his sons, Yidi and Yida, at Ocean City, MD.

The Clinical Corner

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

Getting to Know our Staff Clinicians

The main goal of this new section is to increase the participation of Staff Clinicians, and make their work better known at NIH. In this issue, we decided to interview an accomplished, well known and respected clinician, who has been a role model for many of us that became Staff Clinicians. He answered some of our questions and gave some advice.

An Interview with Ravi A. Madan, M.D.

What was your general role as Staff Clinician?

As a Staff Clinician, roles may vary significantly from team to team and branch to branch. My role really exists on multiple levels. One is to oversee the clinical operations of trials under other PIs within my branch. But in addition, I have also had the opportunity to develop my own translational research as primary investigator. In addition, as the Clinical Director of the Genitourinary Malignancies I facilitate the clinical operations of the group.

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

All clinical trials are different, but at the NCI clinical trials generally start with home grown science that can be developed in an accessible population of patients

and translated in a clinically meaningful way. The difficulties are equally variable, but it often starts with a willing pharmaceutical partner with whom you can align scientific and industry priorities. Once agreements are in place, the next steps involve development of a concept and scientific review, followed by protocol development and IRB/safety review. This process can be as quick as four months, but can also take years. Each protocol goes through its own life cycle with different challenges and even once it opens, requires frequent oversite and regulatory management.

What was your contact with the Staff Scientists? Have you collaborated on bench to bedside projects?

I have had great collaborations over the years with the staff scientists in multiple labs including the LTIB (under the direction of Jeffrey Schlom, Ph.D.), as well as W. Douglas Figg, Pharm.D. lab and Jane Trepel's lab. Often I have had input in preclinical modeling, while the Staff Scientists have had input on clinical trial design. Then we work together to develop correlative data from patients and put to it in a clinical context. These interactions work best when communications among Staff Clinicians and Staff Scientist are open, frequent and a two-way street.

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

Patient care at the NIH is unique in that we are a research hospital. Therefore, we lack some things that every hospital has, like an emergency room. But the benefits far exceed the limitations with world class expertise in many fields with state of the art imaging and patient sample analysis.

What is the career path of a Staff Clinician? Where do they go from here?

The career path for Staff Clinicians can be variable and that is one of the exciting things. For those who are more clinical, they can be in the clinic frequently and manage patients on multiple clinical trials. For those more inclined to develop translational research studies of their own, those opportunities also exist. Experienced staff clinicians also have ample opportunities to further their career outside of the NIH leading academic, regulatory (FDA) and industry initiatives.

Any final advice for new Staff Clinicians regarding collaborations with other Staff Clinicians and/or Staff Scientists?

My advice is to develop a career strategy and find mentors and collaborators (including other Staff Clinicians and Staff Scientists) who can help you achieve those goals. Being at the NIH is a unique experience with unique resources that allows staff clinicians to have career paths that would not be possible elsewhere.

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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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