THE DOSSIER

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

From the Editor

SSSC Roundtable organizers (L to R) Brunilde Gril, Swati Choksi and me, after the event.

In July, the second roundtable conversation with the CCR Director was organized by the SSSC Professional Development Committee. SSSCs had the unique opportunity to speak about their concerns directly with Dr. Misteli. In a large organization like the NCI, it is not uncommon for senior leadership to appear to be inaccessible. However, the openness around discussing SSSC concerns that marked our roundtable discussion is a testament to the continued commitment of our Director to SSSCs. This engaging discussion left SSSCs feeling motivated that their concerns were heard and that they can be part of the decision-making process in the CCR. These efforts to set in place an empowering workplace culture can serve as a powerful motivator. This is a topic covered in the interview with Lawrence Levy, former CFO of Pixar, in the personal development corner for this issue. Moving forward, I hope that we all recognize and are able to articulate and share what it is that makes us feel empowered and motivated in our environments to reach our creative potential.

One concern that came up during the roundtable was information dissemination about resources available to SSSCs. In this issue, we have an article about the CCR Central intranet. CCR Central is a centralized platform to access information about the multitude of resources available to us. Since hearing about it a few months back, I have found it to be an indispensable site, and now it is the first place I go when in search of a CCR resource. I hope you find it valuable too.

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

In This Issue

Mark your calendars

Annual SSSC Professional Development Day

October 4th 2019

Registration opens Sept 4th

Information session for PIs on preparing SSSC Quad Review Packages

October 4th 2019

3pm Bldg 37 Room 6041/6107
video conf to Frederick: Bldg 549 Room A.

Find Resources

- CCR CENTRAL

PC: Look for this icon in the START menu under NCI CCR

Mac: Look for this icon in your dock

- SSSC WEBSITE

The Office of the Director

Second SSSC Roundtable Conversation with CCR Director

I was glad to meet last month with CCR staff scientists and staff clinicians (SS/SCs) in a second roundtable meeting hosted by the NCI SS/SC Association. As I have come to expect from the SS/SC community, I was impressed by the level of passion and dedication, but also professionalism, that was evident during our conversation.

In conversation at the recent SSSC Roundtable Meeting

The meeting was a good opportunity for me to get an update on what the most pressing issues in the SS/SC community are. Much of the conversation centered around the continuing need, and our efforts, to develop more structured and transparent career ladders and development opportunities for SS/SCs. These efforts, such as the recently launched SS/SC Technical and Career Enrichment Programs (STEP), which grew out of the last roundtable discussion, must and will continue, and the conversation yielded several ideas for new initiatives which we will explore.

I particularly valued the very frank discussion on the difficult topic of how to best ensure open and constructive dialogue between PI and SS/SC. Communication with the PI is central to just about all aspects of a SS/SC's career, particularly around opportunities for growth such as funding and time for independent research, mentoring opportunities and travel to conferences. Letters of agreement (LoAs), as recently adopted at the NIH level for SCs and their PIs, arose as an example of an effective tool that provides structure and clarity about roles and expectations, and I understand the SS/SC Association is further developing this idea.

An ongoing challenge for us as an institution remains to provide comprehensive information about what resources are available to SS/SCs, including grant and funding opportunities, training courses, quad review and promotions. We have now included some of this information in CCR's new intranet, CCR Central, and more information is available on the SS/SC website, which is now also linked to CCR Central. I have asked my communications staff to continue conversations with SS/SCs to help improve awareness of what is available and to address what is still missing.

An important topic of discussion, and one which I am very sensitive to, was uncertainty regarding job security for SS/SCs, which may arise due to departure of a PI or lab closure. SS/SCs are particularly vulnerable to these transitions due to the term-limited nature of their appointments. CCR remains fully committed to helping each and every SS/SC find a new opportunity either within NCI or in other institutes. This personalized approach has worked well for us, and we have a very good track record of placing SS/SCs in new laboratories when these difficult situations arise.

The roundtable discussion of last month once again highlighted the very unique nature of the SS/SC position and the irreplaceable role SS/SCs play in our research and clinical enterprise. The dedication and

quality of CCR's staff scientists and staff clinicians truly embodies the values of the NIH intramural program to freely explore the most important research problems and to conduct research of the highest quality. SSs and SCs are integral to the success of our research program, and I look forward to continuing my commitment to working with all of you.

Useful Links:

About CCR Supplemental Funding

SSSC Career Enrichment Program

SSSC Technical Enrichment Program (STEP)

Tom Misteli, Ph.D.
Director, CCR

Check out the new and improved CCR central intranet

CCR Central is a "one-stop shop" to easily access the vast amount of online information that staff scientists and staff clinicians need every day to get things done. In one convenient location, it consolidates the many sources of information which have previously been available in different places in cyberspace and some new ones. If you don't immediately see what you are looking for in the bullets under each section, click View All Topics or simply use the CCR Central search bar. Or take a spin through the site with one of the quick video tutorials.

The staff scientists and staff clinicians subsection on the Scientific Networks/Groups section provides links to the SS/SC web site and more. Under the Training section, you can learn more about the Staff Scientist/ Staff Clinician Technical Enrichment Program, which provides CCR staff scientists and staff clinicians an opportunity to compete for funding to gain access to comprehensive training in state-of-the-art techniques available through CCR cores and facilities.

Take a look at the Scientific Resources section, which connects you to CCR's vast array of cores. Be sure to also check out the Site Visits, Tenure, and Quad Review section where you can find review checklists, forms and appropriate contacts.

Staff clinicians may be particularly interested in the Conducting Clinical Trials Section, which has information about CCR's clinical infrastructure and resources such as the Protocol Support Office, the Office of Education and Training, links to clinical information systems, and procedures relating to common patient issues such as Severe Adverse Events, staying at the Safra Family Lodge and working with Walter Reed.

Wish we had added something that's not there? Let us know via the feedback button on every page.

On a PC?	On a Mac?
Look for this icon in your START menu under NCI CCR	*Look for this icon in your dock*
	

Lianne Priede, Ph.D.
Communications Specialist
Office of Research Operations and Planning

2019 Annual SSSC Professional Development Day

The Professional Development committee of the CCR Staff Scientist Staff Clinician Organization is excited to bring you 2019 Annual Professional Day. The CCR SSSC Organization conducts an annual one-day meeting addressing the professional development needs of the Staff Scientist and Staff Clinician community. This year we have an exciting agenda that touches on a wide range of topics from Leadership and Team Building in Science to Mentoring.

We are trying some new things this year. Do not miss!

Flash Mentoring will be an interactive session where attendees will move "speed dating" style from table to table every 15 minutes meeting with 6-10 mentors.

Develop Your Personal Elevator Pitch will focus on how to powerfully convey your work in just a few minutes. Last year we had Scott Morgan show us the do's and don'ts of giving an Elevator Pitch – how to convey the key points of your work in a few minutes. This year you will have the opportunity to give your elevator pitch. Use your skills and sign up!

2019 Annual SSSC Professional Development Day

October 4th 2019

Bethesda: Porter Neuroscience Center (Building 35, Room 610)

Frederick: NCIF B549, Conf B

Registration opens September 4th

Swati Choksi, Ph.D. (SS)
Chair, Professional Development Committee

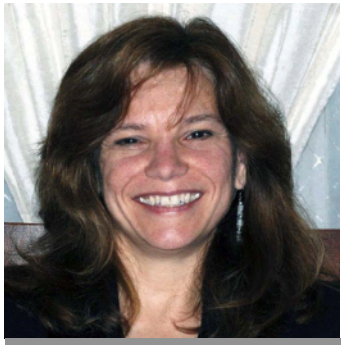
2020 Staff Scientist and Staff Clinician Quadrennial Review

The next Staff Scientist (SS) and Staff Clinician (SC) Quadrennial Review will be held in March of 2020. SSs and SCs undergoing review and their PIs will receive an email from me in September informing them of the review and providing links to important review information. The Quad Review is comprised of three parts: the recommending memo from the PI, the SS/SC's CV and Bibliography and two letters of recommendation from collaborators. To assist PIs and Supervisors in assembling their SS's package, I will hold an information session on preparing Quadrennial Review packages. Supervisory credit is available. The presentation is scheduled for **October 4th at 3:00pm** in building 37 room 6041/6107 with video conference to Frederick, building 549 room A.

Just a reminder that Associate and Senior Associate Scientist promotion packages are also reviewed at the March meeting. SS should review the criteria found on the CCR ARC webpage (https://nciconnect.nci.nih.gov/sites/CCR/HR/FTE/Pages/Staff-Scientist.aspx) and if they feel they are qualified discuss submitting a request with their PI and branch chief.

For information concerning Staff Scientist and Staff Clinician positions and associated forms please go to: https://nciconnect.nci.nih.gov/sites/CCR/HR/FTE/SitePages/Home.aspx.

If you have questions or need more information, please contact me at masisonc@mail.nih.gov or 240-781-3356.



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

The Core Corner

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

The Mouse Modeling and Cryopreservation Core

The use of genetically-engineered mouse (GEM) models for the study of in vivo gene function has been instrumental to investigating genetic interactions and biochemical dynamics aiming at understanding cancer biology. Traditionally, transgenic technologies and gene targeting by homologous recombination in embryonic stem (ES) cells, have been utilized to generate mice that model human diseases. More recently, application of the CRISPR/Cas9 technology has opened new doors and limitless possibilities for the generation of GEMs and goes beyond the boundaries of conventional gene targeting, allowing for more accelerated progress in biological sciences.

The Mouse Modeling and Cryopreservation (MMC) Core, provides expert services to the NIH scientific community for generation of GEMs as well as for cryopreservation of murine germplasm. The core is comprised of the following laboratories: Transgenic Mouse Models (TMM), Cryopreservation & Assisted Reproduction, and Cell Culture.

TMM offers a complete array of services aimed at successfully generating transgenic, knockout, and knock in mouse models. TMM support includes consultation with experimental design, preparation of DNA, microinjection, and genotypic evaluation by Southern blot analysis. Germline-competent C57BL/6NCr ES cells utilized for gene targeting have been generated DeNovo within TMM. The laboratory has also advanced its technical capabilities to successfully generate GEMs via CRISPR/Cas9 technology, working closely with the CCR-dedicated Genome Modification Core, where the CRISPR reagents (guide RNAs and donor constructs if applicable) are designed and generated.

Preservation and archiving of valuable GEM models is carried out by the Cryopreservation and Assisted Reproduction Laboratory. It is critical that unique mouse models are protected against genetic drift or loss due to unforeseen events. Highly skilled technical staff perform assisted reproduction techniques (in vitro fertilization, IVF), as a means to rescue mouse lines, or for expansion of colonies to produce large age-matched cohorts for experiments. Both sperm and embryos can be cryopreserved, the modality recommended based on the genetics of the strain, complexity of genotype, as well as its natural reproductive characteristics.

The experienced technical team at the Cell Culture Laboratory, working closely with the Animal Research Technical Support (ARTS), process mammalian cell lines for expansion, harvest and preparation for experiments, as well as possess the ability to isolate and establish primary cell lines.

MMC, directed by Roackie Awasthi, is a part of the Laboratory Animal Science Program (LASP, Director: Dr. Stephen Jones) at the Frederick National Laboratory (FNL). To learn more about the program, visit the MMC website: https://ncifrederick.cancer.gov/Lasp/MMC.aspx,. You can direct your questions and inquiries to Roackie Awasthi, awasthipp@mail.nih.gov . You may also access the LASP website https://ncifrederick.cancer.gov/Lasp/Default.aspx for information on other expertise at FNL that are available

From L to R: Keith Smith, Herb Hagenau, Dawn Crummitt, Roackie Awasthi, Alicia Carey, Jennifer Harrison and Debbie Peters.

The Author's Corner

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

A Prime-Pull-Amplify Vaccination Strategy To Maximize Induction of Circulating and Genital-Resident Intraepithelial CD8(+) Memory T Cells.

Çuburu N, Kim R, Guittard GC et al. J Imm. 2019 Feb 15;202(4):1250-1264.

Adenovirus vector-based prime-boost vaccination via heterologous routes induces cervicovaginal CD8(+) T cell responses against HPV16 oncoproteins.

Çuburu N, Khan S, Thompson CD, et al. Int J Cancer. 2018 Apr 1;142(7):1467-1479.

Recent advances in the understanding of CD8+ T cell memory has revealed that long-lived memory CD8+ T cell populations reside in most non-lymphoid tissue. Resident memory CD8+ T cells (CD8 T_{RM}) do not circulate and play key role in immunity against viral pathogens in particular at epithelial surfaces. Notably, they contribute immediate effector T cell functions and induce a broad innate antiviral response in surrounding tissue (1). CD8+ T_{RM} exhibit a distinct set of markers from other circulating memory populations which also varies with tissue localization. Maintained expression of the activation marker CD69 defines most CD8+ T_{RM} in non-lymphoid tissues whereas the expression of the integrin CD103 is generally restricted to intraepithelial CD8+ T_{RM} in pluristratified epithelia and plays a role in long-term retention. In addition to their antiviral role, CD8+ T_{RM} can also control intraepithelial tumors and might constitute a subset of tumor infiltrating lymphocytes (2).

"Dr. Cuburu's focus is the development of vaccination approaches to maximize CD8+ T cells against HPV-associated neoplasia"

Human papillomavirus (HPV), a non-enveloped virus with a double stranded DNA genome, is the cause of almost all cervical cancer and is responsible for a substantial fraction of other anogenital and oropharyn-geal cancers. Persistent HPV infection and maintained expression of the oncoproteins E6 and E7 can lead to transformation of cervicovaginal keratinocytes and development of cervical intraepithelial neoplasia (CIN). Most HPV infections are cleared naturally, and CIN2/3 lesions often regress overtime. Infiltration of high-grade lesions by mucosal T cells can predict lesion regression whereas exclusion of T cells from the lesions was linked with persistence of intraepithelial disease (3). These obser-vations suggest that a therapeutic vaccine against persistent HPV infections and intraepithelial lesions should induce cell-mediated immunity against viral antigens at the lesion site. Nicolas Çuburu, Ph.D., joined John T. Schiller, Ph.D., Deputy Chief at the Laboratory of Cellular Oncology (LCO) to develop a new type of viral vector for mucosal immunization based on epitheliotropic properties of HPV and taking advantage of a versatile pseudoviruses production system developed previously in the lab. Indeed, intravaginal immunization with HPV pseudo-viruses induced preferentially intraepithelial cervico-vaginal CD8+ TRM compared to other established immunization modalities (4). This initial study allowed Dr. Çuburu to further characterize cervicovaginal CD8+ T_{RM} and to apply this technology to an HSV infection model in collaboration with Jeffrey Cohen, M.D., and Kening Wang, Ph.D., in the Laboratory of Viral Diseases, NIAID (5).

Dr. Çuburu's focus is the development of vaccination approaches to maximize systemic and cervicovaginal intraepithelial CD8+ T cells against HPV-associated neoplasia. In collaboration with Janssen Vaccines & Prevention BV, under a CRADA, Dr. Çuburu showed that adenoviral vector type 26 and 35 expressing the oncoprotein E6 and E7 could efficiently transduce the cervicovaginal mucosa. Contrary to intramuscular immunizations, intravaginal immunization with adenoviral vectors, elicited long-lived intraepithelial resident CD69+CD103+CD8+ T cells against the E6 and E7 oncoproteins. In parallel, the development of HPV pseudoviruses as an alternative platform for delivery of various viral antigens including the oncoproteins E6 and E7 was pursued. During the course of experiments testing different routes of administration, intramuscular priming followed by an intravaginal booster immunization was the best regimen to induce concomitantly strong systemic and intraepithelial CD8+ T

Using flow cytometry, confocal microscopy and adoptive T cell transfer of TCR transgenic T cells Dr. Çuburu showed that the local amplification of cervicovaginal intraepithelial CD8+ T cells required in situ antigen presentation, which triggered the recruitment of circulating CD8+ T cells and their local proliferation within the cervicovaginal mucosa. Systemic and genital CD8+ T cells share the same TCR-repertoire suggesting that local amplification does not select for specific TCR-clonotypes. Importantly, this prime-pull-and-amplify immunization approach was quantitatively and qualitatively superior to other approaches based on prime-and-pull approach using various immuno-modulators (Figure 1). In particular, Imiquimod is being investigated in clinical trials against high grade lesions caused by HPV infection alone or together with HPV therapeutic vaccines given systemically.

"All together these studies were made possible thanks to the remarkably collaborative environment at NCI and especially due to the NCI core facilities"

These results underscore the importance of the order route usage in prime-boost immunization with non-replicating vectors in order to shape the tissue distribution of CD8+ T cell responses. In addition, they underscore the importance of local antigen presentation to elicit genital CD8+ T_{RM} and provide a rationale to develop novel vaccines against sexually transmitted infections and to treat human papillomavirus neoplasia. In order to evaluate further therapeutic vaccines there is a need for more accurate intraepithelial neoplasia animal models. Most efficacy studies of therapeutic vaccines against HPV-induced lesions rely on transplantable tumor cell lines driven by E6 and E7 onco-proteins. Although useful to assess cytotoxic agents, the fast growth of orthotopic tumor models makes it unsuitable to evaluate and compare most vaccines at the time the tumor mass is established. Current efforts in the lab are tailored towards the development of a mouse model that recapitulates the slow pace of transformation, intra-epithelial tumor growth, and the establishment of an immunosuppressive environment seen in human cervical intraepithelial neoplasia (CIN). This model could be useful to study the mechanisms of immunosuppression in situ and for the evaluation of therapeutic vaccines. All together, these studies were made possible thanks to the remarkably collaborative environment at NCI, and especially due to the support of the NCI core facilities. Notably, the Genomic core for Nanostring analysis, the Flow Cytometry core for cell sorting, the Confocal core for microscopy analysis and the Laboratory Animal Science Program (LASP) provided continuous support.

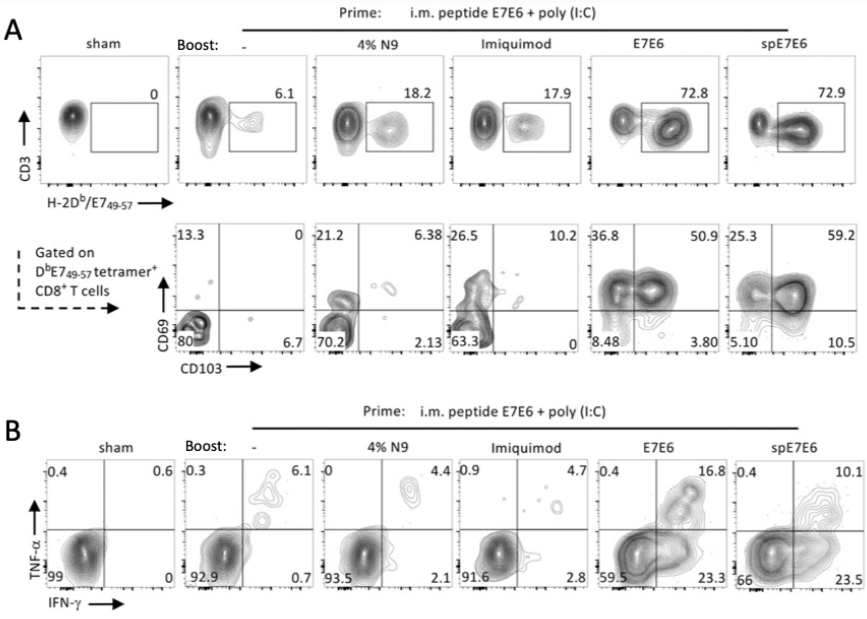


FIGURE 1. Prime-pull-amplify immunization preferentially elicits functional cervicovaginal CD8+ T_{RM} against the HPV oncoproteins E6 and E7. Two HPV PsV expressing E6E7 and spE6E7 were generated. C57BL/6 mice were immunized i.m. twice 5 d apart with $E7_{44-62}$ and $E6_{43-60}$ long peptides and poly(I:C) in saline. Two weeks later, mice were immunized Ivag with 10^8 iu of HPV PsV expressing the E7E6, 5% imiquimod, and 4% N-9 or remained untreated. Two weeks after the booster immunization, genital and blood E7-specific CD8+ T cell responses were assessed by H-2D^b/$E7_{49-67}$ tetramer staining. (A) Representative FACS plots of E7-tetramer staining and expression of CD69 and CD103. (B) Production of IFNg and TNFa by cervicovaginal CD8+ T cells was analyzed by FACS after in vitro stimulation with E7 peptide.

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4. Çuburu N et al. 2012. Intravaginal immunization with HPV vectors induces tissue-resident CD8+ T cell responses. J Clin Invest *122*, 4606-4620.
5. Çuburu N et al. 2015. Topical herpes simplex virus 2 (HSV-2) vaccination with human papillomavirus vectors expressing gB/gD ectodomains induces genital-tissue-resident memory CD8+ T cells and reduces genital disease and viral shedding after HSV-2 challenge. J Virol *89*, 83-96.

Nicolas Çuburu is a SS in the Neoplastic Disease Section of the Laboratory of Cellular Oncology, NCI. He is involved in several ongoing projects in the lab, by providing both scientific and technical training to Postdoctoral Fellows and students. He has recently developed a new line of research and is actively involved in seeking, establishing and maintaining collaborations with NIH or extramural labs. He was involved in the organization of the SSSC 2019 retreat and is looking for more opportunities to be involved in the SSSC community.

Nicolas Çuburu Ph.D. (SS)
Lab of Cellular Oncology

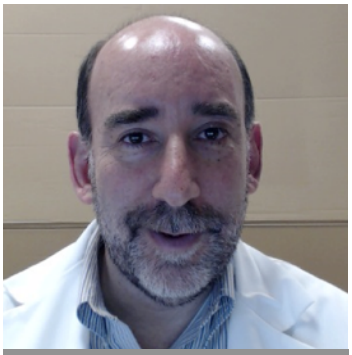
The PI Corner

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

After a 24-year career at the University of Pennsylvania, I came to the NCI Center for Cancer Research in 2011 to become Deputy Chief and Senior Investigator in the Laboratory of Pathology (LP). As the LP Deputy Chief, I work closely with the LP Chief (Kenneth Aldape, M.D.) to oversee three interdependent missions:

1. Clinical – providing diagnostic pathology services for all institutes of the NIH
2. Research – investigating basic and translational pathobiology
3. Education – training future pathology clinicians and researchers

Beyond my duties as Deputy Chief, I participate actively in all three missions. In the clinical realm, I serve as the LP Medical Director and a staff pathologist in the COMPASS clinical genomics program. In the research realm, I direct the LP Cancer Molecular Pathology section, which uses a multidisciplinary approach to study recurrent genetic and epigenetic alterations in the soft tissue cancer rhabdomyosarcoma and then apply our findings to more generalizable questions in cancer biology. Finally, in the educational realm, I serve as Associate Program Director of the Anatomic Pathology Residency and as mentor to postdoctoral fellows and students training in my laboratory. In all these activities, I have the privilege to work with a dedicated group of staff clinicians and scientists, who provide much of the diagnostic, techno-logical and scientific foundation of our clinical, research and educational programs. It has been particularly gratifying to see trainees from our educational program attain positions as staff clinicians and scientists and to truly witness the continuity of the LP tripartite mission.



Frederic G. Barr, M.D., Ph.D.
Deputy Chief
Senior Investigator

The Clinical Corner

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

An interview with Miloš Miljković, M.D., M.Sc. (SC, ARP) Lymphoid Malignancies Branch

Miloš Miljković, M.D. (SC, ARP) Lymphoid Malignancies

Alexandra Zimmer: What is your general role as staff clinician?

Miloš Miljković: My main role is to help transfer the findings from the Waldmann Laboratory into clinic in order to discover effective new treatments for T cell malignancies, which are the Lab's focus. My secondary task is to evaluate the role of IL-15, a cytokine which Dr. Waldmann codiscovered and which has been produced and extensively studied as a single agent by the NCI – in cancer immunotherapy. One could say I study two aspects of T cells: how to use them to fight cancer, and how to fight them when they themselves become malignant.

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

MM: The first and the most important step is knowing why the trial is being done in the first place. For phase I trials that means understanding the preclinical data, which will help guide trial design and point to the kinds of correlative studies that could give some hints about the drugs' pharmacodynamics. It also means knowing what compromises you are allowed to make when designing the trial: not all drugs tested in the lab will be available for use in investigator-initiated trials (IITs), and finding a suitable replacement is often a challenge.

That leads me to the second step: obtaining the drug. This is usually done by directly contacting the manufacturers, who often make drugs available for IITs along with budget support. At NIH we are privileged in how many resources we already have for implementing clinical trials, and "drug-only" requests from companies are usually granted. Even so, the contract negotiations between our Technology Transfer Office and the companies' lawyers can take months in the best of circumstances (and years if there is money involved). Federal law dictates what agreements we are allowed to make, especially pertaining to intellectual property, and some companies have been more understanding of that than others.

NCI's Cancer Therapy Evaluation Program (CTEP) is another potential drug source. They act as an intermediary between companies, evaluate requests on their behalf, and can provide support with protocol development. They also bring another layer of trial design experience, oversight, and review, which has mostly benefits, but also some challenges. Finally, if a drug is being used for its approved indication, the Clinical Center Pharmacy will often obtain it from a commercial source. Cancer drugs are notoriously costly, with total costs per trial in the millions of dollars, so this is the avenue of last resort. But we are so grateful that it exists.

"The easy-to-give but not easy-to-follow advice is to know what related research is ongoing in your lab, branch, institute, and the NIH"

The writing of the clinical protocol itself is straight-forward once we know what questions we want answered and what the drug source is, since those will guide trial design, treatment schedule, correlative studies, and safety reporting requirements. Our Protocol Support Office is invaluable during this step, as they will have the most up-to-date information on regulatory requirements and will often know from their experience with other protocols what the best avenue is for ours if any questions arise.

There are many regulatory steps once the protocol is written, including internal quality control followed by many different reviews: scientific, manufacturer, FDA, and finally IRB (institutional review board). This is much like a journal peer review in that it can take months, and often comes back with conflicting recommendations.

All of the preceding steps are actually just Step 1: Open the trial for enrollment. That's when the real work begins,

and the real challenges arise. Subsequent steps would comprise a whole chapter, and to go over all the difficulties would require a book.

AZ: What is your contact with staff scientists? Any report of bench to bedside cooperation?

MM: You could say that everything we do in the Branch is bench to bedside (and bedside to bench) cooperation. An anti-CCR4 CAR T-cell construct we are trying to get into clinic comes directly from the work of L. Para Perera, Ph.D. an LYMB staff scientist. Another staff scientist, Sigrid Dubois, Ph.D. is instrumental for all of our IL-15 trials, as her main interest is on regulation of NK cell function. She is also interested in the NK cell dysfunction that many patients with T-cell malignancies have, so our next project together will be analyzing viably frozen cells of patients with adult T-cell leukemia the lab has collected.

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

MM: We have the privilege of the almost unlimited time we can spend with our patients, discussing their issues and our thought process in depth. We do not have to worry about insurance coverage, for the most part, and we are not being hounded about prior authorization and dis-charge planning. On the other hand, there are many inefficiencies in how things are being done, from clinic flow to ordering imaging studies, which can be striking for somebody just out of residency who thinks that the Clinical Center is "just another hospital". Between fellowship training and my current position, I've been at the NIH for five years now, so my memory of how things are done elsewhere is starting to fade. Fortunately, we have new fellows coming each year to remind us of the world.

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

MM: It depends on the person, and their particular position, so it is hard to give a generalizable answer. If you derive satisfaction from patient care and clinical research, and don't want to be bogged down with even more administrative responsibilities than those that come from running a clinical trial, this is a great job. Being on the tenure track, at the NIH or elsewhere, does give you more independence, but also many additional responsibilities. I've never worked at an academic medical center, but what I hear from colleagues who are there is that it can be a challenge even for investigators with multiple R01s to keep protected time for research. NIH does have many resources and workshops on preparing grants, but they are underused by MDs (at an NCI grant writing workshop three years ago there were two of us among dozens of PhDs).

Other paths from staff clinician position are mostly sideways trajectories in which we can leverage our skill set and knowledge: FDA and the industry. I don't know enough about either to comment further.

AZ: Any final advice for new staff clinicians or about collaboration between staff clinicians & staff scientists?

MM: The easy-to-give but not easy-to-follow advice is to know what related research is ongoing in your lab, branch, institute, and the NIH in general. Especially while you're still new, and don't have a full patient panel with numerous trials and several committee obligations, it pays to attend lectures, seminars, journal clubs (especially trans-institutional) in your field of interest.

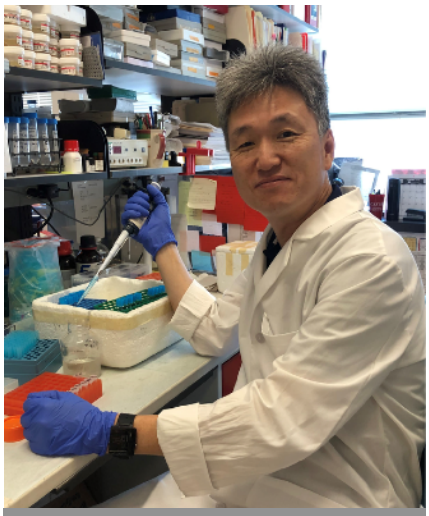
AZ: Do you identify any personal issues or challenges in being a medical scientist? Any specific advice to others starting in that path?

MM: I thought of myself as a patient person until I tried to open my first trial, when every regulatory step felt like an insurmountable obstacle. Patience and persistence win out, eventually.

Lastly, any scientist will do well to remember the words of the physicist Richard Feynman: "The first principle is that you must not fool yourself, and you are the easiest person to fool."

The SSSC Corner

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



Yang Jo Chung, Ph.D. in the laboratory

I started to work with Peter Aplan, M.D. as a post-doctoral fellow in fall 2005. Before joining Dr. Aplan's Lab, I was interested in hematopoietic stem cell biology, which I studied during my Ph.D. program and first post-doc period. During that period, the concept of leukemia stem cell had emerged in the field of leukemia biology, especially Acute Myeloid Leukemia. Experimental evidence demonstrated the existence of a leukemia stem cell in Acute or Chronic Leukemia. However, in Myelodysplastic syndrome, known as pre-leukemic myeloid malignancy, the disease stem cell had not been fully proven at that time due to low successful rate of xenografting cells derived from human patients and lack of animal model for the disease. When I joined Dr. Aplan's lab, his group had just published a paper on the mouse model of Myelodysplastic syndrome (Blood, 2005). I discussed my research project with Dr. Aplan and proposed to identify Myelodysplastic syndrome stem cell.. The project progressed so successfully under the supervision of Dr. Aplan that I published the evidence of pre-leukemic stem cell existence in PNAS, 2007. Since then, my research has focused on disease pathogenesis of hematopoietic malignancy and I have published several articles. Currently my research interests are on the progression of pre-leukemic to leukemic state and clonal dominance mechanism of leukemic cells.

I was promoted to a staff scientist in 2011. From the viewpoint of experienced hematologist, Dr. Aplan's Lab has excellent research environment due to Dr. Aplan's knowledge for clinical hematology and resources including transgenic mice. Dr. Aplan is very good mentor with good insight in science. He has an excellent ability to analyze scientific data, especially in the field of molecular medicine. I am learning a lot from him about understanding leukemia biology, especially the aspect of molecular pathogenesis. We discuss how to design new experiments to pursue my research project.

In addition to my own research projects, I am providing technical help such as bone marrow transplantation for postdocs and younger trainees. I work with postbac students as well, teaching and supervising them.

Dr. Chung with his landscapes

Outside the lab, I like oil painting and my main subject is landscapes. Spending some time in front of the canvas over the weekend makes me feel good and takes me to a different world from science. I also enjoy running regularly and playing golf sporadically.

Yang Jo Chung, Ph.D. (SS)
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The Personal Development Corner

Section Editor: Brunilde Gril, Ph.D., M.P.S. (SS)

From Pixar to Juniper - Lessons on Leadership, Creativity and Culture: An Interview with Lawrence Levy

Lawrence Levy, a graduate of Harvard Law School and former CFO and Board member of Pixar Animation Studios, was a major player responsible for bringing the talented team of Pixar to the world. Following this impressive achievement, Lawrence took a different path and became a student of renowned Tibetan Buddhist Master Segyu Choepel Rinpoche under whom he has studied for almost twenty years. Together with Segyu Choepel Rinpoche and three others, Lawrence co-founded the Juniper Foundation with the vision of embedding the essence of Buddhist methods for developing the mind into modern culture. In his book *To Pixar and Beyond: My Unlikely Journey with Steve Jobs to Make Entertainment History* (2016), *An Amazon Best Book of 2016 in Business and Leadership*, Lawrence reveals the *tour de force* leading to the success of Pixar and why he eventually left to pursue a different course. Interweaving reflections on corporate culture, creativity and eastern philosophy, Lawrence highlights challenges and key aspects to unleash our potential.

Brunilde Gril: As Staff scientists/Staff clinicians, we often lead and mentor a small team of scientists; post-doctorate fellows and/or students. In your article entitled *"Finding the Healthy Tension Between Being Confident and Collaborative"* in Harvard Business Review, you identified key assets characterizing the outstanding leadership style of both Steve Jobs and Segyu Rinpoche. Could you summarize your insights here?

Lawrence Levy: My years in Silicon Valley taught me that really innovative work, true breakthroughs, is the product of opposing forces coming together and working things out. Typically, on the one side, you have the confidence of the vision and dream of a founder or group of founders that is essential to try anything new and crazy. On the other side, that confidence has to know when to bend to reality; when to shift, adapt and change. Vision has to be put to the test of reality. The really good leaders know how to do this.

At Pixar, for example, we had the vision of creating the next generation of animated entertainment. As I describe in my book, the realities came close to destroying that vision several times and we had to bend and adapt until we made it, while maintaining the essence of our vision. At Apple Steve Jobs had the vision of building the next generation of consumer electronics. Apple almost went out of business before Steve returned and they finally married the bigness of that vision with the realities of the market and technology.

Lawrence Levy, near his house in California

My later work is in an entirely different field but the same dynamic is present. Segyu Choepel Rinpoche is a remarkable Buddhist master, and his vision is nothing short of changing humanity for the better. He sees that our relentless focus on materialism and consumption is too one-sided—it produces too much mental anguish.

To solve that we have to unfold a different dimension to our lives, an inner dimension. Only then can we fully flourish both outwardly and inwardly. Segyu Rinpoche is in many ways ahead of everyone else – a person from the future! – but he is also pragmatic. He knows we have to fit advanced ideas for developing the mind into our modern life, and he is very patient in allowing that to happen.

BG: Visionary skills, as you just described, are keys to inspire and motivate people. In addition, an ability to empower employees/colleagues seems also very important. Could you share your perspective on how to best empower people?

LL: If I were to summarize the attributes that empower people I would have to use the words *vision*, *appreciation*, and *respect*. We have to lead with vision; to make people feel they are part of something that matters. We have to show people appreciation; make them feel that their contribution to that vision, no matter how small, matters. Just a small amount of appreciation can go a long way towards making others feel empowered.

Finally, respecting the dignity of others is another ingredient in making people feel empowered. This doesn't mean we always have to agree, but we ought to strive for environments in which we are respectful even when we disagree. It is amazing how much difference merely the tone of our voice influences how others feel. I think we would go a long way to reduce stress and empower others if managers and leaders were more aware of how to treat others with dignity and respect.

"If I had to summarize the attributes that empower people I would have to use the words *vision, appreciation* and *respect*"

BG: In your book, you articulated beautifully the importance of nurturing an environment for creativity while answering the demand and the reality of business imperatives. I can see a parallel in the scientific world, in which we need creativity to think out of the box to uncover biological phenomena or develop new techniques while still facing the reality of a harsh and competitive world. Can you elaborate on your insights about the best culture to encourage creativity in a competitive workplace?

LL: I find that the best culture is one that is unafraid to examine and resolve the competing tensions that it takes to do great work. For example, creative out-of-the-box thinking is almost never linear or formulaic. It comes with many false starts, setbacks and wrong directions. There is always some battle between creativity and practicality, as represented by business, production or other administrative needs.

It helps to have a culture where these tensions can be aired openly, without blame or anger. Usually, there is some legitimate point to understand from each side of the discussion. Even if we don't agree on things, we can still cultivate a culture in which we feel we are working together, on the same team. It is challenging to collaborate in this way because it is easy to become defensive or political. The best teams understand how to give constructive feedback and learn from each other without it being offensive or political. That is a great aspiration for a workplace I think.

BG: The Buddhist philosophy called the Middle Way is about harmonizing opposing forces that cause tension in our lives. Can you explain how to use this ancient philosophy to our modern world? For example, we have self-centered metrics of success in science (e.g., need to be a first author in many publications, need to get invited to talks) while we know that flourishment/ eudemonia comes from pursuing goals beyond self-interest ("Philosophical and Scientific perspective of well-being", the Dossier June 2018). How do we reconcile these divergent goals?

LL: The Middle Way is a philosophy of harmony. Its central idea is that we become frustrated or miserable when we cling to fixed, rigid ways of thinking because reality is not fixed and rigid. The self-centered metrics you mention are a great example of that. The problem isn't with the metrics per se; it is when we define our self-value by those metrics. Then it becomes an extreme way of thinking that the Middle Way would say will get us in trouble.

For example, if we identify our value as a human with, say, being a "successful scientist" then we have limited ourselves to a pretty narrow formula, much of which is out of our control. We have also excluded many other possibilities that make life rich and fulfilling, like being a good friend, parent, partner, neighbor, etc. According to the Middle Way, to flourish we have to get beyond these inner narratives that limit and narrow our lives; we have to see how deceptive they are. Then we can live a more expansive version of life, one that depends not on outer metrics for valuing our lives but in which we cultivate a well-spring of strength and nourishment from within. That takes inner awareness and practice, which is the aim of the methods for developing the mind we teach at Juniper.

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