THE DOSSIER

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

November 2010 Issue 3

From the Editor

Welcome to the third issue of The Dossier, a newsletter dedicated to the Staff Scientists and Staff Clinicians (SS/SC) of the CCR!

This issue contains important messages from the Director's Office and a special article by Dr. Miriam Poirier. A summary of our first SS/SC Mid-Year Training Event is also presented along with details on the quadrennial review and information on bioinformatics resources at NCI. This issue also highlights the work of Dr. Luowei Li (SS) and her successful experience with the Confocal Microscopy Core, headed by Susan Garfield (SS). We hope to continue to provide relevant and pertinent information to aid in the success of SS/SCs. Please send your contributions and suggestions to budhua@mail.nih.gov.

Anuradha Budhu, Ph.D. (SS)
Editor-in-Chief
Laboratory of Human Carcinogenesis

In This Issue

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From the Office of the Director

Well organized enterprises commonly address continuity as part of their strategic planning, and the Center for Cancer Research is no exception to this practice. Building continuity into our organization is challenging, though, because we have an unusual infrastructure. We often are working on long-term, high-impact questions about cancer mechanisms by employing, in part, large numbers of short-term staff. To succeed under these conditions, we must maintain the continuity of our research focus, sometimes for decades, while factoring in the influx and efflux of hundreds of post-doctoral researchers who pass through our doors for 3 to 5 years of training. During this unending parade of change, we also must preserve the network of ideas that our scientists generate, whether they come from visiting or staff researchers.

Fortunately for our organization, we have career Staff Scientists and Clinicians who perform this vital service to CCR by meeting our continuity needs. They are our custodians of continuity. Thanks to their institutional memory, they give visiting post-docs information and advice about earlier projects completed in their respective laboratories, all while working alongside them as they address their own research questions.

"Fortunately for our organization, we have career Staff Scientists and Clinicians who perform this vital service to CCR by meeting our continuity needs. They are our custodians of continuity."

Our Staff Scientists and Clinicians also perform another critical function for CCR. They help us to fully exploit our network of ideas. Research itself does not progress in linear fashion. It evolves in many expected—but often some unanticipated—directions from an initial hypothesis. Visiting researchers often work on a single aspect of an overall complex problem without always being fully aware of all the related research ongoing here in CCR, or in labs outside of CCR. Staff Scientists and Clinicians provide this needed intramural and extramural networking. In many cases, they contribute needed perspective, expertise, and assistance running complex experiments.

Staff Scientists and Clinicians are an integral part of CCR's culture and intellectual vitality. CCR leadership is grateful for their important role in creating and passing on our progress and in building connections from one researcher to another.

***Robert Wiltrout*, Ph.D.**
Director, Center for Cancer Research

Please share this newsletter with your colleagues and visit the SS/SC website at
https://ccrod.cancer.gov/confluence/display/CCRSSSCArchive/Home

The 2010 Staff Scientist and Staff Clinician Mid-Year Training Event

The Career Development Committee held the first NCI Mid-Year Training Event for SS/SC on September 13, 2010 in the Natcher Building, NIH.

The first NCI Mid-Year Training Event for Staff Scientists and Staff Clinicians was held on September 13, 2010 in the Natcher Building at NIH. This training session was a great success with over 100 participants and was articulated around 3 blocks.

The first block was about how to organize effective meetings. It started with a lively presentation by Sandra Thomas and Shannon Connolly from the NCI Office of Workforce Development (http://mynci.cancer.gov/workforce). Sandra and Shannon projected a DVD showing a very ineffective professional meeting followed by discussion of the basic ingredients of effective professional meetings. This presentation was followed by a panel discussion with Sandra, Shannon, Karen Kochersberger, Tim Sakemiller and Alison Rattray. Karen, our meeting coordinator for this training event, described SAIC's approach to organizing NIH events (http://mynci.cancer.gov/workforce). Tim, who is an ARC manager in NCI-Frederick, described the administrative steps needed to participate in the organization of an outside Scientific Meeting and Alison described her experiences in organizing FASEB meetings.

The second block was a presentation about grants available to SS/SC. Jonathan Wiest, Director of the Center for Cancer Training (http://cancer.gov/cct) moderated a presentation of grants for which SS/SC may be eligible. As an introduction, Jonathan gave a very detailed presentation about available funding mechanisms and how to become a successful candidate, stressing the fact that he is the only CCR signing official for grant applications. Following Jonathan, Donna Kimbark, Program Manager at the Congressionally Directed Medical Research Program (CDMRP), Department of Defense (https://cdmrp.org/), gave a very complete presentation of all grants and mechanisms offered by CDMRP. She explained that their mandate is to cover specific aspects of health care research where other federally funded programs are lacking. After these needs are assessed, grants are announced throughout the year. Potential candidates should pay careful attention to the grant requirements, which often differ from past offered grants. Yong Yao, Director of the NIH Roadmap Molecular Libraries (http://mli.nih.gov/mli/), presented the NIH R03 grant mechanism for solicitation of assays for high-throughput screening, which offers $50,000 for assay development. The last speaker for the first part of the session was Jacqueline Roberts, Program Specialist at the Intramural AIDS Targeted Antiviral Program who presented the funding mechanism offered by this NIH program. The second part of the program included success stories from invited SS/SC who are currently grant recipients. Christophe Marchand (Staff Scientist, recipient of a NIH R03 grant), Nadya Tarasova (Staff Scientist, recipient of a CDMRP-DOD grant) and Frank Maldarelli (Staff Clinician, recipient of a NIH Bench to Bedside award) all shared their experience about applying to these grants and being successful. A stimulating panel discussion with all participants was established as a conclusion for this block.

The third block in the afternoon was organized in the format of four mini think tanks. Each group was given the mission of developing ideas about particular professional development related issues for SS/SC. This block generated a large amount of information, which will be presented in a future issue of the Dossier.

Christophe Marchand, Ph.D. (SS),
Laboratory of Molecular Pathology and
Victoria Virador, Ph.D. (SS),
Medical Oncology Branch

The PI Corner

The contributions of the Staff Scientists and Staff Clinicians are absolutely critical to the mission of the CCR and the NCI. Years ago PIs frequently had a "right hand person" who functioned independently within a program, devised innovative approaches to answering questions within that program, and was both competent and committed to the line of research directed by the PI. However the Promotion Committees were always faced with the same conundrum: how independent are they and how far can they be promoted under the current Civil Service System? Unfortunately these very important and accomplished staff persons never seemed to get the recognition that they deserved. It has been, therefore, gratifying over the years to see this problem addressed by the creation of Staff Scientist/Staff Clinician positions. As a PI I am most appreciative for the Staff Scientists in my group who have made critical contributions by their dedication and hard work. Time and time again I have heard similar sentiments voiced by other PIs, and although we probably do not thank you sufficiently, please know that your work is highly valued and essential to our progress in the fight against cancer.

Miriam Poirier, Ph.D.
Head, Carcinogen-DNA Interactions Section
Laboratory of Cancer Biology and Genetics

The Bioinformatics Corner

Software solutions to mine large datasets are constantly being expanded as new sequence annotations are being updated and high-throughput platforms are being developed. If you are new to high-throughput data analysis, take a look at the Office of Science and Technology Partnerships Wiki (https://ccrod.cancer.gov/confluence/display/CCROSTP/Home) and click on the "Bioinformatics Tab". You will find a series of software that are available to NCI. In addition to commercial software, the open source community is also very active, and can oftentimes provide more flexible software (at the cost of having to reformat your data a bit more or perhaps requiring a bit of programming). Here are three very useful open-source tools:

- R (http://cran.r-project.org/): free software environment for statistical computing and graphics. This requires a bit of programming but there are lots of well documented packages that can be used (http://www.bioconductor.org/). Still don't know where to start? Try one of the hands-on courses offered through the Computer Training Program (http://training.cit.nih.gov).
- BRB Array Tools (http://linus.nci.nih.gov/BRB-ArrayTools.html): uses an Excel front end for visualizing and analyzing microarray data, developed by Dr. R. Simon and the BRB-Array Tools Development Team at NCI.
- Weka (http://www.cs.waikato.ac.nz/ml/weka/): collection of machine learning algorithms for data mining (i.e. classification, regression, clustering, visualization, ect). This software is flexible (appealing for developers as well as non-developers), user-friendly, and is very well documented.

Ewy Mathé (SS)
Laboratory of Human Carcinogenesis

The Quadrennial Review Corner

2011 Quad Review Packages Due in January, Get Started!

Based on the lists compiled last year, the following Staff Scientists and Staff Clinicians are scheduled to be Quad reviewed in 2011. Specific deadlines have not yet been set, but plan to submit your Quad packages to your AO in January for the review in March. If you're on the list below, please confirm your review date with your AO.

The Quad package is assembled by you and your PI, so it is essential that you both are clear about what you need to do. Templates and forms are available online, choose Staff Scientist or Staff Clinician (http://home.ccr.cancer.gov/intra/arc/fte/index.asp). Your PI writes the recommending memo and requests letters of recommendation. In addition to discussing your achievements, awards, and publications, it is essential that the recommending memo describes your responsibilities in the Lab/Branch and how you have fulfilled them. Every effort is made to fairly evaluate all Staff Scientists and Staff Clinicians despite their various roles, but those roles must be explained. The letters of recommendation are extremely important and should come from collaborators or other scientists who have worked directly with you and can comment knowledgably and enthusiastically on your work. Your primary responsibility is to create a CV that includes all your scientific activities and accomplishments over the last four years. The Quad review panels have strived to ensure that contributions to team science receive appropriate credit. The panels also recognize and reward outstanding training and mentoring, and service to the NIH and scientific communities. Make sure to include these activities on your CV, in addition to your publications and presentations. Outstanding Staff Scientists and Staff Clinicians provide scientific leadership and specialized scientific expertise within their Lab/Branch. Overall, your Quad package should illustrate how your efforts have contributed to the success of your research team.

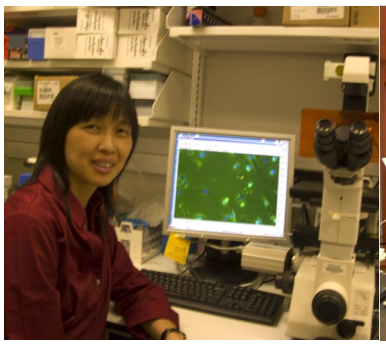
Lynne Rockwood, Ph.D.
Office of Scientific Programs

SS/SCs Scheduled for 2011 Review:

Staff Scientists	Staff Scientists	Staff Clinicians
ANURADHA BUDHU	YILI YANG	KAROLL CORTEZ
YUAN JIANG	YUK SING CHENG	JASON LEVINE
DALE LEWIS	DAVID DAVIS	STEVEN PAVLETIC
NADIM MAJDALANI	MARK DUDLEY	PETER PINTO
PAUL MITTELSTADT	STEVEN FELDMAN	MARTHA QUEZADO
AHMED RAAFAT	MARIA PARKHURST	SUPARNA WEDAM
CHIN HSIEN TAI	LISA RIDNOUR	CONSTANCE YUAN
DEBORAH HODGE	WANPING XU	
ABDUL WAHEED	SVEN BILKE	
	PAOLA SCAFFIDI	

The Core Corner

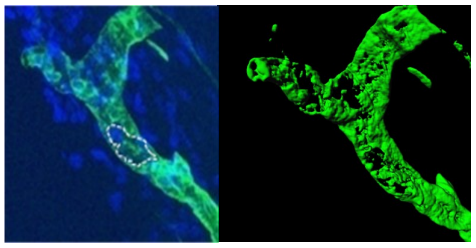
Reference: Li L, Shukla S, Lee A, Garfield SH, Maloney DJ, Ambudkar SV, Yuspa SH. Cancer Res. 2010 Jun 1;70(11):4509-19. Epub 2010 May 11.



The skin cancer chemotherapeutic agent ingenol-3-angelate (PEP005) is a substrate for the epidermal multidrug transporter (ABCB1) and targets tumor vasculature. Ingenol-3-angelate (PEP005), extracted from *Euphorbia peplus*, is currently in clinical trials to eradicate basal cell carcinoma, actinic keratosis and squamous cell carcinoma (SCC) in situ by topical application. A preclinical study of PEP005 demonstrated that topical treatment of PEP005 effectively eradicates a number of subcutaneously xenografted human and mouse tumors. PEP005 is structurally related to phorbol esters and activates protein kinase C (PKC) in vitro and in vivo. To elucidate the molecular target(s) of PEP005, we compared the biological and biochemical function of PEP005 and phorbol 12-myristate 13-acetate (PMA) using cultured mouse tumor cell lines and two strains of hairless mice. We found that topical PEP005, but not PMA, inhibited the growth of subcutaneous tumors derived from PAM212 (mouse SCC) and B16 (mouse melanoma). PEP005 and PMA both induced acute neutrophilic infiltration on mouse skin, but only PEP005 caused subcutaneous hemorrhage and vascular damage. Both PEP005 and PMA activated Erk1/2 in epidermis, but PEP005 also activated Erk1/2 in skin dermal fibroblasts and endothelial cells. Pretreatment with topical cyclosporin A (CsA), verapamil or XR9576, modulators of P-glycoprotein (P-gp), prevented PEP005-induced hemorrhage, but not neutrophil infiltration. CsA also impaired PEP005's anti-cancer activity while the anti-inflammatory dexamethasone did not. PEP005, but not PMA, blocked photoaffinity labeling of human P-gp with [^{125}I]-Iodoaryazidoprazosin and inhibited P-gp mediated drug resistance to HCT-15 cells. The intracellular levels of PEP005 were significantly lower in P-gp expressing cells and treatment with XR9576 increased the levels to those of cells that do not express P-gp, demonstrating that PEP005 binds to and is transported by P-gp. Taken together, our results suggest that P-gp mediated absorptive transport, dermal penetration and vascular damage contribute to the anti-cancer activity of PEP005 *in vivo*.

PEP005-induced hemorrhage was observed within 3 hours after topical application. Immunohistochemistry of CD31 and electron microscopy studies demonstrated the loss of the structural integrity of the cutaneous blood vessels and activation of endothelial cells. To visualize whole blood vessels in mouse skin, the blood vessels in mouse were labeled with FITC-lectin. After fixation, the skin samples were sectioned, transversely to hair follicles, into 100 µm section, and then mounted with mounting medium containing DAPI for visualization by confocal microscopy (Zeiss NLO510). A series of images were taken and projected in three dimensions using the ZeissLSM Image Browser. Fluorescent images showed FITC-lectin labeled blood vessels from control and PMA treated mice displayed continuous green fluorescence. However, loss of continuous FITC-lectin staining in PEP005 treated mice was detected 40 minutes after initial treatment, well before the appearance of hemorrhage on the treated skin. To get a better view of the 3D images of FITC-lectin labeled blood vessels, Susan Garfield from CCR Confocal Core Facility in building 37 performed a surface rendering technique (Imaris 6.1 software) to reconstruct FITC-lectin labeled vessels. The reconstructed blood vessels from PEP005 treated skin was markedly damaged leading to discontinuous patterns appearing as "holes". The use of the surface rendering reconstruction technique clearly enhanced the images of FITC-lectin labeled cutaneous blood vessels and delivered a powerful picture that is worth a thousand of words. The results were of our recent publication supports the conclusion that the anti-cancer agent PEP005 eradicated subcutaneous xenografted tumors by targeting and directly damaging cutaneous blood vessels and tumor blood vessels.

Luowei Li, Ph.D. **(SS),** Laboratory of Cancer Biology and Genetics;
Susan Garfield **(SS),** Laboratory of Experimental Carcinogenesis, Head, Confocal Microscopy Core



Original fluorescent image

Image after surface rendering

Announcements

The CCR Confocal Microscopy Core has a new location

The CCR Confocal Microscopy Core Facility is located in a newly renovated Imaging Suite (B114) in the basement of Building 37. Three confocal systems, 2 environmental chambers (heat, humidity and CO_2 control) with x,y scanning stages (multiple locations during time lapse) and 2-photon lasers for deep tissue imaging are available to users as well as specialized software and several computer work stations. Susan Garfield, the Facility Head, provides imaging expertise/advice and users are trained on the instruments by core facility staff.

Moving on……

John Morris, M.D., SC Co-Chair and Metabolism Branch researcher, joined the Division of Hematology/Oncology, Department of Medicine at the University of Cincinnati as a Tenured Professor of Medicine. He will be Chief of the Lung and Head & Neck Cancer Section, directing a translational research program with both clinical and laboratory aspects.

John Janik, M.D., an SC member of the Metabolism Branch, joined Bristol-Myers Squibb as their Medical Director in the Discovery Medicine Oncology Group. He will work with Dr. Jon Wigginton.

Vote!

The candidates for the SS/SC Co-Chairs for the 2011-2012 term have been announced. Please check the SS/SC web site this month to get information on the nominees and place your vote.

Bethesda Candidates

Olga Aprelikova, Ph.D.
Swati Choksi, Ph.D.
Christophe Marchand, Ph.D.
Christina Stuelten, M.D., Ph.D.

Frederick Candidates

Jianbo Chen, Ph.D.
Anu Puri, Ph.D.

Clinical Candidate

Marybeth Hughes, M.D., FACS

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 regarding 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 manner and we will do our utmost to include your material in upcoming issues.

Join one of these SS/SC Committees

Career Development
Communications
SS/SC Retreat

Please share this newsletter with your colleagues and visit the SS/SC website at
https://ccrod.cancer.gov/confluence/display/CCRSSSCArchive/Home