THE DOSSIER

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

December 2014 Issue 18

From the Editor

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

This issue contains important messages from the Director's Office, a special article by Scott Durum, Ph.D., and information on the 2015 SS Quadrennial Review from Cynthia Masison, Ph.D. A summary of the 3rd Biennial SSSC Professional Development Day is presented by Christophe Marchand, Ph.D. We feature Constance M. Yuan, M.D., Ph.D., in our SSSC Corner, while Sergey G. Tarasov, Ph.D., and Yien Che Tsai, Ph.D., describe their collaborative efforts at the Biophysics Resource. In addition, the published work of Myong-Hee Sung, Ph.D., is highlighted in our Author's Corner.

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

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

In This Issue

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From the Office of the Director

The Impact of the Intramural Research Program

From its humble beginnings in a one-room laboratory on Staten Island in the late 1880s, the NIH Intramural Research Program, or IRP, has now become the world's largest biomedical research institution. Other government, academic, and nonprofit groups wishing to establish productive research laboratories have used the IRP model, which is designed to maximize the impact of basic research advancements on improving human health.

As Staff Scientists or Staff Clinicians, you know that being a part of the IRP provides an array of unique opportunities. Here, researchers have the freedom to pursue high risk, but potentially rewarding, projects that might otherwise not receive grant funding or seem unprofitable to commercial entities but may provide fundamental insights into the nature of living systems. IRP scientists and clinicians can devote years or, in some cases, decades to the development of a particular line of exploration. At the same time, scientific rigor is maintained through oversight by Boards of Scientific Counselors made up of objective, external reviewers.

Avenues to translate basic discoveries from the laboratory into the clinic also exist, even for those investigators with no prior clinical experience. Having access to patients with rare diseases through the Clinical Center can facilitate discoveries that may be impossible anywhere else. Add to this the availability of state-of-the-art facilities, carefully maintained by many of you, and resources, including leading experts in their fields, and the exceptional environment of the IRP becomes obvious.

Some fruits of IRP researchers' labors have been in the news recently, such as discussions of potential vaccines for the Ebola virus, all of which rely on a basic understanding of the molecular events involved in the virus life cycle. Closer to home in CCR, Douglas Lowy, M.D., and John Schiller, Ph.D., received the National Medal of Technology and Innovation from the President for their work on the development of human papillomavirus (HPV) vaccines. In efforts spanning 30 years, Drs. Lowy and Schiller along with members of their research teams discovered that HPV L1 proteins, like the bovine papillomavirus proteins they originally studied, spontaneously assemble into spheres of virus-like particles (VLPs) and these VLPs are capable of inducing potent anti-HPV antibody responses. After licensing the VLP technology, two pharmaceutical companies went on to produce the commercially available vaccines, Gardasil and Cervarix. Drs. Lowy and Schiller continue to pursue novel anti-HPV vaccine constructs and methods of administration as well as the topical antimicrobial carrageenan, which may extend HPV infection prevention to those without access to vaccination.

Without the IRP environment, the translation of a single HPV protein into an effective vaccine and ultimately commercial products might never have been made, since vaccines against sexually transmitted infections were met with considerable skepticism at the time. Likewise, research into the Ebola virus might not have progressed as far as it has. Staff Scientists and Staff Clinicians, like you, play a critical role in making the IRP a successful research enterprise. Thank you for the valuable work that you do. I look forward to seeing what we discover next.

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

The Quadrennial Review Corner

The 2015 Quadrennial Review for Staff Scientists

All Staff Scientists that are being reviewed in 2015 have been notified by email. The email contained a checklist of items needed for the review package, a curriculum vitae template and a link to the CCR SSSC webpage. As indicated in its name, the quad review process evaluates the Staff Scientist's scientific activities and accomplishments over the last four years for appointment extension and salary adjustment purposes. If you think the timing of your quad review is not accurate, please contact your AO for clarification. The deadline for submission of the complete review package to CCR is December 12, 2014. **Please contact your AO for local ARC submission deadlines**. It is anticipated that formal review of the packages will be conducted in March 2015 and the results of the review reported back to the Staff Scientist and supervising PI no later than April 24, 2015.

The quad review package consists of three parts: the recommending memo from the supervising PI, the Staff Scientist's CV, and at least two letters of recommendation from collaborators who know the Staff Scientist and his/her work. A revised recommending memo has been designed this year to facilitate the review process and highlight the importance of the contributions the Staff Scientist makes to their laboratory. In their recommending memo, the supervising PI is asked to indicate the specific role(s) the Staff Scientist plays in the laboratory. An accompanying letter detailing the Staff Scientist's scientific productivity, presentations, participation in special interest groups, mentoring/teaching, Tech transfer, involvement in GMP production and/or CRADAs, collaborations, continuing education, awards and significant achievements is also completed by the supervising PI.

The Staff Scientist should be proactive in this process by providing examples to his/her PI of how he/she has contributed to each of these areas. The Staff Scientist should ensure that the CV is up to date and provides specific details of his/her involvement and contributions. The reviewers only have the information provided by the supervising PI and the Staff Scientist to conduct the review. It should not be assumed that the reviewers will take into consideration any information that is not specifically provided in the package. For example, in addition to providing a list of mentees, indicate how the Staff Scientist's mentoring benefited the fellows' careers (publications, posters, educational opportunities) and where mentees are now should also be provided. While a list of collaborators indicates the Staff Scientist's involvement in team science, describing the contributions to the project provides important details by pointing out the Staff Scientist's specific roles in moving projects forward. Although reviewers have recognized how budget and travel constraints have limited everyone's ability to attend meetings, there are still many opportunities at the NIH and in the local area. To summarize, strong supporting memos from your PI and collaborators and a detailed CV are the most important ways to demonstrate how your efforts have contributed to the success of your research team and to the greater scientific community.

Cynthia Masison, Ph.D.
Scientific Program Analyst, Office of The Director

The PI Corner

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

Our American scientific research establishment, for all its collective intelligence, ignored, for a generation of scientists, a fundamental flaw in its structure. We were conducting research with trainees. If budgets periodically increased, we increased the trainees. When all these trainees eventually looked for research jobs and submitted grant applications, it was like balloon mortgages triggering the housing crisis. The system needed to change. Creation of the Staff Scientist position has greatly improved the system, allowing us to conduct critical research without procreating scientists every year. That is the benefit to the establishment.

The benefits of Staff Scientists to the Investigator and the research projects cannot be exaggerated. Perhaps if my own experience were different, my opinion would be less extravagant. The Staff Scientist in our group, Wen Qing Li, Ph.D., brings an intellectual and technical expertise, and a professional standard into the lab every day. She knows how everything works, really everything, and how, and why. She runs the research, I write the grant applications. WQ teaches the postdocs and students how to do everything and this patience is sometimes tested with difficult visitors from time to time. We discuss each postdoc applicant, and together review everyone's progress. While she loves to focus on her own projects, we continually discuss every project in the lab. Collaborators who really know us email WQ and cc me.

This level of synergy, trust and reliance developed over a number of years. Like many NIH Staff Scientists, WQ came to our lab as a postdoc. Her accomplishments clearly marked her as a high achiever and, when the Staff Scientist position was created, she was identified as an ideal candidate. If creating this kind of position were an experiment, it would be judged a huge success, the enterprise and the scientists have all benefitted from the Staff Scientist system. I think the next step should be to create more of a contractual permanency to the position, like that of our Biologists and tenured Investigators.

Scott Durum, Ph.D.
Head, Cytokines and Immunity Section,
Deputy Chief, Laboratory of
Molecular Immunoregulation

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The SSSC Corner

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

My father, a Biochemistry Professor, instilled in me a love of science and the joy of "playing" in the laboratory. As a little girl, I learned to pipette, use a spectrophotometer, and perform experiments with leukemia-derived cultured cells for science projects. Thirty-some odd years later, I am still examining leukemia, only now, as a hematopathologist, with expertise in clinical flow cytometry. I have the chance to make life changing diagnoses every day, and also generate and interpret research data that directly impacts the understanding of disease biology, treatment and outcome of leukemia and lymphoma patients here at NCI.

I joined the Laboratory of Pathology (LP) in 2006 as a Staff Clinican for the Flow Cytometry Unit, led by Maryalice Stetler-Stevenson, M.D., Ph.D. Every day is a surprise, you never know what will show up! The cases are unusual, and don't follow the textbooks (but why would leukemia bother to read a book?). Plus, I work with a bright, motivated and all-around fabulous group of people (pictured on this page). That is, and continues to be, a powerful motivation to wake up every morning and come to work.

Previously, I was an Assistant Clinical Professor at the University of Florida, where we often examined marrows from patients with myeloma. Since joining LP, I have seen this previously incurable disease become potentially curable. I remember examining a bone marrow from a patient with myeloma, whose disease completely regressed on the drug carfilzomib, and almost couldn't believe my eyes, certainly one of the highlights of being here at NIH. Another highlight: a few years ago, there was a patient who was the first to respond to CD19 CAR T-cell therapy. I will never forget that evening, when I identified a population of CD19 CAR positive T-cells not only expanding within the patient, but also the disappearance of the acute lymphoblastic leukemia (ALL) cells. This was the only therapy to have ever been effective; she was finally able to undergo a bone marrow transplant and remained disease-free for a little over two additional years.

Even though we don't have direct patient contact, we collaborate closely with clinicians, and they connect us to the patients we serve. Their stories reinforce our vital role at NIH, the medical community at large, and most importantly, "humanize" our daily work. I recall a pediatric oncologist who was so excited that the CD22 recombinant immunotoxin treatment was working in one of the ALL patients. His patient said "why don't they give this stuff to all the kids? It doesn't make your hair fall out and it works!". These stories are exciting and keep me going. They demonstrate that our work makes a tangible and direct impact in the lives of others.

The Flow Cytometry Laboratory, LP, NCI, NIH. Back row (left to right): Gregory Jasper, Robert Honec, Cathy McCoy. Middle row: Margo Santiago, Constance Yuan, Maryalice Stetler-Stevenson. Front row: Linda Weaver, Dalia Salem.

Outside of work, I enjoy spending time outdoors with my friends, both human and equine. Whether riding the trails, competing in local shows, or volunteering at farm events, I enjoy every moment with my four-legged companions. There is no perspective quite like seeing the world from the back of a horse. I've also had the opportunity to participate in outreach work with Throughbred ex-racehorses. This area has a deep tradition of racing, and it's very satisfying when these magnificent creatures find new homes and second careers once their time on the racetrack is over. As a little girl, I always loved horses. To this

The SSSC Corner Con't

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

Connie enjoys the company of her equine friends. "Juice Box" (left, Factory Direct) is a Throughbred ex-racehorse, owned by Addie and Sheri Thornley of Damascus, MD. "Zipper" (right, Zips Dancing Queen) is an American Quarter Horse, owned by Erin Reilly and Steve Gunnulfsen of Laytonsville, MD.

day, my family continues to tease me that I would've been a very good veterinarian.

Constance M. Yuan, M.D., Ph.D. (SC)
Flow Cytometry Unit
Laboratory of Pathology

The Professional Development Corner

The Third Biennial NCI SSSC Professional Development Day

The 3rd Biennial Professional Development Day was held on September 26, 2014, in NCI Shady Grove. After a few welcome remarks, Eric Hale, J.D., opened the morning session with a detailed presentation on grant submission, where he described the new regulations in place at NCI. Following Eric's presentation, Kelly Leonard animated a very interactive workshop on how to network using the social media LinkedIn. The afternoon session was opened by Shannon Connolly and Jennifer Chloupek, M. Ed., with a stimulating workshop on managing up or how to interact efficiently with your supervisor.

Lastly, a panel composed of CCR Deputy Directors from Frederick and Bethesda, the CCR ARC Deputy Director and four recently displaced Staff Scientists was convened for discussion on SSSC displacement. During this panel discussion, several issues were brought forth that relate to how SSSC displacement is handled in Bethesda and Frederick. Based on the information gathered during the panel discussion, the Professional Development Committee sent a memo to the CCR Senior Staff just before their October meeting. CCR considers this to be a very important issue and is actively working on clarifying the process of SSSC displacement and updates will be provided in upcoming issues of *The Dossier*.

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

The Author's Corner

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

Switching of the Dominant Feedback on NF-κB in Macrophages

Switching of the relative dominance between feedback mechanisms in lipopolysaccharide-induced NF-κB signaling. Sung, MH, Li, N, Lao, Q, Gottschalk, RA, Hager, GL, Fraser, ID. Sci Signal 7(308), 2014.

As part of an early innate immune response during microbial infection, macrophages use Toll-like receptors (TLRs) to recognize molecular patterns such as the Gram-negative bacterial product lipopolysaccharide (LPS). Receptor activation initiates a complex signaling network that involves NF-κB and other pathways. The complexity of this network has hampered our understanding of how macrophages resolve conflicting signals to determine when to mount an immune response. To make matters even more complicated, the signaling dynamics of NF-κB in individual cells have been shown to be oscillatory and to influence the biological response in the few cell types examined (*1, 2*). Having shown the biological relevance of NF-κB oscillations in fibroblasts (*2*), Myong-Hee Sung, Ph.D., Staff Scientist in the Laboratory of Receptor Biology and Gene Expression (LRBGE) headed by Gordon Hager, Ph.D., hypothesized that immune cells utilize the complexity of NF-κB dynamics to achieve their intricate function. The project benefitted from the collaboration with Iain Fraser, Ph.D., in the Laboratory of Systems Biology at NIAID, who offered a valuable tool for live microscopy, a dual reporter clone generated for genome-wide siRNA screens in macrophage lines. Dr. Fraser and his coworkers had devised a reporter system to simultaneously monitor NF-κB nuclear localization and transcription in living cells. Dr. Sung performed live cell microscopy on macrophages expressing GFP-tagged RelA, a subunit of NF-κB, under the control of the RelA promoter and a rapidly degraded mCherry fluorescent protein under the control of the TNF-α promoter, an NF-κB target (*Figure 1*) (*3*).

Interestingly, in macrophages, the NF-κB dynamics were distinct from those seen in fibroblasts, suggesting previous models of LPS-induced signaling may not apply to macrophages. In addition, there was little correlation between nuclear NF-κB and target reporter induction at any single time point. However, the activity of nuclear NF-κB integrated over time (only available from real-time assays) was well correlated with mCherry reporter activity, despite the variety of other transcription factors at work in macrophages. To understand how cells decode LPS signaling information, the team varied the concentration of LPS stimuli. In contrast to the response in non-immune cells, nearly all the macrophages responded regardless of the LPS dose. Above a threshold dose, however, LPS increased RelA mRNA and protein. The authors later showed that RelA is a direct target of NF-κB, identifying a previously unknown NF-κB positive feedback loop. Microarray analysis of expression suggested that the LPS dose threshold may correspond to the turning point at which macrophages commit to mounting an immune response (*Figure 1*). The newly identified positive feedback loop was then incorporated into a novel mathematical model of LPS-induced NF-κB signaling, generated by Dr. Sung. The switch from predominantly negative feedback to positive feedback allowed the cells to discriminate between various levels of LPS. To test the model experimentally, the team asked whether

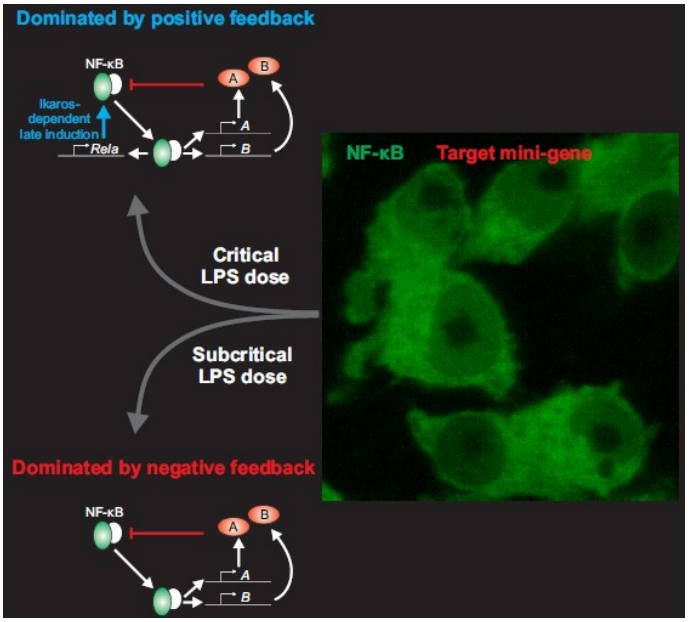


Figure 1. **Re-wiring of the NF-κB regulatory circuit at a critical dose of LPS.** Lower Panel: Sub-critical doses of LPS induce predominantly negative feedback genes and genes with conflicting functional consequences, preventing a coherent response in macrophages. Upper Panel: Above a critical dose of LPS, Ikaros-dependent amplification of NF-κB becomes a dominant feedback loop, which overcomes the various negative feedback loops and enables a full-blown innate immune response.

The Author's Corner Con't

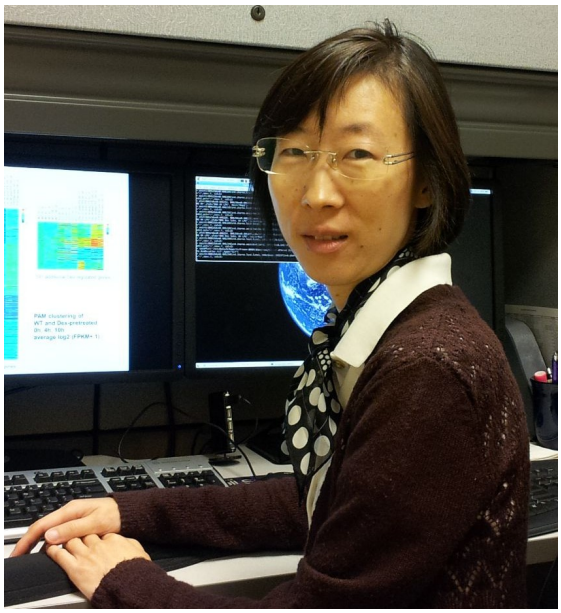
Section Editor: Cristina Bergamaschi, Ph.D. (*SS*)

the transcription of LPS-induced genes was affected by a prior dose of LPS, a phenomenon known as hysteresis. Indeed, macrophages treated with a high dose of LPS and switched to a low dose showed more transcription of these genes than cells pre-treated with a low dose. Finally, to look for factors involved in RelA induction by LPS, Sung combined expression microarray data with data from the genome-wide siRNA screen in Dr. Fraser's lab. The cross-comparison identified the transcription factor Ikaros. Indeed, in experiments knocking out the factor Ikaros, the positive feedback pathway was inhibited, hampering LPS dose discrimination.

Together, the authors revealed a novel positive feedback pathway for switching on NF-κB in macrophages in response to physiologically relevant concentrations of LPS. This multidisciplinary investigation exemplifies how quantitative single-cell analysis, combined with high throughput profiling approaches, can lead to a series of new and sometimes unexpected discoveries even from extensively studied molecular systems. It represents the first example of stimulus-induced transcriptional activation of RelA, a key NF-κB gene that amplifies the overall activity of NF-κB. The discovery raises new questions: In what other contexts is NF-κB activity amplified to support important biological responses? What regulates this master regulator at the level of transcription? Although the study revealed Ikaros as one regulator, there may be other factors important for the transcriptional regulation of RelA.

Myong-Hee Sung, Ph.D. (SS)
Laboratory of Receptor Biology and Gene Expression

Myong-Hee (Mia) helped establish the bioinformatics staff in LRBGE by recruiting talented computational scientists over the last several years. She develops new computational algorithms for the genomics community, especially for the recently introduced assays that lack proper statistical tools (4-7). Numerous studies in Dr. Hager's lab have benefitted from her mathematical and computational expertise. She has contributed to a large number of important publications since she joined LRBGE in 2005. Mia advises students, postdoc fellows, and junior Staff Scientists for various projects, from study designs to writing manuscripts, and consults for PIs in and outside of NIH. In addition to computational genomics, Mia has been interested in understanding the complex dynamic activities of transcription factors. This paper, exemplifying her interest in NF-κB dynamics, grew out of a study that she initiated with Dr. Fraser. Mia hopes to continue this line of research by addressing unexplored questions with quantitative single cell approaches.



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Studying Mechanisms for Ubiquitination Through Protein-Protein Interactions

In the Weissman lab (Laboratory of Protein Dynamics and Signaling), we study post-translational regulation of proteins by the ubiquitin system and its role in cancer and other diseases. The ubiquitin system is a complex system that regulates almost all cellular processes. In this pathway, ubiquitin is conjugated onto specific substrate proteins, determining the fate of these substrates in the cell. Ubiquitination is a complex process that involves a hierarchical system of three enzymes: a predominant ubiquitin-activating enzyme (E1), around 40 ubiquitin-conjugating enzymes (E2s) and over 500 ubiquitin-protein ligases (E3s). In addition, around 100 de-ubiquitinating enzymes (DUBs) can remove ubiquitin from substrates, reversing the effects of E3s. Understanding how this complex system of enzymes functions is critical to understanding how perturbations of this system lead to disease and designing new therapeutic approaches.

We have focused mainly on the E3s, which together with the E2s, determine substrate specificity. One area of interest is characterizing the interaction of E3s with their cognate E2s. RNF45 (also known as gp78) is a multi-membrane spanning E3 involved in degrading proteins from the endoplasmic reticulum (ER). RNF45 regulates sterol metabolism by degrading Insig proteins and promotes the spread of sarcoma by degrading the metastasis suppressor CD82/KAI1 (*1, 2, 3*). Increased expression of RNF45 in African American breast cancer patients suggests that higher levels of RNF45 may contribute to poor outcome in this group of patients (*4*). Understanding how RNF45 interacts with its cognate E2, UBE2G2, in protein degradation will enhance our ability to target RNF45 for treatment. In collaboration with the laboratories of Andrew Byrd, Ph.D., and Xinhua Ji, Ph.D., at CCR, we have characterized the interaction between RNF45 and UBE2G2 (*5, 6*). The activity of RNF45 depends on a short region of RNF45 called the E2G2 binding region (G2BR) that recruits the E2 with high affinity (K_D = 21 nM).

Isothermal titration calorimetry (ITC) has been a major tool for studying the interaction of the E3 with the E2 or substrate. One limitation of ITC is the ability to purify a large amount of the individual proteins. In some cases, it may be necessary to express the E3 in complex with the E2 to obtain the functional protein. In this situation, we have used competition experiments with fluorescently labeled E2 to determine binding affinity. In addition to ITC, the Biophysics Core also provides access to several instruments for fluorescence-based assays. We are developing assays based on fluorescence resonance energy transfer (FRET). FRET requires specific labeling of both proteins and the efficiency of energy transfer depends on the proximity as well as relative orientation of the fluorophores when the two proteins interact with each other. A new technique, microscale thermophoresis (MST), which measures the movement of a fluorescently labeled protein in the presence of a temperature gradient, may simplify the assay. Using MST, we have determined the K_D for G2BR and UBE2G2 to be 28 nM, similar to that obtained by ITC. Moving forward, it is likely that MST can be developed for measuring binding affinity for complex systems, including crude cell extract and membrane proteins.

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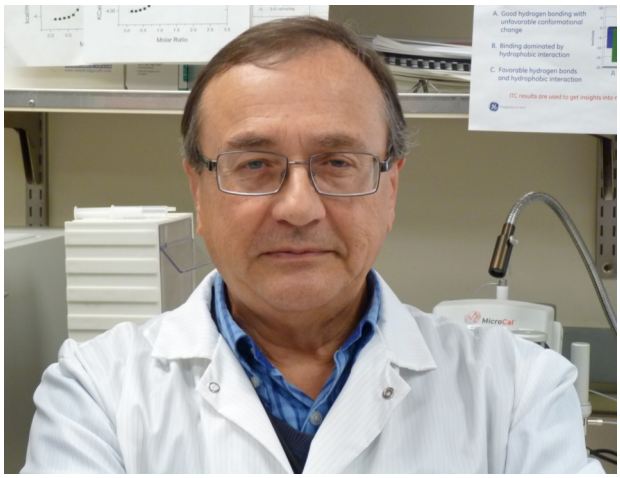
The Biophysics Resource

The Biophysics Resource (BR) (http://ccr2.cancer.gov/resources/sbl/BR/Default.aspx is an open, shared use facility. CCR scientists get training from BR staff members (Sergey Tarasov and Marzena Dyba) to run their own experiments using nine modern biophysical techniques. For the most complex studies, BR staff members collaborate with users by providing experimental design, data analysis and interpretation. Since 2001, more than 160 CCR scientists have conducted collaborative research with BR or have been trained to use BR instrumentation. In addition, 157 scientific publications and patents have been prepared in collaboration with BR or with BR acknowledgement.



Sergey G. Tarasov, Ph.D. (SS)
Head, Biophysics Resource
Structural Biophysics Laboratory

Yien Che Tsai, Ph.D. (SS)
Laboratory of Protein Dynamics and Signaling

Announcements

Attend!

The NCI Intramural Investigators Retreat
Tuesday, January 13, 2015
Ronald Reagan Building & International Trade Center
8:30am-5:40pm
Registration Deadline: December 15, 2014

Congratulations!

Your votes are in for our new SSSC Co-Chairs and Vice-Co-Chairs!

Bethesda SS Co-Chair: Smitha Antony, Ph.D.
Bethesda SS Vice-Co-Chair: Connie Sommers, Ph.D.

Staff Clinician Co-Chair: Christopher Heery, M.D.

Frederick SS Co-Chair: Abdul Waheed, Ph.D.
Frederick SS Vice-Co-Chair: Yien Che Tsai, Ph.D.

Looking for Editorial Experience?

The Dossier is looking for SSs or SCs to participate as Section Editors. If interested, please contact Anuradha Budhu at budhua@mail.nih.gov

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.

Join a SSSC Committee

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