NCI CENTER FOR CANCER RESEARCH

FELLOWS & YOUNG INVESTIGATORS NEWSLETTER

Volume 13 Issue 2 July 2014

From the Editor's Desk

Majda Haznadar, PhD

Welcome to the Spring/Summer edition of the Fellows and Young Investigators Newsletter. The Spring was very busy with the preparations for the 14th Annual Fellows and Young Investigators Colloquium, which ended in success and drew many CCR trainees to network with their colleagues and present interesting research in a friendly atmosphere. You can read about the highlights from the FYI Colloquium in this issue. The Annual Food, Toy and Gift Drive once again showed that the NIH employs many generous people who made this event a great success once again. Thank you to all of you who have contributed. Other topics of interest in this issue include the Spring Research Festival, USA Science and Engineering Festival, as well as our recurring sections comprising conference highlights and CCR research highlights. If you are interested in contributing to the FYI Newsletter, please email haznadarm@mail.nih.gov. Enjoy!

Writers:

Kimberley Boelte, PhD
Rami Doueiri, PhD
Julie Heinecke, PhD
Sukhbir Kaur, PhD
Pradeep Kota, PhD
Nadia Pereira de Castro, PhD
Koreen Ramessar, PhD
Barbara Rath, PhD
Jessica Roberts, PhD
Emilee Senkevitch, PhD

TABLE OF CONTENTS

CCR-FYI NEWS

14th Annual Fellows and Young Investigators Colloquium 2
Reflection on the 2nd Annual Food, Toy, and Gift Drive 4
The Spring Research Festival 2014 5
OTE Scientific Management Training 6

Articles

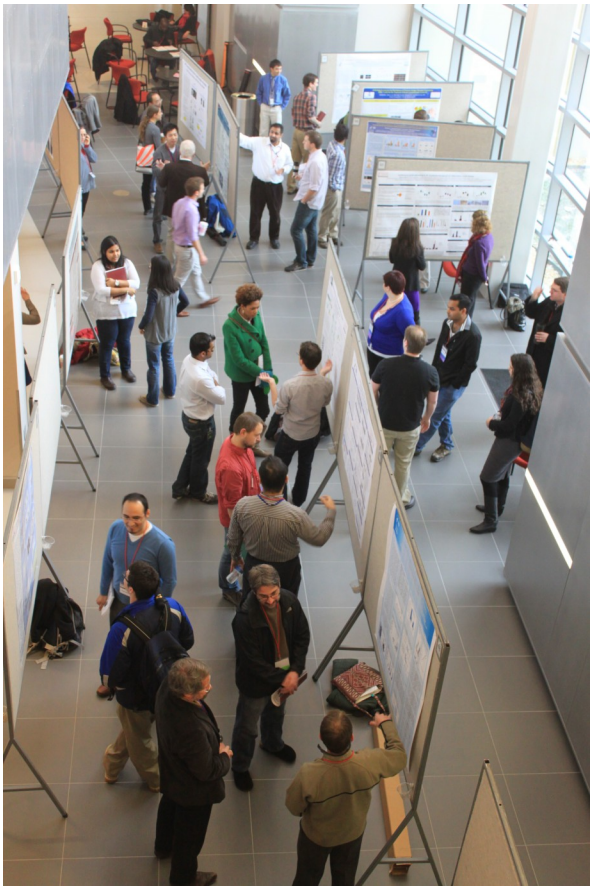
Conference Highlights of Spring/Summer 2014 7
USA Science and Engineering Festival 8
Transition from a PhD to a Postdoc at the NIH 9
CCR Research Highlights 11

IF YOU HAVE ANY COMMENTS, SUGGESTIONS OR WOULD LIKE TO CONTRIBUTE TO FUTURE NEWSLETTERS, PLEASE EMAIL US AT nciccrfyi@mail.nih.gov, or majda.haznadar@nih.gov

CCR-FYI News

14th Annual CCR-FYI Colloquium: Making Research Count – From the Bench to the Bedside

The 14th Annual CCR-FYI Colloquium was held on March 24th and 25th at the Advanced Technology Research Facility in Frederick, Maryland. The members of CCR FYI association organize this event annually to foster career development of young fellows. The program began with a welcome address from the CCR-FYI Co-Chairs, Dr. Vijay Walia and Dr. Barbara Rath, highlighting the current and past accomplishments of CCR FYI. Dr. Jonathan Wiest, Director of the Office of Training and Education, CCR, NCI, delivered the opening remarks and encouraged fellows to take full advantage of the resources available at CCR for career and scientific development. Dr. Robert Wiltrout, Director of CCR NCI, continued the meeting with remarks on the current status of the intramural training program. There were four keynote talks spread out over the two days. On the first day, we heard about control of oncogenic Ras from Dr. Peter Johnson (NCI), and NF-kB in myeloid cells in the tumor microenvironment from Dr. Ann Richmond (Vanderbilt University Medical Center). On the second day, keynote talks were given by Dr. Eric Holland (Fred Hutchinson Cancer Research Center) on brain tumor models in mice and how they relate to human medicine, and Dr. Shyam Sharan (NCI) on the functional significance of breast cancer susceptibility genes. Both days had excellent oral and poster presentations from postbacs, graduate students and postdoctoral fellows. The concurrent workshops covered a range of topics, including networking skills, managing up, resources available for research at the NIH, and information on becoming an entrepreneur. The first day ended with a great talk by this year's Outstanding Postdoctoral Fellow, Dr. Ryan Holland, whose work is on a drug that his group designed, created, and translated into clinical practice. This competitive award is given to a fellow who is nominated by their mentor, and is selected by a peer-review process. On the second day, we heard an excellent talk about cancer survivorship by Ms. Kim Norris, Founder/President of the Lung Cancer Foundation of America. She ended with a challenge addressing the audience and asking for the advancement of lung cancer research. As usual, the colloquium ended with the awards being presented. Dr. Ryan Holland was selected as the Outstanding Postdoctoral Fellow in January, and was presented with a certificate. Ms. Katie Stagliano received the Outstanding Postgraduate Award. The best oral presentation awards were presented to Dr. Lars Boeckmann and Dr. Lei Sun, and the best poster presentation awards were presented to Dr. Mairi McLean and Dr. Heekyong Bae. Congratulations to everyone who won an award, and thank you to all who participated! Both days were capped off with social networking events at Brewer's Alley in Frederick,



Attendees of the FYI Colloquium at the poster session discussing fellows' research in a friendly, relaxed atmosphere.

(Continued on page 3)

(Continued from page 2)
Maryland, which featured good food, beverages, conversation, and great company. Many invited guests and CCR fellows attended social networking events. The CCR-FYI Steering Committee would like to thank the members of the Colloquium Committee – Kimberly Boelte, Barbara Rath, Vijay Walia, Smita Kakar, Emilee Senkevitch, Rami Doueiri, Amy Wahba, Diane Foreman, Andrew Huehn, Uday Maachani, as well as Kathy Augustin, LaTasha Beasley, and Jonathan Wiest from the CCR Office of Training and Education for their hard work in planning and executing the meeting. The Colloquium Committee worked very hard on this year's meeting, and would like to invite anyone interested in planning next year's event to join the committee.

Submitted by:
Kimberly Boelte, PhD
Laboratory of Molecular Immunoregulation
Cancer and Inflammation Program
and
Barbara Rath,
MsE, PhD
Radiation Oncology Branch
and
Vijay Walia, PhD
Laboratory of Cell and Developmental Signaling
Membrane Trafficking and Signaling Section

2014 FYI Colloquium planning subcommittee (from left): Amy Foreman, Rami Doueiri, training director Jonathan Wiest, Smita Kakar, Kimberly Boelte, Andrew Huehn, Emilee Senkevitch, Vijay Walia, Uday Maachani, Barbara Rath. (not pictured—Diane Kambach)

Reflection on the 2nd Annual Food, Toy and Gift Drive

The CCR-FYI Outreach Committee hosted its 2nd Annual Food, Toy, and Gift Drive to benefit the NIH Children's Inn on the Bethesda campus. The Children's Inn is an invaluable resource that serves as a hospitality house, where children receiving treatment at the biomedical facilities can come to stay with their families at a "place like home". The food and toy donations are essential to keeping the Inn operating and they help bring a comforting experience to each sick child. The drive was held from December 2 -19, 2013 on the Bethesda, Advanced Research Technology Facility (ATRF), and the Frederick National Laboratory for Cancer Research (FNLCR) Main and Industry Lane campuses. This year's drive was an enormous success! We collected over 850 food and toy items, which well exceeded last year's donations of 500 items. In fact, Emilee had to make two trips down from Frederick because her car could not hold all of the donations. The food donations go into the Help-Yourself Pantries that are 24 hour accessible, into Welcome Bags, and into the kitchen of the Inn. The gifts will be used in the Inn's game room, as well as for the Thoughtful Treasures program, where each incoming child receives small gifts. This year we had several new donation sites thanks to helping hands extended from the NIH community. We would like to thank April Kennedy for her enthusiasm for this project, and going out of her way to set up donation boxes on the Industry Lane campus of the Frederick National Laboratory for Cancer Research. We plan to include this location in the drive next year. Patricia Fetsch of the CCR Laboratory of Pathology volunteered to help with the donations on the Bethesda campus, and we would like to thank her for her time. Julie would like to specifically thank the members of the Radiation Biology Branch, of which she is a part, for their huge contribution to this year's success. We would also like to thank the members of the Outreach Committee that helped with collection of the donations including Dr. Smita Kakar, Mr. Ingold Huang, Dr. Steven Cuss, and all those who helped spread the word about this exciting drive.

Julie Heinecke, PhD, and Emilee Senkevitch at the Children's Inn with the generous donations collected throughout the NIH.

Submitted by:
Julie Heinecke, PhD
Cancer and Developmental Biology Laboratory
Renal Differentiation and Neoplasia Section
NCI-Frederick
and
Emilee Senkevitch, PhD
Laboratory of Molecular Immunoregulation
Cytokines and Immunity Section

The Spring Research Festival 2014

The 2014 National Interagency Confederation for Biological Research (NICBR) Spring Research Festival was held in Fort Detrick, Frederick. This was the eighteenth annual event and the second sponsored by the NICBR agencies. The NICBR organizations includes:

- United States Army Medical Research and Materiel Command (USAMRMC) and United States Army Medical Research Institute of Infectious Diseases
- National Institute of Allergy and Infectious Diseases (NIAID), Integrated Research Facility (IRF)
- National Cancer Institute at Frederick
- United States Department of Agriculture (USDA), Agricultural Research Service (ARS)
- United States Department of Homeland Security (DHS), National Biodefense Analysis and Countermeasures Center (NBACC)
- Centers for Disease Control and Prevention (CDC)
- United States Navy, Naval Medical Research Center (NMRC)
- Food and Drug Administration (FDA)
- United States Army, Installation Management Command

The Festival took place on May 5-8th including two seminar sessions, a keynote speaker with Poster Blitz and two poster sessions. Scientific staff, including students, technical support staff, postdoctoral fellows, and principal investigators, presented their research to the joint scientific communities. The event started with the NICBR Scientific Symposium where short talks were presented from twelve speakers chosen from a pool of submitted abstracts. The presenting fellows represented the USAMRIID, NCI, ARS, USACEHR, USDA-ARS. The following day I had the opportunity to attend the NICBR Research Collaboration Forum, where presenters were considered for the award for any article published in 2013 that was a result of collaboration between two or more NICBR partners at Fort Detrick (e.g. NCI and USAMRIID). NCI-Frederick was represented by Barry O'Keefe and Sreejith Raran Kurussi. The keynote speaker of the Spring Research Festival was Dr. Jacques Ravel. He highlighted this year's theme, The Microbiome: Impact on Health and Disease with his talk "The Vaginal Microbiome Impact on Health and Disease". Following this event, we had the Poster Blitz with brief overviews of selected posters displayed during the Scientific Poster Presentations. Twenty-seven poster awardees and three best oral presentations were selected. The three post-doctoral fellow poster award recipients were:

- Ms. Jackie Blanc, USDA-ARS. *Genomic and Proteomic Characterization of Rathayibacter toxicus.*
- Dr. Balamurugan Kuppusamy, NCI. *C/EBPdelta Links Hypoxia and Inflammation to the Promotion of Cancer Stem Cell Characteristics and is a Target for HDAC Inhibitors.*
- Dr. Elaine Morazzani, USAMRIID. *Characterization of Humoral and Cell-mediated Immune Responses to Gamma-irradiated V3526 Vaccine Candidate.*

The 2013 Best NICBR Collaborative Publication went to Dr. Shannon L. Taylor, USAMRIID and Dr. Victoria Wahl-Jensen, formerly NIAID, now NBACC on the article entitled: *"Endothelial Cell Permeability during Hantavirus Infection Involves Factor XII-Dependent Increased Activation of the Kallikrein-Kinin System"* and published in PLOS Pathogens. 2013; 9 (7), p 1-13.

Congratulations to all 2014 NICBR Spring Research Festival award winners! Stay tuned for the event next year; you can be the next awardee!

Submitted by:
Nadia Pereira de Castro, PhD
Laboratory of Tumor Growth Factor Section
Mouse Cancer Genetics Program

OTE Scientific Management Training Session

On June 6, a three hour Scientific Management Training session was held on both Frederick and Bethesda campuses. The goal of this course is to help post-doctoral fellows develop skills necessary to lead a scientific research laboratory. This workshop is organized by Dr. Terry Moody in the Office of Training and Education, and led by Tim Quigg, currently the Special Assistant to the Vice Chancellor of Research at UNC-Chapel Hill. Prior to retiring as Chair of the Computer Sciences Department at UNC, he worked in the North Carolina state government and managed two software companies. Therefore, Mr. Quigg has many years of experience as a manager in a variety of environments, and able to offer plenty of insight and examples of situations he encountered in a managerial role. The workshop was packed with lots of information related to management. First, Mr. Quigg started by explaining the three "schools" or organizational theory; this lead to a discussion on which "school" our lab or department falls into, and which ones might be best when managing a lab. Mr. Quigg then offered us advice on how to align our personal goals with the goals of the organization we may work for, and how to effectively manage our time. Lastly, Mr. Quigg offered insight on how to develop skills that would enhance our ability to simultaneously be a supervisor and a subordinate in an organization. He stressed that effective supervision is a learned skill, and then offered multiple scenarios we may encounter, including hiring practices, managing difficult employees, understanding our boss' motives, being an effective team leader, and setting goals. I thought this was an excellent workshop; Mr. Quigg provided the attendees with a lot of material to discuss and reflect upon. As post-doctoral fellows, we are highly trained in science, but rarely do we get any formal training in management. Most of us will find ourselves in a management position following our fellowships, and I appreciate The Office of Training and Education giving us fellows an opportunity to learn skills beyond bench work. Any fellow who is interested in becoming a supervisor at any level from supervising summer students to managing a lab should strongly consider taking this workshop. For more information contact Dr. Terry Moody, by e-mail (moodyt@mail.nih.gov) or by phone (240-276-7785).

Emilee Senkevitch, PhD

Submitted by:
Emilee Senkevitch, PhD
Laboratory of Molecular Immunoregulation
Cytokines and Immunity Section

Opportunities to Practice Talks for Conferences, Seminars & Job Interviews

The **PASS (Presentation and Seminar Skills)** series has teamed up with Scott Morgan to provide CCR scientists with an hour-long session of one-on-one tutoring. During this session, you will go through your presentation with Scott, where he will provide feedback on style, content, delivery of message, etc. A week or two later, you will have the opportunity to present your talk in front of your colleagues and to receive constructive feedback. Scott will also attend and provide additional feedback following the presentation. Scott has over 15 years of valuable experience in science communication and has recently co-authored a book, 'Speaking about Science'.

We will work with you and Scott to arrange a suitable time and schedule. This is a wonderful opportunity for anyone who wishes to improve his/her presentation skills either for a meeting presentation or job talk.

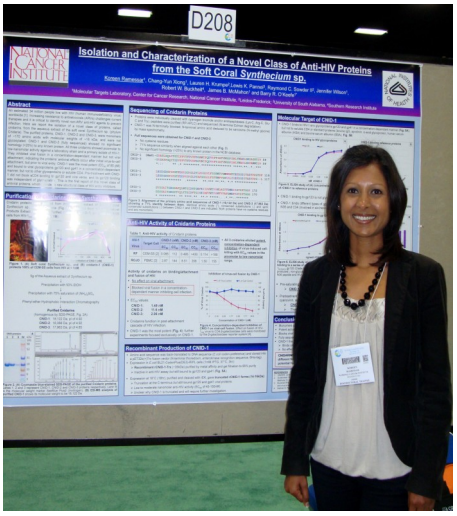
If you are interested in taking advantage of this opportunity or have additional questions, please contact Leigh Greathouse (kristen.greathouse@nih.gov). Available slots will be filled on a first come – first served basis.

Articles

Conference Highlights of Spring/Summer 2014

The Experimental Biology EB2014 Annual Meeting

The Experimental Biology (EB2014) annual meeting was held at the San Diego Convention Center from 26-30 April 2014. As one of the largest meetings to date, it comprised over 14,000 national and international scientists and exhibitors representing six sponsoring societies and multiple guest societies. The sponsoring societies were American Association of Anatomists (AAA), the American Physiological Society (APS), American Society for Biochemistry and Molecular Biology (ASBMB), American Society for Investigative Pathology (ASIP), American Society for Nutrition (ASN), and American Society for Pharmacology and Experimental Therapeutics (ASPET). This multidisciplinary, scientific meeting featured plenary and award lectures, pre-meeting workshops, oral and posters sessions, on-site career services and exhibited an array of equipment, supplies and publications for research labs. The majority of scientists represented university and academic institutions as well as government agencies, non-profit organizations and private corporations. Unsurprisingly, there were over a thousand talks, workshops and poster presentations to choose from. An online itinerary builder tool (available a few weeks before the conference) which I personally used, easily facilitated developing a customized itinerary. Talks were held all day with poster sessions in the afternoon, and covered basic and applied research in the fields of anatomy, physiology, biochemistry, pathology, nutrition, and pharmacology. I attended and enjoyed several sessions highlighting areas such as gene expression, protein folding and processing, localization, quality control, post-translational modification and glycans in vaccine development to name a few. In addition to the over 400 exhibitors present, there were also career development seminars and workshops held which had topics ranging from writing grant proposals to job hunting, job talk and interview preparations, as well as negotiation strategies. The poster sessions amazed me as they spanned over 1300 categories. Being one of the NIH 2014 FARE award recipients, I used my travel award to attend EB2014 where I presented a poster on our discovery and characterization of a novel class of potent anti-HIV fusion inhibitor proteins from a soft coral, at the Mode of Action Natural Products poster session (Tuesday, April 29, 2014). I was also privileged to have been selected from thousands of attendees and have our work showcased in one of the conferences' press releases entitled "Coral reefs provide potent new anti-HIV proteins: discovery raises hope for new methods to prevent the spread of HIV", which can be found at www.newswise.com/articles/coral-reefs-provide-potent-new-anti-hiv-proteins. The novel proteins we discovered (from a marine extract in the NCI natural product extract repository) represent a new structural class of HIV entry inhibitors, and provide a new candidate for non-ARV anti-HIV microbicide development. My poster was well received by many interested scientists, students and journalists and I had the chance to discuss my research and gain some valuable input and feedback. I would definitely recommend attendance to this conference not only for the fantastic, innovative and up to date research talks, but together with the career development symposiums and the many social events organized by guest societies, this conference provides a great opportunity to share your research and network with the world's best scientists.



Koreen Ramesar, PhD, standing in front of her poster at the EB2014 in San Diego.

Submitted by:
Koreen Ramessar
Molecular Targets Laboratory
Protein Chemistry and Molecular Biology Section

USA Science and Engineering Festival

The 3rd USA Science and Engineering Festival was held on April 24-26 2014, at the Walter E. Washington convention center in Washington DC. This three day event was sponsored by Lockheed Martin, and more than 500,000 people attended. More than 750 STEM organizations participated for hands on science and engineering activities for people of all ages. This event was a great opportunity to learn about the participating educational and research organizations and an added bonus was that the event was free of charge. The overarching theme of the festival was to create public awareness about the importance of science and math education. The main objective of the festival was to encourage the next generation of engineers and scientists among the young high school and college students. Many well-known research organizations were in attendance, such as NIH, NSF, NASA, National Academy of Engineering, National Academy of Sciences, AAAS, American Physical Society, American Chemical Society, Harvard, MIT, Princeton, Georgetown, University of California San Diego, University of California, Berkeley, Johns Hopkins, U.S. Naval Academy, Duke, University of Maryland Office of Naval Research and many more. These organization exhibits were clustered under various pavilion themes such as astronomy and space exploration, career, earth sciences, energy, engineering kids, Lockheed Martin, math and science, national security, natural science, NSF and friends, social sciences, steam and sustainability. Attendees had an opportunity to explore NASA robotics, which allowed for excellent hands-on training. The attending youth participated in hands-on trials that increased their curiosity, but also allowed for fun and enjoyment. In addition to experimental activities, there were many tourist attractions such as lunch with Nobel Laureates, autographs from celebrities and from authors of science and math books. Young students were amazed and fascinated with a magic school bus, Einstein stage shows by Bill Nye the science guy and Lynn Brunelle.

NIH Volunteers at the USA Science and Engineering Festival enthusiastically talking to the curious, young future scientists.

Twenty Institutes of the NIH participated under the 'health and medicine pavilion' and over 4000 future scientists participated in 'X-STEM-Extreme STEM Symposium' on Friday, April 24th. To inspire youth careers in STEM, group presentations and live demonstrations were organized and distinguished speakers were invited, such as Dr. Francis Collins. Twenty five hands-on mind astonishing activities were carried out such as 'a noisy planet, DNA and brain, isolation of strawberry DNA, regenerative medicine etc. Some of the highlights that were especially interesting to the youth were watching 3D digital printing and learning about how the body works by identifying body parts, measuring lung capacity, etc. In addition to hands on experimental activities, NIH also hosted the event 'Meet the NIH staff' on April 26th. Hundreds of NIH staff volunteered for this event. I had the opportunity to serve as an NIH volunteer on April 25 for the 'trait tree' event. It was a great pleasure to be able to inspire young students. I would like to recommend other fellows to consider attending this festival next year.

Submitted by:
Sukhbir Kaur, PhD
Laboratory of Pathology
Biochemical Pathology

Transition from a PhD to a Postdoc at the NIH

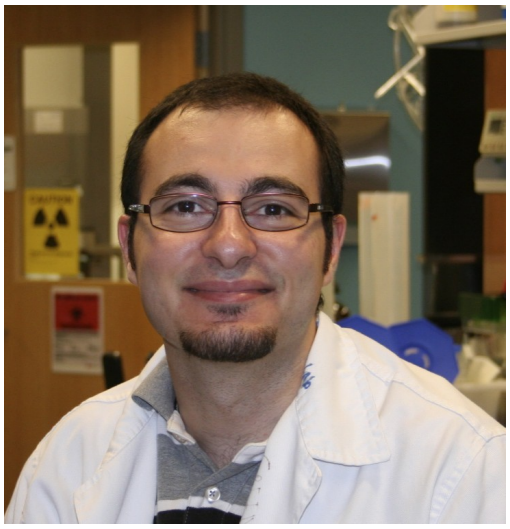
Like hundreds of new postdocs coming to the NIH, I was extremely excited, yet worried. I was happy that my graduate school training paid off after so many years, but now I had to work in a highly competitive setting where I was a complete stranger. Before starting my postdoctoral training, I met an old friend who recently became a faculty member. This friend advised me to spend 24/7 of my first 2 years in the lab. He stopped his social life in order to get as many publications as possible for his next step. However, I asked myself: Is socializing and building networks mutually exclusive with lab work and productivity? Having read about the top 100 successful companies' policies, I realized that a large part of success comes from forging friendships and socializing. Therefore the advice I am going to give here is based on my own experience, although others might have different opinions on the matter and might have been more successful following their own advice. At least my own advice helped me to survive my first nine months at the NIH.

The first thing I had in mind after coming to the NIH is a plan for the post-postdoc life. I am interested in entrepreneurship or a tech transfer career. So from the beginning, I shared my idea with my advisor and coworkers, and it paid off. I was informed about the "INNoVATE" program at UBMC, BioBuzz and BioBeer groups, technology transfer groups on LinkedIn, technology transfer classes offered by FAES and guidance from OITE. I felt a certain relief having seen some light in the dark tunnel called "how well are you prepared for the next step?"

The next crucial step was to make friends. I feel energized by friendships and human interactions and thus I enjoy a cohesive work environment. After being introduced to the lab members, I went personally and introduced myself to others, socialized over lunch, or sometimes outside the lab environment, in order to establish a connection with a variety of colleagues. Becoming friends with my lab-mates made it easier for me to get a sense of the nuts and bolts of the lab, and to feel that I am part of a bigger entity than the trio: me, my project and advisor. So my advice to the postdocs is: get to know whom you are working with, and if you know one or two words in their language (if they are foreigners) throw them out on multiple occasions; this helped me to break the ice.

The next step was getting involved in campus activities, so I joined the CCR Fellows and Young Investigators Steering Committee (FYI-SC), which allowed me to meet new people that shared the similar interests and concerns that I had. In addition, the CCR FYI-SC is helping me expand my networks and connections; as much as papers and achievements are important, networking is as important, in my opinion.

Last but not least, work hard, extremely hard for your research, but give yourself a day off per week and do something you enjoy or have never done before. This might sound like a pitch from a self-help book, but good advice is good advice. Whether you are in Bethesda or Frederick,



Rami Doueiri, PhD

you are not far away from amazing walking trails, rivers, beaches and big cities to visit, and if you don't have anyone to accompany you on a trip, you can always invite people on a social networking site such as Facebook!

Humans have a great ability to adapt to new environments, and by forging friendships and becoming familiar with our surrounding, we can quickly loose the blues and get a sense of belonging, which in turn will make our postdoc years more productive and enjoyable.

So for all new postdocs, I say welcome to a great experience, you are learning how to be great scientist so try to benefit the most from this unique opportunity.

Submitted by:
Rami Doueiri, PhD
Human Retrovirus Section
Vaccine Branch

CCR Research Highlight: Parkinson's disease and cancer: two public health problems, one common solution?

Cancer arises from a population of cells that divide and grow uncontrollably. Thus, therapies are designed to promote tumor cell death by blocking parts of deregulated growth signaling pathways from communicating with other elements of the pathway. Parkinson's disease, in contrast, is a neurodegenerative disorder characterized by the premature death of neurons in the midbrain. Although the debilitating traits of Parkinson's disease including tremor, muscular rigidity, and slowness of movement are well established, the mechanisms leading to cell death are not. Here, the central problem is that cells refuse to die. While we would expect the pathologic mechanisms of Parkinson's disease and cancer to be quite different, emerging genetic and functional studies suggest that strikingly similar and overlapping pathways are involved in both diseases.

The first connection between Parkinson's disease and cancer was reported more than half a century ago, when it was discovered that cancer was unusually rare in people with Parkinson's disease. With these early observations and recent advances in genome-wide association studies, it was found that many genes involved in familial Parkinson's disease were already associated with cancer. Thus, it seemed as if the same mutations leading to the inappropriate neuronal cell death in Parkinson's disease could lead to inappropriate somatic cell survival in cancer. Of the pathways deregulated in these two pathologies, protein misfolding and degradation, cell cycle control and apoptosis, mitochondria and oxidative stress, and the PI3K-AKT-mTOR pathways are the most overlapping. With the recent developments in understanding how mitochondrial dysfunction contributes to cancer progression, the remainder of this article will focus on the role of mitochondria and oxidative stress in cancer and Parkinson's disease.

Cancer cells and neurons utilize mitochondria in fundamentally different ways. Cancer cells alter their metabolism and use glycolysis to a greater extent than neurons, which primarily use oxidative phosphorylation to generate ATP. Mitochondria contain cell death receptors, so how these organelles are removed via mitophagy may have an important role in determining cell survival in these two cell types. Mitophagy is a selective form of autophagy by which mitochondria are degraded in autolysosomes. Mitophagy is regulated by PTEN Induced Putative Kinase 1 (PINK1), a serine-threonine kinase, which accumulates on damaged mitochondria and attracts the E3 ubiquitin ligase, Parkin, to assist in their degradation. Recent evidence by Lazarou *et al.* published in *Developmental Cell* suggests that PINK1 forms a complex with the translocase of the outer membrane (TOM) selectively on depolarized mitochondria, and this tight regulation is responsible for the activation of Parkin, which maintains the balance of healthy mitochondria.

Jessica Roberts, PhD

Mutations in Parkin and PINK1 make up the two most common causes of autosomal recessive Parkinson's disease, respectively. These findings suggest that PINK1 and Parkin function together in a common pathway to regulate mitochondrial integrity. In Parkinson's disease, loss of Parkin or PINK1 can lead to the failure to ubiquitylate target proteins or degrade damaged mitochondria via mitophagy. It has also been shown that heterozygous mutations in Parkin and PINK1 have been identified in several cancer types, although these mutations are often different than the ones identified in Parkinson's disease. Knockdown of PINK1 using RNA interference leads to the accumulation of reactive oxygen species, which can cause severe DNA damage. Parkin mutations, on the other hand, drive tumorigenesis through its regulation of p53 and vice versa. A recent study by Hoshino, *et al.* showed that cytosolic p53 binds to Parkin and disrupts its regulation of mitophagy, causing mitochondrial dysfunction in mice. Apart from modulating mitophagy, loss of Parkin can also lead to inefficient ubiquity-

(Continued on page 11)

(Continued from page 10)

lation of normal or misfolded proteins which could result in the activation of other downstream pathways. One such example includes the failure to ubiquitylate cyclin E. Cyclin E, therefore, accumulates and drives the cell into the S and G2/M phases of the cell cycle.

While loss of PINK1 and Parkin may be responsible for both the progression of Parkinson's disease and cancer, their mechanisms appear to be quite different. In Parkinson's disease, poorly performing mitochondria are associated with the death of nerve cells in the substantia nigra, which plays a major role in movement. However, the accumulation of dysfunctional mitochondria also drives cancer progression. So, how can we explain these differences? Perhaps some of this variation can be accounted for by understanding the differences between neurons and cycling cells. It has been hypothesized that the mutations driving cell survival may cause terminally differentiated cells to try so hard to divide that they eventually die. It is also possible that these mutations disrupt multiple pathways, tipping the balance towards disease by helping to evade any biological redundancy that might have compensated for the effect of the mutation. In both diseases, the regulation of mitochondrial integrity is altered, but the mechanistic details tying the Parkinson's-cancer story together remain unknown. While there are a lot of interesting hints and clues, we need to continue working on connecting the dots.

Submitted by:
Jessica Roberts, PhD
Laboratory of Human Carcinogenesis

NCI-Frederick Postdoc Seminar Series

- Every other Wednesday, watch email for details. Free pizza and soda are provided.
- If you are interested in presenting as a speaker, please contact Linda Brubaker (brubakerld@mail.nih.gov)

The **NCI App for Fellows** is now available and compatible with Android and Apple phones, as well as iPod touch, iPads and Tablets! Search for "NCI Fellows".

To all CCR trainees

Did you know that the *CCR Office of Training & Education*:

- **Assists trainees and mentors with mentoring issues**
- **Assists in submitting applications for various funding mechanisms**
- **Provides opportunities for expanding collaborative interactions**
- **Assists trainees in the transition to different career paths**
- **Provides numerous courses**
- **And much more!**

CCR Office of Training & Education
Jonathan S. Wiest, PhD
Director for Training and Education
Tel: 240.276.5628 wiestj@mail.nih.gov

CCR Research Highlight: Inhibiting Raf Dimerization: When and Why?

Cells respond to external cues by switching on/off specific small GTPase-mediated signaling cascades. The Ras-driven Raf-MEK-ERK kinase cascade regulates many cellular processes including but not limited to proliferation, differentiation and migration. Aberrant signaling through this pathway due to mutation of its members is causative of many human cancers. The importance of this pathway is further underscored by a group of developmental disorders collectively know as the 'Ras'-opathies, which are caused by germline mutations in Raf and other members of the Ras pathway. Mammalian cells encode three members of the Raf kinase family (A-, B- and C-Raf). Upon receiving an external stimulus that activates Ras, Raf kinases dimerize to transduce the signal downstream. However, the physiologic basis and binding preference for dimerization and its importance in normal and disease states is yet to be fully realized.

In a recent study* reported in Molecular Cell, Freeman et al. show that Raf dimerization is a prerequisite for the activation of wild-type and disease-associated mutant forms of Raf in different cell types. Using co-immunoprecipitation assays, the authors set out to determine the molecular composition of Raf dimers and their role in normal and disease-associated Raf signaling. The authors found that among the Raf proteins, B-Raf and C-Raf interact preferentially with each other more than with A-Raf. While B-Raf weakly interacts with A-Raf, no interaction between A-Raf and C-Raf was observed. More importantly, this interaction was induced by receptor tyrosine kinase activation and was required for Raf kinase activation. Using structure-based mutagenesis of the Raf dimer interface, Freeman et al., found that B-Raf homodimerizes constitutively while C-Raf lacks this ability in the absence of a stimulus. Further, the authors identified residues in the interface, which when mutated, modulate the ability of Raf proteins to homo- and heterodimerize. Strikingly, these mutations do not affect the interaction of Raf with its other binding partners such as Ras, 14-3-3 or Cdc37.

Upon establishing the indispensible need for Raf dimerization under normal conditions, the authors asked whether disruption of dimerization by mutagenesis affects the function of mutant Raf kinases in human disease states. By monitoring the focus formation ability upon disruption of the dimer interface, the authors showed that mutant Raf with high catalytic activity (V600E B-Raf) is independent of dimer formation. However, disease-associated Raf mutants with moderate or low catalytic activity were still dependent on dimerization for their biological activity.

Pradeep Kota, PhD

An important aspect of this study is the development and validation of a peptide inhibitor that specifically blocks Raf dimerization, thereby impeding downstream MEK activation under certain conditions. Freeman et al., expressed several peptides derived from the dimer forming face of B-Raf as GFP-fusion proteins in cells. One such peptide (DI1) was able to potently disrupt dimerization of wild-type and mutant Raf kinases (that are still dependent on dimerization), and inhibit the downstream activation of MEK. Realizing the therapeutic potential of DI1 as an inhibitor of Raf signaling in disease states, the authors further characterized its potential use in inhibiting proliferation of non-small-cell lung carcinoma cells. Compared to a scrambled version of the same peptide, DI1 could specifically decrease the viability of cells that expressed activated Ras or, dimerization-dependent B-Raf mutants.

Overall, this study confirms the regulatory role of Raf dimerization in normal and disease-associated Raf signaling. Development of a specific dimerization inhibitor provides proof of principle that the Raf dimer interface is a druggable target for controlling Raf-mediated signaling due to aberrant Raf activation in cancers and Rasopathies.

(Continued on page 13)

(Continued from page 12)

* Freeman, A. K., Ritt, D. A. and Morrison, D. K. Effects of Raf dimerization and its inhibition on normal and disease-associated Raf signaling. **49:** 751-58, 2013.

Submitted by:
Pradeep Kota, PhD
Laboratory of Cell and Developmental Signaling,
Frederick National Laboratory

Opportunities to Practice Talks for Conferences, Seminars & Job Interviews

The **PASS (Presentation and Seminar Skills)** series has teamed up with Scott Morgan to provide CCR scientists with an hour-long session of one-on-one tutoring. During this session, you will go through your presentation with Scott, where he will provide feedback on style, content, delivery of message, etc. A week or two later, you will have the opportunity to present your talk in front of your colleagues and to receive constructive feedback. Scott will also attend and provide additional feedback following the presentation. Scott has over 15 years of valuable experience in science communication and has recently co-authored a book, 'Speaking about Science'.

We will work with you and Scott to arrange a suitable time and schedule. This is a wonderful opportunity for anyone who wishes to improve his/her presentation skills either for a meeting presentation or job talk.

If you are interested in taking advantage of this opportunity or have additional questions, please contact Leigh Greathouse (kristen.greathouse@nih.gov). Available slots will be filled on a first come – first served basis.

NCI Center for Cancer Research
Fellows & Young Investigators

What is the CCR-FYI?

The NCI CCR Fellows and Young Investigators (CCR-FYI) Association was organized to foster the professional advancement of young scientists at the CCR and is supported by the NCI CCR Office of Training and Education (OTE).

Who can participate?

All young investigators including postdocs, postbacs, graduate students, research fellows, clinical fellows, technicians, and staff scientists.