NCI CENTER FOR CANCER RESEARCH

FELLOWS & YOUNG INVESTIGATORS NEWSLETTER

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From the Editor's Desk

Majda Haznadar, PhD

Welcome to the Winter edition of the Fellows and Young Investigators Newsletter. The Fall began with a government shutdown that had a profound impact on the NIH, including the CCR community. Startup took some time, but we are back in full swing. As in the past issues, we continue to bring you Conference Highlights from around the country and the world that our fellows have attended. Additionally, we bring you a highlight of the National Postdoctoral Appreciation Week: if you didn't have a chance to attend, know that you and your hard work are appreciated! You will also be able to hear from our fellows about the first months of their postdoctoral training: we are certain that you will be able to relate. We hope that you will enjoy the articles we have prepared for you in this issue. Please contact us if you are interested in contributing to the CCR-FYI Newsletter!

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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

Providing support for fellows at CCR
CCR-FYI Association is supported by the CCR Office of the Director

CCR-FYI News

National Postdoc Appreciation Week Celebrations

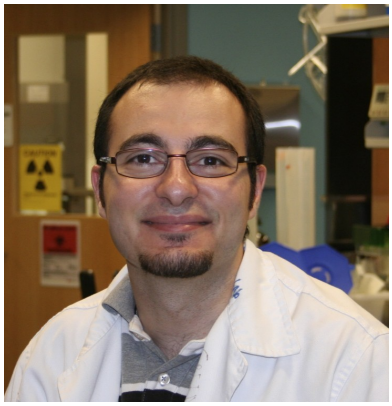
The CCR Fellows and Young Investigators Steering Committee (FYI-SC) celebrated its postdoctoral fellows with a week of events from the 09/16-09/20, including an ice cream give away and a joint social networking with FELCOM at Union Jack's, Bethesda and Brewer's Alley, Frederick. The National Postdoctoral Association (NPA) encouraged both academic and government institutions to plan activities during the National Postdoc Appreciation Week (NPAW). Since 2009, the NPA has sponsored the NPAW to recognize the significant contributions that postdoctoral scholars make to U.S. research and discovery. In 2010, this week was officially recognized by the U.S. House of Representatives. This year, 36 states, Washington DC and Canada, 80 cities, 106 institutions and 255 events took place and were posted on the NPA website, which all recognized the contributions of the postdoctoral researchers. The CCR FYI celebrated the NPAW with free ice cream generously donated by the PIs from the CCR. The ice cream team (big thanks to Kim, Cristina, Amy, Julie, Barb, and Uday, members of the FYI-SC, for organizing this event) handed out approximately 250 ice cream bars and popsicles to postdoctoral fellows in Frederick and Bethesda. A number of PIs stopped by and proudly put on a sticker, donated from the OITE, saying "I ♥ my postdoc". The ice cream give away on both campuses was also a chance for postdocs to meet and network with the current officers of the FYI-SC, Vijay Walia, Barbara Rath, Kimberly Boelte, and Jonathan Wiest, the director of the CCR Office of Training and Education (OTE). The following social networking event at Union Jack's was a huge success: over 60 fellows joined the celebration and networked with food and beverages until late Thursday night. In Frederick, the celebrations of the NPAW started with the FYI Seminar Series with pizza and soda, followed by delicious ice cream social, and a traditional picture-taking event of the present postdocs. The final event in Frederick resulted in a fun social gathering at Brewer's Alley, where around 15 fellows expanded their network and celebrated their own and their colleagues' achievements.

Ice-cream social in front of building 37 in Bethesda. Fellows have enjoyed the festivities that the FYI-SC had organized in their honor.

Submitted by:
Barbara Rath, MsE, PhD
Radiation Oncology Branch

HIV/AIDS and Cancer Virology Fall Think Tank

On November 14th 2013, the HIV/AIDS and cancer virology Think Tank meeting was held on the NIH Bethesda campus. This one-day meeting was a great opportunity to meet other scientist working on various aspects of HIV/HTLV biology and other cancer causing viruses such as HPV and KSHV. The majority of the talks and all the posters were presented by the NIH scientists and ranged from HIV/SIV vaccines and analyzing various aspects of the immune response, to identification of novel types of koala retroviruses to host-virus protein interactions. This meeting was also a great opportunity to listen to two talks given by extramural researchers, Dr. Christophe Nicot from the University of Kansas and Dr. Bryce Chackerian from the University of New Mexico. Dr. Nicot is a former NIH postdoc and did his training in Dr. Franchini's lab. He has since built a successful career in academia working on HTLV accessory protein functions and DNA damage repair. Meeting Dr Nicot was of special interest to me since I was familiar with his work during my PhD but never had the pleasure and an opportunity to meet him personally. Dr. Bryce's was very informative and gave an exceptional and interesting talk on virus-like particles (VLP) and how they can be used for vaccine design. This Think Tank meeting, although short, was packed with a wide range of topics, allowing one to easily find posters and talks of interest.



Rami Doueiri, PhD

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

Articles

Conference Highlights of Fall/Winter 2013

Cytokines 2013: From Molecular Mechanisms to Human Disease

The Cytokines 2013 conference was held at the Hyatt Regency in San Francisco, September 29-October 3. This was the Inaugural Meeting of the International Cytokine and Interferon Society (ICIS) formed by the merger of the International Cytokine Society and the International Society of Interferon and Cytokine Research. The major focus of the conference was to highlight the great advances being made to bridge the gap between understanding molecular mechanisms of cytokines and translating it into effective treatments. This goal was achieved by covering the role of cytokines in health and disease with presentations on basic science as well as clinical research. Major topics discussed included the biology, gene regulation, and epigenetics related to cytokines and cytokine receptors in innate and adaptive immunity, host-pathogen interactions, inflammation, autoimmunity, tumor immunity, hematopoiesis, and stem cell biology. Presentations were given in plenary symposia, concurrent symposia, and poster sessions. The conference attendees included scientists from academia, biotechnology, and pharmaceutical industries, as well as clinical investigators, postdoctoral fellows, and graduate students. During a time when money for travel is not always readily available, it is fortunate that ICIS members who attend the annual meeting are eligible for Travel Awards. These awards are provided through a grant from the Milstein Family based on the scientific merit of the abstract and financial necessity. I, along with several other NCI-CCR fellows, was fortunate to receive this award which covered lodging expenses. I encourage any fellow who plans to attend a future Cytokine conference to apply for this award or any of the other number of awards offered. Unfortunately, the conference began two days before the threat of a government shutdown. Much to the dismay of NIH attendees, the federal government did shut down on October 1, which led to the mandatory exit of all NIH scientists. Despite the early departure, I was still able to hear some phenomenal talks, some of which were given by leaders in the field such as David Artis, Richard Flavell, and Warren Leonard. In addition, I had the opportunity to present my research at a well-attended poster session and enjoy some of what the city of San Francisco has to offer. I highly recommend this conference to trainees interested in immunology and inflammation. Hopefully the next conference will not take place during the first day of the government's new fiscal year!

Submitted by:
Miranda Hanson, PhD
Laboratory of Molecular Immunoregulation
Cancer and Inflammation Program

Miranda Hanson, PhD

The 2nd FEBS Special Meeting – JAK/STAT Signaling: Model Systems & Beyond

In this era of ever-shrinking budgets and governmental shutdowns, I was quite fortunate to attend the FEBS meeting on JAK/STAT signaling recently held in Nottingham, UK from the 12th to 15th of September. Hosted by the University of Nottingham at Albert Hall, just a scant walk from the good Sheriff's castle, this four-day meeting brought together a dynamic international cross-section of the field's top researchers. With 42 speakers and 85 posters, the gathering was rather small in size but proved to be a collegial and intimate scientific experience. During session breaks and meals, the setting was very conducive to discussing the recent talks and learning from well-established and respected scientists. Despite its small size, the meeting was packed with talks across the many areas of research that encompass JAK/STAT biology, often leaving a short time for the question and answer sessions that followed the oral presentations. Due to the numerous interesting talks that were very well attended, the poster sessions were, unfortunately, less well visited. I fortunately had a chance to receive helpful critical feedback at my poster session, and to meet and speak with our international collaborator to discuss the mouse model he recently shared with us.

The breadth of topics covered ranged from David Levy's (NYU) demonstration of the controversial presence of Stat3 in mitochondria to Uwe Vinkemeier's (University of Nottingham) suggestion that Stat molecules likely oligomerize in excess of the canonical dimer and tetramer paradigms. Lothar Hennighausen (NIH) delivered an interesting talk where he described the chicken-and-egg phenomenon of the timing of Stat5/DNA binding and the appearance of "active" transcriptional histone marks on mammary-specific genes. Further, Veronika Sexl's (University of Vienna) elucidation of the role of serine phosphorylated Stat5 in Chronic Myelogenous Leukemia lent further support to the understudied role of serine-specific phosphorylation of Stat molecules and the relationship to human disease. To my great interest the meeting was anchored by Norbert Perrimon (Harvard) who described a systematic and whole-organism approach to local and distant JAK/STAT signaling and the effects on normal development in *Drosophila*. It seems that his lab is truly pushing the field forward, looking for new roles for JAK/STAT rather than continuing to dissect the minutiae of what is largely already understood. I was very interested in learning about the JAK/STAT pathway's role in developmental biology; however, this topic was not very well represented at the meeting. However, there was a copious amount of information and knowledge shared about the pathway's importance in embryonic stem cell maintenance, mainly focused on the established canonical roles in the immune system and cancer biology. It is not a farce to suggest that a basic understanding of their roles in normal development will unlock the answers to their viability as therapeutic targets in human disease. The meeting was a worthwhile whirlwind and as relaxing a work-weekend as I've had in a long time. And, as Nottingham is a beautiful and walkable city, I can see why Robin Hood fought to preserve her.

Michael D. Hall, PhD standing in front of his poster at the conference.

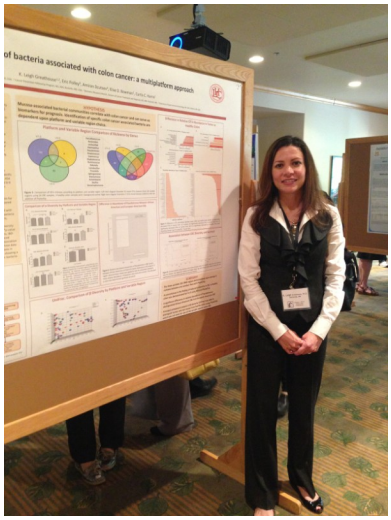
Submitted by:
Michael D. Hall, PhD
Cancer and Developmental Biology Laboratory
Renal Differentiation and Neoplasia Section
NCI-Frederick

28th Annual Aspen Cancer Conference

Amidst the beautiful backdrop of the snow-capped mountains in Aspen Colorado, the Aspen Cancer Conference commenced on the evening of July 13th to discuss the "Mechanisms of toxicity, carcinogenesis, cancer prevention and cancer therapy". The ASPEN CANCER CONFERENCE is a series of yearly meetings begun by Drs. Benjamin F. Trump and Curtis C. Harris in 1985. This conference has continued annually with its mission to assemble the leading scientists from all disciplines to discuss cutting edge research that emphasize the relationship between toxicity and carcinogenesis. This conference is composed of a small curated group of scientists, and fellows that attend are chosen from nominations by their mentors. I and my colleagues, Majda Haznadar and Brid Ryan, were therefore honored to be chosen to attend this year's conference, along with 12 other fellows.

Sunday morning the conference was kicked off by a great talk from the keynote speaker, Jim Allison, who discussed "Immune checkpoint blockade in cancer therapy". Dr. Allison, who is chair of the Immunology Department at MD Anderson Cancer Center, discussed the existence of multiple non-redundant inhibitory pathways that limit T cell responses, which could offer new strategies for directing the immune system to attack cancer cells. Specifically, PD-1, an immune checkpoint, recruits a phosphatase and interferes with T cell antigen receptor mediated signaling. Its two ligands, PD-L1 and PD-L2, are both expressed on dendritic cells PD-L1 and tumor cells. Importantly, antibodies to PD-1 and PD-L1 have shown responses against several tumor types in clinical trials, and an anti-PD-1 antibody, nivolumab, produced sustained responses in about 25% of late stage melanoma patients, and when given together with anti-CTLA-4 antibody produced sustained responses in about 40% of patients. Dr. Baeuerle, of AMGEN research in Munich, Germany, continued the discussion on immunotherapy. He reported on a new class of T cell-engaging antibodies, called BiTE antibodies, one of which is in Phase II trials. This antibody, Blinatumonab showed response rates in patients with non-Hodgkin's lymphoma in the range of 69-80%, and is currently being tested in Phase I trials for refractory NHL patients.

The next session focused on the topic, the microbiome, which was lead off by a fun introduction by Stuart Yuspa. The session continued with a talk by Johanna Lampe, from the Fred Hutchinson Cancer Research Center, in which she discussed how the host diet influences the amount and types of microbes in the gut. Key, she indicated, was the compounds that the microbes produce which can both benefit and harm the host. She noted important examples such as equol, which is produced by bacteria and is associated with risk of breast and prostate cancer. Also, she reported that her lab had found that plant enterolignans were significantly different in their excretion from women, which correlated with bacterial diversity, an important biomarker of overall health. Another great talk was given by Dr. Scott Bultman, who discussed his work on dietary fiber, colorectal cancer and butyrate. He outlined how high v low fiber diet was protective in a chemically-induced mouse model of colon cancer, and this was dependent on the mouse being colonized with a cocktail of bacteria that were high butyrate producers. Furthermore, he went on to demonstrate that due to the Warburg effect, malignant colonic epithelial cells become addicted to glucose allowing butyrate to accumulate and act as a histone deactylase inhibitor (HDAC), which increased apoptosis.



Leigh Greathouse, PhD, MPHD, standing in front of her poster at the conference.

Another special perk of this conference was the networking opportunity that was offered to fellows in the form of room sharing, afternoons off for activities like hiking and biking and time to experience the nightlife of Aspen with other fellows. During this same day, the fellows were treated to a lunch with the senior scientists on the organizing committee. This was a great opportunity that allowed the fellows to ask critical questions in a relaxed atmosphere. Fellows asked questions regarding career advancement, work-life balance,

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and navigating the academic waters as a female principle investigator. That evening we were treated to a musical dinner reception to accompany our poster session, which lead to many great discussions with the attendees and other fellows.

The following day, the sessions included

Beautiful backdrop in Aspen, CO, the location of the 28th Annual Aspen Cancer Conference.

the topics of protein degradation and non-coding RNA. The co-founder of the Aspen Cancer Conference, Curt Harris, started off the non-coding RNA session with a brief overview of the functions of non-coding RNAs, which was followed by a great talk from Dr. Sharp, from MIT. He discussed how the more specific the drug, "the less likely it is that a particular cancer cell will possess the mutations and more likely it is that a compensating mutation will arise". However, targeting an essential function in tumor cells as the result of oncogenic transformation could be more useful in treating more cancers. As such, he described how critical miRNAs are in controlling the carcinogenic process, whereby loss of miRNA control is a common observance in cancer. And disease survival is dramatically reduced when miRNA levels are reduced, which can occur as the result of mutations in Dicer that controls production of miRNAs. He noted that targeting these types of master control proteins for miRNAs could be a target of new therapies for several types of cancer.

That evening we were treated to a fascinating talk from the Director of the new Texas A&M Center for Innovation in Advanced Development and Manufacturing, Dr. Brett Giroir. This endeavor arose from a $285.6 million US Department of Health and Human Services contract that initiated a public-acedemic-private partnership that was designed to bolster the preparedness of the U.S. to successfully defend against emerging infectious diseases, pandemic flu outbreaks or biological threats. This new state-of-the-art facility will, he said, be able to "provide a strategic national vaccine response to pandemic influenza (50 million doses delivered within four months of pandemic strain notification, with initial doses delivered within 12 weeks), which an amazing feat by any international standard. However, they will also be tasked with development and clinical testing of vaccines or small molecule therapies for hospitals that could not otherwise afford to develop and test these new laboratory discoveries. By collaborating with other industry leaders including GSK, Kalon, and Sabine Vaccine Institute etc., they will be able to quickly translate novel therapies from the bench to the clinic and therefore expedite new cancer therapeutics to the public by reducing time to clinical trial, lowering cost of development and manufacturing and increasing quality standards.

On the last day we heard from great scientists such as Thea Tlsty, who impressed the audience with beautiful pictures demonstrating her lab's ability to derive all three tissue lineages from adult human somatic cells. Additionally, Joe Gray, spoke about a new way of studying breast cancer using "spatial systems biomedicine".

Overall, the Aspen Cancer Conference was an amazing experience that combined the fun outdoor activities offered by the picturesque town of Aspen with high caliber scientists and fellows in attendance. Furthermore, the small intimate nature of the meeting is what truly makes the Aspen Cancer Conference such a unique and rewarding experience I hope to be able to experience again next year.

Submitted by:
K. Leigh Greathouse, PhD, MPH
Laboratory of Human Carcinogenesis

Off-the-Bench Careers: Scientific Program Manager

Kristin is currently working as a Scientific Program Manager at the NIH National Center for Advancing Translational Sciences. She served as the CCR-FYI steering committee chair from 2011-12. She received her PhD from Colorado State University post which she worked as a postdoctoral fellow at the NCI/NIH for four years. During her stay at NIH, she volunteered to lead various organizations such as CCR-FYI and also the outreach committee. She explored her interest in careers away from bench and really loves what she does today.

When did you decide to move away from bench?

I was a postdoctoral fellow at the NIH for a little over 4 years and wanted to try something different than lab work, but still stay connected to the scientific community. In addition to the great science at the NIH, there are a plethora of opportunities for the fellows to explore and find their area of interest. I started to volunteer for various activities at the NIH and gradually started thinking about a career away from the bench.

Did you take any special training or courses to better prepare yourself for the current position?

In addition to research, the NIH gives you plenty of opportunities to explore your interests. I was actively involved in CCR-FYI committee and also served as the steering committee chair which helps in organizing the Annual NCI-CCR colloquium. It was a wonderful experience which gave ample opportunity for networking and to hone management skills. I was also the founder and chair of the Outreach committee. All this exposure better prepared me for the current position.

Do you miss working at the bench?

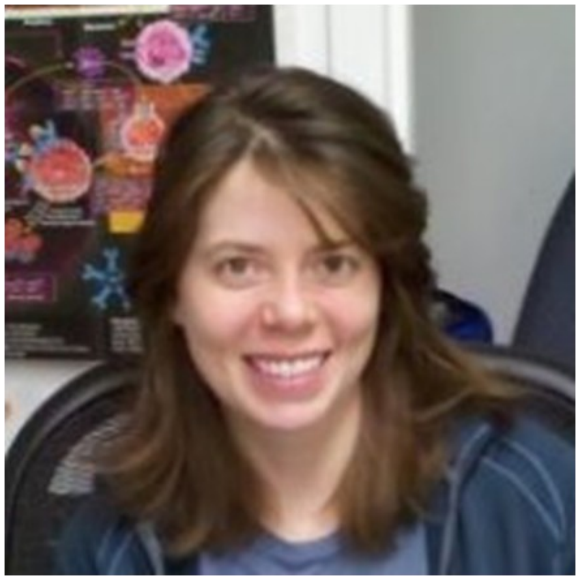
Not at all. I love my job. While I was a postdoctoral fellow at the NIH, I learned that I had a great interest in science but I never wanted a career in bench science. My current job as a Scientific Program Manager at NIH/NCATS seemed like a good fit. This keeps me close to cutting-edge research without actually performing experiments at the bench.

How much science is involved in your current position?

I work to manage a Program called Microphysiological Systems or "Organ-on-a-chips". We interact with scientists almost on a daily basis. We are consistently engaged with the investigators, discussing concepts, providing resources and fostering partnerships within the Consortium. This offers me opportunities to work with researchers, doctors, administrators and the general community toward a common goal of improving human health. I have to keep myself updated with the current literature in the field and design projects as a part of a team. But I do not run any experiments myself.

What is the most fun part of your job?

The most fun aspect is to interact with leading researchers who are doing cutting-edge science and knowing that it will definitely improve human health.



Kristin Fabre, PhD

How much networking was involved to get your current position?

Networking is the key in today's job market. Being

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a chair of the CCR-FYI colloquium put me into an advantageous position where I met the right people who helped to channel my efforts in the right direction.

Would you recommend this career to other fellows at the NCI/NIH?

If you are outgoing and like fast-paced projects, then definitely yes!. Being at the NIH provides you an advantage of exploring your interest in both bench and non-bench careers. I would advise the fellows to participate in the wide range of non-bench opportunities which are available at NIH. Explore your strengths and likes and then make a decision for your career. I liked management and science programs but initially I was not sure about which career would be the best fit. This is where the guidance from the OITE also helped a lot. Take advantage of the fabulous resources available to you at the NIH.

Submitted by:
Khyati Kapoor, PhD
Laboratory of Cell Biology
Transport Biochemistry Section

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

From a PhD to a CRTA: A Year of Transition

A little over a year ago, I arrived at the NIH to begin the next phase of my scientific career as a postdoc at the NCI. I was elated to be done with my Ph.D. after six long years. Yet I was nervous about moving away from the support network I had built in graduate school. To succeed as a postdoc, I realized I had to rebuild it – from the ground up.

Because of the skills gained during a postdoc fellowship, it is now quite common to transition to one following graduate school. This worthwhile experience is invaluable whether you decide to stay in academia or to move towards other endeavors. This is because postdoc fellowships are an opportunity to improve your technical skills, enhance your critical thinking skills, and investigate your career prospects. Yet, it can be very challenging to acclimate to your new position and to determine what you want to achieve from it.

Starting a Ph.D. program, in which all the students are in the same situation, it can arguably be much easier than starting a new postdoc position. As a postdoc, you do not come in with an entire group of students in the same position as you are, and you have to construct your own support network without the aid of graduate advisory committees. So it can be difficult to adjust to a non-student life and to your new lab environment. But what does one focus on first? Starting strong in the lab? Getting to know your coworkers? Making new friends? Building your network?

This past year in transition has taught me that there is no correct order for starting and adapting to your new postdoc position. I spent part of my time reading up on my new topic of interest and most of my time experimenting, but I tried to balance it with non-scientific activities. I found that engaging in such extracurricular activities that I enjoy helped me to maintain a healthy work-life balance and also allowed me to come back to the bench motivated.

But how do you build that support network? It all starts with your lab-mates and your mentor. They and other postdocs in your department are a great source of information for when you are beginning in your new position. After all, they were new members once, too, and they went through similar experiences. It is also crucial to find a mentor. This can be someone other than your supervisor, but oftentimes, they are one in the same. A mentor can help introduce you to your new scientific community and often has a vested interest in your success. In fact, one can find multiple mentors and use them as a resource.

Finally, one should spend some time thinking about a future career choice. The NIH has numerous resources to help you determine which professional career path is right for you. Also, talk to your mentor(s) about their scientific journey. These are all strategies to help to assure you that you will get the most out of your new postdoc fellowship.

So to all the new postdocs out there – go to postdoc happy hours, meet new members of your department, and utilize all the resources this place has to offer. I hope you enjoy your time at the NIH as much as I am.

Want more information? Here are some useful resources for postdocs at the NIH:

https://www.training.nih.gov/trainees/postdocs
https://www.training.nih.gov/felcom
http://ccr.nci.nih.gov/careers/

Submitted by:
Monica Markovski, PhD
Laboratory of Molecular Biology
DNA Molecular Biology Section

Monica Markovski, PhD

CCR Research Highlight: A game of thrones, dictated by inflammation, crowns the king of colon tumorigenesis

The mono-layered epithelia of the intestine tissue have to maintain a constant delicate balance. This balance has to take into account radical changes at the luminal end of the intestines. Throughout this continuous battle, the cells are exposed to harsh conditions of mechanical, chemical and biological forces. During these processes, the intestinal epithelia are required to juggle between the absorption of nutrients and metabolites, while also restricting the penetration of any infectious agents. Such conditions suggest that meticulous multifaceted regulation plays a major role in this fragile junction. Additionally, several homeostasis-preserving mechanisms are involved. To that end, signals from stromal and immune compartments, as well as from commensal bacteria are channeled to the stem-cells-containing crypt niche, This niche, otherwise known as the "headquarters" of the tissue, is where a dynamic "tango" between the Wnt and the BMP signaling pathways dictates the proliferation/differentiation balance. Importantly, the high apoptotic rate, resulting in constant tissue renewal, coincides with high levels of oxigenative stress and free radicals, which all add up to an increased risk of DNA damage that can lead to a cell transformation. Furthermore, this mutagenic risk becomes even more threatening when a chronic inflammatory response is a preceding condition. All the aforementioned processes lead to an increased DNA damage and allow pathogenic bacterial species to take over the commensal population of the microbiota, thus exposing the epithelia to yet another oncogenic factor.

On top of the environmental factors contributing to the risk of colorectal cancer, genetic predisposition is also reported to play a major role. One of the most prominent examples would be the Adenomatous polyposis coli (APC) gene, which functions as a negative regulator of the Wnt pathway and, once mutated or lost, can become the initiating molecular event of tumorigenesis in the colon tissue. Another profound characteristic of a full-blown colorectal cancer (CRC) is the high abundance of p53 mutations, whose late appearance in this histotype suggests a role in promoting cell invasion and, contributing to the pre-metastatic stages.

Strikingly, this sequence of pre– and tumorigenic events seems to get reshuffled in patients suffering from inflammatory bowel disease (IBD), eventually resulting in colitis-associated colorectal carcinoma (CAC). High frequency of mutations in p53 would arise early in the inflamed tissue of those patients, before cancerous lesions are observed. The early occurrence of such mutations indicates a shift in their role, which are no longer considered a late promoting factor but an initiating event. Moreover, the incidence of APC mutations drops down dramatically in CAC, which mostly occur in a later stage of the disease, reinforcing the postulation that APC is no longer in the driver's seat. As a result, one can expect to find less adenomateous polyps in CAC but rather escalating grades of flat dysplastic lesions progressing to invasive carcinoma.

Interestingly, the similarity in many aspects of colon tumorigenesis between humans and rodents, both on the molecular and the pathological levels, had generated ample scientific effort studying this malignancy in mice and rats. To that end, azoxymethane (AOM) affects the colon (primarily on its distal end), inducing the accumulation of β-Catenin in the nucleus/cytosol. Due to such disruption of the Wnt pathway yielding high rate of adenomas in mice and rats, the AOM model had become a standard in studying CRC. The investigation of CAC is centered around a combination of AOM with colitis inducing agents, an example of which is dextran sodium sulfate (DSS). The fact that the conjugation between AOM and DSS decreases the period of tumor latency together with the fact that clear chronic build-up in all pro-inflammatory parameters have broadened the use of this model have led to a definitive proof for the link between cancer and inflammation. Nevertheless, the remarkable efficiency of AOM/DSS is compromised by the notion that, similarly to the APC/min mouse model, all treated animals are bound to accumulate either APC or β-catenin mutations during cancer progression, through a certain path which bypasses p53 mutations.

In a recent publication (Pubmed # 23680148), we challenged mice that harbor mutant p53 (a "knock-in" model) with DSS colitis, and monitored the pathological aspects of cancer development. Interestingly, not only was the addition of carcinogen dispensable and cancer development detected in almost all treated mutant p53 (mutp53) mice, but also the tumorigenic pattern

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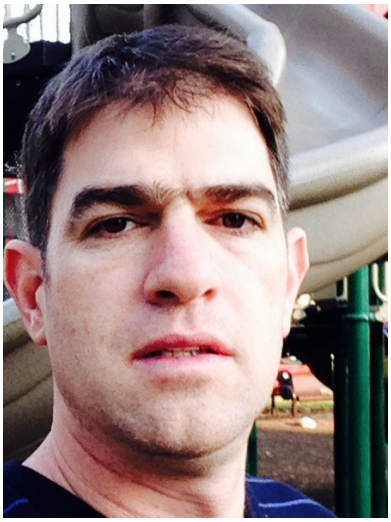
reflected exclusively a flat non-adenomateous evolvement of dysplasia eventually trespassing trough the muscularis mucosa and invading out of the colon. It is also well worth mentioning that when mutp53 mice were treated with both AOM and DSS, no evidence for such flat dysplasia was recorded. However, the entire cohort of treated mutp53 mice was observed with adenomas, which were equally advanced when compared to wild-type mice that underwent the same procedure. This absolute difference in outcome was completely dependent on the presence or absence of AOM and led to the conclusion that whenever this carcinogen is a part of the experimental system, the colon is bound to display a CRC subtype of tumorigenesis, regardless of the p53 mutation status.

Setting aside the findings stemming from this study, suggesting that mutations in p53 gain function in CAC by sharing a molecular cross-talk with NF-κB, future CAC research in mice must take into consideration that any model that would involve early defects in the Wnt pathway will most likely reflect the sporadic/familial colorectal cancer pattern. The development of sporadic/familial CRC includes multiple contributions from the inflammatory effects leading to tumorigenesis. Since the existence of early p53 mutations in IBD patients is a key factor, that should not be overlooked. Disconnecting APC or β-catenin aberrations and the early onset of smoldering inflammation in the colon tissue will help to understand the malignant process of this significant subtype of CAC. Addition of the mutp53 will further enhance the ability to form invasive carcinomas, which will faithfully mimic the course of the disease in human patients.


Tomer Cooks, PhD

Cooks T, *et.al.* Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated colorectal cancer. Cancer Cell. 2013 May 13;23(5):634-46.

Submitted by:
Tomer Cooks, PhD
Laboratory of Human Carcinogenesis

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.

Upcoming Events

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".

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.