



Graduate Research Highlights • Publication Update

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RASSF1A Is Part of a Complex Similar to the *Drosophila* Hippo/Salvador/Lats Tumor-Suppressor Network

Cai Guo, Stella Tommasi, Limin Liu, Jiing-Kuan Yee, Reinhard Dammann and Gerd P. Pfeifer

Summary

The Ras Association Domain Family 1A (*RASSF1A*) gene is one of the most frequently silenced genes in human cancer. *RASSF1A* has been shown to interact with the proapoptotic kinase *MST1*. Recent work in *Drosophila* has led to the discovery of a new tumor suppressor pathway involving the *Drosophila* *MST1* and *MST2* ortholog, Hippo, as well as the Lats/Warts serine/threonine kinase and a protein named Salvador (Sav). Little is known about this pathway in mammalian cells. We report that complexes consisting of *RASSF1A*, *MST2*, WW45 (the human ortholog of Sav), and *LATS1* exist in human cells. *MST2* enhances the *RASSF1A*-WW45 interaction, which requires the C-terminal SARAH domain of both proteins. Components of this complex are localized at centrosomes and spindle poles from interphase to telophase and at the midbody during cytokinesis. Both *RASSF1A* and WW45 activate *MST2* by promoting *MST2* autophosphorylation and *LATS1* phosphorylation. Mitosis is delayed in *Rassf1a*^{-/-} mouse embryo fibroblasts and frequently results in cytokinesis failure, similar to what has been observed for *LATS1*-deficient cells. *RASSF1A*, *MST2*, or WW45 can rescue this defect. The complex of *RASSF1A*, *MST2*, WW45, and *LATS1* consists of several tumor suppressors, is conserved in



First author, Cai Guo, is a graduate student in Dr. Gerd Pfeifer's laboratory.

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Faculty Spotlight

The Stark Truth: A Young COH Professor Talks About His Research and Offers Some Advice

The Helix knows how tough it can be for 1st year graduate students to choose a thesis lab. To help make the transition easier, we'll strive to highlight interesting and innovative faculty members who would make good mentors. In this issue, Assistant Professor Jeremy Stark answers a few questions so that we might get to know him better. Don't miss his good advice!

What does your lab study and what excites you about your research?

Our lab works on mechanisms of chromosomal double-strand break (DSB) repair in

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THE CAREER CORNER

How to Work Job Fairs for Positive Results

Jonie Watanabe Tsuji,
Career Counselor

What do you think of when you think of career fairs? Cool giveaways? Free food from companies? Door prizes? I hope that aside from all of the "fun" stuff associated with a career fair you also think of the practical reason to attend—finding a job or internship!

But why should you go to a career fair? For career fairs, the obvious reason is to search for a job or internship. Even if you are not currently in the market for a job, go anyway! Use the opportunity to get information on a company, find out about a particular industry, and become knowledgeable about what the "real world" has to offer!

How should you prepare yourself? The most important thing is to plan ahead! Your #1 priority: your **RESUME**. See a career counselor and have it critiqued, lest you be embarrassed by a recruiter who points out that you misspelled a word. If the organization hosting the fair lists companies attending, see who is coming, write the company names down, check their websites, and prioritize a list of the companies you most want to see.

When the big day arrives, walk around the booths, pick up company literature and job listings, listen to other students as they speak with recruiters, and

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Tenured COH Graduate and Radiopharmaceutical Scientist, Michael R. Lewis, Tells The Helix What it Takes to Stay Hot

As COH's first tenured graduate, Michael Lewis holds a special place in our school's history. We recently got in touch with him to shed some light on the tenure process from an insider's perspective.

What does your lab study?

My research program focuses on the synthesis, development, evaluation, and application of metal-based radiopharmaceuticals for molecular imaging and targeted radiotherapy of cancer. The immediate relevance to the clinical imaging and therapy of cancer is provided by attachment of radiometal chelates to biomolecules that bind with a high affinity and specificity to cell surface or oncogene molecules overexpressed by tumor cells. People often ask me, "What kind of cancer do you study?" to which I answer, "It depends." The new area of molecular medicine, imaging and therapy is often based on specific interactions between a targeted agent and a target molecule overexpressed in cancer. What we do is find an attractive new cancer target, design molecules, such as peptides and nucleic acid analogues, with high affinity and specificity for a molecular target, then ask, "In which types of cancer is that target clinically relevant?" We are studying molecular imaging of oncogene expression in non-Hodgkin's lymphoma and breast cancer, as well as evaluating multistep strategies for therapeutic targeting of colon cancer.

What were some of the major obstacles and frustrations you had to overcome during your graduate studies?

I was out of school and worked in academic research labs for six years before I started the graduate program at City of Hope. Consequently, the first major obstacle I had to face was how to study for and take exams again. That was not fun, but I survived! However, the most important "obstacle," in terms of



Associate Professor Michael R. Lewis is City of Hope's first graduate student to achieve tenure. He studies radiopharmaceutical chemistry and biology at the University of Missouri, Columbia.

educational and career success, that I had to address was not being afraid to try new things. Learning how to be versatile, flexible, and persistent in an independent process of inquiry and discovery is one of the most important goals of graduate education, in my opinion. Those qualities are especially important in the context of a project that is unsuccessful: that is, knowing when to cut losses and try a different approach. I had one project during my Ph.D. studies that never worked at all. It cost me a year, but I did not give up hope for alternatives that were ultimately successful. Ironically, one student in my group is in the same boat, and I am drawing on personal experience to find new ways to accomplish his research goals, as well as new projects to try.

What kind of sacrifices did you have to make in order to become an associate professor?

Well, I really must qualify my answer by saying everyone is different and has to make different sacrifices differently, meaning not everyone has to do what I chose to do. The goal of promotion to Associate Professor with tenure is, at most institutions, very nebulous and poorly defined from the point of view of a junior faculty member, what we half-jokingly call "a moving target inside a black hole." A new faculty

member will almost never be told how to do his or her job; the expectation is the faculty member will either know or learn what he or she doesn't know. Furthermore, the outset of the tenure track is usually the first time one has to confront the concurrent responsibilities of teaching, research, and service. Learning how to balance those responsibilities in an environment where expectations of outstanding performance in each seem overwhelming creates a considerable amount of

pressure. However, it was very important for me to realize that, in context, the vast majority of that pressure is self-generated. That is not to say the sacrifices weren't great. Thirteen- to sixteen-hour work days were the norm for most of my first six years, and from 1993 to 2006 I estimate that I worked three years longer than the average American during that time period. My exercise routine went out the window in February 2002, and I have yet to find it again. When I took a joint appointment with the Department of Veterans Affairs, I lost seventy-two days of unused University vacation time. I could go on and on, and I know all that must sound horrible, but I feel the sacrifices were worth being in a place where, by and large, I get to pursue my own interests and decide what to do from day to day. Also, lest those sacrifices sound horrible, things get better with time. The only way I can explain it is that there is something about experience that breeds efficiency. Now I can accomplish as much or more in eight or ten hours as I could in thirteen or sixteen hours previously. In August 2004 I got tired of the "all work and no play" existence I created for myself. I formed a band with some friends and began touring around the state about

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Alumni News: Associate Professor Michael R. Lewis takes time to speak to *The Helix*

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once a month, and I am also studying classical double bass. So it is possible to be a professor and have a life after all; it just takes finding the right balance to relax and recreate without compromising academic productivity.

What motivates you to keep going during a tough week?

In that regard I'm an eternal optimist, always thinking that next week, next month, next semester, etc., will be better! However, the best motivator is knowing that my graduate students and postdocs are going to walk into my office periodically with major breakthroughs in their research projects, and there is nothing I enjoy more than seeing their eyes light up when they make that discovery or realize what relevance their work has to radiopharmaceutical sciences and nuclear medicine. Finally, I always look forward with great enthusiasm to those few days when I can get out and do experiments with my own hands. The worst days injecting rabbits with

samarium-153 to study its radiation biology or positioning a canine cancer patient and running the gamma camera are better than the best days doing paperwork in the office!

What is your outlook for young graduate students today in terms of job placement and funding?

My opinion is that the outlook is as bad, possibly even worse than it was in the early 1990s, when I was a graduate student. The NIH funding pool has been drying up for a while now, even as more "fish" struggle to stay or get in the water. Thus far I have been fortunate to have not only NIH but also other funding agencies to support my research, such as the Department of Defense and the Department of Veterans Affairs. Increasingly more investigators are turning to those agencies and other alternatives for funding. In other words, it's incredibly competitive everywhere. On the other hand, now can be a great time to be a young graduate student or postdoc. I was in a similar situation:

funding and job prospects were bleak when I was a graduate student, but they became much better when I was a postdoc and junior faculty member, enabling me to move to a career position and achieve tenured faculty status. In the big picture, these things go in cycles. The colleagues I admire most have survived through the best and worst of times, again and again. Funding and job prospects will eventually get better, even if survival has to become the main short-term objective. On perhaps a brighter note, I have not noticed much of an effect of funding or the economy on job prospects in my field and those related to it. I believe that job placement opportunities for graduate students and postdocs are still somewhat promising, even if not as quite as good overall as in recent years.

The Helix would like to sincerely thank Dr. Lewis for his time and insightful contribution to this issue. Please come back and visit soon!

Graduate Research Highlights: RASSF1A

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mammalian cells, and appears to be involved in controlling mitotic exit.

The Helix asked graduate student and first author, Cai Guo, a few questions about her publication.

How did the idea of this work originate? Did you anticipate it developing into such a nice publication when you started?

Before I started my work, a novel signaling pathway that is responsible for regulating cell proliferation was discovered in *Drosophila*. This pathway involves a protein named "Hippo." The protein I was studying, RASSF1A, was reported to be associated with the mammalian homologue of Hippo. So my mentor, Dr. Pfeifer, suggested that I should look into the possible mammalian pathway and find out whether RASSF1A plays a role. When beginning the work, I really didn't

think too much about where it would be accepted for publication.

How long did it take to complete the whole work? Was there any particular frustrating or exciting moment you would like to share?

It didn't take me awfully long to complete this project. I made it within two years. One of the most frustrating experiences I had was making the lentiviral plasmid for MEF cell line transfection. I spent about 4 or 5 months on this experiment alone. One would never imagine being stuck on such a seemingly simple step.

How do you evaluate the impact of this publication?

This publication suggests that RASSF1A is a component of the Hippo tumor suppressor network similar to the one that exists in *Drosophila*. It is the first demonstration that mammalian components of the Hippo pathway

interact with each other, and that defects in this pathway may lead to abnormal mitosis and a failure to induce apoptosis. We anticipate that further investigation, especially study of the function of mammalian RASSF1A, will give us further insight into cell cycle progression, apoptosis, and tumorigenesis.

What is the most important lesson you have learned through the work and the publication process?

What I have learned is that in order to succeed, one really has to read and think as much as possible before even starting an experiment. Although failure is inevitable in scientific investigation, extensive reading and thorough thinking always help one to succeed.

The Helix would like to thank Cai for her generous contribution to this issue. Best wishes for a successful career!

Stark Lab: resolutions, suggestions and avoiding traps

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mammalian systems. This work is relevant to cancer biology, since failure to repair such damage can result in mutations that lead to cancer development. As well, a number of cancer therapies function by causing DSBs, such that as understanding the mechanism of DSB repair, we hope to uncover therapeutic targets to improve the efficacy of these therapies. Specifically, we take the approach of monitoring the repair of a single DSB generated by the rare cutting endonuclease I-SceI, whose cut-site has been introduced into a specific chromosomal locus. Many different cellular response pathways likely influence how a DSB is repaired, including the replication machinery, chromatin remodeling factors, and cell cycle checkpoint pathways. So, a lot of what excites me about our work is that we are able to investigate the functional interplay of a variety of different cellular pathways.

What is one resolution that graduate students should make to achieve contentment in 2008?

Resolve to enjoy the daily challenges of bench science and not to be too afraid to try a new approach/technique in the lab.

Do you have any suggestions for students regarding developing communication skills?

Using the results of your bench work to develop a seminar is critical for career

advancement in science, where the most compelling seminars often provide the clearest biological context for the experimental results. In considering how to describe the importance of your data, there are a number of traps I would suggest trying to avoid. For instance, try not to use a “straw-man” argument to describe the importance of your work, where you build up a “straw-man,” or false-argument, and then “knock it down” with your experimental evidence. For example, the “straw-man” can be a popular model that your data may contradict such that it is tempting to first describe this model in detail, followed by a description of how you think this model is wrong based on your data. I feel that such a structure is problematic in a seminar situation for a number of reasons. To begin with, you are asking the audience to learn something that you suspect is not correct, which is inherently confusing. More importantly, simply debunking a common model may not be very interesting in itself, and avoids the question of why your data/model is inherently compelling in a broad biological sense. Along these lines, it can also be tempting to try to make your



Assistant Professor Jeremy Stark with 2nd year graduate student, Nicole Bennardo. Nicole chose to do her thesis work in Dr. Stark's lab.

seminar interesting by generating “surprises” during the talk, such as making the audience wait until the end of a given section to know your conclusions. In contrast, I suggest stating the key conclusions at the start of each section. In summary, compelling seminars often begin with a focused description of the fundamental biological relevance of the work, followed by a presentation of the benchwork in a straightforward manner.

Many thanks to Dr. Stark for his contribution to this issue of The Helix.

Mission Statement:

The Helix newsletter seeks to inform, empower, and connect our student body in order to focus and promote our graduate school's growth and accomplishments.

Through The Helix, we inform City of Hope and its faculty about graduate program accomplishments in research, ultimately reflecting the caliber of our students and our program.

The Helix also seeks to empower. To inspire, motivate, and give confidence to our graduate students as they explore and accomplish their goals.

Furthermore, by connecting our students, we can nurture an academic environment, establish collaborations, and initiate scientific progress.

The Funny Pages



What Graduate Students are doing away from the lab

Each term, the Graduate Student Organization elects one gregarious student to uphold the position of Social Chair, a responsibility not to be taken lightly. All you need to do is go on one outing to realize that this job entails more than just organizing social events. Take a closer look. The Social Chair is charged with the demanding task of mixing the glue that keeps our student body connected and, quite frankly, sane. If you haven't already, be sure to go to a graduate school social event in the near future. You'll be pleasantly surprised. Below are some highlights from fun past events, each of which was organized by a dedicated graduate student.



▶ Graduate students enjoy a recent trip to the Snow Summit Ski Resort in Big Bear, Calif. (from left) Su Yang, Julie Kanjanapangka, Jane Zhang, Tangsheng Yi, James Young, Lin Wang, Rafael Flores, and Chen Wu.

▶ GSO Secretary, Megan Prosser, and LEL Coordinator, James Young, take time out from their research to unwind at a Beckman Pub gathering. The Beckman Pub offers students, post-docs, and faculty a comfortable and informal environment in which to interact. Refreshments and games help dissipate some of the stress brought-on by a hard day's work.



▶ Sridhar Samineni (2nd year) and Jane Zhang (3rd year, background) prepare for launch during a recent trip to Magic Mountain sponsored by the Graduate School. The School encourages off-campus social events by often defraying expenses.



▶ Every Halloween, COH graduate students don their best costumes and pass out candy to children participating in the Pediatric Halloween Parade. The school's contribution to the parade is always very rewarding and graciously well organized by Serina Ortiz (center, wearing the witch costume).

Job Fairs

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most importantly, drop off your resume and ask intelligent questions. Once you have successfully navigated the career fair and made some great contacts, follow up by getting business cards from the recruiters, and contact them. Make sure to remind them who you are because they may have seen hundreds of students during the course of the day.

Many of the local schools in the area like Caltech, the Claremont Colleges, Cal Poly Pomona, etc. have career fairs. Check out the websites of these colleges' career centers for the date and time of their event. If you have transportation, visit the career fair and go prepared with your resume. And dress nicely (a suit is not required, but you want to make a good impression!). One word of caution – some schools do check IDs (UCLA for one), but most do not. If you are concerned that you may be turned away, you can always inquire with the college's career center before making the trek over there (Caltech and the Claremont Colleges are open to City of Hope graduate students and postdocs).

So brush off your resume and go to a career fair. You never know what may happen! You just may end up with a job or internship! Have fun!

But if you need help with your resume, or you're just wondering whether you should go the academic or industry route, come see me. I'm here the second and fourth Friday of every month. E-mail me at jtsuji@coh.org and we'll set up an appointment. I look forward to meeting you!

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