15th Annual John B. Little Symposium -
“Cancer stem cells and tumor metabolism”

Humans fear radiation for its power to damage our cells and cause mutations in our DNA: we shield ourselves during dental x-rays and may opt out of low dose X-ray scans at the airport. But radiation can also heal when we direct its damaging power against life-threatening tumors. How cancer cells and surrounding normal tissue adapt to stressors such as radiation is an emerging area of scientific inquiry, and the lessons we learn may apply to other disease conditions as well.

On October 26 and 27, the Harvard School of Public Health welcomed an overflow crowd of about 200 scientists to explore this and related ideas further. Scholars and researchers came together to work toward a better understanding of the differences in local environment and cellular metabolism in tumors and surrounding normal tissues, and the role of stem cells in cancer treatment and progression, at the 15th annual John B. Little Symposium.

The 12 presenters at this year’s conference came from many fields: immunology, systems biology, epigenetics, radiation oncology, tumor metabolism, and stem-cell science. The symposium, named for James Stevens Simmons Professor of Radiobiology Emeritus John B. Little, focuses on radiation biology but aims to bring together basic scientists and scholars with a broad range of perspectives. “When you fill up a room with people who think the same way and work on the same things, it’s unlikely that you will produce something new and exciting,” explains Gökhan Hotamisligil, chair of the Department of Genetics and Complex Diseases and one of the symposium’s hosts. “We try to bring together people who think differently, maybe don’t even agree but they do so in a constructive and creative manner.”

The conference, hosted by the John B. Little Center for Radiation Sciences and Environmental Health, was organized this year by Professor of Radiobiology Zhi-Min Yuan and Assistant Professor James R. Mitchell, both in the Department of Genetics and Complex Diseases, and was assisted by Genetics and Complex Diseases newest staff member, Isade Salcedo.

Dean Julio Frenk first provided opening remarks to commemorate the 50th anniversary of Dr. John B. Little’s appointment to the public health faculty:

“Last year, I had the pleasure at the fourteenth symposium to announce that the Morningside Foundation agreed to establish the Morningside Professorship in Radiobiology at the John B. Little Center at the Harvard School of Public Health. The Professorship honors and advances the pioneering efforts of Dr. Gerald Chan, SM’75, SD’79, and his family, the Morningside Group, and the Morningside Foundation in support of scientific research and the promotion of health and education around the world. The Professorship also recognizes Jack’s intellectual leadership in the field of radiobiology. This year, I would like to invite Jack to join us at the podium for a very special presentation.

On behalf of the school and the department, we would like to recognize you, Jack, for the truly outstanding contributions you have made and continue to make. Please accept this plaque as a symbol of our gratitude. The plaque reads,

(continued on page 2)
John Bertram Little, M.D.,

James Stevens Simmons Emeritus Professor of Radiobiology

An international figure in the field of radiobiology, Dr. Little is widely respected and cited for his intellectual accomplishments, mentoring skills, and collegial leadership.

We celebrate his continued career, including the founding of the annual JBL Symposium in 1997 and its ongoing intellectual leadership, and surpassing fifty years of distinguished service to the Harvard School of Public Health.

We honor our distinguished Professor Emeritus as an ongoing contributor, sage advisor and colleague.

Dr. Gerald Chan also offered his congratulatory remarks to Dr. Little, his mentor, and spoke with energy and enthusiasm about the importance of laboratory science as the driver of research behind the policy and practice of public health.

Dr. Little was one of the first scholars to characterize problems in public health as interactions between environmental stressors and humans’ response to those stressors, says Hotamisligil. That approach has since become a foundational idea in public health and a central piece in the vision of the department that guides the agenda for the symposium each year.

For example, a talk by Hilary Collier, assistant professor of molecular biology at Princeton University, focused on the state of quiescence, in which a cell is not actively dividing. If scientists can isolate the metabolic changes and other adjustments a cell must make to enter this state, she said, they might be able to induce a state of quiescence by transferring those mechanisms to rapidly dividing cancer cells. Michael Yaffe, professor of systems biology at MIT discussed the power of systems biology to decode the Achilles heel of cancer in order to facilitate efficacy of chemotherapeutic agents.

Craig Thompson, President of the Memorial Sloan-Kettering Cancer Center, as well as Tak Mak, Director or the Campbell Family Institute for Cancer Research, Canada, discussed how scientists might use “bottlenecks” in tumor metabolism, which tumors must pass through in order to keep growing, to halt tumor progression. Associate Professor Brendan Manning of Harvard and Professor Celeste Simon of University of Pennsylvania provided the latest updates on molecular mechanisms by which tumor cells sense and respond to their nutrient environments by altering their metabolism. Professor Alan D’Andrea discussed how understanding the genetics of a rare disease, Fanconi’s anemia, can illuminate mechanisms underlying the repair of certain types of DNA damage, and how this knowledge can be exploited to tackle tumorigenesis.

And Ruslan Medzhitov, a Professor of Immunobiology at Yale School of Medicine, discussed inflammation, which can be part of a healthy immune response—but when induced by a tumor, actually creates an environment that encourages tumor growth.

Other speakers included William Matsui, Associate Professor in the Department of Oncology at the Johns Hopkins University School of Medicine. Dr. Matsui found that in the disease multiple myeloma, the malignant cells which form the tumor bulk arise from cancer stem cells resembling normal memory B cells. Memory B cells are meant to help the immune system react more quickly to a disease one has already had. He then discussed certain treatments for targeting these myeloma stem cells. Martin Brown, Professor in the Division of Radiation and Cancer Biology at Stanford University, discussed the effects of radiation on endothelial cells comprising the blood vessels that feed the growing tumor.

Anita Hjelmeland, Assistant Professor in the Department of Molecular Medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, discussed glioblastoma, the most common primary brain tumor in adults and also one of the most aggressive cancers. She stressed the importance of tumor-initiating cells and the microenvironment in which they develop. And finally, Jiri Lukas, Executive Director of the Novo Nordisk Foundation Center for Protein Research at the University of Copenhagen, discussed epigenetic mechanisms involved in the repair of double stranded DNA breaks.

Save the Date! 2013 BPH Retreat
Thursday, April 4 - Friday, April 5
Marine Biological Laboratory
Woods Hole, MA
RSVP by Friday, March 1
For more information, contact:
Holly Southern (hsouthern@hsph.harvard.edu)

All BPH faculty and students are invited to attend.
*Doctoral students affiliated with BPH labs can also attend, but please be sure to submit their names and contact information to the BPH Program Office to be included in the event.
Message from the Chair
Gökhan S. Hotamisligil, M.D., Ph.D.
J. S. Simmons Professor of Genetics and Metabolism

First of all, I wish all of you, your families and friends a happy, healthy, and productive New Year. I hope that you had some time to relax and reflect during the holidays and spend some time with your loved ones. We had another wonderful year at GCD, with many personal and professional achievements. The state of our department stands strong despite continuing challenges in the fiscal environment and the atmosphere remains energetic and pleasant. This issue of the GCD Newsletter features just a few of the exceptional awards and honors earned by our outstanding faculty and fellows in the past few months. Professors Manning and Mair were acknowledged as leaders in the field of aging research by the Ellison foundation, with Wilf’s achievements as a young investigator being highlighted and Brendan’s established career of leadership in the field recognized. Zhi-Min Yuan is halfway through his first year with us and already is contributing at the highest level with his research and mentoring, leadership of a training grant and as the head of our current faculty search committee. Marianne Wessling-Resnick assumed the leadership of the Division of Biological Sciences along with the doctoral program. Jack Little was recognized for his more than fifty years of research contributions and leadership. Prerna Bhargava and Sihao Liu were recently graduated quite successfully from the laboratory of Chih-Hao Lee, setting wonderful examples of student achievements that we all aspire to.

There have also been many wonderful life events of note in this year just past including the births of three babies - Esmé Jane born to Margaret Gregor, Kaiden born to Monica Coleman, and Pablo born to Alessandro Arduini. We have had four weddings – Claudia Garcia Wagner, Caitlin Key Alfaro, Anne Benedicte Mengel, and Mehmet Furkan Burak, and two engagements – Lear Brace and Jordan Gallinetti. Love is in the air!

In my meetings with the other chairs, I have many reasons to be proud of my affiliation with all of you as our department is consistently recognized as a leader in research quality, publications and volume of indirect cost generation. With only 2% of the school’s faculty, for example, we have brought in 17% of the school’s income from non-federal grant indirect costs in the current year, placing us at the top in this category amongst all academic departments. Our department has also generated 4% of the school’s federal funds volume and 4% of its federal grant indirect costs. All of this has been possible while Edward has maintained a steady hand on our expense budget without sacrificing quality or an appropriate level of departmental administrative support and David providing an outstanding stewardship to the entirety of our departmental affairs. In the recently completed employee PULSE survey done university-wide, our staff scored the administrative management of the department highly. The paramount to our success is the quality of work done in our laboratories by our faculty, fellows, and students. In a remarkable feast of science, our department has produced a number of exciting discoveries featured in outstanding publications in Nature, Cell Metabolism, Nature Medicine, Science Translational Medicine, Molecular Cell, Science Signaling, Genes & Development, PloS Genetics, FASEB Journal, JCI, and PNAS, just to name a few. Congratulations to all of you involved in these wonderful projects.

I would like to invite all of you to participate in a good-natured competition. Our newsletter is now standing feature of our department and, as such, truly deserves a name of its own. I want to thank David and our department staff who made this newsletter possible and look forward to seeing the next issue. Therefore, I am officially opening - with the distribution of this second issue - a department-wide competition to come up with the name for this publication. Use your creativity and submit as many names for the newsletter as you would like and we will select the best one. The winning entrant will be handsomely rewarded, though the university auditors have not yet established a suitable limit for the value of the prize . . . All entries should be sent to David using his email address [dhasting@hsph.harvard.edu].

This new year of 2013 promises to present many opportunities and challenges as we enter a new world with some economic constraints. However, with our combined capabilities as a department, we can take positive advantage of these opportunities, meet the challenges, and find creative ways to counter the negative effects of the constraints in which we sometimes operate. We have the great privilege of having the most wonderful collection of human capital in all layers of our department that has and will push the boundaries of science. Genetics and Complex Diseases – making an unceasing and positive contribution to benefit of the health of populations throughout our world.

Warmest Regards,
GCD in the Community:

Caitlin Key-Alfaro
Senior Grant Manager by Day, Teacher by Night

You can work alongside someone for a long time and not know about the other talents they have outside of the normal work day. Caitlin Key is one of those folks. Her work style is known to most of the department – collegial, a bright and sunny disposition, always with warmth to her tone. But, you should also hear her lead a classroom full of adults!

Caitlin has been volunteering at Centro Presente in Somerville for almost three years. She offers English classes at the beginner, intermediate and advanced levels to immigrants living in the Boston area as part of a comprehensive approach by this organization. Centro Presente was founded in 1981 by Sister Rose Marie Cummings in direct response to the rapidly growing community of Salvadoran refugees fleeing violence, government repression and instability during the civil conflicts in Central America in the 1980s.

Their website notes –

In April of 2003, we launched a membership program – now over 1,500 members strong – so that our students, legal clients and broader constituency could have a more powerful voice, both within Centro Presente as an organization, and in the wider sphere of public policies that affect us as immigrants. As part of our transformational process, community organizing and leadership development have become the heart of Centro Presente’s work. While we continue to provide key legal and educational services, that work has become part of our community-organizing model, so that people coming to us to address an immediate and individual need are connected to others with whom they can build collective power.

Caitlin becomes very animated when she talks of her work there.

“We have English classes and Spanish literacy classes for those who did not receive a proper education in their home country. We have legal services, computer classes, and citizenship classes so immigrants can study for the exam. We take action to support immigrant advocacy and rights – getting the word out – talking to congress people, talking to local government officials. All this is an effort to make Massachusetts more friendly to immigrants.”

We asked Caitlin how she got started as a volunteer with Centro:

“When I was an undergraduate student, I taught English to immigrants at another organization. Years later, I missed doing that. I undertook a search for an organization in Boston that was doing similar work and when I found them and chatted with them, I really liked what they were doing – not just offering English classes. They described a nice approach to adult education – really empowering – empowering them to be self-sufficient and feel the power of their own voice – we really want people to know that although they were not born here, they should feel that this is their home now and that they are making a contribution to their new country here.

I LOVE the students and they are really hard workers and I admire them a lot. I provide two classes per week, each as a two-hour session, one on Mondays and one on Wednesday. The number of students varies for each nine-week class cycle, with the usual number around five to a high of twelve. I teach both men and women and the ages range from 19 to around 70. Some of these immigrants have been here a few months, some twenty years or more. They can come to additional classes after their first cycle, and many do.

With every class, we start out as a group of people who do not know each other and always by the end of every nine-week cycle we are really good friends. We share a lot of stories – class is often described as a therapy session – with much conversation, getting them talking and listening. People have told their individual stories about how they got to the US. Sometimes these stories are very heart-wrenching, and sometimes descriptive of very dangerous situations. Some of my students are the only members of their family here. They come here, live by themselves, and work to support their family back at home. Often they have two jobs and are still trying to learn English in addition. They really miss their families. That is one reason I really admire them – they are working to improve their own arsenal of skills. Often times they really do not have to learn English – they may be in work places where their bosses and co-workers all speak Spanish to them. But my students seek bigger opportunities through improving their language skills. How impressive they are as human beings . . . they do everything for their families. Their stories are always very touching. I am comfortable sharing my stories with them and they in turn share with me. I have a lot of repeat students because they get comfortable with the class.”

Can others volunteer at Centro Presente?

“We are always happy to find new teachers to teach basic computer skills, Spanish literacy and citizenship. We train new volunteers at the beginning of each nine week session. I have helped the training coordinators do this in the past. I like sharing my volunteer teaching experience and approaches with other teachers.”

What has brought you joy or laughter in this volunteer experience?

“My students are very light-hearted, even though they are burdened by a lot of stress in their lives. But somehow they are very light-hearted. I think the fact that I can communicate with them in both languages, that they will tell me a story. And once they get really animated they will revert to speaking Spanish and I have to push them back into English, which is the only time “strict profesora” comes out. I think that my students always make me laugh because they laugh at themselves at some of their mistakes, which shows me they are comfortable in class.
I feel good about what I do and when I walk out of the class every night and feel so happy that there are such people on the earth with me — they make me feel better about the future and humanity.”

How did you get fluency?

“I started Spanish classes in junior high, maybe 14-15 years old, then continued all through high school, but I never spoke it well. In college, at 21, I went to the University of Havana for six months and studied there. When I got there I realized that I did not speak or understand the language well despite taking all the classes. After six months there, I began to get better, and returned to the US and took advanced classes in Spanish language and literature. Now, I am married and speak to my husband’s Colombian family only in Spanish. Claudia García Wagner in our department is the one that introduced me to my husband – it is kind of a departmental love story. The Colombian student associations at Harvard and MIT get together once a year. Three years ago at the Harvard Queen’s Head pub at Memorial Hall, after work on a Friday, Claudia took me with her and that is where I met my future husband. His family sometimes tells me, “Oh, your accent is very nice”. Caitlin laughed and said, “I believe Colombians think they have the best accents and so they are happy I that I now have one as I used to have a Cuban accent!”

I sometimes see you sitting with one of our custodial staff at lunch time in individual tutoring situations. Can you tell me about that?

“Harvard has a Bridge program. I contacted the coordinator about getting involved. I was thinking that since we have so many folks as service workers who are also immigrants and are in need of similar language improvement. The coordinator, Jennifer, assigned me to a gentleman named Jairo, who is from Colombia. We meet twice a week for an hour at lunch and we just converse. His Harvard position is just one of his two jobs. He is looking for a promotion at his other job, but was told he needs to improve his English skills.”

When I told Caitlin that Jairo now engages me in conversation when I see him in the hallway – something that he never did months ago, she responded, “That is really good to hear! He definitely has improved and I am happy to know that he is more comfortable speaking to others in English. In order to learn a new language, I absolutely believe you must feel discomfort many, many times. It has to get hard for you. I never felt uncomfortable in school as I was never pushed. When I got to Cuba I understood what that discomfort felt like. I tell my students they need to put themselves through that so that they understand. They are tough people. If anyone is going to learn it, they will.

When I hear you pronounce the country name, Colombia, it always sounds more rhythmic than the typical American would pronounce it. Why is that?

“Colombians write the name of their country with an “o” instead of a “u” – so you hear me pronounce it as it is spelled there – Colombia.”

Then she pronounced it for me, patiently and clearly articulating the different syllables twice, so I could hear the difference.

It’s clear why Caitlin is a good teacher.

Mair Selected as Ellison Medical Foundation New Scholar in Aging

Established by Lawrence J. Ellison to support biomedical research on aging, the Ellison Medical Foundation New Scholar awards are targeted to support new investigators of outstanding promise in the basic biological sciences relevant to understanding lifespan development processes and age-related diseases and disabilities. The award is intended to provide new faculty with support during the especially critical first three years of their independent research career. Harvard University nominated Dr. Mair for candidacy, and the Foundation announced his award starting July 1, 2012.

His proposal was entitled, “Uncoupling positive and negative effects of dietary restriction.”

Dr. Mair describes the research in which he is engaged, and details the positive health impact he hopes it will have for our lives.

“Aging is a universal trait that is observed across the evolutionary spectrum. From a public health perspective, aging is also the critical risk factor for a variety of human pathologies, including neurodegenerative diseases, many forms of cancer and metabolic disease. However, although chronological age is immutable, physiological age is malleable, and mechanisms that modulate it can therefore be exploited to reduce disease risk. Our lab is interested in understanding the molecular pathways underpinning the aging process, with the goal of using this knowledge to develop novel therapeutic strategies to treat age-onset disorders.

In particular, we study the mechanisms by which animals can modulate the rate at which they age in response to changes in nutrition and the environment. The profound ability to slow aging during dietary restriction (DR) is seen in organisms ranging from yeast to primates, and is coupled to a striking protection against a suite of age-related pathologies. Despite the beneficial effects DR can have on health however, it also imposes negative social, psychological and physiological side-effects, making it a difficult regime to maintain and an unlikely choice for patients. The goal of this proposal is to find molecular pathways that uncouple the positive effects of DR from detrimental side effects. By elucidating the genetic and molecular pathways that dictate the DR response, we aim to recapitulate the positive effects of DR on lifespan and health without the need for changes in dietary intake and its associated detrimental side effects.”
An Interview with: Prerna Bhargava

Recent doctoral graduate student from the Lee Laboratory

You are about to start a Postdoctoral Fellowship after almost twelve continuous years of molecular biology laboratory work. Were there any points in time when you wondered if there were alternate pathways for you. Did you stay 100% determined and focused on molecular biology the entire time?

“It has been twelve straight years, yes - four years in high school, four years in college and four years here at GCD. Both of my parents are scientists. My mom put me in touch with one of her mentors when I started high school. I began with gels, then pcrs. I knew I wanted to continue in college but was not sure about forever. In college I was actually a legal studies minor as well, and considered going to medical school ... to law school, or even dancing for a career! I thought about everything... But I just can’t be out of the lab – I think I knew that the whole time ... I just can’t do a nine-to-five job. I still dance and do my artsy stuff on the side, but I know the lab is the place for me. It is really fascinating to answer questions nobody has ever answered before, albeit small, miniscule questions in the grand scheme of things. When I considered medical school vs. research, I realized that medicine is very protocol driven, as opposed to being a scientist where one can say, “What about this idea, what happens when you do this ...” There is a blend of critical thinking, creativity, logic, it’s very formulaic but at the same time not very formulaic... I like that.”

What about the repetitive nature of some of the work involved in the pursuit of science... Have you experienced that?

“There is a repetitive nature to the work but I enjoy that. You get a result that you predicted but you want to be sure it is correct so you have to repeat the experiment. Even getting the same result the second time is exciting because you are confirming your hypothesis. And despite an individual technique being repetitive, the questions you are asking are not, so you always get answers to new questions every time you do an experiment.... Also, I was lucky and I purposely selected a graduate laboratory where I would not have to perform the same experiments over and over again, where I would not have to do Western Blots or QPCR plates in perpetuity. Yes, I did QPCR plates all the time and I can do them in my sleep, but it didn’t feel repetitive to me because I did so many different things on a regular basis... I can use a microscope, a FACS machine... basically you can come to me and say, “do this” and I will figure out how to do it. No day ever was the same, and that was exciting.”

You are starting your postdoctoral work in an engineering laboratory. Tell us about that.

“I have always been interested in the engineering aspect of science. The idea of manipulating a system for use in therapeutics is a very interesting concept to me. The lab I am going to incorporates a lot of new technologies. While my work may not focus too much on engineering, the lab does both basic science and engineering research and I am excited to see how to incorporate the two concepts together. I did the public health/biology intersection, and I did the immunology/metabolism intersection, so now it is just another intersection to study and incorporate into my future research.”

You are coming out of a laboratory that was full of life, photography and music, a community of researchers that seemed comfortable and happy interacting with each other... So look down the road a few years and tell us what the Bhargava laboratory will look and feel like when you are responsible for the creation of the environment...

“Having worked in three laboratories, I experienced similar but different environments. There are some key components to maintaining a cordial and easy-going lab. I think the main thing is letting people do what they want to do... not being locked in to following specific instructions all the time... letting people talk to each other... encouraging people to understand that the work is not “nine to five”. You can work the hours that work for you so you can concentrate 100% on your science when you are at work. This type of flexibility is inherently difficult because of the pressures and importance of publishing, balanced with the need to think carefully plan and execute experiments.

The ability to let people do what they want is not just through experiments, but also through expressing ones personality. One way people express their personalities is through music. I love music. Some people do not work well in that type of environment. However, when you tell people they cannot listen to music as a laboratory group, they put on headphones and then the lab becomes very closed. When someone has headphones on you do not feel comfortable in approaching them. Part of the reason we were all so...
friendly was because we put music on... sometimes people hated individual pieces of music, but everyone had opportunities to contribute different selections. That is definitely one of the things I would encourage. Science is not just hard work. Science requires use of both your right brain and your left brain. A lot of very successful scientists I know have talents other than just their science; they may be artistically or musically oriented. You need to be able to use both sides of your brain to think logically and creatively at the same time.

At the end of the day, though, it is the people in the lab that make it enjoyable. In every lab I have been in, even since high school, I have built personal relationships with all of my colleagues. It is really key that the personalities in a lab work together—not once that community is established—science becomes fun and easy.

Let’s imagine the future, and you have been selected to introduce your mentor, Chih-Hao Lee, as he accepts the Nobel Prize. What would you say?

“When he does win the Nobel Prize, I don’t know if I will be the one to introduce him! But, if I am (and it would be a huge honor to!), I would tell the world what a great scientist and mentor he is! Chih-Hao is an interesting PI. He wants to be involved but understands that we need some distance to grow. I have learned a lot from him, both scientifically and professionally. He cares about everybody in the lab—more than just as a PI—he is a mentor and also treats us all like friends. He treated me like an equal, and we had our moments where we went back and forth on planning experiments...and at times we were frustrated with each other, yet he always ensured that I was able to express my opinions and he respected them. He helped me to develop a project and supported me until the end. He took the time to learn about what I was doing, tried to help me build my ideas (even if they weren’t always the best or most straightforward). That required a lot of patience and trust in me and that’s what made him such an amazing mentor.”

It has been said that ‘music is the silence between the notes’. That silence enables you to anticipate the next note or theme, to be surprised, to trust and to respect, but also to explore. That silence is ‘white space’. Talking with you today, it sounds to me like you sense that same “white space” in science.

“Yes, I think that analogy holds in science. There are moments of silence where nothing is happening. It is frustrating. But this frustration makes the discovery at the end of the day so much more exciting. In that white space, you have excitement, anticipation, some pain, and great expectations—and then something great comes out of it—it is so exhilarating!”

Manning Chosen as Distinguished Senior Scholar

Our colleague, Associate Professor Brendan D. Manning was recently informed that he was selected as an Ellison Medical Foundation Senior Scholar in Aging. The selection process was made by the Scientific Advisory Board and approved by Lawrence J. Ellison as Chairman of The Ellison Medical Foundation.

The Ellison Medical Foundation Senior Scholar in Aging program is “designed to support established investigators working at institutions in the U.S. to conduct research in the basic biological sciences relevant to understanding lifespan development processes and age-related diseases and disabilities. The award is intended to provide significant support to allow the development of novel, innovative research programs by investigators who are not currently conducting aging research or who wish to develop new research programs in aging. The Foundation particularly aims to stimulate new research that has rigorous scientific foundations but is not funded adequately, either because of its perceived novelty, its high risk, or because it is from an area where traditional research interests absorb most funding. Senior Scholar awards provide funding up to $150,000 per year for a four-year period.”

Dr. Manning was asked to provide a summary in lay terminology of the project he proposed to the Foundation as part of the competitive award application process. That summary follows here—

“Aging research in model organisms has revealed three major biochemical pathways that influence longevity across species. These three pathways (insulin/IGF1, AMPK, and mTOR) have the shared features that they are controlled by the nutrient status of the organism, which can likewise impact the aging process, and that they regulate local and systemic metabolism. However, the link between these pathways, as it relates to aging, is poorly understood, especially in mammals. Our project makes use of novel mouse genetic models to critically test the hypothesis that these three pathways converge to influence aging through the same mechanisms. Furthermore, we will identify shared and distinct connections between these pathways and cell, tissue, and organismal metabolism, which we believe underlie their control of the aging process and their effects on aging-related diseases. These studies will provide a deeper understanding of how dietary interventions and chemical compounds that are known to prolong lifespan in mammals exert their beneficial effects. Our ultimate goal in defining pro-longevity mechanisms is to reveal novel, and perhaps more focused, therapeutic approaches to attenuate the aging process and prevent aging-related diseases, such as cancer and diabetes.

Under this project, the Manning laboratory will combine mouse genetics with studies of both systemic and tissue-specific metabolism, including the use of unbiased metabolomic analyses. When asked about why this project is innovative and unique to previous aging studies, Dr. Manning said that “the complexity of the signaling network implicated in aging, especially in mammals where the individual network components are all essential to life, necessitates the development of more sophisticated genetic models to help define the molecular mechanisms influencing longevity. We plan to take advantage of our detailed understanding of the wiring of the major longevity signaling pathways to generate novel separation-of-function mouse models that will allow us to interrogate the genetic and metabolic relationship between these interconnected pathways, as it relates to both health span and lifespan. We believe that this type of genetic dissection will provide a unifying mechanistic picture of mammalian aging and improve our understanding and development of pro-longevity interventions.”
Spotlight: Matthew Gangl

Laboratory Manager/Research Assistant in the Lee Laboratory

What occupies your time outside of work?

“School and staying active. School – I am in a master’s program, starting in my fourth year – an MS in biotechnology through the Harvard Extension School. That, and playing basketball and running. I love playing pickup ball in Jamaica Plain. They have a great court and lots of good players – keeps me in training so I have a chance against my younger brother and my buddies in NY who regularly beat the pants off me.” When asked how often he plays, Matthew responded – “I couldn’t play every night – my knees couldn’t take it.” I asked him about the typical neighborhood player, including their height, and how he compared. “Height wise... [and he laughed] not EVERYONE is bigger than me. Two weeks ago we got schooled by a team of five girls – five girls against five guys – the score was, like, fifteen to five.... You’ve got to stay humble.”

When you visit the Lee laboratory, there is always music playing. Matthew is the ongoing source of our music mixes that are playing at the department’s monthly Joyous 120 gatherings. He was asked,

What is the role of music in the Lee laboratory?

“Ahhh... the role of music... the best way to describe the role of music in the Lee lab is that it is an unchanging factor. Regardless of the day, you are going to have a musical distraction – the only time we make a specific choice in the music is when we are doing something that takes a prolonged period of time during which we need to maintain focus – like doing a rack. We will put on something that is conducive to staying focused. Otherwise, it is up to whoever feels motivated to make the musical selections for the day. These days we do a lot of the internet radio stations. They will have question which you answer like, “do you feel happy, warm, do you want jazz”. You answer the questions and the station responds with appropriate selections.” Matt occasionally makes a playlist – sometimes based on the thoughts in his mind during his bus ride in to work. Dr. Lee can actually sometimes guess who makes the selections by listening to some of it... It’s cool. Sometimes during a visit, he’ll take a moment to reflect on what we are listening to it... Occasionally it is loud enough for him to hear it in his office and he’ll ask, “What the heck are you listening to?”. He was asked, “Does Dr. Lee ever come in and say he likes it?” Not usually. He is pretty well versed in music. He has a better grasp of modern music than I do – he listens to music regularly. It’s not often that he would say he digs it – he might say ‘I just heard this band, do you know about them’. He likes to go to shows.”

If you had the opportunity to have tickets to one sporting event in the coming year, what would it be and why?

“I would go down to Miami – opening day of the Heat vs. Celtics [basketball]. I would stay with a former lab mate – I would be in Miami wearing Celtics gear – it would be a fantastic place to be – early fall – beautiful place to hang out after the game... I would like to give the folks in Miami some trouble! I would have selected the NBA finals but I don’t want to be too presumptive that the Celtics would be in it. I would rather be a road fan at a basketball game rather than a football game...... I’ve been a road fan at an Eagles game, and those fans are .... Yikes!!”

When did you know that you wanted to work on bench science?

“Probably I thought I was fairly confident that I wanted to work in biological research when I left college but it was not until I spent some time in Montana after college. It took some time away because college was intense the last two years. I like the thought process of science, working in a group... expanding the knowledge of ourselves in a way that can help others. This is what excites me about the degree program [Biotechnology] I’m in now – it introduces engineer- ing into science... building things has always been a strength of mine - taking a view of problems and finding a way to make the work easier... applying this approach to tissue fabrication, drug purification – any mechanism where I am excited to find a new manner of taking these skills and putting them to work... I love being around smart people – it keeps me motivated. That’s why I like the Harvard community - a lot of brilliant people - a lot of motivated people.”