

DOCTORS IN THE HOUSE STORIES OF RESEARCH, PATIENCE, AND PATIENTS

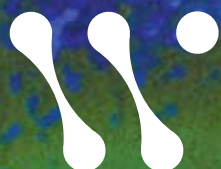
PARADIGM

LIFE SCIENCES AT WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH **FALL 2009**

**MICRORNAs
ON THE WEB**

**TUMORS
ON A DIET**

**CHROMOSOMES
ON THE HOOK**



POPULAR SCIENCE

How do you feel about science? About scientists?

If you're anything like the 2,000 Americans who responded to a survey conducted this past spring by the Pew Research Center for the People & the Press, in collaboration with the American Association for the Advancement of Science (AAAS), you have a positive impression of scientists and their work. According to the results of the survey, which was conducted during the spring of 2009, 84% of respondents view science's effect on society as "mostly positive."

When asked to consider various professions' contributions to societal well-being, 70% of survey-takers indicated that scientists "contribute a lot." Only members of the military and teachers were viewed more favorably, with 84% and 77% of respondents reporting that members of these respective professions "contribute a lot." Equally encouraging for the scientific community: according to the survey, 73% of respondents believe that government investment in basic scientific research "pays off in the long run."

So, how do scientists feel about you?

Well, consider the headline of a press release the Pew Research Center issued this past July when announcing the results of the public survey discussed above and those of a survey among scientists conducted in parallel. The headline reads: "Public Praises Science; Scientists Fault Public, Media."

In this survey of 2,500 scientists across the country (all AAAS members), 85% of participants responded that a lack of scientific knowledge among the general public is a "major problem," while slightly fewer than half (49%) of responding scientists indicated that the public expects solutions to problems too quickly. Taking aim at the media, 76% of scientists responded that the news fails to distinguish "well-founded" findings from "those that are not," and 48% indicated that news media oversimplify scientific findings. (It's worth noting that scientists and the public seem to agree on their impressions of journalists; only 38%

of respondents to the public survey believe journalists "contribute a lot" to society's well-being.)

Although these survey results suggest a potentially vexing disconnect between scientists and the public, when taken together, they also point to remarkable opportunities for teachable moments for both sides. Whitehead Institute faculty long ago recognized the two-way educational importance of public dialog and so have organized or participated in a host of outreach programs over the years on such topics as genetic testing, cloning, and stem cell research. And Whitehead's Partnership for Science Education, aimed at increasing scientific understanding among high school students and teachers, is now in its 19th year.

Such efforts need to continue, and if we're to place stock in these survey data, then the time is right for scientists to bolster their engagement with the public. With the populace so favorably disposed, the scientific community should embrace this opportunity to play before such a friendly audience.

PUBLIC PERCEPTION OF SCIENCE, SCIENTISTS

SCIENCE'S IMPACT ON SOCIETY IS:

Mostly positive	84%
Mostly negative	6%
Other/Don't know	10%

PROFESSIONS CONTRIBUTING "A LOT TO SOCIETY'S WELL-BEING":

Members of military	84%
Teachers	77%
Scientists	70%
Medical doctors	69%

Percentage of survey participants providing each response

Source: Pew Research Center for the People & the Press



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WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH is a nonprofit research and educational institution. Wholly independent in its governance, finances, and research programs, Whitehead shares a teaching affiliation with Massachusetts Institute of Technology.

Whitehead brings together a small group of world-class biomedical researchers in a highly collaborative and supportive environment and empowers them to pursue the questions that engage them most.

PARADIGM reports on life sciences research and innovations at Whitehead and explores public issues related to the conduct of basic biomedical research. To comment or subscribe, please send a note to publications@wi.mit.edu. Text, photographs, and illustrations may not be reused without written permission.

ON THE COVER Fluorescent image of mouse brain tissue genetically engineered to express green fluorescent protein (GFP) in places where the prion protein, PrP, is normally expressed. GFP was detected by its native fluorescence (colored green). Sections were also stained with a dye specific for neuronal cell bodies (colored blue) and a stain to detect the insulating myelin sheaths covering neuronal axons (colored red). The image was captured during research into prion-based, transmissible neurodegenerative diseases. For additional information about such research, please see pages 5 and 6. **Image: Walker Jackson**

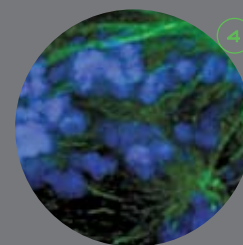
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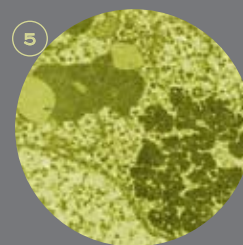
A number of Whitehead scientists bring unique perspective to their research by virtue of their formal medical training. These MD/PhDs, many of whom currently practice in the clinic, feel their experiences in medicine help put their Whitehead projects in broader context



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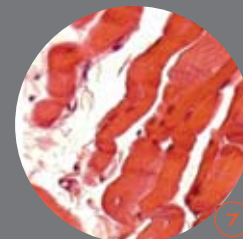


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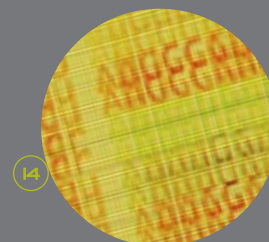
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RESEARCH NEWS

MICRORNA FOUND TO HAMPER ACTIVITY OF TUMOR SUPPRESSOR GENE

A small piece of RNA, or microRNA (miRNA), ratchets down the activity of the tumor-suppressor gene *p53*, according to a study by Whitehead Institute, Genome Institute of Singapore, and the Institute of Molecular and Cell Biology in Singapore.

While *p53* functions to suppress tumor formation, the *p53* gene is thought to malfunction in more than 50% of cancerous tumors.

The study, published in March in *Genes and Development*, reports the first time that a miRNA has been shown to directly affect the *p53* gene, although researchers have previously identified other genes and miRNAs that regulate *p53*'s activity indirectly.

"For critical genes like *p53*, it's important that they are maintained at the right level in the cell," says Beiyan Zhou, a postdoctoral researcher in the lab of Whitehead Member Harvey Lodish and mentor to the paper's first

author, Minh Le. "Le's work describes one more layer of regulatory mechanism that balances *p53* gene expression."

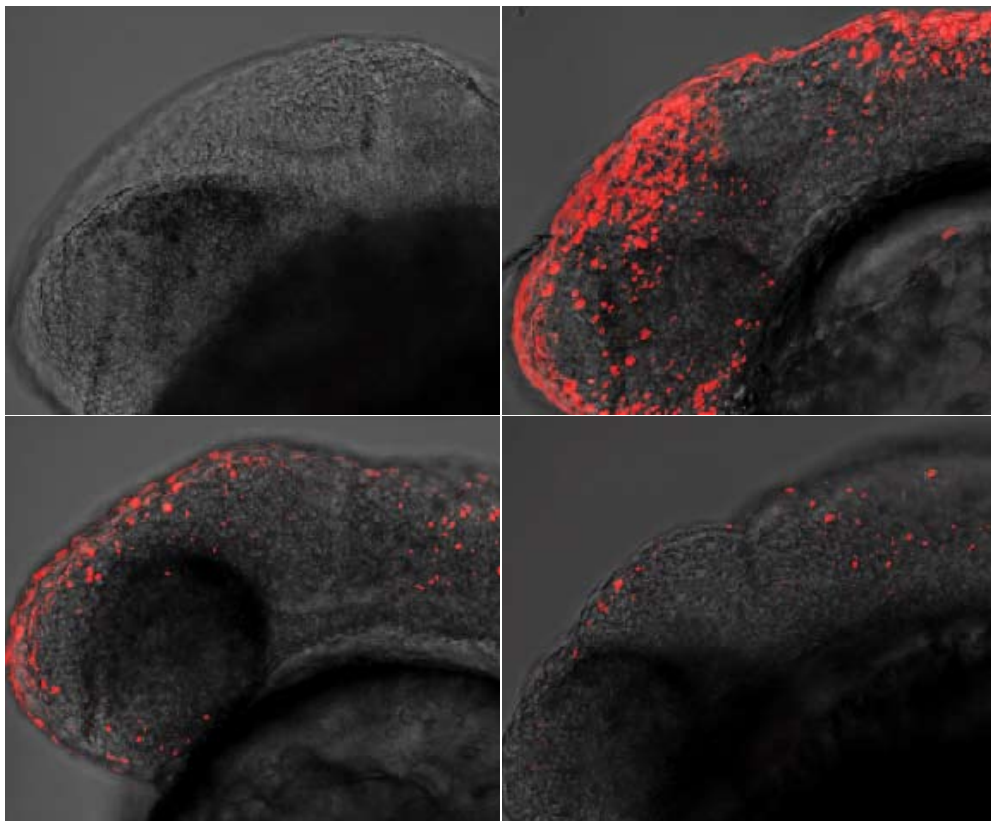
miRNAs, short snippets of RNA, usually reduce how often a certain gene is translated into a protein. When a miRNA matches with and binds to a given messenger RNA coding for a specific protein, it prevents that messenger RNA from acting as a template for protein creation.

To investigate whether any miRNAs directly affect *p53*, Le, who is a joint graduate student in Lodish's lab and in the lab of Bing Lim at the Genome Institute of Singapore and the Institute of Molecular and Cell Biology in Singapore, searched the *p53* gene for any sites that matched with known miRNAs from two databases. Only miRNA125b potentially has *p53* target sites in humans, in zebrafish, and in many other vertebrates, indicating that it was important enough in cellular processes to be conserved through evolution.

Le tested miRNA125b's effects on several types of cells known to express *p53*, including human neural and lung cells. When Le reduced the amount of miRNA125b in the cells, *p53* levels and the number of cells undergoing apoptosis (a type of programmed cell death that can be triggered by *p53*) both increased, whereas an increase in miRNA125b levels decreased levels of *p53* and the number of apoptotic cells.

To confirm that miRNA125b played a similar role in developing organisms, Le changed the miRNA125b levels in zebrafish embryos. When she reduced miRNA125b levels in the embryos, cellular *p53* levels and apoptosis both increased.

"Taking all of this data together, the *p53* pathway is a major target of miRNA125b," says Lodish, who is also a professor of biology and bioengineering at MIT. "Most miRNAs have multiple targets, but there are a few cases that a miRNA has one major target and this is one of them."



UPS AND DOWNS In embryonic zebrafish brains, levels of microRNA-125b (miR-125b) inversely affect the rate of programmed cell death, or apoptosis, in a dose-dependent fashion. This apoptosis is triggered by the ***p53*** tumor suppressor gene, which is thought to malfunction in more than half of cancerous tumors. The control image above (upper left) depicts a zebrafish embryo with baseline levels of miR-125b. In the image to the upper right, levels of miR-125b have been suppressed significantly, leading to an increase in apoptotic cells, displayed in red. The remaining images show the effects of moderate suppression of miR-125b (lower left), which reduces the rate of apoptosis, and minimal suppression (lower right). Thus, higher concentrations of miR-125b result in lower rates of apoptosis. *Courtesy Genes & Development*

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- MICRORNA'S CELLULAR LEVEL MAY PREDICT BREAST CANCER METASTASIS

CELL PATHWAY REGULATES TUMOR RESPONSE TO CALORIC RESTRICTION

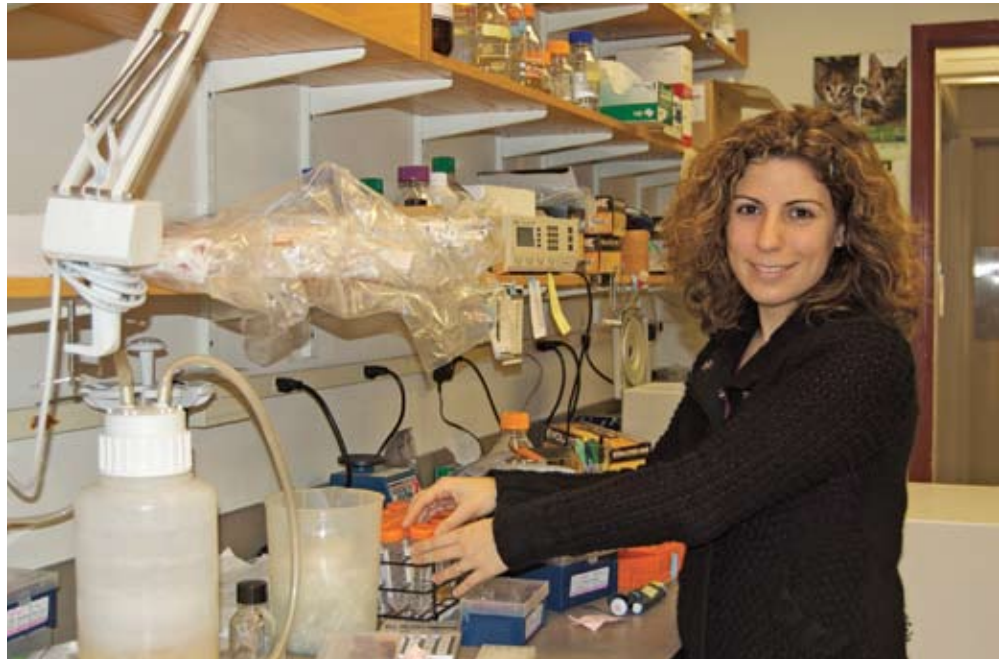
Whitehead Institute researchers have pinpointed a cellular pathway that determines whether cancerous tumors respond to dietary restriction during their development.

Studying human cancer cell lines in mice, researchers have found that when this pathway, known as PI3K, is activated permanently via mutation, tumors grow and proliferate independent of food consumption. However, when the PI3K pathway operates normally, dietary restriction (defined as a 60% reduction in normal intake), results in smaller tumors. The findings were published in March in *Nature*.

“Our findings indicate that each tumor cell bears a signature that determines whether or not that cell will be affected by dietary restriction,” says Nada Kalaany, first author of the paper and a postdoctoral researcher in the lab of Whitehead Member David Sabatini. “We think that mutations in the PI3K pathway are a major determinant of the sensitivity of tumors to dietary restriction.”

The connection between food consumption and tumor growth is not new. In the early 20th Century, scientists first noted the correlation between a restricted diet and decreased tumor size and incidence. However, some cancers’ growth rate was unaffected by a decrease in food consumption. The reason for this difference remained unclear.

To determine how various tumor types are affected by dietary resistance, Kalaany injected cells from human prostate, breast, brain, and colon cancers into mice in an experimental protocol used frequently to study human cancers. The mice then ate as much as they liked (control group) or received 60% of the caloric intake of their counterparts (the dietary restriction or DR group). Both groups ingested the same amounts of vitamins and minerals. After a few weeks, Kalaany saw that the can-



TUMOR STARVATION Nada Kalaany identified a cellular pathway, PI3K, which determines whether cancerous tumors will respond to dietary restriction. **Photo: Ceal Capistrano**

cers could be divided into DR-sensitive tumors, with significantly lower tumor volumes in the DR mice than in control mice, or DR-resistant tumors, whose sizes were apparently unaffected by normal or restricted diets.

Kalaany then grew the same cancer cells in Petri dishes to see how the DR-sensitive and DR-resistant cancers respond to food-related hormones in the body. The cancers were grown in solutions containing increasing amounts of insulin, insulin-like growth factor 1 (IGF1), or in a solution without these hormones. The results supported the previous experiment: those cancer cells that were DR-sensitive in the mice were also stunted by a lack of insulin and IGF1; those cancer cells that were DR-resistant in the mice were unaffected by changes in insulin and IGF1 levels.

Because the difference between the two groups was sensitivity or insensitivity to insulin and IGF1, Kalaany thought the insensitive tumors

may have something amiss in a cellular process called the PI3K pathway, which is activated by insulin/IGF1. A search for mutations in two genes found in the PI3K pathway that are often associated with cancer (*PI3KCA* and *PTEN*), revealed that DR-resistant cells had mutations in one or the other of the genes, while DR-sensitive cells showed no such mutations.

Using a DR-resistant tumor cell line in which the *PTEN* gene could be switched on or off, Kalaany tested whether a change in the *PTEN* gene alone could affect a tumor’s sensitivity to DR. When the *PTEN* gene was turned off, the cancer cells were not affected by dietary restriction, and tumor size increased similarly in control and DR mice. But when *PTEN* was turned on, thereby restoring normal function to the PI3K pathway, the cells became sensitized to dietary restriction and tumor size was smaller in the DR group.

This research was confirmed in two mouse models of cancer, one with prostate cancer caused by *PTEN* deletion and one with lung cancer and a functioning *PTEN* gene. Again, the mice without the *PTEN* gene did not respond to dietary restriction, but the mice with a functioning *PTEN* gene were sensitive to dietary restriction.

Sabatini says that Kalaany's results could lead to cancer treatments tailored to the characteristics of an individual patient's tumor cells.

"Her findings suggest that if we have therapies that mimic dietary restriction, we could better predict which tumors would respond to

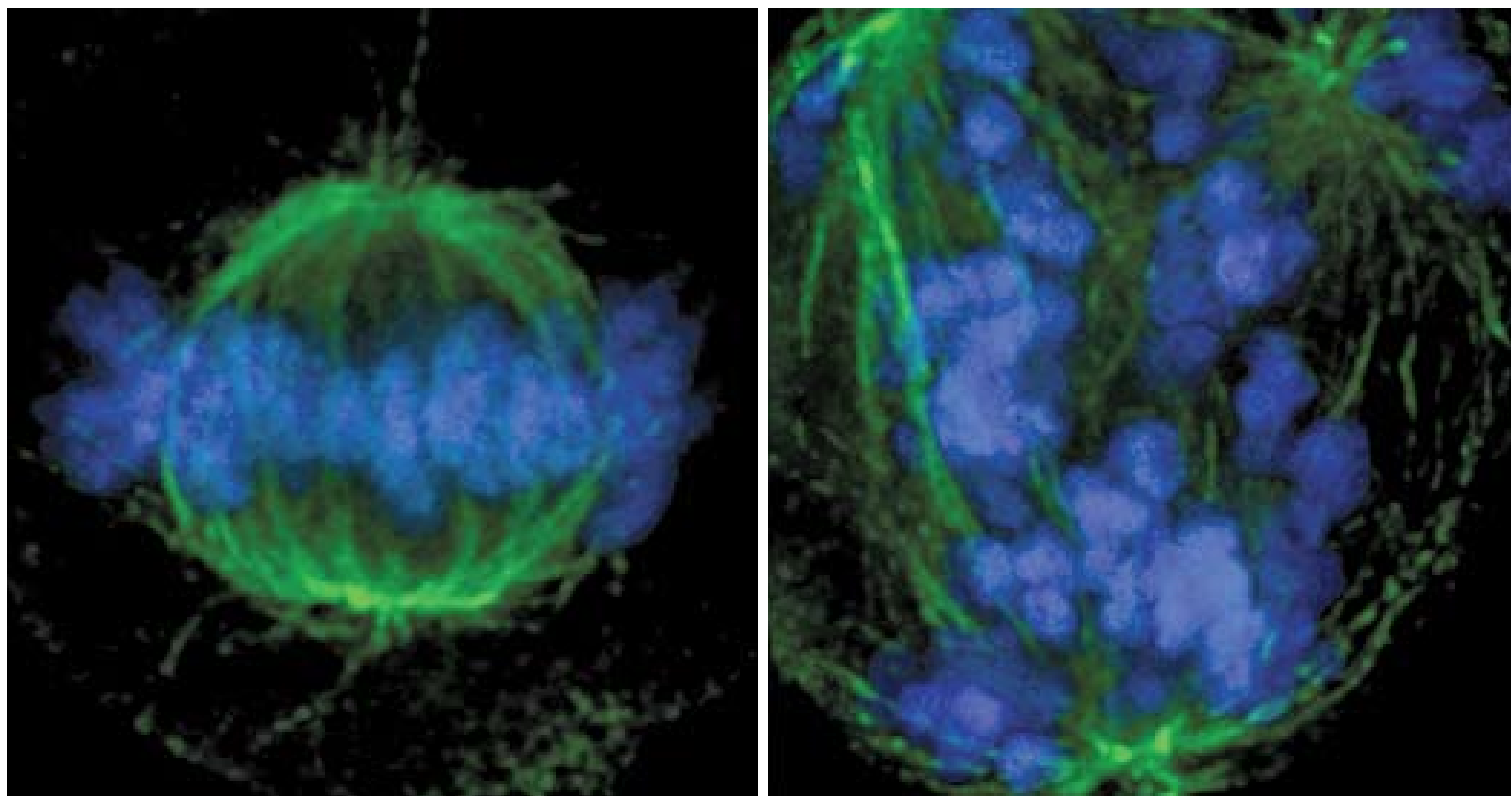
those dietary restriction-mimicking drugs and which ones would not," says Sabatini.

Sabatini is also intrigued by the inverse relationship between too much food and an increase in tumors. "We already know that the United States has an epidemic of obesity and that obesity is probably the biggest contributor to cancer in the U.S., even more so than smoking. Does this research have anything to do with that correlation between obesity and cancer, that if we make animals really obese, that this pathway is also involved in determining their sensitivity to cancer? Answering that question is the next step."

PROTEIN COMPLEX PLAYS CATCHY NUMBER DURING CELL DIVISION

Whitehead Institute researchers have identified a protein complex that harnesses energy from protein filaments, called microtubules, to pull chromosomes to opposite ends of a cell during cell division. This protein complex, known as Ska1, is a component of the kinetochore, a larger protein complex that hitches the microtubule ends to the chromosome.

Although numerous kinetochore proteins have been identified, it was unclear which proteins help facilitate connections to the rapidly shrinking and growing microtubules. The



LINKED IN The Ska1 protein complex is critical for microtubule/kinetochore interaction to function correctly during cell division. When Ska1 is disabled, (above right) cells have disorganized chromosomes (blue) and microtubules (green) arcing from multiple places within the cell. With Ska1 intact, (above left) chromosomes align properly along the cell's center and microtubules arc to them from opposite sides of the cell. *Courtesy Developmental Cell*

RESEARCH POINTS TO POSSIBLE TREATMENT FOR RETT SYNDROME

Using injections of a small derivate of the protein insulin-like growth factor-1 (IGF-1), scientists at Whitehead Institute and MIT's Picower Institute for Learning and Memory have successfully treated a mouse model of the devastating neurological disorder Rett syndrome.

Rett syndrome is an inherited disease affecting one in 10,000 girls. Infants with the disease appear to develop normally for their first 6 to 18 months, at which point their movement and language skills begin to deteriorate. Loss of speech, reduced head size, breathing and heart rhythm ir-

regularities, and autistic-like symptoms are common by age four. Some symptoms may be mediated with prescription drugs, but no cure or truly effective treatment for the disease exists.

In a study appearing in February in the *Proceedings of the National Academies of*

Ska1 complex provides a key missing link between the kinetochore and the microtubules, according to a study published in March in *Developmental Cell*.

“For me, this missing link was one of the really big, outstanding questions of the kinetochore field,” says Whitehead Member Iain Cheeseman. “During cell division, aligning chromosomes and dragging them to two new cells is almost entirely dependent on the ability to hold onto a dramatically shrinking microtubule. We didn’t know how the kinetochore was holding on.”

Cell division is the process one cell (the mother cell) undergoes to ensure that the two resulting cells have a complete copy of the mother cell’s chromosomes. At the beginning of mitosis, each chromosome is bound to its replicated copy. To divvy up the DNA, the microtubules hook onto the chromosomes’ kinetochores and anchor each chromosome in the pair to opposite ends of the cell.

Tugging on the paired chromosomes, the microtubules line up the chromosomes along the middle of the mother cell. Once properly aligned, the bonds between the paired chromosomes break, and the shortening microtubules pull complete sets of the chromosomes to opposite ends of the mother cell.

A microtubule shortens by peeling back narrow molecular strands from its chromosomal end, creating a large amount of force. In yeast, a protein complex called Dam1 harnesses this force to tow the bulky chromosomes through the highly viscous fluid filling the nucleus. Dam1 forms a sliding ring around the shortening microtubule and is also tethered to the rest of the kinetochore. As strands of the microtubule peel back, the fraying end forces the Dam1 ring to slide toward the microtubule’s opposite end, dragging the kinetochore and its attached chromosome behind.

Although Dam1 has been well studied for several years, researchers had been unable to find a comparable protein in higher organisms, including humans. In this study, the Cheeseman lab notes that a newly identified protein, called Rama1, confers upon the Ska1 complex of human cells some of the same properties Dam1 exhibits in yeast cells, including the ability to move a tiny bead down a peeling microtubule.

“It’s exciting because people have been trying to understand for a long time what couples the energy of a fraying microtubule to make chromosomes move in human cells,” says Julie Welburn, first author of the paper and postdoctoral research in the Cheeseman lab. “This research may be a clue to how that coupling works.”

As of now the Cheeseman lab is uncertain if Ska1 forms a ring, like Dam1, or some other shape around a microtubule. “We haven’t seen a specific shape yet,” says Welburn. “That’s work for the future.”

SINGLE GENE MUTATION CAN CAUSE TRANSMISSIBLE PRION DISEASE

For the first time, Whitehead Institute researchers have shown definitively that mutations associated with prion diseases are sufficient to cause a transmissible neurodegenerative disease.

The discovery was reported in August in the journal *Neuron*.

Until now, two theories about the role mutations play in prion diseases have been at odds. According to one theory, mutations make carriers more susceptible to prions in the environment. Alternatively, mutations themselves might cause the disease and the spontaneous generation of transmissible prions.

Prions cause several diseases, including Creutzfeldt-Jakob disease (CJD) in humans,

bovine spongiform encephalopathy (BSE, or “mad cow disease”) in cows, and scrapie in sheep. Some prion diseases, like BSE, can be transmitted from feed animals to humans. Deciphering the origins of prion diseases could help farmers and policy-makers determine how best to control a prion disease outbreak in livestock and to prevent prion transmission to humans.

Prions are misfolded versions of a protein called PrP. In its normal form, PrP is expressed in the brain and other neural tissues. But specific events, such as exposure to prions from the environment, can cause PrP to change from its normal shape to that of a prion. Once in the prion shape, the protein can convert other normal PrP proteins to the abnormal shape. As PrP proteins convert to prions, they form long chains that damage brain and nerve cells, causing the neurodegenerative and behavioral symptoms characteristic of prion diseases.

To determine if a mutation in the PrP gene can cause a transmissible prion disease, Walker Jackson, first author of the *Neuron* article and a postdoctoral researcher in the lab of Whitehead Member Susan Lindquist, engineered a knock-in mouse expressing a PrP gene carrying the mutation associated with the human prion disease fatal familial insomnia (FFI).

In knock-in experiments, the researcher removes a gene of interest, makes specific changes to it in a test tube, and then places it back in its original place in the genome. In this case, Jackson replaced the mouse PrP gene with an altered version carrying the FFI mutation. This version also carried a sequence from human PrP that prevented the mice from acquiring normal mouse prions that could potentially be in the environment.

“It’s more difficult to create a knock-in mouse, instead of randomly integrating the mutated gene into the mouse’s genome,” says Jackson.

Sciences, researchers showed that daily injections of an active fragment of IGF-1 in mice that expressed Rett-syndrome like symptoms could significantly reduce movement and respiratory irregularities. Although treated mice were not cured, the outcome is reason for optimism.

“This is the first realistic way for a drug-like molecule injected into the bloodstream to relieve Rett syndrome symptoms,” says Whitehead Member Rudolf Jaenisch, whose lab collaborated with the lab of MIT and Picower scientist Mriganka Sur in the research.

In approximately 85% of girls with Rett syndrome, the disease is caused by loss of function of the **MeCP2** gene, which is highly expressed during nerve cell maturation. Lack of **MeCP2** expression impedes nerve cell growth, keeping the cells from forming projections, called spines, which are used



PRION GENERATION This section of mouse brain tissue captures an aggregation of prion protein (PrP; highlighted by the arrow) impinging on a neuronal nucleus. The appearance of PrP here is the result of a single gene modification that could result in transmissibility of a neurodegenerative disorder. *Image: Nicki Watson*

“But creating a knock-in like this makes sure the gene is expressed when and where it normally would be. That’s the number one reason we think this disease model worked so well, compared to others’ experiments.”

As adults, the mice exhibited many of the same traits as human FFI patients: reduced activity levels and sleep abnormalities. When Jackson examined the mice’s brains, they resembled those of human FFI patients, with prominent damage to the thalamic region of the brain.

After establishing that the mice have the behavioral and pathological characteristics of FFI, Jackson injected diseased brain tissue from the FFI mice into healthy mice. The healthy mice also carried the same human derived barrier as the FFI mice, preventing their infection by normal mouse prions and ensuring that the only prion they could acquire was the one engineered by Jackson. After injection with the affected tissue, the healthy mice exhibited similar symptoms and neuropathology as the mice with the FFI mutation.

The mutated gene engineered by Jackson had created a transmissible prion disease that could not be attributed to any prions in the environment.

“One of the major tenets of the prion hypothesis is that a single amino acid change in PrP, associated with human disease, is sufficient to cause the spontaneous production of infectious material,” says Lindquist, who is also a professor of biology at MIT and a Howard Hughes Medical Institute investigator. “Many people have tried and come close. But this is the first time it has been nailed.”

for nerve-cell-to-nerve-cell communication. Recent genetic studies have shown that in mice with blocked **MeCP2** expression, turning **MeCP2** back “on” nudges the mice towards normal movement and lifespan—an indication that the disease could be reversible. Although researchers have known which gene causes the vast majority of Rett

syndrome cases, they have until now been unable to promote nerve cell maturation through administration of a drug, protein, or small molecule.

While researchers in Sur’s lab had discovered that increased brain levels of IGF-1 promoted maturation of synapses, the connections between nerve cells that are the basis for brain functions, Emanuela

Giacometti, a graduate student in Jaenisch’s laboratory, was theorizing that IGF-1 might also increase the nerve cell spines in the lab’s mouse model of Rett syndrome. Such mice lack the **MeCP2** gene and at four to six weeks display symptoms quite similar to those in girls with Rett syndrome, including difficulty walking, lethargy, and breathing and heart rhythm irregularities.

MICRORNA'S CELLULAR LEVEL MAY PREDICT BREAST CANCER METASTASIS

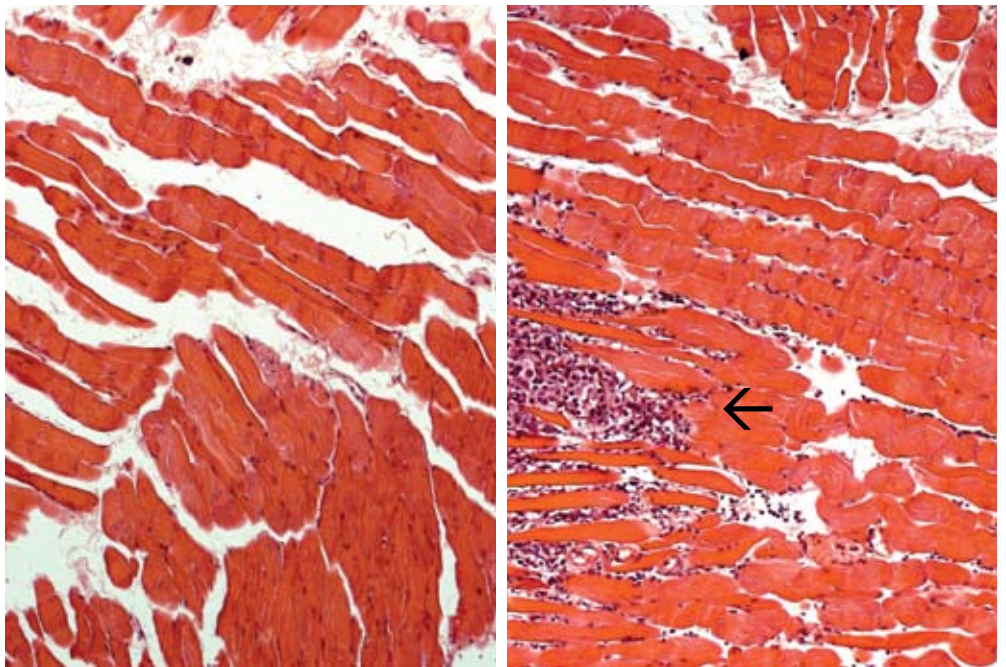
A low cellular level of a tiny fragment of RNA appears to increase the spread of breast cancer in mouse models of the disease.

Measuring levels of this so-called microRNA, which is also associated with metastatic breast cancer in humans, may more accurately predict the likelihood of metastasis (which accounts for 90% of cancer-related deaths) and ultimately help determine patient prognoses.

In the study, whose results were reported in June in the journal *Cell*, Scott Valastyan, a graduate student in Whitehead Member Robert Weinberg's laboratory, screened patient breast cancer samples for microRNAs with potential roles in metastasis. MicroRNAs are single strands of RNA about 21-23 nucleotides long. Within a cell, a single microRNA can fine-tune the expression of dozens of genes simultaneously. This capability could be particularly important in metastasis, a multi-step process that could be influenced by a single microRNA at several points.

The screened samples were classified as either metastatic cancer or non-metastatic cancer. After analysis, the microRNA miR-31 stood out because of its inverse correlation with metastasis. In samples where a patient's original tumor had not metastasized, the cancer cells retained high levels of the microRNA. But where the tumor had metastasized, the cancer cells came to possess lower levels of miR-31.

The functional role of miR-31 in metastasis regulation was then confirmed in mice. When Valastyan removed miR-31 from normally non-aggressive breast cancer cells and implanted those cells into mice, the cells formed highly aggressive tumors. Mice injected with



STOPPING THE SPREAD In the muscle tissue samples above, cancer cells in mice expressing higher levels of microRNA-31 (miR-31) failed to metastasize (left), whereas cancer cells—the small purple dots appearing between muscle fibers—invaded the tissue of mice with low levels of miR-31 (right).

the cancer cells lacking miR-31 had 6 to 10 times more cancer cells that metastasized to their lungs than did their counterparts implanted with unmodified cancer cells.

To see how increasing miR-31 levels could affect metastasis, Valastyan introduced miR-31 into breast cancer cells that readily metastasize. After injecting these altered cells into mice, the mice had 4 to 40 times fewer metastases than mice injected with the unaltered cells.

Valastyan says that quantifying miR-31 levels in a patient's cancer cells could one day support a more accurate prognosis. Currently, breast cancers are divided into three major categories, two of which are typically associated with poor prognoses.

“This microRNA seems to be quite unique, in that it seems to provide some prognostic utility across these existing subclassifications [of cancers],” says Valastyan. A better-defined prognosis could help patients determine whether they might benefit from poorly tolerated cancer therapies.

In addition, miR-31 could be a useful target for cancer therapy. Weinberg, who is also a professor of biology at MIT, is cautiously optimistic. “At present, it's quite difficult to inhibit the action or promote the actions of a microRNA in a whole organism,” he says, “but in the future, microRNAs like this one might prove to be very important in altering the clinical progression of a tumor or causing it to revert to a more benign state.” **P**

In collaboration with the Sur lab to test how IGF-1 might affect these mice, Giacometti administered to two-week-old Rett mice daily injections of IGF-1 fragment. At six weeks, treated mice were significantly more active, had more regular breathing, and had more normal, regular heart rhythms than did untreated mice. In addition, the brains of treated mice were heavier and showed

more nerve cell spines.

“Although the treated mice get better and their symptoms don't progress as fast as they normally would, the treated mice still get the symptoms. So it's definitely not a cure, but it could be a co-therapy,” Giacometti says.

Sur is also excited by the prospect of finding a drug treatment for Rett syndrome and

other forms of autism. IGF1 is approved by the US Food and Drug Administration (FDA) to treat severe IGF-1 deficiency. “This represents a way forward towards clinical trials and a mechanism-based treatment for Rett Syndrome. We very much hope our research can offer some help for the patients who have this terrible disorder.” **P**

DOCTORS IN



CHRISTINA SCHEEL

DEGREE MD MEDICAL SCHOOL University of Muenster, Germany CURRENT POSITION Postdoctoral fellow

Although she grew up in Germany surrounded by medicine (as a toddler, her playpen was set up in an office at her father's medical practice), Scheel began to question her intended career path during her first year of medical training, which is equivalent to the first undergraduate year at an American college or university.

"I was so frustrated because it was all so theoretical and removed from what got me interested in medical school in the first place," says Scheel. "On top of that, I always felt drawn to biomedical research, and was looking for opportunities to get into that. But it wasn't really an option."

At that time in Scheel's native Germany, there was no MD/PhD track and basic research opportunities were quite limited for medical students. Scheel's lab prospects were dim. During a train ride, Scheel struck up a conversation with an American professor who was traveling to a conference in Germany.

"I expressed my frustration to him—how I'd love to work in a lab and get some practical experience, but nobody wants a medical student in their lab for a summer," laughs Scheel.

Scheel was ecstatic when the professor, Dr. Peter Gresshoff of the University of Tennessee, Knoxville, invited her to study Bermuda grass in his lab between semesters.

"After that, I was hooked on cell and molecular biology," says Scheel. "Everybody in medical school thought I was completely insane. But I

also thought I might as well stay in medical school and use some of that knowledge for research."

Before she began her clinical rotations and her final year of medical training, Scheel applied to be a postdoctoral researcher in Whitehead Member Robert Weinberg's lab, an application she made against the advice of many of her professors.

"I was told that if I did this postdoc, I'd screw up my entire career," says Scheel. "Some of the profs who I knew through clinical work even refused to write me recommendation letters."

But by the time she began her first clinical rotation, she had already accepted the postdoc position at Whitehead.

"I really don't want to say I did it against all odds because I was blessed with several great mentors supporting my research extravaganza, including Dr. Gresshoff and my thesis advisor, Dr. Christopher Poremba in Muenster, but

I hope that now it is different, that medical students are more encouraged to do research," says Scheel. "During my time as a medical student, research was always this crazy extracurricular fancy that I was embarking on. Yet I feel that for my life, for my professional development, that 'fanciful stuff' on my CV helped me most, because I got so much more out of an otherwise quite dry and theoretical medical school. And I gained the most from that 'stuff' because now I'm here."



THE HOUSE

BY NICOLE GIESE

Within Whitehead Institute's laboratories—among the many postdoctoral researchers launching their careers, graduate students pursuing advanced degrees, and undergraduates gaining early hands-on experience—is a cadre of scientists bringing unique perspective to biomedical research.

They are the medical doctors, MDs and MD/PhDs, driven to find connections their basic scientific discoveries may one day have for patients in the clinic. Not all have practiced medicine or ultimately plan to. But all have accepted manifold personal and professional challenges along the way, believing that their additional medical training might better equip them to make real differences in their chosen fields.

These are some of their stories.

DUNCAN KUHN

DEGREES ScB, MD MEDICAL SCHOOL Harvard-MIT Health Sciences and Technology RESIDENCY Internal Medicine

FELLOWSHIP Infectious Disease, Pulmonary and Critical Care Medicine CURRENT POSITION Senior Research Associate,

Whitehead Institute; Pulmonologist and Intensivist at Falmouth Hospital

For Kuhn, discoveries in the lab alone aren't sufficient motivation. He needs inspiration from his clinical work, too.

"Doing pure research was not quite the right thing for me," says Kuhn. "And honestly, I fell into medical school because someone else I knew was applying, and I thought, 'Well, this seems like a good idea.'"

Kuhn joined the Harvard-MIT Health Sciences and Technology program to get his medical degree. The interdisciplinary program's research emphasis fit Kuhn to a T.

"I have a fascination with biology, but I really like seeing patients," Kuhn says. "And I like the interplay between the two things. Intellectually, it's stimulating. And it's good for your sanity to break up a slump in the lab with clinic days. And vice versa."

However, he concedes that finding funding to support his research occasionally challenges his sanity. The National Institutes of Health (NIH) offers some grants specifically for medical doctors who want to further their research education. One in particular is the "Mentored Clinical Scientist Development Award," which is better known as the K08. This



grant funds up to five years of research education and laboratory work to "support the development of outstanding clinician research scientists," according to the award's application form. Over the past 10 years, securing K08 funding has gotten tougher.

"Getting the K08 traditionally used to be, from what I understand, kind of an automatic thing," says Kuhn. "But it's gotten much more difficult. Nobody gets that grant on the first pass, generally. People are worried now, because you can only apply for this grant twice."

Even applying for the grant can be difficult. Between working nearly full time in the lab in addition to working in the clinic, physicians who are already stretched thin find little time to fill out a detailed report outlining the next five years of their lives. Funding challenges, coupled with the possibility of earning three times as much in private practice often lure many clinicians away from basic research. But for the moment, Kuhn has no plans to vacate either the laboratory or the clinic.

"It can be the best job in the world, if you like it. And I can't imagine doing anything else," he says.

Everybody in research told me that if they could do it over, they would all study medicine because they were missing that human physiology or patient dimension...

ANDREAS HERRLICH

LUKE WHITESSELL

DEGREE MD, MPhil in Pharmacology GRADUATE SCHOOL Cambridge University MEDICAL SCHOOL Johns Hopkins

RESIDENCY Children's Hospital, Boston FELLOWSHIP National Cancer Institute CURRENT POSITION Research Scientist

Whitesell's interest in cancer comes from his father, a general surgeon. During the 1960s and 70s, his father spent much of his time removing breast and colon cancers from patients, then the only effective treatment for solid tumors. Chemotherapy was in its infancy.

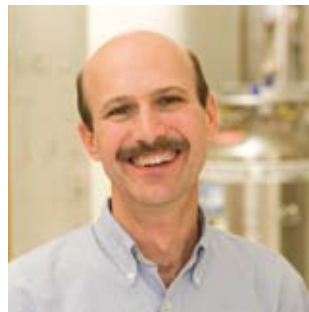
"It definitely impressed me that if more patients were to be cured, it was essential to have medicines that could take care of the problem after removing much of the tumor," says Whitesell.

After majoring in biology at Harvard University, he earned a Master's degree in pharmacology with plans for a career in medical research. He soon found working in a lab just wasn't enough.

"I learned a lot about what I was specifically working on, but not much about the broader context," says Whitesell. "So that's what led to my interest in doing medical school as well."

During medical school and residency, Whitesell spent time in Kenya studying and treating tropical diseases. He grew frustrated by the bureaucracy surrounding international health programs and so turned back to oncology. He went to the National Institutes of Health for a fellowship in pediatric oncology and molecular pharmacology before joining the faculty at the University of Arizona, teaching medical students, running a research lab, and treating children with cancer.

"It was a lot," he says. "It was good while I was younger."



After 10 years at Arizona, Whitesell took a six-month sabbatical in Whitehead Member Susan Lindquist's lab pursuing projects he had only dreamed about. But he couldn't continue his research while on faculty at Arizona. He went back for a year before returning to the Lindquist lab on a fellowship from the Radcliffe Institute for Advanced Study at Harvard.

"That cemented things, and I decided I wasn't going back," he says. After being granted another one year-leave of absence, he finally resigned from the University of Arizona to remain working at Whitehead. Today he studies so-called heat shock proteins, intent on developing truly novel cancer therapies. Although he admits he misses treating his young patients, he is not currently practicing medicine.

"I came to the conclusion that if I wanted to do both (research and clinical care), I'd end up doing both poorly," says Whitesell. "I'd rather do one thing well at a time. I've rationalized the decision by thinking I will do research as long as it continues to be interesting and productive. Then I will return to clinical work, I imagine."

Despite his absence from the clinic, Whitesell says that his medical background contributes to the Lindquist lab in useful ways.

"Each person—and each type of doctor—has his or her own expertise," he says. "Having physician-scientists, basic science postdocs, and grad students in the lab makes for a much richer environment. It takes our lab meetings and discussions to a much higher level."



ANDREAS HERRLICH

DEGREES MD, PhD GRADUATE SCHOOL Freie Universität Berlin MEDICAL SCHOOL Freie Universität Berlin

RESIDENCY Johns Hopkins University FELLOWSHIP Massachusetts General Hospital/ Brigham and Women's Hospital (Nephrology)

CURRENT POSITION Attending physician in the Renal Division at Brigham and Women's Hospital; Instructor at Harvard Medical School; Visiting Scientist

When Herrlich was struggling with the decision to study biology or medicine, he asked a slew of biological researchers and physicians for advice and opinion.

“Everybody in research told me that if they could do it over, they would all study medicine because they were missing that human physiology or patient dimension to gauge what is important and what is the connection between research and the bedside,” says Herrlich. “So I decided to go into medicine, not to become a physician, but to become a better researcher. To my good luck and excitement, I was good at medicine and enjoyed it a lot.”

Now that he's working in both Whitehead Member Harvey Lodish's lab and in the clinic, the drawbacks of working in the two fields are having an impact.

“As an MD doing research, you're doing research seventy to eighty percent of the time, whereas your PhD colleagues do it 100% of the time. So, your research competes with the PhDs' research for grants,” Herrlich says. “That presents a difficulty. Nobody is going to give you credit for time spent practicing medicine when you send your grant in.”

Despite the competition, Herrlich says his medical background is beneficial for his research and for his lab mates.

“I notice it at every lab meeting, when I see my PhD colleagues struggle with understanding the full dimension of their projects. They are missing the human physiology background that could be very useful for interpreting some of their data,” he says. “Of course, there are also examples where PhDs know more than I do, obviously. So it's a give and take. They learn, I learn.”

“Still, my research is very much influenced by my experiences in the medical field,” he continues. “I've chosen to work on a very basic cellular mechanism that is very important in a number of major diseases, like cancer, heart failure, and Alzheimer's disease. It's all the same mechanism, just different proteins that get treated the same way by this mechanism that I'm studying. And so that medical context is why I'm interested in my project.”



SANDRO SANTAGATA

DEGREE MD, PhD GRADUATE SCHOOL Mount Sinai Graduate School of Biological Sciences

MEDICAL SCHOOL Mount Sinai Medical School RESIDENCY Brigham and Women's Hospital

FELLOWSHIP Neuropathology, Brigham and Women's Hospital CURRENT POSITION Instructor, Harvard Medical School

Here's a quick summary of the past 20 1/2 years of Santagata's life:

Four years to complete his undergraduate work as a neuroscience major. Then directly to medical school for two years. Six years for a PhD. Two years of residency completed in 52 straight weeks followed by a one year internship in medicine. Two years training in anatomic pathology and two more years training as a neuropathology fellow. The past 2 1/2 years as a junior attending neuropathologist at Brigham and Women's Hospital in Boston, an instructor at Harvard Medical School, and a Visiting Scientist in the lab of Whitehead Member Susan Lindquist.

And yet, Santagata still needs to put in about two more years of research before he gets his own lab, which means he's roughly eight years behind someone with a PhD who has been pursuing a basic research career exclusively.

"The length of training to be an MD/PhD is one of the biggest problems," says Santagata. "Just the fortitude that one needs to have just to continue to do this... because there are a lot of other attractive things to do outside of this that one perceives as being easier to achieve."

Not everyone makes it through this long, rigorous process.

"Many of my colleagues are no longer doing this," he says. "Even the ones who are very talented at science don't do this anymore."

In fact, Santagata's own fortitude was challenged at one point.

"I almost didn't go back to finish my clinical studies, but I thought having a perspective from being grounded in clinical work would be very helpful," says Santagata. So he endured, and is now happy he did.

"There's great joy to be able to, I think, to do work that's not boring, that's very exciting and stimulating on a regular basis. And to do something that's not been done before and apply that to human health in a very practical way, that's very exciting. But it takes a lot of training, sacrifice, and perseverance to get to the point where you can even begin to entertain the possibility of doing those things. It takes people who are very determined."

I almost didn't go back to finish my clinical studies, but I thought having a perspective from being grounded in clinical work would be very helpful.

SANDRO SANTAGATA

ALAN MULLEN

DEGREE MD, PhD GRADUATE SCHOOL University of Pennsylvania, Immunology Graduate Group MEDICAL SCHOOL University of Pennsylvania School of Medicine RESIDENCY Massachusetts General Hospital FELLOWSHIP GI Unit, Massachusetts General Hospital CURRENT POSITION 4th year Clinical/Research Fellow, GI Unit MGH and Visiting Scientist, Whitehead Institute

Mullen is a master juggler.

The first ball he tosses into the air is his Whitehead research.

"I'm doing a lot of work mainly with human embryonic stem cells to understand some of the signaling pathways that are required for them to maintain their stem cell-ness," says Mullen, a Visiting Scientist in the lab of Whitehead Member Richard Young. "And then trying to understand how the signaling pathways change during early differentiation."

Next up is his clinical rotation (clinic schedule or clinical duties instead of rotation).

As a gastroenterology fellow at Massachusetts General Hospital, Mullen is "in the clinic all day on Thursdays. I split my time between endoscopies in the morning and seeing patients in the afternoon."

Mullen keeps both of these balls in the air with relative ease.

"I like working in both the lab and clinic," he says. "But despite the frustration of not being in the lab for a whole day, it's nice sometimes to switch and focus on a completely different set of problems. I enjoy seeing patients, doing procedures, and the occasions when I can make a diagnosis and concretely say, 'This is your problem. This is how we're going to fix it.'"

But his life is more complicated than just the lab and the clinic. Ball number three comes in the form of his equally accomplished spouse.

"My wife is an MD/PhD, too," says Mullen. "At Brigham and Women's Hospital, she's a hematopathology fellow—she examines blood and tissue samples to diagnose blood diseases like leukemia and lymphoma."

Mullen's wife, Mary (Marian), is primarily interested in clinical work. Her secondary focus is hematopathological research. "It might be a more sane way to balance the clinic and research because she doesn't want to run her own lab," says Mullen with a smile.


For them, family time is particularly important because of the final ball: their daughters, ages 4 and 1.

"It's hard because there's only so much time, and we have to prioritize," he says.

The girls are in day care during the week. Alan drops them off and Marian picks them up. Except for Thursdays, his clinic day, when his wife or mother-in-law picks them up.

"We try to leave weekends open to be with the girls, but I hit the lab during naps or evenings."

Although their schedules are tightly regimented, Mullen admits that there are some advantages to having a spouse who is also an MD/PhD.

"If she's on call or I have to go in on the weekend to start a 24-hour experiment, we both understand and are sympathetic with each other." 



GROUP EFFORT Postdoctoral scientist Andrew Grimson, bioinformatics scientist George Bell, and graduate student Robin Friedman (pictured left to right) joined forces to give TargetScan the capacity and usability it boasts today.



Whitehead scientists team up to create a software tool helping biologists around the world predict the behavior of microRNAs

Whitehead Member David Bartel is many things: a cutting-edge researcher of microRNAs, a Howard Hughes Medical Institute investigator, even a pretty decent volleyball player.

But ask him to develop and maintain a user-friendly resource for communicating and displaying hundreds of thousands of gene-regulatory interactions, and he knows his limits.

“To build a Web site that any biologist could use, that is comprehensive, easily updated, takes advantage of genome databases and other microRNA databases... that is a huge amount of work,” says an appreciative Bartel. “I don’t see any way we could have done that without the people in Whitehead’s Bioinformatics and Research Computing (BaRC).”

Back in 2001, the study of microRNAs was really taking off. First found in the roundworm *Caenorhabditis elegans* eight years earlier, hundreds of microRNAs were popping up everywhere—in worms, insects, mice, humans, and even plants.

With the discovery of these many small RNAs that help the cells regulate their genes, a key question became, which genes are regulated by each microRNA. Together with a student, Matt Rhoades, Bartel was quickly able to answer this question in plants. In plants, each microRNA regulates just a few genes, and these regulatory targets were relatively easy to find. But in animals, finding microRNA targets was much more challenging.

The first breakthrough for predicting targets in animals came when working in collaboration with MIT computational biologist Christopher Burge. A graduate student, Benjamin Lewis, created a computer program that could scan human, mouse, and rat genomes for potential microRNA targets. Lewis’s work predicted microRNA targets based on their conservation between species. This approach rests on the principle that because microRNAs are important regulators of protein production, their targets are likely to be conserved by natural selection from generation to generation and from species to closely-related species. For example, if Lewis found that a microRNA was predicted to target the equivalent genes of human, mouse, and rat, he expected it to be a functional target. A similar strategy was used to gain insights into how microRNAs recognize their targets. Thus, in 2003, was born TargetScan, version 1.

by Nicole Giese

Sometimes it's tricky because a biologist can say something in a single sentence that takes a thousand lines of code to actually execute. GEORGE BELL, BIOINFORMATICS SCIENTIST

In January 2005, Lewis launched a newly refined version of TargetScan with a much more sensitive method of predicting microRNA targets, thereby increasing the number of targets to the point that they could no longer be displayed in a simple spreadsheet.

Bartel had always viewed TargetScan as a living, evolving resource, but the mushrooming research on microRNAs and the increasing number of organismal genomes available for scrutiny threatened TargetScan's long-term viability.

"We realized that our list of predicted targets was becoming more and more complex, more unwieldy," says Bartel. "And we needed a way for the scientific community, including people who aren't experts in computational biology, to easily access all of the data."

After contemplating hiring a programmer to redesign and maintain TargetScan, Bartel decided to work with BaRC. Fran Lewitter, Director of BaRC, thinks that was a wise decision.

"You can't expect one person to have expertise in everything needed to develop and maintain TargetScan—user interface, database design, and software development," she says. "BaRC as a team includes individuals with expertise in these different areas and who collectively have built a robust website."

During 2005 and early 2006, BaRC revamped almost all of TargetScan. Although the user interface was the most visible change, the guts of the program, including its database and operating software code, were also overhauled.

Everyone on the six-person BaRC team has contributed to TargetScan over the years, but Senior Bioinformatics Scientist George Bell has worked most closely with the Bartel lab, in particular graduate students Kyle Kai-How Farh and Robin Friedman and postdoctoral researcher Andrew Grimson. During the redesign, Farh and Grimson took different, complementary approaches to identifying microRNA targets. In some of their earlier work, they had found that the majority of targets responding to microRNAs are not conserved between species. So instead of focusing on conservation, they examined large amounts of experimental data for patterns indicating which potential targets would respond to the microRNA.

"The idea was to integrate the five major patterns that we found into one model, the Context Score Model, or efficacy model, that is capable of looking at potential targets and saying whether they will work or not," says Grimson.

Friedman, who took over the work on conserved microRNA targets from Lewis, believes both the conservation model and the efficacy model are important ways to identify potential microRNA targets.

"Just because a microRNA target is proven experimentally to work, doesn't mean it confers a selective advantage to the organism," he says. "At the same time, a microRNA target may not be very effective experimentally, but it may be effective enough to confer an advantage on the organism and to be conserved. Efficacy and conservation are distinct, but related, questions, which is why they are both useful."

To integrate the efficacy model into TargetScan, Farh wrote the algorithms and analysis code and presented them to Bell. But Bell couldn't

easily insert the code into the redesigned TargetScan infrastructure. So he created new analysis code and added a new feature to TargetScan's display—the Context Score.

"Sometimes it's tricky because a biologist can say something in a single sentence that takes a thousand lines of code to actually execute," says Bell, smiling. "The Context Score was an example of that."

The redesigned TargetScan was unveiled in June 2006. It featured Lewis's original findings, Farh and Grimson's new Context Score, and a more intuitive user interface. Behind the scenes, a flexible database organized the data in a way that was easy to update and expand. TargetScan was now ready to keep pace with the burgeoning field of microRNA research—and none too soon.

The biggest challenge for TargetScan's software and design came last year. Friedman, who is also a joint graduate student with the Burge lab, created an iteration of TargetScan that includes Friedman's more detailed analyses to predict conserved microRNA targets, the probability that a microRNA site has been conserved, and a massive expansion in the number of included genomes, from five to 23. To deal with all of those additional genomes, Friedman rewrote the methods to identify potential conserved microRNA targets. Although the 18 new genomes added vastly more complexity to TargetScan, Bell's design took all of the changes in stride.

"It's kind of adaptable and we can add to it," says Bell. "But our code and the way the data is organized is getting more and more complicated. All of us want to make sure that it's not growing in such a haphazard way that it ends up being a giant mess that's hard to figure out and impossible to maintain. That's one of the challenges for us."


In the meantime, though, all of this hard work is paying off.

"My perception of how TargetScan is used in the wider community, is that it's used a lot now and that wasn't always true," admits Grimson. "What changed it wasn't necessarily our scientific improvements, but Bell and BaRC coming up with a really nice, robust database and Web site. I shouldn't have been surprised, but making the access easy, usable, and reliable seems like it made the biggest difference in the community's adoption of TargetScan."

Madhu Kumar, a graduate student in Tyler Jacks's lab at the Koch Institute for Integrative Cancer Research at MIT, agrees.

"Since I started using it in June of 2005, it's become a lot easier to use," he says. "It's so user-friendly that I use it a couple times a month, like when I read about an interesting cancer-related gene in a journal. I'll look to see what putative microRNAs would target it."

But for Kumar, the data behind that nice user interface is even more important.

"I go to TargetScan because it's pretty clear that, among the different target prediction programs, I'd say its predictions are the most reliable," he says. "If TargetScan makes a prediction, you can design experiments along those lines, and you'll have the best chance of those predicted targets being real. And the Bartel group is constantly adjusting the prediction parameters and seeing whether that leads to better results. It's a work in progress, but that's a good thing because it's always getting better." 

Community

REDDIEN NAMED HHMI EARLY CAREER SCIENTIST

The Howard Hughes Medical Institute (HHMI) has awarded Whitehead Member Peter Reddien an Early Career Scientist appointment, a six-year funded position that allows him to pursue his innovative biomedical research.

Reddien, who investigates regeneration in planaria flatworms, was selected from a pool of more than 2,000 applicants to become one of HHMI's first 50 Early Career Scientists.

"I am thrilled to receive the HHMI Early Career Scientist position," says Reddien. "HHMI has a remarkable history of supporting innovative and creative science, and I am honored to have the future work of my laboratory supported by HHMI."

The selected scientists have been running their labs for between two and six years, a critical period in their careers when they tend to be more creative and adventurous in their work, but are also saddled with the stressful and time-consuming search for grants and other funding. All award recipients work in basic biological and biomedical research and



AN EXCLUSIVE CLUB Peter Reddien is one of just 50 researchers named a Howard Hughes Medical Institute Early Career Scientist. Reddien, who is now one of five Whitehead Members supported by HHMI, was selected from a pool of more than 2,000 applicants. *Photo: Kelly Lorenz*

in areas of chemistry, physics, and computer science that are directly related to biology or medicine.

"We saw a tremendous opportunity for HHMI to impact the research community by freeing promising scientists to pursue their best ideas during this early stage of their careers," says HHMI President Thomas Cech. "At the same time, we hope that our investment in these 50 faculty will free the resources of other agencies to support the work of other outstanding early career scientists."

The prestigious appointment provides Reddien with full salary, benefits, and a total research budget of \$1.5 million over six years. Other expenses, such as research space and the purchase of critical equipment, will also be funded by HHMI.

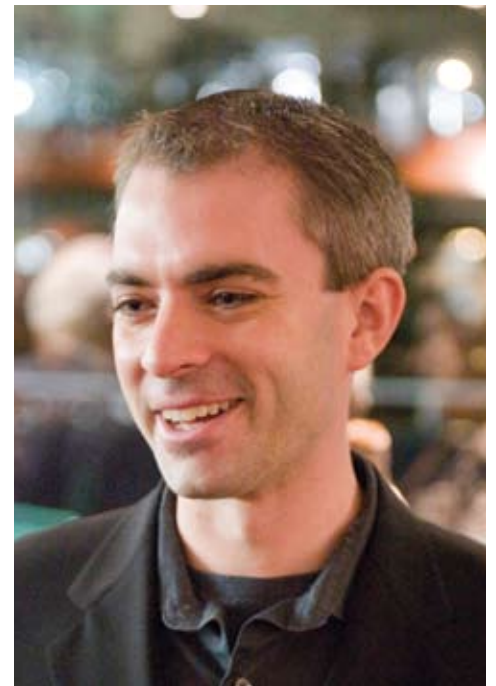
"I'm delighted that HHMI has recognized that Peter, with his rare combination of scientific fearlessness and discipline, is an ideal recipient of their support," says Whitehead Institute Director and HHMI Investigator David Page. "All of us at Whitehead and MIT congratulate Peter on being named to HHMI's first class of Early Career Scientists."

In addition to Reddien, three Whitehead alumni have received HHMI Early Career Scientist awards. They are: Kevin Eggan (Jaenisch postdoctoral researcher), Harvard University; Konrad Hochedlinger (Jaenisch postdoctoral researcher), Massachusetts General Hospital; and Brent Stockwell (Whitehead Fellow), Columbia University.

CHEESEMAN SELECTED AS A SEARLE SCHOLAR

Whitehead Member Iain Cheeseman is one of 15 young scientists nationally to be selected as a 2009 Searle Scholar. Cheeseman was chosen from among a pool of 178 recently appointed assistant professors in the chemical and biological sciences. The prestigious award provides \$300,000 in research support distributed over the next three years to Cheeseman's lab.

"I am really grateful for this support and recognition from the Searle Foundation," says Cheeseman. "This award will allow us to continue focusing on our research instead of worrying about funding. It will have a big impact on the research we have planned."



WHITEHEAD TRADITION In being named a Searle Scholar, Iain Cheeseman follows in the footsteps of Members David Bartel, Terry Orr-Weaver, David Page, Peter Reddien, and Hazel Sive—all of whom were so honored early in their careers. *Photo: Justin Knight*

Cheeseman's lab focuses on deciphering how the protein complex known as the kinetochore functions in a cell undergoing cell division. In preparation for dividing, a cell copies its DNA and compresses it into bundles called chromatids. A kinetochore protein complex is integrated into each chromatid and acts like a hitch, onto which thin, strong protein filaments hook. These protein filaments, termed "microtubules," then drag the chromatids to opposite ends of the cell and partition the DNA equally between the two future cells.

"I'm really delighted that Searle has confirmed what all of us at Whitehead already knew about Iain—that he is a creative, bold, ambitious scientist with enormous prospects for the future," says Whitehead Director David Page, who was a Searle Scholar in 1989. "This award will provide him with not only valuable support, but also valuable opportunities to form strong connections with many peers and future leaders across the country."

Cheeseman, who is also an assistant professor of biology at MIT, has been at the forefront of kinetochore research, helping to identify dozens of the 80-100 individual proteins in the complex and deciphering their specific roles. Most recently, Cheeseman identified that a

collection of kinetochore proteins, called Skai, is key for the kinetochore to tightly grip protein filaments. For Cheeseman, this molecular connection between the kinetochore and the protein filaments was one of his field's great mysteries.

Cheeseman is the sixth Whitehead Member named a Searle Scholar. Others, besides David Page (1989), include Peter Reddien (2006), Terry Orr-Weaver (1988), Hazel Sive (1992), and David Bartel (1997).

Since the program began in 1981, 452 Searle Scholars have shared more than \$88,640,000 in grants. The funds that support the awards come from trusts established under the wills of John and Frances Searle.

CAMARGO ACCEPTS BOSTON-AREA STEM CELL APPOINTMENT

After four years as a Whitehead Fellow, Fernando Camargo has begun a joint appointment in the Stem Cell Program at Children's Hospital in Boston and the Department of Stem Cell and Regenerative Biology at Harvard University.



LOCAL IMPACT Former Fellow Fernando Camargo is putting his Whitehead training to work just a few miles from his old Institute laboratory in his new position in the Stem Cell Program at Boston's Children's Hospital. *Photo: Kelly Lorenz*

The Children's and Harvard programs emphasize exploring the potential of stem cells to better understand and treat human diseases.

Camargo chalks up his bright future to participating in the Whitehead Fellows program.

"The opportunity to pursue and direct my own research endeavors as a Whitehead Fellow has been immensely rewarding and enlightening," says Camargo. "My interactions with all the fantastic scientists here at the Institute have deeply impacted my way of thinking about biological problems."

Camargo's time at Whitehead was marked by frequent interactions with other labs, including those of Members Harvey Lodish, David Bartel, and Rudolf Jaenisch, enabling him to learn from their respective expertise in blood-forming stem cells, microRNAs, and cellular reprogramming. According to Whitehead Director David Page, Camargo's breadth of inter-laboratory work greatly benefited both the Fellows and other Whitehead scientists.

"It's been an enormous pleasure for me to watch Fernando develop as an investigator and launch his research," says Page. "He is a spectacular independent scientist and a highly sought-after collaborator. We're looking forward to celebrating his future achievements."

RUBINS HEADED FOR SPACE

For former Whitehead Fellow Kate Rubins, the sky is no longer the limit.

Rubins was among nine men and women selected by NASA for the 2009 astronaut candidate class. NASA announced its selections in late June after a months-long screening of more than 3,500 applications. Rubins left for NASA's Johnson Space Center in August to begin a training program that, among other things, will require her to master piloting supersonic jet aircraft and to speak Russian fluently.

"I was a bit stunned, humbled, and overwhelmed," says Rubins of her selection. "This is a very exciting time to be joining the space program."

Rubins is no stranger to adventure. Her work at Whitehead in applying cutting-edge technologies to sequence the genomes of deadly viruses with epidemic potential routinely took her to the Democratic Republic of Congo, where she



RAREFIED AIR Former Whitehead Fellow Kate Rubins has traded her lab coat for a flight suit to join NASA's two-year astronaut training program. Rubins was one of nine astronaut candidates selected from a pool of 3,500 applicants. *Photo: Kelly Lorenz*

established a lab to study human outbreaks of monkey pox. She's also experienced in handling samples of lethal Ebola and smallpox viruses in collaborations with the U.S. Army and U.S. Centers for Disease Control.

"Anyone who knows Kate knows she loves adventurous science," says Whitehead Director David Page. "Ordinarily when we speak of adventurous scientists here, they're usually content with biology. But Kate's passions for adventure and science are clearly now taking her well beyond. I suspect she'll bring the most advanced understanding of molecular biology anyone's ever brought to the space program."

"Whitehead was a fantastic place to work on scientific exploration of human biology," adds Rubins. "I will take the wonderful experiences and scientific foundation there into the next phase of discovery."

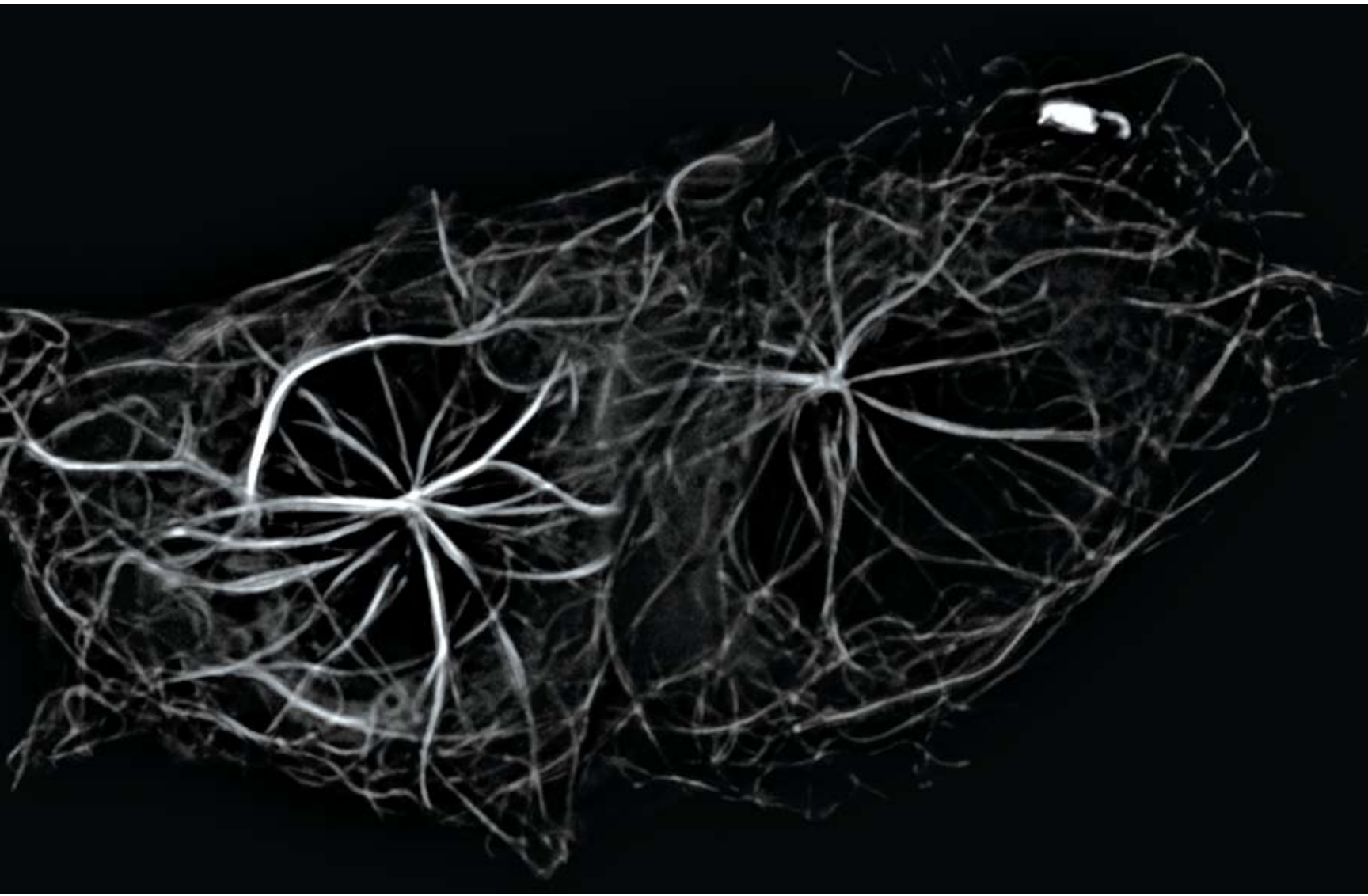
Rubins and her eight astronaut classmates have embarked on an intense two years of training in the U.S. and abroad, after which she hopes to become "mission-eligible" in NASA parlance—and to become the first Whitehead Fellow in space. **P**



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TANGLED WEB Researchers in the lab of Whitehead Member Iain Cheeseman discovered that a protein complex known as Ska1 is necessary for proper chromosome/microtubule attachment during cell division (See page 4). In the image above, Ska1 complex molecules are interacting with each other and binding onto microtubules to form a lacy network. *Courtesy Developmental Cell*