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2013 ASCB Award Essays, Selected Perspectives, and MBoC Paper of the Year

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This special 2013 ASCB Annual Meeting print edition of MBoC collects Perspectives on career choices for scientists that have appeared in the journal since August 2011 and offer readers insiders’ views of science careers away from academic research. Perspectives in this issue focus on careers in patent law, museum work, regulatory science, biotechnology, small-college teaching, grant programs, and K–12 education. Also in this special print edition are essays by seven winners of 2013 ASCB Awards and the 2013 MBoC Paper of the Year. Cover illustration by Johnny Chang.

The Philosophy of Molecular Biology of the Cell

Molecular Biology of the Cell (MBoC) is published by the nonprofit American Society for Cell Biology (ASCB) and is free from commercial oversight and influence. We believe that the reporting of science is an integral part of research itself and that scientific journals should be instruments in which scientists are at the controls. Hence, MBoC serves as an instrument of the ASCB membership and as such advocates the interests of both contributors and readers through fair, prompt, and thorough review coupled with responsible editorial adjudication and thoughtful suggestions for revision and clarification. Our most essential review criterion is that the work significantly advances our knowledge and/or provides new concepts or approaches that extend our understanding. At MBoC, active working scientists—true peers of the contributors—render every editorial decision.

The Society and MBoC are committed to promoting the concept of open access to the scientific literature. MBoC seeks to facilitate communication among scientists by

- publishing original papers that include full documentation of Methods and Results, with Introductions and Discussions that frame questions and interpret findings clearly (even for those outside an immediate circle of experts);
- exploiting technical advances to enable rapid dissemination of articles prior to print publication and transmission and archiving of videos, large datasets, and other materials that enhance understanding; and
- making all content freely accessible via the Internet only 2 months after publication.

Statement of Scope

MBoC publishes studies presenting conceptual advances of broad interest and significance within all areas of cell biology, genetics, and developmental biology. Studies whose scope bridges several areas of cell and developmental biology are particularly encouraged. MBoC aims to publish papers describing substantial research progress in full: Papers should include all previously unpublished data and methods essential to support the conclusions drawn. MBoC will not, in general, publish papers that are narrow in scope and therefore better suited to more specialized journals, merely confirmatory, preliminary reports of partially completed or incompletely documented research, findings of as yet uncertain significance, or reports simply documenting well-known processes in organisms or cell types not previously studied. Methodological studies will be considered only when some new result of biological significance has been achieved or when introduction of the method will significantly accelerate progress within a field.

Note that MBoC places a premium on research articles that present conceptual advances of wide interest or deep mechanistic understanding of important cellular processes. As such, articles dealing principally with describing behavior or modification of specific transcription factors, or analysis of the promoter elements through which they interact, will not generally be considered unless accompanied by information supporting in vivo relevance or broad significance.
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MBcPc PAPER OF THE YEAR
Visualization of actin filaments and monomers in somatic cell nuclei
Want 20,000 eyes focused on your next publication?

David G. Drubin
Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, CA 94720-3202

Molecular Biology of the Cell’s (MBoC’s) electronic table of contents is delivered to more than 10,000 subscribers, including essentially all American Society for Cell Biology (ASCB) members. This means that when you publish in MBoC, more than 20,000 eyes will focus on your work! If you are a cell biologist, these eyes belong to the readers who are arguably the most relevant target audience for your research. So what are you waiting for? Submit your next manuscript to MBoC, where it will be evaluated fairly and expeditiously and will have high visibility by cell biologists when published.

Because MBoC exists to serve cell biologists, we are not looking for reasons to reject manuscripts. Rather, we endeavor to guide authors toward a successful outcome (manuscript acceptance) by providing objective evaluations, constructive feedback, and clarity on which improvements are required. Isn’t this how the manuscript review process should work?

Furthermore, because we refuse to bow down to the journal impact factor, we do not consider in our decision process how many citations they will attract. Fine examples of such Features articles can be found in this special 2013 ASCB Annual Meeting edition. This collection, edited by Features editors Bill Bement, Doug Kellogg, and Keith Kozminski, includes thought-provoking essays by ASCB award winners, whose important discoveries and exceptional service have inspired us all. Also included in this issue are several Perspectives focused on careers. The Perspectives by Doyle and Vale, Sandquist et al., and Yu, along with several that we have published previously (Zatz, 2011; Belmont, 2013; Fields, 2013; Machin, 2013), provide thoughtful firsthand perspectives on diverse career paths pursued by PhD cell biologists, as well as fascinating behind-the-scenes looks at what it is actually like to hold one of these positions.

This year, the ASCB’s executive director Stefano Bertuzzi and I were proud to share the SPARC Innovator Award (www.sparc.arl.org/initiatives/innovator) with Mark Patterson, Bernd Pulverer, Mike Rossner, and numerous other journal publishers and editors who came together at the 2012 ASCB meeting to develop the San Francisco Declaration on Research Assessment (DORA; www.ascb.org/SFdeclaration.html). DORA challenges the obsession of many scientists, journals, administrators, and funding agencies with journal metrics, such as the journal impact factor, and advocates for a cultural change in which research articles are assessed based on their content, rather than on where they are published. The SPARC Innovator Award recognized the authors of DORA for “working to challenge the status quo in scholarly communication for the benefit of researchers, libraries, universities and the public." You can add your support to the DORA movement by signing the declaration here: http://am.ascb.org/dora/index.php/sign-the-declaration. MBoC and the ASCB will be hosting a special panel discussion about DORA at the 2013 ASCB Annual Meeting.

REFERENCES
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And be sure to visit the ASCB Journals booth (201) for opportunities to meet with Editorial Board members and learn about *Molecular Biology of the Cell* and *CBE—Life Sciences Education*.
A chemist building paths to cell biology

Douglas B. Weibel
Departments of Biochemistry, Chemistry, and Biomedical Engineering, University of Wisconsin–Madison, Madison, WI 53706

ABSTRACT Galileo is reported to have stated, "Measure what is measurable and make measurable what is not so." My group's trajectory in cell biology has closely followed this philosophy, although it took some searching to find this path.

BUILDING A PATH TO CELL BIOLOGY

I am honored to receive the 2013 ASCB Early Career Life Scientist Award. Readers will remember a similarly titled essay written by Gia Voeltz and Iain Cheeseman, previous winners of this award—"Building a Path in Cell Biology" (Voeltz and Cheeseman, 2012). I likewise reflect on my journey into cell biology research: my divergence from my formal training as a chemist and informal education as an engineer. My entry into cell biology was rapid and disruptive; I was a chemistry postdoc with George Whitesides in 2004 when a collaborator encouraged me to apply to attend the physiology course at the Marine Biological Laboratory (MBL) at Woods Hole. I hadn't heard of the course, and my only familiarity with Woods Hole came from the deep-sea submersible Alvin (which was from the Woods Hole Oceanographic Institution, not the MBL). Whitesides graciously encouraged me to apply to the 2005 course. I did so and, to my surprise, was accepted. My participation in this course proved to be one of the most important events in my career, and I wish to share my experience with emerging (and emerged) cell biologists.

The 2005 physiology course was a seven-week experience in experimental cell biology under the direction of course directors Tim Mitchison and Ron Vale. The course, now more accurately named Physiology: Modern Cell Biology Using Microscopic, Biochemical, and Computational Approaches, consisted of one week of rotations in core experimental cell biology techniques in cell biology and biochemistry, followed by three, two-week-long research projects in small teams consisting of students, course faculty, and their research assistants.

Science

The 2005 course provided a broad and diverse introduction to cell biology. It covered topics spanning prokaryotic and eukaryotic cell biology and placed a strong emphasis on applying quantitative approaches to experimental biology. In fact, the first week of the course included a weeklong primer in MATLAB and an opportunity to discover how to apply it to analyze, interpret, and quantify experimental data. We wasted no time conducting imaging experiments using marine organisms, and I recall the awe (and, to be honest, some embarrassment at my naiveté) I felt when, for the first time, I watched the process of fertilization and early development of a sea urchin unfold. Those feelings of wonder surfaced repeatedly throughout the course, and I soon learned to see each experience as a cool new opportunity. These experiences included (but were by no means limited to) 1) collecting sea urchins and isolating sperm; 2) performing small interfering RNA studies in Caenorhabditis elegans; 3) learning how to really use a microscope: calculate the limitations of a particular electron-multiplying charge-coupled device and fit the point-spread function back onto the data to increase the resolution of the image; and 4) learning how to take a microscope apart and put it back together. I worked on a range of projects, each with different course faculty. With classmate Ian Schneider and faculty

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Shahid Khan and Ron Vale, I studied the blue-light response of *Escherichia coli* cells. With course faculty Clare Waterman and classmate Andrea Stewart, I studied the dynamics of proteins in mouse fibroblast focal adhesions. With course faculty Tony Hyman and classmates Chi Pak and Léa Trichet, I studied proteins that alter *C. elegans* embryo dynamics during the early stages of development.

The pace of the course was ferocious, and the intensity level was set high to accomplish meaningful science in a short time frame. We pulled sofas into the lab for recovery between 24-hour experiments; rediscovered that, when tired enough, napping on a cement floor is comfortable; and embraced a work-hard, play-hard attitude (Figure 2). It was common for students to dash outside for a swim or to go sailing between experiments, to play pranks on coworkers, or to spontaneously break out into a late-night dance party in the lab. One unfortunate classmate developed stress-induced shingles from his intense work ethic. I was physically and mentally drained and simultaneously euphoric when the course ended. In addition to learning the ins and outs of cell biology, I learned to identify important questions and to use modern cell biology approaches to study them.

Environment

The environment for the MBL—rustic Woods Hole, Massachusetts—is a grand part of the physiology course. It can be difficult to imagine a cutting-edge biological research station located in this part of the state. Beautiful beaches, harbors, and woods surround the MBL, and the town has the slow pace of a coastal New England town. In
the summer, however, the campus percolates with energy and ideas as scientists from all over the world converge on the MBL to populate nearly a dozen courses and many research labs. During any week, a broadly inclined scientist can find multiple talks by world experts in areas of science ranging from microbes to neuroscience. The level of camaraderie at the MBL is high, and students and scientists from different courses and labs meet each other (through sports, eating together, partying) and become fast friends. Local families join MBL scientists for weekly science colloquia on a range of biological topics. Importantly, the MBL has a rich tradition of biological discovery both past and present, and participating in the physiology course enables one to be part of that tradition.

BUILDING A PATH IN CELL BIOLOGY

The physiology course changed my scientific trajectory and shifted my equilibrium slightly away from chemistry and engineering and toward cell biology. We currently use chemical and engineering techniques to study cell biological phenomena in bacteria, with a particular interest in how bacteria control protein localization in space and time. As we pursue questions in this area, we benefit from collaborations with outstanding cell biologists (too many to name here—you know who you are!). As outsiders in the field of cell biology, we have a pragmatic view of our capabilities and have learned that collaborations enable us to penetrate deeper into the field and make sure we are asking broad and meaningful questions.

As our lab has grown, my own graduate students have attended the physiology course (under course directors Dyche Mullins and Clare Waterman), and I anticipate that future students will continue the tradition (under current course directors Jennifer Lippincott-Schwartz, Wallace Marshall, and Rob Phillips). It is safe to say that graduate students from our lab who have attended the MBL have—like myself—experienced a scientific and professional transformation. They returned to the lab with a noticeable scientific confidence, a new perspective, new skill sets, insight into how to identify and address challenging cell biological questions, and refreshed enthusiasm. They brought new ideas to the group and injected them into ongoing projects, and pushed projects in new directions. It is possible that I am imposing my enthusiasm for the course on their experiences, so I suggest you ask them yourself; I would be happy to put you in touch at the ASCB annual meeting.

Galileo is reported to have stated, “Measure what is measurable and make measurable what is not so.” Our path in cell biology has closely followed this philosophy, and, as described above, the process of navigating this field was largely facilitated by the physiology course. At the MBL, my eyes were opened to the field of cell biology, my imagination sparked, and a foundation was created for key methods our lab has developed (and is actively developing) for manipulating bacterial cells, cell walls, and membranes to study protein and lipid localization and regulation in bacterial cells. For example, using these techniques, we have demonstrated that negative curvature causes the accumulation of anionic phospholipids in membranes, which bind to and regulate a broad family of bacterial proteins. To complement these studies, we are developing a toolbox of small-molecule inhibitors of key bacterial proteins involved in division, cell wall assembly, and chromosome segregation, and are applying these tools to study these processes. As the targets of these compounds are essential, modifications to their chemical structures enable us to introduce new families of chemotherapeutic agents for antibiotic development. Confident on our path, we strive to “measure what is measurable and make measurable what is not so.”

More information on the course can be found here: http://hermes.mbl.edu/education/courses/summer/course_physio.html.

REFERENCE
Teaming up: from motors to people

Samara L. Reck-Peterson
Cell Biology Department, Harvard Medical School, Boston, MA 02115

ABSTRACT When I reflect on how I became a cell biologist and why I love being one today, one thing that comes to mind is the many terrific collaborations I have had. The science I am most proud of from my graduate and postdoctoral training would not have been possible without working in teams with other scientists. Now, in my own group, much of our best work is being done collaboratively, both within the lab and with other labs. In this essay, I will highlight my experiences working in teams as a trainee, the role teamwork has played in my own research group, and how important I think collaborative science is for the future of biological research.

COLLABORATIONS AS A TRAINEE

One of my earliest experiences with collaboration across disciplinary boundaries happened when I was a graduate student in the Cell Biology Department at Yale University, working with Mark Mooseker and Peter Novick. During the course of my PhD, work from the Cheney, Mooseker, and Spudich labs showed that single molecules of vertebrate myosin Va can take multiple steps along their tracks (Mehta et al., 1999); this was the first known example of a processive myosin motor. I wanted to determine whether this was a general property of this class of myosin, so I focused on characterizing the motile properties of the two yeast class V myosins. To pursue this goal, however, not only did I need the tools of molecular and cellular biology, which I had, but also those of biophysics, which I didn’t have. I found that the best way to learn a new field was by working closely with someone who already knew it well. One of the postdocs in the lab, Matt Tyska (now an associate professor at Vanderbilt University), was a biophysicist. Over the course of our collaboration, I learned how to analyze, quantify, and interpret in vitro motility data. Ultimately, we showed that, in contrast to their vertebrate counterparts, the yeast myosin Vs are not processive motors (Reck-Peterson et al., 2001). Exciting work from the Trybus lab later showed that
behavior, with Ahmet and Arne focusing on analyzing dynein’s stepping behavior and response to force with high precision. As a group, we discovered that single dynein molecules are processive motors that step more variably than other motors (Reck-Peterson et al., 2006) and that dynein also displays unique force-dependent stepping behavior (Gennerich et al., 2007).

There is nothing more exciting in science than being in the midst of discovery: the intense daily conversations I had with Andrew, Arne, and Ahmet about how dynein might work dramatically fueled our progress. I remember this as one of the most rewarding times of my scientific career. We all brought different skill sets to the team, which allowed us as a group to do what we could not have done alone. However, our close collaboration also posed its own challenges. I found that working closely with peers can create competition, insecurity, and anxiety about recognition. Nonetheless, despite some of the difficulties of working together on a highly competitive project, Andrew, Ahmet, Arne, and I became and remain good friends, and we all left the Vale lab with jobs that would allow us to pursue the science we loved.

COLLABORATIONS AS A PRINCIPAL INVESTIGATOR

When I started my lab at Harvard Medical School in 2007, I knew that I wanted to study intracellular transport ranging from the biophysical properties of the motors to the cell biological functions that require motor activity. As I had learned from Ron’s example, this would require an interdisciplinary team that included people with skills in single-molecule biophysics, genetics, biochemistry, and live-cell imaging. Therefore I recruited both physicists and biologists to the lab. One of the great things about pairing physicists and biologists is that they tend to approach problems from different viewpoints. The physicists tend to first ask “How does it work?,” while the biologists’ first question is often more along the lines of “Why does it matter?” This cultural tension is exciting, because it helps us define problems we might not have recognized working as individuals.

We decided to tackle some big problems. We wanted to understand how dynein steps processively (Qiu et al., 2012), how it is regulated by some of its essential cofactors (Egan et al., 2012; Huang et al., 2012), how teams of motors work together (Derr et al., 2012), and what the structural basis for dynein’s interaction with microtubules is (Redwine et al., 2012). Four of the papers that we published addressing these problems had co–first authors. All four projects also involved collaborations with other colleagues of mine at Harvard. We integrated DNA nanotechnology approaches into our studies by working closely with William Shih (Derr et al., 2012; Qiu et al., 2012) and structural electron microscopy by working with Andres Leschziner (Huang et al., 2012; Redwine et al., 2012). While a great deal of work remains before we can fully answer these four questions, I know that the discoveries we have made so far required teamwork and that our discoveries of the future will too.

Working collaboratively might be vital to success, but that doesn’t make it easy. Just as I had suffered from feelings of competition, insecurity, and worry about recognition, I saw that my students and postdocs had some of these same feelings and concerns. To
foster a culture of teamwork, I invested time in talking to my lab members about the human component of their collaborations. I listened to them and took their concerns seriously. Like any partnership, collaborations in science sometimes require an investment in making the relationship work (Figure 1). Things haven’t always been perfect, but I think we would all say that together we built a strong lab culture that values and respects teamwork. In fact, well before we had published any papers from the lab, I knew that things were on the right track when one of my graduate students came to my office and asked me, “Can I have a collaborator too?”

THE IMPORTANCE OF TEAMWORK FOR THE FUTURE OF THE BIOLOGICAL SCIENCES

While doing science collaboratively is not for everyone, I think teamwork is essential in the modern biomedical research arena. Increasingly, the types of problems that we tackle require more interdisciplinary approaches and larger numbers of people than in the past. Particularly in the culture of the United States, which prizes the individual, it will be challenging to change the ways in which we acknowledge and reward discoveries so that teamwork is appreciated. We need to recognize starred first and cocorresponding authorships as truly equal contributions (which is not always the case), and this recognition should be reflected in how we make decisions about hiring, promotions, and funding allocation. The multiple program director/principal investigator model adopted by the National Institutes of Health in 2006 was an important step toward realizing these goals.

We also need to invest in training principal investigators (PIs) how to manage teams. A decade ago, the Burroughs Wellcome Fund (BWF) and the Howard Hughes Medical Institute (HHMI) recognized the need for this type of training and developed a course, which I took, and published a book on lab management (BWF/HHMI, 2006). I’ve also taken a course run by hfp consulting (www.hfp-consulting.de), a firm specializing in teaching leadership and management skills to scientists. From these experiences, I learned a few important things about how people and teams work. For example, I learned some of the theory behind group dynamics, which has helped me to recognize how individuals within teams may perceive their roles in different ways and that this can change over the course of a project. Through personality assessment analysis, I’ve learned to recognize and appreciate different personality types, which has helped me construct teams and manage conflicts as they arise. The management skills of PIs not only affect scientific productivity but also set examples that will influence the next generation of scientists. Therefore it is important that we invest resources, both human and financial, into this type of training and make it accessible to more people.

I was deeply honored to receive the Women in Cell Biology Junior Award, and I am also grateful for the opportunity that the award provided me to reflect on the work that has brought me to this point. So much of my career thus far has critically depended on working with others, both as a trainee and now in my own lab. In the future, I will continue to encourage and facilitate collaborative science within my lab, institution, and field. I also hope to help break down the cultural obstacles we have toward recognizing and rewarding teamwork in the biological sciences.

ACKNOWLEDGMENTS

I thank Chris Patil, Julie Huang, and Andres Leschziner for conversations about the content and feedback on the writing of this essay. I also thank my mentors Mark Mooseker and Ron Vale for setting great examples of how to foster collaboration.

REFERENCES


A sustained passion for intracellular trafficking

Elizabeth A. Miller
Department of Biological Sciences, Columbia University, New York, NY 10027

ABSTRACT

I am honored to be the first recipient of the Women in Cell Biology Sustained Excellence in Research Award. Since my graduate school days, I have enjoyed being part of a stimulating scientific community the American Society for Cell Biology embodies. Having found myself largely by accident in a career that I find deeply enjoyable and fulfilling, I hope here to convey a sense that one need not have a “grand plan” to have a successful life in science. Simply following one’s interests and passions can sustain a career, even though it may involve some migration.


Elizabeth A. Miller is the recipient of the 2013 ASCB WICB Sustained Excellence in Research Award.

Address correspondence to: Elizabeth A. Miller (em2282@columbia.edu).

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AN EARLY MOVE SOUTH—WAY SOUTH

Although I was born in Princeton, New Jersey, I grew up half a world away in Melbourne, Australia. This was the direct result of the peculiarities of the academic job market, even in the mid-1970s. My father was a mathematician at Princeton’s Institute for Advanced Studies and was lured to the antipodes by an attractive offer from the University of Melbourne. I’m sure my parents expected to come back to the United States in due course, but the relaxed Australian lifestyle suited our family, and we settled permanently in Melbourne. Because I was only three years old when we moved, I developed a deceptive Australian accent that belies my New Jersey heritage!

At high school and university (both publicly funded), I followed a meandering path from biology to mathematics to psychology and back to biology. The broad education that I received as an undergraduate at the University of Melbourne, with an emphasis on systematics and evolution, built a solid foundation that frames the more molecular and mechanistic questions I ask today. Like many others, my laboratory experience was limited to prescribed classes, so my first summer of “real” research at the end of my third year was a revelation. I became fascinated by the elegant beauty of the single-celled algae that were the focus of study in Rick Wetherbee’s lab in the Botany School. I worked with a postdoctoral fellow, Jan Lind, to characterize the extracellular glycoproteins these organisms use as cellular glues (Ludwig et al., 1996). I continued this work as an “honours” student, which in the Australian system is an optional fourth year of university that allows a full year of dedicated bench research. By the end of my honors year, Rick had secured a grant from the U.S. Office of Naval Research to investigate the marine diatoms that are the primary drivers of biofouling on ship hulls. This allowed me to work as a research assistant for a year, while I considered what I wanted to do next with my life, thinking for the first time that one could actually make a living doing this fun research thing.

During my time in Rick’s lab I started to appreciate the problem of how cells move macromolecules (like those secreted glycoproteins) around in very precise ways. With this interest in intracellular protein traffic in mind, I went looking for a lab that would further my training and afford some scientific independence. I was fortunate to join Marilyn Anderson in 1995 as she moved from the University of Melbourne to La Trobe University (located in a suburb of Melbourne). I joined her small group to initiate a new project investigating the delivery of a plant defense protein, NaPI, to the vacuole in tobacco cells. We hadn’t been at La Trobe long when Trevor Lithgow joined the department, introducing me to the benefits of yeast as a model organism. Under the joint supervision of Marilyn and Trevor, I defined the vacuolar sorting signal of NaPI and identified a candidate receptor.
that likely diverts the protein from the default pathway of secretion to an endosome-like prevacuolar compartment (Miller et al., 1999). Aside from the superb scientific training I received from my advisors, graduate school was formative in other ways. Most importantly, I forged lasting friendships with my peers, including my now-husband, Marcus Lee (a fellow graduate student in Marilyn's lab), that enriched my life both at the bench and beyond.

After four years in Marilyn's lab, it was time to move on and find the next step in my own path. Inspired by both of my mentors’ fulfilling overseas postdocs (Marilyn at Cold Spring Harbor and Trevor at the Biozentrum in Basel), I sought out postdoctoral opportunities with those whose work I admired. In retrospect, my approach was very naive, and I am fortunate that I was even invited to interview with so many great labs, coming as I did from a somewhat obscure university in a distant land with (as yet) no publications to my name. Nonetheless, both Marcus and I managed to find excellent opportunities not only in the same city, but in the same lab, this time working with Randy Schekman. So, we gave away our furniture, packed our suitcases, and headed to Berkeley, California.

LIVING THE CALIFORNIA DREAM

Joining the Schekman lab was another revelation. I was suddenly surrounded by a sizable cadre of smart, driven colleagues, both postdoctoral fellows and graduate students, all of whom focused on intellectual problems that fascinated me. The lab was well-funded, and we all had enormous freedom to pursue our own questions, guided always by Randy’s own powerful and creative intellect. After a false start on a project to develop a new in vitro reconstitution assay, Randy suggested I look into the molecular function of one of the coat proteins that drives vesicle formation from the endoplasmic reticulum (Barlowe et al., 1994). Characterization of the COPII coat was pioneered in Randy’s lab, and we had in hand many genetic tools and in vitro assays that facilitated this new project. I used a combination of yeast genetics and biochemistry to delineate the COPII subunit Sec24 as the primary cargo-binding component of the coat (Miller et al., 2002). My findings dovetailed nicely with x-ray crystal structures that Elena Mossessova solved in Jonathan Goldberg’s lab, and we ended up publishing our findings in back-to-back papers (Miller et al., 2003; Mossessova et al., 2003). The panel of mutants that I generated in Randy’s lab still provides interesting new leads (Kung et al., 2012), and we continue to use the powerful approaches of yeast genetics and biochemical assays that mutually inform each other. In retrospect, my postdoctoral years seem like glorious, carefree days when I had the time, resources, and stimulating environment to simply do the very best research I could. Again, a group of like-minded colleagues, especially David Madden, Per Malikus, and Raphael Valdivia, greatly enriched both my bench and leisure lives. Yet, once again, it all too soon became time to move on.

Although the obvious “next step” after a postdoctoral fellowship is an independent faculty position (at least here in the United States), I have to confess that I didn’t necessarily see myself in that role at the end of my postdoc. I didn’t have a long-term career plan, having instead simply been driven by the joy that I derived from doing research and the desire to keep having fun. Nonetheless, I had to find a new position after several years in Randy’s lab. So I went on the job market, looking mainly in larger cities that would also afford opportunities for Marcus, who wanted to change fields and explore protein trafficking in the malarial parasite. Our “two-body problem” was solved in New York City, with Marcus joining a malaria lab on a second postdoctoral fellowship, while I joined the Department of Biological Sciences at Columbia University. Fortunately for me, it turns out that running a lab is also a lot of fun, even if I don’t get to do as much bench work as I’d like.

BRIGHT LIGHTS, BIG CITY, SMALL LAB

My lab continues to explore the molecular mechanisms of vesicle formation from the endoplasmic reticulum, focusing on how protein folding influences this process. It has long been known that misfolded or improperly assembled proteins are not captured into COPII vesicles, but the mechanism by which this quality-control checkpoint works remains unclear. This problem is central to a variety of human diseases, most notably cystic fibrosis, which is often caused by mutations in a chloride channel that cause the protein to misfold. We aimed to use yeast as a model system to probe the cellular pathways that contribute to biogenesis of a related yeast protein, Yor1 (Pagant et al., 2007). I was fortunate to receive pilot funding and a subsequent full grant from the Cystic Fibrosis Foundation, who were persuaded that we could successfully model a human disease in a genetically tractable system. My association with the Cystic Fibrosis Foundation led directly to a fruitful collaboration with John Hartman, an expert in quantitative genomics, who introduced us to the art of high-throughput screening (Louie et al., 2012). This approach has yielded a jackpot of mutants that we continue to characterize mechanistically using our biochemical assays.

It goes without saying that the success of my lab is entirely the result of the fantastic students and postdocs with whom I have worked. I am grateful to my first crop of graduate students, Ray Louie, Leslie Kung, and Mariana Dorrington, who took a chance on a green principal investigator and joined my lab when we were still unpacking boxes. One of my great mentors at Columbia, Marty Chalfie, advised me that initially I would be my own best postdoc. Happily for me, this was not entirely true, as I managed to recruit a former colleague from the Schekman lab, Silvere Pagant, who remains in the lab to this day as a senior research associate, leading our efforts on quality control of Yor1. The work of two talented postdocs, Alenka Copic and Cath Latham, opened up a new view of the problem of quality control, turning our focus to the physical properties of the vesicles themselves (Copic et al., 2012). Another dedicated student, Jenn D’Arcangelo, is well underway with her efforts to follow up on our new model, which proposes that the protein quality-control “checkpoint” is in fact a stochastic product of cargo occupancy and vesicle architecture. There are clearly many exciting discoveries for us to make in the coming years.

Along with the debt of gratitude I owe my lab members, I am also extremely thankful for the support and encouragement of many mentors over the years. In addition to my research advisors, I deeply appreciate the support of my former department chairs and perennial cheerleaders: Carol Prives, Mike Sheetz, Marty Chalfie, and Stuart Firestein. Respected colleagues Bill Wickner, Frances Brodsky, Lois Weisman, and Susan Michaelis are scientific supporters whose enthusiasm for my work is truly gratifying. Indeed, I am grateful to the many talented colleagues who study intracellular membrane traffic and contribute to the supportive nature of the field as a whole. My impression is that this collegial community is, like I am, driven by a passion for science and excited by new discoveries, whatever their sources. Finally, whatever success I have achieved professionally would not be possible without the support—both intellectually and personally—of my husband, who is an equal partner in raising our son and has made career sacrifices of his own to afford me the opportunities I’ve had.
ACKNOWLEDGMENTS
I have had the great fortune to be funded by various private and government agencies for the bulk of my career. My graduate work was supported by an Australian Post-graduate Research Award; my postdoctoral training was funded by the Jane Coffin Childs Memorial Fund for Medical Research. Early work in my lab at Columbia was funded by the Cystic Fibrosis Foundation. Ongoing work is supported by the National Institute of General Medical Sciences under award numbers GM078186 and GM085089.

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Scientific approaches to science policy

Jeremy M. Berg
Department of Computational and Systems Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213

ABSTRACT The development of robust science policy depends on use of the best available data, rigorous analysis, and inclusion of a wide range of input. While director of the National Institute of General Medical Sciences (NIGMS), I took advantage of available data and emerging tools to analyze training time distribution by new NIGMS grantees, the distribution of the number of publications as a function of total annual National Institutes of Health support per investigator, and the predictive value of peer-review scores on subsequent scientific productivity. Rigorous data analysis should be used to develop new reforms and initiatives that will help build a more sustainable American biomedical research enterprise.

Good scientists almost invariably insist on obtaining the best data potentially available and fostering open and direct communication and criticism to address scientific problems. Remarkably, this same approach is only sometimes used in the context of the development of science policy. In my opinion, several factors underlie the reluctance to apply scientific methods rigorously to inform science policy questions. First, obtaining the relevant data can be challenging and time-consuming. Tools relatively unfamiliar to many scientists may be required, and the data collected may have inherent limitations that make their use challenging. Second, reliance on data may require the abandonment of preconceived notions and a willingness to face potentially unwanted political consequences, depending on where the data analysis leads.

One of my first experiences witnessing the application of a rigorous approach to a policy question involved previous American Society for Cell Biology Public Service awardee Tom Pollard when he and I were both at Johns Hopkins School of Medicine. Tom was leading an effort to reorganize the first-year medical school curriculum, trying to move toward an integrated plan and away from an entrenched departmentally based system (DeAngelis, 2000). He insisted that every lecture in the old curriculum be on the table for discussion, requiring frank discussions and defusing one of the most powerful arguments in academia: “But, we’ve always done it that way.” As the curriculum was being implemented, he recruited a set of a dozen or so students who were tasked with filling out questionnaires immediately after every lecture; this enabled evaluation and refinement of the curriculum and yielded a data set that changed the character of future discussions.

After 13 years as a department director at Johns Hopkins (including a number of years as course director for the Molecules and Cells course in the first-year medical school curriculum), I had the opportunity to become director of the National Institute of General Medical Sciences (NIGMS) at the National Institutes of Health (NIH). NIH supports large data systems, as these are essential for NIH staff to perform their work in receiving, reviewing, funding, and monitoring research grants. While these rich data sources were available, the resources for analysis were not as sophisticated as they could have been. This became apparent when we tried to understand how long successful young scientists spent at various early-career stages (in graduate school, doing postdoctoral fellowships, and in faculty positions before funding). This was a relatively simple question to formulate, but it took considerable effort to collect the data because the relevant data were in free-text form. An intrepid staff member took on the challenge, and went through three years’ worth
of biosketches by hand to find 360 individuals who had received their first R01 awards from NIGMS and then compiled data on the years those individuals had graduated from college, completed graduate school, started their faculty positions, and received their R01 awards. Analysis of these data revealed that the median time from BS/BA to R01 award was ~15 years, including a median of 3.6 years between starting a faculty position and receiving the grant. These results were presented to the NIGMS Advisory Council but were not shared more widely, because of the absence of a good medium at the time for reporting such results. I did provide them subsequently through a blog in the context of a discussion of similar issues (DrugMonkey, 2012). To address the communications need, we had developed the NIGMS Feedback Loop, first as an electronic newsletter (NIGMS, 2005) and subsequently as a blog (NIGMS, 2009). This vehicle has been of great utility for bidirectional communication, particularly under unusual circumstances. For example, during the period prior to the implementation of the American Recovery and Reinvestment Act, that is, the “stimulus bill,” I shared our thoughts and solicited input from the community. I subsequently received and answered hundreds of emails that offered reactions and suggestions. Having these admittedly nonscientific survey data in hand was useful in subsequent NIH-wide policy-development discussions.

At this point, staff members at several NIH institutes, including NIGMS, were developing tools for data analysis, including the ability to link results from different data systems. Many of the questions I was most eager to address involved the relationship between scientific productivity and other parameters, including the level of grant support and the results of peer review that led to funding in the first place. With an initial system that was capable of linking NIH-funded investigators to publications, I performed an analysis of the number of publications from 2007 to mid-2010 attributed to NIH funding as a function of the total amount of annual NIH direct-cost support for 2938 NIGMS-funded investigators from fiscal year 2006 (Berg, 2010). The results revealed that the number of publications did not increase monotonically but rather reached a plateau near an annual funding level near $700,000. This observation received considerable attention (Wadman, 2010) and provided support for a long-standing NIGMS policy of imposing an extra level of oversight for well-funded investigators. It is important to note that, not surprisingly, there was considerable variation in the number of publications at all funding levels and, in my opinion, this observation is as important as the plateau in moving policies away from automatic caps and toward case-by-case analysis by staff armed with the data.

This analysis provoked considerable discussion on the Feedback Loop blog and elsewhere regarding whether the number of publications was an appropriate measure of productivity. With better tools, it was possible to extend such analyses to other measures, including the number of citations, the number of citations relative to other publications, and many other factors. This extended set of metrics was applied to an analysis of the ability of peer-review scores to predict subsequent productivity (Berg, 2012a,b). Three conclusions were supported by this analysis. First, the various metrics were sufficiently correlated with one another that the choice of metric did not affect any major conclusions (although metrics such as number of citations performed slightly better than number of publications). Second, peer-review scores could predict subsequent productivity to some extent (compared with randomly assigned scores), but the level of prediction was modest. Importantly, this provided some of the first direct evidence that peer review is capable of identifying applications that are more likely to be productive. Finally, the results revealed no noticeable drop-off in productivity, even near the 20th percentile, supporting the view that a substantial amount of productive science is being left unfunded with pay lines below the 20th percentile, let alone the 10th percentile.

In 2011, I moved to the University of Pittsburgh and also became president-elect of the American Society for Biochemistry and Molecular Biology (ASBMB). In my new positions, I have been able to gain a more direct perspective on the current state of the academic biomedical research enterprise. It is exciting to be back in the trenches again. On the other hand, my observations support a conclusion I had drawn while I was at NIH: the biomedical research enterprise is not sustainable in its present form due not only to the level of federal support, but also to the duration of training periods, the number of individuals being trained to support the research effort, the lack of appropriate pathways for individuals interested in careers as bench scientists, challenges in the interactions between the academic and private sectors, and other factors. Working with the Public Affair Advisory Committee at ASBMB, we have produced a white paper (ASBMB, 2013) that we hope will help initiate conversations about imagining and then moving toward more sustainable models for biomedical research. We can expect to arrive at effective policy changes and initiatives only through data-driven and thorough self-examination and candid discussions between different stakeholders. We look forward to working with leaders and members from other scientific societies as we tackle this crucial set of issues.

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E. E. Just Award Lecture

J. Victor Garcia
Division of Infectious Diseases, Department of Medicine, Center for AIDS Research, University of North Carolina School of Medicine, Chapel Hill, NC 27599

ABSTRACT

What started as a game of discovery for a child with a chemistry set has resulted in a lifetime of fulfillment and dedication to science. It is deeply rewarding to continuously let my curiosity ask questions for which there are no known answers. Equally rewarding has been the opportunity to mentor young students and postdoctorate graduates through their formative years in science.

When I was a child growing up, my parents had an orchard. In the orchard, they cultivated oranges. But my father expanded his one-man operation to other crops including corn, peppers, and tomatoes. At our house, we also had several fruit trees. At nights in the summer, I would be awakened by hard thumps on the tin roof of the building where we parked vehicles and farm equipment. These sounds indicated that either a mango or an avocado had fallen from a tree. Early in the morning, I would climb up on the roof and collect as many of them as I could. Then I would set up a small stall by the door to our house and sell my goods to passersby. When the corn was in and had dried, it would take hours to shell by hand, but it brought a great price. So what did I do with all the money I made? I bought the most amazing chemistry set! It was like magic to me. That was it for me. I was hooked. Even though neither of my parents had a formal education beyond secondary school, and no one in my family at that time had gone to a university, I wanted to be a scientist. My father worked three jobs to take care of my six siblings, my mother, and me. It was a great sacrifice to send me to college. When I first arrived there, I did not do so well. It took me a while to academically catch up with my peers, but eventually I did. The most important lesson I learned in college was to have a good work/study ethic. The second was chemistry. While I was in college, my dad died in a tragic automobile accident that killed two men and left 14 children without a father. My mother took over raising and financially supporting my siblings and me, and she set for us a very high example of success. Even though she did not have a formal high school or college education, she gave us all an education and then helped all of us to obtain postgraduate education. After completing this monumental task, and 10 grandchildren later, she ran and was elected to Congress. Did I say she has been a hard act to follow? She is my source of inspiration.

As an aspiring student of science, I was very fortunate to have outstanding mentors. By the time I arrived at graduate school, I was well prepared for the rigors of the lab. I earned a PhD in chemistry with a focus on nucleic acid/protein interactions in a tremendously rigorous program that provided me with the type of fundamental quantitative skills that have served me well the rest of my academic life. Even courses like molecular dynamics have provided me with the type of broad scientific base that is needed to work in a highly competitive discipline.

If there is one piece of advice I would give to anyone interested in a career in science, or in any other field for that matter, it would be: be flexible. Let everything around you guide you in whatever is your quest. Don’t think the answer you thought up is the correct one. It might be. Yet it might not always be the only one or the complete story. Many years ago, I heard someone say, “the truth is somewhere in the middle.” How can that be in science? Science is about precision. Absolutes. Certainty. Proof. Then I was told that I was “more interested in the middle than the truth.” In other words, many
According to estimates by the World Health Organization (WHO) and the Joint United Nations Program on HIV/AIDS, 34 million people were living with HIV at the end of 2011. That same year, some 2.5 million people became newly infected, and 1.7 million died of AIDS-related causes, including 230,000 children. BLT mice have opened numerous new lines of investigation that were not possible even a few years ago. In addition, they have contributed to our detail understanding of the complex interactions between pathogen and host. The first highly significant contribution using the BLT model was to our understanding of mucosal HIV transmission (Sun et al., 2007). Specifically, in developed countries like the United States, the vast majority of transmission events occur during unprotected anal intercourse. We therefore investigated the reconstitution with human lymphoid cells of the gastrointestinal tract of BLT mice. Our result showed that the gastrointestinal tract of BLT mice closely resembles that of humans and, in addition, that these mice (like humans), if exposed rectally, can be infected by HIV. In addition, we were able to demonstrate the critical role of cryptopatches as the essential anlagen for the development of organized immune tissue in the gut (Nochi et al., 2013). Subsequently, we found that the entire female reproductive tract of BLT mice is reconstituted with human immune cells. Vaginal HIV transmission is responsible for the majority of new HIV infections worldwide. This prompted us to determine whether human immune cells were present in the female reproductive tract of BLT mice. Remarkably, the presence of human immune cells in this tissue rendered female BLT mice susceptible to vaginal HIV transmission (Denton et al., 2008). We subsequently leveraged the fact that BLT mice are susceptible to rectal and vaginal HIV transmission to evaluate a variety of different inhibitors for their ability to prevent HIV acquisition. The results demonstrated that several novel HIV inhibitors, as well as several FDA-approved HIV inhibitors, could efficiently block both rectal and vaginal HIV transmission. Subsequently, the FDA has approved two of these agents for use in HIV prevention.

Despite the availability of numerous antivirals, every day, 1,000 children are newly infected with HIV. A significant number of these children acquire the infection via breast-feeding. Novel approaches to oral HIV prevention are urgently needed. In this regard, we have recently shown that BLT mice recapitulate key aspects of oral HIV transmission, and this information was used to test novel approaches to prevent infection. One unexpected but nevertheless very interesting outcome of these experiments was the demonstration that human breast milk has a very strong and highly reproducible innate inhibitory activity that prevents both HIV infection and its transmission (Wahl et al., 2012). These experiments addressed a paradigm in the field: If milk has an anti-HIV activity, how is it possible for infants to become infected? For this, one has to keep in mind that children born to HIV-infected mothers receive liters and liters of HIV-infected milk during their first six months of life and yet only ~1/10 become infected. Thus the results obtained in the BLT model strongly support the protective effect of milk in preventing HIV transmission and have opened up new avenues of investigation addressing the nature of the innate viral inhibitors present in human breast milk and have provided support for the WHO’s recommendation to provide breast milk to infants of HIV-infected mothers.

Now our research includes a new ambitious goal: to find a cure for HIV/AIDS. In this regard, BLT mice have proven to be an outstanding tool for discovery. BLT mice have been shown to establish the same type of HIV persistence that is observed in HIV patients treated with antiretroviral therapy (Denton et al., 2012). This provides an opportunity to use this model to evaluate novel...
approaches aimed at eradicating HIV from infected patients. Whether or not the observations made in BLT humanized mice can eventually be translated into human clinical applications has yet to be determined. Nevertheless, to date, the information obtained from experiments using BLT mice has been demonstrated to be highly relevant when making evidence-based decisions concerning which novel approaches have the best chance of success when implemented in humans and should be given priority in development pipelines.

What started as a game of discovery for a child with a chemistry set has resulted in a lifetime of fulfillment and dedication to science. It is deeply rewarding to continuously let my curiosity ask questions for which there are no known answers. Equally rewarding has been the opportunity to mentor young students and postdoctorate graduates through their formative years in science. Their curiosity and dedication inspires me, and I have learned from them as much, if not more, than I have taught. I look toward the future with the hope that together we will continue to contribute to the advancement of science in general and ultimately find a cure for HIV/AIDS. For each one of my students and trainees, I have one wish: that they will surpass anything in science that I have accomplished during my lifetime.

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A question of taste

T. J. Mitchison
Department of Systems Biology, Harvard Medical School, Boston, MA 02115

ABSTRACT A career in science is shaped by many factors, one of the most important being our tastes in research. These typically form early and are shaped by subsequent successes and failures. My tastes run to microscopes, chemistry, and spatial organization of cytoplasm. I will try to identify where they came from, how they shaped my career, and how they continue to evolve. My hope is to inspire young scientists to identify and celebrate their own unique tastes.

SCIENTIFIC TASTE AND THE ROLE OF EARLY INFLUENCES

What to work on? How to work on it? There are no right or wrong answers to these questions of taste, but our choices define our trajectories as scientists. Often, we make them early, without thinking, through the influence of opportunities and mentors who came our way as much by chance as choice. Only looking back do we realize their significance. My most important job in the past decade or two has been helping young scientists identify and develop their own tastes. Mine run to microscopes, chemistry, and spatial organization of cytoplasm. Where did they come from? In hindsight, I see the influence of an old brass microscope from the laboratory of my great-grandfather that I was given sometime around my seventh birthday, along with a Kipp’s apparatus. The microscope introduced me to protozoa from the local pond, allowing me to see the insides of a living, moving cell. The Kipp’s apparatus could produce spectacularly smelly or explosive gases, but was less used, because it required parental guidance.

My love of chemistry, and its foundational role in my worldview, is better attributed to my high school chemistry teacher, Mr. Carleton. He provided my first glimpse of a rational underpinning for the natural world in the periodic table, and later explained how it arose from the Schrödinger equation. Neither of us understood the math, but what an inspiration to contemplate an abstract principle that explains reality! My interest in cytoplasm was kindled early, but it took the influence of my PhD mentor, Marc Kirschner, for me to develop a taste for interesting and tractable problems in how it is organized.

DISCOVERY OF DYNAMIC INSTABILITY

I was inspired to join Kirschner’s lab at the University of California, San Francisco (UCSF), after hearing Kirschner give a series of lectures on space and time in biology. I felt then, and still do, that he aims at principles, although getting there entails a lot of wading through details. I chose to work on centrosomes, hoping they might be the brain of the cytoplasm, but our immediate goals were to purify them and figure out how they nucleate microtubules. This nucleation problem lies at the heart of cell organization and is still unsolved, although we probably do know the major protein players. I succeeded in purifying centrosomes, but the technologies then available were too insensitive to identify their components. Somewhat in desperation, I turned to the assay I had been using, and ended up discovering dynamic instability, wherein individual microtubules exhibit large length fluctuations powered by GTP hydrolysis (Mitchison and Kirschner, 1984). This discovery defined my subsequent career and my taste in subsequent research. “You can always get a

Timothy J. Mitchison is the 2013 Keith R. Porter Lecturer for the American Society for Cell Biology.
Address correspondence to: T. J. Mitchison (timothy_mitchison@hms.harvard.edu).
Abbreviations used: HMS, Harvard Medical School; MBL, Marine Biological Laboratory; RNAi, RNA interference; UCSF, University of California, San Francisco.
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paper out of your assay” is something I tell students to this day. It came from analyzing individual microtubules, rather than average behavior, which was natural, given my taste for microscopy, but the key innovation was to freeze the tubulin in tiny aliquots. Every time I thawed one, it behaved the same way, so I could make measurements on multiple days and plot them on the same graph (Figure 1A). I think I learned that from Bruce Alberts. He favored 50% glycerol stocks at −20°C but drilled into me the idea that, if you are careful with your proteins, they will reward you with consistent and interesting behavior. Measuring individuals rather than averages turns out to be generally good taste. Systems biology, my current departmental affiliation, has prospered by quantifying the dynamics of individual cells, which is often more interesting than the population average.

Dynamic instability occurs when two chemicals, tubulin and GTP, self-organize—a complex process that is lifelike in the sense that it generates form and motion. I owe a huge debt to Marc Kirschner for pointing me at this problem and for his obsessive work on treadmilling theory with Terrell Hill, which set up a large applecart for me to overturn. I acknowledge the pioneering work of Marie-France Carlier on the biochemistry of GTP hydrolysis by tubulin, and her prior idea of a kinetic lag between polymerization and hydrolysis. The American Society for Cell Biology also plays an important role. I will never forget preparing for my first big talk at the 1983 meeting in San Antonio. Marc and I were still debating what to call it the night before. “Dynamic Instability” was his idea, and he prevailed, thank goodness! My idea was “Microtubule Jerking”—think on- and off-rate. Only later, when I became friends with Ted Salmon, did I realize to what an extent both dynamic instability and treadmilling were presaged by the work of Shinya Inoue and his big polarization microscope. MBL has been an inspiring place to pursue cytoskeleton dynamics and an important relief from faculty tedium at Harvard Medical School (HMS).

FIGURE 1: My taste in molecules. (A) The remarkable dynamics of tubulin. This graph shows microtubule growth rate as a function of soluble tubulin concentration. Microtubules shrink much faster than expected from extrapolating their growth rate to zero tubulin, because GTP hydrolysis destabilizes them. (Adapted from Mitchison and Kirschner, 1984.) (B) Caged fluorescein, used to measure microtubule sliding in mitotic spindles (Mitchison, 1989). The sulfo-NHS ester portion at the bottom is for labeling lysine residues. (C) Monastrol, the first small-molecule inhibitor of kinesin-5 (also known as Eg5, KSP, and Kif11; Mayer et al., 1999). (D) DMXAA, a drug that was effective for cancer treatment in mice but not humans. We and others recently found that it is a mouse STING agonist (Conlon et al., 2013; Kim et al., 2013). The normal function of STING is to activate an innate immune response to DNA or bacteria in the cytoplasm (reviewed in Paludan and Bowie, 2013).

CHEMISTRY FOR RESEARCH AND THERAPEUTICS

My taste for organic chemistry was subdued by boring university lectures but reawakened when I moved to the Medical Research Council at Mill Hill in London after my PhD. There, I tried to synthesize a photoactivated fluorescent probe for spindle dynamics, encouraged by David Trentham. I finished caged fluorescein (Figure 1B) after moving back to UCSF, and used it to prove that spindle microtubules slide poleward, with important implications for chromosome segregation mechanism (Mitchison, 1989). Synthesizing fluorescent probes is great fun, but chemistry applied to perturb biology is more important, especially since the introduction of green fluorescent protein. I became interested in drug development during a sabbatical visit to Stuart Schreiber’s lab at Harvard in 1996, and moved to HMS to start the Institute of Chemistry and Cell Biology with him and Rebecca Ward in 1997. Back then, we had few tools for perturbing dynamical processes in human cells. Stuart and I imagined that cell-permeable small-molecule “tool compounds” could fill this void. We set out to develop lots of them, using combinatorial chemistry and high-throughput screening, imagining one for every protein. In retrospect, that was ludicrously overambitious, but we did generate some useful tools, notably the kinesin-5 inhibitor monastrol (Figure 1C) and the myosin II inhibitor blebbistatin. In the early 2000s, RNA interference (RNAi) emerged as a general tool for knocking out protein function. It does not replace what you can do with a good drug, but it weakened the rationale for large-scale tool compound development for basic research. Post-RNAi, and my realization of how much effort is needed, I now feel that tool compound development is most justified when it will test a therapeutic hypothesis.

What is a therapeutic hypothesis, and how might you test one? These are application-oriented questions that I have come to find fascinating, although, like many of my contemporaries, I worry that the drive to “translate” basic discoveries into disease treatments is overwhelming the more important long-term mission of advancing fundamental knowledge. My emerging tastes are strongly
influenced by a failed experiment. After monastrol, several companies made potent and specific kinesin-5 inhibitors in the hope of broad-spectrum anticancer drugs that would kill cancer cells by blocking mitosis but that would lack the neurotoxicity caused by microtubule-targeting drugs like Taxol. In hindsight, this was an invalid therapeutic hypothesis. As I discussed in a 2012 *Molecular Biology of the Cell* essay (Mitchison, 2012), mitosis-specific drugs have strong anti-proliferative action in the human body. They cause neutropenia and lack strong anticancer activity at the exposure limit, presumably because preneutrophils in the bone marrow divide much more frequently than cancer cells. Taxol was developed on the basis of an older and simpler therapeutic hypothesis: drugs that efficiently kill cancer cells in culture may work in man. Many important therapeutics were developed this way, but the hypothesis is far from universally valid—most poisons lack selectivity for killing cancer versus noncancer cells. We are now looking for mechanisms by which Taxol kills cancer cells in interphase that are either absent in standard tissue culture or masked by the high proliferation rate. We are also investigating mechanisms for converting tumor-resident leukocytes from pro- to anti-tumor phenotypes, following up on target ID of the failed cancer drug DMXAA (Figure 1D). Time will tell whether these choices of direction in the therapeutic arena are good taste.

**FIND YOUR OWN TASTE!**

A life in science is a long and interesting path, and our trajectories are determined as much by our tastes as by skill and luck. For those of you near the start of this path, I don’t have advice for what kinds of questions you should ask or what techniques you should learn to answer them. I rather suggest you identify your own tastes, celebrate their uniqueness, and trust them to guide you.

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An enduring enthusiasm for academic science, but with concerns

John R. Pringle
Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305

INTRODUCTION
I turned 70 this year and started graduate school shortly after turning 20. Thus, at this writing, I have spent 71.3% of my life in academic science. I have no regrets and hope to continue for years to come, because I remain an unabashed enthusiast for both the research and education components of this profession. The high honor of the E. B. Wilson Medal and the accompanying request to write this essay give me an opportunity to reflect on why this is so, as well as on my concerns about the fouling of the nest that has made it harder for any of us—but particularly for younger people—to enjoy academic science as I have over the past 50 years.

My enthusiasm should not be misunderstood as naïveté. I well understand that not every aspect of the job is fun; some tasks are inevitably tedious or even painful. It hasn’t always been easy for me personally; like most people, I struggle with my own limitations, notably an incurable perfectionism and the frequently linked traits of avoidance and procrastination, which have often made it difficult for me to finish papers and other tasks. I have had papers and grants rejected and seemingly great ideas that turned out to be lousy when actually tested. As a graduate student, postdoc on two continents, faculty member at three universities, and dean for graduate students and postdocs, I have seen plenty of nasty stuff: subcompetent people obstructing progress at all levels; arrogance and self-centered insensitivity to the feelings of others; exploitation of students and postdocs by faculty; dishonesty ranging from exaggerated claims and the concealment of inconvenient data to gross fabrication; pointless and demeaning squabbles about priority and authorship; abuse of the still-critical tenure system; inappropriate behavior by editors and reviewers; and behavior driven by lust for power, money, and fame rather than by any desire to understand nature and (perhaps) improve human well-being in the process. And, in recent decades, I have seen the environment in which science is done erode in ways that I deplore.

 Nonetheless, I still feel that doing science is fundamentally Good (even noble) and that universities are wonderful places. I still look forward (almost) every day to going to the lab, and I have liked (to various degrees) almost every scientist I have known over a long career. How can this be? My attempt at explanation follows.

A DEEP AND ABIDING BELIEF IN THE SCIENTIFIC ENTERPRISE
Already as a child, I realized (sometimes during conflicts with my teachers) that I simply hated opinions that were illogical, irrational, or based on appeals to authority. Thus, I was ineluctably drawn to math and science and the rule of reason and evidence. I haven’t changed, and I feel deeply proud to be, in a small way, a successor to Galileo, Darwin, Pasteur, E. B. Wilson, and the host of others who have helped to push back the fog of ignorance and open ever more of the universe to human understanding. As I watched the Nobel Prize ceremonies in 2001, I found tears running down my cheeks, not because of my personal connections to the laureates and the work for which they were being honored, but because the language of the citations—about the importance of science for the human spirit and the betterment of the human condition—was so incredibly moving. It was a vivid reminder that the scientific enterprise is bigger and grander than its often-flawed individual practitioners, and it is our shared commitment to this enterprise that it has made it so easy for me to like other scientists regardless of their personal idiosyncrasies. This all may seem sentimental and wildly idealistic, but I think it is the truth, and it still sustains me during times of frustration.
Meanwhile, the human condition seems more precarious than ever. I’m not sure that science can save us, but I am confident that it can help, and I am equally confident that irrationality and superstition will not. Scientific medicine saves lives (mine, for one), science-based engineering creates marvelous devices (like the laptop computer on which I write this), and rational planning can save local ecosystems (e.g., the Guanacaste Dry Forest in Costa Rica), so there is surely hope for our species and our planet. To succeed, however, we will need more good scientists and—even more importantly—a public that understands scientific evidence and reason, which is of course why more and better science education is so critically important for our collective future.

**A CAREER BASED ON LUCK AND JUDGMENT**

That I have enjoyed my own career so much seems to me a matter of good luck with an occasional infusion of good judgment. I wasn’t exactly to the manor born. My parents suffered greatly during the Depression of the 1930s, leaving them very focused on financial security but also with a reverence for the education they had missed. Given his own experiences and concerns, it is remarkable that my father advised me repeatedly (it is among my earliest memories) to “find something to do that you would do for free, and hope that you can make a living at it.” Growing up near Chicago, I first planned to follow this advice by succeeding my hero Ernie Banks as the Cubs shortstop, but I had the good judgment to realize that my inability to hit my weight would be an obstacle. When I was 14, we moved to Evanston, where the honors classes made school fun for the first time and put an academic spin on my ambitions.

High-school math was easy and fun, so I decided to become a mathematician. But by good luck, I went to Harvard, where comparisons to some classmates suggested that I did not have big-league talent in this field either. Fortunately, a spring break spent with my roommate’s evolutionary-biology books (when I was supposed to be doing math and physics) revealed the fascination of biology just as E. O. Wilson was trolling for math students to recruit into population genetics. The department addressed my deficiencies with a five-course load during my first year that included organic chemistry but also, luckily, spectacular courses in genetics (Matt Meselson and Nick Gillham) and cell biology (Keith Porter), and I soon realized that my interests, talents, and temperament were better suited to these fields than to ecology and evolutionary biology.

But I was also temperamentally unsuited to join the crowds then studying *E. coli* and its phages and mammalian cell biology, and I had also glimpsed the potential of yeast in the laboratory portion of the genetics course. There were no yeast groups in the Boston area, but I convinced protein chemist Guido Guidotti to sponsor me for study of “some interesting yeast protein.” But protein chemistry wasn’t right either, and I struggled mightily before producing a thesis (mostly on proteolytic artifacts). In the midst of my agonies, I somehow convinced Herschel Roman to accept me for postdoctoral work in Seattle, then the only center of yeast genetics in the country. Herschel soon began nudging me toward his new recruit Lee Hartwell, but I was not excited by Lee’s studies of RNA and protein synthesis. However, during a September 1969 visit to my medical-resident girlfriend, I heard about the first cell-cycle mutants and had the good judgment to sign on immediately. When I joined the lab in 1970, I somewhat perversely veered away from study of the cdc mutants to focus on control of the cell-cycle by nutrition, cell size, and pheromones. Lee was initially dismayed, I think, but it had a happy ending in the development of the concept of Start (Hartwell et al., 1974).

After two more years of work on the nutritional control of cell proliferation (and much broadening of my knowledge of the world) in Zürich with Armin Fiechter, I started my faculty career at Michigan in 1975. Both Lee and everyone else seemed to be interested in the nuclear events of the cell cycle, so wanting, as always, to be different, I decided to focus on events in the cytoplasm, namely bud formation and cytokinesis. It was not clear that the mechanisms would be of any “general interest,” but I didn’t care, as I found the problems interesting myself, and they were essentially unexplored but clearly approachable using the powerful methods of yeast genetics. The department was not strong in genetics or cell biology, and I had a heavy teaching load, but I believe that these two “problems” were also blessings in disguise. I never worried about all about promotion, a sound strategy for Assistant Professors in general, I think, but one that is no doubt harder to follow in some situations. The teaching was very satisfying (particularly “Biologist for Nonscientists”) and educational, and the nine-month salary that accompanied it freed me from excessive worry about grants. Thirty-eight years later, I have shifted focus many times (actin and microtubules, septins, Rho proteins, positional signals in the cell cortex, cell-wall synthesis, evolution of cytokinesis mechanisms, etc.) and moved twice (to North Carolina in 1991 and to Stanford in 2005). I have also started a totally different project (attempting to transform coral biology by developing, more or less from scratch, a proper model system for its study) that now consumes most of the effort of my lab. But we continue to learn interesting new things from yeast, most of which—mirabile dictu—continue to be very broadly relevant.

In looking back, I think that I have been fortunate in many ways. First, for reasons of deep and incompletely understood psychology, I have always been attracted to problems that other people were ignoring (the blank spots on the map), and I think that this has made science more fun in several ways (the sense of adventure, the lack of any sense of competition). What would be the point of doing the same thing as someone else, even if I could do it a little faster (unlikely in my case anyway)? As a student and postdoc, I had mentors who were supportive but willing to let me find my own way, and as a young faculty member, I felt free to ignore what little advice the senior faculty had the temerity to give me. As a result, I have never felt that I had a “boss,” and I can only imagine how unpleasant I would find this. Although sticking for many years to one general area of research, I shifted focus often enough to stay excited, and at the first hint of boredom in my early 60s, I started something totally new, which was thoroughly rejuvenating. I decided early that science would be more enjoyable (not to mention more effective) if I were always open and willing to share ideas, materials, and credit, and I have never once regretted this decision. I have for the most part had people in my lab who accepted my ideas about how science should be done, so that my interactions with lab members (and alumni/ae) have mostly been harmonious. In each move, I left a fine institution and good friends behind, but was stimulated by the new environment. And last, but not least, I had the good luck to find a partner (that medical resident, now a professor of medicine and cancer-center director) who was both passionate enough about her own work to understand my passion for mine and brave enough to join me in the enormously rewarding collaboration of raising two children, which we did without feeling that we were cheating either them or our work.

**SOME PROBLEMS WITH ACADEMIC SCIENCE TODAY**

Despite my own unabated enthusiasm, I feel that the scientific environment has deteriorated considerably during my 50 years of...
involvement, and I am ashamed that my generation has allowed this to happen on our watch. The problems are complex, interrelated, and not all easily solved, and there is not space here to discuss them all. So I will focus on some lowlights, as I see them (while stressing that no other individual or organization bears responsibility for my views!).

1. The inability of some highly qualified people to find academic positions. Despite the undoubted numbers crunch, which has deep roots and is not easily solved, until recently I felt that the young scientists with the greatest potential could always find positions that would allow them to blossom as independent investigators, teachers, or both. Now I am doubtful, and I think that the problem is due in part to institutions’ hiring not on the basis of candidates’ potential for truly creative work but on whether they are working in fields perceived to be “hot” and well funded, which to me automatically means “less left to be done” and “vulnerable to future changes in funding fashion.” It is also a true shame, given the enormous world of fascinating biology left to be explored. I also suspect that the current financially driven stampede toward massive online courses will worsen this situation, perhaps catastrophically, and will degrade the quality of education and even the understanding of what a good education comprises.

2. Poor performance by most funding agencies. Getting a reasonable amount of funding to do genuinely novel basic research is harder than ever, despite some well-intentioned efforts to counter this problem. Among the reasons are the commitment of excessive portions of the agencies’ total budgets to projects that are top-down, directed toward overly specific practical goals, and/or excessively large (and thus almost inevitably wasteful), rather than to the investigator-initiated, small-group projects that have always brought most genuinely new discoveries (and the technologies that follow them).

3. The rise to power of commercial and non–peer-edited journals. Hartwell et al. (1974) was rejected without review by Nature, leaving a bad taste that has lasted, and I have never again submitted a paper there by choice. I have also watched with horror as a host of other journals has appeared for which the best interests of science and scientists are secondary to financial profit and promotion of the power and influence of the journal itself, and at which decisions on whether to publish, and with exactly what content, are all too often made by people who are ill prepared to make good ones. Even more appalling has been to watch these journals gain influence almost in proportion to how poorly they serve the true interests of science. Until 2000 or 2001, I could truthfully tell young scientists that in all the many search-committee, promotion-committee, and study-section meetings in which I had participated, I had never once heard the names of journals (much less their so-called “impact factors”—a metric so deeply flawed as to be ludicrous) used as a criterion in judgment, but, sadly, this is no longer the case. Fortunately, there is a growing realization that we need to wrest control of our most important decisions back from people who have neither the competence (nor, typically, the motivation) to make those decisions well (Bertuzzi and Drubin, 2013; Johnston, 2013; www.ascb.org/SFdeclaration.html). Reducing the perceived importance of publishing in certain journals should also reduce the temptations toward overstatement, concealment of nuance and doubt, and outright fakery.

4. The increased agonies of publication. Publishing one’s work used to be (mostly) fun and satisfying, but it is now too frequently an excruciating ordeal for all concerned. The multiple reasons for this include: 1) Unrealistic expectations. High standards are fine, but science is a journey, not a destination, and no one paper will provide definitive answers to all of the questions in its purview, so that reviewers and editors need to be reasonable. 2) Too many editors who do not have the confidence, or will not invest the time, to evaluate carefully the reviews that they get and give appropriate decisions and instructions to the authors. 3) Closely linked to the preceding point is the routine use of three reviewers, a new and pernicious practice that slows down the reviewing process, adds to the burden on conscientious reviewers, and typically just adds aggravation for the authors without producing any real improvement in the quality of the paper. My own observation is that a third reviewer should be needed <10% of the time and only when the first two reviewers disagree wildly and the editor does not have the competence to adjudicate the matter (which, ideally, should not happen very often at a well-run journal).

5. The decreased quality of publications. I could rant at length but will restrict myself to just a few of the problems that I find most aggravating. 1) The fundamental error of confusing brevity per se with tight writing. Scientific publications should not waste a single word or figure panel, but arbitrary length limits encourage both the splitting of what should be one thorough paper into two or more logically incomplete ones and the omission (or, almost as bad, dumping into supplemental material) of detailed methods, valuable subsidiary results, and important caveats. Despite the effort required, the authors, reviewers, and editor should share the burden of producing a paper that is just the right length for its content. 2) Careless and sloppy writing. Good, clear writing is hard work, especially if it is not in one’s native language, but anything else is a disservice to the community, as well as to the authors (whose experiments may reasonably be assumed to be as careful, or as sloppy, as their writing). Our programs need to provide more training in good writing, which is also hard work (on both sides), but critical. 3) The devaluation of Materials and Methods sections. The essence of science is its reproducibility, and you can’t reproduce it if you don’t know how it was done. I still almost always read the methods section first (when I can find it!), because I want to know whether there is any reason to believe the results. I think that the movement of the methods section to the rear of the paper sends entirely the wrong message and should be reversed in those journals in which it is allowed or even required. 4) The trend to declarative-sentence titles. Such titles, which were essentially unknown before 1980 (Rosner, 1990), are in part a sequela of the perceptions that it is important to publish in certain journals and that a bold claim about what you have (perhaps) discovered will help you get there. They are not actually needed to convey the most important contents of a paper, and they are objectionable for two reasons. First, they almost always overstate the solidity of the main conclusion(s), whereas a decent humility in the face of the complexity of nature is a more becoming posture for a scientist. And, of course, sometimes the bold statement turns out to be simply wrong, yet it lives on in the databases to confuse others for many years to come. Second, very few papers are so one-dimensional that a single sentence can describe them, so that such a title serves to obscure the true richness of the paper’s contents.
CONCLUSION
Academic science has never been a paradise on earth; there have always been problems and frustrations. Although some of these have become worse over the past 50 years, many of our current problems could be solved, at least in part, by community will and action. In any case, if I were 20 again, I would take my chances and pick the same career, not only because it suits me personally but also because I still believe unshakably in its deep and abiding value to our species.

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So, what's it really like to work in biotech?

Lisa Belmont
Genentech, South San Francisco, CA 94080

ABSTRACT  This essay provides insight into the daily life of a scientist in biotechnology, drawing on experience gained from working in companies ranging in size from four to more than 80,000 employees. The basic scientific training in molecular biology required for the work is similar between academia and industry, but the way in which these skills are applied differs. Biologists in industry settings work as part of large, multidisciplinary teams. This requires relinquishing the degree of intellectual freedom allowed in academia but offers an increased opportunity to see the fruits of one's labor translate into products with the potential to positively impact human or environmental health.

INTRODUCTION
Because I work in biotechnology, I was asked to provide some perspective on careers within the biotechnology industry for graduate students and postdoctoral fellows. After completing a typical PhD and postdoctoral training in basic cell biology using *Xenopus laevis* and *Saccharomyces cerevisiae* as model organisms, I decided I wanted to use my research skills in applied science. I took a blind leap into a tiny biotechnology company at which I was employee number four. The lofty goal of this new venture was to directly convert “sludge,” a waste product from pulp mills, into fuel-grade ethanol with a one-step fermentation process. The year was 2000, and the political climate was conservative with respect to renewable energy. It was hard to get funding, and it became evident within a few months that I should consider other employment options. As it happened, a biotechnology company was looking for biologists with expertise in cytoskeletal biology. I applied for the position in the antifungal group and was surprised to be offered a position as a cancer cell biologist. Having only worked with yeast and frogs, I was intimidated by the thought of accepting a position requiring expertise in human cancer, but decided it was too good an offer to turn down. I joined as employee number 90 in a rapidly growing company and quickly became the expert they needed. This turned out to be a fantastic opportunity to take my expertise in basic cytoskeletal biology and learn how to apply it to cancer research and drug discovery. After 5 years, we had sent three novel investigational drugs off into the choppy seas of clinical trials and wished them well. At this time, it seemed prudent either to transition into clinical development or to seek new opportunities in drug discovery. The opportunity arose when Genentech started building a cell cycle effort. I was hired into the cell cycle group as employee number 10,000 (approximately) and after 2 years transitioned into a new department focused on the discovery of biomarkers to identify responsive patient populations. Shortly thereafter, Genentech became a member of the larger Roche team. Although I wrote this introduction to provide context for my perspective, it already illustrates some of the realities of working in the biotechnology industry, such as the need to adapt and be open to new opportunities as they arise. In the remainder of the essay, I will highlight some of the major facets of a career in the biotechnology industry that may not be obvious from the outside.

CAUGHT IN THE MATRIX
Nearly all industrial projects are carried out by multidisciplinary teams. I love this aspect of industry, as I enjoy working with experts in other disciplines, projects move forward quickly, and you learn about other fields without having to be an expert. Good team members will be interested in the various other aspects of the project. For example, most chemists will want to learn more about the target biology, a biologist should learn about pharmacology, etc. Obviously, some teams function more smoothly than others, and the way in which different companies manage teams can have a profound influence on one’s ability to be productive. Teams can be organized in many different ways. A company could have a matrix organization in which a functional group, such as biochemistry, contributes to all projects through various project leaders, or alternatively, a disease-focused organizational structure where each therapeutic area would have a dedicated group of biochemists. You will hear a lot about organizational structure, but what matters most is whether the teams...
are enabled to move projects forward collaboratively and efficiently. I have been fortunate in this regard overall, but it is something you may want to ask about during an interview. For example, you might ask one of your interviewers: “If you wanted to carry out a project that required help from the mouse group, synthetic chemistry, pharmacology, and structural biology, how would that work?” Pay attention to the length of time and number of acronyms required for the answer and watch closely for expressions of angst or joy.

SAY WHAT?
Jargon is rampant in the biotechnology industry, and it can be quite baffling during an interview and the first few months of a job. Shortly after I started at my second industry job, the project leader told me that a critical goal for the project was to establish a PK/PD relationship. I said I would get right on it and went scurrying back to my computer to try to figure out what a PK/PD relationship was. Eventually, I figured out that it that it meant demonstrating that the molecule of interest gets to the relevant tissue at an efficacious dose and has a biological effect consistent with its mechanism of action. This is something any well-trained biologist would want to demonstrate before promoting a drug candidate; it was the jargon that made it mysterious. Furthermore, there was an expert in pharmacology to handle the PK (pharmacokinetics), while PD (pharmacodynamics) was the responsibility of the biologist, which meant demonstrating on-target mechanism of action in vivo. Do not be intimidated by the jargon; people tend to forget they are using jargon, and it is okay to ask what something means.

YOUR PROJECT WILL BE TERMINATED
This is bound to happen at some point during a scientist’s tenure in the biotech industry. Under the best of circumstances, you will be the executioner of your own project. You will go before your senior management and present a series of brilliantly executed experiments that definitively demonstrate that, although the biology is fascinating, for reasons x, y, and z, the project will not be viable. Perhaps the drug will be too toxic or not efficacious or will have insurmountable technical issues. You will have done the company a favor by identifying these issues, and there is honor but little glory in this act. In the worst case, there will be a business decision that has nothing to do with science that dooms your project. In either case, it helps to be adept at identifying or accepting a new project and moving on. Adaptability is key to survival.

A DAY IN THE LIFE
So what does my typical day look like? Early in my career I did a lot of bench work, and I still do some, but currently the largest fraction of my time is spent analyzing, summarizing, and presenting data. I analyze data from my lab, other groups at the company, private databases, public databases, the literature, collaborators, and contract research organizations. I generally interpret data and give presentations to teams to address questions related to drug candidates or drug targets. If key data are needed to answer a question, I get them by either running experiments in my lab, outsourcing, or collaborating. It is generally the most fun when questions need to be addressed in the lab, as I enjoy designing and performing experiments, as well as supervising and mentoring research associates and scientists. However, the stakeholders are generally not concerned about where the data come from, just that they be rigorous and clearly presented in order to enable decision making. I also spend around 25% of my time attending meetings. Sometimes I present, but much of the time I attend to provide feedback and to stay abreast of what other team members and colleagues are doing. Data and progress need to be communicated frequently for teams and departments to function effectively.

In my current role, my primary job is to determine how to identify patients most likely to respond to our investigational drugs and to identify mechanisms of drug resistance. However, there are many different types of positions in biotechnology that require rigorous training in molecular and cell biology. Whether you are hired to identify new drug targets, screen compound libraries, characterize mechanisms of action of drugs, test drug candidates in animal models, or mine data, it is important to understand that when companies hire PhD biologists they are not just looking for a pair of hands. Whoever is hiring needs someone to take intellectual responsibility for a certain area. That job may allow or require a considerable amount of creativity, or it may be largely technical, but the job will generally require someone who can make decisions, exercise scientific judgment, and solve problems with minimal input. How you go about it is context dependent, but you will be an expert for hire working with a team of other experts. Of course, this work is carried out within the context of the larger company goals. The type of job, position within the company, and the corporate culture determine how much influence an individual researcher will have in setting those larger goals. However, even the executives have to answer to a board of directors.

SO, HOW DO I GET A JOB IN INDUSTRY?
Publish good papers in quality journals. Because this is the same thing you need to do to land an academic position, it means you do not have to choose your career path early in your PhD and postdoctoral training. Choose a good lab in a field about which you are passionate and publish something novel. Other things can help you land an industry job, like becoming an expert in a disease-relevant system, such as genetically engineered mouse models, or specializing in immunology. However, I was hired as a cancer cell biologist after completing a postdoctoral fellowship in a yeast lab, so disease specialization is not essential. PhD students are trained to identify scientific questions, carry out experiments to answer those questions, and present the data in a clear manner to other scientists. The hiring managers in industry are looking for those fundamental skills when they set out to hire a scientist, and peer-reviewed publications are the best way to demonstrate that you have what it takes.
Creating opportunities for science PhDs to pursue careers in high school education

Kari M. H. Doyle and Ronald D. Vale

The Bay School of San Francisco, San Francisco, CA 94129; Department of Cellular and Molecular Pharmacology and Howard Hughes Medical Institute, University of California San Francisco, San Francisco, CA 94158

ABSTRACT The United States is confronting important challenges at both the early and late stages of science education. At the level of K–12 education, a recent National Research Council report (Successful K–12 STEM Education) proposed a bold restructuring of how science is taught, moving away from memorizing facts and emphasizing hands-on, inquiry-based learning and a deeper understanding of the process of science. At higher levels of training, limited funding for science is leading PhDs to seek training and careers in areas other than research. Might science PhDs play a bigger role in the future of K–12 education, particularly at the high school level? We explore this question by discussing the roles that PhDs can play in high school education and the current and rather extensive barriers to PhDs entering the teaching profession and finally suggest ways to ease the entrance of qualified PhDs into high school education.

In many K–12 classrooms, science is presented as a series of textbook facts; students are not exposed to scientific methods of inquiry and lose interest in science. At the very opposite end of the science training pipeline, life science PhDs and postdocs in the United States are experiencing difficulties in finding university jobs, a situation that will likely persist in the coming decade if research funding fails to grow; we cannot expect all PhD graduates to become principal investigators (PIs) at academic institutions.

Might these two problems add up to a solution (or at least a partial solution)? Is there a place for graduates of PhD training programs in teaching K–12 science, particularly at the high school (HS) level (the focus of this article)? We argue that the answer is “yes” and that more PhDs, even if their numbers are small compared with the entire teaching pool, could have a catalytic effect on reinvigorating precollege science education. This topic is not new; the National Research Council (NRC) issued two thoughtful reports on attracting science and math PhDs to secondary school education more than a decade ago (Committee on Attracting Science and Mathematics Ph.D.s to Secondary School Teaching, National Research Council, 2000; Committee on Attracting Science and Mathematics PhDs to K–12 Education: From Analysis to Implementation, Division of Policy and Global Affairs, National Research Council, 2002). Their recommendations were not implemented, however, and the reports have largely been forgotten. Little has changed since then; the roadblocks, both in perception and logistics, that discouraged a PhD from becoming a HS teacher in the year 2000 still exist. Since the NRC reports were released, the topic of a HS teaching career option for a PhD has rarely been discussed or debated in our scientific community. We feel that it is time to reopen this discussion. The focus of this article is on PhDs entering the high school system, but much of this discussion also pertains to graduates of science master degree programs and to individuals with scientific training becoming involved in all levels of K–12 education. Our goal is to make students, postdocs, and senior scientists aware of the value of high school teaching for certain individuals as well as for our nation’s educational system. We also consider how changes at the local level (including the perception of K–12 teaching within research universities), as well as at the policy level of teacher accreditation, might facilitate this career path.

IS THERE A NEED AND ROLE FOR PhDs IN HIGH SCHOOL SCIENCE TEACHING? A HS science teaching position requires a BA or BS degree. This requirement makes sense but raises a host of questions for PhDs. Are PhDs overqualified for a HS teaching position? Does a PhD...
degree make one a better HS teacher? Is it worthwhile for a school to hire a PhD often at higher cost? Can one apply aspects of what one learns during PhD training to teaching at the HS level, and are these elements appropriate for HS students?

In our opinion, encouraging the right type of PhD to enter into HS teaching makes sense, and high schools benefit in the end. Many organizations (e.g., the National Academy of Sciences) and educational leaders advocate for more inquiry-based learning in the K–12 science curriculum (National Research Council, 1996; Committee on Developments in the Science of Learning and Committee on Learning Research and Educational Practice, 1999; Committee on Development of an Addendum to the National Science Education Standards on Scientific Inquiry, Center for Science, Mathematics, and Engineering Education, National Research Council, 2000). Scientific inquiry is difficult to teach without having had an experience of trying to solve an unknown scientific question oneself. Offering research opportunities for HS science teachers (or students in training to become teachers) is one way to provide HS teachers with a deeper understanding of science inquiry. Graduate education in science, however, is predicated upon solving an original research problem, and thus a PhD who enters a HS teaching profession has a strong foundation of understanding research and the processes of scientific thinking.

Furthermore, it is possible to translate many experiences from PhD training into a HS environment, such as the skill of how to set up an experiment. This skill, and a general understanding of experimentation, is sometimes lost with prepared lab kits that do not require students to think about controls and other parameters of their experiment. Many lab kits also are not flexible enough for students to adjust variables of the experiment, which is an important aspect of experimental science. Furthermore, even sophisticated labs that are now available to HS teachers do not always involve inquiry and therefore become more of a recipe for students to follow. A second valuable skill is the knowledge of how to read a scientific paper. Although there are resources that explain how to read primary literature, these do not substitute for the experience of using papers for furthering one’s research and writing scientific papers (Gillen, 2007). In addition, scientific papers that are carefully chosen and explained properly can be understandable and enjoyable and no less difficult than reading a challenging novel. PhDs also can instill a sense of wonder about the many important things that remain to be discovered in the sciences and the discoveries that are being made right now. Furthermore, as concluded by the 2000 NRC report (Committee on Attracting Science and Mathematics PhDs to K-12 Education, 2002), PhDs can provide a bridge to scientific centers, as they are more willing to seek opportunities for students to tour research labs or connect students to research projects.

Some may argue that PhDs will be disappointed by HS teaching and are better off teaching more advanced biology in college. However, many individuals enjoy working with HS students at this influential stage of their lives. Furthermore, there are many opportunities for innovation and creativity in HS science teaching in which PhD training could be beneficial, particularly in developing ideas to make science interesting and introducing scientific thinking into the classroom. Thus, education in HS can be as challenging and interesting as bench science for the right type of person. A survey conducted by the NRC in 2000 also revealed that a surprising 30% of respondents (graduate students and postdocs in the biological sciences) were interested in and had considered a career in secondary education (Committee on Attracting Science and Mathematics Ph.D.s to Secondary School Teaching, 2000). This poll should be reconducted, but since the “holding tank” of postdocs seeking jobs has grown larger in the past decade, it is likely that current interest remains high. Although PhDs are aware that the salary scale for a high school teacher is lower than that for other occupations, the 2000 NRC report identified several positive perceptions of teaching in a secondary school, which included “attractive working hours, a work schedule similar to their children’s school day, and time for research or other activities during the summer” (Committee on Attracting Science and Mathematics Ph.D.s to Secondary School Teaching, 2000).

CATALYZING CHANGE: IMPORTANCE BEYOND NUMBERS

Even if PhDs can provide value to high schools, their numbers will always be small, a mere drop in the very large pool of HS teachers. Some might argue that such a small group does not warrant special attention. We counterargue that impact and change are not always driven by sheer numbers of people. Instead, it is important to identify circumstances in which a few individuals can make important differences to a system. A PhD who has a significant understanding of scientific research and learns to become a great HS teacher would have an unusual opportunity of seeing kids enter their classroom “hating” science and leave with an attitude that science is “okay,” maybe even “awesome.” As a bonus, a few students may want to pursue a science-related career (many science professionals can remember a HS science teacher who affected their career decision). In addition, beyond their own classrooms, good teachers with a deep understanding of science can influence many more students by sharing ideas with and assisting their peer teachers. Through their influence on curriculum development, teachers could reach even more students and teachers in their districts or beyond. A subset of scientist–HS educators also may later become administrators in schools or school boards, where they could have a broader impact on the science curriculum, as discussed in a recent editorial by Alberts (2011).

WHAT ADDITIONAL SKILLS DO PhDs REQUIRE TO TEACH IN HIGH SCHOOL?

The 2000 NRC report concluded that PhDs lack the general skills needed to become an effective teacher (Committee on Attracting Science and Mathematics PhDs to K-12 Education, 2002). Indeed, a PhD graduate is not trained to manage a class of teenagers with raging hormones, deliver learning material in a HS curriculum, or necessarily understand and relate to kids of this age group. In addition, teaching methods have changed since the time when a recent PhD graduate would have been in high school. In addition to traditional assessments and lectures, an excellent HS teacher needs to be able to implement methods that include self-reflection, formative assessment, rubrics, lesson planning, classroom management, and awareness of different abilities and learning styles, as well as many other skills. The crux of the matter is how to teach PhDs effectively and efficiently so that they have sufficient skills to confidently enter a high school classroom, a topic to which we return when we discuss teacher accreditation.

WHAT BARRIERS IMPEDE PhDs FROM ENTERING K–12 EDUCATION?

The NRC report estimated that only 0.8% of PhDs work in K–12 education, a stark contrast to the earlier-noted >30% potential interest in such an occupation (Committee on Attracting Science and Mathematics Ph.D.s to Secondary School Teaching, 2000). Although the K–12 teacher salary can dissuade many PhDs from entering the
K–12 profession, many remain interested but face several barriers in transitioning from research into teaching at secondary schools, as noted in the following sections.

**Negative perception of becoming a high school teacher**

Is K–12 teaching an acceptable career outcome after a PhD degree? The answer to this question is not obvious. In contrast to countries like Finland, where K–12 teaching is a highly respected occupation (Sahlberg, 2011), high school teaching is generally perceived as a low-stature occupation in the United States. That perception is further magnified in the higher academic circles. There is an unspoken perception in the graduate school community that becoming a HS teacher after obtaining a PhD represents a failure, a last resort after other options have not panned out. It is not something that one pursues as an active choice. This perception is expressed in a blog by a PhD HS teacher:

I often feel like the world looks at this choice we’ve made as some sort of failing condition. Once in a while I get a student asking me, carefully, why I’m not teaching college if I’ve got my doctorate. The assumption often seems that it’s because I couldn’t make it as an academic so now I’m stuck teaching high school. If only graduate schools valued and encouraged returning to (or entering) K12 practice as an outcome for the PhD (DOCZ, 2012).

Jeff Shaver (personal communication) also expresses similar views:

I knew I wanted to be a high school science teacher since I was a sophomore in high school. This career aspiration was the result of having outstanding high school teachers and a history of teaching in my family. However, I haven’t always felt supported in my decision to teach high school and often got questions like, “If you have a PhD, why are you teaching high school?” With that said, many students and parents appreciated the fact that I had research experience that enabled me to provide opportunities for students that they would not have otherwise gotten.

The perception of HS teaching as a failure for someone with an advanced degree is damaging to graduate students who entertain the idea of such a career choice and to the culture of the scientific community. Many students would be hesitant about discussing becoming a HS teacher with their advisor or thesis committee, fearing that it will “disappoint” them. HS teaching is not discussed as career option in thesis committees and rarely at career workshops. Most PIs have little idea of what HS teaching involves or what is being or could be taught in HS.

**Lack of classroom experience during PhD and postdoc training**

Beyond the perception problem, additional barriers discourage PhD graduates from entering a HS teaching career. First, it is difficult for graduate students to have a significant HS teaching experience during their PhD training in order to decide whether they might like or might be good at it. Graduate students are busy with their own training and work and therefore have little time to spend in a high school classroom. In addition, this time away from lab might not be acceptable to their PI.

On the other hand, finding a way into a classroom is certainly possible for motivated grad students, and there are some good programs that help facilitate such classroom experiences. The National Institutes of Health (NIH) Science Education Partnership Award (SEPA) Program partners graduate students with high schools in order to elevate the curriculum at the schools (National Institutes of Health, 2013a). The National Science Foundation (NSF) Graduate STEM (Science, Technology, Engineering, and Mathematics) Fellows in K-12 Education (GK-12) Program provides training for graduate students through collaborations with K–12 classroom teachers (American Association for the Advancement of Science, 2013). Both the SEPA and the GK-12 programs are designed more to enrich K–12 classrooms than to provide a route to a teaching profession for the graduate student. In addition, the NSF-sponsored Robert Noyce Teacher Scholarship offers scholarships to graduates of STEM programs and professionals who enroll in certificate programs (National Science Foundation, American Association for the Advancement of Science, 2013). This scholarship requires teachers to work in under-served schools for 2 years for every year of support (~4 years), which may not always be the right fit for an individual. Another program that provides training in college classrooms for postdocs is the NIH-sponsored Institutional Research and Career Development Award (IRACDA; U.S. Department of Health and Human Services, National Institutes of Health, 2013b). This program focuses on connecting postdocs with mentor-teachers at institutions (not high schools) that focus on underrepresented groups. The aforementioned programs are helpful in providing PhD trainees or postdocs with an initial experience in the classroom, but they do not provide a pathway to certification, and many of them restrict the types of schools at which they can teach.

**Difficulty in becoming a high school teacher after obtaining a PhD**

The requirement of a teaching certificate provides the greatest barrier of all for PhDs who want to teach in public schools. The accreditation process often necessitates 2 additional years of training, a significant burden of time and potentially money for someone who has already completed a lengthy PhD training program. Owing to a need for STEM teachers, some states have instituted alternate certification programs to streamline this process for individuals with advanced degrees. The requirements for these programs vary greatly by state, but they generally require that the candidate pass a subject test and enroll in classes on pedagogy, class management, and lesson design. Some of these programs have restrictions, such as requiring candidates to work in rural underserved communities for a given amount of time or that the candidate already be used by a school district.

**CAN WE PROVIDE A BETTER ENTRY PATH FOR PhDs TO TEACH HIGH SCHOOL BIOLOGY?**

As discussed here, PhDs who are interested in secondary school teaching find themselves in a “no man’s land,” not being encouraged by the research community or by the K–12 educational community. In the following, we discuss ideas for how this overall path might be facilitated.

**Expose PhDs to the possibility of high school teaching**

Most PhDs who are currently teaching HS science arrive at this choice in spite of, rather than because of, a good mentoring system. Quite notably, HS teaching is frequently omitted from among the many nontraditional career tracks currently being advocated for PhDs (e.g., patent law, public policy, business or nonprofit administration, college teaching, science writing). This situation can be changed, however, by inviting PhD high school teachers to talk at career workshops aimed at graduate students and postdoctoral fellows and making this career option more visible at national meetings. Having clear information about how to get jobs in this sector...
also is essential. Most Ph.Ds are poorly informed, and information on
the Web is complicated and often state specific. The differences
between public and private school jobs could be explained and pre-
sented more explicitly to Ph.Ds, and perhaps a national job board
(e.g., for private schools seeking Ph.D-trained teachers) could be
organized.

Before they make commitments to pursue HS teaching paths, it
would also be useful to give interested Ph.Ds more opportunity to
see what HS teaching is like. All Ph.Ds have experienced HS, but it is
hard to imagine what it is really like to be on the other side of
the classroom. The NSF’s GK-12 program gets Ph.D students into class-
rooms. In addition to such formal mechanisms, however, it would be
relatively easy to institute low- or no-cost partnerships with local
high schools that are tailored to students interested in the possibility
of a high school teaching career. For example, a 2-week “shadow”
of a high school teacher might give Ph.D students or postdocs a
sense of whether they could imagine themselves teaching several
classes per day, 5 days per week

Restructure a certification program for Ph.D STEM educators
Public schools are losing out. The most prestigious and selective
private high schools in the country hire Ph.Ds to their faculty without
a teaching credential. Private schools allow these teachers to pick
up important teaching skills through professional development op-
portunities and/or mentor programs within their school. And it is
working; in most cases, Ph.D hires become outstanding private
school teachers. Public schools, with their tedious teaching creden-
tial requirements, cannot compete effectively with private schools
for a newly minted Ph.D seeking a job.

In our view, a pipeline of Ph.Ds entering private schools is not in
the best interest of our overall educational system. Furthermore, the
complete lack of training/certification for entering private schools is
not in the best interest of a Ph.D seeking to become an effective
teacher. There is a great need to develop tailored programs that
efficiently train Ph.Ds to enter and become effective teachers in ei-
ther public or private school, recognizing that their backgrounds
and years in training differ from those of someone with a bachelor’s
degree. The current accreditation system is not effectively meeting
this goal. We recommend the creation of intensive certification
courses (~6–10 weeks) designed specifically for Ph.Ds that teaches
pedagogy and high school level teaching methods coupled with a
short teaching internship. Even if the cohort was small (e.g., 50 fel-
lowships per year), it could have a powerful effect. The NRC report
identified “a prestigious national fellowship that provides training
and placement, and covers living expenses” would cause Ph.Ds to
consider secondary school teaching (Committee on Attracting Sci-
ence and Mathematics Ph.D’s to K-12 Education, 2002). In addition
to providing an attractive entry point to teaching, such a program
would send a message that Ph.D trainees have a place in the HS
system.

Implementation of such a program is nontrivial, since some
entity (state or federal government or private) would need to
administer and fund it and help to place Ph.Ds in school systems. If
run at a national level, individual states would need to accept such
training for certification to teach in their schools. In 2002, the NRC
Phase II report proposed such a national level training program for
Ph.Ds to enter K–12 education. In this case, the proposed national
program was to provide 2 years of support of Ph.Ds, structured as a
postdoctoral program, to train and intern in a school. Unfortu-
nately, the NRC recommendations were not followed up by the
U.S. government. At the present time, the NSF would be well
positioned to link such a new Ph.D teacher training program to
their existing efforts (GK-12) that enable Ph.D trainees to have
experiences in K–12 classrooms. Alternatively, a philanthropic
organization with combined missions in research and K–12 educa-
tion (e.g., Gates Foundation, Carnegie Foundation, Howard
Hughes Medical Institute) could make a major impact by establish-
ing a first-of-kind program to facilitate the transition of Ph.D gradu-
ates into HS teaching. After placement in high school teaching, a
possible added feature would be to include a summer stipend for
science curriculum development (perhaps for a limited time of a
few years). In addition to augmenting teachers’ salaries, such a
summer program would provide opportunities for creativity and
innovation that could attract energetic Ph.Ds toward HS teaching.

Networking PhD K–12 educators
Improved networking of Ph.D-trained K–12 educators, both locally
and nationally, could stimulate recruitment and career development.
Because their numbers are small, Ph.Ds involved in K–12 education
rarely encounter one another to share experiences or ideas for the
classroom. Such interactions with one another (and with Ph.Ds in
higher education) could have a powerful effect on their professional
development and have a positive impact on STEM education
overall.

One way to foster a sense of community among Ph.D educators
would be through the creation of a website that would serve as a
source of information (e.g., how to get jobs, job postings, curricu-
ulum ideas) and social networking. The cohort of Ph.D HS teachers
could also interact at a national meeting, where they could present
their efforts and share notes on science curriculum development,
as well as meet senior guest scientists and educators.

CONCLUDING REMARKS
Our scientific and educational communities cannot wholeheartedly
advocate bringing real science into K–12 classrooms and yet discour-
age or make it difficult for trained scientists to enter the precollege
teaching profession. Small changes, however, can alter the status
quo. These include developing better local and national awareness
of career paths in K–12 education and expediting/publicizing training
programs that will allow Ph.Ds to find jobs and be prepared to enter
precollege classrooms. Given the coincident problems of insufficient
number of jobs for new Ph.Ds and the need to bring more exciting
science rather than facts to K–12 education, the time is ripe for seri-
ous thinking on implementation. It also is a good time to break down
traditional barriers that prevent more interactions and partnerships
between “scientists” and “educators.” Critically, any new program
aimed at introducing Ph.Ds into K–12 education must be developed
with the help and guidance of K–12 schools. Only in this way can we
build an education system that can truly bridge K–12 and graduate
institutions and introduce scientist-teachers at all levels of our educa-
tional system.

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Perspectives on an alternative career path in regulatory science

F. Owen Fields
Pfizer, Worldwide Research and Development, Collegeville, PA 19426

ABSTRACT Perspectives are provided on an alternative career path in regulatory science for those currently involved in basic biology research. This path is compared and contrasted with basic research, and factors to be examined if one is considering such a path are discussed.

INTRODUCTION

My goal in this article is to provide some perspective to those currently involved in basic biological research on an alternative career path that others and I have chosen. I relate this perspective as a former basic scientist. That is, I was where the typical readers of Molecular Biology of the Cell now are. Having been you and having known many people in your position, I know that some of you are considering alternative career paths for a wide range of reasons.

I begin with a few relevant facts of my biography. I attended college at a medium-sized school in my hometown of Wichita, Kansas, in engineering and business. I quickly felt the need to get my head out of the weeds, however, and switched to a major in biochemistry. After this, I pursued my PhD at the University of California, Berkeley, where my graduate advisor was Jeremy Thorner. By the time I was finishing up my thesis research and was beginning to think of what direction my career should take, I realized a couple of things. First, I wanted to at least try something away from the bench. Second, I had always been interested in the interface between science and society and specifically in science-related policy. I had no idea, however, how to pursue such a career interest.

At about this time I was at a conference and cutting through a job fair on my way from one scientific session to another and noted a person from the U.S. Food and Drug Administration (FDA) sitting behind an FDA banner at a table. She was recruiting but seemed rather lonely. I initially walked past, but then turned around and sat down, and we talked. She informed me that the FDA was wrestling with how to regulate food biotechnology and needed to hire some molecular biologists. To make a long story short, I decided to take the job and moved to Washington, DC, where I initially worked just off the National Mall before my office moved downtown, north of the White House. There I helped develop U.S. food biotechnology policy, and I wrote the U.S. approval decision for a number of products, including the so-called “Round-up Ready” soybean.

Not long thereafter, the approval system was becoming well-trodden ground, and I decided to move to pharmaceutical research. I started at Wyeth Research, outside of Philadelphia. There I worked on a number of programs, including BMP2, a program I am proud to say won the Prix Galien Award for biotherapeutics in 2008, and many other programs. After some years, as happens in this business, Wyeth became part of another corporation through a merger, in this case Pfizer. Initially I was in charge of regulatory strategy for the Pfizer Biotherapeutics Research Unit, and thereafter I took on responsibility for all of the new drugs in Pfizer’s worldwide research and development organization.

WHAT I CONSIDERED BEFORE I MADE “THE JUMP”

When I made what I now call “The Jump” out of basic research, I wondered about a number of matters, and over the past 22 years I have reconsidered these matters periodically. It occurred to me that anyone at the point I once was would likely consider the same matters, so I address these in the rough sequence in which they occurred to me.

What do you actually do in this role?

This is perhaps the hardest question to answer. New drug development is among the hardest things to do in the realm of human accomplishment. One of the reasons it is so complex is that (appropriately) it is one of the most regulated activities one can engage in; the level of regulation is higher than in any other industry besides, perhaps, the nuclear power and weapons industries. Scientific teams
that accomplish successful new drug development are very large and complicated, and it is your job as the regulatory scientist to lead them through the regulatory science requirements. I use the term “regulatory science” because, in contrast to some other fields, in this industry all of the requirements are driven by scientific considerations. Communication (making it clear to regulatory agencies what you are doing, and why, in what is essentially a massive peer review process) is also an important part of the role.

How does it compare with doing basic science?
Drug development, and especially the regulatory science aspects of drug development, are more analogous to so-called “Big Science.” A drug entering early-stage clinical development has been touched by literally hundreds of people, and the cost of discovering it, manufacturing it, and even conducting the smallest of clinical trials is several times as expensive as a typical yearly laboratory budget in basic biology. By the time it is subject to the approval process, thousands of scientists have touched it, and the level of investment required is unimaginable, unless you run a small country.

What is “the jump” like?
The transition out of basic science can be disorienting to some, and it requires mental plasticity as you go from a role in which you know more about your research than anyone else in the world to a role in which there is a truly vast amount to learn and no mechanism for learning it other than jumping in, getting mentored, and self-teaching. In addition, basic science is all about pure scientific reality, whereas regulatory science is an agglomeration of norms and paradigms that, although science based, have been built up by sometimes random accretion over the past century.

Is a background in basic science useful in this area—will my knowledge and skills be used?
Yes, very much so, in terms of the fundamental skills required in basic biology. The reason is simple: as with basic science, the amount of information required to pass regulatory science hurdles is vast, and if you get your head in the weeds, you will simply get lost. It is also the case that in this area of endeavor the fundamental question is always, “OK, these are the facts, now what does all this actually mean in the big picture, and what then must we do?” Having said this, much of the highly detailed information in your head will atrophy as it is replaced by other things. The important concepts you learned as a scientist will remain fresh in your mind.

Are the people as intellectually talented and creative as the people in fundamental research?
The consistency of intellectual talents of people working in basic research, at least in the environment in which I worked at Berkeley, is very high. The level of talent in this area is not as consistent. However, in this role you do work with tremendously smart and knowledgeable people, including basic scientists involved in discovery and research, as well as physicians, and they can often teach you as much about your work as you can teach them about theirs.

How does one get into such role?
Historically there were no certification or master’s programs. There now are a few around the country, and they can be a useful way to enter the field. However, many people still enter the field from either some other area of pharmaceutical research or academia, and there is no typical path. I seem to represent the rare case of someone entering the field immediately after graduate school. Others enter pharmaceutical research in some manner and then transition to the role. Others were unemployed or underemployed and happened to stumble across the role. In my experience, a minority enter the field by actual design (i.e., they decide they are interested and actively seek such a role), but many discover the nature of the role by working with a regulatory scientist and gain interest in that manner.

SOME EXAMPLE CAREER PATHS
In preparing this article, I thought that some examples of actual career paths would be useful, and I took an admittedly unscientific survey of a series of selected colleagues in regulatory science at Pfizer. The paths of those I polled are noted here, as well as some high-level perspective from these individuals. I have left them anonymous.

Person 1
Parent was in the industry, and therefore this person knew about the role early; attended graduate school; entered industry as a scientific writer, then moved to regulatory science. Relevant quote: “Having a broad scientific background was really useful … but I use my scientific background less now for day to day work … but if I didn’t have it, I would probably feel lost when listening to program scientific discussions. I think my impact has been much greater than if I had stayed in academia and focused on basic science.”

Person 2
Completed graduate school, took a postdoctoral role in academia, entered a research role in start-up company, and then moved into regulatory science. Relevant quote: “Having a broad scientific background was really useful … but I use my scientific background less now for day to day work … but if I didn’t have it, I would probably feel lost when listening to program scientific discussions. I think my impact has been much greater than if I had stayed in academia and focused on basic science.”

Person 3
Completed graduate school, took an academic postdoctoral role, then faculty role in academia, followed by a laboratory head role in industry, then moved into regulatory science. Relevant quote: “I think academic research might have been more intellectually challenging in delving in depth into scientific problems, but regulatory science and strategy requires a breadth of skill sets on multiple levels from the integration of multiple scientific disciplines.”

Person 4
Completed graduate school, then moved to a regulatory consultancy, followed by a regulatory science role in industry. Relevant quote: “I knew in my final year of the PhD that a career in the laboratory was not for me as my desire was to have a broader interface with different aspects of science and drug development. … I found out that roles in regulatory science required all the transferable skills which you gain in graduate school. … I believe that it was a good career choice for me and would have liked to have known about this career route at an earlier point in time.”

Person 5
Completed graduate school, took an academic postdoctoral role, then spent 3 years in research at small biotech, worked 12 years in R&D at a large Pharma, was laid off, and then moved into regulatory science after completing a master’s program. Relevant quote: “I wanted to change career path from ‘great expertise in a narrow area’ to ‘big picture’ view. A background in science is still of great value to me today; however most of the exact science that I did is
irrelevant. I would consider regulatory to be equally intellectually challenging as academic science, but in a different way. Unlike basic science, in regulatory one does not generally choose the problem one wants to tackle. Rather, the problems come to you, frequently unexpectedly, and may require integrating knowledge across highly divergent areas (science, law, etc.). I wish I would have moved earlier.”

Person 6
Attended medical school and a medical fellowship in academia, then worked on a National Cancer Institute fellowship, served as a medical reviewer at FDA, and then moved to a regulatory role in industry. Relevant quote: “All these experiences gave me an appreciation for the need for new treatments and the potential impact on multiple patients that participation in the development process can bring. ... I could be more heavily involved in decision making about the practicalities of program planning and execution in a global environment that integrates business, clinical, and other considerations on an ongoing basis.”

CONCLUSION
Many of the readers of this article, by either choice or necessity, will either seek, or be forced by circumstance, to pursue an alternative career outside of basic research. I have attempted to give some perspective on one such path. I hope this perspective is useful to the reader.
From bench to bar: careers in patent law for molecular biologists

Nathan A. Machin
Intellectual Property & Litigation Group, Amgen Inc., Seattle, WA 98119

ABSTRACT Leaving science to pursue a career in patent law requires a considerable investment of time and energy, and possibly money, with no guarantee of finding a job or of returning to science should the decision prove infelicitous. Yet the large number of former scientists now practicing patent law shows that it can be done. I provide suggestions for investigating the potential opportunities, costs, risks, and rewards of this career path.

The molecular biologist wishing to retool herself or himself as a patent law professional has a number of specific career options to choose from.

CAREERS FOR NONATTORNEYS
One need not become an attorney before beginning a career in patent law. Some patent law firms hire scientists or engineers with advanced degrees or training in a technical field to train as patent agents (sometimes using other names, such as patent scientist or technical specialist). Patent agents must take and pass the same U.S. Patent and Trademark Office (USPTO) registration exam (informally called the patent bar exam; discussed below in Careers for Attorneys) as patent attorneys, and they perform many of the same duties as a patent attorney, but with certain important limitations. Patent agents are, by definition, not attorneys, and so are legally prohibited from practicing law beyond those “tasks which are incidental to the preparation and prosecution of patent applications before the Patent Office” (Sperry v. Florida, 1963). This limits the activities they can engage in without attorney supervision. Also, in the United States, nonattorneys are prohibited from becoming partners in the law firms in which they work, except in Washington, DC, although the American Bar Association is considering whether to urge the state bar associations to follow the District of Columbia’s example (American Bar Association, 2011). But many patent agents are quite satisfied with their careers and are highly valued by their employers, and should an agent wish to become an attorney, matriculation at a part-time law school program might be possible.

Patent examiners work for the USPTO or the patent office of another country or region. Patent examiners are tasked with determining whether the patent applications assigned to them meet the requirements for patentability. The examination of a patent application often goes through multiple rounds of review, with the examiner rejecting it and the applicant (or, more typically, the applicant’s patent attorney or patent agent) amending the application and/or rebutting the grounds for rejection until either the application is allowed to issue as a patent or is abandoned by the applicant.

USPTO employees must be U.S. citizens (USPTO, 2013). The USPTO hires new examiners for their technical expertise and communication skills but does not expect them to know patent law, so every new examiner receives a considerable amount of paid on-the-job training. Traditionally, examiners were required to work at the USPTO’s headquarters outside Washington, DC, but the USPTO is opening satellite offices in other cities and expanding its telecommuting options. The USPTO also allows for a range of creative alternatives to the traditional nine-to-five, Monday-through-Friday work schedule.

CAREERS FOR ATTORNEYS
A patent prosecutor, like a patent agent, spends most of his or her time engaged in activities related to the procurement of patents. This includes talking to clients about their potentially patentable inventions, drafting and filing patent applications, and taking patent applications through the USPTO’s examination process. Ideally, this is done as part of an overarching patent strategy that the patent attorney has developed with his or her client. Patent prosecutors also analyze third-party patents to determine whether they present potential obstacles to their clients’ business plans; evaluate third-party patent assets that might be bought, in-licensed, or acquired through a merger or acquisition; and assist in the out-licensing and sale of their clients’ assets.

A patent litigator specializes in asserting his or her clients’ patent rights against alleged infringers and defending clients who are being sued for patent infringement. In patent litigation, as in civil litigation generally, the actual arguing of a case to a judge or jury is the
relatively short end of a long and complicated process (and many cases are settled or dismissed before they even reach trial). Thus, for any given case, a patent litigator will spend most of his or her time identifying and analyzing the relevant provisions of law, collecting evidence, building a litigation strategy, making or assessing settlement offers, and much else besides.

The line between the duties of a patent prosecutor and those of a patent litigator is not always clearly drawn. The patent prosecutor who shepherded an application through the USPTO might be asked to assist or join a litigation team preparing to assert it against an infringer. Patent litigators sometimes help patent prosecutors to obtain patents that will be easier to successfully enforce against an infringer. Prosecutors and litigators might work together to challenge the validity of a third party’s patent using certain quasi-judicial administrative procedures that are available at the USPTO and other patent offices.

Patent agents and attorneys alike must pass the patent bar exam in order to practice before the USPTO. The aspiring patent agent who has passed the patent bar exam will have an advantage over job-seekers who have not, but it is a difficult test that requires considerable preparation. While the exam itself tests one’s knowledge of patent law, in order to sit for the exam, an applicant must satisfy the USPTO that he or she has the requisite technical background. Possession of a bachelor’s degree in molecular biology, biology, or biochemistry (among many other fields), will suffice (see General Requirements Bulletin [USPTO, 2012]). The USPTO also puts important restrictions on the registration of non-U.S. citizens (USPTO, 2012). Patent attorneys, not but patent agents, also must be admitted to practice law in one or more of the states or in the District of Columbia, and so will have to have taken and passed a state bar exam and satisfied several other criteria. For example, practicing attorneys, unlike scientists, must possess good moral character (Committee of Bar Examiners, 2012). Patent attorneys, but not patent agents, also must be admitted to practice law in one or more of the states or in the District of Columbia, and so will have to have taken and passed a state bar exam and satisfied several other criteria. For example, practicing attorneys, unlike scientists, must possess good moral character (Committee of Bar Examiners, 2012). Most states administer the bar exam only to law school graduates, although some allow for an apprenticeship instead.

**TYPES OF EMPLOYERS**

Patent examiners work for a government-run patent office, as already mentioned, but other patent professionals typically begin their careers with a private law firm. Such employers range from small, specialized patent law firms to enormous international firms that practice every sort of law. At a law firm, one works for several, and perhaps many, different clients. Whether one is an attorney or agent, under the traditional law firm model, one’s time is billed out by the tenth of an hour. Many firms require their attorneys to bill at least a certain number of hours per year. This creates pressure to efficiently use one’s time so as to maximize the amount of one’s workday that can be billed to the client. This pressure has only increased during the lingering global recession, as clients scrutinize their legal bills ever more closely. Consequently, some firms are exploring alternatives to by-the-hour billing, such as prenegotiated fees for specific projects (Zahorsky, 2012).

Most medium-sized or larger biotech and pharmaceutical companies have their own “in-house” patent attorneys and patent agents. In-house legal staff are free of the tyranny of the billable hour (as their employers are their only clients), although their time might be tracked, and they certainly are expected to be productive and efficient. In-house positions are typically available only to attorneys and agents with at least a few years of law firm experience.

The technology transfer offices of many universities and of government research organizations like the National Institutes of Health also employ patent professionals to identify, protect, and license intellectual property generated at their institutions, but their hiring criteria and job descriptions vary widely.

**FINISHING A PH.D.**

The graduate student contemplating a career in patent law will have to make another important decision: whether to finish his or her degree. There are good reasons to stick it out. For nonattorney patent law positions, an employer may require a Ph.D. Even if it is not a job requirement, a Ph.D. will impress potential employers and clients. The years of experience behind the degree ensure technical expertise. And there are intangible personal benefits to finishing a degree program in which one has invested so substantially. But many excellent biotech patent attorneys (and all but a few biotech patent litigators) have limited or no postbaccalaureate scientific training, and the opportunity costs of advanced degrees have been well documented (Chemjobber, 2012). Those costs increase substantially when finishing one’s dissertation delays starting a potentially lucrative legal career. Thus the aspiring patent attorney who does a boldly rational cost–benefit analysis might elect to start his or her legal career as soon as possible rather than finish his or her Ph.D.

**FIRST STEPS**

There is no substitute for talking with a number of patent professionals, preferably including some who themselves made the leap from science to patent law. The best such contacts will be people you share some connection or commonality with: a friend, a friend of a friend, a graduate of your degree program, someone whose dissertation was in the same field as yours—anything that establishes a frame of reference for your discussion. The technology transfer office at your institution might be able to direct you to the patent law firms they work with, or you can find patent professionals online. Ask whether they would be willing to schedule a short appointment for an informational interview about careers in patent law. (Your success rate might increase if you mention that you will not be asking them for a job.) If you are invited to an in-person interview, be sure to wear business-appropriate attire. Be prepared with specific questions for your interviewee: How did he or she decide to enter patent law? What other careers did he or she consider? What information did he or she find helpful in making his or her decision? Why did he or she decide to go, or not, to law school? How does law school compare with graduate school? Does he or she recommend finishing your degree before leaving science? What is a typical day like for him or her? What does he or she find most satisfying and most challenging about his or her work? How would he or she compare his or her patent law career to his or her previous life in science? If his or her professional biography is posted on his or her firm’s website, use this information to select appropriate questions.

These contacts also can provide some insight into the current state of the job market for patent agents or attorneys. Legal recruiters in the geographical region where you wish to practice can be found online and should have an even better sense of this. Note that not all recruiters work with patent agents.

Anyone considering enrolling in a full-time law school program should give this decision very careful thought. Law school graduates can accrue six-figure student loan debts and face uncertain job prospects (Carrns, 2012), especially in the current economic climate. An alternative that might be available is to work for a law firm that allows its patent agents to attend law school in the evenings. But squeezing a full-time job and several hours of law school classes and homework into a single day is a challenge, to say the least (Schwab, 2009). And it usually takes four years to earn a law degree this way, rather than the three years needed for a full-time program of study.
SUMMARY
Reinventing oneself professionally is difficult and should not be attempted casually. Only you can determine whether a career in patent law is right for you. But many molecular biologists have found their scientific training to be a good preparation for a legal career. The law requires an ability to make and analyze arguments, weigh evidence, and communicate clearly in writing and orally—skills that are developed in writing and analyzing scientific papers and presenting results at lab meetings and scientific conferences. One wanting to leave science but still interested in making full use of his or her scientific training would do well to consider a career in patent law.

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Life as a professor at a small liberal arts college

Josh Sandquist\textsuperscript{a}, Laura Romberg\textsuperscript{b}, and Paul Yancey\textsuperscript{c}
\textsuperscript{a}Department of Biology, Grinnell College, Grinnell IA 50112; \textsuperscript{b}Biology Department, Oberlin College, Oberlin, OH 44074; \textsuperscript{c}Biology Department, Whitman College, Walla Walla, WA 99363

ABSTRACT We present a look at what it is like to be a professor at a small college: one professor at Grinnell College, one at Oberlin College, and one at Whitman College.

INTRODUCTION
One of the more common careers for PhDs in the biomedical sciences is that of college professor at an institution where the focus is on teaching but there are nevertheless research opportunities. Such professorships are often found in small (<3000 students) liberal arts colleges, institutions that abound in the United States. In this essay, three faculty from small liberal arts colleges were asked to provide some information about themselves, provide specific information concerning how they spend a typical day or week at work, detail some likes and dislikes, and share some general thoughts on their careers as professors at small college. In an effort to ensure that a breadth of experiences and perspectives is provided, each of the professors is from a different institution, and each is at a different stage of his or her career.

JOSH SANDQUIST, PhD
Assistant Professor of Biology, Grinnell College, started in 2012

Grinnell College basics
Location: Grinnell, Iowa, population 9169
Founded: 1846
Enrollment: 1693
Number of tenure track biology faculty: 14

Personal background
On leaving high school, I attended Drake University, a private school of ~3500 students located in Des Moines, IA, with the intention of becoming a pharmacist. Sometime during my sophomore year I began to realize that I was less interested in the clinical aspect of pharmacy and more interested in the basic science of pharmacology. Fortunately for me, I developed strong relationships with a couple of mentors who helped me to find summer research opportunities and steered me toward a new degree offering, a B.S. in Pharmaceutical Sciences. As my senior year approached and I thought more about what I wanted to do after Drake, I took a closer look at my mentors and their chosen professions. I really valued the interactions I had with them. I also liked that they performed research in addition to teaching and that they used their research program as a tool to expose students to real, unscripted science. I went on to do my graduate work at Duke and then my postdoctoral work at the University of Wisconsin–Madison. While at both places I felt the call of the bench, it was the one-on-one interactions, either as the mentee or later as the mentor, that I prized the most. I came to appreciate two things about science education: better educational experiences occur in small groups, and it is easiest to learn science by doing science. These experiences and realizations led me to a career at a small liberal arts school where teaching, research, and mentoring are all highly valued.

A typical week
Describing a “typical” week in my life is no easy task, in that the 16 weeks of a semester play out in a nonuniform manner. Although there is a certain weekly ebb and flow to the semester, there are also intermittent periods of intense demand on my time and faculties. Moreover, the particular constellation of tasks that consume my time is different each week, although the evaporation of all free time is one common feature. Thus the following is less a description of an average week and more a list of the types of activities that occupy my time in any given week, although I can say that the three broad activities that occupy most of my time are...
course preparation, grading, and interactions with students and colleagues.

I’ll begin my week by describing my Friday afternoon. This is when I tackle things that did not require immediate action when they first came up during the week but cannot be put off any longer. Such tasks may include researching a piece of equipment I need for my lab, responding to email, or posting modifications to reading assignments for next week based on the progress made over the last week. In addition, this is often when I start grading assignments turned in during the week. I usually return to similar activities Friday evening and Saturday. Having a family, I attempt to limit work on the weekends to later in the evenings as much as possible. However, a few morning or afternoon hours on one or both days are often unavoidable, depending on how much grading I have to do and what activities are planned for Monday. Evenings before class days require several hours of class preparation, and Sunday evening is no exception.

At my institution we teach five courses a year, generally resulting in alternating three-course and two-course semesters. Labs count as half a course. So, in my three-course semester, let’s say two classes each with a lab, I will spend ~11 hours in class or lab per week. The amount of time it takes to prepare for these classroom hours varies depending on the nature of the lecture/activities to be given/performed in class. I find that class preparations usually expand to fill whatever time I have to give. Besides physically preparing the lecture slides/notes (which can take several hours for a 50-minute lecture if starting from scratch), at least 1 hour before each class/lab meeting is spent doing one or more of the following: last-minute writing/reviewing of lecture, reading up on subject matter outside my comfort zone, researching questions I was unable to answer during the last class, preparing points for class discussion, reviewing the wording on an assignment/quiz/exam to ensure that there are no ambiguities, making sure all materials and equipment are ready for lab, and so on. On top of preparing assignments, quizzes, and exams, they have to be graded, too. Sometimes the grading can wait until the weekend, but some things require a short turnaround so that the feedback can be used in the next assignment. Thus at times grading can create a major demand on my time, leading to late nights.

Although I spend the majority of my time preparing for class and grading, I spend what I find to be a surprising amount of time in meetings. These include regular meetings of the department and less regular meetings of teaching and learning discussion groups, as well as class-related meetings such as organizational sessions with lab instructors. Of course several hours each week are devoted to office hours with students, which are more or less heavily used by the students at different times during the semester.

The foregoing meetings are mostly scheduled events and thus able to be planned around. However, more impromptu meetings, usually with students but also with colleagues or prospective students or someone else, also take up a surprising amount of time. These may take the form of answering questions immediately after class or a surprise visit in my office. In the latter case I may find myself recapping a lecture, explaining a test answer, discussing summer research internships, or working on a student’s 4-year plan. On top of in-person meetings, emails from students seem to come in 24 hours a day. I also find myself working on things for students no longer in my class, such as letters of recommendation. All of these interactions and meetings consume a significant amount of time. However, extensive interaction with students is one of the things that drew me to a small school, and such interactions are the best experiences I have.

The foregoing descriptions give the impression that weekends are busy but manageable, whereas the workweek comes across as a never-ending litany of tasks, and I have yet to mention scholarship and service, which are two other key aspects of the job. Service involves one or more commitments that can take many forms. As a newcomer I have been shielded from demanding service roles so far, and thus service obligations have not yet taken up much time. Scholarship involves many activities likely to be familiar to the reader—planning and performing experiments, ordering supplies, training students at the bench, and writing papers or grants. So far, most of my scholarship activities have involved getting my lab up and running. The tricky thing with science is that not a lot of experiments fit into sporadic 30-minute windows of time. I am thus finding it difficult to squeeze in meaningful bench work during the semester, and although I will not have lectures to prepare in the summer, I plan to have students in my lab working on independent research. Training these students and helping them design their projects will be fun and exciting but will also eat into research time.

I am not trying to downplay the importance of scholarship and service activities. Eventually, I expect to make time for scholarship and service through increased efficiencies in teaching-related activities. In fact, I felt far more efficient with respect to course preparation after only a semester. In particular, I feel like my ability to frame lectures, write exam questions (writing good exam questions was a surprisingly time-consuming process for me), grade papers, and the like is constantly improving and becoming more streamlined. I still have to work as hard, but instead of simply sprinting to keep up, I now have more time for critical reflection, which results in an increase in the quality of my work.

Likes and dislikes

I would call them stress sources rather than dislikes. Perhaps the biggest source of stress is grading. The work can be grueling at times; there are only so many lab reports I can read in one sitting. However, often the more taxing thing is assigning a grade. Making comments and suggestions are work, but generally the goal of those is still to teach. Assigning a grade, on the other hand, does not really instruct, and the letter at the top of the page is such a source of anxiety for many students. Preparing for class, in particular for a new course when last year’s notes do not exist, can be stressful. Between lecture and lab I essentially have eight deadlines a week, which gets to be draining, particularly as lecture and discussion preparation is open ended, with activities such as finding that one perfect example taking up unnecessary time. Another stress is the intellectual isolation. At a small school each professor is generally the lone representative of a particular area of science. As such, I do not often have the opportunity for in-depth discussions on esoteric aspects of my research.

The sources of stress in my job are actually relatively few. In contrast, there are many things I like. The small-group or one-on-one interactions with students, while demanding, are the best part of the job. Students often have a broad curiosity that is refreshing after my years of focused research on very narrow topic. There are also those “ah-hah” moments at the white board in my office when I find just the right way to explain something and a visible connection is made in the student’s mind. Other virtues of being at small liberal arts school include having the same student in introductory and advanced courses and interacting with more non-science majors, as fewer nonmajors science courses exist. Even in my advanced class several students were double majors, with one major in the humanities. I enjoy teaching on broad topics to broad audiences because I get to learn a lot, too.
Conclusion

In the course of writing this I realized that there are a few aspects to being a professor, especially at a small liberal arts school, that have not quite matched my expectations. For one, I have many more premed students in my classes than I was expecting. Another thing, which I touched on earlier, is that with so many demands on my time I often do not feel that I have the time to be as thoughtful about and creative with my teaching as I would like to be or am expected to be. Although this will change some now that I have a base set of lectures and activities to expand on, service activities will soak up that "spare" time. As I also mentioned earlier, it is a little bothersome how much energy both my students and I spend producing a single-letter grade. It is not that I expect students to be completely oblivious to grades, but I anticipated a little more focus on the process. Together these things sometimes make me feel that my role is to generate some defined product as opposed to provide students an opportunity to expand their minds. Despite these things, I have come to the conclusion that while this job is demanding, the activities that occupy the majority of my time are ones that attracted me to the job in the first place, and those are the activities that will keep me in front of a class for as long as I am allowed.

LAURA ROMBERG, PhD
Associate Professor of Biology, Oberlin College, started in 2004

Oberlin College basics

Location: Oberlin, Ohio, population 8286
Founded: 1833
Enrollment: 2900 (2300 + 600 in the Conservatory of Music)
Science departments: Anthropology, Archeology, Biology, Chemistry/Biochemistry, Computer Science, Environmental Studies, Geology, Mathematics, Neuroscience, Physics and Astronomy, Psychology, Sociology
Number of tenure track biology faculty: 13

Personal background

Coming out of high school, I knew I was interested in science, but not in which discipline. However, in my freshman year at Princeton I took an introductory biology course and found it utterly fascinating. I was never interested in medicine, and I was not initially interested in teaching, in part because I did not (and still do not) consider myself primarily a “people person.” After graduating with a B.A. in Molecular Biology, I earned a PhD from the University of California, San Francisco, and then did postdoctoral work at Duke and then Harvard. In the course of my graduate and postdoctoral work, I noticed several things about myself and what I valued about being a scientist: first, the process of seeking underlying explanations appealed to me; second, I very much enjoyed fitting small pieces into a larger whole; third, I came to find that I enjoyed preparing for and giving lab meetings and the challenge of explaining myself clearly to my lab mates. The last two realizations provided one of my first inklings that I might enjoy teaching, as much of teaching is concerned with preparing the clearest possible explanations for students and helping them fit apparently disparate pieces into an integrated whole. To more explicitly explore what teaching might be like, I taught a class as an adjunct professor during my postdoc and then spent a year as a visiting professor before beginning my tenure-track position at Oberlin. Having taught classes where I was the one in charge (as opposed to being a TA) really helped me decide that this was a job that I wanted. Although not absolutely necessary, these experiences likely made me a more attractive candidate for the position I landed at Oberlin.

Typical day/week

Strictly speaking, any given week can vary quite a bit from any other, so the most accurate way to describe how I spend my time is to first consider those activities and responsibilities that happen every week and then consider those that occur less often.

The first weekly responsibility is, of course, teaching. I teach two or three classes per semester, and these may be lectures, labs, or seminars. The standard lecture class is three 1-hour periods per week, the standard lab class is one 3-hour period per week, and a standard seminar might be two 1.5-hour periods per week. These times represent contact hours, and preparation time must be added to them. Assuming that the lectures are ones that I have already taught a number of times, I use an additional 2–3 hours per course per week for preparation and modification. Lab classes require setup, and although much of this is done by laboratory support staff, not all of it is, and so I usually need at least 1 hour. For seminars, preparation entails reading the relevant papers and preparing handouts, which takes 1–2 hours.

In addition to teaching, I have weekly meetings with students working in my lab and with my colleagues. For seasoned students conducting research in my lab (i.e., students who have at least a semester’s worth of experience), I spend about 1 hour a week with each of them (I usually have two or three students doing independent research with me). I also have a weekly 1-hour faculty meeting.

Some activities take more time when first undertaken. The first time teaching a course is a huge amount of work. For example, it may take 8–16 hours to prepare each new lecture. Similarly, new student researchers take far more time than their more experienced peers: I typically spend up to 8 hours a week with them. For this reason, I usually try to have the new students start in the summer.

Preparing and grading exams and assignments is intermittent but quite time consuming. For exams, besides the exam preparation itself, I have to hold group review sessions, meet one on one with students who need extra help to prepare for the exam, grade the exam, and then meet with any students who wish to go over their exam answers. For paper assignments, I prep the students, read and discuss drafts of their papers, and then grade the papers. Once each semester, I have a series of meetings with student advisees. The meetings are not particularly long, maybe 20 minutes or so, but it is not uncommon to have as many as 20 advisees, so they add up.

After tenure, the amount of committee work increases. Tenured faculty may be expected to serve on a variety of time-consuming committees, including curriculum committees, hiring committees, and grant committees. In addition, everyone is expected to serve a 4-year stint as department Chair at least once.

That’s all during the school years; summers are for research. Nonetheless, the time commitment is significant, and it is not unusual for me to pull 40–60 hours a week during the summer supervising student research and/or conducting my own research.

Likes/dislikes

With respect to “likes,” there are many. At the top of the list is the opportunity to interact with the students. I find that it is possible to get outstanding students here, ones who are not only bright and talented, but also completely engaged in the process of learning. That is, many of the students want to interact with professors and
value the time they spend learning from them. The one-on-one interactions with students are the best part of the job. I get to know the students well, I get to talk serious science with them, and I get to watch them grow into sophisticated thinkers.

While researching, I often felt as if my efforts represented little more than a drop in the bucket. In contrast, with teaching I get direct and often rapid feedback, which makes it clear to me that I am having an impact on a person. Similarly, the hardwired requirements of teaching provides one with a continual sense of accomplishment, assuming of course that one takes care of business. In contrast, in pure research, one can literally work for years on a single topic before a paper comes out of it. I also find that the emphasis on teaching, as well as the relatively small number of faculty, has resulted in me becoming a much more broadly grounded biologist than I used to be. I understand now many things—metabolism and medical applications, for example—for better or worse than I used to as a result of having to teach about them.

A welcome side product of increased breadth and, perhaps ironically, the relatively small size of the campus and faculty is that it facilitates interdisciplinarity. For example, I became involved in a collaboration with a math professor largely because I was sitting next to him at a faculty meeting. Similarly, the fact that we are in the same building as the chemists foment interactions that might not be as likely to happen at a larger institution where a given department is housed within its own building or buildings.

Paradoxically, one of the consequences of being at a small liberal arts school with a heavy teaching load is that you often end up spending more time at the bench than you would if you were running your own lab at an R1 institution, where the principal investigators typically spend most of their time administering science rather than doing experiments themselves.

With respect to dislikes, they often revolve around time allocation. Specifically, it is often hard to balance my teaching and research activities. The teaching comes with hard and immediate deadlines that cannot be missed. In contrast, research deadlines are far more open ended, meaning that the one has to work hard not to procrastinate. Letters of recommendation also come with deadlines, as does grading. Although I am comfortable writing letters of recommendation for students I know well, writing letters for students I do not know well can be irritating, and I dislike grading outright. However, it is better than it used to be. I have learned how to establish and employ grading rubrics and how to write clear questions and other skills that make the grading less painful.

Oberlin and many other small liberal arts colleges are often in the middle of nowhere. Although this may make them safe places to raise families, it comes with a distinct downside: it is often hard for a partner to find a job. In addition, there is the more obvious issue of isolation that comes with transitioning from a place with a large population base (like Boston) to one with a very small population base (like Oberlin).

Then there are the “flip sides”: The flip side of the college smallness issue is that it is harder to find someone with a related specialty to bounce ideas off of, and it may be essential to develop collaborations with others at different institutions both to provide sounding boards and a place to learn new techniques or use more specialized, expensive equipment. The flip side of the student engagement is that some students can be very demanding and even a bit entitled. The flip side of direct, often rapid feedback from teaching is that when it isn’t going well, one may end up the recipient of very public criticism.

Other thoughts and conclusions
My first year was very challenging. I found the job even more time-intensive than research: I was routinely working 80 hours a week my first year. A big chunk of this was lecture prep. Things improved over time as I developed my lectures and acquired test writing and grading skills. I’ve also become more savvy about how I approach my work. For example, I deal with the cyclical nature of the work by getting a jump start on future assignments during times when the load is lighter. That is, if I know that I am going to be presenting a new lab in the spring semester, I might start the reading for it in the fall, during times when I am not swamped with preparing or grading assignments. I also make a point of staggering exams and paper assignments and consider very carefully when to take on new students (usually the summer). I have also learned how to think very hard about what kind of experiments to give my students and how feasible they really are, given the constraints of time, money, and training. Focusing on what is cheap and dependent on repetitive labor is a good way to start. Here’s a simple hierarchy as a guideline: picking colonies—great; subcloning multiple similar constructs—good; developing new protein purifications—not so good; working with sensitive mitotic cell extracts—impossible. Nevertheless, I still have to work fairly hard (~60 hours per week), and anyone who aspires to teach at a small liberal arts school should abandon the notion that it is a cake walk. That being said, I find my job very fulfilling and am more than satisfied with it as a career choice.

PAUL YANCEY, PhD
Professor of Biology, Whitman College, started in 1981

Whitman College basics
Location: Walla Walla, Washington, population 32,148
Founded: 1883
Enrollment: 1596
Science departments: Anthropology, Astronomy, Biochemistry/Biophysics/Molecular Biology, Biology, Chemistry, Environmental Studies, Geology, Mathematics, Physics, Psychology, Sociology
Number of tenure-track biology faculty: 12 faculty, but 2 positions are split by married couples

Personal background
I’ve always been fascinated by biology, especially marine life. My mother is a cell biologist (who later did pioneering work on gap junctions and aquaporins), and our family often took vacations to California beaches and cliffs, where she got me far more interested in tide pool life and seashells than in swimming in the surf. My dad is a chemical engineer who worked on the space program, which also inspired me. My interest in space initially won out, and I went to California Institute of Technology as an undergraduate to major in astrophysics. However, I soon learned of the exciting, new revolutions in biology there: in immunology (Leroy Hood, future inventor of the automated DNA sequencer), homeotic genes (Ed Lewis, future Nobelist), and gene regulation in development (Eric Davidson and Roy Britten). I got hooked on biology and changed majors. As a small institution, Caltech (800 undergraduates) had many opportunities for undergraduate research. I ended up working 2 years in the Davidson/Britten lab under the mentorship of Barbara Hough, who taught me the new techniques in DNA/RNA for studying genes in sea urchin and frog development. I even became a coauthor on a research paper. In my senior year, I got to be a TA in Davidson’s Developmental Biology course and discovered that I loved teaching as much as research.
I decided I wanted to combine my love for marine life with cellular/biochemical/physiological approaches to discover how marine animals are adapted to survive in different environments. I went to Scripps Institution of Oceanography for my PhD and did my post-doctoral work at the University of St. Andrews in Scotland. There I not only worked on the biochemistry and physiology of muscle proteins in marine animals, but also got to teach in a physiology course. After much soul-searching, realizing how much I got out of a smaller institution as an undergraduate and that I wanted teaching, as well as research, to be valued, I started applying to small colleges. I landed a job at Whitman College in Washington State, where I was hired to teach Physiology, Marine Biology, and Developmental Biology.

**Typical day/week**

A week at Whitman College varies considerably. During a teaching semester, workday hours are consumed with teaching preparation, emails, student conferences, teaching itself, committee work, and some research-related activities. I grade papers, write, and catch up on journals at home Monday through Thursday evenings and Sundays, and might also do lab experiments on Sundays. Sometimes I have to work on Saturdays. I try not to work at home or weekends while on sabbatical, except during research trips.

**Log for a teaching semester, spring 2013**

We have a five-course teaching load (lectures, 1.0; seminars and labs, 0.5); mine is as follows:

- Fall, 2.5 load: Physiology lecture and two labs (load, 1 + 0.5 + 0.5); Student Research (0.5 load).
- Spring, 2.5 load: Marine Biology for majors (load, 1) and Marine Biology field trip (for a 45-hour week during spring break; load, 0.5); Bioethics seminar (0.5 load); Student Research (0.5 load). After a fall sabbatical, I lecture in Marine Biology for nonmajors instead of Bioethics (3.0 load)

This particular semester, I am working on the research projects noted earlier and teaching Student Research (eight students), Marine Biology for majors (28 students), Marine Biology for nonmajors (23 students), and Marine Biology field trip (21 students)

**Monday: 10.5 hours**

1) Answer numerous emails from students, research collaborators, and so on (1 hour)

2) Go over and fine-tune PowerPoint lecture (prepared on previous Friday) for afternoon nonmajors class (1 hour)

3) Prepare PowerPoint and extensive handout for Tuesday majors class; I always revise each lecture with new discoveries, which requires searching the Internet searches and reading journals (see evening, below) (1.5 hours)

4) Lunch in my office updating my Deep-Sea website, which is used worldwide by students, reporters, and so on (1 hour)

5) Lecture, 1 p.m., nonmajors Marine Biology (1.5 hours, including 10-minute setup, 80-minute lecture)

6) Write letters of recommendation for a student (1 hour)

7) Read proposals to the IRB (I am a member), writing recommendations (1 hour)

8) Work on paper on eel osmolytes (work done with colleague in Scotland; 1.5 hours)

9) Evening: begin reading this week’s Science, Nature, Science News, New Scientist, and daily New York Times for news stories relevant to class and to my research (1 hour)

**Tuesday: 12 hours**

1) Answer numerous emails (1 hour)

2) Fine-tune morning lecture (1 hour)

3) Lecture 10 a.m., majors Marine Biology (1 hour, including 10-minute setup, 50-minute lecture)

4) Office hour 11 a.m.; meet with various students on their thesis writing (1 hour)

5) Lunch and haircut appointment (1 hour)

6) Administer senior oral exam with another faculty (required of all seniors; 1 hour)

7) Prepare PowerPoints and extensive handouts for Wednesday majors and nonmajors classes (3 hours)

8) Dinner 6 p.m. with selected faculty and the Trustees to discuss “teacher-scholar” model and the effect of our recent reduction in our course load from 6 to 5 (3 hours)

**Wednesday: 11.5 hours**

1) Answer numerous emails (1 hour)

2) Fine-tune morning lecture (1 hour)

3) Lecture 10 a.m., majors Marine Biology (1 hour)

4) Office hour 11 a.m.; meet with some thesis students (1 hour)

5) Lunch during a faculty committee meeting (1 hour)

6) Lecture 1 p.m., nonmajors Marine Biology (1.5 hours)

7) Prepare PowerPoints and extensive handouts for Thursday majors class (1.5 hours)

8) Faculty meeting 4 p.m. (1 hour)

9) Evening: continue reading journals and begin writing exam for Friday (2.5 hours)

**Thursday: 10.5 hours**

1) Answer numerous emails, including one from Scotland colleague on our paper (1 hour)

2) Fine-tune morning lecture (1 hour)

3) Lecture 10 a.m., majors Marine Biology (1 hour)

4) Office hour 11 a.m.; meet with some thesis students (1 hour)

5) Lunch in my office; international conference call on our NSF trench grant (1.5 hour)

6) Answer more emails (0.5 hour)

7) Administer senior oral exam with another faculty (1 hour)

8) Meet with colleague and student on planning new osmolyte-drink experiments (1.5 hours)

9) Evening: finish writing exam (2 hours)

**Friday: 8.5 hours (go home a bit early!)**

1) Answer numerous emails (1.5 hours)

2) Write abstract for summer conference in Scotland on our fish research (1.5 hours)

3) Work on eel paper (1 hour)

4) Lunch during department meeting to go over sabbatical replacement interviews (1 hour)

5) Administer exam in nonmajors class 1 p.m. (1.5 hours); I only use Friday slots for exams; later in the semester, this time slot will be taken with senior thesis presentations
6) Prepare PowerPoints and extensive handouts for Monday nonmajors class (2 hours)  
7) Nonwork: attend Dean’s TGIF party

Saturday  
Day off! I try to get in some exercise (biking, walking), as well as do household errands and read recreational books

Sunday: 7 hours  
1) Morning: bike in (for exercise) to work in my lab with student #1 to conduct first coral analysis; later in the semester, I will have students’ extensive reports from the field trip to grade, which will take all day every Sunday and many evenings

Abbreviated log for a semester sabbatical, fall 2012  
I worked on four research projects and involved eight research/thesis students:
• Analyzing coral tissues from Hawaii (where I and a student worked in June) for sugars potentially important in coral-symbiont attraction  
• Testing a new osmolyte-based sports drink from Danisco-Dupont, which the company based on my research (with two students)  
• Implementing a new collaborative NSF grant with Woods Hole, University of Hawaii, University of Aberdeen, and NIWA New Zealand (and later with James Cameron’s DEEPSEA CHALLENGE for exploration of the world’s deepest oceans (trenches); my part is to investigate biochemical pressure adaptations in proteins (involving osmolytes); with two students  
• Analyzing osmolytes in endangered European eels from Scotland (where a student and I went in July); on an NERC grant to a colleague in Scotland

The sabbatical work included trips to Scotland, Hawaii, and New Zealand; here I describe a week at Whitman in September 2012.

Monday: 9 hours  
Morning: Instrument, reagent prep; conference call with Hawaiian colleagues; meet with thesis student #1 to plan coral analysis; meet with student #2 to help with graduate school applications

Afternoon: Meet with student #1 to conduct first coral analysis; order more research supplies online; answer emails, begin making travel and housing arrangements for research trip to New Zealand for me and student #3.

Tuesday: 8.5 hours  
Morning: Meet with departmental colleague and thesis student #4 to finalize report for Danisco-Dupont for completion of Phase 1 with their sports drink; brainstorm a new grant proposal for a Phase 2 study; finish making travel arrangements; answer emails.

Afternoon: Continue coral sample analysis with student #1; look online for analytical laboratories to help us solve the structure of an unknown molecule we found in the Scotland fish related to osmotic adaptation

Wednesday: 9 hours  
Morning: Drive my pickup truck (while wife follows in our car) to repair shop for tune-up. On the way, a radiator hose ruptures. We go to buy antifreeze and a new hose; install these; finally take truck to shop. Meet with thesis student #5 and a Whitman analytical chemist to plan her analyses of iron in seawater samples she collected over the summer with an off-campus researcher; read an advisee’s Watson Fellowship application and make extensive edits.

Afternoon: Meet with a geologist who brings in a mysterious blob creature from a local stream, which I quickly identify as a bryozoan, then show him its statoblasts in a microscope; take raw HPLC data of fish-osmolyte analyses done previously for the Scotland project and convert to concentrations in tissues, with statistics, with student; answer emails; write letter of recommendation for student.

Thursday: 8.5 hours  
Morning: Confer with director of college alumni office on an alumni trip I will help lead in early November to Florida Keys, which includes two lectures to alumni; book tickets to Miami; help student #7 set up equipment for his separate project on the sports drink (treadmill, refractometer for urine specific gravity, osmometer); go with wife to get pickup truck, then run to office supply store for items needed in the lab.

Afternoon: International conference call (United States, United Kingdom, New Zealand) with all colleagues on our NSF trench-exploration grant: Plan a meeting of grant collaborators and testing in November of the submersible we will use (Nereus at Woods Hole Oceanographic Institute); meet with student #1 to plan next week’s coral experiments; find and book tickets, housing, car for Woods Hole in November; answer emails, including one from Scotland colleague on beginning a research paper on our findings.

Friday: 7.5 hours  
Morning: Answer emails; meet with student #7 and his first volunteer to do initial test on athlete hydration state during workouts with and without the new sports drink (IRB has given permission).

Afternoon: Receive (by express courier) frozen corals from Hawaii and frozen amphipods from the bottom of the Mariana Trench (from Scripps Institute of Oceanography; collected by Cameron’s expedition); meet with students #3 and #8 to do tissue dissections for biochemical analyses; write up draft of grant proposal for Phase 2 to Danisco-Dupont.

Likes/dislikes  
The single duty that makes me most want to retire is GRADING. That has gotten increasingly tedious because 1) I now have seen the same essay answers over and over (despite trying to be creative in varying the essay questions), 2) the most recent generations of students are more demanding in terms of questioning the grades they receive, 3) enrollments in Biology have soared (this year 100 of our college’s 390 seniors are life-science majors), and 4) innovative active-engagement exercises require more work. Grading is the number one reason professors near my age have taken early retirement/tedious activity. This has gotten worse over the years for the college as a whole; for example, there are far more safety protocols with accompanying paperwork. A 4-year stint as Science Division Chair (somewhat like an Assistant Dean) nearly burned me out. However, some faculty enjoy administrative duties and do more over time as their research output slackens.

Whitman’s isolation in a small rural city, a situation for many liberal arts colleges, has engendered both likes and dislikes. There are many benefits that drew us here to raise a family: a safe,
non–rat-race environment, a daily commute of 2 miles with no traffic jams, affordable housing, friendly citizens, and access to great outdoor activities. In addition, the college brings in many cultural events, and the city itself has many activities and amenities that have grown with the phenomenal winery industry here. But there are so many things lacking that one takes for granted in a major metropolitan area; for example, we have no Whole Foods, Costco, high-fashion shopping, large museums, zoo, or wide range of international cuisines. My wife and I have always made up for the things we miss by traveling frequently, often for research, and the College, in recognition of our isolation, provides funds for travel to meetings and research sites. So, overall we’ve been satisfied. But I do wish we were a 1-hour drive from a major city rather than 4 to 5 hours.

Also on the “likes” side, I have found that academic freedom and a flexible schedule make up for a lower salary compared with those in industry and medicine. I still love the teaching itself and research with students and colleagues around the world. In fact, by being at a college that not only does not expect you to do cutting-edge research (freeing you to try things that might not get funded right away) and provides travel funds to overcome isolation, I think I’ve been able to do more-interesting, innovative research and develop more worldwide collaborators than I would have at a large R1 university.

Changes and concluding thoughts
Over my 30-plus years as a professor, a number of things have changed in my job.

Our college has changed loads from six courses, not counting student research, before 1990, then to six courses, with student research counting as one course (1990), then to a five-course load in 2010. Also in 1990, the college increased the frequency of sabbaticals from every seventh semester/seventh year to every fifth semester/fifth year (although the criteria for earning a sabbatical became very strict, with some faculty being denied every year). These changes occurred as my department increasingly emphasized undergraduate research and the college as a whole increasingly emphasized scholarly productivity as a criterion for tenure, sabbaticals, merit pay, and promotion. However, excellence in teaching remains the #1 criterion here. As part of that, we’ve been expected to implement more-active engagement techniques in traditional lecture and even laboratory courses.

When I first started out and certainly through tenure, I often worked 7 days a week during the school year, typically half of Saturday and much of Sunday. Over time, I have become more efficient at exam writing, grading, paper writing, and making time for research. As a result of this and our course-load reductions, I am now able to take off most Saturdays. Evening work is also more feasible and less stressful since our son grew up and moved away.

I’ve witnessed two very different tracks among the full professors here. First, as I noted earlier, there are many senior faculty who have transitioned to doing more service and less (often very much less) research. In contrast, there are those like me who have less committee and other college service work (as younger faculty tend to get elected to committees) concomitant with more research. In my case, earlier successes in research have led to even more research with colleagues around the world, which the five-course load enables me to do.

In conclusion, I feel that the core components of this profession have made it all worthwhile, despite the stresses and long hours. I can’t think of another profession I would have chosen instead.
From bench to museum—an unlikely journey

Kristina Yu
Living Systems, Exploratorium, San Francisco, CA 94111-1456

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I,
I took the one less traveled by,
And that has made all the difference.

Robert Frost

Deciding to “leave the bench” and basic research after committing many, many years to graduate school is not an easy thing to do. There is real pressure from peers, principal investigators (PIs), even parents, to stick it out and follow a more established career path, either to academia or the biotech industry. In my case, I realized fairly early on in graduate school that the traditional options were not areas I was interested in pursuing. I also felt strongly about how science was frequently misrepresented in popular culture and the media. The epiphany—that I was “okay” leaving basic research, despite not really knowing what else was out there—came late one night, in the cold room of all places. I trotted down the hall of our building and announced this to my friend and classmate (also working in a cold room) who was having similar thoughts herself. We high-fived. We would support each other. We would be okay.

Fast-forward 15 years. I now work at the Exploratorium, an interactive science museum in San Francisco, directing the museum’s Living Systems Department. In this essay, I discuss how I wound up at the Exploratorium and what it is like to work in a museum environment, creating science experiences for the general public.

NOT JUST A LABOR OF “LIKE”

Although I knew deep in my heart of hearts that a life of basic research was not for me, it took me awhile to announce this to my PI. When I finally did, I confessed that, although I enjoyed bench work, basic research had always been a labor of “like” for me and, given the rigors of academia and industry, “like” was not enough to base a career on. I wanted to take the training I had received and the enthusiasm I had for science to the public in some way. Fortunately, my PI was incredibly understanding and supportive, recognizing the general need for greater science communication.

Not long after completing a fairly standard PhD in cell biology, I started searching for jobs, with the intention of eventually applying to the science communication program at the University of California, Santa Cruz. Fortunately, I was not entirely certain of what type of job I was searching for, so I cast a wide net. Because my thesis work involved a lot of live-cell imaging and microscopy—which I genuinely enjoyed—I would diligently type “microscopy” into every job search engine I had access to at the time, and every time I would come up empty-handed …

AN ALIQUOT OF GOOD LUCK

Until finally a hit. And what a hit it was—the Exploratorium was looking for a microscopist. Growing up in the San Francisco Bay area, I was very familiar with the Exploratorium and had visited many, many times. Founded in 1969 by Frank Oppenheimer, the Exploratorium—a museum of “science, art and human perception”—pioneered the concept of a science center. The Exploratorium had recently been awarded a grant to develop a microscope facility where the public could control the microscopes to examine live specimens. The position described online was everything I was looking for—but that I did not know could exist in one job. Several months later, I found myself reporting to work as the one and only microscopist at the museum—a place that was at once a familiar childhood memory, yet completely foreign as a workplace.

Address correspondence to: Kristina Yu (kyu@exploratorium.edu).
Abbreviation used: PI, principal investigator.
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quickly learned that the samples that worked for a microscope exhibit in the museum were colorful, moved (but not too fast or slow), had some level of familiarity either as an object or a concept, and could be the subject of a scientific “story” that would be relevant to a broad number of visitors. Our exhibits need to appeal to a range of visitors with diverse backgrounds and interests, so honoring the inherent beauty and “wow factor” of a biological sample viewed with a microscope became incredibly important.

At the Exploratorium, projects for the museum floor are almost always developed by multidisciplinary teams. Depending on the project, there might be scientists, exhibit developers, carpenters, graphic designers, writers, structural engineers, artists, educators, programmers, education researchers, and volunteers involved. Every team member brings a critical expertise or skill to the project, and more often than not, works in some way with every other team member. Developing successful exhibits is also extremely challenging and is a skill unto itself. Seemingly simple exhibits at the Exploratorium are the result of months (sometimes years) of development. Curiosity and respect for other métiers is incredibly important, as are good communication skills and the ability to problem solve, both on your own and with a group. The broad range of expertise and interests represented in the museum never fails to amaze me, and it presents a constant opportunity to learn and appreciate other disciplines. Because the work is highly project-based, a “typical” day is hard to describe; it really depends on the kind of project you are working on and what phase of development it is in. In one of my more recent roles, a colleague and I were asked to curate a new gallery of biology exhibits in preparation for the grand reopening of the Exploratorium (Figures 1 and 2). For this large, multiyear project, I led a team with all the roles

FIGURE 1: The Exploratorium overlooks San Francisco Bay.

A CRASH COURSE
Biology exhibits at the Exploratorium are unique in that they are built in-house and more often than not involve a live specimen or organism. To care for and culture the organisms that are included in exhibits and other activities, the museum has a working laboratory and a staff of biologists who maintain cultures of more than 40 types of organisms all under one roof. Colonies of termites coexist peacefully with tanks of zebrafish and incubators full of mouse embryonic stem cells. A variety of plants, insects, marine invertebrates, and microbes also call the lab at the Exploratorium home. After spending so many years in a fly lab focused on the first 2 hours of development in Drosophila, I got a crash course in husbandry of a much wider variety of “critters and bits,” as I now fondly call them.

In my role as microscopist, I was charged with setting up a microscopy facility so that museum visitors would ultimately be able to “drive” the instruments to examine and explore live biological samples in the way a research scientist might. Choosing samples that the public would actually care to look at, specifying equipment, advising on software design, and prototyping interpretive media for visitors were all part of my new position. The learning curve was rather steep—not long after I started at the Exploratorium, a colleague and I wheeled a brand-new motorized stereo zoom microscope out onto the exhibit floor to try out with visitors. Very quickly we realized that cords, buttons, and levers are extremely tempting to little hands—the Exploratorium being an interactive museum—and that eyepieces look an awful lot like handlebars to anyone under 8 years old. What I naively thought would be amazing to share with visitors (cytoskeletal dynamics and cell cycle regulation, for example) wound up being way too esoteric for the general public. I
described in the paragraph above and more, so good management skills were important as well.

THE ROAD LESS TRAVELED
When I was asked to contribute this Perspective, it was with an emphasis on my career path. It seems that more and more graduates are interested in science education and outreach, or other careers that use a background in biology applied to other areas. After reflecting on my career trajectory and talking with a number of colleagues—all PhD scientists from various disciplines—I cannot really say that there is a defined career “path” from the bench to a museum. Not long ago, I was at dinner with a table full of the scientific colleagues mentioned above. No two of us had arrived at the Exploratorium in quite the same way—some had come straight from grad school to work on a specific project and stayed, others had years of formal teaching experience before coming to the museum. Another had started out with internships in museums and media before landing a series of positions at science museums.

Positions for scientists at museums do not crop up all that often. There are, however, opportunities out there that might increase one’s odds of the right door opening at the right time. There are postgraduate programs in museum studies and internship programs at museums, science centers, and other media outlets. Volunteering can also be a way of gaining some informal science education street cred, and it also puts you in an institution—all the better to network and keep an eye open for positions. There are also professional associations, like the Association for Science and Technology Centers, the American Alliance of Museums, and the Association of Zoos and Aquariums, whose websites have career information and may be places to get familiar with the type of projects in which member institutions are engaged. Scientific publications are not necessarily what one is judged by in the museum world—it is more about demonstrated experience doing the type of work you are applying for (teaching, exhibit design, implementing outreach programs, etc.).

Working outside academia and industry has certainly opened my eyes to what is possible with a background in basic research. There are lots of interesting, very diverse careers out there that draw on the skills one learns at the bench and in working in an academic lab—the challenge is finding a good match for your interests. And although there may not be a defined “road” or even a path to some of these careers (such as in a museum), defining one’s own way can make for a very rewarding journey.
A view from the NIH bridge: perspectives of a program officer

Marion Zatz
National Institute of General Medical Sciences, National Institutes of Health, Bethesda, MD 20892

ABSTRACT This essay is written from my perspective as a program officer for research and training activities at the National Institute of General Medical Sciences (NIGMS) for almost 27 yr. It gives a bird’s-eye view of the job of a program officer, which includes providing advice to applicants and grantees, making funding recommendations, overseeing grantees’ progress, facilitating scientific opportunities in specific areas of program responsibility, and shaping NIGMS and National Institutes of Health (NIH) policy. I have highlighted the numerous rewards of serving as a program officer, as well as some of the difficulties. For those who may be considering a position as an NIH program officer now or in the future, I’ve also described the qualities and qualifications that are important for such a career choice. Finally, this essay addresses some of the challenges for the NIH and the research community in the years ahead as we simultaneously face exciting scientific opportunities and tighter budgets.

INTRODUCTION In the face of record deficits and shrinking National Institutes of Health (NIH) budgets, one might wonder why a sane person would choose a career in government service. As a program officer (PO) at the National Institute of General Medical Sciences (NIGMS) for almost 27 yr, I can say that, despite many swings of the funding pendulum—from the 1990 budget crisis to the 1998–2003 budget doubling to the current fiscal situation—serving the research and training community is an amazing opportunity to support and advance science and to guide trainees, fellows, newly established investigators, and senior scientists.

Although many of you reading this essay have NIH support, you probably don’t have a good idea of what a PO does, or even who your PO is. Because part of my job is to educate the scientific community about how extramural funding and peer review work, I’ll begin with the question, what does a PO do?

THE JOB The NIH comprises 27 institutes and centers (ICs), and the job of a PO will vary with the IC, but the basics are shared across the NIH. In a nutshell, and from the NIGMS perspective, POs advise applicants and grantees, make funding recommendations, oversee the progress of funded grants, encourage scientific opportunities, and help develop NIH policy. However, we are just one part of an NIH team that serves the biomedical community. Our job complements that of the scientific review officer, who shepherds applications through the initial peer review process, appoints reviewers to study sections, runs study section meetings, and prepares summary statements. Once a priority score/percentile and summary statement have been generated, the responsibility shifts to the PO. In addition, POs work with IC grants management specialists on grants policy and business matters.

Advice Applicants may need advice at every step of the way, from whether their project is of interest to an IC’s scientific mission or is responsive to a special initiative, to which study section might have the best expertise to review an application, to what the chances of funding are, or to what next steps are needed to revise and improve an application. Unfortunately, many applicants are reluctant to call their PO, and in this modern era of communication, most inquiries occur by email, where nuances may be lost. Therefore, I consider an important part of my job to be a social worker for scientists, trying to lead investigators and trainees through ever-changing policies, practices, and budgets and providing as much information as possible along the way. This year has been particularly challenging for applicants and POs. With an NIH budget appropriation not finalized until April, 9 mo into the fiscal year, it has been more difficult and more important than ever to provide timely information on funding prospects or the need to revise an application.
Funding
How are funding decisions really made? This is an area that varies considerably among ICs. In NIGMS, the PO plays an active role. As a first step, we listen to study section discussions and read the summary statements for applications in our program area (each of us has what is called a “portfolio” of applications and grants in a defined scientific area in which we are particularly knowledgeable). The next step is preparing for review by the NIGMS advisory council, during which council members may advise us on applicant concerns and the relative merits of the scored applications; every application that is funded by the NIH must receive this second level of review. After council review, NIGMS POs meet to discuss and recommend which applications should be funded. This process is mainly driven by the availability of funds and the initial peer review evaluation. However, many other important factors also are taken into consideration, including the following: information gained from the study section discussion, such as reviewer differences of opinion; council advice; novelty of the scientific area; the applicant’s status as a new or more established investigator; and the availability or lack of other support for the principal investigator. Although NIGMS establishes a “nominal” payline for each council round, based on the availability of dollars to fund all applications through a given percentile, in reality there is little difference in quality between applications that are within a few percentile points of each other. Therefore, we look at a range of applications on either side of the nominal payline and consider all of the relevant factors in making the final funding recommendation. In addition to recommending which applications should be funded, POs recommend the level of funding, making budget adjustments on a case-by-case basis that, on average, must meet NIH-mandated cost-containment guidelines.

Oversight
Once an application is funded, it becomes part of a PO’s portfolio. We review annual progress reports, reading about the most recent research before it is published, and also advise grantees on strategies for their competing renewals, changes in project goals, and other issues that may arise in the course of a 4- to 5-yr grant award. However, a PO’s responsibility for oversight goes well beyond the individual grantees in a program portfolio. We have both the obligation and the pleasure of staying abreast of the latest advances in our area of science by attending conferences, meeting with our grantees, and reading relevant journals. These activities in turn enable us to perform a crucial part of a PO’s job, which is to identify emerging needs and opportunities.

Facilitating scientific opportunities
One of the most gratifying activities for a PO is identifying an emerging area of science and fostering its development. A perfect example from my own experience is stem cell research. The development of human embryonic stem cell lines provided an incredibly exciting opportunity to address some of the most fundamental questions in biology, but one that required nurturing and overcoming technical as well as policy hurdles. As a PO I organized a series of workshops and developed initiatives to encourage scientists with little or no knowledge of stem cells to enter the field, master the necessary methodologies, obtain needed resources, and study the basic biology of stem cells. After the advent of embryonic stem cells came the discovery of induced pluripotent stem cells, and so these efforts continue as this important and fascinating area evolves.

Policy
Many of us also serve on IC and trans-NIH committees tasked with developing or implementing new policies and practices. As an example, I serve on the NIH Stem Cell Task Force and the NIGMS Training Strategic Planning Committee, which provide me with an opportunity to help shape stem cell research and future research training efforts.

THE REWARDS
I’ve briefly addressed the question of what a PO does for a living. The next big question is, what are the rewards, and is this a career that you might want to pursue? The things I enjoy most are 1) the “social worker” part of the job—the gratification that comes from helping applicants and grantees—and 2) being at the forefront of science where one gets a broad overview of how areas connect and evolve over time. The evolution of my program portfolio provides a wonderful example of the opportunities that ever-changing science offers a PO. When I first came to the NIGMS extramural program my background was in immunology, and I had the challenge of both starting a new program in molecular immunobiology and assuming responsibility for a program in cell growth and differentiation, a broad area about which I knew little. This was in 1984, and the field of cell cycle research was about to break wide open. Over time, my portfolio of grants grew and acquired a focus that came to support some of the best basic cell cycle scientists in the field. Then another emerging area, programmed cell death, blossomed, one that connected my immunology background with cell biology. Most recently, my program portfolio has evolved in response to new opportunities in stem cell research. It’s been great fun to learn new areas of science and watch them morph, driven in large part by the scientific community, but also with a little help from the NIH and me.

Although I’ve focused on the roles and rewards of a PO for research grants, equally important are a PO’s responsibilities for research training activities, including individual fellowships and institutional training grants. In a way, being a PO for research training wedds the two parts of the job that I enjoy most, helping people (in this case, trainees) and overseeing change. Although approaches to training may evolve more slowly than research opportunities, training strategies must keep pace with workforce needs as well as the increasingly more complex and multidisciplinary practice of science. It’s been rewarding to develop new Ph.D. training grant programs in two emerging areas, bioinformatics and computational biology, and molecular medicine. Equally important is the challenge of promoting diversity in graduate programs. I’ve been involved in many activities over the last 15 yr with this goal in mind, including organizing a workshop in 2001 for training grant program directors, Achieving Scientific Excellence through Diversity; developing a new NIGMS website for diversity recruitment and retention strategies; and serving on the NIGMS Committee for Biomedical Workforce Diversity. It’s been gratifying to see the trainee diversity of my training grant portfolio increase over time, albeit more slowly than I would like. NIGMS is now engaged in implementation of a strategic plan for training, Investing in the Future, to which I and many others will contribute our philosophy and ideas for the next generation of scientists.

THE QUALIFICATIONS
Perhaps you are wondering at this point what qualifies someone to be a PO and what are the needed skills and attributes? Like many of my colleagues at the NIH, I came to this position following a career as an independent research scientist, where I developed many skills that are essential for being a successful researcher or teacher, and
for being a PO. I believe the most important qualification for the job is a love and appreciation of good science; that is why POs are officially called health scientist administrators. At a minimum, one also needs excellent organizational skills, a talent for verbal and written communication, the ability to work well with others as a team, and good common sense. Needless to say, we all have different strengths. I think I’ve grown in many ways as I’ve gained experience, honed my skills, and benefited from many opportunities for on-the-job training.

BACK TO THE FUTURE
What are the challenges facing the scientific community and the NIH? The future will depend more than ever on a partnership between research and educational institutions and the NIH. Clearly, one challenge is to meet the ever-changing scientific research and training opportunities in the face of limited financial resources. It’s unlikely that we’re going to see another budget doubling anytime soon. Investigators may have to get by with smaller and fewer grants, remembering that the R01 was intended to be a grant-in-aid that should leverage institutional and other resources. The NIH will continue to support the best research and the training of outstanding scientists, preparing them for independent careers in academia and the many other rewarding career options available to them. It’s worth noting that even with the current flat budget, NIGMS, just 1 of 27 ICs, is supporting more than 3500 R01s and roughly 4300 trainees on fellowships and training grants. Although shrinking budgets may make it harder to make funding decisions and more difficult and time consuming to advise applicants and grantees, I believe the job of a PO will be more important than ever in helping to sustain the enthusiasm and progress of the research and training enterprise.

So my view from the NIH bridge is that, despite choppy seas, science has never been more exciting, and, to paraphrase a familiar line, we’re from the government and we’re here to help you!

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Visualization of actin filaments and monomers in somatic cell nuclei

Brittany J. Belin\textsuperscript{a,b}, Beth A. Cimini\textsuperscript{b,c}, Elizabeth H. Blackburn\textsuperscript{c}, and R. Dyche Mullins\textsuperscript{a,b}
\textsuperscript{a}Cellular and Molecular Pharmacology and \textsuperscript{b}Biochemistry and Biophysics, University of California, San Francisco, San Francisco, CA 94158; \textsuperscript{c}Physiology Course, Marine Biological Laboratory, Woods Hole, MA 02543

**ABSTRACT** In addition to its long-studied presence in the cytoplasm, actin is also found in the nuclei of eukaryotic cells. The function and form (monomer, filament, or noncanonical oligomer) of nuclear actin are hotly debated, and its localization and dynamics are largely unknown. To determine the distribution of nuclear actin in live somatic cells and evaluate its potential functions, we constructed and validated fluorescent nuclear actin probes. Monomeric actin probes concentrate in nuclear speckles, suggesting an interaction of monomers with RNA-processing factors. Filamentous actin probes recognize discrete structures with submicron lengths that are excluded from chromatin-rich regions. In time-lapse movies, these actin filament structures exhibit one of two types of mobility: 1) diffusive, with an average diffusion coefficient of 0.06–0.08 μm\(^2\)/s, or (2) subdiffusive, with a mobility coefficient of 0.015 μm\(^2\)/s. Individual filament trajectories exhibit features of particles moving within a viscoelastic mesh. The small size of nuclear actin filaments is inconsistent with a role in micron-scale intranuclear transport, and their localization suggests that they do not participate directly in chromatin-based processes. Our results instead suggest that actin filaments form part of a large, viscoelastic structure in the nucleoplasm and may act as scaffolds that help organize nuclear contents.

**INTRODUCTION**

In the cytoplasm, actin filaments form functional networks that enable eukaryotic cells to transport cargo, change shape, and move. These activities organize components of the cytoplasm and help turn a mob of macromolecules into a living cell. Actin is also present in the nucleus (de Lanerolle and Serebryannyy, 2011), but in this compartment its functions are more cryptic. Early studies revealed high concentrations (100 μM) of actin in oocyte germinal vesicles (Clark and Merriam, 1977; Clark and Rosenbaum, 1979; Scheer et al., 1984), but there is disagreement over whether this actin is predominantly monomeric or filamentous (Gall and Wu, 2010; Kiseleva et al., 2004; Bohnsack et al., 2006), and there is no consensus regarding its function.

Somatic cell nuclei contain much less actin than oocyte germinal vesicles, and the forms and functions of this actin are even more hotly debated. Monomeric actin participates as a subunit in several nuclear complexes that regulate chromatin architecture, but its function within these complexes is mysterious (Farrants, 2008). Nuclear actin has also been proposed to form unconventional filaments that interact with cytoskeletal regulators, including coflin (lida et al., 1992; Dopie et al., 2012), α-actinin (Kumeta et al., 2010), filamin (Loy et al., 2003), coronin 2A (Huang et al., 2011), and nuclear isoforms of myosin (Pestic-Dragovich et al., 2000). There are also reports of unconventional forms of actin in the nucleus, including covalently modified monomers (Hofmann et al., 2009) and nonfilamentous oligomers (Schoenenberger et al., 2005).

Nuclear actin filaments have been proposed to participate in many processes, including control of chromatin architecture, regulation of transcription, and intranuclear cargo transport. Broadly
Progress in understanding the distribution of actin in the nucleus has been limited by the lack of appropriate reporters. No nuclear actin filaments can be detected when cells are stained with fluorescently labeled phalloidin. The data that do exist derive from either 1) immunofluorescence (Krauss et al., 2003; Schoenenberger et al., 2005) or 2) expression of nucleus-targeted, fluorescent actin derivatives (McDonald et al., 2006; Dopie et al., 2012). Neither method discriminates between monomeric and filamentous actin, and, as a result, their use has yielded little functional insight.

The best information on the dynamics of nuclear actin was provided by McDonald et al. (2006), who measured the mobility of nuclear-targeted, green fluorescent protein (GFP)-tagged actin with two different techniques and obtained two different results. Using fluorescence recovery after photobleaching (FRAP), they measured a very low mobility (0.009 μm²/s), whereas using fluorescence correlation spectroscopy (FCS), they obtained significantly higher values (>0.06 μm²/s). Whether these values report on different mobility populations of nuclear actin—for example, the monomer and filament pools—or arise simply from the differences in the techniques used has not been resolved.

To visualize nuclear actin monomers and filaments in live somatic cells and assess their possible functions, we designed, constructed, and validated a set of fluorescent nuclear actin probes. Probes that bind monomeric actin are concentrated in nuclear speckles, globular structures enriched in pre-mRNA splicing factors (Spector and Lamond, 2011). This localization is consistent with proposed interactions between actin and RNA-processing factors. Filamentous actin, however, does not localize to nuclear speckles but forms a set of punctate structures of more or less uniform size. These structures are scattered throughout the interchromatin space and are excluded from chromatin-rich regions, arguing against direct participation of at least the majority canonical actin filaments in gene regulation or chromatin remodeling. In time-lapse movies (Supplemental Movies S1 and S2), most nuclear actin filaments move diffusively (<x²> ~ t³) but very slowly, with mobility ranging from 0.06 to 0.08 μm²/s. A small fraction of filaments moves even more slowly (~0.015 μm²/s) and subdiffusively (<x²> ~ t²). Analysis of filament trajectories demonstrates that nuclear actin filaments do not undergo directed motion but exhibit anticorrelated motions at short time scales, consistent with entrapment in an elastic mesh.

The small size and lack of directed motions of nuclear actin filaments argue against primary roles in either intranuclear transport or maintenance of nuclear mechanics. We argue that nuclear actin filaments form short scaffolds that interact with—and may help assemble—a viscoelastic structure in the nucleoplasm. To our knowledge, this is the first direct evidence for the presence of cytoskeletal filaments in the nucleoplasm of live somatic cells. This finding is an important milestone in mapping the physical geography of the nucleus and may provide clues into how nuclear contents are organized.

**RESULTS**

**Design of nuclear actin reporters**

To visualize actin in nuclei of live cells, we worked against two obstacles: 1) the low concentration of actin in somatic cell nuclei (Stüven et al., 2003), especially compared with the high concentration of actin in the cytoplasm; and 2) the low permeability of the nucleus to fluorescent probes. We dealt with both obstacles by constructing actin reporters localized almost exclusively to the nucleus. We engineered our probes by fusing an actin-binding domain (ABD) to both a fluorescent protein (enhanced GFP [EGFP]) and three tandem repeats of the nuclear localization sequence (NLS) from SV40 (Figure 1a). We tested ABDs from many previously characterized actin-associated proteins (Table 1 and Supplemental Table S1). To distinguish monomeric from polymeric actin, we used ABDs specific for either actin filaments (FABDs) or actin monomers (monomeric [globular] actin–binding domains [GABDs]).

We expressed all our ABD-NLS reporters in human U2OS (osteosarcoma) cells and imaged them with confocal microscopy. We judged the veracity of each construct based on several criteria: 1) whether its localization differed from that of an EGFP-NLS (EN) or NLS-EGFP control; 2) whether it obviously perturbed actin localization or dynamics; and, for FABD-NLS constructs, 3) whether the small amount of reporter remaining in the cytoplasm localized to phalloidin-stainable actin filaments.

**Probes that bind monomeric actin localize to nuclear speckles**

In U2OS cells, our control construct EN localizes throughout the nucleoplasm and is enriched in nucleoli (Figure 1b). Nucleolar enrichment is commonly observed for proteins targeted strongly to the nucleus by multiple repeats of the SV40 NLS (Shirley et al., 1998). Of our monomer-binding constructs, only the RPEL1 and RPEL2 domains from the transcriptional coactivator, MAL, exhibited a pattern distinct from that of nuclear EGFP controls. RPEL1-EN (R1EN) is distributed through the nucleoplasm and enriched in nucleoli but also localizes to small, nucleoplasmic bodies distinct from nucleoli (Figure 1c). Immunofluorescence reveals that these nucleoplasmic bodies also contain SC35, a marker for nuclear speckles (Figure 1d). To determine whether localization to nuclear speckles reflected interaction with monomeric actin, we expressed an RPEL1 mutant (R81D/R82D) incapable of binding actin (Mouilleron et al., 2008). The point mutations completely abolish colocalization of the probe with SC35 (Figure 1d). These results suggest that monomeric actin is a component of nuclear speckles.

**Actin-filament probes identify small particles dispersed through the nucleoplasm**

The distributions of most FABD-NLS constructs we tested (Table 1 and Supplemental Table S1) were indistinguishable from nuclear EGFP controls (Supplemental Figure S1) and also failed to detect actin structures in the cytoplasm, suggesting that they are simply not suited for labeling actin filaments in vivo. This failure could be caused by 1) intrinsically low affinity of the ABD for actin filaments or 2) interference from the attached EGFP or NLS. Two of our constructs, however, produced unique nuclear distributions and also recognized actin filaments in the cytoplasm. These constructs contained either the tandem calponin homology (CH) domains from utrophin (Utr261) or the engineered, actin-binding peptide Lifeact, both of which have been used to study in vivo actin filament dynamics (Riedel et al., 2008; Burkel et al., 2007). These two probes recognize filamentous structures in the nucleus that are not
We could think of no simple way to improve this probe, and so we did not pursue it further. Utrophin does not bind monomeric actin, so the mechanism by which it perturbs nuclear actin architecture must be different. To understand why the utrophin probe might assemble nuclear actin bundles, we expressed Utr261 in *Escherichia coli* and purified it to homogeneity. When mixed with purified actin in vitro, Utr261 potently perturbs actin assembly dynamics by stabilizing and bundling actin filaments, even at relatively low concentrations (unpublished observations). We hypothesized that reducing the valency of this interaction might abolish Utr261's ability to generate ectopic nuclear actin bundles.

Utr261 contains two tandem CH domains, CH type 1 (CH1) and CH type 2 (CH2; Winder et al., 1995). The CH1 domain contains a bipartite binding motif that mediates high-affinity interaction with filaments, whereas CH2 contains a smaller actin-binding motif with weaker affinity (Figure 2, b and c). To create a construct that binds filaments with high affinity but does not bundle them, we made truncation mutants of Utr261. We fused each to EN and expressed them in U2OS cells. The Utr150-EN, Utr165-EN, and Utr205-EN mutants lost the ability to bind cytoplasmic actin filaments and exhibited a nuclear localization similar to the EN control (Figure 2d). However, one truncation mutant, Utr230-EN, bound actin in the cytoplasm and exhibited a remarkably distinct localization pattern in the nucleus: small, distributed puncta. We observed similar localization patterns of Utr230-EN in nuclei of multiple mammalian cell types, including U2OS, UMUC3, and HeLa (Figure 3a).

The amount of ectopic actin created by Lifeact- and Utr261-EN probes is proportional to probe expression level. To determine, therefore, whether the punctate nuclear structures identified by Utr230-EN are artifactual, we quantified their number and size as a function of probe expression level. We created a cell line stably observed in nuclear EGFP controls. These structures, however, can also be visualized by phalloidin derivatives and appear to be created by expression of the probes themselves (Figure 2a and Supplemental Figure S1).

The mechanism by which Lifeact induces formation of nuclear actin filaments is unclear. Lifeact binds actin monomers with high affinity, even higher than for binding to filaments (Riedl et al., 2008), and so the probe probably promotes import of monomeric actin from the cytoplasm. We could think of no simple way to improve this probe, and so we did not pursue it further.

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**FIGURE 1**: RPEL-based monomeric actin reporters localize to nuclear speckles. (a) Nuclear actin reporter construct design. (b) Localization pattern of EN (right) and NLS-EGFP (left) control constructs in transiently transfected U2OS cells. (c) Localization patterns of EN and R1-EN in transiently transfected U2OS cells. Cellular expression levels for each construct, as determined by the total integrated intensity within the nucleus, increase from left to right. (d) Immunofluorescence assays in U2OS cells transiently transfected with R1-EN or an actin-binding-deficient mutant (RR > DD) and stained with an SC35 antibody. R1-EN images in the second row are enhanced for contrast.

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**TABLE 1**: Nuclear actin reporter design.
To further demonstrate that nucleoplasmic puncta identified by Utr230-EN are endogenous structures containing actin filaments, we perturbed nuclear concentrations of actin. Nucleocytoplasmic transport factors importin 9 (IPO9) and exportin 6 (XPO6) shuttle actin into and out of the nucleus, respectively (Stüven et al., 2003; Dopie et al., 2012). We knocked down expression of IPO9 and XPO6 using small interfering RNA (siRNA) and observed the nuclear localization pattern of Utr230-EN puncta. Reduced expression of XPO6 altered the distribution of Utr230-EN from a constellation of small puncta to a handful of much larger, brighter foci (Figure 4, a and b). These large foci appear in the majority (52%) of knockdown cells but only a small fraction of mock-treated (8%) or untreated (9%) cells (Figure 4c). Knocking down expression of the import factor IPO9 produced the opposite effect: the majority of knockdown cells (53%) lack nuclear actin structures, whereas this is true in only a small fraction of mock-treated (12%) or untreated (13%) cells (Figure 4, d–f).

Phalloidin colocalizes with Utr230-EN after latrunculin B treatment

Previous studies used the actin monomer–sequestering drug latrunculin B (LatB) to probe the function of filamentous actin in the nucleus (Zhao et al., 1998; McDonald et al., 2006; Wu et al., 2006; Ye et al., 2008). To study the effects of LatB on nuclear actin architecture, we treated U2OS cells expressing Utr230-EN with a range of
LatB concentrations (0.2–1.0 μM) for 30 min before fixing cells and staining them with 4’,6-diamidino-2-phenylindole (DAPI) and Alexa 568-phalloidin (Figure 5a). After 0.2 and 0.4 μM LatB treatments, significant disassembly of cytoplasmic actin structures occurred while nuclear actin puncta appeared unaffected.

Of interest, even though we detected no change in nuclear actin organization at 0.4 μM LatB treatment, we began to detect phalloidin staining of the nuclear structures recognized by Utr230-EN (Figure 5b). The same nuclear actin puncta were also observed by phalloidin staining in cells treated with 0.4 μM LatB that are not expressing Utr230-EN (Supplemental Figure S2), further arguing that our probe recognizes endogenous actin-containing structures. This concentration of LatB disassembles almost all phalloidin-stainable filaments in the cytoplasm, so the colocalization between Utr230-EN and phalloidin may become visible due to the decreased phalloidin signal from the cytoplasm.

Higher concentrations of LatB perturbed nuclear actin organization. At 0.6 μM the size of nuclear actin puncta actually

FIGURE 3: Utr230-EN binds to native punctate nuclear actin filaments. (a) Confocal sections of HeLa, U2OS, and UMUC3 cells stably expressing Utr230-EN. The second row shows magnifications of the nuclear area. (b) Comparison of average nuclear intensity of U2OS cells stably expressing Utr230-EN with average puncta size (top) and average number of puncta per nucleus (bottom). Data were collected from 97 nuclei. (c) Alignment of the MAL and Myoc RPEL1 domains (adapted from Mouilleron et al., 2008) with actin-binding site 1 of the human α-actinin, utrophin, and dystrophin CH1 domains, revealing a conserved Q/R/K/K/T motif. (d) Localization of Utr230-EN and Utr230-E QKK→DDD in transiently transfected U2OS cells. (e) Nuclear localization of Utr230-EN and of a transiently transfected predicted actin-binding-deficient mutant (QKK→DDD).
We next looked for colocalization between nuclear actin filaments and several actin-associated proteins reported to be in the nucleus: nuclear myosin I (NM1), Baf53a/Arp4 (a marker for all human actin-containing chromatin remodelers), coronin 2A (CORO2A), and lamin A/C (Figure 6, f–i). We observed little or no colocalization of nuclear actin with these proteins or with other chromatin-remodeling markers, including p400 (Swr1 complex), Brg1 (BAF complex), and histone H2AZ (Supplemental Figure S3).

Binding of Utr230-EN to nuclear actin puncta may occlude interactions between actin and chromatin-based complexes. Several reports suggest that the interaction of actin with transcription and remodeling factors is required for normal nucleic acid synthesis (e.g., Ye et al., 2008). To test whether the binding of Utr230-EN with actin blocks the association of actin with chromatin, we performed incorporation assays for 5-bromo-2′-deoxyuridine (BrdU) and 5-ethynyl uridine (EU; a BrUTP analogue) in cells expressing Utr230-EN to determine whether nucleic acid synthesis was inhibited. The distribution of cells in the 4N state as reported by BrdU incorporation, a measure of DNA synthesis, was reduced by Utr230-EN expression (Supplemental Figure S4). However, since a similar reduction was increased, and at 0.8 μM LatB intranuclear actin rods, detectable with both Utr230-EN and phalloidin, appeared in the majority of cells (as previously reported; Pendleton et al., 2003). Even higher concentrations of LatB eventually resulted in disassembly of nuclear actin structures, and at concentrations ≥1.0 μM we could detect no nuclear actin structures with either phalloidin or Utr230-EN. We observed very similar effects on nuclear actin architecture in cells treated with cytochalasin D (Supplemental Figure S2).

Nuclear actin filaments are enriched in the interchromatin space

We used immunofluorescence to look for colocalization between nuclear actin filaments and a variety of nuclear landmarks and nuclear actin-binding proteins. Curiously, we find that the Utr230-EN actin reporter does not colocalize with RNA polymerase I, II, or III and is not associated with H3K9me3 heterochromatin (Figure 6, a–d). DAPI staining of Utr230-EN–expressing cells throughout the cell cycle reveals that nuclear actin puncta are generally excluded from chromatin (Figure 6e). In fact, nuclear actin filaments do not strongly colocalize with any nuclear landmark we tested, including elements of the nuclear lamina, nuclear matrix proteins, nucleoli, nuclear speckles, PML bodies, and telomeres (Supplemental Figure S3).

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observed for cells expressing EN, we believe this effect is a consequence of nuclear protein overexpression. In our EU incorporation assays, there was no significant decrease in RNA synthesis in cells expressing Utr230-EN (Supplemental Figure S4). The absence of defects in nucleic actin synthesis specific to Utr230-EN expression indicates that Utr230-EN-bound actin is likely distinct from the pools of nuclear actin that participate directly in chromatin-based processes.

Dynamics of nuclear actin filaments
We imaged live U2OS cells expressing Utr230-EN by time-lapse confocal microscopy to determine the dynamics of nuclear actin structures. The trajectories of individual particles (Figure 7a) were calculated using the MATLAB particle tracking package u-Track (Jaqaman et al., 2008). On average, nuclear actin particles move with an apparent diffusion coefficient of $\sim 0.07 \mu m^2/s$ and a time-dependent value of $\alpha$, the scaling exponent for the relationship of the mean-squared displacement versus time (Figure 7b, inset, and Supplemental Figure S5). Theoretically, time dependence in the $\alpha$ value can indicate that the particles are confined within a finite volume, in which the displacement of the particles approaches some limiting value. In our case, however, we find that the time dependence of $\alpha$ is simply an artifact of confocal imaging. The fastest and most highly diffusive particles are the most likely to exit the imaging plane early in the time course, resulting in an enrichment of the remaining, less mobile particles as the observed trajectory length increases. This selection for slower particles at long time scales decreases the apparent average particle speed over time, causing the displacement curve to appear to plateau. Consistent with this interpretation, binning our data for particle trajectories by their length reveals that both the apparent diffusion coefficient and $\alpha$ decrease as trajectory length increases (Figure 7, b and c).

Particles with shorter recorded trajectories appear to move diffusively, with an apparent diffusion coefficient of $\sim 0.07 \mu m^2/s$ and $\alpha$ approaching 1. Particles with the longest recorded trajectories are slower and move more subdiffusively, with an apparent diffusion coefficient of $\sim 0.015 \mu m^2/s$ and $\alpha$ of $\sim 0.67$. These diffusion coefficients are unexpectedly low, being at least an order of magnitude below the $0.5–5 \mu m^2/s$ range reported for transcription factors in the nucleus (Gorski et al., 2008) and the $57 \mu m^2/s$ value reported for soluble GFP (Houtsmuller et al., 1999). The particles observed over short and long trajectories might represent...
FIGURE 6: Nuclear actin filaments are enriched in the interchromatin space. Immunofluorescence in U2OS cells stably expressing Utr230-EN and stained with antibodies for (a) RNA polymerase I marker PAF49, (b) RNA polymerase II, (c) RNA polymerase II marker POLR3F, (d) H3K9me3 heterochromatin, (f) nuclear myosin 1 (NM1), (g) Baf53a/Arp4, (h) coronin 2A (CORO2A), (i) lamin A/C. (e) DAPI staining in fixed U2OS cells stably expressing Utr230-EN throughout the cell cycle.
FIGURE 7: Dynamics of nuclear actin filaments. (a) Trajectories of F-actin puncta in a single confocal slice of a live U2OS nucleus over 30 s at 50-ms resolution. 100 pixels = 9.1 μm. (b) Double-logarithmic plot of mean-squared displacement (MSD) vs. time for nuclear actin puncta with variable trajectory lengths. The fitted line is for the longest trajectories only (>15 s in length) and has a slope of −0.67. Inset, linear plot of MSD vs. time, with average values for all nuclear actin trajectories (red) and for a simulated random walk with a diffusion coefficient 0.07 μm²/s (blue). y-axis, MSD in μm²/s; x-axis, time in seconds. N = 25,000 particles for both observed and simulated data. (c) Average apparent diffusion coefficients of all nuclear actin particles as a function of trajectory length. N = 25,000 particles. (d) Distribution of apparent diffusion coefficients for all nuclear actin particles. N = 25,000. (e) SCI values for 10 representative nuclear actin trajectories from a single cell during the first 50 frames (2.5 s) of their trajectories. (f) VCF values averaged from all 0.5-s windows within nuclear actin trajectories (red) and trajectories for a simulated random walk (blue). N = 25,000 particles for both observed and simulated data. (g) Time-lapse image series of U2OS nuclei in cells stably expressing Utr230-mEos2-NLS before and after photoconversion at 405 nm. (h) Average relative mEos2 fluorescence recovery at 488 nm after photoactivation in nuclear and cytoplasmic actin filaments. Cytoplasmic actin, n = 12,000 foci; nuclear actin, n = 16,000 foci.
functionally distinct populations of actin since, in addition to the variation in α, the apparent diffusion coefficients among short- and long-lived particles do not fall into a single uniform distribution (Figure 7d).

We looked for directed motion of nuclear actin filaments by calculating the speed correlation index (SCI) for all of our calculated particle trajectories (Bouzigues and Dahan, 2007). Briefly, the SCI reveals how persistently a particle moves in the same direction; periods of directed motion produce high, positive SCI values across multiple, consecutive time points. Overall we found that nuclear actin particles undergo less persistent directed motion than simulated random walks. In our data, only 0.21% of 3343 nuclear actin trajectories (each with a length of 50–100 frames) scored an SCI of >0.75 for five or more consecutive frames, compared with 1.08% of 5000 trajectories of a simulated random walk. Not only are the positive directional correlations weak, but also our data are generally skewed toward negative correlations. That is, for a particle moving in a given direction at a given time, its movement soon afterward is biased in the opposite direction. This negative bias is clear in plots of SCI values of individual trajectories (Figure 7e). From the absence of directed motion and the small size of the actin-containing structures (Supplemental Figure S5), we conclude that this nuclear actin pool is unlikely to contribute to long-range (micrometer-scale) transport events.

We were intrigued by the negative skew in the speed correlation index of nuclear actin-containing particles. To investigate this phenomenon further, we calculated the average correlation between the direction of particle motion at the beginning of a trajectory (the first two frames) and its direction of motion at all subsequent time points in the trajectory (Weber et al., 2010a,b). The resulting velocity autocorrelation function (VCF) reveals that, over a short time scale, the velocity autocorrelation is indeed negative for actin trajectories (Figure 7f). One physical interpretation of this result is that nuclear filaments are embedded in a viscoelastic medium, such as a cytoskeletal or nucleic acid polymer network, that provides an elastic force opposing motion (Weber et al., 2010a). Because nuclear actin puncta are excluded from chromatin, we conclude that this force must arise from a viscoelastic network within the interchromatin domain, perhaps consisting of nuclear matrix proteins.

Finally, to estimate the rate of filament turnover within nuclear actin structures, we performed photoconversion experiments in cells expressing a photoswitchable variant of our nuclear actin reporter, Utr230-mEos2-NLS (McKinney et al., 2009; Figure 7g). Fluorescence recovery curves for nuclear F-actin puncta show an average t1/2 of 195 s, remarkably similar to the 217 s that we calculated for cytoplasmic actin stress fibers analyzed in the same experiments (Figure 7h). From these curves we conclude that the kinetics of nuclear F-actin assembly and disassembly are comparable to those found in cytoplasmic actin structures.

**DISCUSSION**

Before trusting a nuclear actin probe, one must demonstrate that 1) it actually binds actin in vivo, 2) its localization in the nucleus reflects binding to actin, and 3) its expression does not alter the distribution of nuclear actin. When targeted to the nucleus, the most widely used probes for studying filamentous actin in live cells, Life-act and Utr261, perturb nuclear actin architecture. We therefore designed and tested several new families of probes for nuclear actin. Our best nuclear actin filament probe, Utr230-EN, passed all three of the tests listed. In the cytoplasm it labels actin filaments in a pattern indistinguishable from that of fluorescent phalloidin. In the nucleus, its localization is disrupted by point mutations that abolish actin binding and by perturbation of the nuclear actin concentration. Changes in its expression level do not alter the number or size of particles recognized by Utr230-EN. Finally, when cytoplasmic actin is depolymerized by latrunculin B, fluorescent phalloidin recognizes similar nuclear structures in untransfected cells.

The size distribution of nuclear actin filaments, as judged by Utr230-EN intensity, is approximately Gaussian (Supplemental Figure S5), which suggests that the filaments have a more or less fixed size. Filaments free to assemble and disassemble, in contrast, would eventually achieve an exponential length distribution (Sept et al., 1999), whereas filaments that break and anneal should follow a power-law distribution (Brangwynne et al., 2011; Foret et al., 2012). The peak in the Utr230-EN distribution corresponds to a short (<100 subunit), fixed-length actin filament, possibly similar to fixed-length filaments found in the membrane skeleton of red blood cells or associated with the Golgi apparatus (Colón-Franco et al., 2011). It is tempting to speculate that nuclear actin filaments share functional and regulatory features with these short, membrane-associated filaments.

The localization and morphology of nuclear actin filaments are inconsistent with several functions previously proposed for them. For example, the spatial restriction of actin filaments predominantly to the interchromatin space argues against direct involvement of conventional actin filaments in transcription and chromatin remodeling (Fomproix and Percipalle, 2004). They are also not long enough (Supplemental Figure S5) to serve as tracks for long-range transport of cargo (e.g., genetic loci) through the nucleus (Dundr et al., 2007). In addition, we observed no directed motion of nuclear actin filaments and little or no colocalization between nuclear actin filaments and known nuclear myosins.

Our results shed new light on the physical nature of somatic cell nucleoplasm. Some nuclear actin filaments move diffusively, whereas the motion of others is restricted. The subdiffusive motions we observe for some filaments likely result from interactions with larger nuclear structures of very low mobility. Of interest, at short time scales, the motion of most actin filaments was anticorrelated, characteristic of particles embedded in a viscoelastic medium (Weber et al., 2010a). What is responsible for the viscoelasticity of the nucleoplasm? The mechanics of the cytoplasm are dominated by the properties of actin filament networks, but the actin filaments we observe in the nucleus are too small and dispersed to themselves account for a significant amount of viscoelasticity. One obvious candidate is chromatin, but this is not consistent with the localization of nuclear actin to the interchromatin space. A better candidate is a nucleoplasmic structure consisting of lamins and other filamentous or filament-associated proteins in the nucleus (Shimi et al., 2008). More work is required to determine whether nuclear actin filaments are simply trapped in such a structure or function as scaffolds that help organize it.

Although our results rule out direct participation of actin in motor-directed intranuclear transport, actin filaments may interact with other nucleoplasm components (e.g., lamins) to form a three-dimensional mesh or matrix. Such a structure would explain previous observations of actin’s effect on intranuclear transport. Dundr et al. (2007), for example, tracked the motion of an array of U2 small nuclear RNA minigenes to Cajal bodies after transcriptional activation. They observed two modes of motion: short-range diffusion interspersed with transient periods of high mobility in the direction of the Cajal body. Because these high mobility bursts were absent after expression of the dominant-negative, nonpolymerizing R62D actin mutant, they speculated that the high-mobility bursts result from motor-dependent transport of the U2 array along actin tracks. It is possible, however, that the bursts of higher mobility represent
“hopping” of particles between zones of confinement, or corrals (Saxton, 1995).

Our time-lapse imaging results explain some discrepancies with respect to the previous study on nuclear actin dynamics by McDonald et al. (2006). The different mobilities of nuclear actin that they measured using FRAP (0.009 μm²/s) and FCS (>0.06 μm²/s) correspond surprisingly well to the two distinct populations of nuclear actin filaments we observed: the small subset of subdiffusive puncta (<5% of all particles) with an apparent mobility of 0.015 μm²/s, and the larger, diffusive population with an average diffusion coefficient of 0.07 μm²/s. The FCS measurements of McDonald et al. (2006) likely counts more molecules from the fast-moving pool, whereas the FRAP measurement may be more sensitive to the slow-moving filament pool.

The RPEL domain from MAL binds monomeric but not filamentous actin, so we constructed an RPEL-based probe to study monomeric actin in the nucleus. In addition to a diffuse, nucleoplasmic localization, this probe accumulates in globular, nuclear bodies that contain SC35. This colocalization indicates that actin monomers concentrate in nuclear speckles, a compartment previously shown to also contain phosphorylated forms of myosin V (Pranchevicius et al., 2008). This suggests a role for monomeric actin in RNA processing or the staging of RNA-processing factors, which are believed to be the primary function of nuclear speckles. The difference in localization between nuclear actin filaments and monomers argues that these actin pools are functionally distinct.

Our Utr230-EN– and RPEL-based actin probes represent a significant expansion of the molecular toolbox for the in vivo study of actin dynamics. They gave us the first detailed view of the architecture and dynamics of nuclear actin. Further progress in understanding the function of nuclear actin will require not only nucleus-specific probes, but also nucleus-specific tools for perturbing actin assembly and localization.

MATERIALS AND METHODS

Molecular biology

FABD constructs were cloned from full-length human cDNA using standard techniques. JMY WH2 and MAL RPEL domain constructs were cloned from full-length recombinant human proteins. The VASP GABD was cloned from a full length Dictyostelium recombiant protein, p-RSETA-mEos2 (McKinney et al., 2009) was acquired from Addgene (Cambridge, MA; plasmid 20341). Mutagenesis was performed using the QuikChange mutagenesis kit and primer design tool (Stratagene, Santa Clara, CA). We used pEGFP-C1 (Clontech, Mountain View, CA) as the host vector for all EGFP fusions, with N-terminal EGFP fusions inserted into the unique Agel and Nhel sites. Primer sequences are available upon request.

Cell culture

HeLa, U2OS, and UMUC3 cells (American Type Culture Collection, Manassas, VA) were cultured in DMEM supplemented with 10% fetal bovine serum, 2 mM l-glutamine, nonessential amino acids, and penicillin–streptomycin (University of California, San Francisco (UCSF), Cell Culture Facility) at 37°C with 5% CO₂. For transient transfection of all ABD constructs other than Utr230-EN, cells were transfected using Lipofectamine LTX (Invitrogen, Carlsbad, CA) according to the manufacturer’s protocol. For transient transfection of Utr230-EN, cells were transfected with Xtreme-GENE HP (Roche, Indianapolis, IN) according to the manufacturer’s instructions. All transient transfections were performed 24–72 h before data collection. Stable cell lines of Utr230-EGFP-NLS and Utr230-mEos2-NLS were generated by lentiviral expression constructs based on the plasmids from the Trono lab (see Li et al., 2004) and containing the selectable marker from pSM-PUW-IRES-Blasticidin (Cell Biolabs, San Diego, CA).

siRNA

Mock siRNA and human XPO6 and IPO9 Silencer Select siRNAs were purchased from Invitrogen. Transient reverse transfection using Lipofectamine RNAiMAX was performed on stable Utr230-EN U2OS lines according to the manufacturer’s protocol. At 15–20 h after transient transfection, the cell medium was replaced. Cells were split into flasks and/or fibronectin coverslips 3 d after transfection and were either fixed for imaging or lysed for Western blotting at 5 d after transfection.

Western blotting

About 1 million cells were harvested, washed with ice-cold phosphate-buffered saline (PBS), and pelleted in a microfuge by spinning at 1000 rpm for 5 min at 4°C. Cell pellets were lysed by resuspension in 2× SDS sample buffer with 1 mM Pefabloc and boiled before SDS–PAGE. For each sample we blotted against HSP70 as a loading control. Standard methods were used for immunoblotting, using 1:500 Rb anti-XPO6 (Abcam, Cambridge, MA), 1:500 Rb anti-IPO9 (Abcam), and 1:1000 mouse anti-HSF70 (Santa Cruz Biotechnology, Santa Cruz, CA) with overnight incubation at 4°C. Horseradish peroxidase–conjugated secondaries (Jackson ImmunoResearch Laboratories, West Grove, PA) were used at 1:10,000, and ECL reagent (SuperSignal West Pico; Pierce, Rockford, IL) was used according to the manufacturer’s instructions.

Immunofluorescence and staining

Cells were passaged onto glass coverslips coated with 10 μg/ml fibronectin (Invitrogen) and cultured overnight to 30–60% confluence. Coverslips were fixed at room temperature for 30 min in 3.7% paraformaldehyde (prepared from Formalin; Sigma-Aldrich, St. Louis, MO) in PBS (UCSF Cell Culture Facility). Cells were permeabilized in 0.1% Triton-X-100 in PBS for 3–5 min and blocked in 5% goat serum/PBS at room temperature for 60 min. Primary antibody incubations were performed for 60 min at room temperature in 5% goat serum/PBS. Cells were incubated in Alexa Fluor 568–labeled secondary antibodies (Invitrogen) in 5% goat serum/PBS for 30 min at room temperature and mounted on slides with fluorescent mounting medium (DakoCytomation, Hamburg, Germany). For phalloidin and DAPI staining, cells were fixed as described and stained for 15 min in 0.1% Triton/PBS with 0.5 μg/ml DAPI (Sigma-Aldrich) or 0.7 μl/ml Alexa Fluor 568–phalloidin (Invitrogen). Dilutions and product numbers for antibodies used for immunofluorescence are available upon request.

BrdU and EU incorporation

For BrdU incorporation, cells grown on coverslips were incubated in 1 × BrdU labeling reagent (Invitrogen) in complete medium for 2 h at 37°C with 5% CO₂. After incubation, cells were fixed, permeabilized, and blocked as described. Coverslips were then incubated for 60 min at room temperature in 1:500 anti-EGFP antibody (Abcam) in 5% goat serum/PBS. The cells were washed and incubated for an additional 30 min at room temperature in 1:500 Alexa 562 secondary (Invitrogen). Cells were washed in PBS and permeabilized in 1% Triton-X/PBS for 3 × 5 min. The nuclear BrdU epitope was exposed by treatment with 1 N HCl for 10 min at room temperature, followed by 10 min at room temperature and 20 min at 37°C in 2 N HCl. The acid was neutralized in 0.1 M sodium borate for 12 min at room temperature. The cells were permeabilized in 1% Triton-X/ PBS for 3 × 5 min at room temperature and incubated overnight at...
4°C in 1:50 anti-BrdU (Invitrogen). Anti-BrdU-stained coverslips mounted on slides with fluorescent mounting medium (DakoCyto- mation). EU incorporation was performed using the Click-It RNA Alexa 594 imaging kit from Invitrogen. Cells were incubated in 1 mM EU in complete medium for 45 min at 37°C with 5% CO₂. After EU incubation, the EU detection reaction was performed according to the manufacturer’s protocol, with a twofold reduction in Alexa 594 azide concentration from the recommended procedure to reduce background signal. BrdU and EU incorporation levels in fixed cells were acquired using epifluorescence microscopy. The integrated intensity of the nuclear signals for BrdU and EU nucleic acids was measured in ImageJ (National Institutes of Health, Bethesda, MD). The intensities were normalized by nuclear area and plotted using R.

Microscopy
Confocal images for particle tracking were collected using an Eclipse Ti-E Motorized Inverted Microscope (Nikon, Melville, NY) equipped with a Yokogawa CSU22 Spinning Disk Confocal and Photometrics Evolve electron-multiplying charge-coupled device camera using a 100×/1.40 numerical aperture (NA) Plan Apo objective (UCSF Nikon Imaging Center). Confocal data were acquired with Micro-Manager software (Stuurman et al., 2007). All other images were taken using DeltaVision RT system (Applied Precision, Issaquah, WA) with a CoolSnapHQ camera (Photometrics, Tucson, AZ) using a 100×/1.40 NA UPlanSapo objective (Olympus, Tokyo, Japan). For live-cell imaging, cells were split onto polylysine-coated Mat-Tek dishes and kept at 37°C with 5% CO₂ during image acquisition. Images were processed for contrast enhancement and noise reduction using ImageJ.

Photoconversion
U2OS cells stably expressing the Ut230-mEos2-NLS construct were photoconverted with a 405-nm laser and then imaged at 568 nm in 10-s intervals for 10 min. To reduce bleaching of the highly unstable green state, images were taken at 488 nm only every fifth time point. The time courses for the two channels were then synced and cropped into converted or unconverted regions of interest (ROIs) in FIJi (Fiji is Just ImageJ; http://fiji.sc), and the particles inside each ROI were analyzed in CellProfiler (Carpenter et al., 2005). Normalization for photobleaching and curve fitting were mathematically calculated in Python, primarily with the SciPy package (www.scipy .org). Plots of recovery curves were generated in R.

Particle tracking and analysis
Particle trajectories were calculated using the u-Track MATLAB software package (Jaqaman et al., 2008) using the default parameters. Calculation of the speed correlation index was performed as described in Bouzigues and Dahan (2007) using a window size of three frames for averaging and implemented in Python. Calculation of the VCF was performed as described in Weber et al. (2010a) and implemented in Python. All additional analysis of particle trajectories was implemented in Python, and all figures were generated using R. To briefly expand on the description of VCF calculation given in Weber et al. (2010a) in the velocity autocorrelation function calculation, the velocity of each particle was determined for every pair of adjacent frames within its trajectory (e.g., particle velocity \(v_0\) was calculated between frames 1 and 2, velocity \(v_1\) was calculated between frames 2 and 3, and so on). The velocity autocorrelation was then calculated as the sine of the angles between the particle velocity at each time \(t\) and the velocity at time \(t + \delta\) for \(\delta\) ranging from 50 to 500 ms. Thus a value of 1 indicates a strong positive velocity autocorrelation, in which the particle motion at time \(t\) is in the same direction as at time \(t + \delta\), and a value of –1 indicates a strong anticorrelation, in which the particle motion at time \(t\) is in the opposite direction as at time \(t + \delta\). The plotted velocity autocorrelation function is the average of the velocity autocorrelation values for all particle trajectories. Documentation and code for all particle trajectory analyses are available upon request.

Drug treatments
Latrunculin B (Biomol International, Plymouth, PA) and cytochalasin D (Sigma-Aldrich) were diluted in EtOH and used in warm medium. After replacement of old media with drugged medium, cells were incubated for the indicated time at 37°C with 5% CO₂.

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