Support for a career in science

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ABSTRACT I am so very honored to receive the Women in Cell Biology Sandra K. Masur Senior Leadership Award from the American Society for Cell Biology (ASCB), particularly because many of the previous awardees have served as mentors and sources of inspiration throughout my own career. I also thank the ASCB for always striving to be maximally inclusive, in terms of both the scientists it supports and its broad vision of what constitutes cell biology. As a graduate student I gave one of my first talks at an ASCB meeting, and I am proud to have been an ASCB member for almost 30 years. In this essay, I describe my own career to illustrate the support that I believe is needed to achieve a career in science.

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BECOMING A SCIENTIST

I grew up in central New Jersey, the grandchild of immigrants from Romania, Slovakia, and Belarus. None of my grandparents had more than a sixth-grade education. Both my parents grew up on chicken farms, part of a little-known aspect of American Jewish history in which the Jewish Agricultural Society gave refugees loans and training to become egg farmers. I like to say that I have deep roots in the pharmaceutical industry—one grandfather worked as a cook in the E. R. Squibb & Sons (now Bristol-Myers Squibb) cafeteria. My parents were the first in their families to attend college, and they expected that, as they had done, I would commute to a nearby college and obtain a degree in something that led to a middle-class job. My mother and the few other women who worked were teachers, a career that my mother often said was a good job for a woman.

S. L. Wolin

I don't know whether it is an honest assessment or imposter syndrome, but I believe that I was given opportunities because people saw something in me that I couldn't see in myself. In my senior year of high school, a friend's mother encouraged me to apply to a wider range of colleges, teachers wrote supportive letters, and I was accepted by Princeton University. Although my parents were taken aback by the costs, they supported my attendance.

I entered Princeton without a specific major in mind. However, during my freshman year, I searched for a job on campus in order to avoid an unpleasant summer job, such as scooping ice cream, which I had done in a previous summer at home. The Biology Department needed an undergraduate to maintain *Drosophila melanogaster* stocks, and so I became the "freshman fruit fly flipper." This job came with a daily cookie break, which allowed me to interact with graduate students and faculty. I was enthralled by their dedication and by the concept of experiments—the ability to devise a question and learn something entirely new from your results. This experience led me to major in biochemistry and carry out independent work with then assistant professor Raju Kucherlapati, an incredibly supportive mentor. However, since I was unsure that I could succeed as a scientist, I decided to apply to MD–PhD programs. My rationale was that if I could not make it as a scientist, I could contribute to society as a physician.

I consider myself fortunate to have ended up in Yale's MD–PhD program, where I had several fantastic mentors. All new medical students were assigned a "faculty friend." Mine was Marilyn Farquhar, with whom I had monthly tea in the school cafeteria. George Palade, who taught the cell biology seminar for MD–PhD students, also took me under his wing. At George's recommendation, I carried out my PhD with Joan Steitz, characterizing a newly discovered class of RNPs, known as Ro RNPs, that were targets of autoantibodies in patients with systemic lupus erythematosus (SLE). Although I did not complete my thesis goal of determining their function, I identified

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the major protein (now called the Ro 60 kDa protein or Ro60), cloned two of its associated noncoding "Y RNAs," and identified the site at which Ro60 bound these RNAs (Wolin and Steitz, 1983, 1984). Joan was both a supportive mentor and a role model for running a laboratory in which all members felt respected and empowered. With Joan's encouragement, I decided that perhaps I could make it as a scientist and applied for postdoctoral positions.

In Peter Walter's lab at the University of California, San Francisco, I devised a method to map the positions of translating ribosomes on mRNAs (Wolin and Walter, 1988). Using this method, I showed that ribosomes pause during initiation and termination, as well as over specific codons. I also found that ribosomes stack behind stalled ribosomes, a phenomenon now called ribosome collision. With Peter's encouragement, I gained more confidence in my abilities. Through my interactions with Christine Guthrie (an unofficial mentor), and by watching the Walter lab's initial forays into yeast genetics, I learned of the power of genetics to give insights into biological processes. From Peter, I learned to be unafraid to try new approaches and study unfamiliar organisms.

OUR SCIENCE

Upon starting my own laboratory in the Department of Cell Biology at the Yale School of Medicine, I decided to focus on uncovering the functions of two enigmatic classes of RNPs. My idea was to identify the RNPs in yeast and then combine cell biology, biochemistry, and genetics to elucidate their functions. One class, La RNPs, consisted of a protein called the La autoantigen that bound many newly synthesized RNAs. Although the human La protein was known to bind nascent transcripts synthesized by RNA polymerase III (Rinke and Steitz, 1982), its function was controversial. Our studies in budding yeast revealed that La is a chaperone that stabilizes numerous nascent noncoding RNAs and assists their folding, maturation, and assembly with proteins (Yoo and Wolin, 1997; Pannone *et al.*, 1998; Chakshusmathi *et al.*, 2003). Although my lab embarked on these experiments without any yeast experience, we received much support from colleagues.

The function of the other class, the Ro60 RNPs I studied as a student, proved more difficult to crack. Early on, we discovered that in oocytes of the frog *Xenopus laevis*, Ro60 bound to a large collection of aberrant rRNAs that appeared to be misfolded (O'Brien and Wolin, 1994). With our collaborator Karin Reinisch, we showed that Ro60 is ring-shaped and binds misfolded RNAs via its central cavity (Stein *et al.*, 2005). Our studies supported a model in which Ro60 scavenges noncoding RNAs that, because they are misfolded, fail to bind their specific RNA-binding proteins (Fuchs *et al.*, 2006). However, we did not know the fate of these Ro60-bound RNAs or how Y RNAs contributed.

Since Ro60 RNPs are absent from all sequenced yeast genomes, but are present in some bacteria, we adopted bacteria as our model system. By studying the first sequenced bacterium with a Ro60 orthologue, we discovered that a Y RNA tethers Ro60 to a ring-shaped nuclease, forming a double-ringed RNA degradation machine (Chen *et al.*, 2013). Our recent studies indicate that mammalian Y RNAs function similarly to tether effector proteins to Ro60 (Leng *et al.*, 2020).

Remarkably, our studies of RNPs that are targets of patient autoantibodies ended up leading us back to the field of autoimmunity. We collaborated with Martin Kriegel to provide evidence that the anti-Ro60 autoantibodies in patients with SLE may arise through molecular mimicry with bacterial Ro60 RNPs (Greiling *et al.*, 2018). Moreover, given data that binding of endogenous RNA to innate immune sensors can trigger production of type I interferons (Crow *et al.*, 2019), we have become interested in the role of RNA surveillance pathways in preventing inappropriate activation of these sensors.

In 2017, I began a new adventure. I was recruited to the National Cancer Institute of the National Institutes of Health (NIH) to build a new Laboratory (NIH-speak for a small department) dedicated to RNA Biology. This position has given me the incredible opportunity to hire multiple tenure-track investigators (the NIH equivalent of assistant professors) and to mentor them as they embark on their independent careers.

SUPPORTING OTHERS: IMPROVING THE SCIENTIFIC ENVIRONMENT

Rather than use this platform to give advice to trainees and young faculty, I would like to discuss how we (anyone in a position to help) can improve the environment for these scientists. One obvious way is to pay forward what others have done for us. I am acutely aware of how much it meant to me when more-senior scientists supported me with a few encouraging words, a small act of kindness, or by acting as my advocate. Now that I am a Laboratory Chief (the NIH-equivalent of a department chair), I try to be mindful of the need to provide such support.

To me, mentoring also includes working to create a collegial environment for all. One role of a mentor is to help newcomers navigate unwritten rules of the profession and institution (Bland *et al.*, 2009). This role of mentors would be far less important if the rules and expectations were clear. Many universities have certainly improved in this regard: we now have graduate student and postdoctoral fellow handbooks and promotion websites for faculty with model dossiers. Although this is helpful, there is still a need for mentors to advocate for young scientists by promoting their work and helping to advance their careers.

Another way we can improve the environment is by making women and other groups that are underrepresented in science feel welcome in our fields (National Academies of Sciences, Engineering, and Medicine, 2019). To this end, it is critical that women and scientists from other underrepresented populations be well-represented in our seminar series and scientific meetings (Termini and Pang, 2020). Although there should no longer be any excuse for meetings where women are poorly represented among the speakers, I still see obviously lopsided programs. Personally, as both an attendee and a speaker, I find that there is a world of difference between feeling like you are a guest at someone else's party and feeling like it is also your party.

Due to the support that I received from mentors and family, I have a career that I could not have imagined when I was young. I have had and continue to have the privilege of mentoring fantastic trainees and young faculty. The commitment of these young scientists to improving equity in science and increasing opportunities for all makes me very optimistic for the future.

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REFERENCES

Bland CJ, Taylor AL, Shollen SL, Weber-Main AM, Mulcahy PA (2009). Faculty Success Through Mentoring: A Guide for Mentors, Mentees, and Leaders, Lanham, MD: Rowman & Littlefield Education.

Chakshusmathi G, Kim SD, Rubinson DA, Wolin SL (2003). A La protein requirement for efficient pre-tRNA folding. EMBO J 22, 6562–6572.

Chen X, Taylor DW, Fowler CC, Galan JE, Wang HW, Wolin SL (2013). An RNA degradation machine sculpted by Ro autoantigen and noncoding RNA. Cell 153, 166–177.

Crow MK, Olferiev M, Kirou KA (2019). Type I interferons in autoimmune disease. Annu Rev Pathol 14, 369–393.

Fuchs G, Stein AJ, Fu C, Reinisch KM, Wolin SL (2006). Structural and biochemical basis for misfolded RNA recognition by the Ro protein. Nat Struct Mol Biol 13, 1002–1009.

Greiling TM, Dehner C, Chen X, Hughes K, Iniguez AJ, Boccitto M, Ruiz DZ, Renfroe SC, Vieira SM, Ruff WE, *et al*. (2018). Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus. Sci Transl Med 10, eaaan2306.

Leng Y, Sim S, Magidson V, Wolin SL (2020). Noncoding Y RNAs regulate the levels, subcellular distribution and protein interactions of their Ro60 autoantigen partner. Nucleic Acids Res 48, 6919–6930.

National Academies of Sciences, Engineering, and Medicine (2019). The Science of Effective Mentorship in STEMM, Washington, DC: The National Academies Press.

O'Brien CA, Wolin SL (1994). A possible role for the 60 kd Ro autoantigen in a discard pathway for defective 5S ribosomal RNA precursors. Genes Dev 8, 2891–2903.

Pannone B, Xue D, Wolin S (1998). A role for the yeast La protein in U6 snRNP assembly: evidence that the La protein is a molecular chaperone for RNA polymerase III transcripts. EMBO J 17, 7442–7453.

Rinke J, Steitz JA (1982). Precursor molecules of both human 5S ribosomal RNA and transfer RNAs are bound by a cellular protein reactive with anti-La lupus antibodies. Cell 29, 149–159.

Stein AJ, Fuchs G, Fu C, Wolin SL, Reinisch KM (2005). Structural insights into RNA quality control: the Ro autoantigen binds misfolded RNAs via its central cavity. Cell 121, 529–539.

Termini CM, Pang A (2020). Beyond the bench: how inclusion and exclusion make us the scientists we are. Mol Biol Cell 31, 2164–2167.

Wolin SL, Steitz JA (1983). Genes for two small cytoplasmic Ro RNAs are adjacent and appear to be single copy in the human genome. Cell 32, 735–744.

Wolin SL, Steitz JA (1984). The Ro small cytoplasmic ribonucleoproteins: identification of the antigenic protein and its binding site on the Ro RNAs. Proc Natl Acad Sci USA 81, 1996–2000.

Wolin SL, Walter P (1988). Ribosome pausing and stacking during translation of a eukaryotic mRNA. EMBO J 7, 3559–3569.

Yoo CJ, Wolin SL (1997). The yeast La protein is required for the 3′ endonucleolytic cleavage that matures tRNA precursors. Cell 89, 393–402.