The path from student to mentor and from chromosomes to replication to genomics

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ABSTRACT **The American Society for Cell Biology Women in Cell Biology Sandra Masur Senior Award recognizes leadership in scientific accomplishments and in mentoring, which are intertwined. My development as a scientist reflects important mentors in my life, including my father and Joe Gall, who is my "Doktor Vater." In turn, as an established investigator, my scientific successes in researching 1) chromosomes, their replication and genomics, and 2) ribosomes, their structure, evolution, and biogenesis, reflects the hard work of my students and postdocs, for whom I act as a mentor, guiding them in their research and along their career paths.**

It is a wonderful honor to receive the American Society for Cell Biology (ASCB) Women in Cell Biology (WICB) Senior Leadership Award that is named after my friend Sandra Masur, who has done so much for WICB. I attended the very first WICB meeting in 1971 and served as the chair of WICB in 1991. Subsequently, I led the action to make it a standing committee of ASCB, thus ensuring its longevity and its acceptance by the ASCB as a way to promote women in science. This is also the charge of the Rosalind Franklin Society, of which I am a founding member. In this short article, I will trace my training and key mentors who have impacted my career.

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THE EARLY YEARS

It was natural that I would become a biologist. My father was a physician-scientist who grew up in Italy. After graduating from medical school in Milan, he emigrated to the United States during World War II, arriving by boat during the Great Hurricane of 1938, to pursue research with Harry Goldblatt, who had established the first animal model for renal hypertension. Soon thereafter, Mussolini's Manifesto of Race stripped Jews of their Italian citizenship and professional positions. Unable to practice medicine in Italy, my father remained in the United States and joined the faculty of the College of Physicians and Surgeons (P&S) of Columbia University (serving as a faculty member from 1942 to 1979), where he continued his research on hypertension and saw patients. He wrote an exhaustive review of the field and proposed an explanation for renal hypertension (later proven correct by others), but since it was counter to a hypothesis espoused by his department chair, he was not allowed to publish the work. I vividly remember my father shelving his opus and stating that although he would terminate his research, his patients would be the beneficiaries of his knowledge of the area. At that moment I became determined to become a scientist and carry forward the name of Gerbi in biomedical research. Years later, a study presented at an ASCB WICB meeting showed that successful female biologists hold their fathers as role models. How true this was for me!

At Hunter College High School, I had marvelous teachers for ninth grade biology (Ruth Lilienthal) and for advanced placement biology (Lynn Pasztor). I wrote a term paper about J. Herbert Taylor's discovery published just a few years earlier that chromosomal duplication was semiconservative (Taylor *et al.*, 1957). In that classic

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Abbreviations used: ASCB, American Society for Cell Biology; CNE, conserved nuclear element; MBL, Marine Biological Laboratory; NIH, National Institutes of Health; P&S, College of Physicians and Surgeons; PI, principal investigator; RIP, replication initiation point; snoRNA, small nucleolar RNA; WICB, Women in Cell Biology.

paper, Taylor popularized the use of tritium for autoradiography and was able to follow the label in successive cell divisions. However, he could not imagine how DNA was organized into chromosomes, and this led him to speculate about various models. Thus began my interest in DNA replication and chromosome structure. Little did I know that two years later I would take Taylor's molecular genetics course at Columbia when I was a sophomore at Barnard College. These were exciting times, and Taylor invited Matt Meselson to give a seminar about his demonstration that DNA replication in *Escherichia coli* was semiconservative (Meselson and Stahl, 1958), a study that had been published a year after Taylor's findings of semiconservative duplication of chromosomes (for further discussion, see Gall, 2016). Taylor served as ASCB president in 1970.

As an enterprising Barnard undergraduate, with New York at my doorstep, I registered for a Brookhaven symposium where I was met at the train station by a chauffeur sent from Brookhaven to escort me to the meeting, never dreaming that his passenger was an undergrad and not a professor! The impetus to attend this meeting was to learn more about giant chromosomes. This wish was fulfilled. Joe Gall spoke about his DNase studies on amphibian giant lampbrush chromosomes that supported a unineme model for chromosome structure (i.e., one DNA double helix per chromatid; Gall, 1963), thus settling the issue of DNA arrangement in chromosomes that had puzzled Taylor. At the same meeting, Crodowaldo Pavan spoke about the polytene chromosomes of *Rhynchosciara* larval salivary glands, whose DNA puffs underwent intense DNA synthesis (Ficq and Pavan, 1957). Although I did not introduce myself at the time, I already knew that I wanted to pursue a PhD under Gall's mentorship. Moreover, I became hooked on sciarid DNA puffs, and we are still studying them in my lab.

Early on in my studies at Barnard, I was taught about the experimental basis for biological facts in a developmental biology course given by Lucena Barth. Subsequently, she and her husband moved to the Marine Biological Laboratory (MBL) to continue their research. With her introduction to the MBL, I came to appreciate this very special place, where research is an intense experience shared with colleagues who are incredibly excited by scientific discoveries. As a graduate student, I took the physiology (cell biology) course at MBL, and later, as a faculty member, I did some collaborative research at MBL, taught in an undergraduate January course, and served on several MBL review committees. Lucena Barth was my first role model of a female research scientist, helping me to choose research as a career path. My next female role model was the vivacious Reba Mirsky Goodman at Columbia P&S, under whose guidance I did my senior honor's thesis on polytene chromosomes from the fly *Sciara coprophila*. She had obtained these flies from Helen Crouse, who was a research associate in J. Herbert Taylor's lab. Ultimately, once I had established my own independent lab, Crouse turned over all the *Sciara* stocks to me. Crouse had obtained *Sciara* from Charles W. Metz at Johns Hopkins University, did her PhD research with Barbara McClintock, and spent her career studying *Sciara* (Gerbi, 2007). We now maintain the *Sciara* stock center and welcome new investigators who wish to work with *Sciara* in their labs to explore its many unique biological features (DNA amplification, chromosome imprinting, a monopolar spindle in meiosis, X dyad nondisjunction, chromosome elimination, etc). Such studies are now made possible by our expanded toolbox of the genome sequence and transformation methodology for *Sciara* (brown.edu/go/sciara-stocks).

GRADUATE SCHOOL AND BEYOND

My PhD studies at Yale with Joe Gall were transformative in terms of my career. He is a biologist par excellence who chooses whatever biological system is best suited to answer the question at hand, including frogs, salamanders, fruit flies, beetles, and protozoa (Endow and Gerbi, 2003; Endow *et al.*, 2013). Although I had wanted to study amphibian lampbrush chromosomes with him, he encouraged me to bring *Sciara* to his lab. I wanted to pursue DNA amplification at the polytene chromosome "DNA puffs," but the molecular methodology was not yet available (cloning and sequencing had not yet been invented). Instead, we made use of *Sciara*'s gigantic polytene chromosomes (which undergo more rounds of endoduplication than *Drosophila* polytene chromosomes) as the first chromosomes to be used for in situ hybridization (Pardue *et al.*, 1970). These were exciting times in the Gall lab, as he was developing this method with my classmate Mary Lou Pardue, using an rRNA probe against its amplified extrachromosomal genes in amphibian oocytes (Gall and Pardue, 1969; Pardue and Gall, 1969). The power of new methods to advance the field is a lesson I took with me to my own lab, where we have developed several new techniques, including replication initiation point (RIP) mapping, which allows the start site of DNA synthesis to be mapped to the nucleotide level (Bielinsky and Gerbi, 1998, 1999). The basis for RIP mapping is λ-exonuclease, and we are refining its use to map replication origins genome-wide (Foulk *et al.*, 2015).

Following graduate school I spent two years as a postdoctoral fellow at the Max Planck Institute for Biology in Tübingen, Germany, where Wolfgang Beermann had created a mecca for polytene chromosome researchers. Just as I had wished to work on lampbrush chromosomes for my graduate research but ended up working on *Sciara* polytene chromosomes, at the Max Planck, instead of working on chromosomes, I started my studies on rRNA. Having used *Xenopus* rRNA to probe polytene chromosomes at Yale, I wondered where the regions of evolutionary conservation resided. Beginning in my postdoc and continuing on in my own lab at Brown, I used the relatively new method of molecular hybridization and then the even newer methods of DNA sequencing and cloning to explore this question. My fascination with ribosomes began in college, when my father had taken me to hear a seminar at the New York Academy of Sciences given by George Palade about his isolation and electron microscopic visualization of ribosomes. The dogma of the time was that ribosomal proteins were the enzymes for ribosome function in protein synthesis, but I suspected that rRNA might play an important role, as is now well documented. We derived the first sequence for rRNA from a metazoan (*Xenopus*) and discovered highly conserved sequences of vital importance for ribosome function (peptidyl transferase center, etc.) and "expansion segments" (Gerbi, 1996), whose positions but not sequences are conserved in eukaryotes. Their eukaryotic-specific roles are currently emerging. Our recent bioinformatic study has mined the now extensive database of rRNA sequences from the three domains of life to define conserved nuclear elements (CNEs), some of which are universally conserved. Other CNEs are domain specific, including several that line the wall of the tunnel in the large ribosomal subunit in eukaryotes, suggesting a eukaryotic-specific function (Doris *et al.*, 2015). At Brown we also delved into ribosome biogenesis and used *Xenopus* oocytes to demonstrate the function of U3 small nucleolar RNA (snoRNA) in 18S rRNA processing (Savino and Gerbi, 1990; Borovjagin and Gerbi, 2001) and discovered the conserved elements that guide U3 and other snoRNAs to the nucleolus (Lange *et al.*, 1998, 1999).

Since joining the faculty of Brown in 1972, I have tried to mentor the next generation as payback for the mentoring I received. At the local level, besides the many wonderful undergraduate and graduate students and postdocs mentored in my lab, I served for more than three decades as the director, principal investigator (PI),

and then co-PI of our National Institutes of Health (NIH) graduate student training grant. As the founding chair of the Department of Molecular Biology, Cell Biology, and Biochemistry, I also mentored junior faculty. I have been active in graduate and postdoctoral training at the national level, serving as a founding member and chair of the Association of American Medical Colleges Graduate Research Education and Training Group and as chair of a Federation of American Societies for Experimental Biology conference on this subject, publishing several articles with Howard Garrison (deputy executive director for policy). As part of my activities in ASCB public policy, I testified before the House and Senate Subcommittees on Appropriations about the importance of NIH funding for graduate education. It was awesome to realize how many thousands of scientists would benefit from my three-minute testimony!

The ASCB plays an important role in nurturing the careers of cell biologists from their time as students to established investigators. As a beginning graduate student, I attended my first ASCB meeting in 1965 and later served as program chair (1986), member of the ASCB Council (1988–1990), chair of WICB (1991), and president (1993). It is noteworthy that my PhD advisor Joe Gall, who was ASCB president in 1968, trained three ASCB presidents (Mary Lou Pardue, Liz Blackburn, and me). Moreover, all three of us are women, and for his nurturing of women in science, Gall received the WICB Senior Award in 2006. It is a great honor to follow in his footsteps to receive this honor myself.

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