Princeton University

Honors Faculty Members Receiving Emeritus Status

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The biographical sketches were written by staff and colleagues in the departments of those honored.

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Faculty Members Honored in 2019
for Receiving Emeritus Status

Virginia A. Zakian

Virginia "Ginger" A. Zakian, the Harry C. Wiess Professor in the Life Sciences and a member of the faculty in the Department of Molecular Biology since 1995, is one of the world's most accomplished molecular geneticists. She has contributed groundbreaking insights into the nature and function of telomeres, the unusual structures at the ends of eukaryotic chromosomes. Her lab also discovered and characterized the first eukaryotic accessory DNA helicases, which are enzymes that allow the replication fork to move past hard-to-replicate sites such as stable protein complexes and DNA secondary structures. A forceful champion of expanding the participation of women and underrepresented minorities in science, she has participated in efforts at both Princeton and around the country to bring greater diversity to the discipline. Her commitment to training the next generation of scientists is evident from the large numbers of undergraduates, graduate students, and postdoctoral fellows who have studied in her laboratory, and have gone on to successful careers in science and related fields.

Ginger received her bachelor's degree in biology from Cornell University in 1970, graduating Phi Beta Kappa and cum laude. Her lifelong interest in DNA replication was sparked during her doctoral studies at Yale University with Joseph G. Gall, where she used electron microscopy to measure the distribution of origins of replication in the DNA of the fruit fly *Drosophila virilis*. She demonstrated that the origins of replication in the majority of DNA are clustered, beginning as regularly spaced small circles indicative of bidirectionally replicated segments of DNA that eventually merge into larger "eyes." After receiving her Ph.D. in 1975, Ginger spent a year at Princeton as a postdoctoral fellow in the laboratory of Arnold J. Levine, where she turned her attention to the mechanism of replication of adenovirus, a virus with a simple genome that is a useful model to study mammalian DNA replication.

Ginger moved to the University of Washington in 1976 to study in the laboratory of Walton Fangman on a National Institutes of Health postdoctoral fellowship. It was in Fangman's lab that Ginger encountered the simple eukaryotic model organism, *Saccharomyces cerevisiae,* or baker's yeast, that would engage her attention for the

rest of her career. Like mammalian cells, yeast cells contain nuclei with multiple linear chromosomes, and much of what we know about DNA replication was first discovered by studying yeast. With Fangman, Ginger studied the replication and inheritance of a variety of chromosomal and extra-chromosomal DNAs.

In 1979 she was appointed an assistant member of the Fred Hutchison Cancer Research Center, where she rose through the ranks to become a member in 1987. It was there that she turned her attention to the components of chromosomes that are required for their precise replication and segregation. Toward that goal her laboratory was the first to construct and characterize an artificial chromosome in yeast, which ultimately led to the application of yeast artificial chromosome vectors in the sequencing of the human genome. In the course of these early studies, Ginger discovered an important epigenetic phenomenon called telomere position effect, whereby genes that reside close to the end of chromosomes are silenced by their proximity to telomeric sequences.

It is these unusual ends of chromosomes that most attracted Ginger's curiosity. Nothing that was understood about DNA replication at the time could explain how these last 300 bases of DNA were replicated, nor why they were essential for the stability and the proper segregation of chromosomes during replication. Using a combination of genetic and biochemical approaches to tackle these questions, Ginger and her colleagues were the first to identify proteins that interact with telomeric DNA, first in ciliates and then in yeast. They showed that one of those proteins, Cdc13, is required to recruit Est1, a subunit of the enzyme telomerase, to chromosomal ends by recognizing unique repeated telomeric sequences. Another protein that Ginger studied, Pif1, a helicase that unwinds double-stranded DNA, not only inhibits telomerase at broken DNA ends, which is essential if those breaks are to be successfully repaired, but it also helps to channel its catalytic activity to short telomeres by removing it preferentially from longer telomeres. Ginger also established that Pif1 has the unusual property of preferentially displacing RNA from DNA, a property that is consistent with the obligate RNA-dependent activity of telomerase.

But the story of Pif1 does not end there. Pif1 is also a member of a family of helicases that acts throughout the genome to facilitate the replication of hard-to-replicate regions of DNA, including G-quadruplex DNA structures, four stranded secondary structures held together by non-canonical G-G base pairs. The lab showed that the Pif1 family of helicases accomplish this feat by promoting

replication fork progression at these sites. In the course of these studies the lab made a surprising discovery that highly transcribed regions of the genome, which were thought to be very accessible to the replication machinery, actually impede replication forks as well, a problem that is overcome with Pif1-like activity. The universal importance of Pif1 is suggested from collaborative work in Ginger's lab that showed that Pif1 mutations are associated with increased risk of breast cancer in humans.

Telomeres, it turns out, replicate themselves in completely novel ways. Up to a point they use conventional the DNA synthetic pathway, but at the very end, they use a completely novel process that assembles guanosine-rich tails onto the ends of the chromosome. Ginger's lab established that Cdc13 acts as a switch between the two pathways, thus regulating the length of the telomeres. In searching for other proteins that affect telomere biology, Ginger pioneered a now widely employed technique called chromatin immunoprecipitation, which uses antibodies to identify proteins bound to specific DNA sequences. Using this technique, Ginger showed that another yeast protein, Rap1, is bound to telomeres where it affects both telomere structure and chromosome stability, and confirmed that telomeres are assembled into protein-DNA structures that are different from the structures in the rest of the chromosomes.

The full extent of the complexity of telomeric protein-DNA structures is still being revealed. Ginger's lab has recently made a major contribution to resolving this question by using another powerful technology, mass spectrometry, to identify approximately 70 new proteins in the complex. She has shown that several of these are involved in regulating the level of the telomerase activator Est1 by modulating its rate of protein degradation. Another surprise from her work is the finding that three telomere-associated proteins appear to be necessary to process the active structure of the telomerase-associated RNA TLC1.

Life scientists are always interested in whether their discoveries are unique to the organism they study, or can be generalized to other organisms. Ginger's lab undertook an analysis of telomere structure and function in a distantly related yeast, *Saccharomyces pombe.* They were the first to identify the telomerase-associated RNA in *S. pombe,* and to show that it has features similar to those of the human counterpart. Furthermore much, but not all, of the telomere biosynthetic pathway that she had discovered in *S. cerevisiae* was conserved in *S. pombe.*

Ginger's influential contributions to our understanding of telomeres has been recognized by many honors, including election to the National Academy of Sciences. She is constantly in demand to speak at universities and research institutes, and has given dozens of keynote lectures at important national and international meetings. She has been continuously funded by the National Institutes of Health since 1979, and was awarded a prestigious Merit Award in 2000. Her prominence in the field is reflected by the large number of volunteer leadership roles she has played at the National Institutes of Health, including serving on the Council of the Institutes of General Medical Sciences and on the Board of Counselors at the National Cancer Institute. Within the broader profession, she has served on the Council of the American Society of Cell Biology, the board of directors of the Genetics Society of America, and was a founding member of the board of the Rosalind Franklin Society. She has served on the editorial boards of a variety of journals, and organized key scientific meetings in the field.

Ginger has been an outspoken voice advocating for the greater inclusion of women and underrepresented minorities in science. In 2001 at Princeton she chaired the Task Force on the Status of Women in Science and Engineering that undertook a detailed analysis of the University's efforts to attract and retain highly talented women in the sciences, and made critical recommendations to remedy gender differences. As an affiliate faculty member in the Program in Gender and Sexuality Studies, she brings the perspective of a scientist to the program's teaching and deliberations. She served three times on the University's Target of Opportunity Search Committee, as well as on committees at the National Institutes of Health charged with increasing minority opportunities in life sciences. Within the Department of Molecular Biology, she has effectively advocated for expanding the enrollment of underrepresented minorities in the graduate program, helping to make the department's program one of the most diverse in the country.

Ginger has taught courses at both the undergraduate and graduate level at Princeton, and overseen the theses of 17 graduate students and 39 undergraduates. She has a strong track record of training postdoctoral fellows, who have gone to have successful careers in academia, industry, and communications. She has served the department in a variety of committee roles, including the Executive Committee, the Graduate Student Admission Committee, and the Postdoctoral Fellow Program.

With a remarkable number of scientific advances to her credit, as well as the care she has taken to promote the welfare of her community and the preparation of the next generation of life scientists, Ginger Zakian has been an exemplary member of the faculty of Princeton University.