Lois K. Miller

1945–1999

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

LOIS K. **MILLER**

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By A. Lorena Passarelli, Janet Westpheling, Erin M. Espelie, and Karl Espelie

Lois K. Miller was an outstanding virologist, biochemist, and geneticist, who pioneered the field of molecular baculovirology, the study of a group of insect viruses. Her keen intellect and vision had major and long-lasting impacts inside and outside the traditional realm of virology, influencing other biological fields. She developed new strategies to use baculoviruses as biological pesticides against environmentally and economically costly insect pests, affecting agricultural productivity worldwide. She developed the use of baculoviruses for the expression of heterologous proteins, a creative leap that has facilitated the characterization of a large number of human proteins and the study of their functions. Research from her laboratory also significantly advanced the fields of insect physiology and genetics, and she made major early contributions to understanding the molecular mechanisms of apoptosis, or programmed cell death, an important cellular process in many diseases including cancer. Lois excelled in all areas of professional life, as a scientist, mentor, teacher, colleague, consultant and in professional society and university service activities. She was a role model and an inspiration for young scientists, leaving a strong legacy that set high standards for the many students and colleagues who continue her work today.

Early life

Lois Miller was born in Lebanon, Pennsylvania, on October 8, 1945. Her father, Clarence, was a Lutheran minister and her mother, Naomi, a high school Latin teacher. Lois was the youngest of three children. Lois and her brother, Paul, started taking piano lessons at a very early age, and both excelled in regional piano competitions. Lois' father moved the family to various locations, depending on his church affiliations, including Cincinnati, Ohio, and Harrisburg, Pennsylvania, where Lois attended junior high and high school. Her family affectionately called her "Puddy" or "Pudd," a nickname that came from an early fondness for pudding. Lois attended a small liberal arts college,

Upsala College in East Orange, New Jersey. She spent the summer after her junior year working on a research project at Oak Ridge National Laboratory, gaining an appreciation for science and bench work. Lois graduated *magna cum laude* from Upsala with a B.S. in chemistry in 1967.

For graduate school Lois attended the University of Wisconsin-Madison, funded by a Woodrow Wilson Fellowship. She joined the laboratory of biochemist Robert "Bob" G. Wells in Madison. While still a student she published four articles on the exonucleolytic and associated diphosphokinase activities of the *Micrococcus luteus* DNA polymerase. This work contributed directly to the understanding of the structure and function of DNA polymerase, and led to the discovery that a domain of the polymerase, the "Klenow fragment," was able to synthesize and proofread DNA.

When Lois was not in the laboratory, she could be found riding her newly-purchased Honda motorcycle, playing piano for the annual graduate student parody of the biochemistry faculty, sailing Frisbees onto the rooftops of the greenhouses located next to the biochemistry building, and learning how to play squash with Karl Espelie, a fellow PhD student in biochemistry who became her life-long partner, husband and companion, sharing her strong love of science.

Once while Lois was still a graduate student, she attended an American Association for the Advancement of Science meeting in Chicago. She participated in a program there entitled "Women in Science" that was televised nationwide. Lois was asked to serve on a panel with three other women: the chemist Jean Simmons, her college mentor, the marine biologist Eugenie Clark, and the inimitable Margaret Mead. As a member of this powerful intellectual team, Lois learned about how to deal with the media, address unwanted attention to her gender, and present her science to the public. All of these talents served her well in her future, high profile career.

Lois finished her PhD in November 1971, and accepted an American Cancer Society postdoctoral fellowship with Robert Sinsheimer in the Biology division at the California Institute of Technology. She transitioned from working with bacteria to working with bacteriophages at the molecular level, and moved with her Honda motorcycle to Pasadena. While in California, she took courses in scuba diving, skiing, and sailing. She married Karl in the gardens on the Caltech campus during her lunch break, just a few days before the pair left for a two-month tour of France, Italy, Yugoslavia, and Turkey.

After Caltech she took a postdoctoral position for two years with Mike Fried at the Imperial Cancer Research Fund Laboratories in London, England. In the Fried laboratory she studied polyomaviruses, small DNA viruses, developing similar approaches to those that she would later use with baculoviruses.

While living in London, Lois and Karl took vacations to Copenhagen, Cairo and Luxor, and Moscow and Leningrad. They drove their Volkswagen bug from London to a virology meeting in Madrid. They went on safari to Kenya and Tanzania. Lois and Karl also fell in love with theater; they went to plays, operas, or concerts almost every night, concluding the evenings by strolling across the Thames on the western side of the Waterloo Bridge.

Pioneering baculoviruses

In 1976, Lois and Karl moved to Moscow, Idaho, where Lois had been offered a position as an assistant professor in the department of Bacteriology and Biochemistry at the University of Idaho. Part of Lois' decision for selecting Moscow, beautifully nestled in the hills of the Palouse region, was its proximity to Washington State University, where Karl had secured a faculty position. At the time, spouses in the same field of the sciences were rare and often prohibited from working at the same institution. On her first day at the University of Idaho, Lois astounded her Dean by submitting research proposals to both the National Institutes of Health and National Science Foundation; both proposals were ultimately awarded. Lois' new position encouraged her to address agricultural problems of importance to the Pacific Northwest. So, at the outset of her independent scientific career, Lois decided to change her focus and apply her background in biochemistry and virology to agricultural questions. In addition to the critical timing in her career and risk in changing fields, an impressive aspect of this decision was her cross-disciplinary vision. She searched for a relatively new area with future potential in basic and applied research that would also contribute to the larger scientific community.

Lois' search led her to a group of relatively unstudied viruses called baculoviruses that infected insect pests of economically important crops. She was intrigued by the impact that these viruses might have on agriculture, and by the potential importance of studying viral gene regulatory pathways. Her vision for the use of baculoviruses as models for the study of viral mechanics and insect physiology was extraordinary; it continues to inspire practical genetic applications in research today.

During Lois' first few years as an assistant professor at the University of Idaho, she worked quickly and adeptly to develop the reagents and hone the methodologies needed to study baculoviruses. Lois initially isolated and plaque purified baculovirus variants of *Autographa californica* M nucleopolyhedrovirus (AcMNPV) from the larvae of infected cabbage looper, *Trichoplusia ni*. In 1978, she predicted that cloning and purifying the virus would facilitate its genomic characterization, the ability to isolate mutants, and eventually, benefit the commercial applications of baculoviruses. At this time, other laboratories were also purifying and characterizing variants of the same virus. Having obtained a genetically pure stock of virus, Lois derived a physical restriction endonuclease map of AcMNPV and other related baculoviruses. One of the variants Lois isolated, AcMNPV L1, is still widely used and continues to augment knowledge about these intriguing and complex viruses. Her grant from the National Institutes of Health, titled "Genetic Characterization of Baculoviruses," was funded from 1977 to 1986.

The next set of experiments that Lois conducted show a comprehensive and systematic approach to studying a newly isolated virus, and opened many lines of research for her post tenure academic years. Although she was performing basic molecular biology work, she kept in mind the potential use of baculoviruses as biological pest-control agents. First, she established the virulence of the baculoviruses, an important attribute for using them in agricultural settings. Second, she created and phenotypically characterized panels of temperature sensitive mutant viruses with phenotypes that blocked several steps during the virus replication cycle. Some of these mutants were mapped using newly developed DNA transfection of insect cells, a method whereby a DNA restriction fragment from the wild-type virus would be introduced into cells infected with the mutant virus. After genetic recombination between the fragment DNA and the mutant viral DNA, the defective phenotype was rescued.

Although not all of these temperature sensitive mutants were initially mapped, many were stored in the freezer and retrieved ten to twenty years later when more modern molecular tools could be used, and the viral genome had been fully sequenced. These mutant viruses were later instrumental in assigning gene function in an era where temperature sensitive mutants were old fashioned and targeted gene mutations could be created. Thus, an old tool, originally established by Lois as a junior investigator entering a new field, resurfaced years later and helped define crucial gene functions and viral regulatory strategies.

Lois earned tenure at the University of Idaho and was promoted to associate professor in 1978, less than four years after starting her new research program. As an associate professor she opened new areas in baculovirus research. In her laboratory, viruses were being passaged in cultured cells and genetic maps were being generated. Lois discovered that baculovirus genomes contained transposable elements acquired from the insect host. This discovery was the first report of a virus that infected eukaryotes to incorporate a mobile genetic element derived from its host. It also illustrated that baculovirus transposable element mobility was different from many transposable elements known at the time but similar to Ty1 elements in yeast; the terminal repeats were found separate from the primary body of the transposable element. Furthermore, this was the first example of a copia-like transposable element found in metazoans other than that of the *Drosophila* fruit fly genome.

Lois' vision went beyond this unique finding. She reasoned that if baculoviruses could accommodate a 7.5 kbp insertion, then their nucleocapsids could also hold targeted insertions of other foreign genes of interest. As a publication announcing her findings was going to press, she was simultaneously developing baculoviruses as gene expression vectors. Finding insect transposable elements in AcMNPV was a significant report that advanced the field of baculovirology and genetics. The study was published in the journal *Nature* and further established Lois as an innovator in her field.

Around the same time, in June 1979, Lois and Karl welcomed a daughter, Erin Marie Espelie, after which Lois took two months off from the laboratory. Lois became in equal parts a mother, a wife, and a scientist; she excelled in all of these jobs. The family took every opportunity to enjoy living in the Northwest, traveling with friends to look for mushrooms, cross country skiing and white-water rafting on the Salmon River. Erin and Karl often joined Lois when she went to scientific meetings or when she was invited to deliver seminars in places like Hawaii, Japan, and China. They took Erin to plays in London, where as a young child she developed a love of Shakespeare.

Baculoviruses as gene expression vectors

At the brink of becoming a full professor, Lois, as sole author, published a historic review in 1981[1] in which she discussed work in progress developing AcMNPV as a gene expression vector. She outlined the advantages and disadvantages of using baculoviruses to carry "passenger DNA" and their ability to produce abundant and correctly post-translationally modified products. She carefully contrasted and compared the benefits of baculoviruses and other viral vectors. AcMNPV could accommodate large genes from

plants or animals (vertebrate and invertebrate) into its genome, since it could package it into "expandable" rod-shaped nucleocapsids, similar to packaging large transposable elements as she had determined before. Lois had also figured out how to quickly target genes to specific loci in AcMNPV since she had used recombination techniques between small DNA fragments and the viral genome when mapping temperature sensitive mutants. These inserted genes could be expressed from a strong viral promoter yielding significant amounts of polypeptides.

This strong viral promoter directed transcription of a gene called polyhedrin, which yielded most of the protein that makes up the dense occlusions that form in the nucleus of baculovirus-infected cells. Polyhedrin-composed occlusions house roughly 100 enveloped nucleocapsids. From restriction endonuclease analysis and Southern blots conducted by Walter Doerfler's group, Lois reasoned that the polyhedrin gene was not duplicated in the genome, implying that the production of all those occlusions—and all of that polyhedrin protein—ultimately came from a single strong promoter.

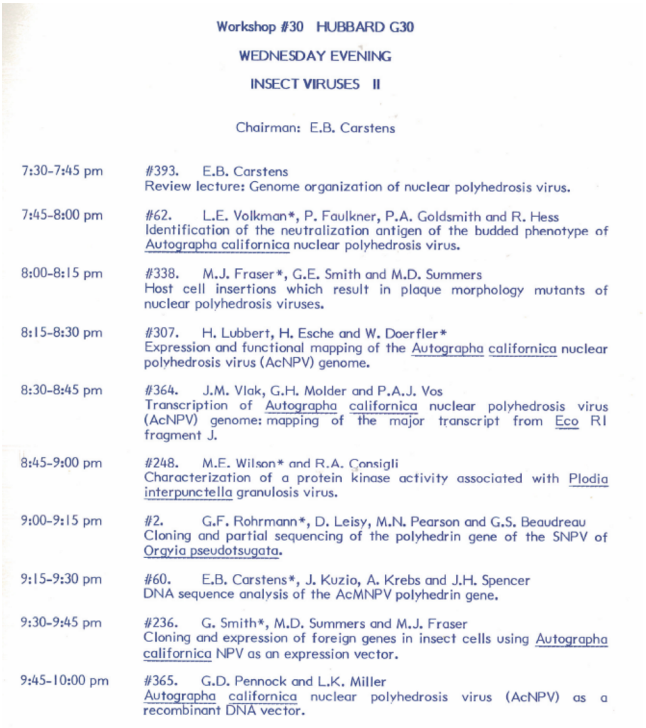
Lois reasoned that polyhedrin was not an essential gene in the propagation of virus in cultured cells, and wisely speculated that it could be used to drive expression of foreign genes. In 1980, Kathleen N. Potter and Lois published a paper mapping mutants that had few polyhedra (so-called FP mutants) or occlusions. These were instrumental in inferring that polyhedrin was not essential for viral replication in infected cultured cells, and could be targeted as a site for foreign gene insertion. Moreover, insertions in polyhedrin could be identified by visual inspection of polyhedra-deficient plaques. Not only had she identified a non-essential gene, but a screening marker. Having a cell culture system allowed the mass-production of susceptible cells and viruses, and large-scale expression of foreign genes.

The early 1980s were exciting years in baculovirus research, crucial in developing baculoviruses as eukaryotic vectors for foreign gene expression. The second American Society for Virology meeting, held in East Lansing, Michigan in 1983, brought together numerous baculovirologists to discuss current research. The Insect Viruses II workshop chaired by Eric B. Carstens revealed growing research on baculovirus genome architecture, transcript mapping, and enzymatic activity of specific viral gene products (Figure).

The last four talks of this historic workshop set the foundation for research that evolved into future trademarks of baculovirology. George F. Rohrmann and Eric B. Carstens presented the nucleotide sequence of polyhedrin in two baculoviruses, *Orgyia pseudotsugata* single NPV and AcMNPV, respectively. The last two presentations described

research on the use of AcMNPV as the effective carrier of foreign genes from the laboratories of Max Summers and Lois Miller. Discussion went long past 10:00 p.m., the time when the workshop was scheduled to end.

Shortly after disseminating her ideas on developing AcMPNV as a vector in review articles and at meetings, Lois published a seminal study describing the insertion of a bacterial gene in the AcMNPV genome and showing that its expression was regulated as that of the viral gene it substituted for.[2] Few would have predicted the impact that this study would have on basic research, the industrial production of proteins, and the delivery of health-related molecules. She submitted the manuscript to the journal *Cell.* In June of 1983, Lois was also preparing artistic photographs of blue-tinted plaques that validated the expression of the inserted lacZ gene for the journal's cover[3]. Lois anticipated that having a color marker would facilitate the study of pathogenesis and other molecular features of the virus, another prediction that was eventually proven to be true. Unfortunately, the study was not accepted by *Cell*, delaying its submission to *Molecular and Cellular Biology* until September of that year and its acceptance until November of 1983; in the meantime, similar work by the Summers group[4] was accepted for publication in September.



Workshop #30 HUBBARD G30

WEDNESDAY EVENING

INSECT VIRUSES II

Chairman: E.B. Carstens

7:30-7:45 pm — #393. E.B. Carstens
Review lecture: Genome organization of nuclear polyhedrosis virus.

7:45-8:00 pm — #62. L.E. Volkman*, P. Faulkner, P.A. Goldsmith and R. Hess
Identification of the neutralization antigen of the budded phenotype of Autographa californica nuclear polyhedrosis virus.

8:00-8:15 pm — #338. M.J. Fraser*, G.E. Smith and M.D. Summers
Host cell insertions which result in plaque morphology mutants of nuclear polyhedrosis viruses.

8:15-8:30 pm — #307. H. Lubbert, H. Esche and W. Doerfler*
Expression and functional mapping of the Autographa californica nuclear polyhedrosis virus (AcNPV) genome.

8:30-8:45 pm — #364. J.M. Vlak, G.H. Molder and P.A.J. Vos
Transcription of Autographa californica nuclear polyhedrosis virus (AcNPV) genome: mapping of the major transcript from Eco RI fragment J.

8:45-9:00 pm — #248. M.E. Wilson* and R.A. Consigli
Characterization of a protein kinase activity associated with Plodia interpunctella granulosis virus.

9:00-9:15 pm — #2. G.F. Rohrmann*, D. Leisy, M.N. Pearson and G.S. Beaudreau
Cloning and partial sequencing of the polyhedrin gene of the SNPV of Orgyia pseudotsugata.

9:15-9:30 pm — #60. E.B. Carstens*, J. Kuzio, A. Krebs and J.H. Spencer
DNA sequence analysis of the AcMNPV polyhedrin gene.

9:30-9:45 pm — #236. G. Smith*, M.D. Summers and M.J. Fraser
Cloning and expression of foreign genes in insect cells using Autographa californica NPV as an expression vector.

9:45-10:00 pm — #365. G.D. Pennock and L.K. Miller
Autographa californica nuclear polyhedrosis virus (AcNPV) as a recombinant DNA vector.

Workshop 30 of the 2nd Annual Meeting of the American Society for Virology in East Lansing, Michigan. (Printed with permission from the American Society for Virology.)

The sequence of events during this crucial period has been documented in published manuscripts, in the submitted conference abstracts, in the contributions from many other groups, and relayed by those who witnessed the competitive and stimulating envi-

ronment of those times. Throughout, Lois always worked steadily and focused on the science, rather than the politics. The development of AcMNPV as a carrier of foreign genes has since been broadened, and continues to be instrumental in the research of many scientific fields, including the improvement of agricultural biopesticides. Although this was a milestone accomplishment in Lois' career, she had others perhaps even more noteworthy, and we are still seeing how far their long-term impact will go.

Equally remarkable was Lois' perspective of baculoviruses as safe vectors to deliver genetic material to mammals as well as insects. In a review published in *Science* in 1983, Lois proposed that insect-specific toxins could be inserted into polyhedrin to increase the efficacy of baculoviruses as biological insecticides. This proposal did not remain theoretical for long. It was translated into an active line of research for the Miller laboratory, resulting in seminar invitations, consultations, and funding support from several agribusiness companies that sought to put the new class of biopesticides into practice.

Over the next few years, Lois worked on the transcription of viral genes, expression of AcMNPV genes in mammalian and dipteran cells, and the use of chemical inhibitors to dissect early and late viral gene expression. The work on mammalian cells was the start of another example of the creative use of baculoviruses as gene delivery systems, while the inhibitor work was fundamentally important in the ability to study early genes independently of late or very late ones. With her postdoctoral fellow Paul Friesen, she dissected early transcriptional units and divergent transcripts of the anti-apoptotic protein p35. This work provided a framework for understanding early genes and some of their functions.

In the middle of an important time in her career between 1983 and 1984, Lois was diagnosed with malignant melanoma. The malignant cells were localized and removed, and Lois continued her productive routine. Eleven years would elapse before a reoccurrence of this cancer.

In 1983, Lois was promoted to full professor at the University of Idaho. The rapid and exceptional work that she had performed was receiving notoriety nationally and internationally. Among Lois' admirers was Arden Lea, a mosquito physiologist at the University of Georgia, in the department of Entomology. Arden convinced Lois and Karl to relocate and join his department. Lois also had a joint appointment in the department of Genetics. Lois moved with her laboratory team and her family to Athens, Georgia, in 1986.

New directions, new discoveries

Athens was a somewhat larger college town than Moscow and provided opportunities for arts and theater, and excellent schooling for Erin. In Georgia, the family exchanged beautiful mountain scenery for mild winters and heated summers, colorful azaleas, stately magnolia trees, and southern hospitality. Their new home was in a rural section of Athens, on seven acres of land with a large pond for their red canoe and an abundance of birds. It was enough space for Lois to go jogging on trails that Karl carved out. They added a swimming pool that served as a gathering place for laboratory get-togethers on hot summer days. Lois often complained, however, about the "long" ten-minute commute between her home and the University that included three stoplights, far too many from her perspective.

Lois rapidly established her laboratory within the departments of Entomology and Genetics at the University of Georgia. Postdocs and advanced graduate students working with Lois relocated from the University of Idaho and, even though it was a major move, research productivity did not halt. The transition was smooth and the laboratory quickly grew to ten active members. With new facilities, resources, and additional personnel, Lois expanded the number and diversity of research projects. These were consistent with the interests of laboratory members joining the team from the department of Entomology or Genetics. The group was energetic and prolific, and life-long friendships developed.

The family continued to travel extensively, visiting Australia, Austria, Germany, Scotland, England, the Caribbean, and more. They found a spot in the British Virgin Islands, Jost Van Dyke, to which they returned many times for snorkeling and pleasure reading. Lois packed pounds and pounds of books into an oversized suitcase for family reading. Her work accompanied the family on their trips, too, as she assiduously kept up on journals and a wide-range of research. She also loved to read novels "reserved for the beach."

The task of developing baculoviruses as efficient pest control agents gained momentum and was supported by industrial companies. Lois and team members, including Russ Eldridge and Michael D. Tomalski, characterized the activity of insect and arachnid toxins, as well as proteins that affected insect development, when they were expressed in AcMNPV. She hypothesized that these toxins could paralyze the host and would improve baculoviruses as pest control agents and further the understanding of insect neurophysiology. The mite neurotoxin was the most potent venom tested, paralyzing infected insects and blocking further feeding, an important attribute in insecticides which was published

in *Nature* in 1999.[5] She also collaborated with her husband Karl in an elegant study that evaluated the safety of expressing baculovirus toxins in non-pest insects.

In addition to directly investigating the potential of baculoviruses as insecticides, Lois' basic research sometimes stumbled upon ways to improve pest control. The key was to step back and realize the potential that basic research could have on applied research. While studying a region of AcMNPV that frequently incurred deletions during serial passage, Lois and a postdoctoral fellow, David R. O'Reilly, discovered that AcMNPV encoded an ecdysteroid UDP-glucosyl transferase (EGT). The enzyme catalyzed the transfer of glucose from UDP-glucose to ecdysteroids, thereby blocking insect molting.[6] This was advantageous for virus replication, but at the same time allowed the insect to consume more food. They reasoned that deletion of EGT would allow molting and reduce crop consumption. This was indeed the case. Using an "EGT deletion" baculovirus to control insect pests was regarded as a more regulation-friendly approach than one expressing exogenous genes. Lois Miller and David O'Reilly obtained two patents from this work and defined the biochemistry of the EGT enzyme.

Lois then defined the promoter region of the polyhedrin gene and found that only eight base pairs defined the promoter and that sequences downstream of the translational start codon provided a burst in gene expression. She mapped mutations that strengthened expression from the polyhedrin promoter referred by her team as "the super promoter" and filed a patent in 1991. She also worked with hybrids of strong promoters to learn about gene transcription and optimize expression from AcMNPV. A tangent of this work included defining the influence of antisense transcripts near polyhedrin. Together, many publications improved the ability to map complex transcription units, understand gene regulation, and develop more efficient expression vectors.

Anew area that was advanced during this period was the identification of the genes necessary for viral late gene expression and genomic replication. Lois and a graduate student, A. Lorena Passarelli, developed a powerful assay that mimicked viral DNA replication to identify these genes. The assay was simple, yet technically delicate. A reporter gene whose expression depended on a late viral promoter could only be expressed in the presence of replicating viral DNA. The viral genes necessary for late expression were eventually narrowed down to cloned viral open reading frames that contained nineteen genes. This assay identified late gene transcription factors called LEFs and viral DNA replication factors, since late gene expression required viral DNA replication in the assay

as during virus infection. Other investigators later confirmed the role of each gene using genetic, in vitro, or in silico methods.

One of Lois' major contributions was identifying viral genes that blocked the ability of the host cells to commit suicide by programmed cell death, or apoptosis. Lois and Rollie Clem, a graduate student, characterized a spontaneous AcMNPV mutant dubbed the "annihilator mutant." The name was cleverly coined since shortly after virus infection, cells died by breaking up into small blebs.

After searching the literature for a process that mentioned "blebs," they learned about apoptosis, which at the time was just starting to become more widely appreciated. Apoptosis is a normal process during development whereby unwanted cells die by breaking up into blebs known as apoptotic bodies. Normally, baculovirus-infected cells survive for several days after infection, and then die by passive lysis. However, annihilator-infected cells die by apoptosis within several hours after infection. The annihilator mutation was mapped to a gene called, p35, which demonstrated that AcMNPV normally blocked apoptosis, and if p35 was mutated, the resulting apoptosis was detrimental for virus replication.

A seminal paper published in *Science* was one of the first examples of a virus manipulating host cell apoptosis.[7] P35 was later shown by Lois and collaborators to be an inhibitor of caspases, the executioner enzymes of cell death, and as such became an important tool for studying apoptosis in *Drosophila* as well as in mammals. A few years later, Lois, Rollie Clem, and a colleague spending a sabbatical in Lois' laboratory, Norman Crook, found that baculoviruses encoded another type of anti-apoptotic gene, which they named inhibitor of apoptosis (IAP).[8] This was another breakthrough in apoptosis research, as this baculovirus IAP became the founding member of a metazoan gene family which also regulate apoptosis and other processes in humans and other organisms. Lois and members of her group went on to carry out some of the first defining work on IAP proteins and how they inhibit apoptosis in insect cells. Her work attracted other investigators to study the process in other systems.

Awards and rewards

Lois' teaching competence was recognized early on with a University of Idaho Alumni Award for Excellence in Teaching in 1982. The University of Georgia also recognized Lois' creativity and sustained accomplishments. In 1992, Lois was promoted to a Distinguished Research Professor, the highest faculty rank awarded by the University. Four

years later, she received the Lamar Dodd Award for outstanding research for her exceptional and internationally recognized work. Her service on the University Research Foundation advisory board was legendary. In her soft-spoken yet direct way, she took the president of the University to task more than once in directing the course of the Foundation.

Also in 1992, she became an American Association of Advanced Science fellow; the following year she was named an American Academy of Microbiology fellow. She received continuous National Institutes of Health funding for almost her entire career (1980-2001), as well as other federally funded research grants.

In 1996 she was awarded the American Society for Microbiology Chiron (now Promega) Corporation Biotechnology Award. Lois took Erin to the awards ceremony and in her usual modest way commented that it was nice to have someone else be the center of attention.

In 1997 Lois was elected to the National Academy of Sciences. Upon receiving congratulations from a former graduate student, she replied "Please celebrate with me since I received this honor only through the very hard work of my students and post-docs. I hope you get direct rewards in the future. Sometimes science seems to have few rewards. The best advice is to enjoy what you are doing while you're doing it."

At a party at the President's house at the University of Georgia to celebrate Lois' election to the Academy many were wondering if she would wear a dress. Karl insisted that she owned one. In the end, as always, she was beautiful without being flashy. Her colleague John Avise, a fellow member of the Academy, commented that "it's not so bad to be a person of no flash and all substance."

While she was at the University of Georgia, Lois' baculovirus research resulted in five patents, illustrating the applicability as well as the creativity of her work. She published over 150 research papers, several books, and contributed to many book chapters. Memorably, she was asked to write a chapter in *Fields Virology*, a compendium and review of virus families, when in prior years baculoviruses and other insect viruses had not been included in this encyclopedic volume.

After her untimely death, Lois was honored by lectureships and awards; the significance of her accomplishments becoming more obvious with time. In 2003, Bob Granados gave a Founder's Lecture at the Society for Invertebrate Pathology in her honor. The American Society for Virology has a yearly lectureship in her name. The University of Georgia also

posthumously awarded Lois the Inventor's Award for her inventions' "originality, innovation, and impact outside the university setting."

Teaching and mentoring

Lois demanded excellence in her teaching and student learning, just as she demanded it in research, yet she had a personable teaching style and when appropriate brought primary literature to illustrate points. Viruses sometimes came in handy as examples of cellular processes and sometimes she illustrated examples by her attire. To explain modifications in mRNA, for instance, she walked into class wearing a baseball cap with an m7G emblem and a ribbon tied to the back of her belt with a series of AAAAAs. Students never forgot these RNA processing events. Given her unusual level of seriousness, casual sharing of personal anecdotes may have been unexpected. But once she wore her sneakers with a small ceramic heart tied to the shoelace. Sitting in the front row, a student timidly asked her about the heart. She said that her daughter Erin had given it to her for Valentine's Day and had asked her to wear it.

Most scientists knew Lois through her publications or from interactions at conferences, but some were fortunate to know her in the laboratory, in the classroom, more informally at gatherings at her home in the company of her family, or during laboratory camping trips in the mountains of Idaho or northern Georgia.

Lois ran a demanding research program and expected nothing but the best from herself and everyone else, but she provided the best education and mentoring anyone could wish for. She was able to blend her serious love for science with her wonderful sense of humor. She had a contagious laugh and would laugh easily. Her graduate student Suzanne M. Thiem recalled being on a weekend canoe trip to Upper Priest Lake - north of Sandpoint Idaho near the Canadian border on a day of heavy rain. She says "we were like drowned rats when we got back to the landing and pulled the canoe out. When I went to get the truck my very distinctive pickup with a "Virginia is for Horse Lovers" bumper sticker on it - to load the boat, I noticed a scrap of paper under the windshield wiper. It was an old envelope with a note written in pencil that simply said, "Suzanne, why aren't you in the lab working?" signed by Lois. I could mentally hear her distinctive laugh…"

Lois mentored many junior scientists from other laboratories regardless of whether they were competitors or not. Her mentoring was unselfish. She cared about advancing science and those who practiced it well. Teaching the next generation was a priority. Malcolm (Mac) Fraser, who co-authored a publication in which polyhedrin was substi-

tuted with b-interferon7 in the laboratory of Max Summers, recalled that Lois, in spite of the competition between the Miller and Summers laboratories, was a one of the most influential mentors of his career, and was, in fact, instrumental in his securing his first NIH grant.

For many years, Lois tolerated her husband Karl's strong interests in sports. She had no interest herself, until an undergraduate student, Brett Pellock, who was also a punter for the University of Georgia football team, joined her research group. After that, Lois became an ardent University of Georgia football fan. She watched or listened to every game with friends and family and voiced her disappointment on specific plays that did not favor the team.

Lois wanted to be an excellent scientist—not an excellent female scientist. There were no female faculty members in the Biochemistry department when she was a student at the University of Wisconsin-Madison or in the division of Biology while she was a postdoctoral fellow at Caltech. She was the first woman in her department at the University of Idaho and the first female professor in the department of Entomology at the University of Georgia. Lois was also the first woman to be elected to the National Academy of Sciences from the state of Georgia. Lois went out of her way to mentor younger female scientists—but then she went out of her way to mentor all younger scientists. She found the time to serve on graduate student committees, on committees for promotion and tenure and for departmental evaluations. She served on the National Institutes of Health Review Panels for many years. Lois was a key and permanent member of the University of Georgia Research Foundation and guided the foundation in difficult financial years in the right direction.

Never slowing down

In 1994, as Lois was forced to reduce her service and teaching activities due to the recurrence of malignant melanoma, she wrote two letters. One was addressed to colleagues, with the subject "My personal health," and one to her "Former Miller Lab Members" with the blunt subject "Metastatic Malignant Melanoma." The letter to colleagues told them "I want to minimize rumors by supplying facts openly," and went on to detail the diagnosis, treatments, and her check-up plans. The letter to her former team members stressed that if any one needed anything at any time, she would make herself available. The word "any" in "any time" was in bold type.

She dedicated hours when she was weak to writing letters for her students in case they needed them in the future to secure positions in other laboratories or academia. She never abandoned her students or postdoctoral fellows; she followed through until the end. Lois faced death with the same courage and unfailing sense of humor she displayed in every other aspect of her life.

In 1995, Lois celebrated her 50th birthday. Laboratory members from all times and places surprised her at a local restaurant wearing T-shirts that said GARSH, a word of her own etymological creation (as far as anyone can tell). It was a joyous event and everyone reminisced, laughed, renewed strong bonds, and celebrated Lois' birthday. It was especially important for those who knew there might not be another such occasion.

Lois faced her battle with melanoma with the same determination and attention to detail that she used to mold her career. She participated in an incredibly grueling and painful experimental immunotherapy program run by Steven A. Rosenberg at the National Cancer Institute Center in Bethesda and survived for more than 4 years from diagnosis. When her former students Lorena Passarelli and Rollie Clem visited after her immunotherapy at the National Cancer Institute, she laughed, discussed her latest scientific findings, and inquired about her students' new paths. Her only regret, she said, was that she would not live to know the function of each of the over 150 genes in AcMPNV. Lorena and Rollie inherited a tradition of mentorship and research ethics, as well as all her clones and viruses to continue Lois' legacy.

Lois decided to spend her last few months at home in a hospice program, with her family and friends. She worked tirelessly from home on manuscripts and arranged to send viral strains and isolates to colleagues around the world. Throughout, she was selfless in deflecting attention from herself and encouraging everyone around her to continue living their lives. This included her daughter, Erin, who was studying biochemistry at Cornell University, and who was in the midst of her junior year when Lois died on November 9, 1999.

The scientific community is still being rewarded from Lois' contributions. If she were still alive, there is no doubt that the field would be significantly more advanced. Perhaps by now we would know the function of each gene in AcMNPV.

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