BIOGRAPHICAL MEMOIRS

Melvin M. Green

August 24, 1916–October 24, 2017
Elected to the NAS, 1980

A Biographical Memoir by Pamela Geyer

Melvin "Mel" Martin Green was a pioneering geneticist whose contributions helped shape our understanding of genes and genomes. Mel was well-known for his genetic intuition and his great admiration for the vinegar fly, *Drosophila melanogaster*, commonly known to others as the fruit fly. Mel firmly believed that the basic principles of genetics were largely derived from Drosophila genetics. Over his remarkable sixty-year career, he practiced his favorite advice from William Bateson to "treasure your exceptions." Mel screened enormous numbers of flies and used his exceptional powers of observation to routinely uncover the unexpected. Mel's groundbreaking studies included important topics of the day, such as heterosis, pseudo-allelism, radiation-induced "back-mutation" (reversion), and intra-allelic complementation, studies that led him to his seminal discovery of Drosophila transposable elements. He uncovered new mutations, created new chromosomes, and shared his ideas broadly, publishing a rich collection of more than 125 papers. His extensive literature imprint was coupled with decades of teaching classes in general genetics, cytogenetics, human genetics, and the history of genetics to thousands of undergraduate and graduate students at the University of California, Davis (UC Davis). Mel's long and dedicated life of scholarship was suffused with his marvelous wit, strong insight, intense candor, and inspiring integrity that influenced career trajectories of generations of trainees and fellow faculty researchers.

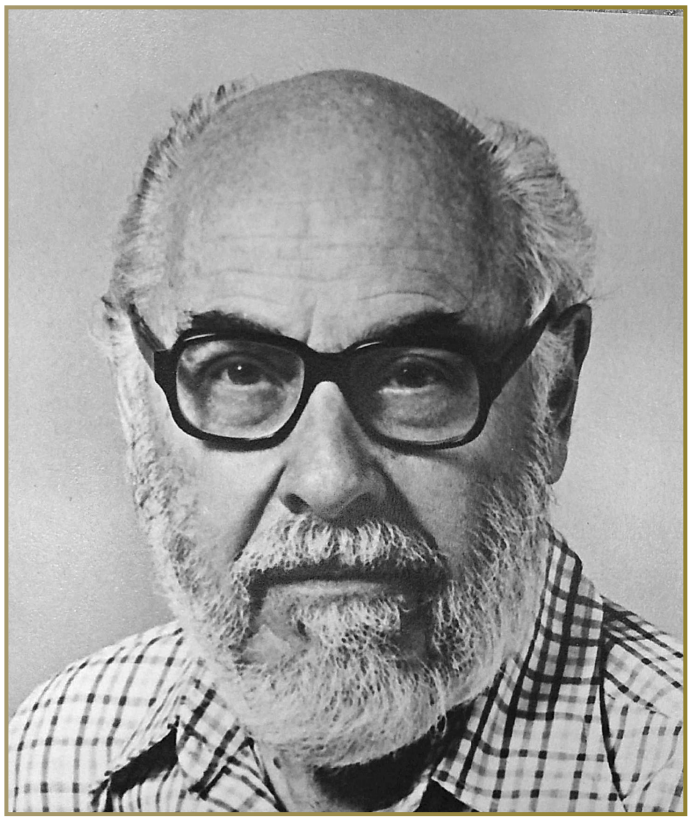

Figure 1 Melvin M. Green.

Family, Education, and Early Academic Career

Born in Minneapolis, Minnesota, Mel grew up during the Great Depression in a Jewish ghetto at a time of flagrant antisemitism. He attended college at the University of Minnesota. As a first generation college student, Mel was unfocused. Although initially considering a career as a historian, Mel switched to the sciences after taking a genetics class taught by Clarence P. Oliver, a former student of Nobel Prize winner Herman J. Muller. In that class, Mel uncovered a passion for genetics. This led him to enroll in advanced science classes and seek a position as an undergraduate assistant

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Figure 2 Mel screening flies, January 1967.

in the Oliver laboratory, marking the beginning of his long and fruitful research career using *Drosophila melanogaster*.

Mel completed his bachelor's degree in zoology and chemistry in 1938. Motivated by his enjoyment of working in the Oliver laboratory, Mel decided to remain at the University of Minnesota and pursue graduate training. He completed a master's degree in 1940 and a Ph.D. (1942) in zoology and biochemistry. Upon entering the Oliver laboratory as a graduate student, Oliver said to Mel, "I have my own research problem, what's yours?" This prompted Mel to design his own thesis project, something that Mel proudly told later generations of trainees, urging them to work independently on topics that they loved. His dissertation focused on heterosis, a term referring to phenotypic variation caused by interactions between genes, an area of active research even today. For these studies, Mel obtained multiple mutations in the *vestigial* gene, a gene that is required for wing structure, and he examined how mutations that slowed development (*Minute* mutations), as well as temperature and starvation affected *vestigial* wing phenotypes.[1] His thesis was entitled "Phenogenetic Studies in *Drosophila melanogaster*." In addition to research, Mel served as a teaching assistant in zoology. In one of his classes, he met the inquisitive Kathleen Cummings. By the time his dissertation was completed, Mel had both acknowledged Kathleen for her "assistance and criticisms in preparation of the manuscript (thesis)" and proposed marriage.

Their marriage was delayed, however, by his induction into the U.S. Army during World War II. Though initially assigned to basic duties, such as mopping floors, Mel recognized that he might be more useful to the army working in a medical laboratory. As such, he approached his commanding officer and told him of his Ph.D. degree. This conversation proved fruitful, because Mel was sent to officer training at the Medical Field Service School in Pennsylvania and graduated as a first lieutenant in October 1943. After this training, he was assigned to the 15th General Hospital and shipped out to London aboard the RMS *Queen Mary*. From England, Mel progressed through France, Belgium, the Philippines, and to occupied Japan, leaving the military in 1946 as a captain.

The Early Academic Years

Upon returning to Minneapolis in 1946, Mel and Kathleen Cummings were married. The couple moved to the University of Missouri in Columbia, where Mel was first appointed an instructor and then promoted to assistant professor in the Department of Zoology. As a new faculty member, Mel had both teaching and research responsibilities. His teaching obligations were broad and included multiple laboratory and classroom courses on general zoology and cellular physiology. Mel's independent research program was built from an unexpected observation made by his former Ph.D. adviser. Oliver had published research noting that heterozygotes with distinct mutations in the *lozenge* gene (required for eye development) occasionally produced non-mutant "wild type" progeny. At the time of this observation, little was understood concerning the nature of the gene and mutations. Oliver's observation led Mel to question whether the *lozenge* mutations were "alleles in the usual sense" or were mutations in two closely linked genes (termed pseudo-alleles). Contemplating how to discriminate between these possibilities, Mel recognized the power of numbers, expanding both the number of *lozenge* alleles that were investigated and increasing the number of F1 progeny, scoring tens of thousands of progeny. With the assistance of Kathleen, Mel found that wild type progeny were produced in crosses of multiple *lozenge* alleles, generated by equal crossing over or recombination.[2] Based on their data, Mel concluded that the "simplest explanation" was that *lozenge* alleles represented a "closely linked multiple allelic series." Subsequently, Mel showed that "pseudo-allelism" occurred at other *X*-chromosome genes, including *forked* (required for bristle structure), *vermilion* (required for eye color), and *white*

(required for eye color). At the time of these studies, Mel's interpretation of pseudo-allelism was reasonable, as these experiments preceded Seymour Benzer's elegant demonstration of recombination within bacteriophage genes.[3] Mel's pseudo-allelism studies also marked the beginning of his large collection of fly stocks that carried *X*-chromosome linked mutations.

During his time at the University of Missouri, Mel spent many rewarding and stimulating hours discussing questions about the nature of the gene and X-ray mutagenesis with Lewis J. Stadler, a renowned plant geneticist. Stadler's long-standing interest in the mutagenic effects of X-irradiation in maize and barley led him to propose that X-rays cause mutations by deletion. Mel and Stadler vigorously debated this conclusion, especially in light of Nikolay Timofeéff-Ressovsky's report that X-rays could produce back mutations (revertants) of an unstable *white* allele in Drosophila.[4] Mel argued that this finding was inconsistent with Stadler's ideas. The argument went unresolved, as Timofeéff-Ressovsky's unstable allele was lost, preventing further exploration of the mechanism of X-ray reversion.

Mel's association with Stadler had a huge impact on his career. In their conversations, Stadler introduced Mel to plant genetics and set a foundation for Mel's appreciation of Barbara McClintock's transformative discovery of transposons in maize. These discussions undoubtedly prepared Mel for his future discovery of Drosophila transposons. Indeed, Mel regarded Stadler as one of his most important mentors.

The UC Davis years

In 1950, after four years at the University of Missouri, Mel was hired by G. Ledyard Stebbins to become the second member of the newly formed genetics department at UC Davis. Again, Mel had both teaching and research responsibilities. In his first year, Mel taught introductory genetics to students on the growing Davis campus. He would go on to teach many courses in genetics to multiple generations of students.

In his early days at UC Davis, Mel continued to study pseudo-allelism and interallelic crossing over. Yet he remained preoccupied by the question of reverse mutability by X-rays and whether the Timoffeéff-Ressovsky *white* allele was special. To address this question, Mel began a search for Drosophila mutants that showed spontaneous reversion, reasoning that such alleles were similar to the original revertible *white* allele and would allow him to access the capacity of X-rays to produce back mutations (revertants). His early investigations centered on two *forked* (*f*) alleles, f^{1} and f^{36N}, both of which spontaneously reverted. Mel found that X-rays increased the back mutation frequency of f^{36N} but not f^{1}, providing some support for Timofeéff-Ressovsky's observation.[5] These findings led Mel to ask whether X-rays could generally enhance back mutation. He tested mutations in the *X*-linked *yellow* (body pigmentation), *scute* (bristle number), and *white* genes, finding that X-rays increased reversion of the y^{2}, *sc* and *white (w)-ivory* (w^{i}) mutations. Nonetheless, he also found that some alleles did not revert (y^{1} and w^{a2}), confirming two classes of Drosophila mutants: those that do and those that do not readily back mutate upon X-ray exposure. Based on these findings, Mel concluded that X-rays were a "potent mutagen" for back mutation.[6]

Back mutation studies of w^{i} were particularly fruitful. While conducting these studies, Mel identified $w^{crimson}$ (w^{c}). Notably, w^{c} arose as a partial X-ray induced revertant of w^{i}. Mel documented that w^{c} was "mutationally highly unstable" and produced both stable and unstable mutations in males and females.[7] Additionally, he recovered w^{c} transpositions from the *X* to the third chromosome.[8,9] Based on the complexity of these w^{c} mutational events, Mel concluded that w^{c} was controlled by a "foreign" regulatory element localized within the *white* gene, drawing parallels between his findings and McClintock's pioneering observations in maize. These studies mark the first demonstration of transposable elements and transposition in Drosophila. It took another fifteen years before the molecular nature of the w^{c} allele was defined. Mary Collins in the Gerald M. Rubin laboratory showed that Mel's "controlling element" was a 10-kb foldback sequence inserted in the *white* gene.[10] Reflecting on his discovery, Mel credited his deduction to McClintock, noting that she had provided the intellectual framework for his insight in Drosophila.[11] He also noted that "the powerful tools of molecular biology" provided an answer to the status of X-ray mutagenesis. He concluded that his data supported the conclusion that X-rays make deletions, because his revertible alleles were associated with transposon insertions.[12] Further, he wrote that "the discovery of mobile DNA elements in Drosophila was the outcome of nature's design and serendipity!"—evidence that Mel cherished his exceptions.

The discovery of transposable elements solidified Mel's fascination with mechanisms of mutagenesis. This led to a productive collaboration with a colleague in the Department of Genetics, James B. Boyd. Together, they isolated Drosophila mutants sensitive to irradiation.[13] Mel was also intrigued by the unusual second chromosome mutator element described by Yuichiro Hiraizumi that was found within a natural Drosophila population in Texas. This mutator promoted recombination in the male germline, a process that is completely absent in wild type flies. Mel's interest was further piqued by findings that the male recombination (MR) second chromosome also caused mutations elsewhere. In collaboration with M. D. Golubovsky, Mel characterized a second *MR* chromosome, this time identified from wild flies in Russia. The Golubovsky mutator increased the rate

of insertional mutations at the *singed* (bristle structure) gene. MR elements puzzled Mel for many reasons. First, they were present in nearly a third of chromosomes isolated from wild flies found throughout the world. Second, the MR elements exhibited hotspots for mutagenesis. Third, MR elements moved to new genomic positions. Although in his early studies, Mel thought that MR elements were of viral origin, his data convinced him otherwise. He ultimately recognized that properties of MR elements matched bacterial insertional mutants.[14] Indeed, later molecular studies established that these mappable MR mutators were indeed full-length transposable *P* elements.[15]

Mel's studies of spontaneous mutagenesis generated a large collection of fly lines, with many carrying *X*-linked mutations. Mel often said that he loved the haploid genetics afforded by the *X* chromosome. Among his collection were multiple alleles of the *yellow* gene, including the spontaneous y^2 mutation. In 1935, Wilson Stone had described a unique example of complementation involving the y^2 mutation.[16] Using his collection of mutants, Mel re-examined *yellow* complementation, demonstrating that complementation occurred between the spatially inseparable y^2 and its derivative allele, y^{59b}.[17] These findings foreshadowed our subsequent collaboration on transvection or interallelic complementation at the *yellow* locus.[18]

Awards and Honors

In recognition of his many research accomplishments, Mel received numerous fellowships that allowed him to conduct research in laboratories around the world. He held both Fulbright and Guggenheim Fellowships at the University of Leiden in the 1950s, a National Science Foundation Senior Postdoctoral Fellowship at the Max Planck Institute in Germany in the early 1960s, a second Guggenheim Fellowship to work in Canberra, Australia, in the late 1960s, a Davis Fellowship to work in Israel in the mid-1970s, and a visiting professorship at the University of Geneva, Switzerland, in the late 1970s. Mel also received an honorary doctorate from the University of Umea, Sweden. His travels led to productive interactions with Drosophila researchers across the globe and added to Mel's impressive collection of mutant strains. Perhaps the most fitting recognition for his distinguished accomplishments and their significant scientific impact was his election to the U.S. National Academy of Sciences in 1980.

Although Kathleen was integral to Mel's early studies of pseudo-allelism at the University of Missouri, upon moving to Davis, California, she turned her attention to raising their two sons (Jeremy and Jonathan) and to making a difference in the Davis community. Kathleen served as a charter member and president of the League of Women Voters in Davis, was the first woman elected to the Davis city council, and

Figure 3 Mel outside Green Hall.

was a member of the board of directors of the Sutter Davis Hospital board. Kathleen's efforts were recognized by receipt of Covell Award as Davis's Citizen of the Year. Mel was proud of Kathleen's accomplishments and endowed a scholarship for women in science, the Kathleen C. Green Scholarship in Biology at UC Davis, to recognize outstanding academic achievements by female biology students.

The Emeritus Years

Mel retired from the UC Davis Genetics Department in 1982. Although this marked the end of his formal teaching responsibilities, Mel remained an active mentor to faculty and students within the department. Indeed, Mel continued to come into the laboratory and set up crosses seven days a week, well into his nineties. His office and laboratory were located on the third floor, and he always walked up the stairs, encouraging the younger generations to avoid the elevators. Mel took special joy in teaching undergraduate researchers both the techniques of Drosophila genetics and his favorite Yiddish words. Mel truly cared about the success of Davis students and his colleagues, and he would often bring colleagues pertinent research articles. Mel was always enormously enthusiastic and engaged in science.

Retirement provided Mel more opportunity to visit Drosophila research laboratories. In the mid-1980s, he came to Johns Hopkins University and the laboratory of Victor G. Corces. During that period, the Corces laboratory was defining the molecular basis of mutations in the *forked*, *yellow*, and *suppressor of Hairy-wing* genes—all genes of great interest to Mel. Notably, *forked* and *yellow* were two of the *X*-linked genes that Mel had studied over the years, and the *suppressor of Hairy-wing* gene was a modifier of mutations caused by insertion of the *gypsy* transposon. Just prior to Mel's visit, I had published a paper reporting the nucleotide sequence and structure of the *yellow* gene, the location of the *gypsy* transposon in the y^2 mutation, and the molecular details of a y^{2+} revertant that Mel had identified. Of course, these studies

Figure 3 Mel's 100th birthday celebration.

generated great excitement for Mel, and when he came to the Corces' laboratory, we entered into a fun and for me, life-changing collaboration. Together, we defined mechanisms of mutagenesis of the *yellow* gene by the *gypsy* transposon and identified the mutagenic element as the *gypsy* insulator, described *P* element mutagenesis by gene conversion at the *yellow* gene, and characterized the consequences of the *suppressor of sable* on *P*-element induced *yellow* mutations.[19] But our most memorable accomplishment was uncovering the molecular basis of interallelic complementation (transvection) at *yellow*. These studies would not have been possible without Mel's rich collection of *yellow* mutants and his prior documentation of complementation.[20] Using our respective strengths, I would define the molecular basis of an individual *yellow* mutant and Mel would set up crosses to quantify its level of complementation with y^2. Before we understood any of the molecular rules underlying transvection, I would make a prediction of whether an individual mutant would complement, and I coupled these predictions with a $1 bet. Mel was delighted to take the first bet, and even more delighted when I lost and had to pay up. But the next bet went my way, and Mel reluctantly returned my dollar. After that time, Mel refused to bet but nonetheless happily crossed the flies. Together, we complement tested y^2 with eleven molecularly defined loss-of-function *yellow* mutants. We discovered that complementation of y^2 depended on the *trans*-action of *yellow* tissue-specific enhancers and disruption of their *cis*-promoters. These findings provided surprising evidence for a novel activity of enhancers, and the importance of promoter competition for shared enhancers.[21]

I learned so much about Drosophila genetics working with Mel. He introduced me to the beauty of the *X* chromosome, the utility of patroclinous inheritance and attached *X* chromosomes, and the power of a large mutant collection. Mel encouraged me, a biochemist and developing geneticist, to "let the fly tell you what is important." My short collaboration with Mel started a lifelong friendship filled with bountiful advice and support. I was delighted to travel to Davis to be part of the celebration of his 100th birthday celebration and again enjoyed Mel's contagious enthusiasm for science. Mel remains an inspiration to me. He is truly one of my scientific heroes.

Mel passed away in 2017 at the age of 101. In 2020, as a fitting tribute to this UC Davis icon and beloved Drosophila geneticist, the UC Davis Life Sciences Building was renamed the Melvin M. and Kathleen C. Green Hall.

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