BIOGRAPHICAL MEMOIRS

Michael Grunstein

August 30, 1946–February 18, 2024
Elected to the NAS, 2008

A Biographical Memoir by Siavash K. Kurdistani

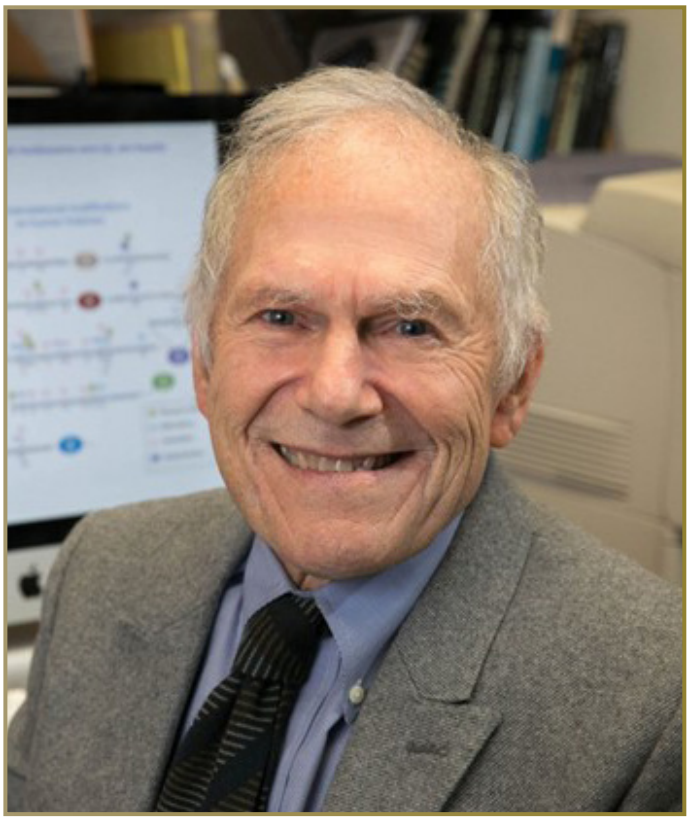

Figure 1 Michael Grunstein.

The clock ticks. The room remains empty. Michael Grunstein hadn't expected Leonard Cohen to accept the invitation to his high school poetry club. But now, Cohen, at the brink of becoming a renowned Grammy-winning songwriter, poet, and novelist, is moments away from performing to an empty room. Michael's excitement turns to apprehension, but he doesn't panic. In a flash of ingenuity, he dashes to a nearby kindergarten and recruits a group of young children to fill the seats, their little feet swinging back and forth, wondering who these men are. As Cohen recites his poems to this impromptu, tiny-tot audience, Michael's creativity and resourcefulness are on full display. These traits not only defined this moment but also foreshadowed the qualities that would drive his scientific career, illustrating that the human elements shaping personal narratives are the same ones that drive scientific breakthroughs.

Born to Holocaust survivors who emigrated from Romania to North America, Michael Grunstein rose from humble beginnings to forge a remarkable scientific career that fundamentally transformed our understanding of histone proteins. He discovered that histones are not simply inert scaffolds for DNA winding, as was widely believed, but play important roles in gene regulation. His pioneering work overturned strongly held beliefs and laid the groundwork for advancements in the field of epigenetics, impacting both biology and medicine. Through tour-de-force genetic and biochemical studies in budding yeast, he demonstrated that histones influence gene activity within living cells and established the basis for understanding how histone modifications contribute to chromatin structure and function. For his seminal discoveries on the role of histones and their modifications in gene expression, Grunstein, along with C. David Allis of Rockefeller University, received many accolades, including the Gruber Genetics Prize (2016) and the Albert Lasker Award for Basic Medical Research (2018).

From Survival to Science: The Grunsteins' Journey

Michael was born in Beclean, Romania, in 1946 into a family of Holocaust survivors. His mother, Elizabeth Pollak, was freed from Auschwitz and his father, David, from a

labor camp. Michael's older brother had passed away during the war, a tragic loss believed to have resulted from the lack of access to antibiotics. Facing a changing political climate and persistent antisemitism, and motivated by a desire for a new beginning, the family relocated first to Israel and then to Canada, settling in Montreal in 1952. Elizabeth found a new vocation as the owner of a grocery store that doubled as a pub at night. David, known as the village dentist in Romania because he possessed a pair of pliers, founded a taxi company. Now six years old, Michael was poised to seize opportunities that had been denied to his family just a few years earlier.

Unbeknownst to Michael, his future partner, Judy Gross (later Grunstein), had followed a remarkably similar path. Born in Cluj, Romania, merely fifty miles from Michael's hometown of Beclean, Judy's family too had left Romania with little more than a watch and a suitcase. They first moved to Israel and then to Montreal, arriving in 1960 and settling just three blocks away from Michael's family. Judy and Michael would meet in high school, marking the beginning of a lifelong partnership that lasted until Michael's passing in February 2024.

Michael was not fond of high school, where his peers saw him as an intellectual. He often skipped classes, preferring to spend his time playing pool. Michael had a passion for writing poetry and founded the poetry club that would one day host Leonard Cohen, offering an early outlet for his creative energy. College was no different. He continued to miss classes, took makeup exams, played tennis, and cruised around in a red MG convertible roadster. His academic trajectory took a pivotal turn when he met John Southern, a biology teacher at McGill University. John's profound passion for experimental biology and genetics ignited Michael's interest in science. This chance encounter with an inspiring mentor proved transformative, leading Michael to seamlessly integrate his creative interests with a newfound scientific curiosity.

Michael built a strong foundation in scientific fundamentals in genetics and chemistry at McGill, receiving his bachelor of science degree in 1967. Following the recommendations of his mentors, he applied to the University of Edinburgh for graduate studies. Michael married his high-school sweetheart, Judy, and the very next day, the newlyweds moved to Edinburgh. There, he joined the lab of Max Birnstiel, recognized for isolating the first gene (rDNA), at the Institute of Animal Genetics. This institute was earlier led by renowned embryologist Conrad H. Waddington, who in 1957 introduced the concept of the epigenetic landscape to illustrate the process of cellular differentiation during development.

Michael then moved to Stanford University for postdoctoral research, beginning in the Departments of Medicine and Biochemistry with Laurence "Larry" Kedes, whose lab

Figure 2 Michael Grunstein in the early days of the Molecular Biology Institute at UCLA, in his office examining an autoradiogram.

was located at the Veterans Administration Hospital in Palo Alto, California. There, Michael applied his insights from rDNA to studies of histone mRNA.[1] He later joined the lab of David Hogness in the Department of Biochemistry at the School of Medicine on campus. It was in the Hogness lab that Michael developed colony hybridization, a powerful method for identifying a specific gene or segment of DNA from very large mixtures that revolutionized gene isolation and mapping.[2] The technique, known colloquially as a "Grunstein-Hogness," was a mainstay of recombinant DNA research for more than two decades.

By the end of his postdoctoral training, Michael and Judy had two young children: Davina and Jeremy. Cognizant of the potential need for frequent relocations owing to Michael's career in science, Judy decided to pursue dentistry, viewing it as a profession suitable for a supporting spouse on the move. Therefore, their decision on where to establish Michael's independent lab was partly contingent on where Judy was accepted into a dental school.

In 1975, Michael and Judy chose the University of California, Los Angeles (UCLA), swayed by the appeal of sunny Southern California and a strong recruitment effort from Winston Salser, a founder of Applied Molecular Genetics Inc., better known as Amgen, and a faculty member in what was then the Department of Biology (later renamed the Department of Molecular, Cell, and Developmental Biology). Their decision was further solidified by Judy's acceptance to the UCLA School of Dentistry, albeit two years after their initial move. Another compelling factor was the opportunity for Michael to establish his lab in the new Molecular

Biology Institute (MBI) (Figure 2), also known as Boyer Hall after prominent UCLA biochemist and Nobel laureate Paul D. Boyer. Boyer was instrumental in founding and building the MBI, envisioning it as a means to enhance healthcare by leveraging the burgeoning field of molecular biology to reveal the mechanistic bases of disease. In this regard, Michael's career fulfilled that vision, as his discoveries laid the genetic groundwork for the development of a new class of anti-cancer drugs that act by impacting the epigenome.

A Stormy Path from Sea Urchins to Yeast

After arriving at UCLA in July 1975, Michael decided to focus his research on the function of histones, driven by his fascination with DNA-packaging proteins and a strategic decision to avoid what he perceived as the crowded field of transcription regulation research. Initially, he continued using sea urchins, a model system he had previously employed in the Kedes lab and one that was favored by many developmental biologists. But this choice soon proved to be challenging. The large genome and lengthy reproductive cycle of sea urchins made genetic analysis both time-consuming and difficult and required a constant supply of fresh specimens for biochemistry. These challenges intensified when in 1976 Hurricane Liza decimated the sea urchin population in the Gulf of California, from which Michael sourced his specimens. This series of events prompted Michael to pivot to the then-emerging model system of budding yeast (*Saccharomyces cerevisiae*). Yeast's much smaller genome and markedly shorter reproductive cycle significantly eased the process of genetic manipulation and analysis. His decision was further catalyzed by the development of an efficient method for DNA-mediated transformation of yeast cells, a breakthrough reported independently by the laboratories of Gerald Fink and Jean Beggs.[3,4]

To acquire expertise in yeast biology and genetics, Michael attended the summer 1979 rendition of the Yeast Genetics and Genomics course at Cold Spring Harbor Laboratory in New York. He also spent several weeks further mastering yeast genetics techniques at Brandeis University under the guidance of Lynna Hereford in the lab of Michael Rosbash, a friend from their days in Edinburgh and a future Nobel laureate. Hereford, who had trained under Lee Hartwell—a pioneer in using yeast genetics to study cell cycle regulation and himself a Nobel laureate—had recently cloned the yeast histone H2A and H2B genes.[5] Her work demonstrated that yeast contains only two copies of each histone gene in its haploid genome, a feature that significantly simplified genetic manipulation compared to other model organisms with a much larger number of histone gene copies. Michael's collaboration with Hereford led to the discovery that the two histone H2B genes in yeast encode proteins with slightly different amino acid sequences.[6]

Unpackaging Histones: How Grunstein Redefined Chromatin Research

By the time Michael established his independent lab, a significant amount of biochemical research was underway to understand chromatin structure. It was established that eukaryotic DNA is wrapped around an octamer of histone proteins, forming the nucleosome, an arrangement that allows the large eukaryotic DNA to be compacted within the confines of the nucleus.[7] Consequently, histones were primarily thought to serve as packaging materials for the eukaryotic genome. But there was limited understanding of the biological functions of histones and little genetic evidence to support any proposed function.

Eukaryotic chromatin is broadly categorized into two types: euchromatin, which is transcriptionally active; and heterochromatin, which is more condensed and transcriptionally silent. It was not suspected that histones played a role in establishing these structural configurations or contributed to gene silencing within heterochromatin.

In the ensuing years, the Grunstein lab fully leveraged the power of yeast genetics to establish that histones are much more than DNA-packaging proteins, also contributing to regulation of gene expression as well as to formation of the silent, heterochromatic regions of chromatin.

A seminal contribution came in 1988, when three trainees in Michael's lab—Min Han, Ung-Jin Kim and Paul Kayne—employed a clever genetic strategy that placed histone gene expression under a repressible promoter that could be shut off.[8] This innovation allowed them to ask what happens when histone levels are reduced in vivo, effectively decreasing the number of nucleosomes. The result was striking. Several genes that normally should not be expressed in the absence of activation signals were unexpectedly turned on and expressed. This was the first in vivo demonstration that dismantling of nucleosomes can facilitate activation of certain genes. They also demonstrated that histone depletion causes a specific cell cycle arrest in cells, affecting chromosome segregation, replication, and global transcription.[9,10,11]

Another set of landmark studies, this time of the N-terminal "tails" of histones, marked the beginning of a new era in our understanding of transcriptional gene regulation. The sequences of the N-terminal tails of histones are highly conserved and protrude from the globular domains around which the DNA is wrapped. These N-terminal tails were also thought to play a structural role in genome organization. Yet, it was known that the histone N-termini undergo extensive post-translational modifications such as acetylation and methylation of the ε-amino group of lysine residues, among

others. Moreover, about two decades earlier, Vincent Allfrey and Alfred Mirsky had established that histone acetylation correlated with gene expression.[12]

Building on this foundation, once again, the Grunstein lab employed yeast genetics to obtain a deeper understanding of the functions of these tails. Paul Kayne, Linda Durrin, and Randy Mann showed that the N-terminal tail of histone H4, though not necessary for viability or growth, is essential for expression of certain genes and, surprisingly, for silencing of telomeres and sub-telomeric regions and the mating type loci, regions of chromatin that adopt heterochromatic features under standard growth conditions.[13,14] Telomeres are specialized sequences at the ends of chromosomes, and the regions near them house genes typically involved in stress response that remain inactive under normal growth conditions. The mating type loci, on the other hand, determine the "gender" of budding yeast and facilitate mating of yeast cells for a form of sexual reproduction. Lianna Johnson, Jeffrey Thompson, and Andrew Carmen revealed that the acetylation state of a single lysine at position sixteen in the N-terminus of histone H4 (H4K16) is critical for gene silencing; this lysine must remain unacetylated to effectively maintain transcriptional repression at these loci.[15,16] Jeffrey Thompson demonstrated an additional requirement for the histone H3 N-terminal tail for repression of heterochromatic regions in yeast.[17]

These findings underscored the regulatory roles of histones through specific modifications of conserved residues on their N-terminal tails. Expanding upon these discoveries, Andreas Hecht and collaborators showed that the histone N-terminal tails serve as binding sites for the silencing proteins Sir3 and Sir4, and that it is these interactions that are influenced by the acetylation state of key lysine residues within the histone tails.[18] These insights led to the development of the first molecular model for heterochromatin assembly in eukaryotes (Figure 3), which identified the Sir proteins as the first chromatin binding factors sensitive to the modifications of histone tails.

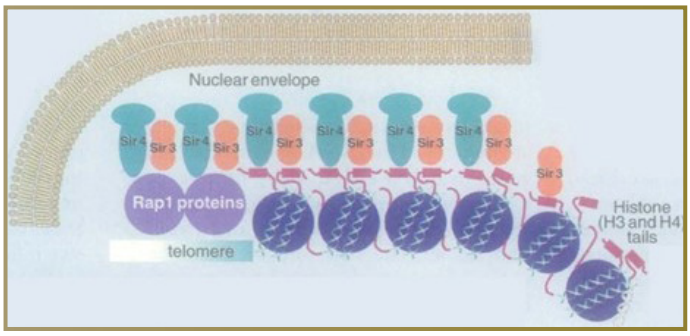

Figure 3 The first molecular model of heterochromatin formation in yeast proposed by Grunstein was highlighted in a Commentary in *Science*. *Image adapted from Nowak, R. 1995. Histones hush yeast mating genes.* Science *270:1590.*

Although Michael's career was marked by numerous breakthroughs, it also faced significant setbacks. One failure, in particular, stood as a persistent source of regret. In the early 1980s, Michael set a goal for his lab to identify a histone acetyltransferase (HAT) in yeast. Over the decade, a generation of trainees, including Gabriel Travis, Maria Colavito-Shepanski, David Kolodrubetz, and Min Han, worked tirelessly to achieve that goal. Despite extensive efforts and substantial purification of the activity, they never succeeded.[19] Ultimately, Michael decided to abandon the effort, a decision he would later regret. Interestingly, many of the experiments with histone depletions were initially conceived as backup plans in case the HAT identification failed, highlighting how failure can be as influential as success in shaping the course of scientific research.

Beyond Genetics: A Technological Renaissance Popularized Chromatin Research

In the mid-1990s to mid-2000s, Michael's appreciation for the power of technology came back full circle. Using antibodies against specifically modified histone residues, Stephen Rundlet and Noriyuki Suka and colleagues developed a method known as chromatin immunoprecipitation combined with PCR, or ChIP-PCR, to identify histones with specific modifications at particular genomic loci.[20] This powerful technology enabled higher-resolution mapping of histone modifications across the genome and their correlation with various gene regulatory regions, such as promoter elements. ChIP-PCR transformed chromatin research, sparking a surge in histone studies across the wider scientific community that continues to this day.

Employing this technology, the Grunstein lab mapped the acetylation patterns of various histone residues at promoters and correlated these patterns with the expression of specific genes. As their studies progressed, Maria Vogelauer discovered that histone acetylation and deacetylation were not confined to promoter regions and affected virtually every nucleosome throughout the yeast genome, including gene bodies. To distinguish this widespread phenomenon from promoter-specific activity, the team coined the term "global histone acetylation and deacetylation."[21]

Michael continued to push the boundaries of technology, quickly realizing the potential of DNA microarrays to scale up ChIP-PCR from analyzing a few genes at a time to thousands simultaneously, an approach that became known as ChIP-Chip, named after the microarray chips used. He invested substantial resources in developing these arrays in his own lab, long before they were commercially available. I joined the Grunstein lab as a postdoctoral fellow in 2000, drawn in part by the opportunity to work with this cutting-edge technology.

Together with Daniel Robyr, Yuko Suka, and Amy Wang, we used our homemade microarrays to explore how different histone deacetylases function across various genome regions.[22] We mapped the acetylation patterns of several residues across all core histones throughout the genome and discovered that co-regulated genes with similar functions often share similar patterns of histone modifications in their promoter regions,[23] a phenomenon now recognized as "chromatin states."[24] Our studies with DNA microarrays also demonstrated that the actions of histone deacetylases extend beyond repressed genes, playing a broader role that includes deacetylating histones associated with transcriptionally active genes.[25,26]

Pioneering Through Pain: A Lasting Scientific Legacy

Throughout the 1990s and early 2000s, Grunstein's accomplishments unfolded against a backdrop of serious health issues, including severe back pain and a potentially lethal lung disease. Despite these personal challenges, he continued to forge ahead, making pioneering discoveries in the field. Legend has it that he once gave a lecture lying on his back on the floor, a measure taken to alleviate his back pain while continuing to convey the latest discoveries from his lab.

Toward the latter part of his career, Grunstein expanded his research to explore the roles of histone modifications in the globular domains of histones and to examine the function of these modifications in mammalian cells.[27,28] These ventures demonstrated his eagerness to follow the science wherever it might lead, embracing the uncertainties of new research areas rather than remaining within the familiar confines of his past yeast work. This willingness to venture into new systems highlighted his adaptability in pursuit of deeper scientific understanding.

In 1994, Michael switched his affiliation to the Department of Biological Chemistry at UCLA. He served as chair from 2007 to 2010 and retired in 2016. Michael always valued groundbreaking discoveries over conventional metrics of academic success. He emphasized this philosophy in faculty recruitment and promotion evaluations, caring little about the quantity of publications or the prestige of the journals where they were published. Paraphrasing his view, he would often remark, "If you've discovered something significant, you could publish it in a letter to your mother, and it would still receive its due recognition."

In 2008, Michael was diagnosed with Parkinson's disease. Despite the gradual and relentless toll it took on his abilities, I never heard him complain about his circumstances. "Considering everything, it could be worse," he would often quip. Judy, who initially worked as a lab assistant and helped Michael set up his lab at UCLA, became an even more crucial source of support as she helped Michael navigate the challenges of his illness. After three decades of practicing dentistry in the community, Judy also retired in 2016 so that she and Michael could devote more time to enjoying their family, which now included four grandchildren: Jasper, Rowan, Emilia, and Josie.

Michael received widespread acclaim for his discoveries, earning him election to the American Academy of Arts and Sciences (2001) and the National Academy of Sciences (2008). Among his many accolades were the Massry Prize (2003), the Rosenstiel Award (2011), the Gruber Genetics Prize (2016), the Albert Lasker Basic Medical Research Award (2018), and the Albany Prize in Medicine and Biomedical Research (2022). He shared these honors with C. David Allis, who isolated the first histone acetyltransferase, linking these enzymes to gene activity for the first time.[29]

Beyond his scientific endeavors, Michael was passionate about his family and friends, fine dining, coffee, and gardening. He approached gardening not just as a leisure activity but with serious dedication. At its peak, his garden was yielding an impressive two tons of avocados annually, alongside a variety of other fruits and vegetables. He made a legendary avocado soup.

As for histones, much remains to be discovered. We now understand that eukaryotes inherited their nucleosomal-based chromatin architecture from an archaeal ancestor that contained histones. These ancient organisms had small genomes and lacked both a nucleus and sophisticated epigenetic regulation, suggesting that many known functions of histones likely evolved subsequently within the eukaryotic lineage. What roles did histones serve in archaea? What advantage did they offer over alternative DNA-binding proteins? Were they instrumental in the formation of the first eukaryotes? Histones still hold many mysteries, and perhaps the most enduring legacy of Michael Grunstein is the generation of scientists he has inspired to continue to explore these DNA packaging proteins.

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