

Obituary

Michael R. Green (1954–2023)

*Consummate passion for research
—and for fishing*

Michael Green was an internationally recognized scientist known for his seminal contributions to several areas of eukaryotic gene regulation, including transcriptional activation mechanisms by both viral and cellular proteins, mechanisms of pre-mRNA splicing, and transcriptional and epigenetic pathways involved in cancer. In more recent years, Michael assumed major administrative leadership positions related to the advancement of science at the University of Massachusetts Chan Medical School. He passed away unexpectedly on February 10, 2023 at the age of 69.

Michael was born in Philadelphia, Pennsylvania and raised in St. Louis, Missouri. He received a BS degree with honors in Biochemistry from the University of Wisconsin-Madison and then returned to St. Louis to earn his MD and PhD degrees from Washington University School of Medicine. As the son of the distinguished molecular virologist Maurice Green at St. Louis University's Institute of Molecular Virology (IMV), Michael gained an early exposure to basic biological science; and his unbound enthusiasm and intellectual and experimental gifts for science were apparent even before he began his PhD work, with publication of a half dozen papers (including first author papers on the oncogenic human adenovirus 12 in *Cell*, *Nature*, and *Journal of Virology*) from work at the IMV.

His PhD studies were carried out in the laboratory of Bob Roeder, where he boldly chose to investigate the transcription programs of the autonomous rodent parvovirus H1 and the human adenovirus-associated virus 2 (AAV2), which were not being studied in the laboratory at the time. In very short order, he identified not only discrete spliced mRNAs but, importantly, primary transcripts and corresponding promoters and initiation sites, which found special relevance decades later with the use of AAV2 as a major gene delivery vector

for gene therapy studies. With his clearly envisioned objectives, superior organizational and experimental skills, and characteristic intensity and rigor, Michael's studies proceeded quickly and successfully, resulting in four first-author publications (including two in *Cell*). Although he enjoyed learning about the practice of medicine in medical school, Michael felt that the opportunities in research were so exciting that he decided to forego additional clinical training and become a full-time researcher.

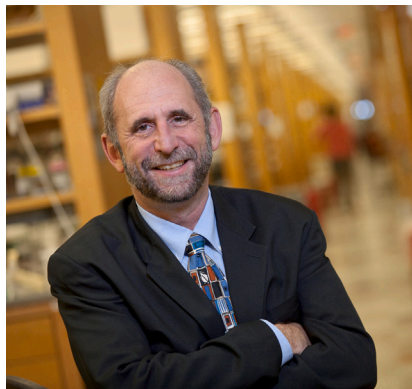
He went on to acquire postdoctoral research training at Harvard University in the laboratory of Tom Maniatis, where he was one of an exceptionally talented and creative group of pre- and postdoctoral scientists that included Adrian Krainer, Rick Myers, Brian Seed, Gary Struhl, and Richard Treisman. In the Maniatis laboratory, Michael investigated pre-mRNA splicing and transcriptional activation by viral immediate early proteins. His contributions in these areas led to his first independent academic appointment in 1984 in the Department of Biochemistry and Molecular Biology at Harvard University, where his lab space and tiny office were sandwiched between the laboratories of James Wang and Mark Ptashne.

Michael was ambitious, competitive, and eager to make significant scientific contributions. Splicing studies occupied

much of his attention during those early years. In collaboration with Maniatis, Michael pioneered efficient *in vitro* pre-mRNA splicing systems, which led to the co-discovery (independently made by Phil Sharp's group at MIT) of the RNA lariat and the two-step pre-mRNA splicing pathway. Michael also discovered the essential splicing factor U2AF, demonstrated how it defines the 3' splice site and initiates spliceosome assembly, and illuminated other mechanistic aspects of U2AF function. In recognition of these formative discoveries, he received the Presidential Young Investigator Award in 1985.

Early on, Michael made equally groundbreaking discoveries in the transcription field. His most significant contribution to viral transcription was showing, contrary to the prevailing view at the time, that adenovirus E1a and several related viral proteins function at the promoter. In particular, he demonstrated that E1a contains a transcriptional activation domain and is recruited by the cellular DNA-binding protein ATF2. Notably, this finding was the first demonstration of coactivator recruitment, which is now a fundamental concept in the field. This work also provided the first clear mechanistic link of a cancer-causing viral protein to the transcription of specific genes. His studies on adenovirus transcription led to his discovery of the CREB/ATF family of cellular transcription factors, which are involved in the regulation of a number of important cellular genes.

Michael left Harvard in 1990 to become a professor at the then relatively new University of Massachusetts Medical School (now UMass Chan Medical School) in Worcester, Massachusetts, where he joined the faculty of the recently formed Program in Molecular Medicine (PMM). Chaired by Mike Czech, PMM was launched with the goal of assembling a world-class cadre of multidisciplinary basic and clinical investigators. As noted by Czech, "Michael's impact was immediate and transformative," a compliment clearly



Michael R. Green



Michael, with a false albacore caught off Falmouth, Massachusetts. His fondness for fishing was almost as intense as his commitment to science. Photo courtesy of Gerry Fink.

warranted by the fact that, soon after joining PMM, Michael led the search committees that recruited Craig Mello and Craig Peterson.

At UMass Chan, Michael continued to make prominent discoveries studying the regulation of gene expression. He developed a powerful Gal4-based *in vitro* transcription system, devised methods to analyze transcription complex assembly *in vitro*, and used these to demonstrate activator-mediated recruitment of basal transcription factors to promoters. In one of the first chromatin immunoprecipitation experiments, he showed that most yeast activators function by recruiting the pre-initiation complex to promoters, the first *in vivo* demonstration of this fundamentally important mechanism (done contemporaneously and independently by Kevin Struhl at Harvard Medical School). Furthermore, he identified the essential *in vivo* target of the prototypical activator Gal4 as the SAGA complex, and his collective work on the Gal4-SAGA interaction arguably represents the most definitive characterization of a functional activator-target interaction to date. In addition, he purified and cloned yeast TATA-box-binding protein (TBP)-associated factors (TAFs), and he subsequently identified TAF-independent promoters (in both yeast and mammalian cells), modifying the generally accepted view of TAFs as general coactivators. Finally, in a very important study, he described the general basis by which multiple unrelated activators can synergistically activate transcription through simultaneous interaction with the general

transcription machinery, a fundamental concept unique to eukaryotes.

In collaboration with Rob Singer (then at UMass Chan and now at Albert Einstein College of Medicine), Michael demonstrated, for the first time, that splicing occurred co-transcriptionally. For these experiments, he presciently suggested developing splice-junction probes that would only hybridize to a spliced mRNA. He argued from energetic principles that a 20-nt probe crossing the splice junction would successfully hybridize at the formamide concentrations used in the assay. At the time, 50-nt probes were the norm and 20-nt probes were not used. To Michael's credit, the experiments worked perfectly, and 20-nt probes eventually became the standard for the FISH field.

In the mid-2000s, Michael began applying his expertise in the regulation of eukaryotic gene expression to studying the role of gene expression in various human disease states, in particular cancer. At the time, a relatively new mechanism for inactivating tumor suppressor genes—transcriptional (or epigenetic) silencing—was emerging as a predominant mechanism in cancer development. Michael's group was among the first to use genome-wide RNAi screening, and he developed functional screening approaches to delineate specific pathways by which oncoproteins, such as RAS, epigenetically reprogram cancer cells to promote transformation. These studies elucidated the first molecular mechanism for DNA methylation of tumor suppressor genes; the discovery of this so-called “instructive” transcriptional mechanism disproved the generally held view that epigenetic alterations in cancer cells occur stochastically. Recognizing that transcriptional silencing is reversible, he sought to develop strategies to reactivate gene expression as a therapeutic approach for cancer and other rare monogenic disorders, such as Rett Syndrome, that arise due to the inappropriate epigenetic silencing of a specific gene. He also employed genome-wide RNAi screening to discover new factors and transcriptional regulatory pathways that promote or prevent cancer and to delineate mechanisms of therapeutic resistance in cancer.

Michael's pioneering research led him to become an investigator of the Howard

Hughes Medical Institute in 1994 and to be appointed Director of the Medical School's MD/PhD Program in the same year. The combination of outstanding achievements in research, institutional service, and steadfast commitment to the Medical School's growth became Michael's hallmark during his 33 years at UMass Chan. In 1999, he left PMM to found the Program in Gene Function and Expression (PGFE), a department-like entity he created as part of a campus-wide expansion of research faculty. He assembled a relatively young cadre of assistant professors and began the process of mentoring these academic novices en route to making PGFE a research powerhouse. The extent to which he spent his time helping people reflected his maturation as a leader and paralleled his faculty members' growth as scientists. Michael's vision and hard work set the tone, and his ability to recognize and develop outstanding scientists paid off, leading one colleague to comment that “Michael didn't hire superstars, he created them.”

In 2014, PGFE merged with the Department of Cancer Biology to form a new Department of Molecular, Cell and Cancer Biology, with Michael appointed as its first Chair. At the same time Michael became Director of the UMass Cancer Center and, shortly thereafter, Co-director of the Li Weibo Institute for Rare Diseases Research. These roles, coupled with his unique leadership skills, high standards of research excellence, formative impact on the faculty, and persistent and visionary fostering of the exceptionally collaborative culture at UMass Chan, led to his appointment as the Vice Provost for Strategic Research Initiatives in 2018. As noted by the institution's Dean and Provost, Terry Flotte, Michael accomplished so much “with his own uniquely parsimonious style, never overly emotive nor reactive. Michael brought a calm, steady rigor to everything he did within our community.” Flotte further noted that “UMass Chan is very indebted to him and his legacy.”

Adding to his many notable accolades, Michael's extraordinary scientific achievements earned him elected memberships to the European Molecular Biology Organization (2010), the National Academy of Sciences (2014), the National Academy of Medicine (2015), and the American Academy of Arts and Sciences (2018).

Michael's stellar attributes and habits were foundational to his success. He was smart as a whip and an outstanding scientist. His dedication and determination, and the focus and intensity he brought to projects, inspired everyone around him. As a young faculty member at Harvard, he worked full weeks and long hours alongside the members of his group. He loved running experiments and seemed happiest with a pipet in his hand, cloning bits of DNA for his next experiment and listening to Jimi Hendrix's music blaring from a boombox. If Michael wasn't in the laboratory, he was working away in his office. He would joke with his trainees, sometimes kibbitzing from his office, while writing a paper or grant on his computer. His excitement about science was unparalleled, as was his intense zeal for data, notoriously wanting daily updates even though most experiments took at least a week. His office door opened into a long hallway that led to the darkroom where researchers would develop their autoradiographs. Michael would see his group members walking back with still dripping, freshly developed autoradiographs, and he would jump up and meet them in the hallway, eager to immediately go over the results. He was always excited when anyone made a discovery, including disproving a favorite hypothesis.

As a mentor, Michael had many unique talents, most notably his uncanny ability to motivate his trainees. One of his former postdoctoral fellows, Joseph Reese, recalled Michael saying, "Someone can always come up with a hundred reasons not to do an experiment, but a good scientist can identify the one or two good reasons to motivate them to try it." Despite overseeing a very large laboratory during most of his scientific career, Michael had an open-door policy and was always ready for spontaneous spirited discussions and debates. His ability to be objective was inspirational, and

he fostered an environment that allowed everyone in his laboratory to share their ideas without fear of rejection, a style that helped to shape his trainees' success as independent and confident scientific thinkers.

Many of Michael's trainees had highly successful careers after leaving his group and, as Michael did, went on to hold leadership roles at their institutions. They give Michael's training and mentorship credit for having fostered both the research and leadership aspects of their careers. His former trainees often reached out for advice, and he was always willing to help, drawing upon his years of experience to guide both their science and scientific careers. The graduate students and postdoctoral fellows who trained under him remember his wit and humor that kept the group environment both competitive and friendly—no simple accomplishment. Despite his self-proclamation that patience was not one of his virtues, Michael was a firm believer in perseverance and persistence, and he would fervently acknowledge when these qualities paid off for his trainees upon their success.

Although he had a consummate passion for research, Michael was not all work and science. He was immensely proud of his accomplished family, including his wife of 33 years, Maria Zapp (also a dedicated scientist at UMass Chan), and his siblings, Wendy Lee (a retired pediatrician) and Eric Green (currently Director of the NIH's National Human Genome Research Institute). He also was a sports enthusiast who delighted in vigorous conversations about his beloved New England Patriots—though he had disdain for golf, which he did not consider a sport. He was a serious fisherman, plying the waters of Vineyard Sound each summer weekend. Every cast was like an experiment in which he hoped to get a positive result. On one fishing venture with his good friend Gerry

Fink, he hooked a huge striped bass and fought it for about 10 minutes—and then in a frantic run, the fish escaped before he could pull it into the boat. His profound disappointment was evident as he slouched down on the boat's deck. Reflective of his humor, Michael's only comment was: "Maybe I should take up golf."

The loss of Michael Green as a distinguished scientist, charismatic leader, valued colleague, respected mentor, and cherished friend and family member are beyond measure. His absence will be felt forever, not only by his friends and colleagues but also by his legacy of an extended scientific community, built over four decades and now dispersed across the globe, whose destiny he presided over with profound wisdom.

ACKNOWLEDGMENTS

We thank Michael's numerous friends, colleagues, and former trainees for reminding us about his many accomplishments and for sharing their personal stories, and we are especially grateful to Gerry Fink for the poignant fishing tale and photo.

Robert G. Roeder,^{1,*}
Sara K. Deibler,²
Allan Jacobson,²
James W. Lillie,³
Michael Rosbash,⁴
Robert H. Singer,⁵
and Narendra Wajapeyee⁶

¹The Rockefeller University, New York, NY, USA

²UMass Chan Medical School, Worcester, MA, USA

³MapLight Therapeutics, Inc, Palo Alto, CA, USA

⁴Howard Hughes Medical Institute, Brandeis University, Waltham, MA, USA

⁵Albert Einstein College of Medicine, Bronx, NY, USA

⁶University of Alabama at Birmingham, Birmingham, AL, USA

*Correspondence: roeder@rockefeller.edu
<https://doi.org/10.1016/j.molcel.2023.06.027>