Greg Hannon: the scientist who changed biology, and the people who practiced it

Gregory J. Hannon photographed outside the McClintock Laboratory building at Cold Spring Harbor Laboratory, 2004. Courtesy of Cold Spring Harbor Laboratory Archives, New York.

This memorial reflects on the extraordinary ability of Gregory J. Hannon (1964–2026) to develop transformative technologies, ask bold biological questions, and repeatedly redefine entire fields. Equally, it celebrates his profound influence as a mentor who fostered originality, intellectual rigor, authenticity, and generosity. Greg's greatest legacy extends beyond his discoveries to the generations of scientists whose approach to science, and to life, continues to be shaped by his example.

Some scientists build careers around a single transformative discovery. Greg Hannon built multiple fields.

Greg's fascination with RNA began during his doctoral training under Timothy Nilsen at Case Western Reserve University, where he studied *trans*-splicing in nematodes (Hannon et al. 1991). Although far removed from the small RNA revolution that would later define his career, his doctoral work reflected a lasting curiosity about how RNA regulates gene expression, a question that remained central throughout his scientific life.

Greg's scientific career accelerated during his postdoctoral training with David Beach at Cold Spring Harbor Laboratory. There, he helped define the molecular mechanisms controlling cell cycle progression by establishing the INK4–CDK4/6 pathway as a central tumor suppressor mechanism in human cancer (Serrano et al. 1993; Hannon and Beach 1994). These studies established Greg as an exceptional cancer biologist with a remarkable ability to recognize questions whose importance extended far beyond the problem at hand.

Even then, Greg was already thinking beyond biology itself. He recognized that one of the greatest limitations in mammalian biology was not a lack of ideas but a lack of genetic tools. While yeast and *Drosophila* genetics had transformed their respective fields, comparable approaches were largely unavailable in mammalian systems. Greg set out to change that.

His first step was MaRX (mammalian retroviral expression cloning), an elegant strategy that introduced forward genetic approaches into mammalian cells (Hannon et al. 1999). Although often overshadowed by his later discoveries, MaRX captured the philosophy that defined Greg's career: When existing technologies limited discovery, he invented better ones.

That philosophy found its fullest expression with RNA interference (RNAi). Greg immediately recognized that RNAi was more than an intriguing biological phenomenon—it was a transformative genetic tool. His laboratory developed vectors, genome-wide shRNA libraries, and experimental platforms that brought functional genetics to mammalian cells at an unprecedented scale (Paddison et al. 2002, 2004). Within just a few years, these technologies had become indispensable throughout biomedical research.

For Greg, however, technology was never the destination; it was the means to answer bigger biological questions.

As RNAi became an established experimental platform, his attention shifted toward the biology of endogenous small RNAs. His laboratory helped establish microRNAs as fundamental regulators of development, differentiation, and cancer (He et al. 2005) and later uncovered the biology of piRNAs, revealing how germ cells protect genomic integrity by silencing transposable elements through specialized small RNA pathways (Girard et al. 2006; Aravin et al. 2007; Carmell et al. 2007). These discoveries fundamentally reshaped our understanding of gene regulation, genome defense, and heredity.

Throughout his career, Greg repeatedly reinvented himself. While many scientists spend decades expanding a single discovery, he continually pursued new biological frontiers. From RNA processing to cell cycle regulation, mammalian genetics, RNA interference, microRNAs,

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Article published online ahead of print. Article and publication date are online at http://www.genesdev.org/cgi/doi/10.1101/gad.354062.126. Freely available online through the *Genes & Development* Open Access option.

and piRNAs, Greg never seemed interested in becoming the world's expert on yesterday's breakthrough. Instead, he was drawn to tomorrow's unanswered questions.

His move to the Cancer Research UK Cambridge Institute reflected another evolution of that vision. There, his laboratory shifted from studying individual genes and pathways to understanding tumors as complex biological systems. By integrating functional genomics, genome engineering, computational biology, and spatial technologies, his group investigated cancer evolution, cell identity, and transposable element biology while pioneering multidimensional "virtual reality" maps of tumors that allowed researchers to explore the cellular architecture of cancer in unprecedented detail. Even as his approaches became increasingly sophisticated, his central goal remained unchanged: to develop better ways of understanding biology.

Looking back, it becomes clear that Greg's career was never defined by a single field. It was defined by a single vision: bringing the power of genetics to mammalian biology. From MaRX to RNAi, genome-wide shRNA libraries, endogenous small RNAs, and functional genomics, every major contribution from his laboratory expanded the ways scientists could ask and answer fundamental biological questions. Greg changed not only what we knew about biology but how biology itself could be investigated.

However, remarkable as Greg's scientific accomplishments were, they tell only part of his story.

For those of us fortunate enough to train in his laboratory, his greatest legacy was the way he shaped the people around him.

Greg possessed an almost uncanny ability to mentor individuals rather than trainees. He understood that every scientist required something different. Some needed confidence. Others needed independence. Some benefited from relentless challenge, while others simply needed someone who believed in them before they believed in themselves. Greg somehow knew what each of us required and quietly provided it.

He encouraged each of us to become the best version of ourselves rather than the next version of him. He believed that originality was as important in people as it was in science and that the best careers were built not by imitating successful scientists but by remaining authentic to oneself.

Perhaps his greatest lesson was that science should never replace one's identity. Greg believed that science was not simply a profession—it was a personality trait. Curiosity, creativity, skepticism, ambition, generosity, and humility were not qualities reserved for the laboratory; they were simply part of who he was. He encouraged us to remain ourselves, to cultivate interests beyond science, to value our families and friendships, and to resist the temptation to define success solely through publications, awards, or prestige. Ironically, it was precisely this authenticity that made him exceptional.

He valued initiative over obedience, boldness over caution, commitment over appearances, and tenacity over convenience. His laboratory was a place where ideas mattered more than hierarchy and where ambitious trainees were trusted with extraordinary independence. He expected excellence, but he never confused excellence with perfection.

Greg also showed us what scientific leadership looked like.

His critiques during seminars were legendary, not because they were intimidating (most of the time), but because they were invariably insightful. He demonstrated that one could be intellectually rigorous, demanding, and uncompromising without ever diminishing another scientist. His questions were not performative but rather sought a deeper understanding. He challenged ideas, never people. There was no need for theatrics or humiliation. Instead, there was clarity, curiosity, and remarkable intellectual honesty.

Many of us quietly positioned ourselves next to Greg during scientific talks, knowing that the conversations afterward would often be as educational as the presentations themselves. Watching Greg dissect a scientific problem in real time was like watching someone solve a puzzle no one else had yet recognized needed solving.

He also taught us another invaluable lesson: It is impossible to please everyone, and trying to do so is rarely compatible with doing important science. Greg remained authentic, even when it meant disagreeing with prevailing opinion. He demonstrated that integrity matters more than popularity and that conviction should never be sacrificed for acceptance.

What perhaps surprised outsiders most was how little Greg cared for the performative aspects of academic success. At conferences, while many senior scientists attended exclusive dinners or carefully navigated networking events, Greg usually chose to spend his evenings with his trainees. Those informal dinners became some of our most memorable lessons, not because Greg intended to mentor us, but because he reminded us that becoming a great scientist never required becoming someone other than ourselves.

Outside the laboratory, Greg reminded us that extraordinary scientists are still human beings. He loved his family deeply and found enormous joy in traveling with his children, riding long distances on his bicycle, fishing, playing music with his band, and simply gathering with friends. He also reminded us that success does not eliminate self-doubt. Despite his extraordinary accomplishments, Greg spoke openly about uncertainty and self-questioning, giving many young scientists permission to acknowledge their own struggles while continuing to pursue ambitious goals.

For countless trainees, collaborators, and friends, Greg became far more than a mentor. He became part of the support system that helped us navigate careers, setbacks, and life itself.

The loss of Greg Hannon leaves a wound that will never completely heal. Perhaps a better metaphor is a scar. A scar reminds us that something painful has become inseparable from who we are. Those fortunate enough to have worked with Greg carry that scar with immense pride because it reminds us that, for a time, we were privileged to exist within his orbit.

Yet Greg's legacy resembles something even more fundamental.

Like DNA, it continues to replicate.

Every trainee who learned from Greg carries forward a small part of how he approached science: how he questioned assumptions, challenged ideas without diminishing people, encouraged originality, valued authenticity, and built laboratories where people mattered as much as discoveries. Those trainees now mentor their own students in much the same way, ensuring that scientists who never had the privilege of meeting Greg Hannon will nevertheless inherit part of his philosophy.

His legacy is therefore written not only in landmark discoveries, revolutionary technologies, or the fields he transformed, it is written in people.

And that may be the greatest legacy any scientist can leave behind.

Acknowledgments

Because no brief memorial can fully capture Greg's extraordinary scientific legacy, the examples and references included here are representative of his remarkable work. Sincere apologies to Greg's many trainees, collaborators, and colleagues whose important contributions and publications could not be individually acknowledged here.

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Genes Dev. published online July 21, 2026
Access the most recent version at doi:10.1101/gad.354062.126