

Alfred Goodman Gilman (1941–2015)

On December 23, 2015, Alfred Goodman Gilman died peacefully at home after a long battle with pancreatic cancer. Though Al was one of the great scientific minds of the past 50 years and is best known for his discovery of guanine nucleotide-binding regulatory proteins (G proteins), anyone who trained or worked closely with Al knew him as much more than that. His greatness extended equally to scientific leadership, mentorship of young scientists, and a relentless pursuit of scientific discovery.

Basic science and its application to pharmacology were in Alfred Goodman Gilman's blood from birth. Al was born on July 1, 1941, in New Haven, CT, the same year his father, Dr. Alfred Gilman, and Dr. Louis Goodman (from whom Al received his middle name) published the first edition of the preeminent textbook, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. Years later, Al would continue his father's work as associate and senior editor of the famous textbook through four subsequent editions. Al often spent time in his father's lab at Albert Einstein College of Medicine, where he watched experiments in action. Al's early education was received at The Taft School in Watertown, CT, which at the time was a strict all-boys prep school. He once noted that while he did not enjoy the rigors of the experience, it did teach him two things: how to learn and how to smoke. With known risks, he enjoyed doing both the rest of his life.

Al received his Bachelor of Science degree (*summa cum laude*) from Yale University in 1962 and his MD and PhD degrees from Case Western Reserve University in 1969 under Theodore Rall, who had worked with Earl Sutherland and was instrumental in the discovery of adenylyl cyclase and cyclic AMP (cAMP). It was in Rall's lab that Al began his life-long interest in signal transduction. An important outstanding question in the field at that time was how an extracellular signal, such as a

hormone, is transduced from binding its receptor on the membrane to activating a second messenger response inside the cell. After receiving his MD/PhD, he knew his fate was to pursue a career in basic biological science, trying to answer that question. Off he went to the NIH for his postdoctoral research in the laboratory of Nobel Laureate, Marshall Nirenberg. There he made his first big impression on the world of signal transduction by developing a remarkably simple and sensitive assay for measuring cAMP, the second messenger discovered by Sutherland and Rall. A telling accomplishment setting him apart from his peers at the time was that Nirenberg communicated the paper describing the transformative cAMP assay to the *Proceedings of the National Academy of Sciences*, with Al as its sole author.

In 1971, Al started his own lab in the Department of Pharmacology at the University of Virginia in Charlottesville. He directed his full attention to understanding the molecular components of the transducer that activated adenylyl cyclase to synthesize cAMP inside the cell in response to receptor activation at the cell's surface. Previous work by Martin Rodbell had shown that an essential ingredient required for this signal transduction was guanosine triphosphate (GTP). The Gilman lab employed a mutant cell line that was deficient in the transducer activ-

ity, and in 1978 the lab purified the missing component from normal cells. The purified component was a multi-subunit protein called Gs, the first of what would become a family of GTP-binding protein switches. Upon activation by a transmembrane receptor, a subunit of Gs was shown to exchange GDP for GTP, dissociate from the receptor inside the cell, and activate adenylyl cyclase —the basic paradigm of information flow in many other hormone and light-mediated signaling events.

Al's early successes led to his recruitment by indomitable forces (Donald Seldin, Kern Wildenthal, Michael Brown, and Joseph Goldstein) to come to the University of Texas Southwestern Medical Center in Dallas in 1981, where at the ripe age of 40, he was appointed chair of the Department of Pharmacology (a position he held for 25 years). He reinvigorated the department by seeding it with two former trainees, Elliott Ross and Paul Sternweis, who made the fundamental discoveries of G proteins and their mechanism. In his own laboratory, Al continued a remarkable progression of work that, over the next decades, elucidated virtually every step in the G protein signaling cycle. The impact of his discovery on basic biology and medicine was transcendent, and it led to a number of accolades, including election to the National Academy of Sciences (1985), the Albert Lasker Basic Medical Research Award (1989), and the Nobel Prize in Physiology or Medicine, which he shared with Martin Rodbell (1994).

So, Al was an exceptional scientist, but as junior colleagues who knew him closely, we would be greatly remiss in a full and proper accounting of his life if we stopped there. In addition to scientific excellence, he also built one of the finest basic science departments in the country—a place that was academically rigorous, highly productive, and fun. As administrator and leader, he was absolutely without equal, earning the non-trivial distinction of being



Alfred Goodman Gilman, circa 1980 (the “crazy pants” days at the University of Virginia), and in 2009 (the UT Southwestern days).

respected by the university administration as well as the faculty, fellows, and students of the department. Indeed, when both authors of this essay were postdoctoral fellows looking for jobs, it was widely known that the Department of Pharmacology at UT Southwestern was *the* place to be—a nursery for good fundamental science, administered with integrity, and run by a respected scientist whose word was good enough to take to the bank. Things got done, promises were kept, and a young investigator could simply focus on the task of building their own research program.

The success of the department deeply reflected Al's qualities both as a scientist and as a person. He built the department on certain core principles. Above all was the dictum, in his own words, "to hire only excellent people." The turn of phrase is subtle but important. It was not sufficient to merely have an impressive pedigree or to be a star scientist; it was also necessary to be a good communicator, to demonstrate citizenship, to be willing to teach, and to contribute to the quality of life within the department. Al steadfastly refused to weigh scientific quality against character, as if deficiencies in one could be counterbalanced by an overabundance of the other. Apparently, this principle derived from his mother, a woman of considerable strength and influence on young Al. In an autobiography, Al wrote "...when my father talked of a colleague and the brilliance of his work, my mother occasionally rolled her eyes and commented on the deficiencies of the colleague's personality. Subsequent personal observations taught me that [she] was almost always correct. I tried to pay attention to both sides of that issue when building a department." He stayed true to this lesson. The result was an unusually vibrant department full of excellent people (in the Gilman sense) in which incisive professional criticism was supported and encouraged, but somehow always

delivered in a manner that was cordial, respectful, and ultimately, productive.

Another principle was that support for young scientists must go well beyond a good start-up package and laboratory space. Al provided ongoing support by investing surplus departmental funds, whenever available, on shared equipment items, by shielding young faculty from the destructive effects of non-research related demands, and by having essentially no departmental meetings. Time was spent in direct conversation with junior scientists, either formally in his office or more often, over an early evening spirit at the faculty club. He listened well, was remarkably quick on the uptake, and did not hesitate to deliver a robust and well-reasoned professional opinion if presented with a bit of data or a new idea. These opinions had great influence, inevitably steering the recipient toward the most interesting (rather than most obvious) scientific directions. But, he balanced his opinions with extraordinary humility as well. He did not tell the faculty what to be interested in and did not pretend to know scientific fields outside of his experience. Through all this, Al enabled originality.

Balancing scientific excellence with humility about the grand mysteries of biology had another productive side effect: it kept Al unsatisfied about his own much lauded research achievements. In the post-Nobel period, he became deeply unsettled with a worry that a life focused on *in vitro* biochemistry—of taking apart specific components of biological systems and studying them in isolation—was not going to tell us how a cell (or any other complex system) worked. As he put it in characteristic vernacular, "...it might not amount to a damn thing..." In 2000, as the last research project of his career, he launched a large-scale effort to study the complexity of cellular signaling in the context of living cells. The goal was to globally map the structure and functional dynamics of networks of signaling pathways in cells, with

a set of well-defined objectives. The effort was scientifically and socially complex and taught more about the difficulties of such an endeavor than producing definitive conclusions. Nevertheless, the work illustrated something important; for Al, prior achievements and big prizes did not cloud the drive to always focus on the next unsolved problem.

In the final stages of his career, Al took on institutional leadership roles. In 2004, he was named Dean of UT Southwestern Medical School, and in 2006 he became Executive Vice President for Academic Affairs and Provost. In 2009, Al retired from UT Southwestern to become the Chief Scientific Officer of the Cancer Prevention Research Institute of Texas (CPRIT), a job that he felt would permit him to use his talents of scientific insight, integrity, and institutional vision to fund one of the largest research efforts in the nation to battle cancer. True to his principles, this effort was characterized by rigorous scientific review, staffed by the best people in science, and was uncompromising in its goals of funding the best work. Anything less was unacceptable, even if it meant, at considerable personal risk, his resignation from the organization when core principles were violated.

There are great scientists and there are great human beings. Al, in rare form, was both. With his passing, one can hope that the principles of excellence (in the Gilman sense) will live on in good departments of biological research.

David J. Mangelsdorf^{1,4,*} and Rama Ranganathan^{1,2,3,*}

¹Department of Pharmacology

²Department of Biophysics

³Green Center for Systems Biology

⁴Howard Hughes Medical Institute
UT Southwestern Medical Center, Dallas,
TX 75390, USA

*Correspondence: davo.mango@utsouthwestern.edu (D.J.M.), rama.ranganathan@utsouthwestern.edu (R.R.)
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