Alfred Goodman Gilman

(1941–2015)

Pharmacologist who won a Nobel prize for his discovery of G proteins.

Alfred Goodman Gilman discovered heterotrimeric G proteins, which help to usher chemical signals into cells. For this work, which reshaped our understanding of hormone and drug action, he shared the 1994 Nobel Prize in Medicine or Physiology with Martin Rodbell.

Gilman's impact on biomedical research and education extended much further. He edited several editions of the definitive textbook *The Pharmacological Basis of Therapeutics* (or 'Goodman and Gilman'), which has served generations of medical and graduate students. At the University of Texas Southwestern Medical Center in Dallas, he chaired the pharmacology department from 1981 to 2004, became dean in 2004 and provost in 2006. And in 2009, he was appointed first chief scientific officer of the Cancer Prevention and Research Institute of Texas (CPRIT), established to disburse US$3 billion in state funding. He died on 23 December 2015.

Gilman was born in July 1941 in New Haven, Connecticut, with, in his words, a "scientific silver spoon" in his mouth. His father was the eminent pharmacologist Alfred Gilman Sr, who wrote the aforementioned textbook with his close colleague Louis Goodman. Gilman Sr, in tribute to his friend, gave his son the middle name Goodman. As a child, young Gilman enjoyed trips to his father's labs at Columbia University and the Albert Einstein School of Medicine in New York.

After completing a degree in biochemistry at Yale University in New Haven in 1962, he enrolled in one of the first MD–PhD programmes in the United States, at Case Western Reserve University in Cleveland, Ohio. The programme was run by Nobel laureate Earl Sutherland, the discoverer of cyclic AMP, a key intracellular messenger molecule. Here, Gilman solidified his interest in cell-signalling mechanisms. A postdoc at the US National Institute of Health in Bethesda, Maryland, with Marshall Nirenberg, another Nobel laureate, followed. In 1970, in Nirenberg's lab, Gilman independently developed a sensitive technique for detecting cAMP that was immediately widely adopted.

But it was his discovery of a family of G proteins made up of three different subunits (known as heterotrimeric G proteins) as a junior faculty member at the University of Virginia in Charlottesville, that transformed the field of cell signalling. In the 1970s, evidence was mounting that the hormone receptors involved in cell signalling were independent entities in the plasma membrane. Gilman and his postdoc Elliott Ross were investigating this problem using membranes from a lymphoma cell line called cyc$^-$. These cells seemed to lack the key enzyme adenylyl cyclase, which catalyses formation of cAMP. The cells retained the β-adrenergic receptor that binds a class of molecules called catecholamines, which includes the hormone adrenaline. This binding stimulates adenylyl cyclase, increasing the formation of cAMP.

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To these cyc$^-$ membranes, Gilman and Ross added an extract of another cell line, mouse L cells, which retained enzyme activity but lacked the hormone receptors. To their delight, this 'reconstitution' system worked and yielded hormone-sensitive adenylyl cyclase activity. However, control experiments indicated that extracts in which the cyclase activity had been inactivated, by heat for example, still led to a fully reconstituted hormone-sensitive enzyme.

Through ingenious experiments they demonstrated that these extracts contained a heat-stable, hitherto unknown regulatory component required for activity of the adenylyl cyclase and that the cyc$^-$ cells actually did contain the catalytic unit of adenylyl cyclase (and hence had been misnamed). They called the new component $G_s\alpha$ — the α subunit of the stimulatory guanine nucleotide regulatory protein (G protein), because it bound guanosine triphosphate (GTP) and conferred both hormone and GTP sensitivity on the adenylyl cyclase.

Using their reconstitution assay, they purified the protein and determined its DNA sequence. Their discovery, published in a series of papers in 1977–78 (E. M. Ross and A. G. Gilman *J. Biol. Chem.* **252,** 6966–6969; 1977; and E. M. Ross *et al. J. Biol. Chem.* **253**, 6401–6412; 1978) confirmed Rodbell's prediction of the existence of such an intermediate protein linking a cell's hormone receptors to adenylyl cyclase and intracellular signalling. Over the next 15 years the family of heterotrimeric G proteins grew to about 20, and their roles expanded to include almost all physiological processes in species from yeast to mammals. Gilman's subsequent work with Stephen Sprang focused on the detailed characterization by X-ray crystallography of several of the G proteins and the adenylyl cyclases that they regulate.

Gilman's writing and speaking style were distinctive. He was critical not just of others' work but also of his own. His wit could border on the acerbic if he felt that the highest standards were not being met. He was beloved by his trainees, to whom he was fiercely loyal. They remember him as a hands-off mentor who was nonetheless approachable and inspirational, and who instilled in them a sense of rigour and integrity. Gilman displayed this personal integrity when, in 2012, he resigned from the CPRIT over concerns that political and commercial factors were exerting undue influence on its awarding of grants.

Al's offbeat sense of humour occasionally made its way into his published work. For instance, he designated the irreversibly activated state of adenylyl cyclase induced by a certain guanine nucleotide as the 'P state' (for priapic) because "the enzyme's rate of catalysis was persistently elevated".

Reflecting on the role of serendipity in scientific discovery, Al once commented: "The trick is to recognize good luck when it happens, embrace it, and then commit whatever it takes to extract its full value." He certainly extracted the full value of his lucky start as a scientific blueblood. ■

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