Developing the Purine Nucleoside Analogue Acyclovir: the Work of Gertrude B. Elion

Thymidine Kinase from Herpes Simplex Virus Phosphorylates the New Antiviral Compound, 9-(2-Hydroxyethoxymethyl)guanine

Inhibition of Purified Human and Herpes Simplex Virus-induced DNA Polymerases by 9-(2-Hydroxyethoxymethyl)guanine Triphosphate. Effects on Primer-Template Function

Gertrude B. Elion (1918–1999) was born in New York City. As a child she had an insatiable thirst for knowledge and enjoyed all of her school classes equally. She skipped two grades and graduated from high school in 1933, at the age of 15. However, because of her widespread intellectual curiosity, when it came time to choose a major in college, she faced a dilemma. Ultimately, the death of her grandfather that summer made her decide to do something that might eventually lead to a cure for cancer, and she became a chemistry major when she entered Hunter College in 1933.

When she graduated from Hunter in 1937, she was unable to attend graduate school because of the depression. Unfortunately, jobs were scarce and the few laboratory positions that were available were not open to women. “Nobody . . . took me seriously,” she recalled. “They wondered why in the world I wanted to be a chemist when no women were doing that. The world was not waiting for me” (1).

Elion managed to get a 3-month job teaching biochemistry to nurses in the New York Hospital School of Nursing. During this time she met a chemist who was looking for a laboratory assistant. Although he was unable to pay her, she decided that the experience would be worthwhile. She stayed there for a year and a half, eventually making $20 a week. By this time she had saved up enough money to attend graduate school and entered New York University in 1939. She was the only woman in her graduate chemistry class.

Gertrude B. Elion

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Elion obtained her Master of Science degree in chemistry in 1941 after which she started working as a quality control chemist in the Quaker Maid Company food laboratory, checking the color of mayonnaise, the acidity of pickles, and the mold levels on fruit. After a year and a half she got a job in a laboratory at Johnson and Johnson synthesizing sulfonamides. Unfortunately, that laboratory was disbanded after about 6 months. Luckily, she was offered a job by *Journal of Biological Chemistry* (JBC) Classic author George Hitchings (2) at the Burroughs Wellcome Research Laboratories (now known as GlaxoSmithKline). While working with Hitchings, Elion continued working toward her doctoral degree, going to school at night at Brooklyn Polytechnic Institute. After 2 years of night school she was informed that she would no longer be able to continue her doctorate on a part-time basis and would need to attend school full time. Elion decided to remain with Hitchings and give up her pursuit of a doctoral degree. However, by the time she died in 1999, Elion had been awarded 25 honorary doctorate degrees.

The recent development of sulfa drugs made Hitchings wonder if other substances that interfered with microbe metabolism could also be used as drugs. Hitchings began examining the nucleic acids and assigned Elion to investigate purines. They soon discovered that bacterial cells were unable to produce nucleic acids unless certain purines were present and started to work on synthesizing compounds that would inhibit the incorporation of these purines into nucleic acids. By 1950 they discovered two compounds, diaminopurine and thioguanine, which inhibited the incorporation of adenine and guanine (respectively) into nucleic acids, and were both eventually used to treat leukemia.

Their success with diaminopurine and thioguanine led Elion to substitute an oxygen with a sulfur atom on a purine molecule, producing 6-mercaptopurine, a molecule closely related to thioguanine, that was also an effective treatment for leukemia. Elion and Hitchings also developed a number of additional drugs including azathioprine, a less toxic form of 6-mercaptopurine used to suppress the immune system after organ transplants, and allopurinol, a drug used to treat gout that blocks uric acid production by competing for xanthine oxidase, an enzyme that converts purines to uric acid. The methods they used eventually became known as “rational” drug design, and Hitchings and Elion were regarded as pioneers in the field.

In 1967, Hitchings retired and Elion was promoted to Head of the Department of Experimental Therapy, making her the first woman to lead a major research group at Burroughs Wellcome. She turned her attention to antiviral medications after learning that adenine arabinoside, which had a structure similar to 2,6-diaminopurine, showed signs of successfully fighting DNA viruses. She began synthesizing new compounds and eventually developed the purine nucleoside analogue 9-(2-hydroxyethoxymethyl)guanine (acyclo-Guo or acyclovir), which proved to be a potent inhibitor of herpes simplex virus type I and type II both *in vitro* and *in vivo*. The two JBC Classics reprinted here deal with Elion’s further investigations of this compound.

In the first Classic, Elion and her colleagues report that acyclo-Guo is phosphorylated at a 30- to 120-fold faster rate in cells infected with herpes simplex virus than in uninfected cells. They determined that the virus-encoded enzyme thymidine kinase was responsible for this phosphorylation and that phosphorylation was necessary for acyclo-Guo to effectively inhibit virus replication. These results explained why the purine nucleoside analogue was such a potent and specific inhibitor of herpes simplex virus.

Elion and her colleagues eventually determined that the triphosphate form of acyclo-Guo, acyclo-GTP, was the active form of the compound that is produced by the herpes simplex virus-induced deoxynucleotide kinase. In the second JBC Classic Elion examined the inhibition of highly purified herpes simplex virus by acyclo-GTP and discovered that it competitively inhibited the incorporation of dGMP into DNA, catalyzed by herpes simplex virus DNA polymerase. Additionally, $^{14}$C-labeled acyclo-GMP residues incorporated into activated DNA by herpes simplex virus-1 DNA polymerase could not be excised by the polymerase-associated 3',5'-exonuclease activity, thus leading to the prevention of further polymerization. Acyclovir is currently one of the most commonly used antiviral drugs and is primarily used for the treatment of herpes simplex virus infections, as well as in the treatment of herpes zoster (shingles).

Although Elion retired in 1983, she remained at Burroughs Wellcome as Emerita Scientist and consultant and in 1984 her laboratory developed azidothymidine (AZT), which was the only drug licensed in the United States to treat AIDS until 1991. In recognition of her
contributions to drug discovery, Elion shared the 1988 Nobel Prize in Physiology or Medicine with Hitchings and Sir James W. Black.

In addition to the Nobel Prize, Elion received many awards and honors for her research. These include the 1968 Garvan Medal from the American Chemical Society, the 1970 President’s Medal from Hunter College, the 1983 Judd Award from Memorial-Sloan Kettering Institute, the 1984 Cain Award from the American Association for Cancer Research, the 1990 Ernst W. Bertner Memorial Award from the M. D. Anderson Cancer Center, the 1990 Medal of Honor from the American Cancer Society, and the National Medal of Science, presented by President George Bush in 1991. She was also the first woman inducted into the National Inventors Hall of Fame (1991). Elion was elected to the National Academy of Sciences in 1990 and to the Institute of Medicine in 1991. She was a fellow of the American Academy of Pharmaceutical Scientists and the American Academy of Arts and Sciences, a foreign member of the Royal Society, and an honorary member of the Spanish Academy of Dermatology and Venereology.

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REFERENCES


1 Biographical information on Gertrude B. Elion was taken from Ref. 1.