

This Week's Citation Classic

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Yarmolinsky M B & de la Haba G L. Inhibition by puromycin of amino acid incorporation into protein. *Proc. Nat. Acad. Sci. US* **45**:1721-9, 1959. [McCollum-Pratt Inst., and Mergenthaler Lab. Biol., Johns Hopkins Univ., Baltimore, MD]

The authors suggest that the antibiotic, puromycin, is an analog of the terminal aminoacyl-adenosine portion of aminoacyltransfer RNA. They show that puromycin is an inhibitor of protein synthesis and, by a study of separate steps in the *in vitro* process of radioactive amino acid incorporation into protein, provide evidence that the inhibition occurs at a step following the charging of transfer RNAs with amino acids. [The *SCI*[®] indicates that this paper has been cited over 560 times since 1961.]

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"Having been asked to comment on or explain why an article I coauthored with Gabriel de la Haba has been so often cited, I am beset with conflicting desires, to express irritation at the computer-assisted trivialization of renown and to express pleasure at receiving an honor, however dubious.

"The work came about as a consequence of a review, which I prepared for a few colleagues in 1957, of the then meager literature on protein synthesis. The antibiotic, puromycin, had been shown (by a team at Lederle Laboratories in 1953) to consist of a methylated adenosine linked by a peptide bond from an amino group replacing the hydroxyl group on carbon 3 of the ribose to a methylated tyrosine.¹ In 1955 E H Creaser had noted that puromycin inhibited the induction of β -galactosidase in staphylococcus.² I called attention to these results in a seminar delivered to my colleagues in the Laboratory of Cellular Pharmacology at the National Institute of Mental Health, suggesting that puromycin might specifically inhibit protein synthesis at a reaction involving both a nucleic acid and an amino acid component. The proposal was perhaps too vague to

awaken much interest at a time when the role of transfer RNAs as 'adaptor molecules' was not recognized. Among those present at this seminar were Gabriel de la Haba and a visitor, Edward Reich.

"It was de la Haba who, two years later, encouraged me to take my proposal seriously. We had both returned to our alma mater, Johns Hopkins University, as postdoctoral fellows. The structure of the business end of 'charged' (aminoacyl) transfer RNA had just been published; the resemblance to puromycin was striking. De la Haba had promising ideas of his own concerning the possible sensitivity of protein synthesis to esterase inhibitors such as diisopropyl fluorophosphate (DFP). On a part-time basis the two of us embarked on a collaboration to study the action of DFP and puromycin. The DFP experiments were disappointing, but the puromycin experiments justified our weekend labors. After our results were published, we learned that similar efforts were being planned at the Rockefeller Institute. The unfortunate investigator was Ed Reich.

"Our findings provided a glimmer of rationality in a murky empirical field. But it is not this achievement that accounts for the frequent citations. It is rather our demonstration that puromycin can be a convenient tool. It has been used (often with skill and effectiveness) to dissect molecular events in protein synthesis in prokaryotes and in eukaryotes. It has been used (often with recklessness and subsequent regret) to dissect the role of protein synthesis in more complex physiological phenomena.

"The puromycin article summarises an isolated undertaking. Other articles of mine, closer to the line of my subsequent scientific development, mean more to me. One such article, coauthored with Max Gottesman, is about integration-deficient mutants of bacteriophage lambda.³ Its citation success is unknown to me, but I would not be surprised if its rating is largely a reflection of a trivial happenstance; the article provides the first published mention of a now widely used recombination-deficient mutant of *E. coli* kindly sent to us by a scientist whose renown requires no certification by computer, Matthew Meselson."

1. **Waller C W Frythh P W, Hutchings B L & Williams J H.** Achromycin. The structure of the antibiotic puromycin. I. *J. Amer. Chem. soc.* **75**:2025, 1953.
2. **Creaser E H.** The induced (adaptive) synthesis of β -galactosidase in *Staphylococcus aureus* *J. Gen. Microbiol.* **12**:288-97, 1955.
3. **Gottesman M E & Yarmoliasky M B.** Integration-negative mutants of bacteriophage lambda. *J. Mol. Biol.* **31**:487-505, 1968. [The *SCI*[®] indicates that this paper has been cited over 205 times since 1968.]