

August 19, 1969

Dr. Leslie Orgel
Dr. Francis Crick

Dear Leslie and Francis:

It was a pleasant surprise to get ideas about DNA polymerase from Spetsai. From Paul's account, you all had a wonderful mixture of science and frolic.

Both your suggestions have seemed reasonable to me too; I think implications are made in the recent Science paper along these lines.

1) Correct base pairing and the function of the 3' → 5' nuclease (formerly Exo II): I think that base-pair matching of template and incoming nucleoside triphosphate followed by base-pair recognition by the enzyme could be virtually error-free. However mismatching might be edited out by exonuclease (3' → 5').

2) The 3' → 5' nuclease does prefer frayed or single-stranded ends. The activity disappears very rapidly as the temperature is reduced, although we have not (and really should have) related this more accurately to the helical-random coil states of chains. I've wanted to know in such studies whether we were saturating the enzyme before comparing rates and the multiple sites within the active center present difficulties in interpretation. However I'll guess you're right about the alkaline pH optimum being due to fraying.

The experiment you suggest in which poly(dT)_n - poly(dA)_npdG* is used as a substrate would be worthwhile if we had a series like this to compare but unfortunately they're not easy to come by.

A new possibility for correction of mismatching by the enzyme emerges from our studies of the 5' → 3' exonuclease function. (Preprint of Nature article is enclosed). The "cut and patch" scheme for removing pyrimidine dimers should be applicable to other lesions.

Warm regards,

Sincerely,

Arthur Kornberg

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