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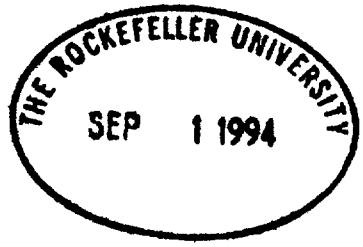

Professor Joshua Lederberg
The Rockefeller University
1230 York Avenue
New York, NY 10021

Dear Professor Lederberg:

Thank you for your note and reprint in regard to our recent determination of the structure of *E. coli* β-galactosidase.

One of the most pleasing aspects of the structure determination has been the ability to rationalize many of the observations in the literature regarding the enzyme. I am afraid, however, that at this point we are not in a position to say very much about the K^+/Na^+ competition. With this present definition of the structure we are quite confident about the overall fold of the polypeptide chain and are developing some information on solvent binding. It is, however, practically impossible to distinguish a bound solvent molecule from, for example, a bound sodium ion. In principle, we could try to replace any bound sodium ions with potassium, but the additional electron density would not give us much to work with. Substitution with, for example, rubidium or cesium could be tried, but their larger size might make them poorer mimics. Unfortunately, the unusually large size of the β-galactosidase unit cell precludes us from data collection in-house. We have to go to a special facility (the "Photon Factory") in Japan and, because of the pressure of other users, are limited to two days every 12-15 months. Our priority at the moment is to get information on the binding of substrates but we will certainly want to look into the roles of metals as data collection can be arranged.

You might ask why, if we are so equivocal as to possible sodium binding sites, we feel reasonably confident regarding the binding of magnesium. This is in part serendipity. During the determination of the structure we first exposed crystals of the enzyme to EDTA in an attempt to remove magnesium and then added thallium, thinking that it might act as a magnesium replacement. On working up the data, thallium was observed to bind at one site, while at a different site, consistent with studies from Huber's and Withers' laboratories we observed negative density consistent with the removal of magnesium.

We have just received reprints of our article. As you requested, a copy is enclosed.

Thanks again for your interest in writing.

With best regards,

Brian W. Matthews

Enclosure
BWM:jlp
cc: Ray Jacobson