

α

STANFORD UNIVERSITY
MEDICAL CENTER
PALO ALTO, CALIFORNIA

DEPARTMENT OF GENETICS
School of Medicine

January 22, 1962

Dr. Giovanni E. Magni
Institute of Genetics
Via S. Epifanio 14
Pavia, Italy

Dear Giovanni:

Thank you for your letter of the twelfth; I am returning the signed acceptances as you suggested. Of course I am agreeable to any procedure according to what is most convenient for you. I hope the lawyers don't waste too much of your time.

I hope the implication that you will be doing your own fluorinations are favorable for the more rapid progress of this program. Have you been able to get a good chemist who is trained in this kind of organic synthetic work? On the whole I would thoroughly agree with you that it is far better to do such procedures in your own laboratory, and I would not be at all sure that the experience with the fluorination of steroid derivatives would be especially pertinent to our problem here.

A thought occurred to me that another area of specific chemotherapeutic activity might be found in those biosynthetic pathways which we know to be blocked in man, but which operate in microorganisms. I would have particularly in mind the steps in the biosynthesis of the essential amino acids, for example, phenylalanine. Derivatives like p-fluoro phenylalanine are incorporated into protein in place of phenylalanine, and have consequent toxicity. This compound itself therefore has no useful chemotherapeutic activity. If, however, we could find a fluorinated analogue earlier in the synthetic chain, and this either prevented the endogenous phenylalanine by the microorganism or was incorporated into lethal synthesis, it should then have selective therapeutic activity. You must know this scheme for the biosynthesis of the aromatic amino acids which comes mainly from Bernie Davis's work. It has been proven to apply mainly to *E. coli*. We also have some evidence that at least part of the earlier steps are also characteristic of *Bacillus subtilis* although we have some fairly definite indications that in *B. subtilis* tyrosine is derived from phenylalanine through a phenylalanine hydroxylase. Anyhow, my suggestion would be to look specifically at some of the fluorinated analogues of the precursors of prephenic acid as likely selective inhibitors. Substituted fluorobenzoic acid derivatives should behave metabolically very much like the corresponding hydroxy benzoic compounds. If the purified and characterized compounds can be obtained and prepared so much the better, but along these lines of our previous discussions, it might be equally agreeable to simply submit shikimic acid to fluorine replacement and look for whatever compounds may then show antimicrobial activity. I have not done any literature search for the indicated substances.

This suggests that it might be quite valuable to collect an index of fluorinated analogues of biosynthetic intermediates from the literature* more generally. This could give us more insight into the conditions for definite activity, even information on the lack of biological activity would be of considerable interest. Outside of the steroids, which are probably beyond the scope of our present interest, the only derivatives I can readily think of are fluoroacetate, fluorouracil and fluorophenylalanine. Since you will hopefully be isolating a number of other fluorinated derivatives, it

FOLD SIDES OVER AND THEN FOLD BOTTOM UP.
MOISTEN FLAP WELL AND APPLY PRESSURE TO SEAL.

Magni, G.

would be valuable to collect

Dr. Giovanni Magni

2

January 22, 1962

we have already discussed.

If you don't already have them, you will be interested in the following books - "Metabolic Pathways" (two volumes) by David Greenberg, Academic Press; "Handbook of Microbial Metabolites", from Pfizer, by Max Miller, published by Blakiston Division, McGraw-Hill, and a rather naive, but perhaps useful textbook "Chemobiodynamics and Drug Design" by Schueler published by McGraw-Hill. I would, of course be happy to get these books sent to you if this would be of any help, but I hesitate to attempt a possible duplication.

In discussing analogues of aromatic metabolites, I should have stressed that we have our own special interest in this metabolic area for two reasons. 1) That the corresponding genes are the best mapped and constitute the main linkage group so far in bacillus subtilis, and 2) that Kretchmer here is also very much interested in the metabolism of phenylalanine from the standpoint of the etiology and treatment of phenylketonuria. In fact, a drug that in some magical fashion could prevent the assimilation of phenylalanine would give us the most direct approach to treatment of this disease.

We were sorry to hear that Luca had to change his possible plans about visiting in March, but hope that some other occasion will arise. As he, if not we, may already have told you our definite plan for our Japan trip is now for the interval between April 7 and May 20. I hope you will also have been giving some thought yourself to your ultimate visit to Stanford.

Thank you very much for the leather gloves which fit me beautifully. I am still jealous of your ostrich skin and if you could sometime run into a pair of the same size, I would be very grateful for them - but please send me the bill for both pairs at that time.

With our best wishes,

As ever,


Joshua Lederberg

Joshua?