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Philip J. Migliore, M.D.
Chairman and Research Director
The Moran Foundation
Department of Pathology
Baylor College of Medicine
Houston, TX 77030

Dear Dr. Migliore:

I am writing this letter to report to you, and to the Scientific Advisory Committee of the Moran Foundation, on the status of my projects supported by The Foundation.

I- "Specific Diagnosis of Celiac Sprue by Immunohistochemistry and/or Immunofluorescence" (4-93-0068):

This project is still active. After inquiring from our clinical colleagues, we were told that they do not see many cases of this disease in the Houston area. Contact with colleagues in Europe, who have access to a good number of cases with celiac sprue, has been initiated. We hope to start receiving tissues and begin our experiments soon. We are hoping to conclude this project within the coming year, and the results will be reported in the next progress report.

II- " Biopsy-based prediction of stage and prognosis in colorectal cancer":

This project is concluded, with the exception of a small but significant part related to TGFB-RII as explained.

Results of the studies on biopsies of human colon cancer are as follows:

p53, MDM2, and nm23-H1: Our results showed no correlation between the expression of any of these markers in pre-operative biopsies of colon cancer and stage or prognosis.

TGF-B1 and EGFR: There were technical problems that rendered the results useless. Specifically, there were nuclear staining in many of the cases, and nuclei should be negative for TGF-B1 or EGFR.

Transforming Growth Factor alpha (TGF-a): Significant results were obtained with this part of the study. These results are summarized in the following abstract, which was published in the Proceedings of the American Association for Cancer Research (1995, 36:629):

Predicting the outcome of patients with colorectal adenocarcinoma (CRCA) prior to surgery would be of help in selecting high-risk individuals who may benefit from pre-operative adjuvant therapy. We studied the expression of TGF α in preoperative biopsies of 106 patients with CRCA, who had at least 5 years follow-up, using an anti-TGF α monoclonal antibody and utilizing the ABC immunoperoxidase technique. For survival analysis, we used the actuarial survival method and the Log Rank test for statistical significance. CRCA with low TGF α expression (less than 25% of the tumor cells immunoreactive for TGF α) had a significantly poorer survival than those with high TGF α expression ($p=0.0412$). After excluding from analysis biopsies showing mucinous or poorly differentiated CRCA, known predictors of poor prognosis, the results remained significant ($p=0.0289$). It is concluded, therefore, that low or absent expression of TGF α in pre-operative biopsies of patients with CRCA, as detected by immunohistochemistry, is a significant predictor of a worse outcome.

This was presented as a platform presentation at the annual meeting of the American Association for Cancer Research in Toronto, Canada, in March of this year (1995). The Moran Foundation support was acknowledged in the title slide. The manuscript is in preparation, and the support of The Moran Foundation will also be acknowledged in the paper.

TGFB-RII:

Our results show that only 3 of 100 cases of colon cancer were positive for TGFB-RII. Initially we were disappointed with this negative result (low expression), because no statistically significant correlation with stage or prognosis could be done. However, with the recent publication in Science about loss TGFB-RII gene in 20% of adenocarcinomas of the right colon, we think that our findings should be of interest to investigators in the field, and should be submitted for publication. The authors concluded that since TGFB-RII stimulation or binding by TGF-B inhibits the growth of cancer cells, then the loss of expression of this receptor may have an important role in the evolution of these cancers. Our finding of absent TGFB-RII expression in 97% of our colon cancer biopsies does not seem to agree with that assumption. We decided to support our findings by investigating TGFB-RII expression in frozen sections of 100

resected carcinomas and 20 normal or inflamed colons, and correlate the expression with cell type (epithelial or non-epithelial), histology (cancer, normal colon, inflammatory bowel disease), and also with the site of carcinoma (right side vs. left side). The results then will be submitted for publication, and The Moran Foundation support will, of course, be acknowledged.

Thank you for your support

Sincerely,

Mamoun Younes

Mamoun Younes, M.D.
Assistant Professor