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TO: Philip J. Migliore, M.D.
Research Director, The Moran Foundation

SUBJECT: Progress Report for The Moran Foundation Project
"A knockout mouse model for the study of tumor suppressor activity of the C/EBPα gene."
Principal Investigator: Gretchen J. Darlington, Ph.D.

DATE: September 24, 1997

The Specific Aims for the proposal submitted to The Moran Foundation in 1996 were the following:

Specific Aim 1, to rescue the liver specific defects in the knockout animals. The application proposed two methods for replacing expression of C/EBPα in the liver of transgenic animals. We have completed these studies and have successfully generated a transgenic line containing C/EBPα under the direction of the albumin promoter. These transgenic animals express C/EBPα in the liver. The transgenic animals have been crossed back into the C/EBPα deficient mouse line. The phenotype of the C/EBPα knockout animals containing the albumin C/EBPα transgene, is as predicted. That is, the viability of the animals through the perinatal period is greatly increased. This animal model will enable us to examine the effects of loss of C/EBPα in other tissues than the liver. We will also be able to examine the effects of C/EBPα deficiency in animals of older age. To date, we have had animals survive for as long as 8 weeks carrying the transgene. Thus, the Specific Aim 1 has been completed successfully. We are currently preparing a manuscript describing the phenotype of the older knockout animal which is highly interesting in that the animals fail to develop white adipose tissue.

Specific Aim 2 was to characterize the cell types involved in the abnormal growth in the liver and lung in order to determine the cell type that is responsive to the loss of C/EBPα growth suppression. We are currently continuing these studies and are carrying out histologic analysis of these two tissues in the newly generated mouse model described above. These studies are ongoing and will be completed within the next few months. To date, we have seen abnormal proliferation in the liver but no tumor formation.

The Moran Award enabled our laboratory to conduct pilot experiments to generate an animal model system that will provide a new approach to analyzing the role of nuclear transcription factors of the C/EBP family. I am very grateful for The Moran support which came at a critical time for my research program. The data gathered with the support of The Moran Foundation has enabled me to apply for additional Federal funding which will support long-term studies of this mouse model.

Sincerely,

Gretchen Darlington

Gretchen J. Darlington, Ph.D.
Professor of Pathology, Cell Biology and Molecular Genetics

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