

**9th ANNUAL DEPARTMENT OF PATHOLOGY YOUNG INVESTIGATORS' DAY
POSTER SESSION**

Thursday, April 5th, 2007

TURNER CONCOURSE

REGISTRATION FORM

E-mail COMPLETED Registration form and abstract to:

Stacey Morgan (smorgan9@jhmi.edu) on or before

Friday, March 16th, 2007

If you have questions or problems regarding your submission, please contact Stacey Morgan via e-mail (smorgan9@jhmi.edu)

Applicant's Name: _____ YEN-CHUN LIU _____ Degree: ___MD___

Applicant's Division: _____ Pathobiology Graduate Program _____

Faculty Preceptor: _____ Chi.V.Dang _____
(Must hold a primary appointment in Pathology)

Appointment Category: _____ House Staff _____ Clin Fellow _____ Research Fellow
_____ Medical Student _____ Graduate Student X (Program:Pathobiology)

Register for: _____ Clinical Research _____ Translational Research ___X___ Basic Research

Full Poster Title *

Coupling Control of Cell Proliferation and Nucleotide Metabolism through MYC, E2F1 and their Target Genes

Where has the work been presented?

Meeting Name _____

Meeting Date _____

Not Previously Presented _____ X (AACR 2007 , LA) _____

Where is this work being published? _____

Journal Name, Volume, Page, Date _____

In Preparation _____ X _____

Author(s) (First & Last) _____ Yen-Chun Liu, Chi.V.Dang _____

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***INCLUDE A ONE-PAGE ABSTRACT (including title and all authors) OF THE WORK YOU WILL BE PRESENTING**

Coupling Control of Cell Proliferation and Nucleotide Metabolism through MYC, E2F1 and their Target Genes

c-Myc and E2F1 are two key transcription factors that are involved in tumorigenesis by activating target genes involved in cell cycle progression and cell death. We recently identified target genes common to Myc and E2F1 by chromatin immunoprecipitation (ChIP) coupled with pair-end ditag sequencing analysis (ChIP-PET), computation and microarray expression studies in a MYC-inducible model of human B lymphoid tumor. We found genes, which are putatively regulated by the Myc-E2F1 transcriptional network, encoding enzymes involved in both purine and pyrimidine metabolism. Subsequent ChIP experiments with quantitative PCR characterized direct MYC and E2F1 binding to the promoter and/or first intron region of these target genes. The expression of these genes could be induced by increased MYC level but not all of them responded to decreased E2F1 level in the E2F1 knockdown study. Hence, despite of the direct binding of these two transcription factors, gene expression regulation among the nucleotide metabolism genes varies. We focused on inosine monophosphate dehydrogenase 2 (IMPDH2) involved in de novo purine synthesis and dihydroorotate dehydrogenase (DHODH) involved in pyrimidine synthesis, since overexpression of IMPDH2 appears to be a common feature in human malignancies and both enzymes have known small molecule inhibitors available for loss-of-function studies. Mycophenolic acid (MPA) inhibits IMPDH, causing S phase cell cycle arrest and delayed cell apoptosis in Myc-overexpressing B cells. On the other hand, significant cell death instead of cell cycle arrest was found by inhibiting DHODH with leflunomide. The fact that the end nucleotide product (guanosine or uracil) of each pathway could rescue both phenotypes demonstrated the specificity of the inhibitory effects. Presumably, differences in nucleotide pool depletion by the specific inhibitors led to significantly different phenotypes. To determine the potential therapeutic role of these inhibitors, we studied mycophenolic mofetil, a prodrug of MPA, and found that it significantly inhibited tumorigenesis in the P493 human B lymphoid tumor xenograft model. Since efficient nucleotide synthesis is critical to dysregulated tumor cell growth, these results link transcriptional regulation of nucleotide metabolism by factors central to tumorigenesis to small molecule inhibitor and provide a solid base for potential cancer therapy targeting the nucleotide metabolism pathways in cells with dysregulated Myc or E2F1 transcriptional networks