Summary for Office of Rare Disease, NIH
FASEB Summer Research Conference on Biological Methylation

Dr. Dennis Vance chaired the first session "Greasy Methyltransferases" of the Biological Methylation Conference. The first speaker, Dr. Rene Jacobs discussed a fascinating phenotype in a homozygous mouse deficient in the liver-specific enzyme phophatidyl ethanolamine N-methyltransferase. This enzyme is responsible for the methylation of phosphatidyl ethanolamine (PE) to produce phosphatidyl choline (PC). When the *pemt -/-* mice are fed a choline-deficient diet, the mice develop non-alcoholic steatohepatitis (NASH), which tends to precede development of hepatocellular carcinoma, a rare cancer. The NASH liver phenotypes in the *pemt -/-* mice can be attributed to an increased ratio of PE/PC. Intriguingly, human patients with NASH also have an increased PE/PC ratio. Drs. Christine Hrcyna and Stephen Young talked about another class of greasy methyltransferases, the isoprenyl-cysteine methyltransferases (ICMTs). Using a chemical biology approach, Dr. Hrycyna identified new inhibitors of ICMT. Dr. Young presented exciting findings implicating the precursor of lamin A as the cause of phenotypes associated with the Hutchinson Gilford Progeria Syndrome, a rare disease resulting in accelerated aging phenotypes. His research reveals that farnesyl transferase inhibitors can prevent both the accumulation of prelamin A (which is isoprenylated and methylated, but is not completely processed to mature lamin A) and slow development of the progeria symptoms. ***Drs. Young and Hrycyna are now collaborating in order to test the effects of the ICMT-inhibitors in this system.***

The focus of talks in Session 3 was "Human Genetic Diseases that Affect Synthesis and Degradation of AdoMet." Each of the four speakers in this session spoke about rare diseases. Dr. James Finkelstein, the session chair gave a wonderful overview of the methionine cycle of metabolism; including enzymes required for remethylation of homocysteine and the trans-sulfuration pathway. Dr. Finkelstein discussed rare inherited genetic diseases in enzymes of these pathways including a fascinating discussion of the S-adenosylhomocysteine hydrolase deficiency. Despite the rarity of this deficiency, the topic is of great interest to the scientific community, because the hydrolase step is reversible, and so accumulation of homocysteine can also produce elevated levels of S-adenosylhomocysteine. Thus, the symptoms exhibited by the hydrolase patient provide insights into the effects of hyperhomocysteinemia, which is well known as being associated with adverse clinical outcomes. Dr. Zigmund Luca described human patients with inherited deficiencies in Glycine-N-methyltransferase. Because Glycine-N-methyltransferase is a major consumer of S-adenosylmethionine (AdoMet), these patient's symptoms derive from elevated levels of this metabolite. One of the interesting symptoms is mild hepatitis-like liver disease, which seems to depend on high levels of AdoMet, because other patients with hypermethioninemia do not manifest liver disease. ***This phenotype was especially interesting in light of the previous talk by Dr. Jacobs (Session 1). A lively discussion resulted at the end of this session regarding the implications that high AdoMet that may result from deficiencies in enzymes that represent major metabolic consumers of methyl-groups***!Drs. Corrales and Mato completed Session 3 by discussing how deficiencies in production of AdoMet (due to defects in methionine adenosyltransferase isozymes, MAT1A and MAT2A) can lead to development of liver cancer. AdoMet levels in livers of the MAT1A -/- mice are 25% of normal, and by eight months the animals exhibit steatohepatitus, and by 18 months the animals develop hepatocarcinoma. Proteomic analyses revealed mitochondrial respiratory abnormalities. There was much discussion about the mechanisms by which altered ratios of AdoMet/AdoHcy may influence liver disease and development of hepatocarcinoma.

In Session 7, Drs. Mario Fraga and Kathrin Muegge discussed the role of methylation and acetylation as post-translational modifications of histones. The global loss of monoacetylation and trimethylation of histone H4 is a common hallmark of tumor cells, including leukemia cells as compared to normal lymphocytes.

It is the policy of FASEB not to publish conference proceedings. This policy fosters an environment that encourages presentation of the newest results and hypotheses. A business meeting was held and plans were made to hold another Biological Methylation in the summer of 2008.