

Description of Research	<p>The Maclean lab studies the etiology and pathogenesis of cystathionine beta-synthase deficient homocystinuria (CBS DH), Down syndrome (DS) and Fragile X syndrome (FXS). All three of these conditions involve a component of cognitive impairment for which the mechanisms are unknown and current treatment is either lacking or non-existent. Our efforts focus a range of genomic, proteomic, biochemical, behavioral, genetic and molecular techniques upon mouse models of these diseases with a view towards delineating pathogenic mechanisms and the rational design of novel treatment strategies.</p> <p>With regard to CBS DH we have generated a novel transgenic mouse model of the disease and using behavioral analysis, hippocampal microarrays and proteomic analysis we have uncovered a number of novel pathogenic mechanisms that we have subsequently confirmed in human CBS DH tissue samples. This work has lead to the discovery of a novel treatment for CBS DH, for which a limited clinical trial will start at the Children's hospital in Denver in February 2009.</p> <p>In our work on DS we have used a number of behavioral tests to investigate the effects of choline supplementation upon cognitive function in the Ts65Dn mouse model of the disease. We have found that while perinatal treatment with choline is unable to improve the ability of these mice to form a conditioned taste aversion (a functional test of learning and memory in mice) this treatment does ameliorate attentional dysfunction. This work is now being extended into the use of anticholinesterase inhibitor drugs in pre-clinical studies using the Ts65Dn mouse model. In addition to this work, we have been involved in a collaborative project with Dr Kim Bjugstad's laboratory investigating the possible application of mouse neural stem cell therapy to improving cognition in Ts65Dn mice.</p> <p>Our studies on FXS have used behavioral and biochemical investigations of the FMRP1 knockout mouse model to investigate the hypothesis that aberrations in the hypothalamus-pituitary-adrenal axis HPA axis contribute to the clinical sequela observed in humans with FXS. We observed no significant changes in corticosterone or expression level/location of the glucocorticoid receptor as a consequence of knocking out the FMRP1 gene indicating that this is probably not a promising therapeutic avenue for this condition. Working in collaboration with Barbera Strupp at Cornell, we were able to show that the FMRP1 mouse does suffer from increased attentional dysfunction and is thus a suitable model for testing novel therapeutic strategies.</p>
Methodology	Genetics; Molecular and Cellular Biology
Clinical and special developmental populations	Developmental Disorders
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