# THE ROLE OF GENETIC BACKGROUND ON THE PHENOTYPIC SEVERITY OF THE OSTEOGENESIS IMPERFECTA MURINE (*OIM*) COL1A2 GENE MUTATION THROUGHOUT POSTNATAL DEVELOPMENT

Stephanie Carleton

Dr. Charlotte L. Phillips, Dissertation Advisor

## ABSTRACT

Osteogenesis imperfecta (OI) is a diverse disease of type I collagen, the main structural protein in the body. It has been well documented that related individuals harboring the same OI-causing mutation can have very different clinical outcomes. However, the relationship between genotype and clinical outcome remains unclear.

The goal of this study was to further examine the genotype-phenotype relationship with the long-term goal of identifying modifier genes that impact the quality of bone. Modifier genes influence clinical outcome by interacting with genes known to impact bone quality such as the type I collagen genes. As gene expression changes throughout development, we sought to determine if age-related changes in bone quality occurred. To this end, the same OI-causing mutation was studied on two genetic backgrounds, one with reduced bone strength (C57) and one with variable bone strength (outbred). Wildtype and *oim* animals of each strain were then analyzed at one, two and four months of age to assess bone shape and strength as well as biochemical parameters.

This work showed strain related differences at all ages examined, but the presence of the *oim* mutation overrides these differences. Bones from *oim* animals of either strain have altered bone geometry and reduced biomechanical strength as compared to wildtype, with C57-*oim* animals having a more severe phenotype than outbred *oim* animals. *Oim* animals also had altered mineral composition and reduced amounts of type I collagen, which were strain specific. Taken together, these data indicate a role for genetic background in determining phenotypic severity, although some parameters are more affected by genetic background than others.