Sex chromosome-modified mice and rats to identify factors causing sex differences in physiology and disease

Arthur P. Arnold[1], Xuqi Chen[1], Vincent R. Harley[3],
Melinda R. Dwinell[2], and Aron M. Geurts[2]

[1] Dept Integrative Biology & Physiology, UCLA, Los Angeles CA USA
[2] Dept Physiology, Medical College of Wisconsin, Milwaukee, WI, USA.
[3] Hudson Institute of Medical Research, Monash Medical Centre, Melbourne, Australia.

Novel therapies may result from improved understanding of sexually unequal factors that protect from or exacerbate disease. Two classes of proximate factors are root causes of phenotypic sex differences: gonadal hormones and sex chromosome genes. Sex chromosome effects on phenotypes have been uncovered in the last 20 years because of the advent of rodent genetic models that allow comparison of animals with the same type of gonad but with different sex chromosomes (e.g., XX vs. XY). The Four Core Genotypes (FCG) and XY* mouse models have led to the discovery of sex chromosome effects in many models of disease, including cardiovascular, autoimmune, metabolic, neural, and cancer.

The FCG mouse model involves deletion of the testis-determining gene *Sry* from the Y chromosome (making XY gonadal females) and insertion of an *Sry* transgene onto an autosome (making XX gonadal males). XX and XY mice with the same type of gonad differ in numerous disease phenotypes. When such a sex chromosome effect is discovered, it can be attributed to effects of X or Y genes using the XY* model, which compares XO vs. XX, XY vs. XXY, XO vs. XY, and XX vs. XXY. Finally, manipulation of the dose of individual X or Y genes establishes specific genes that are factors causing sex differences.

In the last 5 years, we have also manipulated *Sry* dose in laboratory rats, making XY and XXY gonadal females, and XX and XXY and XYY gonadal males. We introduced an *Sry* transgene onto an autosome, and used CRISPR-Cas9 to reduce the dose of *Sry*. The novel availability of these new rat models increases the number of species in which sex chromosome effects can be studied relatively easily, and will broaden understanding of the role of sex chromosome genes in disease.