The Long-legged mouse and the Impossible Hybrid – genome evolution in the mouse from molecules, stem cells to organisms

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The genome is in constant evolution. Despite this on-going change, the genome also has to maintain essential functions. Discovering the evolutionary process underlying genome evolution is thus a central goal in evolutionary genetics and medicine. I will discuss two studies, where we take a systems genetics approach to understand how the genome evolves in the mouse. First, I will present our novel approach of generating *in vitro* "crosses" in interspecific F1 hybrid mouse embryonic stem (ES) cells. By inducing mitotic recombinants with genome-wide random breakpoints, we have developed a simple tissue culture system that allows genetic mapping between the reference strain BL6 (mostly *Mus musculus domesticus*) and *M. castaneus, M. spretus* and *M. caroli* that span 1, 2 and 6 million years of divergence. I will discuss how we use *in vitro* recombination to generate "Impossible Hybrid" mouse stem cells and directly investigate which genetic changes underlie species differences. Next, I will discuss the "Longshanks mouse", a unique genetic resource created by Campbell Rolian at the University of Calgary. We combined whole genome sequencing, modelling and molecular genetics to dissect this mammalian evolve-and-resequence experiment. In a final section, I will also introduce haplotagging, a new technique invented by our group, which allows rapid, simple and low-cost generation of linked read sequencing libraries that match or surpass the leading commercial options. We anticipate haplotagging will enable genome assemblies at scale and population genomics projects involving hundreds to thousands of samples. I will showcase the novel biology enabled by haplotagging. Together, these studies illustrate our research program of identifying and mining these special systems in the mouse for their unique insights in our overall goal to link genotype to phenotype in an evolving genome.