1 in 400 people has a maternally-inherited mutation in mitochondrial DNA (mtDNA) potentially causing severe, incurable disease. MtDNA is exclusively maternally inherited and mutant and normal mtDNA co-exist in carrier women (heteroplasmy). The severity of the disease in their offspring depends on the proportion of abnormal mtDNAs that they inherit.

Families who have had a child die of severe, maternally-inherited mtDNA disease need reliable information on the risk of recurrence in future children. However, prenatal diagnosis and even estimates of risk are fraught with uncertainty because of heteroplasmy. This results in a mtDNA bottleneck, whereby unpredictable fluctuations in the proportions of mutant and normal mtDNA may arise between generations. We demonstrated that in humans, significant fluctuations are already apparent in oocytes in both controls and carriers of mtDNA disease.

In "Mitochondrial donation" disabled mitochondria are replaced with healthy ones in early human development using nuclear transfer. We are testing whether non-invasive alternatives can be used, notably activating autophagy, a cellular quality control mechanism, in which damaged cellular components are engulfed by autophagosomes.

Using mice that are transgenic for fluorescent LC3 (the hallmark of autophagy) we quantified autophagosomes in cleavage stage embryos. We confirmed that this reaches a maximum in 4 cell embryos and are correlating it with mtDNA copy number.

Following up our results showing that mtDNA mutants are specifically eliminated from cultured fibroblasts under energetic stress by mitophagy (mitochondria-specific autophagy) {Diot, 2015 Pharmacological Research} we hypothesise that modulating heteroplasmy by activating mitophagy may be a useful complement to mitochondrial replacement therapy.