Enhancing mitochondrial DNA fidelity to improve mammalian lifespan and healthspan

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Animal mitochondrial DNA (mtDNA) has a higher substitution rate than nuclear DNA, with the accumulation of mtDNA mutations being one of the hallmarks of ageing. This discrepancy in the rates of evolution is partially due to the lack of mismatch repair activities in the mitochondria. Octocorals – a group of cnidarians – have a reduced rate of mitochondrial evolution and encode a MUTS-like protein (mt-MutS) in their mtDNA. Previous analyses suggested that this enzyme was acquired from a virus and has been universally retained among octocoral taxa. Its function, however, remains unknown. The project will combine comparative, structural, and experimental approaches to investigate the function of mt-MutS and to test whether mt-MutS expression results in lower mutation rates in mtDNA and improve heath in ageing. Comparative analysis of octocoral mtDNA will be used to identify distinct mutation patterns among its lineages and correlate them with the changes in mt-MutS. Partial mt-MutS sequences will be used to identify clades with unusual or accelerated rates of mtDNA evolution for additional sampling. Site- and taxa-specific evolutionary rates in mt-MutS will be analyzed to infer functional and structural constraints and to optimize the choice of the mt-MutS for transgenesis. Ancestral sequences of mt-MutS for the nodes of interest will also be reconstructed and analyzed. A structure-function approach will be utilized for in vitro dissection of mt-MutS functions. The full-length proteins from several species and a reconstructed ancestral sequence will be tested for stability and for amenable structure determination. Isolated domains will also be used for high-resolution structural analysis by diverse biophysical techniques to probe molecular details of binding and nuclease activity for understanding and improving function. Finally, we will generate transgenic mice that express a mitochondrially-targeted version of this optimized mt-MutS enzyme to test its effects on mtDNA mutation rate. The transgene construct will be knocked-in to mice by directed Easi-CRISPR template repair or BAC-transgenesis. mtDNA mutation rate analyses in wildtype and mice with enhanced mitochondrial mutation rates will be undertaken. An ageing study on mice expressing mt-MutS will determine if enhanced mtDNA fidelity can positively affect organismal lifespan and healthspan.

The research team:

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Open positions in the MACKERETH group:

Postdoc (Structural Biology, Biochemistry) - starting November 2019, duration 24-30 months
Technician/Engineer (Molecular Biology, Protein Expression) – starting November 2019, duration 24 month

Interested candidates should send a curriculum vitae and the contact information for two referees to cameron.mackereth@inserm.fr before 31 July 2019.