Biological effects of the loss of homochirality in a multicellular organism

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Homochirality is a fundamental principle of all living organisms. Accordingly, biomolecules occur in only one chiral form, L-amino-acids in proteins and D-sugars in DNA/RNA. While D-amino acids are thought to be non-proteinogenic, pieces of evidence demonstrate that proteins can undergo spontaneous chiral post-translational modifications under conditions of stress and ageing, leading to homochirality loss. Despite its pivotal importance for life, the biological and pathological consequences of homochirality loss remain to be elucidated.

Combining interdisciplinary chiral-selective techniques with genetic, cellular and biochemical approaches we identified novel heterochiral protein motifs that accumulate in Protein-L-isoaspartate (D-aspartate) O-methyltransferase mutant (*Pimt KO*) chiral-deficient animals. We show a direct link between D-amino acids and protein dysfunction in vivo, which in turn promotes a progressive 'heterochirality syndrome', through a cascading effect across biological scales spanning from loss of molecular homochirality to increased resistance to caspase activity, increased tumour susceptibility, and shortened lifespan (Previously published in: Banreti et al. (2022) Nat Commun 18, 13(1):7059).

Our recent advances broaden our understanding of the underlying molecular and cellular mechanisms connecting heterochirality to biological sequelae.