Preclinical development of a novel gene-based therapy for alkaptonuria

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Alkaptonuria (AKU) is a rare disorder of the tyrosine degradation pathway that qualifies for gene therapy due to a deficient homogentisate 1,2-dioxygenase (HGD) enzyme. AKU stops patients' bodies from breaking down the tyrosine-derivative homogentisic acid (HGA) that the body naturally produces during the digestion of food. HGA builds up in the body and, over time, leads to black and brittle bones and cartilage, and early onset osteoarthritis. NTBC, a potent inhibitor of the key enzyme 4-hydroxyphenylpyruvate dioxygenase (HPD), is undergoing clinical trial as potential treatment for AKU patients. Although NTBC ameliorates the biochemical deregulation, it leads to tyrosine accumulation in the blood associated with debilitating side-effects. In this PhD project, Sien undertakes a Darwinian approach to overcome the current therapeutic limitations by developing the best possible gene therapy strategy to cure AKU and study its efficiency in human cell models and mice. First, Sien applies directed protein evolution to drastically improve the catalytic activity of HGD (eHGD) in order to reach therapeutic efficacy without the use of high viral titers. Second, she investigates whether combination therapy of eHGD with NTBC further improves the therapeutic outcome. To achieve this, eHGD is co-expressed with an NTBC-insensitive HPD enzyme variant (HPDΔNTBC). This not only corrects the metabolic defect inflicted by the disease, but also removes the drug side-effects of NTBC.

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