GENETICALLY ENGINEERED PROBIOTIC *E. COLI* NISSLE TO CONSUME AMINO ACIDS ASSOCIATED WITH ORPHAN METABOLIC DISEASES

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Orphan metabolic diseases are rare genetic defects that interfere with metabolism due to ineffective or missing enzymes. Two of them, Phenylketonuria (PKU) and Maple Syrup Urine Disease (MSUD) are defined by accumulation of amino acids to toxic levels due to defective metabolism of protein break down products. PKU is caused by a defect in the gene encoding phenylalanine hydroxylase (PAH). MSUD is caused by a defect in a multi-enzyme complex found in mitochondria called branched chain α-ketoacid dehydrogenase "BCKDH". Without the activity of these enzymes, the amino acid phenylalanine (Phe) in the case of PKU or the branched-chain amino acids leucine (Leu), isoleucine and valine for MSUD build up to neurotoxic levels in the blood and brain, leading to neurological deficits. Current treatment options focus on dietary protein restriction, are insufficient and, unfortunately, can lead to a failure to thrive. Lifelong compliance with a prescription diet is also a concern. We have genetically engineered Nissle, a probiotic strain of E. coli, to reduce serum phenylalanine and leucine levels in patients with PKU or MSUD; preclinical data supporting the activity of these strains are described.