

Commentary

## New approaches to treat PKU: How far are we?

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Exactly 50 years after Bickel et al. [1] initiated dietary treatment by phenylalanine restriction clinicians and researchers worldwide are still searching for an alternative approach to the treatment of phenylketonuria (PKU). Today we know that maintaining the restricted diet is beneficial if not essential to prevent brain damage, but there are still disagreements as to how long this diet should be continued. A number of nutritional products with improved quality are available in most countries, but many adolescents and young adults generally do not comply with the recommendations for monitoring and control of phenylalanine concentrations [2], and two thirds of pregnant women in the United States did not follow the diet before becoming pregnant [3]. There is a need for an alternative approach to the treatment of PKU.

As for many other inherited metabolic disorders, somatic gene therapy for PKU offers hope for the future. The paper by Ding et al. published in this issue of *Molecular Genetics and Metabolism* summarizes the present knowledge of different strategies in PKU gene therapy. With the help of the recently available animal models for PKU and hyperphenylalaninemia [4] it became possible to test different gene transfer vehicles, however, the reality is quite different from what had been expected. Both, liver phenylalanine hydroxylase (PAH) gene transfer in vitro and in vivo, as well as autologous non-hepatic gene targeting attempts failed due to poor efficiency of gene delivery and/or lack of essential cofactor tetrahydrobiopterin (BH<sub>4</sub>). The final statement by Ding et al. is rather sobering: "... despite different non-viral and viral gene transfer approaches that have been examined, none of them seems to hold

great promise for future clinical trials until an appropriate gene transfer vector is designed."

A totally different approach to the treatment of PKU is phenylalanine degradation with recombinant phenylalanine ammonia lyase (PAL), a non-mammalian enzyme that degrades phenylalanine [5]. In *Pah<sup>enu2</sup>* mouse both i.p PAL injection and oral administration lowered plasma phenylalanine concentrations and genetically engineered *Lactococcus lactis* for expressing PAL was used successfully to treat hyperphenylalaninemia rats [6]. Although it is still a long way to first clinical trials in humans, this approach seems to be somewhat more promising.

While still facing technical difficulties to replace the defective gene and/or enzyme, one new approach to treat at least some PKU patients seems to be a close reality. A relative high percentage of patients with mild PKU may benefit from substitution with BH<sub>4</sub> in that oral administration of the natural cofactor for PAH reduce their plasma phenylalanine levels [7]. BH<sub>4</sub> can obviously activate the specific mutated PAH by either increasing the affinity for BH<sub>4</sub>, by three-dimensional structure stabilization, or by its chaperon-like activity. It has been shown that a number of mutations correlate with BH<sub>4</sub> responsiveness [8] and a number of patients with mild PKU or hyperphenylalaninemia are presently on BH<sub>4</sub> treatment without the low-phenylalanine diet [9]. The main disadvantage of this approach is the relative high costs of BH<sub>4</sub> and enabling regulations in some societies.

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