

Editorial

## Five years of synergistic scientific effort on phenylketonuria therapeutic development and molecular understanding

From March 1st to the 4th of 2005, 85 top phenylketonuria (PKU) researchers from 13 countries in academia, hospitals, and industry gathered on a Caribbean cruise ship for 4 days to discuss the past, present, and future efforts on PKU. The ship's name "Imagination" was very fitting for the name of the conference, since imagining the future of PKU, with the possibility that  $\text{BH}_4$  may soon change the face of treatment for some families, was what it was all about.

Approximately 1 in 10,000 Caucasians are born with PKU or the milder form, hyperphenylalaninemia (HPA). Most forms of PKU and HPA are caused by mutations in the phenylalanine hydroxylase gene, resulting in a non-functional enzyme that in turn leads to an accumulation of the L-phenylalanine (L-Phe) substrate in blood and brain. Over 400 disease-causing mutations have been identified in patients with PKU or HPA (<http://www.pahdb.mcgill.ca>). Scientific talks and discussions at this historical meeting focused on the basic science behind PKU and therapeutic options under development to assist in the management of the disorder. In particular, there was a great deal of open discussion surrounding the use and molecular effects of tetrahydrobiopterin ( $\text{BH}_4$ ).

Somewhat surprisingly but now better understood, a significant number of PKU patients respond to an oral ingestion of  $\text{BH}_4$  with a lowering in their plasma L-Phe levels. These observations have been in place for many years. However, until the publication by Kure et al. (*J. Pediatr.* 135 (1999) 375–378), not much attention was paid to these phenomena. Following the report in 1999, many other cases from Europe quickly appeared and greatly accelerated this line of discovery. A database that contains a current listing of the  $\text{BH}_4$ -responsive genotypes has now been established at <http://www.bh4.org>. Several possibilities have now been put forward to explain the  $\text{BH}_4$  response in mild PKU: (i) a decreased affinity of the mutant PAH for  $\text{BH}_4$ ;

(ii) stabilization of the active tetramer/dimer forms of the mutant proteins and protection from proteolytic cleavage, i.e.,  $\text{BH}_4$  can act as a chemical chaperone preventing misfolding and subsequent ubiquitin-dependent proteosomal degradation; (iii)  $\text{BH}_4$ -induced change in  $\text{BH}_4$ -biosynthesis; and (iv) PAH mRNA stabilization, as shown for nitric oxide synthase. From the meeting, it was clear that  $\text{BH}_4$  responsiveness is a multi-faceted mechanism, with the chaperone folding affect being a significant contributor.

Of particular importance with the group of researchers who attended this landmark Caribbean meeting, is the teamwork and open communication that has allowed for these approaches to be fully pursued and understood in rapid fashion. The end results of these synergistic and open communications will benefit the patients and families with PKU. Although  $\text{BH}_4$  is proving to be one approach the field has rallied behind, other efforts from enzyme replacement therapy to gene therapy are on the horizons. With an improved understanding of PKU in general, these other efforts will benefit significantly. With ongoing efforts, we will one day get to the point of seeing all patients with PKU having treatment options. In this special issue of Molecular Genetics and Metabolism, the scientific findings of the PKU-related research presentations of the meeting are described in detail. As guest co-editors of this issue of MGM, we are very grateful to the active participants of the meeting, authors in this special issue, and the financial support of BioMarin Pharmaceuticals, all who contributed significantly to a very successful and critically important meeting.

Nenad Blau  
Richard Koch  
Reuben Matalon  
Raymond C. Stevens

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