Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2015-2016

Project Nº 33

Title: Stabilization and cerebral and hepatic localizations of a fusion protein of the aminolevulinate dehydratase for early treatment of acute attacks in hepatic porphyrias.

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Summary

Acute porphyrias are rare genetic diseases caused by reduced activity of the specific enzymes of the heme synthesis pathway[1]. The dominant clinical feature is life-threatening neurovisceral attack when hepatic heme synthesis is activated by endocrine or environmental factors. Acute attacks are associated with serum accumulation of neurotoxic porphyrin precursors (aminolevulinic acid, ALA, and porphobilinogen, PBG) of hepatic origin[2].

The aim of this project is the development of a fusion protein of aminolevulinate dehydratase able to metabolize the neurotoxic ALA compound, accumulated in serum during the acute attack. The advantages over current therapy (repeated intravenous administrations of hemin) were: (i) it can be administered subcutaneously by the patient himself when the first signs of acute attack appears, (ii) increased half-life and (iii) it acts simultaneously in the three compartments involved in porphyric crises: serum, liver and nervous system. We will evaluate the pharmacokinetic and pharmacodynamic properties of the fusion protein when administered intravenously and subcutaneously in a mouse model of porphyria[3]. Next, we will assess the therapeutic efficacy of the fusion protein for the early treatment of porphyria attacks in the murine model of acute porphyria. Finally we will analyse the ability to cross the blood-brain barrier and the protective effect on the neurological abnormalities observed in the AIP mouse model.

References

1.-Anderson, K. E., J. R. Bloomer, et al. (2005). "Recommendations for the diagnosis and treatment of the acute porphyrias." Ann Intern Med 142(6): 439-50.

2.- Unzu, C., Sampedro, A., Mauleon, I., Alegre, M., Beattie, S.G., de Salamanca, R.E., Snapper, J., Twisk, J., Petry, H., Gonzalez-Aseguinolaza, G. et al. (2011) Sustained enzymatic correction by rAAV-mediated liver gene therapy protects against induced motor neuropathy in acute porphyria mice. Mol Ther, 19, 243-50.

3.- Lindberg, R.L., Porcher, C., Grandchamp, B., Ledermann, B., Burki, K., Brandner, S., Aguzzi, A. and Meyer, U.A. (1996) Porphobilinogen deaminase deficiency in mice causes a neuropathy resembling that of human hepatic porphyria. Nat Genet, 12, 195-9.

POSSIBILITY OF PhD

NO

* (PhD grant required)