New drugs for the treatment of primary Hiperoxaluria (PH-1)

Resumen: Primary hiperoxaluria (PH-1) is a human genetic disease consisting on a deficiency of alanine-glyoxylateaminotransferase (AGT) activity in hepatocytes. This enzyme metabolizes glyoxylate and a lack of its activity leads to an excessive production of oxalate. Oxalate accumulation damages kidney and liver functions at first and other tissues and organs later. This disease is lethal and no effective pharmacological treatment exists nowadays; renal and hepatic transplants become necessary to preserve the life of the patients. Several mutations on AGT gene, leading to protein misfolding that avoids enzymatic activity, have been described as responsible for this disease. Our objective in this project is to develop an effective treatment for PH-1, based in a strategy of pharmacological stabilization of AGT. This novel approach is the state of the art for protein misfolding, and it is based in the use of pharmacological chaperones to recover protein active conformation. In this Memory we include the design, synthesis and biological evaluation of a series of chaperones for AGT. The synthesis has been designed following a Diversity Oriented Synthesis-like scheme, based on the knowledge of the recently described enzyme active site and it is an application of the skills that the applicant acquired during her postdoctoral stay at Cambridge University (UK) as a Marie Curie IEF-Fellow. The project is a multidisciplinary approach with a synthetic chemical part to be developed at the University of Granada, where the applicant is Assistant Lecturer, and a biological part to be developed during short stays at the University of La Laguna (Canary Islands, PH-1 endemic zone) in collaboration with Prof. Eduardo Salido, a specialist in PH-1. The project deals with a topic of interest in European Research as it faces the treatment of an orphan disease that is endemic in some regions of Europe, and it meets a part of the therapy not fully covered by the pharmaceutical industry

Objetivos: Primary hiperoxaluria (PH-1) is a human genetic disease consisting on a deficiency of alanine-glyoxylateaminotransferase (AGT) activity in hepatocytes. This enzyme metabolizes glyoxylate and a lack of its activity leads to an excessive production of oxalate. Oxalate accumulation damages kidney and liver functions at first and other tissues and organs later. This disease is lethal and no effective pharmacological treatment exists nowadays; renal and hepatic transplants become necessary to preserve the life of the patients. Several mutations on AGT gene, leading to protein misfolding that avoids enzymatic activity, have been described as responsible for this disease. Our objective in this project is to develop an effective treatment for PH-1, based in a strategy of pharmacological stabilization of AGT. This novel approach is the state of the art for protein misfolding, and it is based in the use of pharmacological chaperones to recover protein active conformation. In this Memory we include the design, synthesis and biological evaluation of a series of chaperones for AGT. The synthesis has been designed following a Diversity Oriented Synthesis-like scheme, based on the knowledge of the recently described enzyme active site and it is an application of the skills that the applicant acquired during her postdoctoral stay at Cambridge University (UK) as a Marie Curie IEF-Fellow. The project is a multidisciplinary approach with a synthetic chemical part to be developed at the University of Granada, where the applicant is Assistant Lecturer, and a biological part to be developed during short stays at the University of La Laguna (Canary Islands, PH-1 endemic zone) in collaboration with Prof. Eduardo Salido, a specialist in PH-1. The project deals with a topic of interest in European Research as it faces the treatment of an orphan disease that is endemic in some regions of Europe, and it meets a part of the therapy not fully covered by the pharmaceutical industry

Impacto: To establish collaborative research for the discovery of a PH-1 treatment, encourage research on orphan diseases, develop new DOS methodologies and supply new molecular libraries for biological screening

2 Participantes

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Presupuesto: 4,500,000.00

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