CIC bioGUNE
Biozientzietako Ikerkuntza Kooperatiboko Zentroa
Centro de Investigación Cooperativa en Biociencias

PRESS RELEASE

One of our groups opens the way to combatting dermatological disorders associated with Gunther's disease

- *The prestigious scientific journal PNAS has published a study from Dr. Oscar Millet's group, in collaboration with the University of Bordeaux, which shows that drugs can be used to fight this extremely rare disease.*

- *Gunther's disease is a metabolic disorder that affects less than 300 people worldwide, attacking their blood system, skin and eyes and even causing skeletal deformations.*

- *This study has shown that a stability defect in the enzyme uroporphyrinogen III synthase is responsible for the two known types of this disease.*

(Bilbao, October 2013).- Gunther's disease is considered to be an extremely rare disease, affecting some 200 to 300 people worldwide. It is one of the most aggressive disorders in the porphyria “family”, a heterogeneous group of metabolic diseases classified on the basis of the enzyme affected, and can cause painful erosions and continual scarring of the skin.

After several years investigating a number of ways to combat this disease, around three years ago the research group led by Dr. Oscar Millet at the Center for Cooperative Research in Biosciences (CIC bioGUNE) patented a novel system that can help to alleviate its symptoms. Now, Dr. Millet's group, in collaboration with researchers from the University of Bordeaux, has made further progress in this field by publishing their finding that inhibition of a cell mechanism for eliminating proteins helps to combat the dermatological problems associated with this disease in the prestigious journal PNAS.

Gunther's disease, which is how congenital erythropoietic porphyria is more commonly known, is a rare haem-group metabolic disease that aggressively attacks

the blood system, skin and eyes and even causes skeletal deformations. The metabolic problem caused by this disease is associated with a loss of activity of the enzyme *uroporphyrinogen III synthase (URO-synthase)*, and the majority of symptoms reported in patients are partly related to the low residual activity of this enzyme.

According to Oscar Millet, “our group has spent many years investigating the molecular basis of this disease. One of our most important findings is the phenomenon known as *stability defect*, which means that the mutation destabilises the enzyme and may prevent it from working properly.”

In a previous study, Millet's group discovered that inhibition of the proteasomal route, one of the pathways by which proteins are eliminated from the cell, allows protein levels to be re-established and some degree of enzyme activity to be recovered. The study published recently in PNAS has gone one step further by showing that, in mice, this inhibition may be a specific target that allows the dermatological problems associated with this disease to be controlled.

The results of this research at CIC bioGUNE are relevant for three reasons. Firstly, this study by Millet's group opens up new ways to combat Gunther's disease using drugs by establishing a link between pharmacological activity in higher animals and an improvement in disease-related symptoms.

Moreover, this research suggests possible new strategies for combatting this disease. “As the main problem is enzyme stability, we consider that future studies could be aimed at developing a molecule that binds to the protein to stabilise it, thereby obtaining better results in the treatment of this disease”, states Dr. Millet.

Finally, this study has shown that the tests undertaken with the two most common mutations (C73R and P248Q) responsible for congenital erythropoietic porphyria provide similar results, thereby confirming that the *stability defect* concept is generalised.

The origin of the disease

The proteins and metabolites used by cells to undertake their key functions are synthesised by the human body rather than being ingested. This synthesis is the result of a complex manufacturing process in the body involving a chain of enzymes that are responsible for transforming some molecules into others until the target molecule is obtained. The enzyme URO-synthase, the malfunction of which causes Gunther's disease, is essential for the correct formation of certain molecules responsible for oxygen transport.

“If this enzyme fails, the chain stops at this specific point. The substrate for this enzyme is very unstable and spontaneously decomposes into another compound that accumulates in the body. There is no way of getting rid of this compound. Consequently, if a person has a deficiency in this enzyme, this creates a blockage in the natural pathway and the build-up of a catabolite, thus causing the disease”, notes Dr. Oscar Millet.