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# CIC bioGUNE patents a new system to treat Günter's disease

- *Formally known as congenital* erythropoietic porphyria*, it is the most aggressive variant of porphyria. It is degenerative, with no available treatment.*

- *The project, led by Dr. Oscar Millet, could lead to a new drug which helps to improve the quality of life for patients with this disease.*

(*Bilbao, November 2010*). CIC bioGUNE, the Centre for Cooperative Research in Bioscience, has patented a new system that can help alleviate the symptoms of a rare, aggressive disease, congenital *erythropoietic porphyria*, more commonly known as Günter's disease. The Centre is examining the possibility of developing a new drug that improves the quality of life of patients suffering from this disorder.

Congenital *erythropoietic porphyria*, or Gunther's disease, is considered an extremely rare disease (200-300 cases worldwide), and one of the most aggressive within the porphyria 'family'. Porphyria is a heterogeneous group of metabolic diseases with different variants, depending on the enzyme that is damaged. There is no effective treatment to manage this disease.

The key to the understanding of this disease lies in elucidating the controlling mechanism of heme biosynthesis. Heme is a molecule which, among other functions, has the property of carrying oxygen in the blood. The **heme group** is a prosthetic group that is a part of several proteins, such as haemoglobin. Haemoglobin is found in the erythrocytes in the blood, whose function is to store and transport molecular oxygen from the lungs to the tissues and carbon dioxide from the peripheral tissues to the lungs. The heme groups are responsible, for example, for the red colour of blood.

The heme group is not ingested in food but rather it is synthesized. This synthesis is the result of a complex production process executed by a chain of enzymes whose function is to transform certain molecules into other molecules, until eventually the heme group is produced. If just one element in this chain, one enzyme, fails, it is enough for the entire production of heme to be altered.


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The production of heme group is important for normal functioning of the human body; its lack causes serious symptoms, such as haemolytic anaemia, as the sufferer cannot absorb iron necessary for oxygen capture. Depending on which enzyme fails in the heme production chain, the result is a type of porphyria, manifesting itself as a more or less aggressive disease variant. Günter's disease is the most acute variant of all those in the porphyria family.

The enzyme involved in this disorder, *uroporphyrinogen III synthase* (UROIIIS), is the subject of the study led by Dr. Oscar Millet's laboratory in CIC bioGUNE.

"If the enzyme fails, the chain stops at that specific point. The substrate of this enzyme is very unstable and spontaneously breaks down into another compound which accumulates in the body. There is no way to get rid of it. When you are deficient in this enzyme, there is an impediment in the natural route and a harmful catabolite accumulates", said Dr. Oscar Millet, manager of the project patented by CIC bioGUNE.

The symptoms of this disease are already present in the first months of life. The first warning sign is the red colour of the babies' urine, followed by an extreme sensitivity to sunlight which, from early childhood, manifests itself as skin lesions on the exposed areas. Repeated erosions and scarring may end up causing epidermal atrophy, scleroderma, bone and cartilage retractions and destruction, most pronounced on the face and hands.

Dr. Millet proposes to partially inhibit the enzyme (*porphobilinogen deaminase*) preceding the one affected in the chain, so that without breaking the still working part of the route, the toxic catabolite accumulation is reduced.

"What we propose is the partial inhibition of the preceding enzyme so the catabolite does not accumulate. The aim is to regulate the chain at a previous step, before the failing enzyme, without affecting the preceding enzymatic chain and so producing the least possible disturbance in the system", says Oscar Millet.

"In short, the aim is to turn Günter disease into a less aggressive form of porphyria (acute intermittent porphyria), which should improve the quality of life for the patients suffering from this disorder", concludes Millet.

CIC bioGUNE continues to work on the next phase of this project to develop what is now an inhibitor into a potential drug. If the *in vitro* tests with some of the inhibitor molecules are successful, and they can demonstrate that there is also an *in vivo* inhibition, the project would enter into the possible drug development phase. The development of such a drug should help to alleviate some of the more aggressive effects of this disease.


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