GENE THERAPY AGAINST RETINOSIS PIGMENTARY
TERAPIA GÉNICA CONTRA LA RETINOSIS PIGMENTARIA

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For many years, pigmentary retinosis has been one of the lesser known eye pathologies and only when we began to understand it we learned of its complexity, derived from the diversity of mutations which can cause the disease and the different progression in its progress, which makes it very difficult to predict when it will express a more severe form.

As with many other pathologies, one of the hurdles which must be overcome to understand the disease fully is the lack of animal models for researching the ways in which the disease develops. Obviously, the best animal models are those in which the disease occurs naturally. Here, acknowledgement is due to veterinarian ophthalmologists who made it possible to diagnose the disease in dogs. Research with these animals proved that, just like in humans, canine retinosis expresses in many different forms, with the presence of mutations equivalent to those occurring in humans (Aguirre et al., 1978) (1). It is a paradox that dogs, who are guides for humans affected by retinosis, have also guided researchers in their efforts to determine the causes of this disease.

For many years researchers studied affected dogs with all sorts of details at the molecular, cellular, ophthalmological and behavioral level in order to find the only therapies against retinosis which are being tested at this date. The first clinical trials were carried out in the nineties with gene therapy and encapsulated cells in dogs with very positive results which paved the way for the FDA authorizing clinical trials in humans. The therapies being developed for humans originated in the studies developed by the group led by Dr. Gustavo Aguirre of Pennsylvania University based on encapsulated cells (Tao et al., 2002) (2) and with gene therapy (Acland et al., 2001) (3).

At present, there are two therapies in clinical trial stages against human pigmentary retinosis. In stage 2, the clinical essay utilizing modified encapsulated cells for releasing trophic factors, particularly CNTF and gene therapy with associated adenovirus carrying the right gene which encodes for protein RPE5 in stage 1. This mutation gives rise to a form of Leber’s congenital amaurosis. If the results of these essays which began last May in Great Britain yield positive results, we would have the first a la carte effective therapy against a retinal mutation which could continue with the treatment of other mutations in order to apply it to other mutations in genes involved in pigmentary retinosis.

Gene therapy with AAV Adeno-associated virus carrying the gene which causes the disease paves the way to the long-awaited a la carte therapy for the «rare disease» of pigmentary retinosis. A recent editorial comment published in the prestigious Nature journal made reference to statistics on the type of molecular strategy utilized in clinical essays with gene therapy for different diseases. Accordingly, 4% of 284 clinical essays were carried out utilizing AAV adenoadsociated virus (as in the case of RP65 therapy) without observing any adverse effects.

The research by Dr. Aguirre’s group, which led to the initiation of gene therapy in humans, demonstrated the restoration of visual function in animals treated with gene therapy (Acland et al., 2005) (4). In the course of a recent collaboration with his group and with the funding of FUNDALUCE and the ONCE Foundation we were able to study the retinas of dogs treated with gene therapy in which the restoration of the visual function had already been demonstrated and verified that, after gene therapy with RPE65-AAV, the molecular structure and

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distribution of the retina was almost entirely restored (Hernández et al., 2007) (5).

Doubtlessly, the main challenge now is to determine the type of mutation the disease causes in order to draw an international map of the amount of people affected by the same mutation. At the time of writing, some institutions are busy identifying the mutation of pigmentary retinosis patients, initially offering identification if the patients have a known mutation because the characterization of new mutations would require a work covering several years (which, even so, is being undertaken by some research groups). Clearly, this is the challenge for the next few years, and the effort to this end should not originate only in patients (who have a strong motivation) but in institutions which, by means of special budgetary allocations, would facilitate organizing the phenotype of the population affected by pigmentary retinosis as well as continued support for research in the field of rare diseases which was established in recent years.

After over thirty years of research, therapy against retinosis is closer than ever before. However, we must proceed with caution. It is crucial to await the publication of results with the first patients in order to perfect the treatment before applying it in our routine practice.

REFERENCES