Window Into Retinal Studies

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Window Into Retinal Studies

Abstract
Professor Gustavo Aguirre discusses the context of his research studies at the University of Pennsylvania, which are currently concentrating on the degenerative disease, retinitis pigmentosa.

Keywords
blindness, dogs, animals, Retinitis Pigmentosa GTPase Regulator, X-linked RP

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Can you provide an overview of the discovery of X-linked retinitis pigmentosa (XLRP) diseases?

There are several retinal diseases in humans that are known to have X-linked inheritance. There are only two where the gene has been found: RP-3 and RP-2. The pioneering work on the mapping of these diseases was done in the UK by Professors Alan Wright (University of Edinburgh) and Shomi Bhattacharya (Institute of Ophthalmology) beginning in the 1980s. It took a long time to refine the disease intervals, and many groups were working on this difficult area. Eventually, the Wright and Meitinger groups published a seminal paper identifying a very complex gene called RPGR (Retinitis Pigmentosa GTPase Regulator). They also found part of the gene which had previously been very difficult to sequence. This DNA region – ORF-15 – accounted for about 70 per cent of mutations in patients with RPGR. After this finding, my team collaborated intensively with Wright and found that dogs had the mutation in the same ORF15 region as patients. When you take most populations of patients with X-linked RP, up to 70 or 80 per cent have mutations in RPGR. Thus it is recognised as the most common cause of X-linked RP. It is a very severe problem, not least because the regions in questions are very difficult to clone and sequence.

The first gene therapy clinical trials in human patients affected with a severe form of childhood blindness were reported 2008. Can you highlight the developments which have been made in this regard, and any further challenges clinical trials have thrown up?

The Phase 1 studies in human patients have confirmed that treatment of the study population is safe which is the primary goal of any Phase 1 clinical trial. In addition, the studies have shown efficacy in some patients. What we now need is to determine the patient population that is amenable to treatment, and the long-term safety and efficacy in treated patients.

In the studies with LCA-affected dogs over the past 10 years, we have shown stable correction and safety over this period of time. What we still need to know are the structural correlates of the restored function. In other words, does the treated retina remain normal and, if so, can it restore the chemical connections with other cells that ultimately are responsible for transmitting the visual information to the brain.

The new studies under the direction of Dr András Komáromy use a different model of severe visual impairment – achromatopsia – that occurs at birth. Patients with this severe disease have an aversion to light; they are totally blind in bright light; their fovea and macula – which contain the cone cells that enable colour vision and high visual acuity – do not function normally.

We have published a paper which details that this disease can be cured and, with collaborators at the University of Florida, are planning to develop clinical trials for this disease. In this disease, the studies are directed at treating cones – the main class of cells involved in macular degeneration. If we can develop a treatment targeting cones, there is the exciting possibility that we can treat other diseases also.

What major, long-standing challenges does your field of research present?

From a scientific point of view, a main challenge now is in eliminating proteins that have an adverse effect on tissue, not only in relation to X-linked RP, but other dominant diseases in which the actual genetic defect produced a protein that has a deleterious effect on the retinalphotoreceptors. One such disease is caused by mutations in the rhodopsin gene which is an extremely common cause of autosomal dominant RP.

Many disease-causing mutations that are inherited as dominant or X-linked result in what is known as gain-of-function, where the abnormal proteins produced cause disease. For therapy, you must prevent production of the abnormal protein and then replace it with the normal version. In the X-linked RP model, which is applicable to a large number of dominant diseases, the need to eliminate the undesirable mutant protein is a challenge of utmost importance.

To what extent has genome sequencing been integral in enabling the team to identify likely targets for intervention, and can you outline the support offered by the Penn Genome Frontiers Institute (PGFI)?

The progress made in this regard is remarkable. When I first started work in this field in 1992, there were absolutely no genome resources available for the dog. So we had to carry out cloning for ourselves, taking information gained from the cloning of genes in mice, cows and humans. When I look over the lab books, I recall that people would spend several years cloning genes; today you simply access the information through a web browser. We can use SNP-chips to track diseases or you simply access the information through a web browser. We can use SNP-chips to track diseases or identify new diseases, and arrays to look at gene expression. The resources available at the PGFI have been critical in providing the infrastructure and resources needed to do this work.
A research team based at the University of Pennsylvania are conducting essential research which could lead to promising therapies for X-linked retinitis pigmentosa, an hereditary disease that leads to blindness.

FOR THE BEST part of two decades, Dr Gustavo Aguirre of the School of Veterinary Medicine at the University of Pennsylvania, Philadelphia, has dedicated his research efforts to the long-term development of therapies for degenerative retinal diseases. Presently, Aguirre and his collaborators are conducting studies in relation to retinitis pigmentosa (RP) linked to the X-chromosome. RP represents a group of hereditary and degenerative eye conditions that invariably induce total blindness in patients. In general terms, this group of diseases is associated with dystrophies of the photoreceptors of the retina and/or the pigment epithelium.

Aguirre and his associate, Dr William Beltran, are employing dog models in identifying the genes and pathways associated with a form of RP known as X-linked PRA2 (XLRP). This naturally occurring canine disease is a close correlate of early-onset XLRP in humans. This work has great potential for translational studies to harness a novel therapy for XLRP caused by mutations in the ORF-15 region of the RPGR gene. Significantly for XLRP, mutations in this gene account for 8-10 and 15-20 per cent of early onset retinal diseases in the U.S. and Europe respectively. With this in mind, it is clearly manifest that Aguirre’s studies bear enormous potential and relevance in clinical terms; however, the industry and dedication shown by Aguirre and his team up to this point also warrant attention.

CURRENT INVESTIGATIONS

While a considerable proportion of patients with retinal diseases carry mutations in the RPGR gene, significant gaps persist in our understanding of the function of the protein, as well as the molecular mechanisms that lead to photoreceptor degeneration.

In addressing this issue, part of Aguirre and his investigators’ latest research involves the identification of genes and pathways associated with Retinal Dysfunction (RD) in dogs affected with XLRP2, also known as RPCR2. This is a canine model of early-onset XLRP caused by an RPCR exon ORF15 microdeletion. The connection between RPCR2 in dogs and RPCR in humans is extremely useful: should the team determine that the molecular mechanisms underlying XLRP2 in dogs are the same as those of XLRP in humans, it is anticipated that therapies proven effective in canine models will be likely to induce comparable effects in patients.

The team’s investigations in canine models will run in parallel with a comprehensive study in patients seeking to enhance knowledge regarding the range and history of XLRP. This corresponding study, carried out by Drs Samuel Jacobson and Artur Cideciyan at the University of Pennsylvania,
INTELLIGENCE

MODELS OF X-LINKED RETINITIS PIGMENTOSA

OBJECTIVES

- To develop specific gene-based therapies for RPGR-XLRP past the proof-of-principle stage so that clinical trials are then generated
- To assist collaborators, Drs S Jacobson and A Cideciyan, to conduct prospective studies in RPGR-XLRP patients to assess the feasibility or facility of translating pre-clinical therapy to the clinic
- To carry out complementary in vivo studies in the canine model to quantify photoreceptor laminar structure and function, with emphasis on the central retina, at comparable disease stages as the patients, to establish the morphological/immunocytochemical correlates to the observations made in dogs that can be extrapolated to patients

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