Major advances in vision research and clinical ophthalmology have occurred because of seminal findings by individual investigators, usually though only after years of persistent, hard work. I believe this to be the case with the work of Dr. Gustavo Aguirre in developing, characterizing, and subsequently using his unique animal models of inherited retinal degeneration (RD) in preclinical safety and efficacy trials. These models have been the basis of most of the current clinical trials for inherited RD diseases and, more broadly, many treatments for other tissues of the eye and body. Because of this long-term, groundbreaking body of work, he now fully deserves recognition through the Proctor Award (Fig. 1).

Dr. Aguirre has a long history of discovering and characterizing large-animal models of RD and developing the most appropriate ones for translational studies. This has proceeded over the past 3 decades, such that, by my count, he has given us at least 17 important models that can be used to study gene mutations, cellular protein changes in photoreceptor cell degeneration and death, and also in establishing preclinical criteria for subsequent clinical trials. Of course, this is just what the Food and Drug Administration (FDA) wants as a prelude to a clinical trial. He has done this not only in his own laboratory, but by his skill in forging productive relationships with a long list of distinguished collaborators. Figure 2 shows Gus with some of his principal collaborators, William Beltran on the left, Art Cideciyan next to Gus, and then Samuel Jacobson. The only one missing is Bill Hauswirth, master of the gene vector.

In fact, his work on canine inherited RDs began back in the mid-1970s, with seminal publications on a progressive retinal atrophy in Irish setter dogs that he called rod-cone dysplasia (rcd1) in which the underlying problem in this early-onset RD was found to be in the cyclic GMP phosphodiesterase gene, just as in the rd1 mouse and later human patients. All this work, and then throughout the 1980s and early 1990s, was accompanied by a meticulous description of cellular changes in the degenerative process in the animal models and similarities to human RD disease pathophysiology that later would be crucial in establishing the dog diseases as authentic therapy models for the human. At about this time, Dr. Aguirre established his credentials in the gene therapy arena by first showing that retroviral-mediated transfer of normal β-glucuronidase cDNA to mutant RPE cells in culture completely reversed the disease and, with colleagues at Penn and other institutions, showed that the ocular disease phenotype in MPSI and MPSVII animal models was corrected by either systemic gene therapy or bone marrow transplantation. All this groundwork led to the spectacular finding that gene therapy could, in fact, restore vision in a canine model of childhood blindness: the RPE65 mutation. I believe that this publication forms the basis for most of the subsequent gene therapy studies we now have in the human on the RPE65 mutation and many other diseases as well.

In the mid-1990s, Dr. Aguirre began to establish the genetic underpinnings of the canine models, for example, the X-linked nature of what we now know as XLPRA. He established molecular diagnostic tests for the rcd1 dysplasia, and the cloning and characterization of the cDNA as well as the locus homology between canine prcd and RP17 in the human. He also mapped and described the pathology of canine X-linked progressive retinal atrophy, pinpointing the locus homolog of human RP3.

As with the gene therapy breakthrough using the RPE65 dog model, 2002 saw the publication of another groundbreaking study by Dr. Aguirre and his collaborators, that is, establishing that delivery of the neurotrophic agent CNTF using encapsulated cell technology reduces photoreceptor degeneration in the rcd1 model of RD. This work clearly established preclinical proof of concept for safety and efficacy, a necessary prelude to current human clinical trials on both RP and AMD. Many more advances came in the decade between 2000 and 2010, cementing in, for example, the safety of ocular gene therapy using AAV2 vectors and validating their use for human trials of Leber congenital amaurosis (LCA), as well as giving a further green light in proceeding with human therapy trials by demonstrating the intactness and responses of canine and human visual cortices in early retinal blindness caused by RPE65 gene mutations.

Building on decades of this basic work, there has been an explosion in further movement to clinical trials and ultimate

FIGURE 1. Dr. Gustavo “Gus” Aguirre.

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human treatments in the past few years from Dr. Aguirre and his collaborators as well as several other groups. First, Dr. Aguirre and his team have demonstrated that gene therapy rescues photoreceptor blindness in two dog models of X-linked RD, paving the way for treatment of human X-linked RP (XLRP).11 On a related and very positive note, Dr. Aguirre and his colleagues have recently found that, in XLRP caused by a mutation in the RPGR gene, gene replacement therapy successfully arrested both photoreceptor and vision loss when therapeutic interventions were timed for both early and later phases of intermediate-stage disease.12 Under these conditions, there was improved structural preservation of rods, cones, and bipolar cells as well as correction of opsin mislocalization. Thus, these studies give us much information as to the basic pathology in XLRP and also substantially widen the window of time in which successful therapy in human patients with RPGR-XLRP can be conducted. This gives hope for the first time to older RP patients for functional sight restoration.

Finally, some of Dr. Aguirre’s core work provides new large animal models for the future study of some of the rare but devastating RDs that, because of their rarity, have received little attention. Terrier canine models are now available, for example for I/QCB1 (NPHP5) mutations13 and critical time points have been pinpointed in mutant dogs that will allow defining a “potential time window for testing novel therapies for translation to patients.”14 This again provides hope for those with rare RD diseases that there is indeed a path to clinical translation and restored vision in previously hopeless patients.

The measure of a person’s scientific contributions is not just in their body of work itself but in the vistas opened up to other researchers and clinicians by that work and how it can be applied to treating and curing human diseases. A case in point is the LCA clinical trials described above that would not have been possible or would have been markedly delayed without Dr. Aguirre’s pioneering work in not only providing a large animal model for the RP655 mutation, but spearheading all the preclinical work needed for moving on to an FDA-approved human trial. Positive results in this and many other preclinical studies have led to a number of actual clinical trials that are now well advanced. Thus, there has been rapid translation of basic research findings into the development of new therapies for patients with RD diseases, such as LCA, because of the availability of well-characterized large animal models that can convince the FDA of preclinical safety and efficacy. The broader implication being that, with proof-of-principle established in these cases, treatment of many ocular diseases by gene therapy and neurotrophic therapy will now be hastened.

In summary, Dr. Aguirre’s decades of ground-breaking and meticulous work has given us a way to actually study the basic genetics, biology, and pathophysiology of gene mutations that cause hereditary blinding retinal disease in a large animal model of human disease. Moreover, it has also allowed us to do the preclinical studies for safety and efficacy that have given us a direct pathway for the restoration of sight to previously hopeless people with vision loss and blindness due to inherited RD diseases.

References