RETINA INTERNATIONAL

Seeking A Cure For
Retinitis Pigmentosa (RP), Macular Degeneration, Usher Syndrome and Allied Retinal Dystrophies

Agenda and Talk Summaries for Retina International Scientific and Medical Advisory Board Meeting

Date: Monday, 30 April, 2018
Time: 1:30 – 3:00 p.m.

Location: Honolulu Convention Center - Room 324

Agenda

A) Introduction

1 Welcome - Ms. C. Fasser, President, Retina International

2 Scientific Programme Introduction – Drs. E. Zrenner and J. Hollyfield, co-chairs, Scientific & Medical Advisory Board

B) Scientific Programme

Age-Related Macular Degeneration

1 Clinical trial for Geographic Atrophy using APL-2, a complement inhibitor – *Dr. Ramiro Ribeiro, Apellis*

2 Phase III studies of brolucizumab versus aflibercept in AMD: 48-week primary and key secondary outcomes from HAWK/HARRIER *– Dr. Glenn Jaffe*

Artificial Vision

3 Artificial Vision Update - *Dr. Eberhard Zrenner*

Cell- and Drug-Based Therapies

4 **Stem cell therapy for RP: Phase 1 and II clinical trial** - *Dr. Henry Klassen*

5 **Phase 1 clinical study of an embryonic stem cell–derived retinal pigment epithelium patch in Age-related Macular Degeneration** - *Dr. Peter Coffey*

6 **Gene therapy trial for X-linked Retinoschisis** - *Dr. Catherine Cukras*

7 **Horanama gene therapy trial PDE6B** - *Dr. Guylene Le Meur, Horama*

8 **Achromatopsia CNG3B Clinical Trial** - *Dr. Dominik Fischer*

9 **Update on gene therapy for choroideremia and X-linked RP** - *Dr. Robert Maclaren*

10 **Phase 2 study of gene therapy for Choroideremia** - *Dr. Rachel Huckfeldt*

11 **LUXTURNA (voretigene neparvovec-rzyl) for biallelic RPE65 mutation-associated retinal dystrophy** - *Dr. Thomas Ciulla, Spark Therapeutics*

12 **Update on treatment for Inherited Retinal Degenerations due to mutations in the RPE65 and RLBP1 genes** - *Kali Stasi, Novartis*

Planned Gene Therapy

13 **Preclinical gene therapy for Leber Congenital Amaurosis caused by NPHP5 mutations** - *Dr. Gustavo Aguirre*

14 **LCA10 clinical trial** - *Dr. Artur Cideciyan*

15 **New generation optogenetics vision restoration** - *Dr. John Flannery*

Other Business

16 **ERN - European Reference Network** - *an update - Dr. Helene Dollfuss*

17 **The Eye-Risk Programme** - *Dr. Marius Ueffing and Dr. Carolyne Klaver*

18 FFB's approach to collaboration with industry on late stage research - *Ben Shaberman, FFB*

16 RD 2018 in Ireland - *Dr. Christian Grimm*

Attendees
Retina International Officials

SMAB co-chairman:	Dr. Eberhart Zrenner
SMAB co-chairman:	Dr. Joe Hollyfield
SMAB secretary:	Dr. Gerald Chader
Retina International president:	Mrs. Christina Fasser
Retina International CEO:	Mrs. Avril Daly

Speakers
Aguirre Gustavo; Cideciyan Artur; Ciulla Thomas; Coffey Pete; Cukras Catherine; Dollfuss Helene; Fischer Dominik; Flannery John S.; Grimm Christian; Huckfeldt Rachel; Jaffe Glenn; Kali Stasi; Klassen Henri; Klaver Caroline; Le Meur Guylene; Maclaren Robert; Ribeiro Ramiro; Shaberman Ben; Stasi Khali; Ueffing Marius;

Participants
Biel Martin; Boeni Barbara; Boye Shannon; Ballios Brian; Brady Laura; Bredup Cecilie; Carmichael Trevor; Cremers Franz; Daly Avril; Duncan Jacque; Fletcher Erica; Ghosh Fredrik; Heon Elise; Humphries Marian; Humphries Peter; Kalloniatis Michael; Kellner Ulrich; Kjellstrom Sten; Klaver Caroline; Koenekoop Robert; Kondo Mineo; Laties Alan; Lorenz Birgit; Lotery Andrew; Marigo Valeria; Murakami Akira; Natharian S.; Neidhart John; Perce Erick; Porto Fernanda; Prener Holtan Josephine; Sales Mariana; Sallum Juliana; Sankila Eva-Marja; Silva Eduardo; Takahashi Masayo; Tumminia Santa J., Wie Liisa; Worsley David;

Meeting Minutes

A) Introduction

1) Greetings - Ms. C. Fasser, President, Retina International

2) Scientific Program Introduction – Drs. Eberhard Zrenner and Joe Hollyfield, co-chairmen, Scientific & Medical Advisory Board

B) Scientific Program - Clinical and Preclinical Trials: Updates and New Trials

Age-Related Macular Degeneration

1) Clinical Trial for Geographic Atrophy using APL-2, a complement inhibitor.
Dr. Ramiro Ribeiro – Apellis Pharmaceuticles, Waltham, MA, USA

Apellis is a company focused on the complement system, in particularly, the inhibition of complement C3. Our lead candidate drug, APL-2, is being investigated in C3-mediated conditions such as paroxysmal nocturnal hemoglobinuria and geographic atrophy.
The Filly phase 2 trial was a 246-patient multicenter, randomized, single-masked, sham-controlled study to evaluate the safety, tolerability and efficacy of APL-2 in subjects with geographic atrophy associated with age-related macular degeneration (AMD). APL-2 was administered either monthly or every other month, via intravitreal injection, for 12 months followed by six months of safety monitoring without medication. The primary endpoint was the growth of GA lesions measured by fundus autofluorescence at different time points. Monthly administration of APL-2 showed a 29% reduction (p=0.008) in the rate of GA lesion growth compared to sham. With the every other month administration, a 20% (p=0.067) reduction was observed. A more pronounce effect was seeing between month 6 and month 12. During the 6 months of off-drug treatment, the growth rate between groups was similar. The most frequently reported adverse events were associated with the injection procedure. Subjects in the APL-2 arm were at higher risk of conversion to neovascular AMD.

2) Brolucizumab: A Novel Anti-Vascular Endothelial Growth Factor Agent to Treat Neovascular Age-Related Macular Degeneration.

Dr. Glenn J. Jaffe – Duke University, Durham, NC, USA

The wet form of age-related macular degeneration, termed neovascular AMD (nAMD) is a chronic, progressive disease and a leading cause of vision loss in individuals over 55 years old. Currently, intraocular drug injections directed towards the protein called vascular endothelial growth factor (VEGF) which are typically given every one-two months, are the current FDA-approved treatments for this form of AMD. These therapies have greatly improved patient outcomes. However, these treatments require frequent clinic visits and, coupled with the anticipated increased prevalence of AMD and high treatment cost, portend a scenario that is not sustainable. Factors leading to treatment nonadherence include travel to appointments, patient dissatisfaction, and the burden of numerous visits, which may contribute to suboptimal vision outcomes. Real-world studies across several countries revealed lower treatment frequencies and poorer vision outcomes when compared to results in clinical trials. An ongoing challenge is to maintain nAMD treatment efficacy while reducing clinic visits. A novel anti-VEGF agent, brolucizumab, has been developed that has potential to increase the drug activity duration, and thus could reduce the treatment burden on patients with nAMD.

Two randomized clinical phase 3 trials, called HAWK and HARRIER, were conducted at clinical sites around the world, and were recently completed. These trials assessed the safety and efficacy of brolucizumab to treat nAMD. In addition to the novel drug tested, brolucizumab, the trial design was unique, as it gave the investigators the opportunity to test whether an injection given every three-months would be effective for a given patient, or whether the patient would need to be treated more frequently. The key study findings were that broluziumab was as effective as a standard FDA-approved treatment, aflibercept, to preserve the patients' visual acuity. In addition, more than half the patients could be treated every three months, and the treating physician could predict with more than 80% certainty, which patients could be maintained on every three-month therapy over at least two years, based on their response to treatment within the first four months after the drug was first administered. Finally, the safety profile was similar to that of the FDA approved treatment.

The data from these clinical trials suggest that brolucizumab, a novel molecule, is effective in treating nAMD with an extended treatment duration in a large proportion of patients with nAMD. These results offer hope that this therapy may reduce the treatment burden in patients with nAMD, which could lead to better patient compliance, improved outcomes, and decreased drain on valuable health-care resources.

3) Artificial Vision Update

Dr. Eberhart Zrenner, Universityn of Tuebingen, Tuebingen, Germany

The following text is limited to advances in development and use of the two electronic devices now commercially available. Several other prostheses are currently in different stages of construction or testing in countries around the world and are comprehensively reviewed by Cheng et al. in Current Eye Research 42, 334-347. 2017.

Retina Implant Alpha AMS

Interim results from a multicenter clinical trial using the new Alpha AMS device from Retina Implant AG were published by Stingl et al. (Front Neurosci 11, 445, 2017). Alpha AMS is an improved version of the previously developed Alpha IMS device. Fifteen patients blind with inherited retinal degeneration were used in the study. Follow-up period was 12 months. During the observation period, implant-mediated light perception was observed in 13 of the 15 patients, as well as visualization of visual targets, e.g. tableware and cutlery. Two patients were able to distinguish Landolt C-rings up to 20/1111 and 20/546. Many patients reported spontaneously about perceiving moving objects such as car lights, animals or persons. The majority of adverse events were transient and of mild to moderate in impact. The authors conclude that “Psychophysical and subjective data show that Retina Implant Alpha AMS is reliable, well tolerated and can restore limited visual function in blind patients with degenerations of the outer retina.” Compared with the previous implant, Alpha AMS, longevity has been considerably improved. It has been certified as a “commercially available device, reimbursed in Germany by the public health system”

A very recent publication by Edwards et al., (Ophthalmology 125:432-443, 2018) assesses Alpha AMS as to restoring vision in blind patients with end-stage RP. Six patients were implanted and tested up to 12 months. Light perception and temporal resolution were achieved in all participants when the device was operative. Correct grating detections (which were at chance level with the implant OFF) were recorded in 5 participants, ranging from 0.1 to 3.33 cycles/degree

The device was successful in improving visual performance in 5 of the 6 patients with ongoing function for up to 24 months. Patients reported being able to locate or see balls on a billiards table, outlines of windows and doorways, metallic kitchen appliances (e.g., kettle and toaster), black and white laundry items, the outline of a Scottish highland mountain against the setting sun, a passing car, Christmas lights, and building edges.

Argus II and Orion

The Argus II prosthetic system from Second Sight Medical Products (SSMP) uses an external camera to transmit visual information to an intermediate processor and finally to an implant placed on the front surface of the retina. This positioning near the ganglion cells bypasses most of the damaged retinal cells with the ganglion processes passing the visual signals to the brain. Clinical trials using the Argus II were successful and the device has now been implanted hundreds of times around the world at many clinical sites. Advances in design are still being made though. Caspi et al. (Invest Ophthalmol Vis Sci 59, 792, 2018) have tested an eye tracker to see if use of eye movements reduce head movements and increase visual stability. They found that "integrating an eye tracker into the Argus II is feasible and reduces head movements …… and improves pointing precision." Improvements have also been made in surgical techniques used to place the implant on the retinal surface. A "sheets-glide-assisted intraocular placement" procedure has been described by Finn and Vaizovic (Ophthalmic Surg Lasers Imaging Retina 49,132, 2018) that seems to be a useful tool in "aiding the retinal surgeon to successfully and easily place the electrode array" on the retinal surface,
SSMP has also announced the development of an Orion cortical visual prosthesis system with implantation directly into the brain. Visual information is received from a wearable video camera as with the Argus II device. The device could theoretically bypass the eye completely and treat virtually all forms of ocular blindness.

Cell- and Drug-Based Therapies

4) Retinal Progenitor Cell Therapy for RP: Phase I and II Clinical Trial.
Dr. Henry Klassen – University of California, Irvine, Irvine CA USA.

Extensive laboratory studies have been performed with respect to the isolation of retinal progenitor cells (RPCs) and subsequent transplantation to the retina of animal recipients with retinal degenerations. These studies have revealed the therapeutic potential of this approach in the setting of otherwise incurable blinding diseases. One mechanism of action consists of photoreceptor cell replacement, while another involves neurotrophic preservation or reactivation of host photoreceptors. We have focused on this latter approach and undertaken the manufacturing of human RPCs under GMP-compatible conditions, along with formal IND-enabling preclinical studies. A phase 1/2a open label safety study of intravitreal RPCs in 28 patients with retinitis pigmentosa was initiated in 2015 and completed in August of 2017. The data showed a favorable safety profile and included subjective reports of visual benefits. BCVA showed statistically significant improvement for treated eyes versus untreated eyes, with indications of a

dose-response relationship. A controlled phase 2b clinical proof-of-concept trial is currently underway to further explore these early findings.

5) Phase 1 Clinical Study of an Embryonic Stem Cell-Derived Retinal Epithelium Patch in Age-Related Macular Degeneration (AMD). Dr. Peter Coffey, Moorefields Eye Hospital, London

The following was derived from notes taken during Dr. Coffey's talk and from information published in Nature Biotechnology 36:328-37, 2018.

Dr. Coffey and his group have designed and constructed a small patch consisting of a coated synthetic basement membrane on which are attached human embryonic stem cells (hESC) differentiated into retinal pigment epithelial (RPE) cells. For the trial, the patch is implanted into the subretinal space of one eye in each of 2 patients with severe, exudatative AMD. The primary endpoints are 1) safety, including the incidence and severity of adverse events and 2) improved best-corrected visual acuity of 15 letters or more. Local immunosuppression was used long term.
Over a 12 month period, there was successful delivery and survival of the RPE cells on the patch as assessed by biomicroscopy and Optical Coherence Tomography. Functionally, there was a gain in visual acuity of 29 letters in patient 1 and 21 letters in patient 2. Surgical safety, cell safety and tumor safety studies support the decision to move on in the trial and the use of hESC-RPE patch transplantation as a "regenerative strategy for AMD".
A more in-depth review was published by Dr. Coffee and coworkers in *Progress in Brain Research* 231:225-44, 2017. Initial proof-of-concept studies are reviewed as to the use of stem cells in replacing degenerated RPE cells in AMD patients. Also, regulatory and manufacturing challenges are considered in the path of moving a potential treatment from the laboratory bench through a clinical trial.

Gene Therapy

6) Gene Therapy Trial for X-Linked Retinoschisis.
Dr. Paul Sieving and Dr. Lisa Wei, National Institutes of Health, Bethesda MD, USA

We conducted a phase I/IIa study to evaluate the safety and tolerability of an AAV vector delivering the human retinoschisin (RS1) coding sequence to individuals with X-linked retinoschisis (XLRS). XLRS is a monogenic trait affecting only males, caused by mutations in the RS1 gene. Retinoschisin

protein is secreted principally in the outer retina, and its absence results in retinal cavities, synaptic dysfunction, reduced visual acuity and susceptibility to retinal detachment. This phase I/Iia, single-center, prospective, open-label, three dose escalation clinical trial administered vector to nine participants with pathogenic *RS1* mutations. The eye of each participant with worse acuity received the AAV-*RS1* gene vector by intravitreal injection. Three participants were assigned to each of three dosage groups: 1e9 vector genomes (vg)/eye, 1e10 vg/eye, and 1e11 vg/eye. The AAV-*RS1* gene was generally well tolerated, in all but one individual. Ocular events included dose-related inflammation that resolved with topical and oral corticosteroids. Retinal cavities closed transiently in one participant. Additional doses and immunosuppressive regimens are being explored to pursue evidence of safety and efficacy (see ClinicalTrials.Gov NCT02317887).

7) Phase I/IIa Study of Gene Therapy for PDE6B Mutation.
Dr. Guylène Le Meur, University Hospital of Nantes, Nantes, France

The *PDE6B* gene, encoding the β subunit of rod phosphodiesterase accounts for about 4-5% of autosomal recessive retinitis pigmentosa (RP) cases (Hartong et al., 2006). Currently there is no effective treatment for this condition. HORA-PDE6B (AAV2/5.hPDE6B) is a gene replacement therapy product which aims to deliver the non-mutated gene to the target retinal cells leading to synthesis of the functional protein. Recently, a clinical study (NCT03328130), support by Horama, for evaluating the HORA-PDE6B product in patients with an RP harbouring mutations in the *PDE6B* gene has just started at the University Hospital of Nantes. This prospective study is a Phase I/II clinical study, over three years, evaluating the safety and biological activity of a unilateral subretinal administration of HORA-PDE6B. The treatment is administrated in the worst affected eye. At least twelve patients of 18 years of age or older will be enrolled in three consecutive cohorts of patients. The first cohort will receive a low dose of the product. The second cohort will receive the high dose of the product. The third cohort will be injected with the maximum tolerated dose. The first elements, that will be looked at will be the results of safety and tolerance. Then in the background, the results of visual function and anatomical tests will be evaluated. The first cohort enrolment is ongoing.

8) Achromatopsia CNB3B Clinical Trial.
Dr. Dominik Fischer, University of Tuebingen, Tuebingen, Germany

The CNGA3 gene therapy trial is the first ocular gene therapy trial in Germany and was the first achromatopsia gene therapy trial initiated worldwide. It is the product of the RD-CURE consortium, a group of clinicians and scientists coordinated by Bernd Wissinger (Tübingen) and Martin Biel (Munich). The consortium aims to bring CNGA3 and PDE6A gene therapy into clinical phase I, is funded by the Tistou and Charlotte Kerstan Foundation (advisor for the foundation: Prof. E. Zrenner) and advised by Drs. Molday, Hamel, Humphries, Wijnholds, Hagemann and Bennett.

In 2015, we started the CNGA3 trial after extensive toxicology and BD studies in NHPs. The study is a first in man, open label, phase 1/2 trial with a staggered, dose escalation study with 3 patients in each dose cohort and 3 such cohorts. Using the AAV8 vector system, we started with a dose of $1x10^{10}$ in the first 3 patients. There was one case in the low dose cohort of potential inflammation in the treated area (i.e. hyperreflective dots) one month after treatment. This was subclinical, completely reversible under steroid treatment and did not impact on visual function at any point of time. We judged this not to be a reason to halt the trial and the independent data monitoring committee (DMC) agreed to a dose escalation to $5x10^{10}$. One patient from the intermediate dose cohort developed symptoms of mild iridocyclitis one month after treatment, which was also completely reversible under steroid treatment and did not impact on visual function at any point of time. Again, the DMC agreed for us to move ahead and escalate the dose to the highest dose ($1x10^{11}$). All patients have now been followed up for a minimum of 12 months and we have not observed any inflammation in any patient from the high dose cohort as of today. Last patient, last visit was in Q4 2017 and consecutive analysis of trial results is ongoing.
As top-level results we can report:

1) 1^0 endpoint was met. Our product can be applied safely, and the procedure is well tolerated.

2) 2° endpoint (efficacy) exploration of endpoints gives a consistent picture of improved cone function (e.g. visual acuity, contrast sensitivity, color vision) that matches results from patients reported outcome measures

9) Update on Gene Therapy for Choroideremia and X-linked RP.
Dr. Robert MacLaren, University of Oxford, Oxford, England

Dr. MacLaren provided an update on the Nightstar choroideremia gene therapy program which is now in Phase III clinical trial running across 11 different countries. The endpoint of the Phase III is to achieve a clinically significant gain in visual acuity in at least 6 patients by 1 year after gene therapy treatment. He also presented long-term data from the original Oxford-

led clinical trial which showed that all 12 patients who were treated per protocol had maintained visual acuity up to 5 years in their treated eyes whereas 8 of 12 had visual acuity losses in their untreated eyes during this period. In the 7 patients in whom the visual acuity had been reduced at baseline, 3 gained 3 lines or more of visual acuity which was consist and sustained up to 5 years. Anatomical features showing slowing of degeneration also became evident beyond the 2-year follow-up period. These results were also presented in the main ARVO session. He also explained that the gene therapy trial for X-Linked Retinitis Pigmentosa (XLRP) was going very well, following the first patient being treated in Oxford in 2017. Several centers in the USA will be joining the trial this year. Dr. MacLaren mentioned that the AAV8 vector they are using encodes a codon-optomized version of human RPGR that avoids deletions in the open reading frame (ORF) 15 region of the transgene. Referring to Fischer et al. (2017), he confirmed that the degree of glutamylation in the codon-optomized construct was the same as in the wild-type human RPGR gene as evidenced by the recent observation of cone-rod dystrophy in TTLL5 mutations in which RPGR is not fully glutamylated. The trial has almost completed the dose-escalation phase with no serious adverse events reported to date.

10) Update on Safety and Dose Escalation Study of AAV2-hCHM for Treating Choroideremia.
Dr. Rachel Huckfeldt, Massachusetts Eye and Ear Infirmary, Boston MA, USA

Spark Therapeutics initiated an open-label, dose-escalating Phase 1/2 trial in 2015 to assess the safety and tolerability of a subretinal gene therapy, using AAV2-hCHM, for the treatment of choroideremia. Additional objectives of the trial are to understand any effects on clinical endpoints that may signal activity of the transferred gene.

Fifteen patients have now been enrolled and dosed. Each participant received a one-time administration of the study drug with the fellow eye serving as a control. Dose escalation proceeded as planned after the initial five subjects were treated at the lower dose as safety data did not reveal any concerns. The second cohort of five patients thus received a higher dose. An interim analysis in March 2017 showed encouraging signs but no statistically significant differences between the injected and control eyes. The lack of conclusive evidence was attributed to the brief and variable follow-up (1.5 years or less for 9 patients) as well as the later stages of disease represented by the patients.

The trial was expanded in mid-2017 to include an additional five patients with less advanced disease to further understand the effects of AAV2-hCHM.

These individuals also received the higher dose. There have been no drug-related adverse events (Aes) in the overall study. The secondary objective continues to be evaluated with assessments of retinal function and structure. Additional analyses of both dose groups are anticipated later in 2018.

11) Luxturna (voretigene neparcocec-rzyl) for biallelic RPE65 mutation-associated retinal dystrophy.
Dr. Thomas Ciulla, Spark Therapeutics, Philadelphia PA, USA

In December 2017, the US FDA approved Spark Therapeutics' Biological Licensing Application for LUXTURNA™ (voretigene neparvovec-rzyl), an adeno-associated virus vector-based gene therapy, for the treatment of patients with confirmed biallelic *RPE65*-mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s). The open label Phase 3 study included 31 participants randomized 2:1; 21 intervention and 10 control. Intervention subjects received subretinal injection of LUXTURNA dosed at 1.5×10^{11} vector genomes per eye, 6 to 18 days apart. Control subjects crossed over to receive LUXTURNA after one year. Efficacy was based on a multi-luminance mobility test (MLMT) score change from Baseline to Year 1. MLMT was designed to measure changes in functional vision, as assessed by navigating a course at different levels of environmental illumination.
At Year 1, a median MLMT score change of 2 was observed in the intervention group for bilateral eyes (p=0.001), showing a statistically significant and clinically meaningful difference between the intervention and control groups. In clinical studies, ocular adverse reactions occurred in 66% of subjects, and may have been related to LUXTURNA, subretinal injection, concomitant corticosteroids, or a combination of these. Warnings and precautions include endophthalmitis, permanent decline in visual acuity, retinal abnormalities, increased intraocular pressure, expansion of intraocular air bubbles, and cataract. The most common adverse reactions were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula) Treatment with LUXTURNA is not recommended for patients younger than 12 months of age.

12) Update on Treatment for Inherited Retinal Degenerations Due to Mutations in the RPE65 and RLBP1 Genes,
Dr. Kali Stasi, Novartis Institutes for Biomedical research, Cambridge, MA, USA

***RPE65* update:** In January 2018, Novartis and Spark Therapeutics entered into separate licensing and supply agreements covering development, registration and commercialization rights to and supply of voretigene neparvovec (Luxturna™) in markets outside the US. Novartis is committed to ensure that patients outside the US have access to this innovative gene therapy treatment for patients with biallelic *RPE65* mutation-associated retinal dystrophy, a progressive disease that eventually leads to complete blindness in the majority of patients and for whom there is no other pharmacotherapy available.

***RLBP1* update:** Retinaldehyde-binding protein 1 (*RLBP1*) retinitis pigmentosa (RP) is a rare progressive retinal degenerative disease currently without any treatment. It is a form of autosomal recessive RP caused by mutations in the *RLBP1* gene on chromosome 15, resulting in either the absence or dysfunction of cellular retinaldehyde-binding protein (CRALBP), a protein that is important in the visual cycle. *RLBP1* RP is characterized by early, severe night blindness and slow dark adaptation from childhood, followed by progressive loss of visual field, visual acuity, and color vision. Most patients are legally blind by middle adulthood. Preclinical research was performed in *Rlbp1*$^{-/-}$ (knockout) mice with the genetic defect causing slow dark adaptation leading to night blindness, one of the typical clinical manifestations of the disease. A single subretinal injection of self-complementary human *RLBP1* genome with an adeno-associated vector capsid improved rod-mediated dark adaptation for one year, in a dose dependent fashion. (Choi VW et al. Mol.Ther.Methods Clin. Dev. 2015;2:15022). In a non-human primate study, it was shown that CPK850 at an initial subretinal dose of ~3x10^{7} vg/µL can safely be used in clinical trials (MacLachlan TK et al Molecular Therapy: Methods & Clinical Development 2018 PMID: 29359172). A Natural History study showed no significant progression of the disease during a 2-year follow-up period (ARVO 2017 posters 3244, 3246, 3249, 3251, 3254 and 3255). A Proof of Concept (PoC) Phase 1/2 trial is currently described at clinicaltrials.gov NCT03374657.

13) Long-Term Preservation of Photoreceptor Function and Structure Following Early-Stage Treatment by AAV-Mediated Gene Therapy in a Canine Model of *NPHP5* Leber Congenital Amaurosi

Dr. Gustavo Aguirre, University of Pennsylvania, Philadelphia, PA, USA

A C-terminal truncation of the *NPHP5* (*IQCB1*) gene causes a photoreceptor ciliopathy with an early onset, rapidly progressive retinal degeneration in dogs. By 6 weeks of age, rod responses are markedly reduced in amplitude

or absent and cone responses are not recordable. The absence of cone function correlates with the lack of cone outer segments even though there is preservation of cone inner segments. This preservation offers the possibility for successful gene therapy. We now report on long-term efficacy of early-stage treatment.

Subretinal injections of 70 µl of cNPHP5 therapeutic vectors, AAV2/5-hIRBP- or scAAV2/8 (Y733F)-hGRK1-, at titers ranging from 1.5 – 5 E11 or E12 vg/ml were made into one eye of affected dogs at 5-6 wks of age, with fellow eyes serving as untreated controls. PR structure and function were quantified by sdOCT and full-field ERGs. Visual behavior was assessed after ~ 1 year following treatment using an obstacle avoidance course to separately test the treated and contralateral control eyes. Gene therapy restored cone function and improved rod function within 6-7 weeks after treatment, and there were no treatment related complications. Post treatment functional evaluation showed sustained preservation of ERG rod and cone function for time periods ranging from 1.4 to 2.7 years after therapy. Testing in an obstacle avoidance course under scotopic and photopic illumination showed retained functional vision in the treated eyes under all illumination conditions. Treatment blebs were associated with significantly retained photoreceptor layer areas which was robust with better ONL preservation at the higher vector concentrations. Thus, iIn spite of the very severe and rapidly progressive photoreceptor degeneration in *NPHP5*-LCA affected dogs, AAV-mediated gene augmentation restores rod and cone function, preserves vision and photoreceptor structure for time periods greater than 1.4-2.7 years without any deleterious effects. As the extent of photoreceptor disease is quite severe and advanced at the time of early-stage treatment, the results augur well for future translational applications.

14) CEP290 – LCA 10 Clinical Trial: CEP290 Gene Mutation
Dr. Artur Cideciyan, University of Pennsylvania, Philadelphia, PA, USA

CEP290 is a cilial protein expressed in rods and cones and mutations in the *CEP290* gene cause non-syndromic LCA as well as Joubert syndrome and related disorders. Mutations in CEP290 are relatively common explaining about 20% of all LCA. An intronic mutation between Exons 26 and 27 that creates a splicing defect insertion of a pseudo-exon and premature truncation of the protein is very common.
In 2012, two groups showed that anti-sense oligonucleotides (AONs) designed for the common mutation can prevent the aberrant splicing in pre-mRNA, correct the mRNA and lead to the translation of the functional CEP290 protein. ProQR has produced such an AON, and designed a multi-center Phase I/II international clinical trial (NCT03140969) to evaluate the

safety and tolerability of the investigational product administered thru an intravitreal injection. The trial is an open-label, single arm, multiple dose, dose escalation study.

Investigational material is injected as a standard intravitreal injection, every 3 months, for one year. The primary outcome measure is ocular safety. Secondary outcome measures include systemic safety, visual efficacy parameters and pharmacokinetics. The clinical trial is being performed in Iowa and Philadelphia, USA, and in Ghent, Belgium. The first injection was performed in November of 2017, and as of May 2018, eight patients have been enrolled. Results are to be evaluated.

15) New Generation Optogenetics Vision restoration.
Dr. John Flannery – University of California, Berkeley, Berkeley CA, USA.

Current reports are that a small number of patients with last-stage severe IRD were treated by RetroSense in a phase I/II clinical trial. The RetroSense product, RST-001, is an AAV2 virus vector with the cDNA encoding channelrhodopsin-2 (Chr2) that is administered by intravitreal injection. It is designed to deliver the gene for the photosensitivity Chr2 protein to the retinal ganglion cells (RGC). Studies suggest that RGCs can survive in a functional state for many years after vision loss from photoreceptor or RPE cell death. Transferring a visual signal to surviving RGCs is the operating principle for the SecondSight retinal electronic prosthesis as well. Retinal physiologists suggest that there are over 20, and perhaps 80 different functional subtypes of retinal ganglion cells. The RetroSense treatment is hypothesized to convert all of the RGCs that are transduced by the AAV vector into the same functional type, the ON-transient responding cell. This type of cell responds to the initiation of light by a brief (transient) action potential signal to the visual cortex. Other types of RGC will respond in the opposite way to a light flash, in that they fire a brief action potential to the cessation of the light – these are called Off-transient. There are also RGCs that are ON-OFF transient and several additional types of responses. Channelrhodopsin responds to blue light, maximally at 480nM, and is much less light sensitive than healthy retinal photoreceptors. This low sensitivity will need to be compensated for by having the patient wear light-intensifying goggles that emit a bright light to activate the Chr2 in the RGCs. It is unclear what will be the patient's experience from this treatment, and it may change with time after the initiation of the treatment as the visual cortex plasticity may adapt to the new, novel input. This plasticity of the brain often occurs with the cochlear implant patients, as their hearing quality improves over weeks and months post-implant.

GenSight is preparing to initiate 2 clinical programs in optogenetics. The GS030 product is a combination of two complementary components: 1) a gene therapy product encoding a photoactivatable channelrhodopsin protein, delivered via a modified AAV2 vector known as AAV2 7m8; and 2) biomimetic goggles that stimulate the engineered retinal cells. Images are projected onto the retina by a light source that uses a specific wavelength. GS030 uses a channelrhodopsin variant, ChrimsonR, that is activated by red light. The goggles will provide a red light to activate the ChrimsonR in the RGCs. The change from a blue wavelength sensor, Chr2 to a red-shifted sensor, ChrimsonR, is to reduce the potential for retinal light damage from the biomimetic goggles, as red wavelengths have been shown to be much less damaging to the retina than blue light. GenSight has initiated the PIONEER study, a dose-escalation study to evaluate the safety and tolerability of GS030 in subjects with Retinitis Pigmentosa.

GenSight is developing a second optogenetic approach, in which halorhodopsin, a yellow light sensitive optogenetic sensor will be expressed via an AAV vector in cone photoreceptor inner segments. The hypothesis here is that there are a subset of patients that have severe vision loss due to loss of the rod photoreceptors, and some patients retain cone inner segments that have lost their light-sensitive cone outer segments. Photoreceptors hyperpolarize in response to light, whereas RGCs respond to stimuli by depolarizing. As a result, the GenSight cone-targeted therapy will use halorhodopsin, which has the opposite polarity response to illumination as does channelrhodopsin-2 or ChrimsonR. This therapy is thought to have the potential to restore more visual capability for the subset of patients that it may be applicable to (patents with observable surviving cone inner segments by OCT imaging) as it should be able to use some of the intrinsic retinal image processing functions, as it is delivered “upstream” of the RGC-directed therapies. Halorhodopsin therapy will also require the use of image intensifying biomimetic goggles to activate the halorhodopsin sensor, as it, like Chr2, is much less sensitive than normal, healthy rod and cone photoreceptors.

Acucela, Inc., a clinical-stage ophthalmology company has licensed from The University of Manchester, UK (UoM) a human rhodopsin-based optogenetic gene therapy for the treatment of retinal degenerative diseases. This genetic mutation-independent therapy, initially developed by Drs Jasmina Cehajic-Kapetanovic, Robert Lucas and Paul Bishop at UoM, will utilize a viral vector to transduce the ON-bipolar cells of the retina with human rhodopsin, a light sensitive protein normally expressed in the rod photoreceptors. This technology has been shown to be effective at restoring visual response in a mouse model of retinal degeneration and is significantly more sensitive in the mouse work than the Chr2, ChrimsonR or halorhodopsin sensors, and may provide functional vision at normal lighting conditions without the requirement for light intensifying goggles.

Overall, there is the challenge to try to restore as much of the normal vision as possible. In designing such a system, there is a necessary balance between a system that has high light sensitivity, such that goggles are not necessary, one that can respond over a broad range of intensities, and one that has response speed adequate for motion vision.
Other research groups are currently testing cone opsins and other light sensing proteins with the hope of identifying a sensor system that can provide adequate light sensitivity over a broad range of light intensities and, at the same time, have response speed adequate for patients to regain visually guided motility.

16) ERN – European Reference Network: an Update.
Dr. Helene Dollfus – University Hospital of Strasbourg, Strasbourg, France

European Reference Networks are dedicated to improve care and research for patients with rare diseases. Twenty-four of them were launched in the Spring of 2017. ERN-EYE is focused on rare eye diseases and involves 29 hospitals in 13 member states of the European Union.

ERN-EYE activities for the past year have been mainly focused on an inventory phase. Moreover, one main achievement has been to work with ORPHANET and HPO (Human Phenotype Ontology) to collectively revisit the ontologies concerning rare eye diseases. This was done over the year with a peak event being the Odile Meeting (Mont Saint Odile, France) where more than 60 ERN-EYE participants with main actors of ORPHANET and HPO, curated the current classifications and ontologies. Overall, 184 new HPO terms related to ocular disease were added with over 600 terms being revised to include definitions or synonyms, correct errors, or to remove/merge obsolete terms. The ORPHANET classification was fully restructured with more than 70 groups created, 40 disorders introduced, 90 entities removed/merged and 140 modifications made in the nomenclature.

Another main action is the implementation of the virtual clinic driven by the European Commission tools launched during 2018 and that will improve the care of patients with rare eye diseases across the EU. Many other fields are being currently covered such as genetic testing, registries, research within the specific working groups‘ topics such as retina, pediatric ophthalmology, anterior segment and neuro-ophthalmology.

We would like to thank Retinal International for their continued support.

17) Update on the EYE-RISK Programme.

Dr. Caroline Klaver, University of Rotterdam, Rotterdam, The Netherlands and Dr. Marius Ueffing, University of Tuebingen. Tuebingen, Germany

Eye-Risk is a consortium focusing on unraveling the pathogenesis of age-related macular degeneration (AMD) and defining patients based on the underlying pathogenesis rather than phenotype. EYE-RISK consists of 10 partners from various countries in Europe, including basic scientists, epidemiologists, geneticists, and industrial partners. It is funded by the EU as a Horizon2020 project and started in 2015. One of the first goals was the establishment of a comprehensive epidemiologic database consisting of the raw data from the European epidemiologic eye (E3) cohorts and biobanks (total study population N greater than 40,000).This enabled us to develop prediction tools to predict frequency of AMD for the next 30 years, and to assess the relationship with serum lipids and lipid genes in great detail. We are currently establishing overall prediction algorithms growth rates for GA and turn-over rates for neovascular AMD. We have also developed a platform for comprehensive AMD genotyping at low cost. Molecular scientist have been working on the cell-specific consequences of genetic variants and system experts are currently defining molecular networks for AMD. Future deliverables will be a web-based prediction tool which incorporates information on genotype, serum biomarkers, and phenotype which will be usable for scientists and clinicians, as well as the general public. Other future goals are to create new clinical guidelines based on molecular signatures for AMD and new targets for prevention and therapy based on an in-depth understanding of pathogenetic drivers.

18) FFB's New, Emerging Strategy for Translational and Clinical Research.

Mr. Ben Shaberman, Foundation Fighting Blindness, Columbia, MD, USA

With the advent of numerous, emerging therapies which are ready for costly translational studies and early clinical trials, the Foundation Fighting Blindness (FFB) is planning the launch of venture capital fund(s) to support these endeavors.

FFB is continuing its traditional fundraising activities including VisionWalk, Dining in the Dark, direct mail and major gift solicitations to support earlier, lab-based research. The venture capital fund(s) will target more advanced

research projects. FFB has recently made major investments in biotechs such as:

- SparingVision which is developing rod-derived cone-viability factor for RP.
- Nacuity which is developing a modified form of N-acetylcysteine for RP and
- ProQR which is developing an antisense oligonucleotide for USH2A mutations in exon 13.
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While FFB has not launched a venture fund as of yet, these are the types of translational and/or early-clinical projects that would comprise the venture-fund portfolio.

Stay tuned for more details on FFB's emerging venture-capital strategy as it develops

C) Announcements, New Business and Conclusions

1) New Business and Announcements from the floor

RD 2018 in Ireland Dr. Christian Grimm – University of Zurich, Zurich, Switzerland

Commented [CC1]:

The XVIIIth International Symposium on Retinal Degeneration (RD2018) will be held September 03-08, 2018 in the beautiful town of Killarney in Ireland. Attendees will be housed in the marvelous Victorian hotel 'Great Southern Killarney' in downtown Killarney. The Great Southern not only has unique rooms, exceptionally good food and a very friendly staff, it also has a spacious conference center with comfortable seating, up-to-date audio-visual equipment and sufficient space for poster sessions.

As in past meetings, the program will focus on age-related macular degeneration and inherited retinal degenerations with several keynote lectures, three full days of oral presentations, evening poster sessions, a full day excursion and a gala dinner to round off the meeting in a social setting.

We raised money to fully support about 60 young scientists at the level of students, post-doctoral fellows, and young faculty lower than the rank of Associate Professor. Awardees will be chosen according to their submitted abstracts by a dedicated Travel Awards committee. Women and underrepresented minorities are encouraged to apply for Travel Awards and to attend the meeting.

People who wish to attend also the ISER meeting in Belfast will have time to translocate to Northern Ireland on Saturday, Sept 09, in time for the opening of ISER 2018.

For further information, please visit our website on http://rdmeeting.net. The organizing committee and the local organizers are excited to welcome the RD research community to Killarney this fall.

2) Final Comments – Ms. Christina Fasser

Ms. Fasser thanked all the speakers for their excellent presentations. She wished that all would have a very successful ARVO meeting and that we would all meet next year at the SMAB meeting in Vancouver, Canada.