RETINA INTERNATIONAL

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

Minutes of the 2017 Meeting of the Scientific and Medical Advisory Board of Retina International

Date: Monday, 8 May, 2017
Time: 1:00 - 2:30 p.m.
Location: Baltimore Convention Center - Room 342

Agenda

A) Introduction

1. Welcome - 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 Introduction – Breaking News in clinical trials for retinal degenerative diseases

Gene Therapy

1) Update on the Novelion (previously QLT) RPE65/LRAT clinical trial- Dr. Hendrick Scholl
2) Spark RPE65 gene therapy clinical trial update –Dr. Katherine High
3) DRUGSFORD evolves into Mireca Medicines and progresses to clinical trials– Dr. François Paquet-Durand
4) Update on gene therapy for choroideremia and X-linked RP- Dr. Robert MacLaren
5) Achromatopsia CNG3B clinical trial update - Dr. Dominik Fischer
6) Gene therapy trial for X-linked Retinoschisis - Dr. Catherine Cukras
7) Gene therapy trials at Moorefields Eye Hospital - Dr. Robin Ali
8) The NACA project - an update - Dr. Brian Mansfield

Artificial Vision

9) Artificial Vision Update – Dr. Eberhard Zrenner

Optogenetics

10) Channel rhodopsin treatment for RP and Dry AMD – Dr. David Birch

Cell- and Drug-Based Therapies

11) Stem Cell Therapy in Wet AMD: Clinical trial update – Dr. Masayo Takahashi
12) PDGF and VEGF in Neovascular AMD: Clinical trial update – Dr. Glenn Jaffe
13) ReNeuron clinical trial for RP – Dr. Eric Pierce

Patient-reported outcome measures

14) Functional Vision vs. Visual Function: Integrating the Patient Perspective Into Treatment for Retinal Degenerative Diseases – Meeting Report – Dr. Elise Heon

New clinical networks

15) ERN: European Reference Network accreditation and kick off – Dr. Helene Dollfus

C) Retina International Announcements, New Business and Conclusions

1. New Business and Announcements – from the floor
2. Final Comments – Ms. C. Fasser

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
Ali Robin; Birch David; Dollfuss Helene; Fischer Dominik; Heon Elise; High Katherine; Maclaren Robert; Mansfield Brian; Paquet-Durand François; Pierce Eric; Scholl Hendrik; Takahashi Masayo; Wei Lisa; Jaffe Glenn unable to attend but sent abstract

Participants
Aguirre Gustavo; Badura Franz; Bainbridge James; Becker Steven; Biel Martin; Bishop Paul; Boeni Barbara; Boye Shannon; Bredup Cecilie; Brady Laura; Bragadottir Ragnheidur; Carmichael Trevor; Cideciyan Artur; Colombo Leonardo; Cremers Franz; de la Rosa Enrique; Duncan Jacque; Flannery John; Fletcher Erica; Herrnandez-Sanchez Catilina; Humphries Peter; Kali Stasi; Keegan David; Kellner Ulrich; Kessel Line; Kjellstrom Sten; Klaver Caroline; Koenekoop Robert; Kondo Mineo; Larsen Michael; Laties Alan; Lorenz Birgit; Lotery Andrew; Michaelides Michel; Michalakis Stylianos; Munier Francis; Neidhart John; Murakami Akina; Pinilla Isabelle; Porto Fernanda; Preisig Markus; Prünte Christian; Richardson Jim; Sahel José; Sallum Juliana; Sankila Eva-Marja; Schorderet Daniel; Shaberman Ben; Simonelli Francesca; Thiadens Alberta; Tsilimbaris Miltiades; Tumminia Santa J.; Ueffing Marius; Uusitalo. Hannu; Vaklavic Veronika; Vincent Andrea; Wenzel Andreas

Meeting Minutes

A) Introduction

1. Christina Fasser welcomes the participants to the Retina International SMAB Meeting

2. Dr. Hollyfield and Dr. Zrenner welcome participants to the scientific part of the Retina International SMAB Meeting

B) Scientific Program Introduction – Breaking News in clinical trials for retinal degenerative diseases

Gene Therapy

1. Update on Novelion (previously QLT) RPE65/LRAT Clinical Trial.

Dr. Hendrick Scholl – Department of Ophthalmology, University of Basel, Basel Switzerland

Changes in company's business and management structure:

The last few months have brought changes in the business and management structure of QLT Inc, including the change of name from QLT Inc. to Novelion Therapeutics Inc. This change occurred in November, 2016, when QLT completed a merger with Aegerion Pharmaceuticals, Inc., a US-based global company that specializes in orphan drug products. Dr. John Orloff is the new Executive VP and Head of Research and Development. He has a lengthy career in clinical development and orphan product experience and will support the zuretinol program team as lead by Lana Janes out of Vancouver.

Clinical program

With this change in structure, a review of the study design and endpoints has been carried out to maximize the chance of study success and potential approval.

As a reminder, Novelion has been developing zuretinol acetate (formerly known as QLT 091001) as an oral, chronic replacement therapy targeted for patients with Retinitis Pigmentosa (RP) and Leber Congenital amaurosis (LCA) due to underlying mutations in LRAT and RPE65. It is proposed to replace/supplement endogenous 11-cis retinal in the visual cycle. In the past, the company has conducted three studies in subjects with these mutations and is working towards advancing to the next stage of studying the drug as a potential therapy.

To that end, the study team has been diligently working on putting the building blocks into place that will allow the successful start-up and enrolment of subjects in the company's next study. A rate limiting element to study start has been putting the finishing touches on the complex analysis pieces for the visual field reading center. That work is now actively ongoing and is progressing well. Recently, a meeting with the FDA took place in order to clarify a few important aspects of the future study design, including our study's primary and secondary endpoints including functional outcomes, as well as target study population, dose assessment, and study design, The FDA meeting was very productive and we are intending to move forward with our study and advance into the clinic this year.

Natural History Study

Results were presented by Dr. Koenekoop on Monday, May 8th at the ARVO meeting. The study confirms that patients with LCA or RP due to RPE65 or LRAT mutations experience progressive and significant declines in Visual Acuity and Visual Field without treatment, starting at an early age (median age at diagnosis of 4 years).

2. Spark RPE65 Gene Therapy Clinical Trial Update.

Dr. Katherine High, Cofounder, President and Chief Scientific Officer, Spark Therapeutics, Philadelphia, PA USA

Katherine A. High, M.D. presented an overview of the results of the Phase 3 trial of the company's investigational For etigene neparvovec, an AAV vector expressing RPE65. This study is the first randomized controlled trial in gene therapy for a genetic disease. The clinical trial included participants with a confirmed genetic diagnosis of biallelic mutations in RPE65.

Participants who met all enrolment criteria were randomized in a ratio of 2:1 to enter either the intervention group (total of 20), where they underwent sequential bilateral injection of vector to both eyes, or to a control group (total of 9), where they completed the same series of assessments at baseline, 30 days, 90 days, 180 days, and 365 days after randomization, but without having been injected. Those in the control group were permitted, at the one year conclusion of the trial, to cross over and receive sequential, bilateral injections in both eyes.

The trial endpoints were the comparison between intervention and control groups on a series of endpoints at the one-year time point. The pre-specified endpoints included the primary endpoint, which was the change in lowest light level at which subjects could pass a multiluminance mobility test (MLMT) at one year compared to lowest passing light level at baseline under bilateral testing conditions; and three secondary endpoints: change in full-field light sensitivity from baseline to one year; change in performance on MLMT using the assigned first eye only; and visual acuity. Additional pre-specified endpoints included Goldmann and Humphrey visual field testing, contrast sensitivity, and a community-based functional vision assessment by an orientation and mobility expert.

For the primary endpoint, participants in the intervention group improved by 1.8 light levels on the MLMT, while those in the control group improved by 0.2 light levels, for a p value of 0.0013. Thirteen of 20 intervention participants (65%) were able to pass the MLMT at 1 lux, the lowest light level tested, at the one year time point, while none of the control participants were able to.

For the secondary endpoints, mean full field light sensitivity in the intervention group improved ~100-fold, while there was little to no change in the control group ($p = 0.0004$), and the monocular MLMT results were similar to the bilateral results (primary endpoint). Visual acuity showed a trend toward improvement in the intervention group (improvement by 8 letters in best corrected visual acuity) vs. the control group (improvement by 1.6 letters), but this did not reach statistical significance ($p = 0.27$). Goldmann visual fields using the III4e test stimulus improved from 332 sum-total degrees at baseline to 673 degrees on average at the one year time point in the intervention group, whereas visual fields in the control group decreased (from average of 427 to 398 sum-total degrees) over the one year time period.

No serious adverse events (SAEs) associated with voretigene neparvovec or deleterious immune responses were observed. Most ocular events were mild in severity with the most common ocular adverse events being transient mild ocular inflammation, transient elevated intraocular pressure, cataracts, and intraoperative retinal tears. Spark Therapeutics has taken advantage of its FDA Breakthrough Therapy Designation to conduct a rolling submission of the Biologics License Application (BLA) with the U.S. Food and Drug Administration (FDA). Spark also intends to submit a Marketing Authorization Application to the European Medicines Agency.

3. DRUGSFORD Evolves into Mireca Medicines and Progresses to Cinical Trial.

Dr. François Paquet-Durand, University of Tübingen, Tuebingen, Germany for MIRECA Medicines

The EU-funded DRUGSFORD project (www.drugsford.eu) ran from September 2012 to August 2016 and aimed to produce new drugs for the treatment of hereditary retinal degeneration (RD). To overcome the problem of genetic heterogeneity in RD, DRUGSFORD focused on cGMP signalling as a therapeutic target and developed novel cGMP analogues as therapeutic agents. For efficient delivery across the blood-retinal-barrier, cGMP analogues were encapsulated into an innovative liposomal drug delivery vehicle so that they could reach the photoreceptor cells and exert their beneficial effect.
The DRUGSFORD consortium was built around three industrial and three academic partners from four different countries. The company BIOLOG (Bremen, Germany) is the world leader in producing nucleotide analogues that can target and modify cGMP-signalling. BIOLOG´s compounds were encapsulated into a liposomal drug delivery vehicle proprietary to the company 2-BBB (Leiden, The Netherlands). The novel compounds and their liposomal formulations were tested in a step-wise fashion in three different systems of increasing complexity, initially *in vitro* in photoreceptor-like cell cultures (V. Marigo, University of Modena, Italy), then in organotypic retinal explant cultures (P. Ekström, University of Lund, Sweden), and finally *in vivo* in various RD animal models (F. Paquet-Durand, University of Tubingen, Germany). Finally, the company SP Process Development (Now: RISE Process Development), established good-manufacturing-practice (GMP) production for the active pharmaceutical ingredient (API).

After four project years, DRUGSFORD has produced over 250 novel cyclic nucleotide analogues. More than 180 of these were tested in cell-free assays, 35 were tested in photoreceptor-like cell cultures, 16 compounds were tested in retinal explants, and 5 were tested *in vivo* in the *rd1* mouse. One liposomal compound formulation – LP-DF003 – resulted in significant photoreceptor rescue in *rd1, rd2, rd10*, and *cpfl1* mice. Importantly, in the *rd2* and *rd10* models carrying RD causing mutations in two different genes (*Prph2*, *Pde6b*,

resp.), the morphological rescue also resulted in a highly significant improvement of retinal function, as assessed in ERG recordings. Consequently, the consortium selected LP-DF003 as the first lead to be developed for clinical testing.
LP-DF003 was granted orphan drug status from the European Medicines Agency (EMA; EU/3/15/1462), and the consortium has filed three different patent applications for API and formulations. DRUGSFORD also finalized a toxicological test programme which detected no safety issues so far, including in an exploratory toxicity and pharmacodynamic (PD) study in non-human-primates. DRUGSFORD then developed a clinical trial programme that was positively reviewed by the EMA (protocol assistance procedure) and that could allow market registration in 8-10 years from today.
To forward the clinical development of LP.DF003 and its eventual commercialization, the DRUGSFORD partners have jointly founded the new company Mireca Medicines GmbH in April 2017. Mireca is incorporated in Tübingen/Germany, and is currently working on a structured business and financial development plan. The first financing round is expected to be completed before the end of 2017. In summary, the highly successful pre-clinical DRUGSFORD project has now been converted into the commercial endeavour Mireca Medicines, to rapidly advance to clinical testing.

For further information please refer to:

- DRUGSFORD website: www.drugsford.eu
- Mireca Medicines GmbH: www.mireca.eu

4. Update on Gene Therapy for Choroideremia and X-Linked RP. *Dr. Robert MacLaren University of Oxford, Oxford, UK*

At the University of Oxford we are currently coordinating two retinal gene therapy trials. A Phase 2 study sponsored by the University of Oxford explores gene therapy in choroideremia in early-stage patients and is a collaboration between Moorfields Eye Hospital and the University of Oxford. So far, 18 patients have been recruited into the study and have undergone successful gene therapy surgery. This is in addition to the investigator-led choroideremia gene therapy trials linked to Oxford which are ongoing at the University of Alberta in Edmonton, the Centre for Ophthalmology in Tübingen in Germany and the Bascom Palmer Eye Institute in Miami. Nightstarx Ltd is also planning further clinical trials which are international and independent of the University of Oxford.
In March of this year, we also started gene therapy for X-linked retinitis pigmentosa caused by mutations in RPGR. The clinical trial is sponsored by NightstarX Ltd using gene therapy technology developed at the University of Oxford. The project was originally funded by the Medical Research Council (UK) and led by Prof Dominic Fischer, who is now in Tübingen. The science

behind the trial includes a complex codon optimisation algorithm that provides stable RPGR protein and has overcome many of the problems of deletions and splicing when using the wild-type sequence in AAV vectors (Fischer et al., Mol Therapy 2017). This 'first in man' clinical trial delivers the full-length wild-type RPGR protein, which distinguishes it from other clinical studies in which use of a stabilised RPGR containing random deletions has been proposed. Several patients have now undergone uncomplicated gene therapy surgery in Oxford. Any other sites wishing to join the next phase of the trial should contact Nightstar, via their London or Boston offices.

5. Achromatopsia CNG3B clinical trial update

Dr. Dominik Fischer. Department of Ophthalmology, University of Tubingen, Tubingen, Germany

The CNGA3 gene therapy trial is the first ocular gene therapy trial in Germany and was approved after extensive pre-clinical work by members of the RD-CURE consortium. This group is coordinated by Drs. Bernd Wissinger and Martin Biel and consists of Martin Biel's group in Munich, who engineered the knock-out mouse in 1999, several groups at the Centre for Ophthalmology in Tubingen (Drs. Wissinger, Kohl, Zobor, Seeliger, Paquet-Durand, Peters, Ueffing, Wilhelm and Fischer) and Stephen Tsang at Columbia. 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 2016, 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 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 ($1x10^{11}$). Those last patients have now been followed up for a minimum of 6 months and we have not observed any inflammation in any patient from the high dose cohort as of today. Last patient, last visit is scheduled for Q4 2017 with consecutive analysis of trial results.
The aim of the study is to proof the safety and efficacy of rAAV.hCNGA3 in patients with achromatopsia. The primary endpoint of the study is safety and

will be assessed by clinical examination of ocular inflammation. Systemic safety is assessed by vital signs, routine clinical chemistry testing (including CRP, ESR) and differential blood counts. Immunopathology essays include ELISA and lymphocyte activity assays. Biodistribution is monitored by qPCR studies on rAAV8 genome in blood, urine, saliva and lacrimal fluid.
Efficacy tests include BCVA, contrast sensitivity, flicker fusion frequency, color vision (color constancy, anomaloscopy, Cambridge Colour Test), pupillography, microperimetry, dark adaptation, GF-ERG and VFQ25 and A3-PRO as patient reported outcome assessments.
Preliminary results show good safety. We did not see any surgical or post-surgical complications such as retinal detachment, hemorrhage or inflammation unresponsive to treatment. In term of secondary outcome measures, a preliminary analysis of efficacy data was approved in an amendment as of April 2017. We are currently performing this analysis and are excited about the final results in early 2018.

6. Gene Therapy Trial for X-linked Retinoschisis.

Dr. Catherine Cukras (presented by Dr. Lisa Wei) - National Eye Institute, National Institutes of Health, Bethesda, MD USA

X-linked Retinoschisis (XLRS) is a monogenic trait caused by mutations in the RS1 gene encoding a 224 amino acid secretory protein called Retinoschisin. The clinical phenotype of XLRS is quite broad at the time of clinical onset or, more precisely, in the sympromatic awaremess by the affected young boy or his parents and in the extent of the peripheral retinal pathology. Central visual acuity reduction with the presence of schisis cavities in the plexiform and nuclear layers of the retina, as seen by OCT imaging, is one of the hallmarks of XLRP. Concomitantly, there is a reduction in the ERG b-wave/a wave (B/a) amplitude, another clinical hallmark of XLRS.
Slow progression occurs and may continue into the 5th and 6th decades and even in later age. Further central degeneration commonly causes additional visual failure. XLRS patients over 50 years of age frequently have macular pigmentary changes and/or macular atrophy.
We are in the midst of a phase I/IIa clinical trial investigating safety and tolerability of a single intravitreal delivery of AAV8.RS1 in dose escalation. We have dosed participants at 3 dose levels. Outcome measures include visual acuity, microperimetry, full field ERG. OCT, fluorescein angiography and hematologic testing. Neutralizing antibody titers for viral vectors and anti-RS1 serologic treating are being measured.
Parameters for outcome measures for both safety and efficacy must be based on the knowledge of natural variation of diseases. We have reported short-term repeatability of functional and anatomic parameters of interst including visual acuity, OCT measurements of central thickness and ERG parameters. For central visual function, both visual acuity and microperimetry (given the patient’s nonpfoveal fixation) are targeted to capturing the impact

of macular disease. Since RS1 is involved in synaptic transmission, full field ERG and especially the b/a ratio are attractive measures.

7. Gene therapy trials at Moorefields Eye Hospital

Professor Robin Ali - UCL and Moorfields Eye Hospital, London and CSO, MeiraGTx Ltd

Over the past year we have substantially expanded our infrastructure for conducting gene therapy trials that includes expansion of GMP facilities for manufacturing clinical grade vectors as well as a major expansion of our clinical trials team.

We have 2 clinical trials currently underway:

1) LCA2 due to RPE65 deficiency.

We believe the first generation of vectors that have been used to treat this condition are sub-optimal and do not generate sufficient RPE65 to restore normal retinal function and therefore provide long term protection against degeneration. We have therefore developed a new vector comprising an AAV5 capsid and optimised RPE65 promoter. The new vector is at least 500-fold more potent than our original vector. The clinical trial started in May 2016 and to date, seven adult participants have received the new vector. We have completed low- and mid-dose cohorts and have just initiated the high-dose cohort. Once we have completed dose escalation in adults, will enroll children. We aim to expand this into a multicentre study involving the Kellogg Eye Centre, University of Michigan by autumn 2017. We anticipate completion of the trial of up to 18 subjects within 12 months.

2) Achromatopsia due to defects in CNGB3. We are using an AAV8 vector and a cone arrestin promoter.

We started the trial in Feb 2017. To date, we have administered vector to three adults. Again, this is a dose escalation study – we will test a medium and high doses before enrolling children. We anticipate completion of the trial of up to 18 subjects within 2 years and it soon is to become a multicentre study involving the Kellogg Eye Center

New Trial: X-linked RP due to RPGR deficiency. We are using an AAV5 vector and a rhodopsin kinase promoter

This trial is due to begin in July/August 2017. Although a very challenging gene defect to treat, after 10 years of optimisation, we have now finalised the development of a gene therapy vector in collaboration with Drs. Tiansen Lee and Alan Wright. We have also spent many years carrying out extensive studies of patients with X-linked RP to determine the most practical trial outcome measures to assess the effectiveness of this gene therapy within a viable trial timeframe. We have now completed manufacture of a clinical grade vector, tested its safety and are awaiting regulatory approval to start a clinical trial that will involve up to 36 subjects, a 2 year enrolment stage and a

2 year follow-up. This study will also become a multi-centre study involving the Kellogg Eye Center in Michigan and the and Massachusetts Eye and Ear Informary.

Other clinical trials and experimental therapies:

We have now started to manufacture clinical grade vector for a fourth inherited retinopathy (another form of LCA) and we aim to start this trial in 2018. We have many more indications that we want to treat and our aim is to initiate a number of other trials over the next couple of years.

As well as clinical trials, we are using another route to develop gene therapy. In the UK, it is possible to provide an experimental therapy under a **"Hospitals Exemptions" route rather than through a clinical trial.** We are using this route to explore the safety and efficacy of gene therapy for LCA4 due to deficiency in AIPL1. This is very severe LCA for which it would be difficult to carry out a trial because it so rare. We have now manufactured clinical grade vector under a "Hospitals Exemptions" licence and we should be in a position to administer this experimental therapy at Moorfields Eye Hospital to children with LCA4 on a case-by-case basis stating from September 2017.

8. The NACA project – an update

Dr. Brian Mansfield. Foundation Fighting Blindness, Columbia, MD, USA

With the increasing genetic diversity being observed in the inherited retinal degenerative diseases, the Foundation Fighting Blindness has been very interested in supporting therapeutic approaches which are less dependent on specific genes and mutations and more general in their applicability. One initiative we have supported has been the work of Dr. Peter Campochiaro (Johns Hopkins University, Baltimore, MD) who has been examining the potential of various antioxidant molecules and the development of biomarkers of oxidative stress that could be used to monitor such therapies. Dr Campochiaro recently published promising preliminary data on two potential markers for oxidative stress that can be measured in the aqueous humor of human RP patients. Based on this study, he is now examining the therapeutic potential of one of the most promising anti-oxidant molecules, N-acetyl cysteine (NAC) in a small clinical trial. This is an FDA approved drug for acetaminophen overdose and the use in retinal dystrophies is a repurposing study.

As an approved drug, NAC could move to clinic quickly. There is a precursor to NAC called N-acetyl cysteine amide (NACA) that, in preclinical testing also undertaken by Dr. Campochiaro, appears more effective, and has the additional advantage of crossing barriers like the blood-retina barrier more easily. This molecule is not FDA approved. In collaboration with the privately held company Nacuity Therapeutics, the Foundation is co-funding IND-enabling studies of toxicity and biodistribution for NACA with the goal of

entering clinical trials for RP in 2018, led by Dr. Campochiaro. It is hoped information from the current NAC study will help guide the design of the NACA clinical trial.

Artificial Vision

9. Artificial Vision Update.

Dr. Eberhart Zrenner – Department of Ophthalmology, University of Tuebingen, Tuebingen, Germany

A summary of Dr. Zrenner's talk is not available. Data below have been obtained from relevant websites and new scientific publications. Information is delimited to progress in the use of the two commercially available retina implants.

Retina Implant AG:

The Alpha AMS system is a relatively new device that is an upgrade to the initial Alpha IMS cleared in Europe in 2013. The system features 1600 pixels (dots of light) which is 100 more than in the Alpha IMS model. This provides patients with improved visual clarity. There is no external camera so vision is more natural than in systems that capture the visual field using cameras. Also, the patient looks with the eyes rather than having to turn the entire head to change the point of view.

The system consists of three components: 1) the implant 2) a receiver and 3) a control unit. The Alpha AMS implant is surgically placed beneath the retina so that the function of the degenerated retinal photoreceptors can be replaced. The external receiver contains a power source in a ceramic coil implanted behind the ear under the skin. The control unit is essentially a transponder that sends energy from the handheld device to the implanted coil. Through this, the patient can adjust the brightness and contrast of the signal. The system has been approved for implantation by the EU.

Second Sight Medical Products:

The ARGUS II system works by converting images captured by a miniature video camera mounted on the patient's glasses into a series of small electrical impulses which are transmitted wirelessly to a grouping of electrodes called an "array" that are implanted on the surface of the retina. These impulses stimulate the retina's remaining cells resulting in the perception of patterns of light in the brain. The patient learns how to interpret these visual patterns, thus having the potential to regain some visual function. Five-year safety and performance results for the ARGUS II clinical trial have now been published (Ophthmology vol 123, p2248, October 2016). The results support the long-term safety profile and benefits of the system for patients blind as a result of RP.

The ARGUS II is the first Artificial Retina to receive approval for implantation in both the USA and the EU. To date, there have been well over 200 implantations of the ARGUS II system. For example, Dr. Stanislao Rizzo in

Italy has now completed over 30 implantations. In April, SSMP announced its first implantation in Asia completed by Dr. Hwang Y.-S. in Taiwan.

Optogenetics

10. Channel Rhodopsin Treatment for RP and Dry AMD. *Dr. David Birch – Retina Foundation of the Southwest, Dallas, TX, USA*

We're conducting a trial with RST-001, a gene therapy product based on the light-gated ion channel, channelrhodopsin-2 (ChR2). This approach was originated by Dr. Zhuo-Hua Pan at Wayne State Univ., who showed that it was possible with gene therapy to insert ChR2 into ganglion cells in rd1 mice. He showed that, with sufficient stimulation, he could produce ChR2-driven ganglion cell responses. Subsequently, OKN and VEP responses have been shown in ChR2-treated mice and the Tomita group has shown similar finding in the RCS rat.

After extensive toxicology and biodistribution studies, RetroSense Therapeutics received regulatory approval for a trial entitled "A Phase I/IIa open-label, dose-escalation study of safety and tolerability of intravitreal RST-001 in patients with advanced retinitis pigmentosa (RP)". The RFSW is the first site with a team of investigators including Dr. Yi-Zhong Wang, who helps with psychophysical and low vision testing. Since this is the first time a non-human gene has been expressed in a patient, we've involved retinal specialists at Texas Retina Associates including Drs. Spencer, Coors, and Wong, who is an expert in uveitis.

This is primarily a safety trial but ultimately the goal is to convert blind patients to low vision patients. To test efficacy in the trial, we're using a battery of tests other than the traditional acuity, etc. These include an ultra-high intensity LED display panel with either blue or red LEDs that can be uzsed to display patterns, movement, letters, etc. We're also testing patients with the full-field sensitivity test, with pattern VEPS, and a light-guided walking task.

The trial is enrolling 15 patients. The first 9 are in a 3 group dose escalation phase going from $4.3 * 10^{10}$ to $4.3 * 10^{11}$ vg through a single 100 mL intravitreal injection. The subsequent 6 will be treated with the highest tolerated dose. To be eligible, vision in the study eye can be no better than hand motion. The 1st patient was treated in March 2016 and the 3rd patient in Group 1 was treated on August 2016. The DSMC had no safety concerns with the low dose and no inflammation was seen.

In Sept 2016, Allergan acquired RetroSense Therapeutics and put a hold on the study while all the procedures and forms were converted. After a pause of several months, we restarted the trial with a patient receiving the mid-dose in April 2017.

Cell- and Drug-Based Therapies

11. Stem Cell Therapy in Wet AMD: Clinical trial update.
Dr. Masayo Takahashi MD, PhD - CDB, RIKEN, Japan

Induced Pluripotent Stem Cells (iPS) are a type of stem cell that can be generated directly from adult cells. In this way, mature cells can be reprogrammed to become plutipotent cells that can give rise to all of the cell types that make up the body such as retinal pigment epithelial (RPE) cells. In our clinical trial, an autologous iPSC-derived RPE sheet was successfully transplanted. The primary endpoint of safety was achieved one year after surgery in the first patient who received autologous iPS-RPE sheet transplantation in wet age-related macular degeneration (AMD). Her visual acuity is still stable without anti-VEGF injections or immune suppression. The HLA 6 loci homozygous iPS cell line was established that covers 17% of the Japanese population. We observed that MHC-DR-matched iPS-RPE cells did not cause any immune rejection in animal experiments. We are now preparing to perform clinical research on allogeneic iPS-RPE transplantation to evaluate the immune reaction to the HLA-matched or -mismatched iPS-RPE cells.

12. PDGF and VEGF in Neovascular AMD: Clinical trial update.
Glenn J. Jaffe, MD, Department of Ophthalmology, Duke University, Durham, NC USA

Neovascular age related macular degeneration is the leading cause of visual acuity loss in the United States among individuals aged 55 and older, and is a major cause of vision loss around the world. Anti-vascular Endothelial Growth Factor (VEGF) therapy has been effective in treating this condition over the first two years after therapy has been initiated. However, in several studies, visual acuity declined over the ensuing years to a level that was at or below the initial baseline visual acuity. According, there is a significant unmet need to develop treatments that can provide sustained visual acuity improvement beyond the initial 2 years of treatment. Fibrotic scar is an important reason for visual acuity loss, as is continued VEGF angiogenesis drive. Platelet-Derived Growth Factor (PDGF) together with VEGF serve to coordinate angiogenesis, and PDGF is a fibrosis-inducing protein. It has been hypothesized that dual-antagonism of VEGF and PDGF could more effectively inhibit angiogenesis in neovascular AMD, and would reduce scar tissue formation, when compared to anti-VEGF monotherapy.
In animal models of pathogenic neovascularization, combined anti-VEGF/PDGF therapy induced greater reduction in neovascularization than anti=VEGF treatment alone. These pre-clinical studies prompted human ant-VEGF/PDGF clinical trials. Phase I and a large phase II human trial showed promising results that suggested a benefit of dual antagonism over anti-VEGF

monotherapy. Accordingly, three large phase III trials were conducted by Ophthotech and a large phase II trial was conducted by Regeneron. Data from two of the three Opthotech phase III trials and from the phase II Regeneron trial have now been reported. Unfortunately, the reported data from these trials was disappointing - none of the trials met their endpoint to show a benefit of combination treatment when compared to monotherapy. The reason(s) for the failure of these clinical trials is unclear. It could be that the hypothesis regarding dual antagonism therapy does not translate from pre-clinical animal models to human disease. It is also possible that the PDGF drug concentration, formulation, dosing frequency, or timing relative to PDGF therapy was not correct. Data from currently ongoing anti-VEGF/PDGF clinical trials may shed some light on these possibilities. Regardless, there remains an unmet need for neovascular AMD treatments that can prevent fibrosis, that can enhance the anti-VEGF effect, and that can provide durable visual acuity improvement over the patients' lifetime.

13. ReNeuron Clinical Trial for Retinitis Pigmentosa.
Dr. Eric Pierce, Massachusetts Eye & Ear Infirmary, Harvard Medical School, Boston, MA USA

Reneuron is conducting a clinical trial testing tolerability and safety of human retinal progenitor cells ((hRPCs) in patients with retinitis pigmentosa. This is trial NCT0264436. This is a first, in-human, dose escalation study in which participants with advanced pigmentosa receive a single subretinal injection of hRPC cells in one eye to evaluate safety and tolerabiligy. This trial is in progress.

Patient-Reported Outcome Measures

14. Functional Vision vs. Visual Function: Integrating the Patient Perspective Into Treatment for Retinal Degenerative Diseases – Meeting Report
***Dr. Elise Héon. SickKids Hospital, Toronto, Canada*.**
On behalf of Eberhart Zrenner, Christina Fasser, Patricia Zillox and all the presenters of the PROM meeting held in Washington DC Nov 2016.

The purpose of the meeting was:
It has become clear that there is an increasing need to develop Patient Reported Outcomes (PROs) tailored to the Inherited retinal Degeneration (IRD) population to best reflect not only the natural history of the effect of vision loss but as an added outcome measure for the assessment of treatment response. A PRO is any report (endpoint) of the status of a patient's health condition that comes directly from the patient without

interpretation by anyone else. This is measured by self-report or interview. For example: „Does a 1-line acuity gain make a difference to the patient?“ These are usually obtained through validated questionnaires. Robust PROs are becoming important also for reimbursement purposes. It's really all about optimizing clinical endpoints.
The objective of this meeting was to analyze the status of PRO development and to form a working group focused on harmonizing the perspectives of the regulators, scientists, and patients in a report on appropriate PROs to be considered in upcoming studies. Participants included members of the NIH, regulatory agencies, Industry, the scientific community and Academia.

Issues addressed included:

1. PPs vs PRO, what is use in drug trials vs. devices?
2. What are the tools currently available for different patient populations?
3. What questionnaires and measurement systems are available?
4. Discussion about the knowledge gap and what should be the next step to get to a Best Practice for the evaluation of patients with IRDs.

What we learned was that:

- PROs are increasingly used as outcome measures in clinical trials of other specialties, such as Pain, Oncology, Rhumatology, Respiratology etc. In Ophthalmology, the filed of cataract, AMD and Glaucoma have used PROs. In fact, 121 ophthalmic PRO instruments have been identified, which can make results hard to compare. Many PROs are used but are not necessarily based on good measurement properties.

- PROs should be developed early in the study, and tailored to the condition studied. Although generic PROs, are more readily available, they provide less valuable information.
- PRO data have been included in European product information with NEIVFQ featuring in the summary of product characteristics for Humira, Lucentis, Eylea, Jetrea.

- Regulatory endpoints in the EU-EMA are similar to those in the USA-FDA in that they need to reflect clinically-relevant treatment benefits. The methods for measurement of the endpoint should be valid, reliable and responsive. Both the organ of interest and the whole person need to be considered. A collaboration EU-USA led to the development of a new program:, the „**Innovative Medicines Initiative**“ (IMI) established in 2016 in which Patient Preference plays a prominent role. This was designed to establish recommendations to aid guidance development for industry, regulators and health technology assessment (HTA) bodies on how and when in the product life-cycle to consider patient perspectives on benefits and risks and to inform the decision-making process.
- A roadmap to **Patient-Focused Outcome Measurement** in clinical trials requires 1) understanding the disease condition 2)

conceptualizing treatment benefits and 3) selecting and developing the outcome measure. There are several concepts that a PRO measure should capture such as 1) symptoms 2) symptom impact and tolerability 3) functioning 4) satisfaction and 5) vision-related QOL.

- There is a scientific process to develop these tools, which must then be validated. The methodology to do this properly is complex, costly and evolving This process is **iterative** with many reasons for changing items during development. Some of these are:
  1) clarity or relevance
  2) response range
  3) variability
  4) reproducibility
  5) inter-item correlation
  6) ability to determine change
  7) item discrimination
  8) redundancy, etc.
- We must include the different types of visual impairments, in some cases involving age, environment, degree of disability, etc.
- Choice of PRO: validity, reliability and sensitivity are applicable to the target population (children, elderly, severity, changes over trial period). Patients are actively involved in the development of these tools.
- There are tools available to develop PROs, and experts to drive them. E.G.: **PROMIS: The NIH Patient-Reported Outcomes Measurement System.**
- We are learning the importance of the difference between visual function and functional vision.

The next step:
A white paper is being considered for publication and discussions are ongoing to develop PROs suitable for our patient populations.
We will build on experiences of other therapeutic areas for PROs e.g. Neurology, Respiratory, Gastroenterology, Endocrinology and Oncology and what has been done in Ophthalmology to develop appropriate tools.

I would like to thank C Fasser, E Zrenner, and P Zillox for spearheading this initiative.

New Clinical Networks

15. ERN: European Reference Network Accredidation and Kick-off.
Dr. Helene Dollfus. Service de Genetique Medicale, Hospital de Hautepierre, Strasbourg, France

A summary of Dr. Dollfus' talk was not available. Following is information on ERN taken from relevant websites:

European Reference Networks (ERNs) are virtual networks involving healthcare providers across Europe. They address the complex and rare diseases and conditions that have a low population prevalence but require highly specialized treatment and concentrated knowledge and resources. Patient diagnosis and treatment is reviewed by virtual advisory boards convened by ERN coordinators. These are medical specialists across different disciplines and they use a dedicated IT platform and telemedicine tools.

Thus, ERNs create a clear government structure for knowledge sharing and care coordination across the EU. They are networks of centers of healthcare providers and laboratories that are organized across borders. A Center of Expertise could be a clinical team, a medical center or a hospital and must be formally accredited by its Member State.

Separate ERNs cannot be created for each rare disease but, rather, similkar diseases are grouped together within a single ERN. This groupings of diseases does not prevent a patient from being able to go to a disease-specific center of expertise nor from benefiting from the expertise of several ERNs. If there is no Center of Expertise for a patient's specific condition in their country, patients can still benefit from the knowledge that their doctor can get from Centers of Expertise in different countries. Thus. ERNs provide the structure that facilitates a doctor's ability to access critical knowledge across borders.

A special network has been developed to establish a virtual clinic known as EyeClin to guarantee the best coverage of Rare Eye Diseases and facilitate cross-border dissemination of expertise. Rare Eye Diseases are the leading cause of visual impairment and blindness for children and young adults in Europe. ERN EYE addresses these conditions in 4 thematic groups: rare diseases of the retina, neuro-ophthalmology rare diseases, pediatric ophthalmology rare diseases and rare anterior segment conditions. In addition, 6 transversal working groups are addressing issues common to the 4 main working themes. Additional working groups focus on specific areas such as genetic testing, registries, education communication and patients. The Network Coordinator is Dr. Helene Dollfus.

C) Announcements, New Business and Conclusions

1. New Business and Announcements – from the floor

All are reminded to attend the **20th Retina International Congress** to be held 10-11 February at the University of Aukland, Aukland, New Zealand. Through a fast-moving programme of short scientific presentations, expert panels, treatment approach plenary sessions, practical guidance presentations and

social events. Retina 2018 New Zealand will present the most up-to-date knowledge in fields such as scierntific and clinical research, treatment advocacy and access, rehabilitation best practices, blindness-specific technologies and peer support.

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 Hawaii.

Gerald Chader

Baltimore, 8th May, 2017