RETINA INTERNATIONAL

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

Minutes of the 2016 Meeting of the Scientific and Medical Advisory Board of Retina International

Date: **Monday, 2nd May, 2016**
Time: **1:00 - 2:30 p.m.**
Location: **Washington State Convention Center, Room 3AB, Seattle WA**

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 Trials: Updates and New Trials

1. Stem cell clinical trial in wet AMD: iPS cell-derived RPE - transplantation for age-related macular degeneration-*Dr. Masayo Takahashi*
2. Stem cell use in RP-*Dr. Henry Klassen*
3. Update on long-term consequences of subretinal gene therapy for *RPE65*-LCA-*Dr. Artur V. Cideciyan*
4. Valproic Acid (VPA) clinical trial-*Dr. David Birch*
5. New trial of gene therapy for RPE65 deficiency (LCA2) initiated at Moorfields Eye Hospital, London, UK-*Dr.Robin Ali PhD*
6. RLBP1 Retinitis Pigmentosa: preparation for clinical trial-*Dr. Kali Stasi*
7. Choroideremia NightstaRx clinical trial-*Dr. Robert MacLaren*
8. Ocular gene transfer for human X-linked retinoschisis (XLRS)-*Drs. Lisa Wei and Paul A. Sieving*
9. Current Status of the achromatopsia CNG3B gene therapy clinical trial-*Dr. Dominik Fischer*
10. Update on clinical trials for RPE65/LRAT-related inherited retinal degenerations – the QLT Inc retinoid program-*Dr. Robert Koenekoop*
11. Usher gene therapy clinical trial-*Dr. Jose-Alain Sahel*
12. Retinal electronic prostheses-*Dr. Eberhard Zrenner*
13. Pixium retinal implant trial-*Dr. Serge Picaud*
14. The DRUGSFORD project-*Dr. François Paquet-Durand*

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

President:	Ms. Christina Fasser
SMAB co-chairman:	Dr. Eberhart Zrenner
SMAB co-chariman:	Dr. Joe Hollyfield
SMAB secretary	Dr. Gerald G. Chader

Speakers

Robin Ali, David Birch, Artur V. Cideciyan, Dominik Fischer, Henry Klassen, Robert Koenekoop, Robert McLaren, Serge Picaud, Francois Paquet-Durand, Jose-Alain Sahel, Paul Sieving represented by Lisa Wei, Kali Stasi, Masayo Takahashi

Roster of Participants at the RI SMAB meeting, 2 May 2016, Seattle WA USA.

Aguirre, Gustavo
Andreasson, Sten
Ballios Brian
Banfi, Sandro
Becker, Steven
Bernstein, Paul
Biel, Martin
Bishop, Paul
Boeni, Barbara
Bredup, Cecilie
Carmichel, Trevor
Cremers, Frans
Daly, Avril
de la Rosa, Enrique
Flannery, John
Fletcher, Erica
Grimm, Christian
Heon, Elise
Herrnandez-Sanchez, Catilina
Hickey, Fionnuala
Humphries, Pete
Kalloniatis, Michael
Keegan, David
Kellner, Ulrich
Kjellstrom, Sten
Klaver, Caroline
Laties, Alan
LaVail, Matthew
Lottery, Andrew
Lorenz, Birgit
Michaelides, Michel
Mullins, Anmol
Munier, Francis
Murakami, Akira
Michalakis, Stylianos
Neidhart, John
Pierce, Eric
Pinilla, Isabelle
Porto, Fernanda
Preisig, Markus
Sallum, Juliana
Sankila, Eva-Maria
Shaberman, Ben
Simonelli, Francesca
Thiadens, Alberta
Tsilimbaris, Miltiades
Tumminia, Santa
Ueffing, Marius
Uusitalo. Hannu
Vallim Salles, Mariana
Vincent, Andrea
Vingolo, Enzo Maria
Weber, Bernhard
Wenzel, Andreas
Worsley, David

Meeting Abstracts

1. Stem cell clinical trial in wet AMD: iPS cell-derived RPE - transplantation for age-related macular degeneration

Dr. Masayo Takahashi MD, PhD CDB, RIKEN, Japan

In a 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 an 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 submacularly reansplanted RPE sheet survives well without any findings of immune rejecction or adverse proliferation for more than a year. Retinal imaging examinations showed improvvement of the pre-existing exudative cbange. Best-corrected visual acuity was stabilized at 0.09 (= 18/200) without addditional anti-VEGF therapy. A score of VFQ (Visual Function Questionairre)-25 improved from 40.7 to 58.3. Since autologous transplantation is time consuming and the cost is high, next, we are preparing clinical research for HLA 6 loci matched allogenic transplantation.
An 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 for clinical research of allogeneic iPS-RPE transplantation to evaluate the immune reaction to the HLA-matched or -mismatched iPS-RPE cells.

2. Stem cell use in RP

Dr. Henry Klassen, UC Irvine, Irvine CA USA

Extensive laboratory studies have previously 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. Recently, we have focused on this latter approach and extended such work to the production of human RPCs under GMP-compatible conditions and formal IND-enabling preclinical studies. Following IND approval from the FDA, we began a Phase 1/2a open label safety study of intravitreal RPCs in retinitis pigmentosa. This trial includes 2 patient cohorts based on residual visual function, as well as a dose escalation component. The study is ongoing. A total of 19 patients have been enrolled as of April 18, 2016, including 4 dose levels. No serious adverse events have been reported to date. Initial clinical experience supports the safety of the approach in late stage RP.

3. Update on long-term consequences of subretinal gene therapy for *RPE65*-LCA

Dr. Artur V. Cideciyan, University of Pennsylvania, Philadelphia, PA

One of the more severe forms of inherited retinopathy causing congenital vision loss is Leber congenital amaurosis (LCA). The *RPE65* mutation form of LCA is a complex disease resulting from a biochemical block of the visual cycle with substantial loss of light sensitivity of rod and cone photoreceptors as well as a progressive time course of retinal

degeneration and worsening vision. Starting in 2007, several independent groups initiated subretinal gene augmentation therapy in patients with *RPE65*-LCA with the goal of reversing the biochemical block and improving vision in the short term and arresting retinal degeneration in the long term. More than 20 primary research papers and numerous reviews/editorials have been published by different groups.

Our group at the University of Pennsylvania and University of Florida performed an NIH-supported clinical trial in one eye of 15 *RPE65*-LCA patients who were 11-30 years old at the time of the surgery. We have continued to follow both the treated and the untreated eyes of these patients to better understand the long-term consequences of the interaction of gene therapy with the underlying natural history of disease. To date, 11/15 patients have been evaluated serially at least for 4 years and up to 8 years after the treatment.

Our most recent published results have suggested a complex interaction of gene therapy and natural history. We found that rod and cone sensitivities improve quickly over days to weeks after treatment, followed by further improvements over 1-3 years. This, however, is followed by a slow spatial constriction of the area of vision improvement over 3-5 years. Throughout these complex changes, the retinal layer with photoreceptor nuclei continues to thin at similar rates in treated and untreated regions. With continued expansion of the number of patients seen long term, we have continued to observe the same dynamics of vision and retinal structure changes.

4. Valproic Acid (VPA) clinical trial

Dr. David Birch, Retina Foundation of the Southwest, Dallas TX, USA

Valproic acid (VPA) is an approved drug used as a broad-spectrum anticonvulsant.It also has interesting characteristics in cell culture: it can increase the yield of misfolded mutant rhodopsin and stimulates the release of cell protective (neurotrophic) factors. By 2010, preliminary reports of efficacy in improving visual fields in retinitis pigmentosa led to the frequent use of VPA as an off-label treatment for retinitis pigmentosa. However, these reports of efficacy were based on a small number of patients and were controversial. A randomized clinical trial was clearly needed to separate fact from fiction. In 2011, the Foundation Fighting Blindness Clinical Research Institute (FFB-CRI) began a multicenter trial with six sites in the United States. The goal was to identify 90 patients with an autosomal dominant gene mutation. In order to recruit these patients, the sites had to contact over 700 patients with known dominant inheritance and screen over 190 for inclusion and exclusion criteria. Among the 90 patients eventually recruited, 50% were male and the average age was 50 years.

Since initial reports suggested VPA might increase visual field size, the primary outcome measure was the change in area to an intermediate spot size (III4e) after 12 months of VPA treatment compared to the change in the placebo (untreated) group. Using statistical methods that take into account the differences between patients, between eyes, and between sites, the initial analysis of the data failed to show a significant benefit from VPA. Many more sub-analyses need to be completed to look, for example, at differences in the way patients with specific mutations may have responded. Nevertheless, the first high level analysis of the data suggests that VPA does not lead to improved visual fields.

5. New trial of gene therapy for RPE65 deficiency (LCA2) initiated at Moorfields Eye Hospital, London, UK

Robin Ali PhD, FMedSci

In April of this year, we opened a new gene therapy trial at Moorfields Eye Hospital, London. This is a phaseI/II dose escalation study to test safety and efficacy of a new gene therapy vector to treat LCA2 due to defects in RPE65. It will involve up to 18 subjects and will include children. We aim to open a US arm of the study at the Kellogg Eye Centre at the University of Michigan in the autumn of this year. The principle investigator in London is Prof. James Bainbridge and‘ in Michigan, it is Dr Cagri Besirli. The UK study is being funded by the UK Medical Research Council.

We are initiating a new trial because in all the trials to date, efficacy has been limited compared to what has been achieved in dog and mouse models. It is our view that data from all the clinical trials to date suggest that the demand for RPE65 has not been fully met with the current generation of vectors and that the current treatments do not prevent degeneration. Although there have been improvements in retinal sensitivity as measured by highly sensitive tests like FST, microperimetry, the levels of RPE65 are not sufficient to generate enough 11-cis retinal chromophore to drive a substantial ERG response even in young subjects in whom a large part of the retina has been treated. A small increase in the level of 11-cis retinal is sufficient to improve rod sensitivity to allow better night vision, but it seems likely that higher levels of chromophore are required to ensure the opsins are folded properly to prevent photoreceptor degeneration. A more potent vector, expressing higher levels of RPE65 is likely to generate higher levels of 11-cis retinal and therefore protect against progressive degeneration and preserve daylight vision.

We have now developed an AAV2/5 vector with a new optimized RPE65 promoter and codon optimsed cDNA that provides several thousand fold higher levels of expression than the vectors used in previous trials. GMP vector has been manufactured in our facilty at UCL and the first subject will receive this new vector in late June.

6. RLBP1 Retinitis Pigmentosa: preparation for clinical trial

Dr. Kali Stasi, Novartis Institute for Biomedical Research, Cambridge, MA, USA

Retinaldehyde-binding protein 1 (*RLBP1*) retinitis pigmentosa (RP) is a rare progressive retinal degenerative disease currently without any treatment. It is a rare 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, without retinal degeneration. A single subretinal injection of AAV8-p*RLBP1*-h*RLBP1* (self-complementary genome with an adeno-associated vector (AAV) serotype 8 capsid) improved rod-mediated dark adaptation for one year in a dose dependent fashion. This compound also exhibited an improvement in cone electroretinogram (ERG) function starting 4 to 10 weeks after injection. CRALBP was detected in the neural retinal lysates from these mouse eyes, indicating vector-mediated

protein expression in the mouse retina. These results were recently published in a peer-reviewed journal (Choi VW et al AAV-mediated *RLBP1* gene therapy improves the rate of dark adaptation in *Rlbp1* knockout mice Mol.Ther.Methods Clin. Dev. 2015;2:15022). It is our hope that this compound will similarly improve retinal function in patients with *RLBP1* RP.

We are currently conducting a Natural History study to better understand the disease itself and its progression in support of a future development program. No data on the Natural History study have been published or released yet, but will be released when available. A Proof of Concept (PoC) Phase 1/2 trial is currently in preparation and we are committed to test it in patients as soon as feasible. Details will be found when available at https://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/search.

7. Choroideremia NightstaRx clinical trial
Dr. Robert MacLaren, Oxford University, Oxford, UK

Choroideremia is an X-linked recessive disease that mainly affects males within a family. Mutations in the CHM gene lead to progressive vision loss due to degeneration of the retinal pigment epithelium, which results in loss of the choriocapillaris blood vessels and photoreceptor cells. The prevalence is estimated at 1:50,000.

The University of Oxford choroideremia gene therapy program is led by Professor Robert MacLaren and is funded by the UK Department of Health and the Wellcome Trust. The trial builds on the key achievements of Professor Miguel Seabra who elucidated the function of the choroideremia protein (REP1) and who is also a coinvestigator on the clinical study. It is a trial of a gene therapy procedure that replaces the patient's defective CHM gene with a normal copy of the gene with the potential of stopping or slowing the progression of choroideremia. The procedure uses an adeno-associated (AAV) virus as a vehicle (vector) to carry the replacement gene into cells of the eye, specifically targeting the retinal pigment epithelium cells. After retinal detachment, injection of the gene in a tiny amount of liquid to an area beneath the central retina called the fovea. In the initial phase of the clinical trial, six patients were treated with the new gene. Assessment of visual function included visual acuity tests, microperimetry and retinal sensitivity tests. Results at 6 months were published in the journal the Lancet (2014) and were "consistent with improved rod and cone function that overcame any negative effects of retinal detachment." Two patients were able to read more lines on an eye chart after treatment. With this success, the scope of the trial was expanded to 14 patients in a Phase 1/2 clinical trial. The objective of this trial is to test for both safety of the procedure and efficacy of 2 different doses of the gene with its vector. The latest results have recently been published in the New England Journal of Medicine (May 2016) showing that the initial improvements in visual acuity have been sustained for up to 4 years.

Following on from the success of the academic research programme, in 2014 the University of Oxford together with the Wellcome Trust co-founded NightstaRx Ltd, a new choroideremia gene therapy company based at the Wellcome Trust offices in London that has the specific remit of gaining worldwide regulatory approval for choroideremia gene therapy. The name 'Nightstar' arose from patient 9 in the current trial who describes being able to 'see the night stars' after his gene therapy treatment. Most importantly, the establishment of Nightstar has enabled further phase I/II clinical trials at international centres outside of the UK, including the USA, Canada and Germany. The Oxford team is currently developing surgical aspects of choroideremia gene therapy further in a specific

Phase II clinical trial involving 30 UK patients at earlier stages of the disease and which is funded by the NHS. In parallel with this, Nightstar is setting up an international pivotal trial, the 'STAR' study based mainly in the USA and following on from the natural history 'NIGHT' study, which many international centers have so far participated in.

8. Ocular gene transfer for human X-linked retinoschisis (XLRS)
Drs. Lisa Wei and Paul A. Sieving. National Eye Institute, NIH, Besthesda MD USA

X-linked retinoschisis (XLRS) is a monogenic form of juvenile macular degeneration and is one of the more common hereditary causes of vision loss in young men. There are no approved treatments for XLRS. We are evaluating the safety, tolerability, and biologic signal of intravitreal administration of an adeno-associated virus (AAV)-based vector containing a normal human retinoschisin transgene (AAV-RS1) in individuals with XLRS in a Phase I/IIa trial.

This is a prospective single-center, unmasked, uncontrolled, dose-escalation phase I/IIa trial (ClinicalTrials.gov; NCT02317887). The study involves a single intravitreal administration of AAV-RS1 in a standard three dose-escalation design. Participants are evaluated at baseline and periodically afterward out to 18 months. The trial is designed to explore primarily safety and potential efficacy. Testing includes ophthalmic evaluation, microperimetry, full-field electroretinography, optical coherence tomography, fundus photography, fluorescein angiography, and hematologic testing. Neutralizing antibody titers for viral vectors and anti-RS1 serologic testing are being measured.

To-date, three doses have been explored (1e9 vector genomes (vg)/eye, 1e10 vg/eye, 1e11 vg/eye) with three participants per dose cohort. One eye (eye with worse visual acuity) of each participant was given the single intravitreal administration of the gene transfer vector containing the human retinoschisin transgene (AAV-RS1). Ages of the nine participants enrolled currently ranges from 23-72 years. The longest available follow-up to date is 9 months following AAV-RS1 injection. Preliminary results show that ~10% of participants have measurable pre-existing antibodies to the vector. The trial is continuing to enroll additional patients.

9. Current Status of the achromatopsia CNG3B gene therapy clinical trial
Dr. Dominik Fischer, University Tuebingen,Tuebingen, Germany

The CNGA3 gene therapy trial is the first ocular gene therapy trial using rAAV8 and was approved after extensive pre-clinical work by members of the RD-CURE consortium. This group 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, Seeliger, Zrenner, Paquet-Durand, Peters, Ueffing and Fischer) and Dr. Stephen Tsang at Columbia University in the USA. The consortium aims to bring CNGA3 and PDE6A gene therapy into clinical phase I. It is funded by the Tistou and Charlotte Kerstan Foundation and advised by Drs. Molday, Hamel, Humphries, Wijnholds and Bennett.

In 2014, we started the NHP studies after successful proof of concept studies in the knockout mouse using rAAV8.hCNGA3. The 90-day study with subretinal vector dose of $1x10^{11}$ or $1x10^{12}$ vector genomes (vg) showed no test-item related changes. Specifically, there were no degenerative, inflammatory or hyperplastic abnormalities in the retina from any animal.

Led by the STZeyetrial (local CRO), an IND application was submitted to the relevant national authority (PEI) after consultations with the EMA and FDA. Approval was granted in October and the first surgery was performed in November, 2015. Since then, all three patients from the low dose group ($1x10^{10}$) underwent surgery without complications. DMC reviewed clinical data one month after 3rd patient and approved dose escalation. First patient was treated with $5x10^{10}$ without complications, second and third patients are scheduled for May and June. High dose group ($1x10^{11}$) is scheduled for second half of 2016 with a close out after 12 months and post-trial annual follow up for 4 additional years.

Surgery is performed under general anesthesia using standard 23G ppV and a two-step, semi-automated injection protocol, which creates a bleb involving the full anatomical macula to maximize the number of potentially transduced cone photoreceptors. The aim of the study is to prove 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 (slit lamp, fundus biomicroscopy, angiography, microperimetry and electrophysiology). 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, FST, GF-ERG and VFQ25 and A3-PRO as patient reported outcome assessments.
Preliminary results show no surgical or post-surgical complications such as retinal detachment, hemorrhage or inflammation unresponsive to treatment. In terms of secondary outcome measures, BCVA reached baseline levels as soon as 14 days post treatment, but did not improve significantly within the first month.

10. Update on clinical trials for RPE65/LRAT-related inherited retinal degenerations – the QLT Inc retinoid program

Dr. Robert Koenekoop, McGill University, Montreal, Que, Canada

Dr. Koenekoop said that he has been with this program since 2009 and was thrilled to update the progress of the QLT retinoid program at the SMAB meeting. In 2000 and 2010, animal studies were performed by the Palczewski and Gearhart groups, in which mice and dogs with RPE65 deficiency received 9 cis-retinal replacement. The results showed significant functional and structural rescue, including an improved ERG and improved mobility.These studies were followed in 2008 by testing oral 9 cis-retinal in human volunteers, and in the same year, the program received Therapeutic Products Directorate (TPD) of Health Canada approval to test the investigational drug on children and young adults with RPE65 and LRAT deficiency. The investigational drug demonstrated an acceptable safety profile.

At the Montreal Children's Hospital of McGill University, in 2009, fourteen autosomal recessive LCA patients (in a single center) and in 2010 to 2012, 18 older autosomal recessive RP patients (in a multicenter study) entered the QLT trial. We showed significant improvements in the sizes of the GVF, improvements in ETDRS VA and improvements in the fMRI measured visual cortex activities in this non-placebo controlled trial. Most patients responded while some patients did not. The patient's testimonies correlated with the improvements in the visual function parameters and their response status. These results were published in *The Lancet* in 2014 and *PLOS-one* in 2015.

We then teamed up with Drs. Peter Humphries and Paul Kenna in Ireland, who with Dr Steve Daiger had just discovered dominant mutations in RPE65. We brought the patients to Montreal and showed efficacy and safety of the QLT 091001 drug in autosomal dominant RP secondary to heterozygous RPE65 mutations, expanding the disease population.

We then performed a repeat dosing study in 27 patients from the phase 1b study and have just completed a natural history study which enrolled 59 subjects total. We are now planning a multicenter, placebo-controlled trial for LCA and RP patients with autosomal recessive LRAT and RPE65 mutations.

11. Usher gene therapy clinical trial
Dr. Jose-Alain Sahel/Dr. Isabelle Audo, Quinze-Vingts Eye Hospital, Paris, France

A clinical trial is underway in patients with Retinitis Pigmentosa associated with Usher Syndrome Type 1B. It has two principal investigators, Dr. Jose Sahel at the Hopital Nationale des Quinze-Vingt in Paris, France and Dr. Richard Weleber at the Casey Eye Institute in Portland, OR, USA.

The study uses gene therapy to replace the MYO7A gene that is defective in patients affected with Usher Type 1B. The MYO7A gene produces a protein called Myosin VIIA that is critical for photoreceptor health and function. Loss of Myosin 7A also leads to progressive hearing loss. Oxford Biomedica has developed a gene therapy method, “UshStat gene therapy” that delivers the replacement MYO7A gene through a proprietary delivery system.

The trial is a Phase I/IIa dose escalation safety study in which two different doses of the gene are studied for any negative effects (adverse events) on the patients. For this purpose, the Primary Outcome Measure of the trial is the study of the incidence of adverse events. Secondary outcome measures include the determination of delay in retinal degeneration progression. Also, changes in function of the treated eye relative to the patient’s contralateral, untreated eye are determined using standard retinal analytical techniques. The Foundation Fighting Blindness is funding work at the Paris site and had funded preclinical laboratory work that led to the trial. Overall, the trial is sponsored by Sanofi, a leading global health-care provider.

12. Retinal electronic prostheses
Dr. Eberhard Zrenner, University Tuebingen, Tuebingen, Germany

There are presently three approaches of electronic retinal implants:
epiretinal, subretinal and suprachoroidal.

Use of a retinal prosthesis is only suited for patients who are blind or have bare light perception; the optic nerve and the visual centers in the brain must be intact. Usually they are only suited for late stage Retinitis Pigmentosa. The current aim is not to make patients reading again etc. but to help them with improved mobility and localization of objects by providing some visual input.

At present, two different types of approved registered retina implants are available to patients as medical devices, in some countries already financed by public health insurance.

1. **ARGUS II (Second Sight Medical Products, USA**) is an epiretinal device with sixty electrodes providing a 25° diagonal visual field, approved for European and US markets. The image is captured by a video camera attached to electronic goggles. The image is sent to a pocket computer and fed back via a transmitter system in the goggles and receiver system attached to the eyeball. Almost 200 patients have been operated on already in centers in Europe and USA, as well as in other countries. The visual acuity is 20/1.200 in best case; observation time is >5 years. Clinical results have been published (Humayun et al.)

2. **Retina Implant Alpha AMS, Reutlingen** is a subretinal implant with 1.500 electrodes and a 15° diagonal field. It has been approved for the European market. Clinical trials have been performed in 53 patients, operated on in seven sites in Europe and Asia. The initial version, Retina Implant Alpha IMS, had a limited survival time. A new overhauled version Retina Implant Alpha AMS has been recently approved for marketing and is now available in six centers in Germany with more centers to be established in France, England and Spain. The “camera chip” device of this Alpha AMS is implanted directly beneath the retina at the level of the degenerated photoreceptors, without electronic goggles outside. Best visual acuity achieved so far is 20/540 in best case.Observation time so far is up to 2,5 years (Retina Implant Alpha AMS).

   Results in 29 patients have recently been published in Stingl et al in Vision Res)

<u>Implants available only in clinical studies:</u>
Pixium Vision, Paris: This is an rpiretinal implant with 150 electrodes and camera outside. The first patient was operated on in February 2016
Bionic Vision, Australia: This device uses a suprachoroidal approach for implantation. So far, three patients have been operated on: now further developed by private bionic vision technologies.
STS implant, Japan: This device also uses a sprachoroidal approach with 49 electrodes. So far, three patients have been studued with observation time > 1 year.

13. Pixium retinal implant trial
Dr. Serge Picaud, Vision Institute, Paris, France

Dr. Picaud reported for the Vision Institute in Paris, France headed by Professor J.-A. Sahel on a novel prostheses that is aiming at restoring vison. They are working with the French company, Pixium Vision. Pixium Vision has started clinical trials with the epi-retinal system, IRIS II that is comprised of 150 electrodes. It is designed to be explantable and potentially upgradeable, and integrating a smart bioinspired camera sensor. Interim results with IRIS I (49 electrodes) showed improved perception for object recognition and grasping. These clinical trials are realized with the clinical department of Professor Sahel at the Fondation Ophtalmologique Rothschild (Paris, France) and at the clinical trial center within the National Hospital Center for Ophthalmology of the XV-XX (Paris, France).

In addition, Pixium Vision is currently developing a new generation of wireless subretinal implant, PRIMA, in partnership with Professor Palanker's team at Stanford University and the Vision Institute in Paris. This photovoltaic implant has been fabricated in France in preparation for clinical studies. These French chips were validated on an ex vivo model of blind primate retinas at the Vision Institute. Pre-clinical in vivo tests are in progress on non-human primates in preparation for the first human studies.

In parallel, the Vision Institute and Gensight Biologics together are developing an optogenetic therapy, taking advantage of microbial opsin to reactivate the blind retina. Using the red-sifted microbial opsin isolated by Dr. Ed Boyden at MIT in the USA, the Vision Institute showed in living primates a sustained expression of ChrimsonR-Td-Tomato in retinal ganglion cells. The expression level was sufficient to drive the ganglion cells at very high spiking frequencies upon light activation below the radiation safety limit. To prepare clinical trials,goggles are finalized to normalize light levels at the proper light intensity with a biomimetic sensor. These results pave the way for clinical trials.

14. The DRUGSFORD project

Dr. François Paquet-Durand, University of Tübingen, Tuebingen, Germany - for the DRUGSFORD consortium

The EU-funded DRUGSFORD project (www.drugsford.eu) aims to produce new drugs for the treatment of hereditary retinal degeneration (RD). To overcome the problem of genetic heterogeneity in RD, DRUGSFORD focuses on cGMP signalling as a therapeutic target and develops novel cGMP analogues as therapeutic agents. For efficient delivery across the blood-retinal-barrier, cGMP analogues are encapsulated into an innovative liposomal drug delivery vehicle so that they can get into the photoreceptor cells and exert their beneficial effect.

The DRUGSFORD consortium is built around both industrial and academic partners. The company BIOLOG (Bremen, Germany) is the world leader in producing nucleotide analogues that can target and modify cGMP-signalling. BIOLOG´s compounds are encapsulated into a proprietary liposomal drug delivery vehicle originally developed by the company to-BBB (Leiden, The Netherlands). The novel compounds and their liposomal formulations are tested in a step-wise fashion in three different systems of increasing complexity, initially *in vitro* in photoreceptor-like cell cultures (Dr. V. Marigo, University of Modena, Italy), then in organotypic retinal explants cultures (Dr. P. Ekström, University of Lund, Sweden), and finally *in vivo* in various RD animal models (Dr. F. Paquet-Durand, University of Tübingen, Germany).

Now in its fourth project year, DRUGSFORD has produced over 250 novel cyclic nucleotide analogues. More than 180 of these were tested in cell-free assays, 35 compounds were tested in photoreceptor-like cell cultures, 13 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,* and *rd10* 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 a corresponding patent application, with further patents currently in preparation. Taking full advantage of orphan drug regulations, DRUGSFORD has developed a clinical test strategy that can potentially achieve drug registration within an 8-9 year time-frame.

To establish the GMP-grade production of LP-DF003, DRUGSFORD has recently included SP Process Development (Södertälje, Sweden) as a new partner. In parallel to GMP production, DRUGSFORD is pursuing a toxicological test programme which has detected no potential safety issues so far. Toxicological assessment will continue with a non-human-primate study set to start in the coming months.

In summary, DRUGSFORD has identified cGMP signalling as a new common target for the treatment of RD. It has produced new compounds with unique and highly target specific properties and it has developed drug delivery technology for efficient delivery to retinal photoreceptors. DRUGSFORD has obtained orphan drug status for its first lead compound formulation and aims to take full advantage of the corresponding regulations to rapidly advance clinical testing.

For further information please refer to:

- DRUGSFORD website: www.drugsford.eu

Orphan Drug Designation: EU/3/15/1462, *cf*. www.ema.europa.eu

1. Announcements, New Business and Conclusions

A – several new clinical trials were discussed

B - Dr. Matt LaVail reminded the group that the **XVIIth International Symposium on Retinal Degeneration (RD2016)** will be held in Kyoto, Japan on September 19-24, 2016. The venue is the historic Kyoto Conference Center and the adjoining Grand Prince Hotel. Meals are provided and the facility allows for maximal interaction of all the attendees during the meeting. An exciting scientific program covering many aspets of retinal degeneration is being organized. Please visit the RD2016 website for more details.

2. Final Comments – Ms. Christina Fasser

Christina thanked all the parrticipants for the excellent summaries of their ongoing or prospective clinical trials**.** She noted that this was the first SMAB program in which all talks were about clinical trials. She wished that the remainder of the ARVO meeting woruld be very successful for all thhe participants in the SMAB meeting. Finally, she hoped to see them all at ARVO 2017 in Baltimore.