

# USH2018

## **International Symposium on Usher Syndrome**

**July 19-21, 2018**

**Atrium Hotel Mainz | Mainz, Germany**



## **PROGRAM & ABSTRACTS**



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## Organizing Institutions



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**The USH2018 Symposium is dedicated to  
Steffen Suchert and Ted Welp  
for their lifework on Usher syndrome.**

In 2015, the Usher syndrome community lost two of our best: Steffen Suchert suddenly passed away from a heart attack in November 2015. A few months earlier in March, "Ted" Welp was tragically killed together with his wife Elaine and their son Thomas at their home.

Ted's investment in *USH1B/MyosinVIIa* research had a direct impact on bringing the USH1B gene therapy to clinical trial. Steffen began to take on the challenge of finding a therapy for this hitherto incurable disease right after his sons Andreas and Matthias were diagnosed. Steffen approached the task very systematically, purposefully and with a unique view of the global trends. In the words of Hermann Hesse, he tried "the impossible, so that the possible arises". For him, his visionary activities to find a therapy was a "family project". Beside other activities, he built on the FAUN Foundation, a unique family foundation dedicated to the research and development of therapies for Usher syndrome, particularly for USH1C.



H. Steffen Suchert  
1945 - 2015



"Ted", Elaine, and Thomas Welp  
- died March 2015

Ted and Steffen teamed up in the Board of Trustees of Foundation Fighting Blindness for their common interests in Usher research. The Usher research and therapy perspectives are where they are today, in no small part, because of these two pioneer men. And where we are today is closer than we have ever been to treatments, real treatments, for all types of Usher syndrome. Ted and Steffen's activities and successes supported the important research on Usher syndrome being initiated and carried out anywhere in the world and have given hope to the entire Usher community. UW



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## Program

| Thursday, July 19 <sup>th</sup> |   | Scientific Symposium |
|---------------------------------|---|----------------------|
| 11:00 - 13:30                   | Registration  |                      |
| <b>13:30</b>                    | <b>Welcome Addresses &amp; Introduction</b>   |                      |
| 13:30 – 14:00                   | <b>Sabine Bätzing-Lichtenthäler</b> , State Minister of Social Affairs, DE<br>& <b>Mark Dunning</b> , Usher-Coalition, US<br>“Patient’s View to Usher Syndrome” |                      |
| 14:00 – 14:25                   | <b>Bill Kimberling</b> , Boys Town, Omaha, US<br>“A history of Usher syndrome research & prospects of new research directions”                                  |                      |
| <b>14:25</b>                    | <b>Scientific Session I: Genetics and Diagnostics of Usher Syndrome</b><br>Chair: Jose Millan, Valencia, E  |                      |
| 14:25 – 14:55                   | <b>Anne-Françoise Roux</b> , Montpellier, FR<br>“Genetics of Usher Syndrome”  |                      |
| 14:55 - 15:10                   | Short oral presentation selected from abstracts<br><b>Carla Fuster García</b> , Valencia, ES (# 38)<br>“USH2A Gene Editing Using the CRISPR System”             |                      |
| 15:10 – 15.35                   | <b>Isabelle Audo</b> , Paris, FR<br>“Clinical diagnosis of Usher Syndrome”  |                      |
| 15:35 – 16:05                   | Short oral presentations selected from abstracts<br><b>Margaret Kenna</b> , Boston, US (# 15)<br>“Challenges of making a correct diagnosis of Usher”            |                      |
|                                 | <b>Adam M Dubis</b> , London, UK (# 11)<br>“Longitudinal phenotypic characterization of type II Usher syndrome caused by mutations in USH2A”                    |                      |
| 16:05 - 16:45                   | <b>Coffee break</b>   |                      |

|               |  |
|---------------|--|
| <b>16:45</b>  | <b>Scientific session II: Usher models &amp; Cell and molecular biology (part I)</b><br>Chair: Gwenaelle Geleoc, Boston, US  |
| 16:45 – 17:15 | <b>Aziz El Amraoui</b> , Paris, FR<br><b>Introduction: “The retinal phenotype of Usher syndrome: pathophysiological insights from animal models”</b>   |
| 17:15 – 17:30 | <b>Short oral presentations selected from abstracts</b><br><b>Nikolai Klymiuk</b> , LMU Munich, DE (# 34)<br>“Generation and preliminary analysis of USH1C transgenic pig model”                                 |
| 17:30 – 17:45 | <b>Adem Yildirim</b> , JGU Mainz, DE (# 19)<br>“The human Usher syndrome protein SANS regulates pre-mRNA splicing by direct interaction with key components of the spliceosome”                                  |
| 17:45 – 18:10 | <b>Jun Yang</b> , Salt Lake City, US<br><b>“The USH2 protein complex in photoreceptors and hair cells”</b>   |
| 18:10 – 18:25 | <b>Short oral presentation selected from abstracts</b><br><b>Jennifer Phillips</b> , Eugene, OR, US (# 32)<br>“Analysis of the functional relationships among Usher Type 2 proteins in zebrafish photoreceptors” |
| 18:25 – 18:55 | <b>Matthew J Tyska</b> , Nashville, US<br><b>“ Shaping the intestinal brush border with adhesion links ”</b>   |
| 19:00 – 21:30 | <b>Poster session - exhibition with wine and cheese - finger food</b>  |



| Friday, July 20 <sup>th</sup> |   | Scientific Symposium |
|-------------------------------|---|----------------------|
| <b>08:00</b>                  | <b>Early bird: Posters - exhibition</b>   |                      |
| <b>09:00</b>                  | <b>Scientific session III: Cell and molecular biology (part II)</b><br>Chair: Uwe Wolfrum   |                      |
| 09:05 – 9:35                  | <del>Bechara Kachar, Bethesda, US</del> <b>Aziz El Amraoui, Paris, FR</b><br><b>“USH proteins in hair cell struction and function”</b>                      |                      |
|                               | <b>Short oral presentations selected from abstracts</b>   |                      |
| 09:35 – 9:50                  | <b>Marisa Zallocchi, Omaha, US (# 20)</b><br>“Integrin alpha8 modulates hair cell maturation through its association with Pcdh-15 (USH1F)”                  |                      |
| 09:50 - 10:05                 | <b>Fred Schwaller, Berlin, DE (# 26)</b><br>“USH2a is a vibration sensor involved in touch and hearing in Usher syndrome”                                   |                      |
| 10:05 – 10:35                 | <b>Mingjie Zhang, Hong Kong, HK</b><br><b>“Structures of the USH1 complexes and their homologues in other tissues”</b>                                      |                      |
|                               | <b>Short oral presentation selected from abstracts</b>  |                      |
| 10:35 – 10:50                 | <b>Daniele Dell’Órco, Verona, IT (# 28)</b><br>“A magnesium-triggered conformational change in CIB2 is impaired in Usher Syndrome type 1J”                  |                      |
| 10:50 – 11:20                 | <b>Coffee break &amp; exhibition</b>  |                      |
| <b>11:20</b>                  | <b>Scientific session IV: Usher models &amp; Therapy (part I)</b><br>Chair: Monte Westerfield   |                      |
| 11:20 – 11:45                 | <b>Alberto Auricchio, Naples, IT</b><br><b>“Dual AAV vectors for gene therapy of USHIB retinitis pigmentosa ”</b>   |                      |
|                               | <b>Short oral presentations selected from abstracts</b>   |                      |
| 11:45 – 12:00                 | <b>Jeffrey Holt, Boston, US (# 41)</b><br>“Next generation gene therapy hearing, balance and quality of life in mouse models of genetic inner ear disorder” |                      |
| 12:00 – 12:15                 | <b>Alaa Koleilat, Rochester, MN, US (# 36)</b><br>“Development of the first pharmacotherapy for the treatment of Usher Type I due to variants in MYO7A”     |                      |
| 12:15 – 12:40                 | <b>Kerstin Nagel-Wolfrum, JGU Mainz, DE</b><br><b>“Translational read-through as therapy for Usher syndrome caused by nonsense mutations”</b>               |                      |
|                               | <b>Short oral presentation selected from abstracts</b>  |                      |
| 12:40 – 12:55                 | <b>Muna Naash, Houston, US (# 33)</b><br>“An Usher Syndrome type IIA knock in model exhibits hair cell abnormalities, and late-onset Retinitis pigmentosa”  |                      |
| 12:55 – 14:30                 | <b>Lunch - coffee - poster session – exhibition</b>   |                      |

## Welcome

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**14:30**

### **Scientific session V: Usher models & Therapy (part II)**

Chair: Mariya Moosajee

14:30 – 14:55

**Erwin van Wijk**, Nijmegen, NL

**“Antisense oligonucleotides for the treatment of Usher syndrome caused by splice site mutations”**

**Short oral presentations selected from abstracts**

14:55 – 15:10

**Jennifer J. Lentz**, New Orleans, US (# 37)

“Antisense Therapy Rescues Hearing and Vision in Usher syndrome”

15:10 – 15:25

**Erik de Vrieze**, Nijmegen NL (# 25)

“Identification of consistently elevated autophagy as pathogenic mechanism of retinal degeneration in Usher syndrome”

15:25 – 15:50

**Yoshikazu Imanishi**, Cleveland, US

**“A small molecule mitigates hearing loss in a mouse model of Usher syndrome III”**

**Short oral presentations selected from abstracts**

15:50 – 16:05

**Anai Gonzalez Cordero**, London, UK (# 31)

“Using hiPSC-derived retinal organoids to model Ush2a pathophysiology”

16:05 – 16:20

**Scott Dorfman (Odylia)**, Atlanta, US (# 42)

“A Non-Profit Mechanism for moving Proof-of-Concept Studies to Clinical Therapies for rare retinal disorders”

16:20 – 16:45

**Mike Cheetham**, London, UK

**“Retinal organoids as disease models”**

16:45 – 17:45

Poster awards & Wrap-up scientific meeting

**Gwenaëlle Géléoc & Uwe Wolfrum**

**“Prospects in human Usher Syndrome research and treatment”**

17:45

End of scientific meeting

**Rhine River Cruise ;board dinner (ticketed event)**

**18:15**

**Bus departure Atrium Hotel to Mainz to boat landing site**

19:00

Mainz – St. Goar and Dinner

23:30

Return to Mainz

| Saturday, July 21 <sup>st</sup> |   | Patient's Symposium |
|---------------------------------|---|---------------------|
| <b>09:00</b>                    | <b>Welcome Addresses &amp; Introduction</b><br><b>Christina Fasser</b> , Retina international, CH<br><br><b>Mark Dunning</b> , Usher Syndrome Coalition, US<br><b>“The Power of an Usher Syndrome Community”</b><br><br><b>Irmgard Reichstein</b> , Deutsche Gesellschaft für Taubblindheit gGmbH<br><b>Dominique Sturz</b> , Usher Initiative Austria, Forum für Usher-Syndrom, Hörsehbeeinträchtigung und Taubblindheit |                     |
| <b>09:25</b>                    | <b>Summary scientific part in layman's terms</b><br>Chair: <b>Irmgard Reichstein</b>  |                     |
| 9:25 – 9:50                     | <b>Margaret Kenna</b> , Boston, US<br><b>“Summary: Diagnostic and genetics of Usher Syndrome”</b>   |                     |
| 9:50 – 10:15                    | <b>Uwe Wolfrum</b> , Mainz, DE<br><b>“Summary: Cell and molecular biology of Usher Syndrome”</b>  |                     |
| 10:15 – 10:40                   | <b>Gwenaëlle Géléoc</b> , Boston, US<br><b>“Summary: Therapy of Usher Syndrome”</b>   |                     |
| 10:40 – 11:30                   | <b>Coffee break with scientists, exhibition</b>   |                     |
| <b>11:30</b>                    | <b>Oral presentations: Therapy in Focus</b><br>Chair: <b>Mariya Moosajee</b>  |                     |
| 11:30 – 11:55                   | <b>Isabelle Audo</b> , Paris, FR<br><b>“Update USHStat Myo7 and other clinical trials”</b>  |                     |
| 11:55 – 12:20                   | <b>Thomas Lenarz</b> , Hannover, DE<br><b>“Cochlear implant technology”</b>   |                     |
| 12.20 – 12:45                   | <b>Eberhart Zrenner</b> , Tübingen, DE<br><b>“Retina implant and electrostimulation”</b>  |                     |
| 12:45 – 13:00                   | <b>Darija Udovicic Mahmuljin</b> , Perkins International, US<br><b>“Steps Toward Better Life: Improving access and quality of education for DB and MD children and youth through partnerships – global campaign”</b>  |                     |

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|               |  |
|---------------|--|
| 13:00 – 14:00 | <b>Lunch with scientists – exhibition</b>  |
| <b>14:00</b>  | <b>Inclusion through Innovation</b><br>Moderator: Sebastian Klaes  |
|               | <b>Mariya Moosajee</b> , UCL, UK<br>“Clinical trial design for nonsense mutations treatment of USH2A”  |
|               | <b>Annamarie Dillon</b> , ProRQ, NL<br>“Clinical trial design for AON treatment of USH2A”  |
|               | <b>Dorothea Kohlhaas</b> , Argus II user, DE<br>“My experiences with Argus II and the better quality of life”                                  |
|               | <b>Alfred Stett</b> , Retina Implant AG, DE,<br>“Subretinal Implant Alpha AMS – recent developments and achievements”                          |
| <b>15:00</b>  | <b>Patient’s View, Diagnosis, Health, Psychological Aspects, Healthcare</b><br>Chair: Dominique Sturz  |
| 15:00 – 15:25 | <b>Julia Moser</b> , Vienna, AT<br>“Patients view to Usher Syndrome”   |
| 15:25 15:50   | <b>Kimberley J Smith</b> , Uxbridge, UK<br>“Psychosocial well-being and health-related quality of life in a UK population with Usher Syndrome” |
| 15:50 – 16:30 | <b>Coffee break, exhibition</b>  |
| 16:30 – 16:55 | <b>Claas Möller</b> , Örebro, SE<br>“The urgency of interdisciplinary healthcare and support for people with Usher Syndrome”                   |
| 16:55         | <b>Podium discussion</b>   |
| 17:30         | <b>End of the symposium – farewell</b>   |
| 19:30         | <b>Family dinner</b> (Haus des Deutschen Weines, downtown Mainz)   |

## Welcome

Welcome to the 4th International Scientific Symposium and the International Patient Symposium (10th Annual USH Connections Conference) on Usher Syndrome at the Johannes Gutenberg University of Mainz, Germany. Welcome to the international leaders in Usher syndrome research, to the young investigators and students who are joining the field and to the individuals and families with Usher syndrome in attendance. Welcome, everyone, to the first gathering of the international Usher syndrome community in Germany.

This symposium provides an opportunity for all. Over the course of the next few days, ideas will be shared, friendships will be forged, and our Usher syndrome community will grow stronger. The knowledge exchanged between researchers from different disciplines and families from across the globe will help bring us closer towards a molecular understanding of Usher syndrome and the design of therapies for treatments and cures of Usher syndrome - the ultimate goal of all of us.

We encourage you to foster new relationships; between scientists and clinicians founding new research programs and careers within the field of Usher syndrome research. Families, take the opportunity to make new friends, both with others living with Usher syndrome and researchers working tirelessly towards therapies. Researchers and clinicians, take the opportunity to be inspired by the people your work impacts. To our entire global community, take the opportunity to be hopeful about the future. This is a time of progress and discovery.

Thank you again for joining us. We look forward to meeting you all.

Uwe Wolfrum, on behalf of the USH2018 organization committee.

## Conference Information

### ORGANIZING COMMITTEE

**Mark Dunning**

Usher Syndrome Coalition, Boston,  
United States

**Gwenaëlle Géléoc, PhD**

Assistant Professor, Department  
of Otolaryngology, F.M. Kirby  
Neurobiology Center, Boston, Children's  
Hospital and Harvard Medical School,  
United States

**Barbara Hein**

Leben mit Usher-Syndrome e.V., Berlin,  
Germany

**Margaret A. Kenna, MD, MPH**

Sarah Fuller Chair for Hearing Loss and  
Hearing Restoration, Director of Clinical  
Research, Dept. of Otolaryngology and  
Communication Enhancement, Boston  
Children's Hospital, United States

**Sebastian Klaes**

Leben mit Usher-Syndrome e.V.,  
Braunschweig, Germany

**Julia Moser**

Forum für Usher Syndrom,  
Hörsehbeeinträchtigung und  
Taubblindheit, Austria

**Kerstin Nagel-Wolfrum, Dr.**

Translational research, Department for  
Developmental Biology and  
Neurobiology, Johannes Gutenberg  
University of Mainz, Germany

**Irmgard Reichstein**

Deutsche Gesellschaft für Taubblindheit  
gGmbH, Essen, Germany

**Dominique Sturz**

Usher Initiative Austria, Forum für Usher  
Syndrom, Hörsehbeeinträchtigung und  
Taubblindheit, Wien, Austria

**Krista Vasi**

Usher Syndrome Coalition, Boston,  
United States

**Uwe Wolfrum, Prof. Dr.**

Molecular Cell Biology,  
Institute of Molecular Physiology (IMP),  
Johannes Gutenberg University of  
Mainz, Germany

### Wolfrum Lab (IMP) & JGU interns

Liliane Clermont Wocker  
Jecek Krzysko  
Deva Kusuluri  
Ananya Samanta, Dr.  
Jessica Ries  
Elisabeth Sehn  
Nasrin Sorousch, Dr.  
Gabriele Stern-Schneider  
Daniel Sturm  
Lars Tebbe, Dr.  
Ann-Kathrin Wallisch  
Kirsten Wunderlich, Dr.  
Adem Yildirim

Christine Seemann

## CONFERENCE LOCATION - VENUE

The symposium will take place at the Atrium Hotel, Mainz

<http://www.atrium-mainz.de/en/>

### **Atrium Hotel Mainz**

Flugplatzstr. 44

D-55126 Mainz

Phone +49/61 31/4 91-0 . Fax +49/61 31/4 91-128

E-Mail [info@atrium-mainz.de](mailto:info@atrium-mainz.de)

### **Transportation**

**By car**, you reach the Atrium Hotel via motorway A 60, exit Mainz-Finthen. Follow the road straight through the village. At its end, you will find the hotel on the right hand side.

**By train**, you arrive at Mainz central station. From there, you reach the Atrium Hotel either by bus no. 55 (direction Finthen/Theodor-Heuss-Straße, bus schedule) or no. 58 (direction Wackernheim/Rathausplatz, bus schedule). Exit the bus at bus stop “Atrium Hotel Mainz”.

**By plane**, you arrive at Frankfurt (Rhein-Main) Airport. From there, you reach Mainz central station by suburban train (S 8, direction Wiesbaden, travel time approx. 30 minutes). Arriving at Frankfurt-Hahn Airport, you reach Mainz central station by bus shuttle.

For discounted and reliable taxi fares from the airport or the train station please contact our taxi-partner **AC-Fahrservice** (06131/6037497 or 0171/4013502).

**Our GPS coordinates: N 049° 58.969, E 08° 10.090**

### **Distances**

Motorway A60 -> 1km /

ICE, IC,EC railway station -> 6 km

City centre -> 6km

Frankfurt Airport -> 29 km

Frankfurt exhibition centre -> 35 km

**CHILDCARE** will be organized by “Lottchens Event“(<https://lottchen-events.de>). Lottchen Events is a modern and creative Children’s events planning agency based in Wiesbaden. Paying great attention to detail, they provide professional childcare services for company events, conferences, weddings and other occasions. Their young and dynamic team of qualified professionals look after children aged 0-12 addressing all of their needs. They offer all-inclusive services providing meals, entertainment and arts and crafts till late at night. On July 19th and 20<sup>th</sup> child care will be provided at the Layenhof, „Am Finther Wald“, 2.5 km away from the Atrium Hotel. The multifaceted mission of the (Interessengemeinschaft) Layenhof e.V.-association is to promote and strengthen social connections in the community, via multicultural engagements, development of conservation projects and supporting the youth and elderly. On July 21th, child care will be on the Ground floor, at the Atrium Hotel.

### **USH2018 Symposium WIFI ACCESS**

Network: Tagen@atrium

Password: Zusammen.2018



### THE ORGANIZERS

**The Usher Syndrome Coalition's mission** is to raise awareness and accelerate research for the most genetic common cause of combined deafness and blindness. The Coalition also provides information and support to individuals and families affected by Usher syndrome

**Johannes Gutenberg Universität (JGU) Mainz** is, with around 31,500 students from over 120 nations, one of the largest and most diverse universities in Germany. JGU unites almost all academic disciplines under one roof with its University Medical Center, its Academy of Arts and School of Music and the Faculty of Translation Studies, Linguistics and Cultural Studies in Germersheim. In over 150 institutes and clinics, 4,400 academics teach and carry out research. With 75 fields of study and more than 260 degree courses, JGU offers an extraordinarily broad range of courses. Since 1999 JGU scientists around Prof. U. Wolfrum are working at the Faculty of Biology on diverse aspects related to the Usher syndrome, from basic science of Usher protein function to translational projects of gene-based therapy options.

**Boston Children's Hospital's community mission** is to improve the health and well-being of **children** and families in our local community. The hospital leverages its resources with community partnerships to address health disparities, improve child health outcomes and enhance the quality of life for children and families.

**Leben mit Usher-Syndrom e. V.**, "Living with Usher Syndrome" is a non-profit organization. We aim to support people with Usher Syndrome and their families. The idea of peer-to-peer-counseling by individuals with Usher Syndrome is fundamental.

**Deutsche Gesellschaft für Taubblindheit gGmbH**, "The "German Association for Deafblindness" is a non-profit organization. Goal is the improvement of support and assistance offers for deafblind people in Germany. Organizations of deafblind people are strongly involved as partner's and associates.

**Usher Initiative Austria** advocates for early diagnostics of Usher Syndrome and for access to emerging therapy options for all Usher individuals. The initiative acts as a link between and expert for European Expert Centres, patients and patient organisations and European Institutions. (former Usher Syndrome Coalition Forum Austria 2014)

**The Forum for Usher Syndrome, Combined Hearing and Vision Loss and Deafblindness** connects individuals with Usher Syndrome and other forms of DeafBlindness, provides a platform for mutual support and exchange and raises awareness about deafblindness.

We thank all our partners and sponsors for making the USH2018 symposium possible.

*Thank you!*

**PARTNERS**



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[faun-stiftung.de](http://faun-stiftung.de)



[www.fondationpourl'audition.org](http://www.fondationpourl'audition.org)

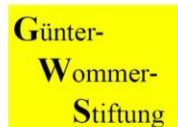


Forschung contra Blindheit  
Initiative Usher-Syndrom e.V.

[ushernet.org](http://ushernet.org)



[www.fondave.org](http://www.fondave.org)



[www.foerdersuche.org](http://www.foerdersuche.org)  
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Stiftung für Kinder mit  
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## Partners & Sponsors



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### MISSION STATEMENTS:

#### **Association For Research In Otolaryngology (ARO):**

“The aims of the association shall be encouragement and promotion of research, both basic and clinical, in the broad field of otolaryngology and related areas; to foster friendly assembly and stimulate scientific interest among its members.”

#### **National Institute on Deafness and Other Communication Disorders (NIDCD):**

“Funding for this conference was made possible in part by grant number 1R13DC016829-01 from NIDCD. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.”

#### **Translational Research Program (TRP):**

“The mission of the translational research program (TRP) at Boston Children's Hospital is to stimulate the development of non-clinical and human clinical trials that seek to improve the care of children, and to ensure adequate infrastructure to support non-clinical and clinical translational research projects.”

## SPONSORS

### Silver Sponsors



#### Retina Implant AG

After fifteen years of research and development it is certain: a person who loses their sight through degenerative retinal disease does not have to remain without a therapy-option. With our RI

Implants and RI Therapies we want to achieve what, until now, appeared to be impossible: we are researching and developing opportunities to help people suffering from retinitis pigmentosa. It is our goal to retain their residual vision or give them back a certain degree of sight.



**Second Sight Medical Products** develops, manufactures and markets implantable visual prosthetics to restore some functional vision to blind patients. Our product, the Argus II<sup>®</sup> Retinal Prosthesis System, is intended to provide electrical stimulation to the retina to induce visual perception in blind people with outer retinal degenerations, such as Retinitis pigmentosa.

### Bronze Sponsors



**Usher 1F Collaborative** is a U.S. 501c3 nonprofit foundation whose mission is to fund medical research to find an effective treatment to save or restore the vision of those with Usher Syndrome type 1F. Founded in 2013 in response to minimal research specific to Usher 1F, we have now funded over U.S. \$1 million in research at four labs, have two animal models, and several potential paths to a cure in development. Learn more: <http://usher1f.org>



#### Oticon - Because sound matters

Oticon Medical is a global company in implantable hearing solutions, dedicated to bringing the magical world of sound to people at every stage of life. As a member of one of the world's largest

groups of hearing healthcare companies, we share a close link with Oticon and direct access to the latest advancements in hearing research and technologies. Our competencies span more than a century of innovations in sound processing and decades of pioneering experience in hearing implant technology. Learn more: [www.oticon.de](http://www.oticon.de)



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## Meet the Speakers



**Alberto Auricchio** is a principal investigator and coordinator of the Molecular Therapy Program at Telethon Institute of Genetics and Medicine (TIGEM) in Pozzuoli/Naples, Italy. He is also professor of Medical Genetics at the Department of Advanced Biomedicine, University of Naples "Federico II". His major research focus is gene therapy of inherited forms of blindness and inborn errors of metabolism using adeno-associated viral (AAV) vectors. His group has contributed to the clinical development of Luxturna, the first gene therapy product approved in US for a genetic disease, and is coordinating a clinical trial of gene therapy for the lysosomal storage disease Mucopolysaccharidosis VI. His lab is developing strategies to overcome the limited cargo capacity of AAV to apply AAV-mediated gene therapy to forms of blindness due to mutations in large genes like Stargardt or Usher IB.



**Isabelle Audo** is a clinician scientist specialized in inherited retinal diseases. She is a group leader in the Dept. of Genetics at the Institut de la Vision in Paris, France. With her co-group leader Dr Christina Zeitz, she is conducting genetic studies applying high throughput next generation sequencing to decipher the underlying gene defect for inherited retinal diseases. At Quinze-Vingts Hospital, she supervises the Electrodiagnostic Unit, is a consultant at the Reference Centre for Rare Diseases and active Investigator at the Clinical Investigation Centre (CIC1423). She is PI and co-PI in several phenotype genotype correlation studies and gene-based clinical trials. She completed her ophthalmology residency at Lille University before joining the group of Prof. Sahel in Strasbourg for a Master. From 1999 to 2003, she spent her time at the Department of Ophthalmology at the University of Madison, Wisconsin, USA, under Prof Albert's supervision, where she completed a research fellowship and her PhD work defended at Strasbourg University. She then performed a Medical Retina Fellowship at Moorfields Eye Hospital, London, UK, with Profs. Bird and Holder. In 2007, she obtained a European Master of Genetics degree at Paris VII University while she was a postdoctoral fellow with Dr Léveillard at the Laboratory of Cellular & Pathophysiology Molecular Retina, in Paris. She received a carrier development award from the Foundation Fighting Blindness and, after the opening of the Institut de la Vision, she became a successful group leader within the department of genetics in addition to developing a busy practice in the Reference Centre for Rare Diseases of CHNO des Quinze-Vingts. There, she is following a large cohort of patients with Usher syndrome. She was involved in the FP7 European project Treatsrsh and the current French project Light4deaf, both aiming at a better understanding of Usher syndrome and at developing innovative therapies. She is a prolific researcher and writer having authored many scientific peer-reviewed papers.



**Mike Cheetham** is a Professor of Molecular Cell Biology at the University College of London (UCL), Institute of Ophthalmology (IoO). Mike completed his PhD on Alzheimer's disease at the Institute of Psychiatry, London and worked on other forms of dementia before moving to the IoO as a lecturer in 1995 when he started working on inherited retinal dystrophy. He was promoted to Professor in 2005. Research in the Cheetham lab is focused on the cell biology of protein folding and proteostasis in neurons. A major research focus is understanding the mechanisms of inherited retinal degeneration. Recently, we developed human iPSC 3D organoid models of retinal dystrophy and used them to probe retinal development, disease mechanisms and test therapies and this will be the focus of his presentation.



**Aziz El-Amraoui**, Associate Professor at the Institut Pasteur, Paris, France. After a PhD in Neuroscience from the University of Lyon-I in 1995, he joined the laboratory of Prof. C. Petit at the Institut Pasteur where resorting to dozen identified deafness genes, several of which are involved in Usher syndrome (deafness and blindness in humans), as entry points has enabled him to enlighten both fundamental and medical aspects of hearing & vision functioning and related disorders. Multidisciplinary approaches owing to the biochemical properties of the encoded proteins, identification of their molecular networks, animal modelling of the disease have provided major cues for understanding how the sensory organs develop and function (Jean-Valade Prize 2005, Fond Mazet-Danet Fondation de France, 2006; Chaire of Excellence Charles Nicolle, Institut Pasteur (2017-2019). In his team "Progressive Sensory Disorders", the member's current efforts are focused on late-onset and/or progressive hearing and vision impairments, aiming to i) elucidate the underlying molecular mechanisms, and ii) identify therapeutic targets to delay, prevent and/or cure progressive hearing and/or vision loss in animal preclinical models, and accelerate their transfer into clinics.



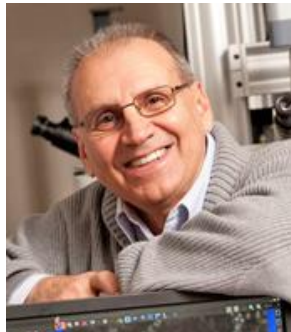
**Gwenaëlle Géléoc**, PhD, is an Assistant Professor in the department of Otolaryngology at Boston Children's Hospital and Harvard Medical School. Dr. Géléoc received her PhD from the University of Montpellier, France. Following postdoctoral work at University College London and Harvard Medical School, Boston, Dr. Géléoc, setup her research lab at the University of Virginia, Charlottesville. There, she studied the development of the sensory cells in auditory and vestibular organs. Her work has brought insight into the developmental maturation of the sensory function and led to the identification of novel proteins involved in sensory reception. After her move back to Boston, Dr. Géléoc, along with her colleague, Dr. Jeffrey Holt, started to explore the use of viral vectors to develop therapeutic treatments for deafness. Some of her pioneering work was published last year in Nature Biotechnology. Dr. Géléoc demonstrated successful restoration of auditory sensitivity in a mouse model of Usher Syndrome type IC. She is now continuing her



work assessing various approaches to restore auditory function caused by mutations that affect the sensory cells of the ear, in particular those associated with Usher syndrome.



**Yoshikazu Imanishi** is currently an Associate Professor in the Department of Pharmacology at Case Western Reserve University School of Medicine. Dr. Imanishi earned his PhD in 2000 from Osaka University. From 2000 to 2005, he conducted his postdoctoral studies at the University of Washington. During the early stage of the career, he invented a novel multiphoton imaging method to visualize dynamic biochemical states in living mammalian retina, and discovered retinosome which is the vitamin A storage structure within the eye. He has solved several critical questions regarding the mechanisms and processes of photoreceptor outer segment development and maintenance, elevating the understanding, treatment and diagnosis of eye disorders. He and his laboratory team developed the photoconversion technique that enables fluorescent labeling of newly synthesized proteins. His work has dramatically increased the understanding of the etiology of Usher syndrome type III for which he has discovered a potential therapeutic molecule. In pursuing the goal of discovering new therapies for the Usher syndrome type III, Dr. Imanishi has also invented a new method of drug screening, which is applicable to inherited disorders caused by protein-destabilizing gene mutations. He is the recipient of 2017 Pisart Award in Vision Science, which was established in 1981 to recognize leadership and outstanding research contributions of independent vision research scientists.



**Bechara Kachar**, M.D. received his M.D. degree from the University of São Paulo, Brazil in 1977. He did postdoctoral research on membrane structure and intercellular junctions with Pedro Pinto da Silva at the National Cancer Institute, and on cell structure and motility with Thomas Reese at the National Institute of Neurological Disorders and Stroke. He joined the National Institute on Deafness and other Communication Disorders (NIDCD), NIH in 1986 and is currently Chief of The Laboratory of Cell Structure and Dynamics (LCSD). Kachar's laboratory seeks an integrated molecular understanding of the architecture,

dynamics, function, and renewal of specialized cellular structures - in particular, those underlying the mechanosensory function of auditory and vestibular sensory cells. The long-term goal of the program is to develop a framework for understanding the different forms of loss of mechanosensory function and to explore opportunities for preventive and therapeutic interventions.



**William Kimberling** recently retired after a long and distinguished career as a human molecular geneticist at Boys Town National Research Hospital in Omaha, Nebraska, and from a faculty position at the University of Iowa which he held in the last years. As a pioneer in Usher syndrome research he mapped the locus for Usher type 2A in 1999. Over his long working life he gathered medical records of hundreds of individuals who have been followed for many years to determine the "natural history" of all Usher syndrome subtypes. By this

he paved the way for founded therapies for treatments and cures of the Usher syndrome disease.



**Margaret Kenna**, MD, MPH, Professor of Otolaryngology at Harvard Medical School and Director of Clinical Research in Otolaryngology at Boston Children's Hospital. Dr. Kenna received her BS from the University of Pennsylvania, her MD from Boston University School of Medicine, and her MPH from the Harvard School of Public Health. She completed a residency in Otolaryngology-Head and Neck Surgery at the University of Arkansas for Medical Sciences and a Pediatric Otolaryngology Fellowship at the Children's Hospital of Pittsburgh.

Before coming to Boston Children's in 1995, Dr. Kenna was on the academic faculty at Children's Hospital Pittsburgh and Yale University School of Medicine.

Over the past 20 years Dr. Kenna's research has focused on the etiologies of pediatric hearing loss, including genetic, structural inner ear anomalies, and ototoxicity. She has recently focused on the early and accurate molecular diagnosis of Usher Syndrome, as well as studying molecular therapies in animal models of Usher Syndrome. She is a founding member of the Harvard Medical School Center for Hereditary Deafness.



**Claes Möller** MD, PhD, is an Otolaryngologist (ENT) and Professor in Audiology and Disability Science at Örebro University and the Audiological Research Centre Örebro University Hospital. Prof. Möller has some 200 publications in international journals, 24 book chapters, and around 1000 presentations. The research encompasses genetics, otolaryngology, oto-neurology, pediatrics and audiology. A special interest for more than 30 years has been research in syndromic deafness and deafblindness. A special interest during the years has been Usher syndrome where Prof. Möller together with Prof. Kimberling

and co-workers during the years have described audiological, vestibular and visual features and made discoveries of genes in USH type 1 and 2. In the last 10 years the focus have been focused on inter-disciplinary bio-psycho-social research in deafblindness within the Swedish Institute for Disability Research at Örebro University.



**Julia Moser** is co-founder and chairwoman of the Forum for Usher Syndrome and Deafblindness (Forum für Usher Syndrom, Hörsehbeeinträchtigung und Taubblindheit), the first self-help organization connecting patients and their families in Austria.

Her work on improving the lives of those affected by Usher syndrome and deafblindness includes creating awareness, connecting patients and their families throughout Austria and lobbying for social change. She is driven by the vision, that every person with Usher syndrome and deafblindness should be able to lead a self-determined life.



**Kerstin Nagel-Wolfrum**, Dr. phil. nat, is Team leader of the Therapy Group (Translational Research) at the Institute of Developmental Biology and Neurobiology of the Johannes Gutenberg University (JGU) Mainz. She received her Diploma in Biology at the Technical University of Karlsruhe and did her PhD at the Goethe University of Frankfurt, Germany. After her PhD, she started at the JGU Mainz working on the human Usher syndrome, and performed her postdoctoral research at the Gene Therapy Centre, University of Florida, Gainesville (W.W. Hauswirth). Her research includes the expression analysis of retinal proteins in human and non-human primates as well as the functional characterization of proteins related to retinal disorders. Her main research interests are the development of gene-based therapies for hereditary retinal disorders. These strategies include i) Gene addition by adeno-associated virus (AAV) ii) Gene repair by homologous recombination and iii) Read-through of nonsense mutation with translational read-through inducing drugs. In 2012, she obtained a research award from the PRO RETINA Deutschland e. V. and Retina Suisse. From 2013 – 2016, she was the coordinator of the E-RARE-2 granted consortium “European young investigators for Usher syndrome (EUR-USH)”.



**Anne-Francoise Roux** works at the Hospital and the University in Montpellier (France) and is the Head of a group carrying out diagnosis and translational research on a number of sensorineural disorders, particularly on various forms of syndromic and non-syndromic deafness. Over the last 15 years, she has developed exhaustive molecular diagnosis for Usher syndrome making her unit a reference laboratory in France. Her group has particular expertise in the interpretation of missense DNA mutations and has published key papers demonstrating

splicing changes as a mechanism for Usher mutations. In addition, she is a board member of the European Management and Quality Network (EMQN) promoting quality management and quality control in molecular diagnostic laboratories.



**Kimberley Smith** completed her BSc in Psychology and Neuroscience at the University of Liverpool (2004). She obtained her PhD from Trinity College Dublin in 2010, and thereafter completed a postdoctoral fellowship in Psychiatry at McGill University in Canada (2011-2014). She was a lecturer in Life Sciences at Brunel University London (2014-2016) prior to joining the University of Surrey in 2016.

Her main research focus is research that examines healthy ageing, with a focus of vulnerable populations such as those who live with chronic conditions, those who have poorer social relationships and those who live with mental illness. She has recently started to look more at the impact of living with a chronic physical disability on ageing and mental wellbeing and has published work on the association of Usher syndrome with mental and social wellbeing and is part of a large ongoing project looking at Cerebral Palsy and mental illness.



**Matthew J. Tyska**, Ph.D. Following graduate studies with Dr. David Warsaw at the University of Vermont and postdoctoral training with Dr. Mark Mooseker at Yale University, Dr. Tyska joined the Department of Cell and Developmental Biology at Vanderbilt University as an Assistant Professor in December of 2004. He is currently the Cornelius Vanderbilt Professor of Cell and Developmental Biology and Scientific Director of the Vanderbilt Cell Imaging Shared Resource. Dr. Tyska's research program focuses on understanding how the cytoskeleton controls cell shape and function, specifically in the context of the transporting epithelial cells that line the intestinal tract. Over the past 14 years, the Tyska Laboratory has made a number of fundamental and field-leading

discoveries on the assembly and function of the enterocyte brush border, the apical specialization responsible for intestinal nutrient uptake. Although light and electron microscopy serve as principal discovery tools, investigations are decidedly broad in scope, ranging from studies in mouse model systems to single molecule imaging in live cells. Recent investigations have focused on defining the function of an adhesion complex of proteins related to the Usher syndrome that appears to be essential for normal brush border assembly. Because this complex has striking similarities to the one that links stereocilia tips in the inner ear, these studies also hold important implications for understanding hair cell morphogenesis.



**Erwin van Wijk** is an Assistant Professor at the Radboud University Medical Center (department of Otorhinolaryngology) in Nijmegen, the Netherlands. In 2009, he obtained his PhD in Medical Science (*Cum Laude*) from the Radboud University Nijmegen. His research has been mainly focused on Usher syndrome since 2004, after he identified the *USH2A* gene in its current form, and contains four major branches: 1. **Usher syndrome-associated proteomics** to obtain novel insights into the pathogenic mechanism underlying Usher syndrome and associated disorders. 2. **Identification of disease genes.** His studies to model

inherited (retinal) disorders in zebrafish, combined with homozygosity mapping and next-generation sequencing yielded several new disease genes (*ZNF408*, *CNNM2*, *POC1B* and *KIAA0556*). 3. **Clinical evaluation of Usher syndrome.** He has been involved in the phenotypic analysis of Usher syndrome type 2A patients and patients suffering from *USH2A*-associated non-syndromic retinitis pigmentosa. These data serve as the basis for the development of standard operating procedures in preparation of the first phase Ib/II clinical trials. 4. **Development of personalized medicine.** He obtained pre-clinical proof of concept for antisense oligonucleotide-based splice modulation as a future treatment option for *USH2A*-associated retinal dysfunction. These results have been patented and successfully valorized in a license agreement with ProQR Therapeutics (Leiden, NL).



**Uwe Wolfrum**, Univ.-Prof. Dr. rer. nat., holds a full professorship for Zoology and Cell Biology at the Johannes Gutenberg University (JGU) of Mainz, Germany since 1999. He received his Diploma in Biology from the Univ. Bayreuth and his Dr. rer. nat. in from the Univ. Regensburg. After a fellowship of the German Research Council (DFG) at the Mayo Clinic Foundation, Rochester, MN, he obtained his habilitation (*Vena legendi*) in 1998 from the University of Karlsruhe, Germany. He is interested research on molecules and protein networks related to the human Usher syndrome (USH) since the first USH gene has been identified in the nineties. At the JGU, his team further

emphasized "Photoreceptor Cell Biology" and aims to understand the basic molecular mechanisms underlying the function of primary sensory cilia in the eye. For his contribution towards defining the role of USH proteins in photoreceptor biology he received in 2008 the Directors Award from the Foundation Fighting Blindness. Since 2005, in addition to protein network analyses, the JGU therapy team evaluates gene-based strategies for the therapy of the USH in the eye.



**Jun Yang**, Ph.D. is currently an Associate Professor for Ophthalmology and Visual Sciences in the John A. Moran Eye Center at the University of Utah. She received her B.S. degree in Medical Biology from Nankai University, Tianjin, P.R. China. After working in the pharmaceutical industry in China for 7 years, Jun went to the University of Massachusetts, Amherst, in the USA for her graduate studies. She obtained her Ph.D. degree in Molecular and Cellular Biology in 2001. Jun was then trained in the retinal field as a postdoctoral fellow in the Berman-Gund laboratory, Harvard Medical School. Jun joined the Moran Eye Center at the University of Utah as

an independent investigator in 2008.

Jun is now studying the molecular mechanisms underlying Usher syndrome in both the retina and inner ear. Her team investigates the multiprotein complex involved in Usher syndrome type 2 using various molecular, cellular, biochemical, and mouse genetic approaches. Their research has been published in prestigious peer-reviewed scientific journals. Jun was awarded Nelson Trust for Retinitis Pigmentosa Scholar from Research to Prevent Blindness in 2013.



**Mingjie Zhang** is currently a Kerry Holdings Professor of Science, Senior Fellow of the Institute for Advanced Study, Director of Centre for Systems Biology and Human Health, and Chair Professor in the Division of Life Science, HKUST.

Research in Zhang's laboratory has been focusing on structural and biochemical basis of synaptic signalling and plasticity, and how neurons develop polarity in early development and maintain polarity in their adulthood. Zhang's lab has been approaching these two fundamental questions in neuroscience by a combination of structural biology, biochemistry, and cell biology approaches. Zhang's lab has also been

systematically investigating how the Usher1 complex in stereocilia and its homologous complex in microvilli are assembled. They have recently discovered that the condensed postsynaptic

density signalling assemblies in neuronal synapses are formed via liquid-liquid phase transitions, a finding that may have far reaching impact in understanding neuronal signalling.



**Eberhardt Zrenner** is Distinguished Professor of Ophthalmology at the Institute for Ophthalmic Research at the Centre for Ophthalmology of the University of Tuebingen. His research interests include: hereditary retinal dystrophies, retinal physiology and pathophysiology, neuro-ophthalmology, ophthalmic toxicology, electrophysiology and other methods of non-invasive function testing, neurodegeneration, ophthalmogenetics and gene therapy and in particular electronic retinal implants, so far tested in 29 study patients in an international multicenter trial, including Oxford, London and Hongkong and others. Prof. Zrenner has studied electronic engineering as well as medicine at the Technical University of Munich, where he obtained his MD degree in 1972. Subsequently he worked within the Max-Planck-Society and received a Fogarty fellowship at the national Eye Institute, NIH, Bethesda, MD. After Habilitation he did a residency at the University Eye Hospital in Munich, later on receiving there an associated professorship. He became full professor and Chairman at University Eye Hospital in Tuebingen in 1989, now Center for Ophthalmology. There he founded the Institute for Ophthalmic Research and runs a special clinic for hereditary retinal degenerations. He is Chairman of the Tuebingen Center for Neurosensory System. He has received numerous grants and awards, two honorary Doctoral Degrees and has published approximately 530 peer reviewed papers

## Scientific Oral Presentations

### INTRODUCTION

#### **A history of Usher syndrome research & prospects of new research directions on day 1 of the scientific program**

W J Kimberling, Y Lundberg

*Boys Town Research Hospital, Omaha, NE*

Usher syndrome is a genetically heterogeneous disorder causing retinitis pigmentosa, hearing loss, and variable vestibular dysfunction. The first recorded instance of Usher syndrome was made by von Graefe in 1858 in Germany. Clinical and genetic data accumulated slowly over the following century. The disorder was named after Charles Usher, an English ophthalmologist, who described the phenotype in detail and presented evidence of its recessive inheritance. In 1959 Bertil Hallgren carried out a study of the Swedish deaf-blind population that supported the concept of heterogeneity. Subsequent progress in understanding the genetic nature of Usher syndrome was slow until around the last decade of the 20<sup>th</sup> century. The discovery of first RFLPs and then SNPs made gene mapping research much more effective, even for recessive traits like Usher syndrome. The first localization of Usher syndrome was of type II to chromosome 1q. This finding also established that the clinical heterogeneity was due to genetic heterogeneity and that at least 2 genes were responsible. To date, twelve loci have been identified as associated with Usher syndrome. Localization was quickly followed by gene identification. For example, the USH1B locus was identified as coding for myosin 7a (MYO7A). Several animal models were developed and these were used to characterize the gene expression and tissue distribution. The USH proteins were found to interact with one another to form complexes that were responsible for their function in the inner ear and retina. Current researches on therapy have focused on gene augmentation, gene editing, translational read through aminoglycosides, prostheses, and retinal and photoreceptor grafting. Accurate and affordable genetic diagnosis is now available using a variety of nextgen sequencing platforms. Overall, the amount of Usher research has increased considerably since the first localizations were made. This is evidenced by the increase in publication rate from about 1.5 papers per year in the 1990s to 137 publications in the last 18 months. This is a remarkable increase and bodes well for future progress in the field. Future progress in therapy should increase on several fronts. It is to be expected that treatment will depend upon a variety of factors: The USH genetic type, the nature of the mutation(s), and the degree to which the eye and ear have been damaged. Gene augmentation, for example, will be most effective early in the life of an Usher patient. Later in life, it may slow progression but is unlikely to restore much sensory ability. Prostheses are already being used to correct the hearing loss and progress is being made to develop effective prostheses for the eye. Clinical trials of these potential treatments requires a pool of appropriate and willing test subjects. Data bases listing potential subjects and with good genetic and clinical data will be extremely helpful. More studies on natural history, by genotype, are necessary in order to plan clinical trials by giving the investigator tools with which to test whether a significant clinical improvement occurs. There is always room for more clinical studies, such as, for example, is there an olfactory component to any of the USHs. The effect in

the heterozygote has been studied but only before the genetic subtypes were identified. This should be revisited. Rehabilitation research should be continued since treatments will be slow in being developed and people with Usher syndrome need to cope with their lives today. In conclusion, a rapidly growing amount of basic and clinical research promises a brighter outlook for individual and families dealing with Usher syndrome.

## GENETICS AND DIAGNOSIS

### Genetics of Usher Syndrome

Anne-Françoise Roux

*CHU Montpellier, FR*

Usher syndrome (USH) refers to recessively inherited disorders that associate hearing loss (HL) and retinitis pigmentosa (RP). It represents the first cause of deaf-blindness with an average frequency of 1/30 000. Three clinical subtypes are defined with respect to the degree of HL, the age of RP onset and the occurrence of vestibular areflexia. Ten genes, that when mutated lead the development of the disease, have been identified: six (MYO7A, USH1C, CDH23, PCDH15, USH1G and CIB2) are involved in Usher type 1, the most disabling form, three (USH2A, ADGRV1 (GPR98) and WHRN) in Usher type 2, the most frequent form, and one, CLRN1, in Usher type 3. For many years, molecular diagnosis of Usher syndrome was laborious as many of these genes consist of numerous exons (e.g. 49 for MYO7A and 72 for USH2A, the most frequently involved genes). Furthermore the lack of reliable “mutational hot-spot” does not allow to prioritize analyses. As a result, and for many years, cascade sequencing by Sanger technology of all coding exons of target genes was the standard approach.

However, even if the identification of a clinical subtype would point to a group of genes to be sequenced, the phenotypic variability could shuffle the cards and resulted in negative results for the expected target genes. Consequently, molecular diagnosis required time-consuming sequencing of all USH genes.

In the last five years, the implementation of MPS (Massively parallel sequencing) in diagnosis laboratories permits simultaneous sequencing of all the USH genes, thus making molecular studies of Usher patients much easier and faster. Yet, additional tools to search for hidden mutations or to classify the numerous variants of unknown clinical significance are needed in order to offer a proper comprehensive diagnosis.

When gene panels also include additional genes mimicking USH syndrome, it becomes possible to address subtle differential diagnoses. On the other hand, since several USH genes are involved in non-syndromic HL as well, they can now be screened in patients presenting with apparent non-syndromic form. Then, the challenge is to provide the most accurate genetic counselling as whether a child carrying two USH1 pathogenic variants will develop Usher syndrome or not.



Finally, in addition to providing families with proper care, elucidating the molecular causes of Usher syndrome remains the essential step to build patient cohorts and to develop therapeutic approaches.

## **Clinical diagnosis of USH**

Isabelle Audo

*Institute de la Vision, Sorbonne Université, Paris, France &  
CHNO des Quinze-Vingts, DHU Sight Restore, Charenton, France.*

Usher syndrome is a group of clinically and genetically heterogeneous disorders that are diversely affecting the cochlea, the vestibule and the retina. The degree of dysfunction of these three types of tissues defines the three type of Usher syndrome. The presentation will review the necessary steps to achieve an accurate diagnosis which is subsequently confirmed by molecular genetics. An emphasis will be given to retina phenotyping and the current state of the art examination to precisely document retinal dystrophy.

## CELL AND MOLECULAR BIOLOGY

**The retinal phenotype of Usher syndrome: pathophysiological insights from animal models**

Schietroma C<sup>1</sup>, Michel V<sup>1</sup>, Patni P<sup>1</sup>, Trouillet A<sup>2</sup>, Cortese M<sup>1</sup>, Papal S<sup>1</sup>, Bahloul A<sup>1</sup>, Picaud S<sup>2</sup>, Petit C<sup>1</sup>, and El-Amraoui A<sup>1</sup>

<sup>1</sup> *Institut Pasteur, Génétique et Physiologie de l'Audition, Sorbonne Université, INSERM UMRS1120, Collège de France, 75015 Paris, France*

<sup>2</sup> *Institut de la Vision, 17 rue Moreau, F-75012, Paris, France*

The Usher syndrome (USH) is the most prevalent cause of inherited deaf-blindness in humans. Three clinical subtypes, USH1-3, have been defined, and ten USH genes identified. Animal mouse models mimicking the abnormal hearing phenotype are available for all USH genes. The USH hearing impairment has been shown to result from improper organization and functioning of the hair bundle, the sound receptive structure of sensory hair cells. In contrast, until recently, the molecular & cellular bases of the visual defect have been less understood as this phenotype is absent in most of the Usher mouse models. Retinal cell degeneration and vision loss have only been unambiguously reported in some Ush2 mutant mice. The three USH2 proteins have been detected in the periciliary ridge complex region, where vesicles dock with the plasma membrane during translocation to the outer segment of photoreceptor cells. By contrast, almost all other Usher mice display no visual defect. Interestingly, creation of two Ush1 mouse models on an albino background revealed that, unlike pigmented mice, *Ush1g<sup>-/-</sup>* and *Ush1c<sup>-/-</sup>* albino mice have dysfunctional cone photoreceptors. The key involvement of oxidative stress in photoreceptor apoptosis and the ensued retinal gliosis was confirmed by prevention of retinal abnormalities when Ush1 mice are reared under darkness or supplemented with antioxidants, such as taurin. Strikingly though, interspecies comparative studies on the retina enabled us to show key differences about USH1 proteins' association with microvillar structures, the calyceal processes, that are present in primate, but not mouse, photoreceptors. An USH1-mediated adhesion belt, similar to that operating in the inner ear stereocilia, has been proposed to ensure normal coupling between the calyceal processes and the outer segments; its defect probably causing the USH1 retinopathy. Our recent studies in Ush1-deficient frogs revealed impaired photoreceptor function and abnormally shaped outer segments, linked to altered and/or absent calyceal processes. Together, these findings indicate that USH1-containing links are essential for their development and/or maintenance of the calyceal processes, which control the sizing of rod disks and cone lamellae throughout their daily renewal. Accordingly, to enable adapted therapies for USH vision, there is an urgent need of preclinical models in appropriate animal species that faithfully reproduce the Usher retinopathies.

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## The USH2 protein complex in photoreceptors and hair cells

Jun Yang

*University of Utah, USA*

Usher syndrome (USH) is the leading cause of inherited deaf-blindness and is currently incurable. Our study focuses on understanding the pathogenesis of USH2, the most common clinical type of USH. ADGRV1, usherin, and whirlin proteins are encoded by the three known USH2 causative genes, and PDZD7 protein is encoded by the known USH2 modifier gene. Biochemical studies have demonstrated that the PDZ domains of whirlin and PDZD7 can directly bind to the PDZ-binding motif of ADGRV1 and usherin *in vitro*. Additionally, ADGRV1, usherin, and whirlin are colocalized at the periciliary membrane complex in retinal photoreceptors, and the three proteins, together with PDZD7, are colocalized at the ankle link complex in inner ear hair cells. The normal subcellular localization of the four USH2-related proteins depend on each other *in vivo*. Therefore, the USH2-related proteins are thought to form a multiprotein complex, the USH2 complex, in both photoreceptors and hair cells. However, our study further demonstrated that the USH2 complex is not exactly the same in photoreceptors and hair cells. First, whirlin plays a role in assembling the complex in photoreceptors, while PDZD7 plays the equivalent role in hair cells. Second, PDZD7 is a component of the USH2 complex only in hair cells. Third, myosin VIIA, an USH1 protein that directly interacts with all four USH2-related proteins *in vitro*, is essential for USH2 protein subcellular localization in hair cells, but not in photoreceptors. In summary, the USH2 complex probably functions and acts in a mechanism similarly but not exactly the same in photoreceptors and hair cells. To understand the pathogenesis of hearing and vision loss in USH2, it is necessary to conduct the studies on the USH2 complex in both the retina and inner ear.

## Shaping the intestinal brush border with adhesion links

Matthew J. Tyska

*Dept. of Cell & Developmental Biology, Vanderbilt University School of Medicine, USA*

During intestinal epithelial differentiation, the packing and organization of apical microvilli are driven by adhesion between two protocadherins, CDHR2 and CDHR5, which drive strong heterophilic interactions between the distal tips of neighboring protrusions. CDHR2 is also capable of weak homophilic interactions. Two cytoplasmic scaffolding proteins, USH1C and ANKS4B, are thought to link CDHR2 and CDHR5 to the actin-based motor, myosin-7b (Myo7b), which promotes accumulation of the resulting “intermicrovillar adhesion complex” (IMAC) at microvillar tips. Interestingly, the IMAC bears a striking resemblance to the tip-link complex that connects the distal tips of adjacent hair cell stereocilia in the inner ear, with USH1C being the only shared gene product. Previous loss-of-function studies in intestinal epithelial cell lines led to the hypothesis that delivery of adhesion links to microvillar tips may be a mechanism that enterocytes use to generate protrusions of uniform length, a defining characteristic of the brush border. To test this hypothesis, we developed a heterologous assay using HeLa cell filopodia,

which normally exhibit great variability in length. To study the consequences of CDHR2 tip delivery in this heterologous system, we generated a chimera containing the motor domain of filopodial myosin, Myo10, and the cargo-binding tail domain of Myo7b. IMAC components that interact with Myo7b, including ANKS4B and USH1C, become enriched at filopodial tips when coexpressed with the chimeric motor. Interestingly, we also found that the chimeric motor alone, without the assistance of USH1C or ANKS4B, delivers CDHR2 and CDHR5 to filopodial tips. Tip enrichment of CDHR2 increased filopodia number and stability, and promoted interactions between adjacent filopodia, resulting in inter-filopodial adhesion and the formation tepee-like clusters of dorsal filopodia, which resemble the clusters of microvilli found on differentiating epithelial cells. Remarkably, tip enrichment of CDHR2 also promoted filopodial length uniformity. These studies highlight default functions for tip-enriched adhesion complexes and their impact on protrusion and cell surface morphology.

## **Variable Number of TMC1 Molecules Underlie Tonotopic Variation in Bundle Morphology and Conductance Gradients in the Cochlea**

Runjia Cui, Seham Ebrahim, and Bechara Kachar

*Laboratory of Cell Structure and Dynamics, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD 20892, USA*

Transmembrane channel-like isoform 1 and 2 (TMC1 and TMC2) are essential components of stereocilia mechano-electrical transduction (MET) channel complex and are required for normal hearing. However, what role TMCs play within the MET molecular machinery, and how they regulate stereociliary bundle morphology during development remain unclear. We examined the relative contributions of TMC1 and TMC2 to the hair bundle morphology development and tonotopic conductance gradients along the organ of Corti.

For the morphological analysis of the stereocilia development and quantitative analysis of the expression of TMC1 and TMC2 at the sites of mechanotransduction we used high performance confocal microscopy of organ of Corti from transgenic mice exhibiting mosaic expression of fluorescently tagged TMC1 and TMC2 on a TMC1/TMC2 null background.

In the presence of both TMC isoforms at postnatal day 6 (P6), the number of TMC1 molecules expressed at each MET channel site had a small increase from apex to base in inner hair cells (IHCs) but showed a 3-fold linear increase in outer hair cells (OHCs). Interestingly, the fluorescence intensity of TMC2 exhibited a significant change in the opposite direction to TMC1 gradient in both IHCs and OHCs. The graded expression of TMC1 in OHCs was maintained through adulthood with the average number of TMC1 molecules calculated to be 8 at apex to 20 at base, while the expression of TMC2 started to decline from base to apex around P6 and can only be detected in apical IHCs at P10. Our data from mice with mosaic expression of TMC1 and TMC2 showed that the presence of either TMC1 or TMC2 was sufficient to produce normal stereociliary bundle development. At P6, hair cells lacking both TMCs had immature phenotype characterized by multiple rows of stereocilia in IHCs and rounded bundles in OHCs. Compare to hair cells expressing both TMCs, a significant upregulation of one isoform was detected in stereocilia in the absence of the other.

The data analysis reveals a correlation between the number of TMC1 molecules and the reported tonotopic gradient in single channel conductance in OHCs. This insight suggests each MET site contains varying numbers of channels each requiring multiple TMC1 molecules. Our results also show that the expression of either TMC1 or TMC2 is required for proper hair bundle maturation. Moreover, we observed an upregulated TMC2 expression in the absence of TMC1 during hair cell development, suggesting the removal of TMC2 may be facilitated by the increased level of TMC1.

## **Structures of the USH1 complexes and their homologues in other tissues**

Mingjie Zhang

*Division of Life Science, State Key Laboratory of Molecular Neuroscience, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong*

Usher syndrome 1 (USH1) is the most common and severe form of hereditary loss of hearing and vision. Genetic, physiological, and cell biological studies, together with structural investigations, have not only uncovered the physiological functions of the five USH1 proteins, but also provided mechanistic explanations for the hearing and visual deficiencies in humans caused by USH1 mutations. Brush border microvilli, actin-based protrusions lining the apical surface of epithelial cells in intestines and proximal tubules of kidneys, resemble the stereocilia of hair cells. Interestingly, many of the protein components that regulate stereocilia development and maintenance have their corresponding counterparts in microvilli, suggesting that the underlying molecular mechanisms for the developments of stereocilia and microvilli might be similar. In this talk, I will discuss our systematic biochemical and structural characterizations of the USH1 protein interaction network and provide structural evidence that the tip-link complex in brush border microvilli shares striking similarity with the stereocilia tip-link complex. Finally, I will show our unpublished findings on the possible mechanism governing the formation of the tip-link densities in stereocilia and microvilli.

## USH MODELS & THERAPY

### Gene addition therapy

Alberto Auricchio

*TIGEM (Telethon Institute of Genetics and Medicine) and Dept. of Advanced Biomedicine,  
"Federico II" University, Napoli, Italy*

Given its small size and enclosed structure, the retina is an attractive target for gene therapy with adeno-associated viral (AAV) vectors. Our group and others have shown that subretinal administration of AAV is safe and effective in patients with congenital forms of blindness. To apply this successful approach to other similar conditions caused by mutations in genes whose coding sequence exceeds AAV cargo capacity, we have recently developed strategies based on co-delivery of two AAV vectors each carrying one of the two halves of a large gene. We have demonstrated that this is effective in animal models of commonly inherited blinding conditions like Stargardt disease and Usher IB, and efforts are under way to develop a clinical trial to test dual AAV in the retina of patients with Usher IB.

### Translational read-through as therapy for the Usher syndrome caused by nonsense mutations

Kerstin Nagel-Wolfrum

*Institute of Neurobiology & Developmental Biology, Johannes Gutenberg University of Mainz,  
Germany*

The Usher syndrome (USH) is the most common form of inherited deaf-blindness. Cochlear implants can compensate the hearing deficiency, however currently no effective treatment is available to stop the retinal degeneration. Nonsense mutations in USH related genes are frequent causes of USH. They introduce a premature termination codon in the coding sequence and lead to the expression of truncated, non-functional proteins. TRIDs (translational read-through inducing drugs) mediate the read-through of nonsense mutations and thereby induce the expression of functional full-length proteins. One such TRID - Ataluren (Translarna) - is already classified as an orphan drug for Duchenne muscular dystrophy caused by nonsense mutations.

Several studies revealed recovery of functional proteins after Ataluren treatment for different ocular disorders, including USH-causing mutations in vitro and in cell culture assays. To analyze read-through efficacy in a patient specific background, we are currently using patient-derived cells, such as fibroblasts, induced pluripotent stem cells and their derivatives as preclinical test systems. We have shown the efficacy of TRIDs to restore aberrant protein expression in several patient-derived cells from patients with USH type 2A and type 1C. Due to the lack of an animal model harbouring a USH nonsense mutation, in vivo studies were

performed in mouse models of other ocular disorders, demonstrating the efficacy of Ataluren in the retina.

In summary, we and others demonstrated the efficacy of TRIDs targeting nonsense mutations for hereditary retinal dystrophies and in particular for USH. Therefore, targeting nonsense mutations has the potential to benefit a substantial proportion of USH patients, making such an approach both practical and economical. Recent findings support the use of patient-derived fibroblasts as a platform for preclinical therapy validation paving the way for clinical trials for the treatment of USH.

Support: FAUN-Stiftung, Nuremberg; ProRetina

### Splice modulation to treat *USH2A*-associated retinal degeneration

Erwin van Wijk<sup>1</sup>, Margo Dona<sup>1,3</sup>, Ralph Slijkerman<sup>1,3</sup>, Erik de Vrieze<sup>1</sup>, Hannie Kremer<sup>1,2</sup>, Peter Adamson<sup>4,5</sup>, Janne Turunen<sup>4</sup>, Kalyan Dulla<sup>4</sup>, Stephan Neuhauss<sup>7</sup>, Hester van Diepen<sup>4</sup>

<sup>1</sup> Dept. of Otorhinolaryngology, Donders Institute for Brain, Cognition and Behaviour, <sup>2</sup> Dept. of Human Genetics, Radboudumc, Nijmegen, Netherlands; <sup>3</sup> Radboud Institute for Molecular Life Sciences, Nijmegen, Netherlands; <sup>4</sup> ProQR Therapeutics, Leiden, Netherlands; <sup>5</sup> Institute of Ophthalmology, UCL, London, UK; <sup>6</sup> Institute for Molecular Life Sciences, University of Zürich, Zurich, Switzerland

Mutations in *USH2A* exon13 are the most frequent cause of both syndromic and non-syndromic retinitis pigmentosa (RP), for which currently no treatment options exist. It is generally believed that RP due to mutations in this gene is caused by a loss-of-function mechanism. In total, over 600 different mutations have been identified in *USH2A* that are spread throughout the gene. Most mutations in *USH2A* are unique or are only found in a few patients. However, at least three mutations are known to be derived from a common ancestor and are therefore seen more commonly: c.2299delG (p.Glu767fs\*21), c.2276G>T (p.Cys759Phe) and c.7595-2144A>G (p.Lys2532Thrfs\*56).

The size of the coding sequence (15,606 bp) and the presence of multiple alternatively spliced *USH2A* transcripts with unknown significance, respectively, hamper the development of gene augmentation therapy. Another difficulty in the development of a therapy for the associated retina degeneration is the lack of a suitable animal model. The currently available *Ush2a* mouse model displays only mild retina degeneration with a very late age of onset. Zebrafish *ush2a* mutant models however, show an early onset retinal dysfunction and are as such provide a unique opportunity to evaluate future therapeutic strategies.

Antisense oligonucleotide (AON)-based splice modulation has been proven to hold great promise as a therapeutic strategy for a number of hereditary conditions, including Usher syndrome. AONs are small modified single-stranded RNA or DNA molecules that are complementary to splice enhancer or silencer target sites. Upon pre-mRNA binding, AONs will prevent or stimulate binding of the spliceosome thereby modulating splicing events. AONs can be designed and applied for different genes and genetic disorders as the specificity depends on their nucleotide sequence.

In this study we explored the therapeutic potential of AON-induced splice modulation as a therapeutic approach for the future treatment of *USH2A*-associated retinal degeneration using a combination of zebrafish and iPSC-derived photoreceptor models.

Disclosures: This work has been patented under number PCT/EP2015/065736. Radboudumc has licensed the rights to the patent exclusively to ProQR Therapeutics.

## **A small molecule mitigates hearing loss in a mouse model of Usher syndrome III**

Kumar N. Alagramam<sup>1</sup>; Suhasini R. Gopal<sup>1</sup>; Ruishuang Geng<sup>1</sup>; Daniel H.-C. Chen<sup>1</sup>; Ina Nemet<sup>1</sup>; Richard Lee<sup>1</sup>; Guilian Tian<sup>1</sup>; Masaru Miyagi<sup>1</sup>; Karine F. Malagu<sup>2</sup>; Christopher J. Lock<sup>2</sup>; William R. K. Esmieu<sup>2</sup>; Andrew P. Owens<sup>2</sup>; Nicola A. Lindsay<sup>2</sup>; Krista Ouwehand<sup>2</sup>; Faywell Albertus<sup>2</sup>; David F. Fischer<sup>2</sup>; Roland W. Bürli<sup>2</sup>; Angus M. MacLeod<sup>2</sup>; William E. Harte<sup>1</sup>; Krzysztof Palczewski<sup>1</sup>; Yoshikazu Imanishi<sup>1</sup>

<sup>1</sup> Case Western Reserve University; <sup>2</sup> Charles River, Cleveland, USA

Usher syndrome type III (USH3) is characterized by progressive deafness and blindness, with variable difficulty in maintaining balance. It is frequently caused by destabilizing missense mutations in the gene encoding the clarin-1 protein (CLRN1). Here we report a novel strategy to mitigate hearing loss associated with a common USH3 mutation CLRN1N48K that involved a cell-based high-throughput screening of small molecules capable of stabilizing CLRN1N48K, a secondary screening to eliminate general proteasome inhibitors, and finally an iterative process to optimize structure activity relationships. These efforts resulted in a new molecular entity BF844. To test the efficacy of BF844, a mouse model was developed that mimicked the progressive hearing loss of USH3. BF844 effectively attenuated progressive hearing loss and prevented deafness in this model. Because the human CLRN1N48K mutation causes both hearing and vision loss, BF844 could in principle prevent both sensory deficiencies in USH3. Moreover, the strategy described here could help identify drugs for other protein-destabilizing monogenic disorders.

## **Retinal organoids as disease models**

Mike Cheetham

*London GB*

The ability to reprogramme human cells into induced pluripotent stem cells (iPSC) and then differentiate them into a wide range of different cell types has revolutionized our ability to study human disease and offers great potential for regenerative medicine. We have used iPSC derived from inherited retinal dystrophy (IRD) patients to study the mechanisms of disease and to test potential therapies. In particular, I will describe how differentiating iPSC to retinal pigment epithelium (RPE) and 3D retinal organoids that contain photoreceptors can explain the retinal specificity associated with some inherited changes, revealing why retinal cells are more susceptible to disease than other cells that also express the disease gene. Furthermore, iPSC derived retinal cells are ideal for testing gene and mutation specific therapies that cannot be tested on knock-out animal models. This technology also offers the potential for quick translation to the clinic by showing not only efficacy, but also safety in the target human cells.



## THERAPY IN FOCUS

### Update on UshStat trial and associated studies

Isabelle Audo

*Institute de la Vision, Sorbonne Université, Paris, France &  
CHNO des Quinze-Vingts, DHU Sight Restore, Charenton, France.*

UshStat is a Phase I/IIa dose escalation safety study consisting of a subretinal injection of a viral vector for MYO7A gene delivery. The clinical trial is a bicentric study (Quinze-Vingts hospital in Paris, France, and Casey Eye Institute, Portland, Oregon, USA) administered to patients with Retinitis Pigmentosa associated with Usher Syndrome Type 1B. The presentation will review the biological process, the inclusion criteria, the protocol and deliver some preliminary results.

### Retina implant and electrostimulation

Eberhart Zrenner

*Institute for Ophthalmic Research, Centre for Ophthalmology, University of Tuebingen,  
Germany*

Electrostimulation can be used in several ways, either to release endogenous growth factors that may be beneficial for slowing down retinal degeneration or for restitution of visual perceptions by electronic retinal prostheses.

1. Electronic retinal prosthesis. There are three concepts being pursued: a) *epiretinal electrode arrays* b) the *subretinal approach* c) the *suprachoroidal approach* to implant electrode arrays for spatially ordered stimulation of inner retinal neurons.

*Epiretinal*: The Argus<sup>®</sup> II implant with 60 electrodes (Humayun et al., Ophthalmology, 2012), developed by Second Sight (Sylmar CA, USA) has been implanted during clinical trials in approx. 200 patients in both Europe and the US where it has also been approved for commercial use. A similar approach has been pursued by Pixium company in Paris with the IRIS II system, that has the receiver electronics positioned in the lens capsula.

*Subretinal*: The Retina Implant Alpha-IMS system with 1500 Electrodes (Zrenner et al. Proc Roy Soc B, 2011) of Retina Implant AG has been implanted during clinical trials in 29 IRD patients (Stingl et al., Vision Res. 2015). The new model Retina Implant Alpha AMS with 1600 electrodes and considerably longer survival time has received CE approval for commercial sale in the EU in 2016, meanwhile financed in Germany also by the public health system.

*Suprachoroidal devices* were developed by the Bionic Vision Australia consortium (Ayton et al., PLoS One 2014) and Nidek Ltd. (Fujikado et al. IOVS 2011); due to the position further away from neurons, spatial resolution is very limited in this approach.

2. Electrostimulation. It has been shown that transcorneal electrostimulation releases endogenous growth factors (BDNF, CNTF, FGF) which prolongs survival of neurons. Meanwhile devices are available (OCUSTIM by Ocuvision GmbH) for patients to stimulate weekly both eyes with electrical currents. Several clinical trials have shown positive effects on the cone system in patients with IRDs (Schatz et al. IOVS, 2011, 2017).

The various approaches will be presented and indications, applications and limitations will be discussed.

## **Steps Toward Better Life Improving access and quality of education for DB and MD children and youth through partnerships - global campaign**

Darija Udovicic Mahmuljin

*Perkins International, Boston, US*

Perkins was founded in 1829 in Boston and is a world-renowned school serving students who are multiply disabled and visually impaired and deafblind. Perkins International (PI) has for 40 years been a global leader in global education, working around the world to help train teachers of MDVI and DB children and empower families.

Children who have multiple disabilities and visual impairment and those who are deaf-blind (MDVI/DB) require specialized education services. They are often left out of education, family and community life. A child who has MDVI needs a teacher who is trained in specialized strategies to meet their unique needs.

**The 2030 United Nations Sustainable Development Goals (SDGs)** have called for quality education for all children. To make a true effort to combat social inequity, SDG4 goal states, it is imperative that all countries work in harmony to “ensure inclusive and quality education for all,” Yet, global efforts are leaving behind children with multiple disabilities and vision impairment as well as deafblind children.

As a global leader in education of children with multiple disabilities, Perkins International is committed to making quality education accessible to 6 million MDVI/DB children. The SDGs provide a window of opportunity to create the systemic changes required to achieve that goal.

**To build on this momentum, Perkins has designed a global strategy to achieve quality education for some of the world’s most vulnerable children.** Perkins International has consolidated 97 years of global teacher training expertise into **Perkins International Academy (PIA)** that was launched in 2017 in UN as global campaign to help governments meet their commitments to SDG 4. The courses establish the first-ever international competency standard for teachers working with children with multiple disabilities.

Perkins designed the **Perkins International Academy** to be implemented in partnership with governments, Universities and other organizations. With this blueprint, Perkins International has endeavored to train 1 million teachers worldwide – one teacher for every six children with MDVI. But we cannot navigate the next frontier of education in accordance with the U.N.’s timeline without building long-term partnerships. We need to build partnerships with countries that know every child has the capacity to learn. We need to build partnerships with countries who can set an example for others to follow.

## INCLUSION THROUGH INNOVATION

### Clinical trial design for nonsense mutations treatment of USH2A

Mariya Moosajee

*Moorfields Eye Hospital; UCL Institute of Ophthalmology, London, UK*

Dr Mariya Moosajee is focused on developing small molecule drugs, such as ataluren, that can be used for overriding nonsense mutations as a treatment for Usher syndrome. In order to progress to clinical trials, natural history studies are required to highlight the correct outcome measures that should be used to inform the efficacy of potential treatments. The use of optical coherence tomography and fundus autofluorescence together provide stronger evidence of disease progression. Based on these findings and the oral administration of the drugs, we can design trials that are long enough with a crossover design to ensure that patients all get the opportunity to take the drug. This was based on feedback from Usher syndrome patient discussion groups, who felt it was not ethical to leave half of the recruited patients on a placebo.

### My experiences with Argus<sup>®</sup> II and the better quality of life since I got the Argus<sup>®</sup> II

Dorothea Kohlhaas

*Argus<sup>®</sup> II user*

As a patient with Retinitis Pigmentosa and a user of the Argus<sup>®</sup> II Retinal Prosthesis System, Dorothea will explain how to handle the equipment (the glasses and a Video Processing Unit). She will then share her daily experiences: how she can use it in different situations and the better orientation and mobilisation it gives her.

“The quality of life changes in a good way with Argus II”, she says. It is an important help for Dorothea to feel more safe when she goes out alone and gives her more self-confidence.

At the end, she would like to present the so-called “A-Team”. It is a team of Argus<sup>®</sup> II users. They meet to exchange, to help each other and to support each other and interested persons.

### Subretinal Implant Alpha AMS – recent developments and achievements

Alfred Stett

*Retina Implant, Reutlingen, Germany*

Subretinal inserted electronic implants replace the function of photoreceptors by converting images incident on the fundus into electrical impulses, which stimulate the retina of people who suffer from severe retinitis pigmentosa.

The CE certified RETINA IMPLANT Alpha AMS utilises an active chip, 3.2 x 4 mm size, with 1600 light detecting and stimulating pixels. It is placed subretinally. No external means for image capturing and processing are required. Since the chip is placed under the fovea, it follows the eye movements. The natural combination of head rotation, eye movements and microsaccades are utilised for image localisation and fixation. Based on a clinical validated aging model, we expect a median lifespan of the implanted system of 5 years.

Psychophysical and subjective data obtained in clinical trials and in daily use show that RETINA IMPLANT Alpha AMS is reliable, well tolerated and can restore limited visual functions in blind people. Regular use of the implant is related to outcome improvements.

The presentation will show recent developments and achievements in implant technology and vision rehabilitation and how the implant positively affects the individuals in their daily life

## Poster / Short Talk Abstracts

### DIAGNOSTICS

#### # 1 Psychological and Physical Health in Persons with Usher Syndrome Type II – A population study

Asmin Sha Valiyagath; Al Hind hospital, India

#### # 2 Inclusion of Deaf-Blind Adults in Patient Reported Outcomes Research

Poorna Kushalnagar<sup>1</sup>, <sup>1</sup>Gallaudet University, Washington, DC, USA

#### # 3 Health-related quality of life and Psychosocial welfare in patients with Usher syndrome

Sabin Katpattil<sup>1</sup>, <sup>1</sup>Ramdas nursing home, India

#### # 4 Health and work in persons with Usher syndrome type 1

Mattias Ehn<sup>1</sup>; Moa Wahlqvist<sup>1</sup>; Berth Danermark<sup>1</sup>; Örjan Dahlström<sup>1</sup>; Claes Möller;

<sup>1</sup> Audiological Research Centre Örebro University Hospital, Örebro, Sweden.

#### # 5 Colour vision in Usher syndrome

Anne Kurtenbach<sup>1</sup>; Gesa Hahn<sup>1</sup>; Christoph Kernstock<sup>1</sup>; Stefanie Hipp<sup>1</sup>; Ditta Zobor<sup>1</sup>; Katarina Stingl<sup>1</sup>; Susanne Kohl<sup>1</sup>; Crystel Bonnet<sup>2,3</sup>; Saddek Mohand-Saïd<sup>2,4</sup>; Ieva Sliesoraityte<sup>5</sup>; José-Alain Sahel<sup>2,3,4</sup>; Isabelle Audo<sup>2,4</sup>; Ana Fakin<sup>6</sup> Marko Hawlina<sup>6</sup> Francesco Testa<sup>7</sup>; Francesca Simonelli<sup>7</sup>; Christine Petit<sup>2,3,8</sup>, Eberhart Zrenner<sup>1</sup>,

<sup>1</sup>Centre for Ophthalmology, Institute for Ophthalmic Research, University of Tuebingen, Tuebingen, Germany; <sup>2</sup>Institut de la Vision, INSERM UMR51120, Paris, France; <sup>3</sup>UPMC-Sorbonnes Universités, Paris, France; <sup>4</sup>Centre d'Investigation Clinique, Direction de l'Hospitalisation et de l'Organisation des Soins, Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, Paris, France; <sup>5</sup> Institut Arthur Vernes, 36 Rue d'Assas, 75006 Paris, France; <sup>6</sup>Eye Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; <sup>7</sup>Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences, University of Campania Luigi Vanvitelli, Naples, Italy; <sup>8</sup>Institut Pasteur, Collège de France, Paris, France; <sup>9</sup>Werner Reichardt Centre for Integrative Neuroscience (CIN), University of Tübingen, Tübingen, Germany.

#### # 6 Correlation between the horizontal visual field size and the dimension of the photoreceptor layer in patients with Usher syndrome type II

Sandra Pujanek<sup>1</sup>; Melanie Kempf<sup>2</sup>; Fadi Nasser<sup>2</sup>; Katarina Stingl<sup>2</sup>; Susanne Kohl<sup>3</sup>; Bernd Wissinger<sup>2</sup>; Marius Ueffing<sup>2</sup>; Eberhart Zrenner<sup>2</sup>; Christoph Kernstock<sup>4</sup>

<sup>1</sup> Beuth University of Applied Sciences, Berlin; <sup>2</sup> Institut for Ophthalmic Research, Center for Ophthalmology, Eberhard Karls University Tuebingen, Germany; <sup>3</sup> Molecular Genetics Laboratory, Institut for Ophthalmic Research, Center for Ophthalmology, Eberhard Karls University Tuebingen, Germany

### # 7 Adaptive optics retinal imaging in patients with Usher syndrome

Melanie Kempf<sup>1</sup>; Susanne Kohl<sup>2</sup>; Katarina Stingl<sup>1</sup>; Marius Ueffing<sup>1</sup>; Eberhart Zrenner<sup>1</sup>; Fadi Nasser<sup>1</sup>

<sup>1</sup> Institute for Ophthalmic Research, Centre for Ophthalmology, Eberhard Karls University, Tuebingen, Germany; <sup>2</sup> Molecular Genetics Laboratory, Institute for Ophthalmic Research, Centre for Ophthalmology, Eberhard Karls University, Tuebingen, Germany

### # 8 Molecular Analysis of twenty-six Iranian Patients with Usher Syndrome

Paulina Liliana Bahena Carbajal<sup>1</sup>; Barbara Vona<sup>1</sup>; Reza Maroofian<sup>2</sup>; Thomas Haaf<sup>1</sup>

<sup>1</sup> Julius-Maximilians-Universität Würzburg; Germany; <sup>2</sup> St George's University of London, UK

### # 9 Targeted high-throughput sequencing for the molecular diagnosis of Usher syndrome reveals 41 novel mutations.

Gema García-García<sup>1</sup>; Carla Fuster García<sup>1</sup>; Teresa Jaijo<sup>1</sup>; Carmen Ayuso<sup>2</sup>; Miguel Fernández-Burriel; Elena Aller<sup>1</sup>; José María Millán<sup>1</sup>

<sup>1</sup> Health Research Institute Hospital La Fe; <sup>2</sup> Fundacion Jimenez Diaz University Hospital (IIS-FJD, UAM), Valencia, Spain

### # 10 Genes and mutations in the Tübingen Usher cohort

Susanne Kohl<sup>1</sup>; Nicole Weisschuh<sup>2</sup>; Katarina Stingl<sup>3</sup>; Anne Kurtenbach<sup>3</sup>; Eberhart Zrenner<sup>4</sup>; Bernd Wissinger<sup>1</sup>

<sup>1</sup> Institute for Ophthalmic Research, Centre for Ophthalmology, Eberhard Karls University, Tuebingen, Germany; <sup>2</sup> Institute for Ophthalmic Research, Center for Ophthalmology, Eberhard Karls University Tuebingen, Germany; <sup>3</sup> Institute for Ophthalmic Research; Germany, <sup>4</sup>Werner Reichardt Centre for Integrative Neuroscience (CIN), University of Tübingen, Tübingen, Germany

### # 11 Longitudinal phenotypic characterization of type II Usher syndrome caused by mutations in USH2A

Adam Dubis<sup>1</sup>; Andreas Mitsios<sup>2</sup>; Maria Toms<sup>2</sup>; Andrew Webster<sup>1</sup>; Mariya Moosajee<sup>1</sup>; Moorfields Eye Hospital; <sup>2</sup> Universty College London (UCL), Institute of Ophthalmology, London, UK

### # 12 retina functional damage in Usher syndrome type 2: A long term follow up using focal electroretinogram

Giorgio Placidi<sup>1</sup>; Lucia Galli Resta<sup>2</sup>; Benedetto Falsini<sup>1</sup>;

<sup>1</sup> Universita Cattolica del S. Cuore; <sup>2</sup> Consiglio Nazionale delle Ricerche, Roma, Italy

### # 13 Usher Syndrome 3A; Literature Survey

Mohamed Tleis<sup>1</sup>, <sup>1</sup>Leiden University, Leiden, NL

### # 14 Health for people with Usher syndrome

Moa Wahlqvist<sup>1</sup>, <sup>1</sup>Audiological research center, University Hospital and Swedish Institute of Disability Research, Örebro University, Örebro, Sweden

## Poster Abstracts

### # 15 Is Usher Syndrome the Correct Diagnosis? Challenges in Genetics

Margaret Kenna; Devon Barrett; Anne Fulton; Harvard Medical School and Director of Clinical Research in Otolaryngology at Boston Children's Hospital, Boston, USA

### # 16 Genetic Testing in patients with USHER syndrome. The Great Benefit of NGS Diagnostics

Heinz Gabriel<sup>1</sup>; <sup>1</sup>Praxis für Humangenetik Tübingen; Germany

### # 17 Comprehensive analysis of transcripts of the *USH1C* gene in the human retina

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## CELL BIOLOGY

### # 18 SANS and Cep290: a molecular alliance linking the human Usher syndrome to a variety of ciliopathies

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### # 19 The human Usher syndrome protein SANS regulates pre-mRNA splicing by direct interaction with key components of the spliceosome

Adem Yildirim<sup>1</sup>; Sina Mozaffari-Jovin<sup>2</sup>; Ann-Kathrin Wallisch<sup>1</sup>; Jessica Ries<sup>1</sup>; Henning Urlaub<sup>2</sup>; Reinhard Lührmann<sup>2</sup>; Uwe Wolfrum<sup>1</sup>

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### # 20 Integrin alpha 8 modulates hair cell maturation through its association with protocadherin-15

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### # 21 The interaction of SANS (USH1G) with Kif2a regulates length and maintenance of primary cilia

Lars Tebbe<sup>1</sup>, Adem Yildirim<sup>1</sup>, Nasrin Sorousch<sup>1</sup>, Kirsten Wunderlich<sup>1</sup>, Aziz El-Amraoui<sup>2</sup> and Uwe Wolfrum<sup>1</sup>

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### **# 22 In vivo validation of USH1g-Cep290 interaction in the retina**

Sebastian M. Siegner; Jennifer Phillips<sup>1</sup>; Jeremy Wegner<sup>1</sup>; Monte Westerfield<sup>1</sup>

<sup>1</sup>University of Oregon; Eugene, USA

### **# 23 Usher syndrome proteins VLGR1 (USH2C) and CIB2 (USH1J) associate with the BBS/CCT chaperonin complex**

Barbara Knapp; Jacek Krzysko<sup>1</sup>; Deva Kusuluri<sup>1</sup>; Karsten Boldt<sup>2</sup>, Marius Ueffing<sup>2</sup> Uwe Wolfrum<sup>1</sup>  
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### **# 24 The Usher syndrome 2C protein VLGR1 regulates focal adhesions**

Deva Krupakar Kusuluri<sup>1</sup>, Barbara Knapp<sup>1</sup>, Karsten Boldt<sup>2</sup>, Gabi Aust<sup>3</sup>, Marius Ueffing<sup>2</sup>, Uwe Wolfrum<sup>1</sup>

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### **# 25 Identification of consistently elevated autophagy in as pathogenic mechanism of retinal degeneration in Usher syndrome**

Erik De Vrieze<sup>1</sup>; Ralph Slijkerman<sup>1</sup>; Margo Dona<sup>1</sup>; Sanne Broekman<sup>1</sup>; Lisette Hetterschijt<sup>1</sup>; Theo Peters<sup>1</sup>; Hannie Kremer<sup>1</sup>; Erwin Van Wijk<sup>1</sup>

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### **# 26 USH2a is a vibration sensor involved in touch and hearing in Usher syndrome**

Frederick Schwaller<sup>1</sup>; Valérie Bégay<sup>1</sup>; Gema García-García<sup>2</sup>; Rabih Moshourab<sup>3</sup>; Johannes Kühnemund<sup>1</sup>; Julia Anai Ojeda Alonso<sup>1</sup>; James F Poulet<sup>1</sup>; Jose M Millan<sup>2</sup>; Gary R Lewin<sup>1</sup>

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### **# 27 Characterization of CLRN1 mutant proteins in the mouse retina**

Frank Dyka<sup>1</sup>; Susan Bolch<sup>1</sup>; W. Clay Smith<sup>1</sup>; William Hauswirth<sup>1</sup>; Astra Dinculescu<sup>1</sup>

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### **# 28 A magnesium-triggered conformational change in CIB2 is impaired in Usher Syndrome type 1J**

Daniele Dell'Orco<sup>1</sup>; <sup>1</sup>University of Verona, Verona, Italy



## Poster Abstracts

### **# 29 Role of the oxidative stress in the degeneration of cone photoreceptors in two Usher animal models and on purified cones**

Serge Picaud; Institut de la Vision, INSERM/CNRS/Sorbonne Université, Paris, France

## ANIMAL MODELS

### **# 30 Developing mutations in *ush1c* and *ush1f* genes in the amphibian *Xenopus tropicalis* to model human mutations in these genes**

Robert Grainger<sup>1</sup>; Takuya Nakayama<sup>1</sup>; <sup>1</sup>University of Virginia, Charlottesville, USA

### **# 31 Using hiPSC-derived retinal organoids to model Ush2a pathophysiology.**

Anai Gonzalez Cordero<sup>1</sup>; Arifa Naeem<sup>1</sup>; Ms Magdalena Kloc<sup>1</sup>; Paromita Majumder<sup>1</sup>; Milan Fernando<sup>1</sup>; Ian Shum<sup>1</sup>; Joana Ribeiro<sup>1</sup>; Alexander J. Smith<sup>1</sup>; Robin R. Ali<sup>1</sup>

<sup>1</sup>UCL Institute of Ophthalmology, London, UK

### **# 32 Analysis of the functional relationships among Usher Type 2 proteins in zebrafish photoreceptors**

Jennifer Phillips<sup>1</sup>; Jeremy Wegner<sup>1</sup>; Kimberly Lerner<sup>1</sup>; Taylor Howat<sup>1</sup>; Monte Westerfield<sup>1</sup>

<sup>1</sup> University of Oregon, Eugene, USA

### **# 33 An Usher Syndrome type IIA knock in model exhibits hair cell abnormalities, and late-onset retinitis pigmentosa**

Muna Naash<sup>1</sup>; Maggie Mwoyosvi<sup>1</sup>; Carl Nist-Lund<sup>2</sup>; Gwenaelle Géléoc<sup>2</sup>; Muayyad Al-Ubaidi<sup>1</sup>

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### **# 34 Generation and preliminary analysis of USH1C transgenic pig model**

Nikolai Klymiuk<sup>1</sup>, Kirsten A. Wunderlich<sup>2</sup>, Georg Dhom<sup>1</sup>, Andreas Blutke<sup>3</sup>, Helen May-Simera<sup>2</sup>, Andrea Fischer<sup>3</sup>, Anna Döring<sup>3</sup>, Ralf S. Müller<sup>3</sup>, Janet Plutniok<sup>1</sup>, Eckhard Wolf<sup>1</sup> and Uwe Wolfrum<sup>2</sup>

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### **# 35 Loss of *ush2a* causes rhodopsin mislocalisation and adult onset photoreceptor degeneration in a zebrafish model of Usher syndrome**

Maria Toms<sup>1</sup>; Matthew Hayes<sup>1</sup>; Adam Dubis<sup>2</sup>; Andrew Webster<sup>2</sup>; Mariya Moosajee<sup>2</sup>

<sup>1</sup> UCL Institute of Ophthalmology; <sup>2</sup> Moorfields Eye Hospital, UK

THERAPY

**# 36 Development of the First Pharmacotherapy for the Treatment of Usher Syndrome Type I due to Variants in MYO7A**

Alaa Koleilat<sup>1</sup>; Trace Christenson<sup>1</sup>; PhD Aaron Lambert<sup>2</sup>; Jeffrey Bellah<sup>3</sup>; Mark Masino<sup>2</sup>; PhD Stephen Ekker<sup>1</sup>; Lisa Schimmenti<sup>1</sup>

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**# 37 Antisense Therapy Rescues Hearing and Vision in Usher syndrome**

Jennifer Lentz<sup>1</sup>; Russell J. Amato<sup>1</sup>; Robert F. Rosencrans<sup>1</sup>; Marianne Hathaway<sup>2</sup>; Abhilash Ponnath<sup>1</sup>; Christopher Tran<sup>1</sup>; Bhagwat Alapure<sup>1</sup>; Ms Katelyn Robillard<sup>1</sup>; Francine Jodelka<sup>3</sup>; Frederic F. Depreux<sup>3</sup>; Bifeng Pan<sup>4</sup>; Carl Nist-Lund<sup>4</sup>; Nicolas Bazan<sup>1</sup>; Hamilton E. Farris<sup>1</sup>; Frank Rigo<sup>5</sup>; Gwenaëlle G.S. Géléoc<sup>4</sup>; Michelle L. Hastings<sup>3</sup>

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**# 38 USH2A Gene Editing Using the CRISPR System**

Carla Fuster García<sup>1</sup>; Gema García-García<sup>1</sup>; Elisa González Romero<sup>1</sup>; Teresa Jaijo<sup>1</sup>; M Dolores Sequedo<sup>1</sup>; Carmen Ayuso; Rafael P Vázquez Manrique<sup>1</sup>; José María Millán<sup>1</sup>; Elena Aller<sup>1</sup>

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**# 39**

**Gene Therapy for Vision Loss in a Murine Model of Usher Syndrome Type 1C**

Katelyn Robillard<sup>1</sup>; Marianne Hathaway<sup>1</sup>; Nicolas Bazan<sup>1</sup>; Jennifer Lentz<sup>1</sup>

<sup>1</sup>Louisiana State University Health Sciences Center, New Orleans, USA

**# 40 In vitro evaluation of the CRISPR/Cas9 and antisense oligonucleotides for treatment of a deep intronic CLRN1 splice mutation**

Elvir Becirovic<sup>1</sup>; Lisa Maria Riedmayr<sup>1</sup>; Martin Biel<sup>1</sup>

<sup>1</sup>LMU München, Institut für Chemie und Pharmazie, Germany

**# 41 Next generation gene therapy restores hearing, balance and quality of life in mouse models of genetic inner ear disorder**

Bifeng Pan<sup>1</sup>; Amy Patterson<sup>1</sup>; Yukako Asai<sup>1</sup>; Wu Zhou<sup>2</sup>; Hong Zhu<sup>2</sup>; Sandra Romero<sup>3</sup>; Jennifer Resnik<sup>3</sup>; Daniel B Polley<sup>3</sup>; Gwenaëlle Geleoc<sup>1</sup>; Jeffrey R. Holt<sup>1</sup>

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**# 42 A Non-Profit Mechanism for Moving Proof-of-Concept Studies to Clinical Therapies for Rare Retinal Disorders**

Harrison Brown<sup>1</sup>; Luk Vandenberghe<sup>2</sup>; Scott Dorfman<sup>1</sup>

<sup>1</sup> Odylia Therapeutics; <sup>2</sup> Grousbeck Gene Therapy Center, Schepens Eye Research Institute and Mass Eye and Ear, Boston, USA

### **# 43 Targeting TNF $\alpha$ pathway in Retinitis Pigmentosa**

Lorena Olivares González<sup>1</sup>; Yeray Ibáñez Marco<sup>1</sup>; José María Millán<sup>1</sup>; Regina Rodrigo Nicolás<sup>1</sup>  
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### **# 44 AAV mediated gene therapy restores partial auditory sensitivity in mouse models of autosomal recessive non syndromic deafness DFNB31 and Usher syndrome type IID.**

Hannah Goldberg<sup>1</sup>; Yukako Asai<sup>1</sup>; Bifeng Pan<sup>1</sup>; Wade Chien<sup>2</sup>; Jun Yang<sup>3</sup>; Gwenaëlle Geleoc<sup>1</sup>; Jeffrey R. Holt<sup>1</sup>

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### **# 45 HIF-1 $\alpha$ STABILIZATION REDUCES RETINAL DEGENERATION IN A MOUSE MODEL OF RETINITIS PIGMENTOSA**

Regina Rodrigo Nicolás<sup>1</sup>; Ms Lorena Olivares González<sup>1</sup>; Cristina Martínez-Fernández de la Cámara<sup>2</sup>; José María Millán<sup>1</sup>; <sup>1</sup> Instituto de Investigación Sanitaria La Fe (IIS La Fe), Valencia, Spain; <sup>2</sup> University of Oxford, Oxford, UK

### **# 46 Mutations in exon 13 of USH2A in 53 patients with Usher syndrome: clinical data in the aim of exon skipping therapy.**

Audrey Meunier<sup>1</sup>; Catherine Blanchet<sup>2</sup>; Vasiliki Kalatzis<sup>3</sup>; Béatrice Bocquet<sup>3</sup>; Anne-Françoise Roux<sup>4</sup>; Isabelle Meunier<sup>2</sup>

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### **# 47 Small molecules for targeting nonsense mutations as treatment option for the Usher syndrome**

Ananya Samanta<sup>1,2</sup>, Susanne Kohl<sup>3</sup>, Westley Friesen<sup>4</sup>, Fabian Möller<sup>1,2</sup>, Bernd Wissinger<sup>3</sup>, Pieter Gaillard<sup>5</sup>, Kerstin Nagel-Wolfrum<sup>1,2</sup>

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