USHER 1b
Works in progress and knowledge gaps

José-Alain Sahel

Paris, Pittsburgh

What we (don’t) know

- **The pathobiology of the disease :**
  - gene discovery
  - Animal models
  - Protein function
  - Stages of the disease
- **The implications of multisensory impairment**
  - Communication issues
  - Impact of visual loss on balance
  - Holistic care
- **The development of efficient gene therapies**
  - What vectors (size, tissue diffusion)
  - What promoters
  - When is it too late ?
- **The development of gene independent approaches**
  - Neuroprotection
  - Optogenetics
  - Prosthetics
  - Cell replacement
- **The demonstration of a therapeutic benefit**
  - The need for natural history data
  - Outcome measures
  - PROs, PBTs

The pathobiology of the disease

- Genetics
- Animal models and their limits
- Protein function
- Phenotype-Genotype

The Usher syndrome (USH)

First cause of deafness-blindness in humans

(50% of all monogenic deaf-blindness)

Three clinical subtypes : USH1, USH2 and USH3

	Hearing loss	Vestibular dysfunction	Retinitis Pigmentosa
USH1 (5-6 genes)	**Profound and congenital**	**Severe**	**Prepubertal onset**
USH2 (3 genes)	**Mild to severe and congenital**	**absent**	**Postpubertal onset**
USH3 (1+ gene)	**Postlingual, mild and progressive**	**variable**	**variable**

First identification of an USH gene

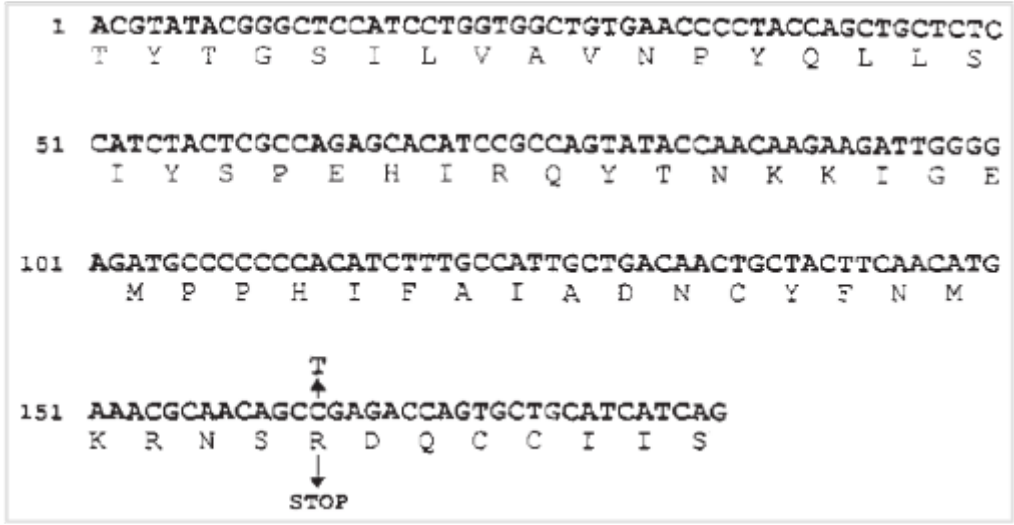
1995: The Usher Syndrome type IB gene, USH1B/*MYO7A*, encoding for myosin VIIa

LETTERS TO NATURE

NATURE · VOL 374 · 2 MARCH 1995

Defective myosin VIIA gene responsible for Usher syndrome type 1B

Dominique Weil, Stéphane Blanchard, Josseline Kaplan*, Parry Guilford, Fernando Gibson†, James Walsh†, Philomena Mburu†, Anabel Varela†, Jacqueline Levilliers, Michael D. Weston‡, Phillip M. Kelley‡, William J. Kimberling‡, Mariette Wagenaar§, Fabienne Levi-Acobas, Dominique Larget-Piet*, Arnold Munnich*, Karen P. Steel‖, Steve D. M. Brown† & Christine Petit¶



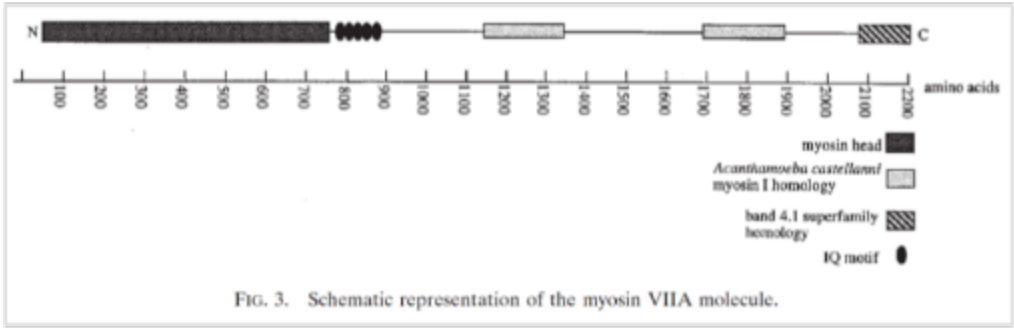


FIG. 3. Schematic representation of the myosin VIIA molecule.

Genes responsible for Usher syndrome (USH)

USH1

USH1B (*MYO7A*, 11q13.5 - OMIM 276903) : **myosin VIIa**

USH1C (*USH1C*, 11p15.1 - OMIM 605242) : **harmonin**

USH1D (*CDH23*, 10q22.1 - OMIM 605516) : **cadherin-23**

USH1F (*PCDH15*,10q21.1 - OMIM 605514) : **protocadherin-15**

USH1G (*USH1G*, 17q25.1 - OMIM 607696) : **Sans**

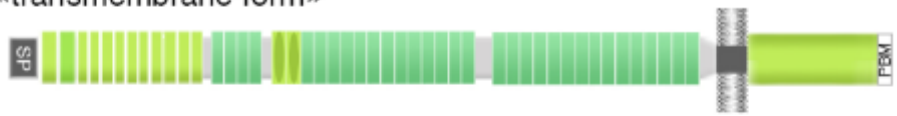
Atypical form

DFNB48/USH1J (*CIB2*, 15q25.1 - OMIM 605564) :
calcium integrin binding protein 2

USH2

USH2A (*USH2A*, 1q41 - OMIM 608400) : **usherin**

«transmembrane form»



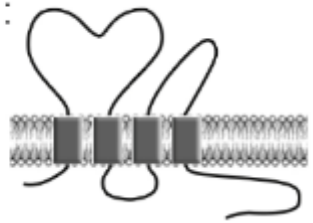
USH2C (*GPR98*, 5q14.3 - OMIM 602851) : **ADGVR1**
(adhesion G-protein coupled receptor V1)

USH2D (WHRN, 9q32 - OMIM 607928) : **whirlin**

Long isoform (L)

USH3

USH3A (*CLRN1*, 3q25.1 - OMIM 606397) :
clarin-1



Geleoc G & El-Amraoui A, Hear Res. 2020

European Journal of Human Genetics (2016) 24, 1730–1738
Official journal of The European Society of Human Genetics
www.nature.com/ejhg

EJHG Open

ARTICLE

An innovative strategy for the molecular diagnosis of Usher syndrome identifies causal biallelic mutations in 93% of European patients

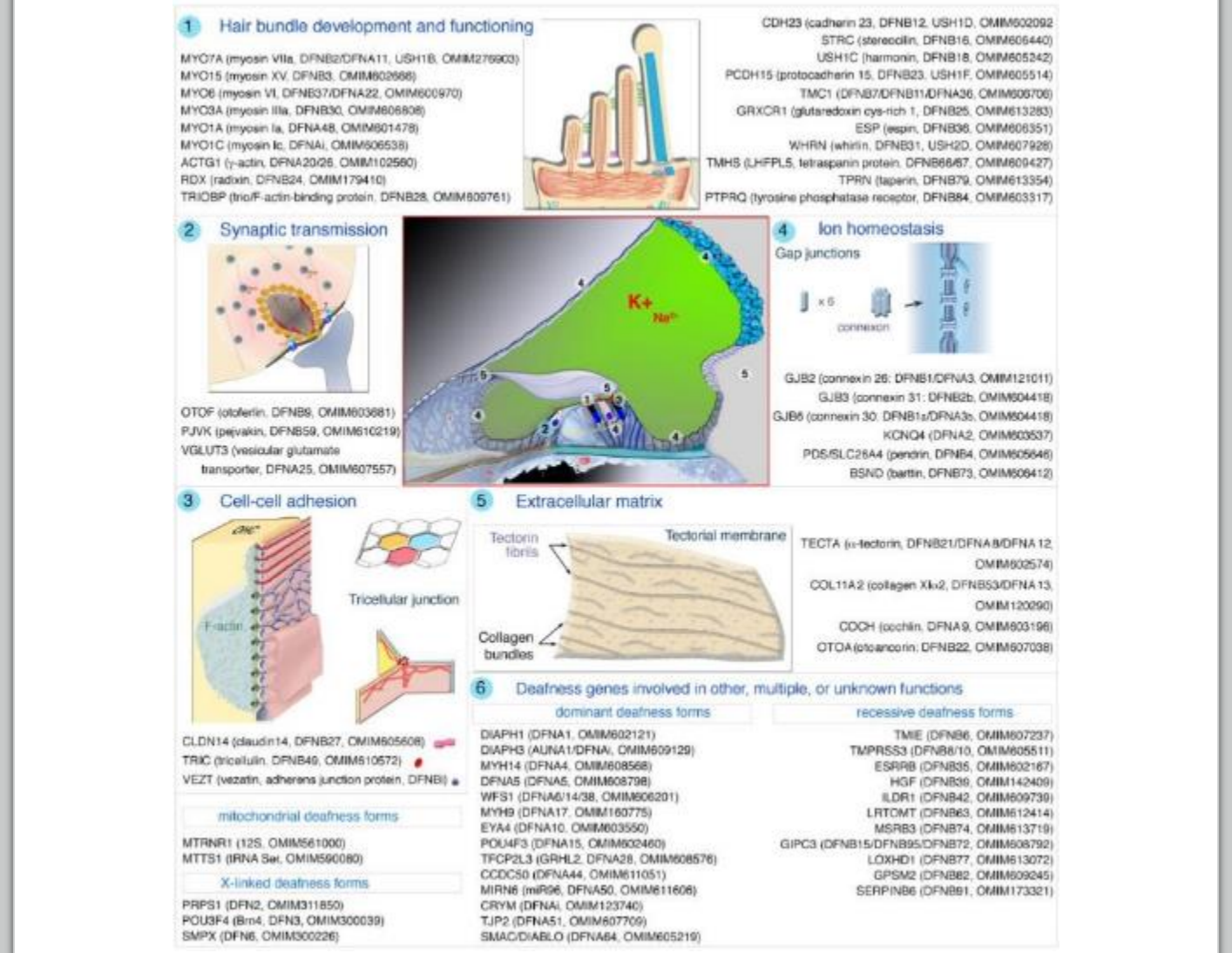
Crystel Bonnet[1,2], Zied Riahi[1,2], Sandra Chantot-Bastaraud[3,4], Luce Smagghe[1,2], Mélanie Letexier[5], Charles Marcaillou[5], Gaëlle M Lefèvre[1,2], Jean-Pierre Hardelin[6], Aziz El-Amraoui[6], Amrit Singh-Estivalet[1,2], Saddek Mohand-Saïd[2,7,8], Susanne Kohl[9], Anne Kurtenbach[9], Ieva Sliesoraityte[8,9], Ditta Zobor[9], Souad Gherbi[10], Francesco Testa[11], Francesca Simonelli[11], Sandro Banfi[12,13], Ana Fakin[14], Damjan Glavač[15], Martina Jarc-Vidmar[14], Andrej Zupan[15], Saba Battelino[16], Loreto Martorell Sampol[17], Maria Antonia Claveria[17], Jaume Catala Mora[17], Shzeena Dad[18], Lisbeth B Møller[18], Jesus Rodriguez Jorge[17], Marko Hawlina[14], Alberto Auricchio[12,19], José-Alain Sahel[2,7,8], Sandrine Marlin[10], Eberhart Zrenner[9,20], Isabelle Audo[2,7,8] and Christine Petit*[,1,2,6,21]

Usher syndrome (USH), the most prevalent cause of hereditary deafness–blindness, is an autosomal recessive and genetically heterogeneous disorder. Three clinical subtypes (USH1–3) are distinguishable based on the severity of the sensorineural hearing impairment, the presence or absence of vestibular dysfunction, and the age of onset of the retinitis pigmentosa. A total of 10 causal genes, 6 for USH1, 3 for USH2, and 1 for USH3, and an USH2 modifier gene, have been identified. A robust molecular diagnosis is required not only to improve genetic counseling, but also to advance gene therapy in USH patients. Here, we present an improved diagnostic strategy that is both cost- and time-effective. It relies on the sequential use of three different techniques to analyze selected genomic regions: targeted exome sequencing, comparative genome hybridization, and quantitative exon amplification. We screened a large cohort of 427 patients (139 USH1, 282 USH2, and six of undefined clinical subtype) from various European medical centers for mutations in all USH genes and the modifier gene. We identified a total of 421 different sequence variants predicted to be pathogenic, about half of which had not been previously reported. Remarkably, we detected large genomic rearrangements, most of which were novel and unique, in 9% of the patients. Thus, our strategy led to the identification of biallelic and monoallelic mutations in 92.7% and 5.8% of the USH patients, respectively. With an overall 98.5% mutation characterization rate, the diagnosis efficiency was substantially improved compared with previously reported methods.

European Journal of Human Genetics (2016) **24**, 1730–1738; doi:10.1038/ejhg.2016.99; published online 27 July 2016

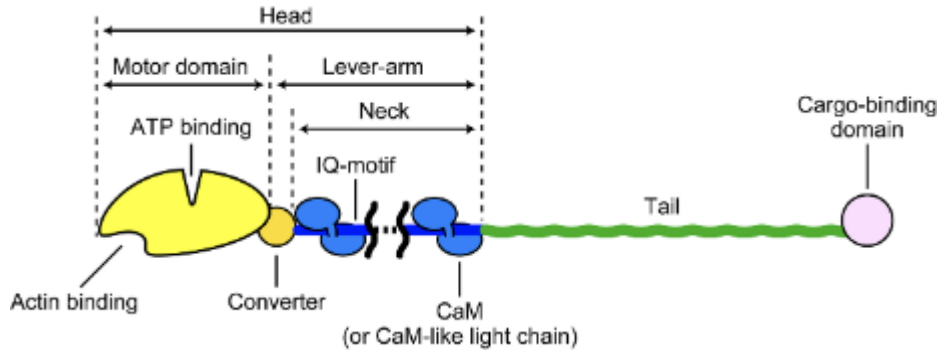
Cochlear defects in Usher

- *adapted from Safieddine S et al., 2012, Annu Rev Neurosci.*

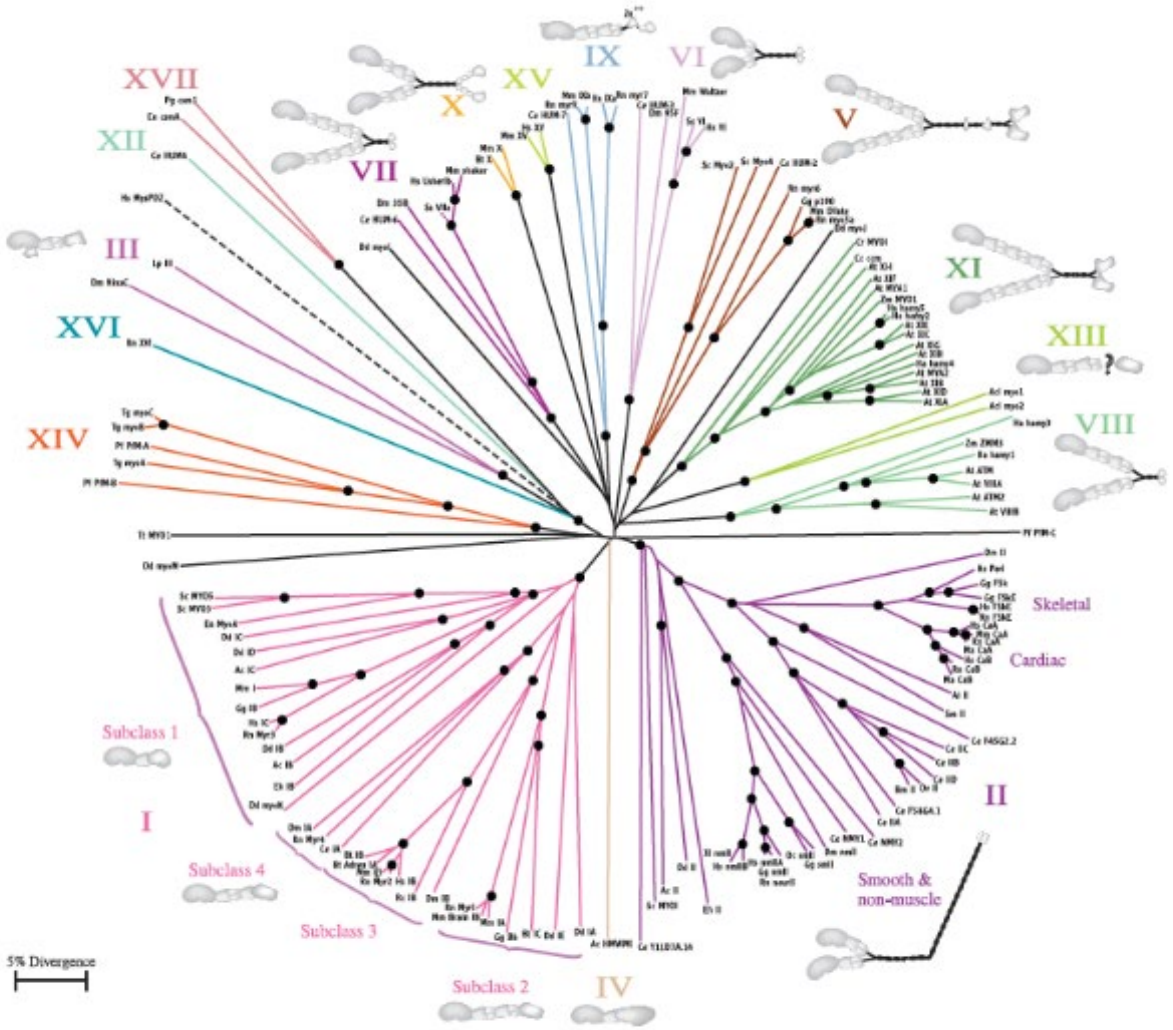


What are myosins?

- **Superfamily of motor proteins**
- Expressed in all eukaryotes
- Properties:
  - actin binding
  - ATP hydrolysis (ATPase enzyme activity)
  - transduction force

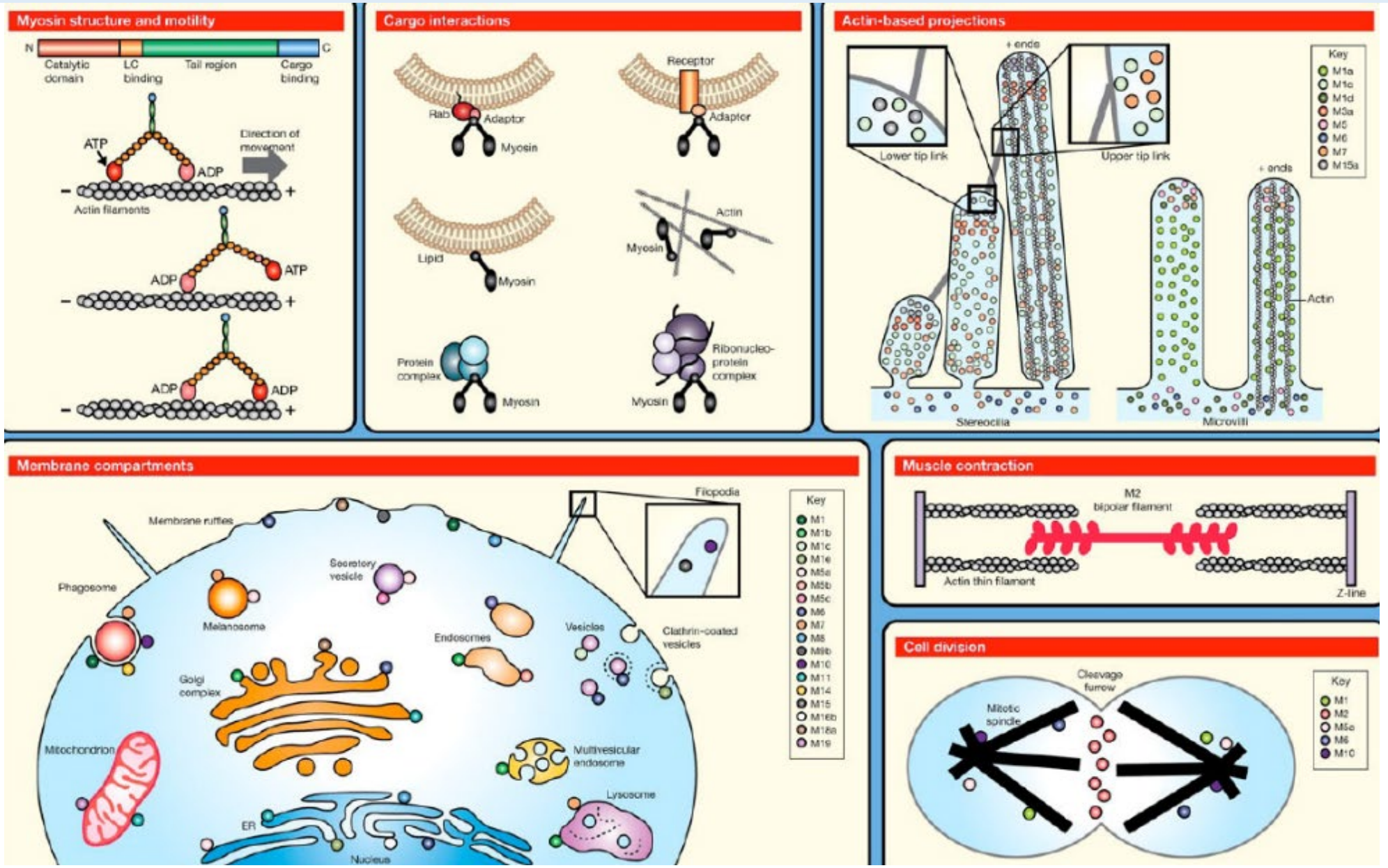


Kodera, N., & Ando, T. (2014)



Hodge, T., & Cope, M. J. (2000)

Functions of myosins?

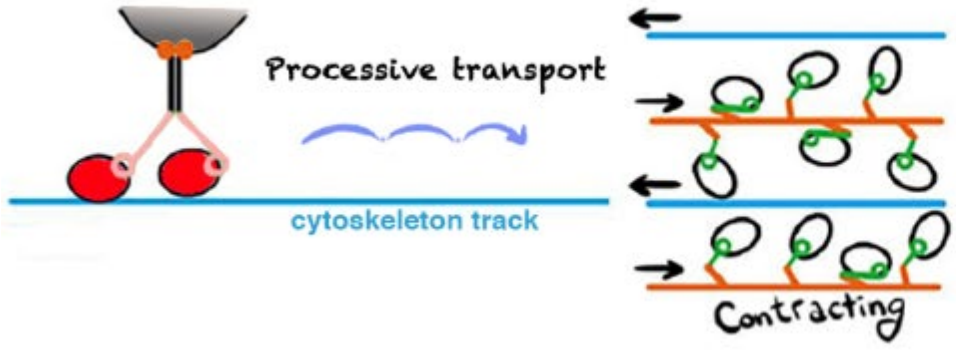


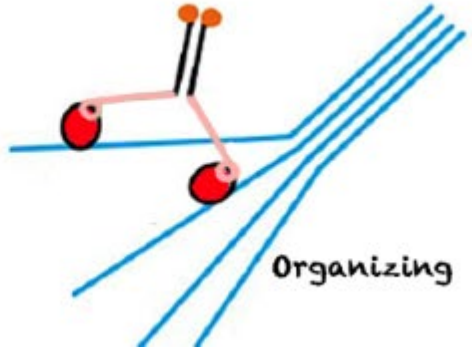
Hartman A & Spudich JA, JCS 2012

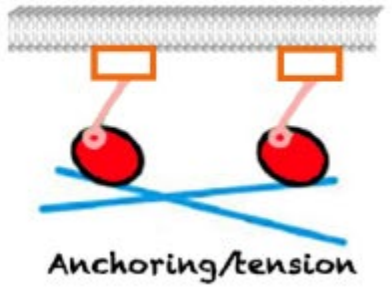
Understanding Myosin VIIa properties

- Non-conventional myosin
- Multidomain containing protein:
  - Motor head domain
  - Neck region: 5 IQ (Isoleucine/glutamine) motifs
  - C terminal region
    - Dimerization domain
    - MyTH4 (myosin tail homology)/FERM (4.1, ezrin, radixin, moesin)
    - SH3 (Src homology domain)

What function ?



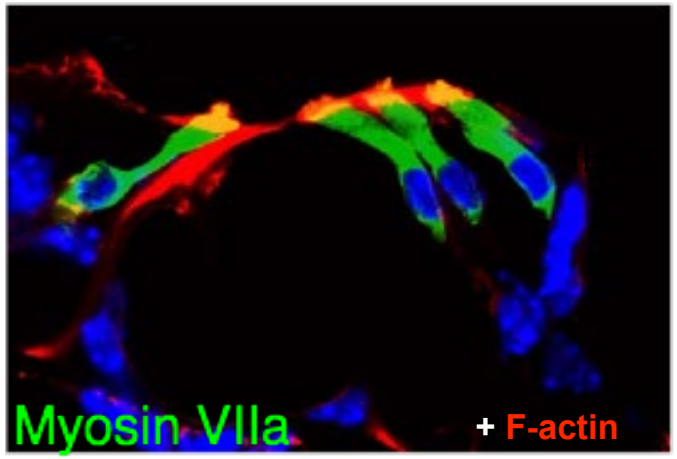


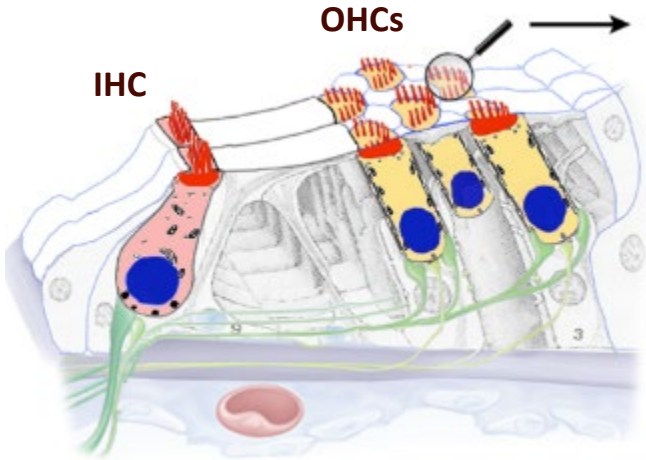


Cellular and subcellular targets of USH1B protein ?

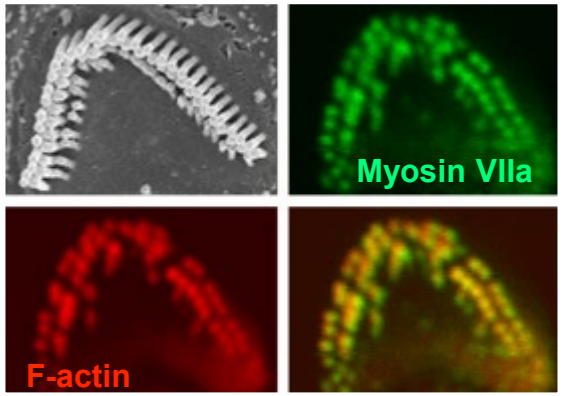
☐ Inner ear: the sensory hair cells & the mechano-sensitive hair bundles

Auditory hair cells





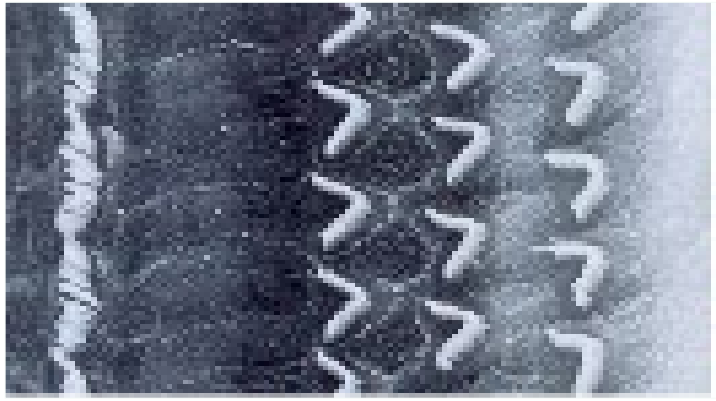
Auditory sensory organ: organ of Corti



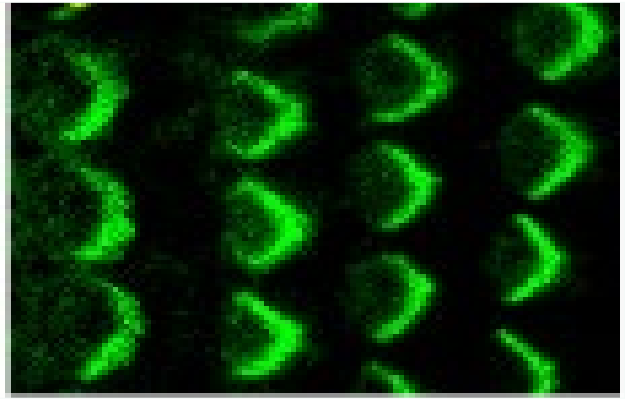
Top view
of the
auditory sensory organ

IHC
(inner hair cells)

OHCs
(outer hair cells)



Auditory hair bundles

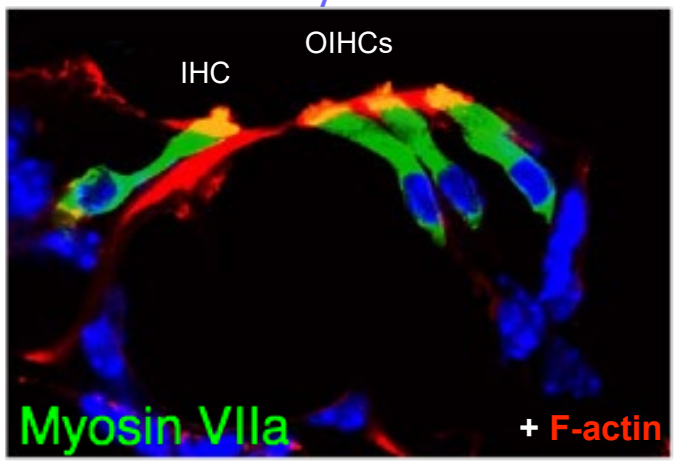


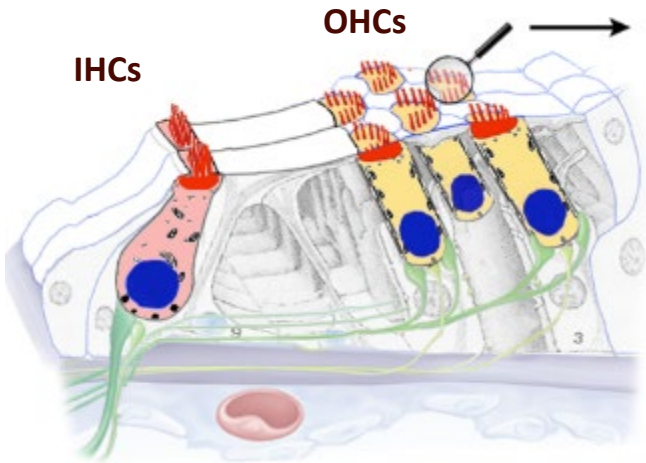
El-Amraoui A, *et al.* -> Petit C, *HMG* 1996

Cellular and subcellular targets of USH1B protein ?

❖ Inner ear: the sensory hair cells & the mechano-sensitive hair bundles

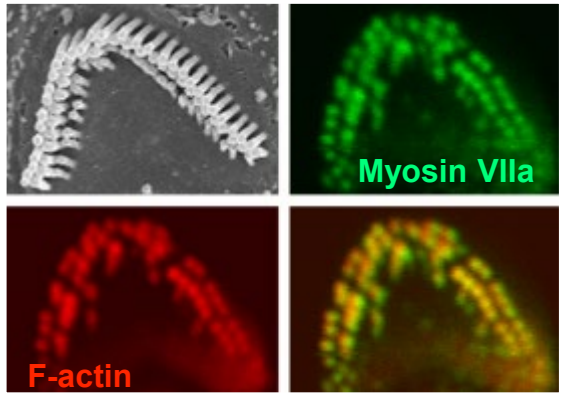
Auditory hair cells





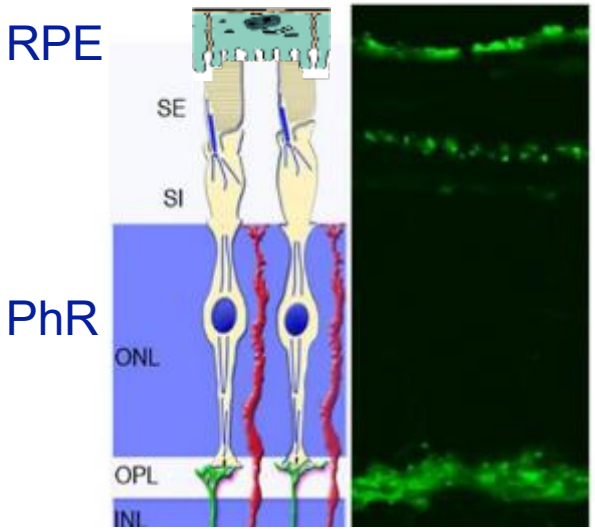
Auditory sensory organ: organ of Corti

Sound receptive-hair bundle

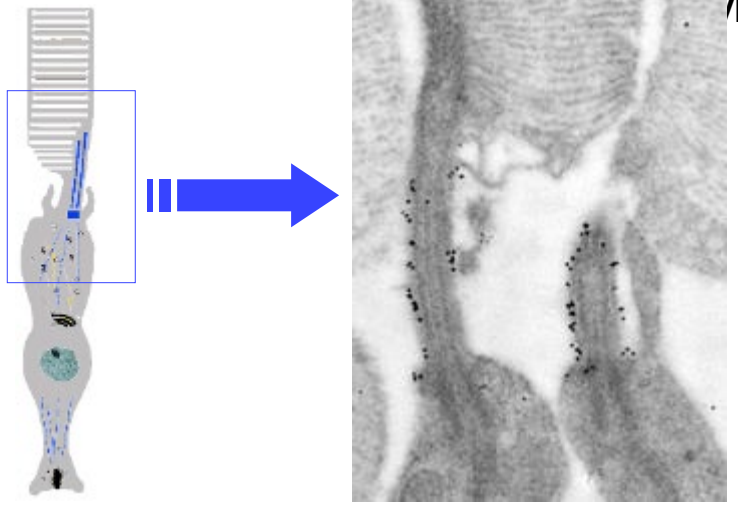


El-Amraoui A, *et al.* -> Petit C, *HMG* 1996

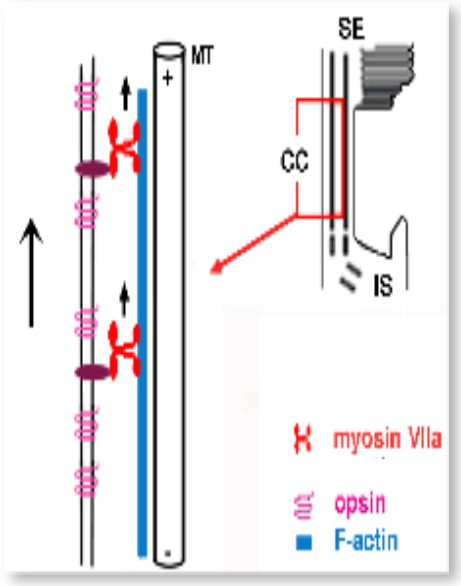
❖ Retina: Photoreceptors (PhR) & retinal pigment epithelial cells (RPE)



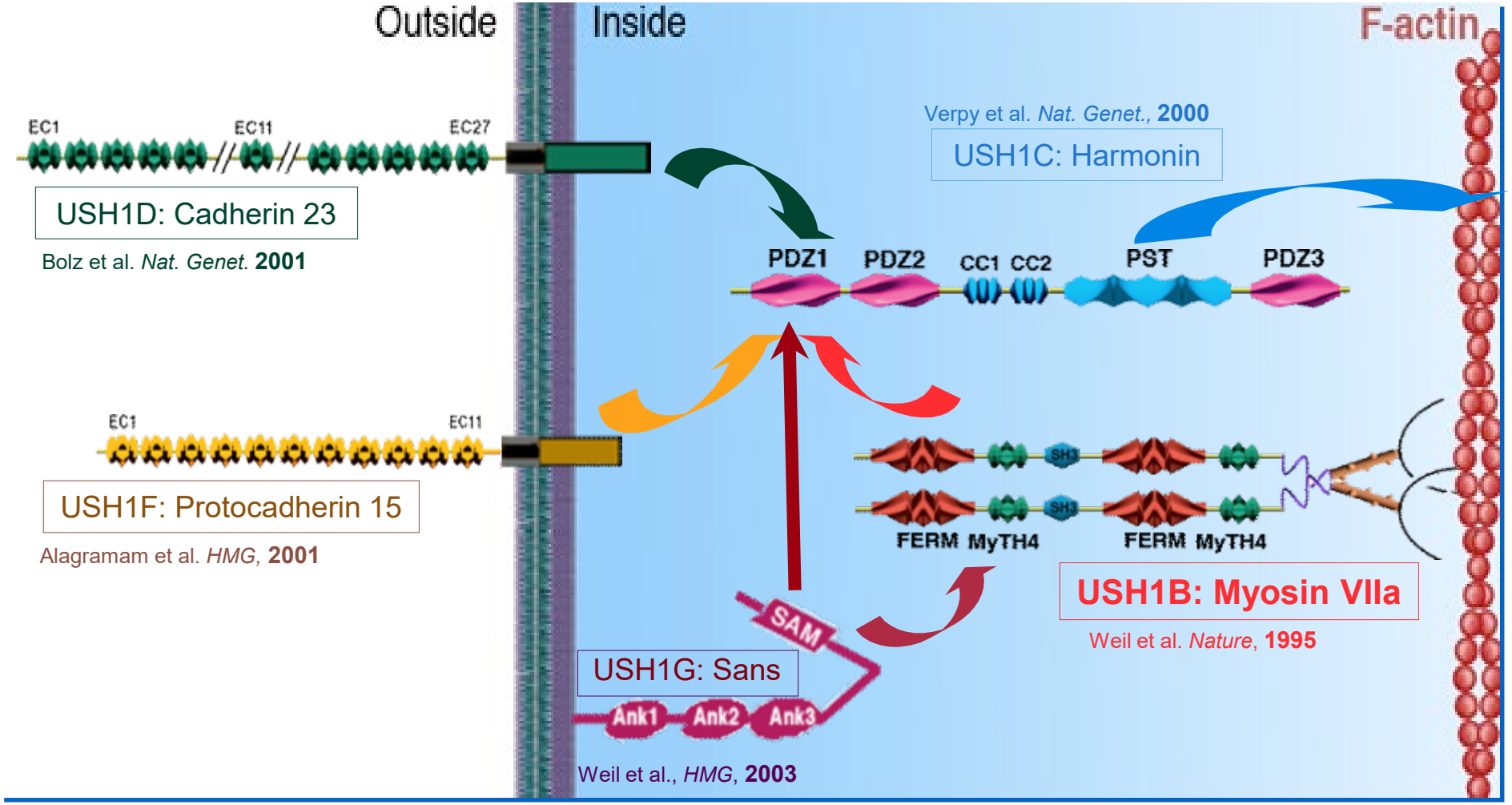
Reiners et al. 2003
Liu X et al. 1997



Source:
U. Wolfrum 2000



All five USH1 proteins are integrated into a protein network, where every USH1 protein can bind to at least one other USH1 protein



Weil D *et al. PNAS* (1996); Verpy E *et al. Nat. Genet.* (2000); Kussel P *et al. EMBO J* (2000); Boëda B *et al. EMBO J.* (2002); Weil D *et al. Hum. Mol. Genet. (2003);* Adato A *et al. Hum. Mol. Genet.*(2005); Michel V *et al. Dev Biol.* (2005); Lefèvre G *et al. Development* (2008), Bahloul A et al. Hum Mol Genet. (2010); Bonnet C & EL-Amraoui A, Curr Opin Neurobiol.. 2012; El-Amraoui A & Petit C, CR Biol, 2014; Geleoc G & EL-Amraoui A, hear. Res. 2020

Myosin VIIa cooperates with other USH1 proteins to shape properly the hair bundle

USHER 1 PROTEINS form the apical inter-stereocilia links

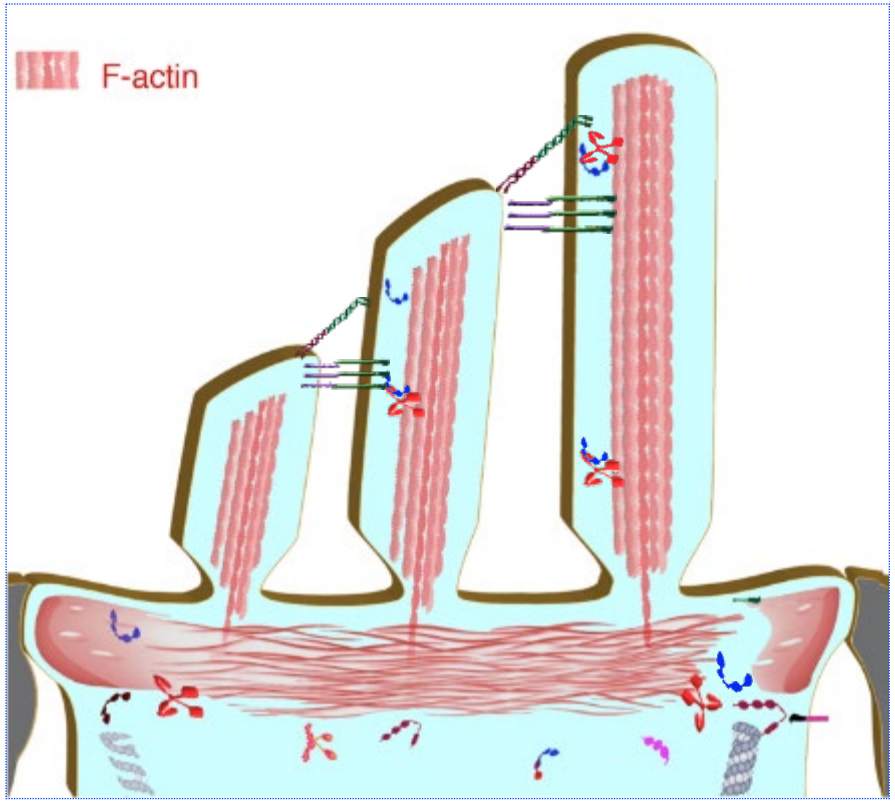
Myosin VIIa (USH1B)

Harmonin (USH1C)

Protocadherin-15 & cadherin-23

USH1F/USH1D heterodimers

SANS (USH1G)

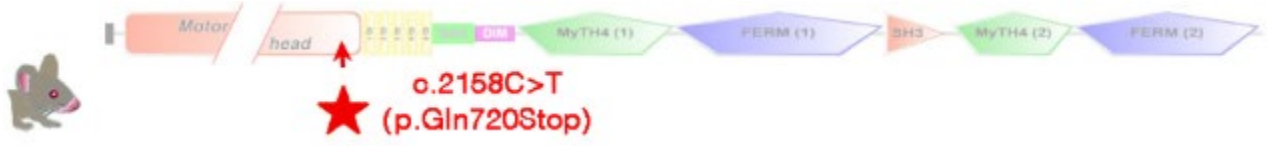


- ✓ **Myosin VIIa (USH1B) is required for the transfer of some USH1 and USH2 proteins into the stereocilia**
- ✓ **Myosin VIIa (USH1B) and Harmonin (USH1C) anchor the inter-stereocilia fibrous links to actin filaments**
- ✓ **Myosin VIIa (USH1B) is necessay for normal mechano-electrical transduction in mature hair bundles**

Weil D *et al. PNAS* (1996); Verpy E *et al. Nat. Genet.* (2000); Kussel P *et al. EMBO J* (2000); Boëda B *et al. EMBO J.* (2002); Weil D *et al. Hum. Mol. Genet. (2003);* Adato A *et al. Hum. Mol. Genet.*(2005); Michel V *et al. Dev Biol.* (2005); Lefèvre G *et al. Development* (2008), Bahloul A et al. Hum Mol Genet. (2010); Bonnet C & EL-Amraoui A, Curr Opin Neurobiol.. 2012; El-Amraoui A & Petit C, CR Biol, 2014; Geleoc G & EL-Amraoui A, hear. Res. 2020

Myosin VIIa defective shaker-1 mutants

Shaker-1 Myo7a $^{-/-}$ mice



Mutant mice for each of the five main USH1 genes are all profoundly deaf and display balance defects

PNAS

Human myosin VIIA responsible for the Usher 1B syndrome: A predicted membrane-associated motor protein expressed in developing sensory epithelia

Vol. 93, pp. 3232–3237, April 1996

Dominique Weil*, Gallia Lévy*, Iman Sahly†, Fabienne Lévi-Acobas*, Stéphane Blanchard*, Aziz El-Amraoui*, Fabien Crozet*, Hervé Philippe‡, Marc Abitbol†, and Christine Petit*§

Myosin VIIa, harmonin and cadherin 23, three Usher I gene products that cooperate to shape the sensory hair cell bundle

The EMBO Journal 24 pp. 6689–6699, 2002

Batiste Boëda, Aziz El-Amraoui, Amel Bahloul[1], Richard Goodyear[2], Isabelle Perfettini, Karl R.Fath[4,5], Spencer Shorte[6], Jan Reiners[4], Anne Houdusse[1], Pierre Legrain[3], Uwe Wolfrum[4], Guy Richardson[2] and Christine Petit[7]

Interactions in the network of Usher syndrome type 1 proteins

Human Molecular Genetics, 2005, Vol. 14, No. 3 347–356

Avital Adato[1], Vincent Michel[1], Yoshiaki Kikkawa[2], Jan Reiners[3], Kumar N. Alagramam[4], Dominique Weil[1], Hiromichi Yonekawa[3], Uwe Wolfrum[2], Aziz El-Amraoui[1] and Christine Petit[1,*]

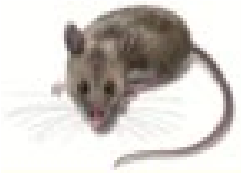
Usher I syndrome: unravelling the mechanisms that underlie the cohesion of the growing hair bundle in inner ear sensory cells *2005*

Aziz El-Amraoui and Christine Petit *Journal of Cell Science 118, 4593-4603*

A core cochlear phenotype in USH1 mouse mutants implicates fibrous links of the hair bundle in its cohesion, orientation and differential growth

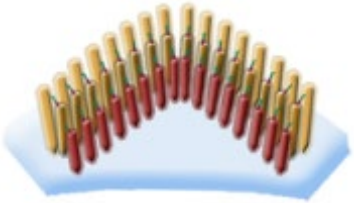
Gaelle Lefèvre[1], Vincent Michel[1], Dominique Weil[1], Léa Lepelletier[1], Emilie Bizard[1], Uwe Wolfrum[2], Jean-Pierre Hardelin[1] and Christine Petit[1,3,*]

Development 135, 1427-1437 (2008)

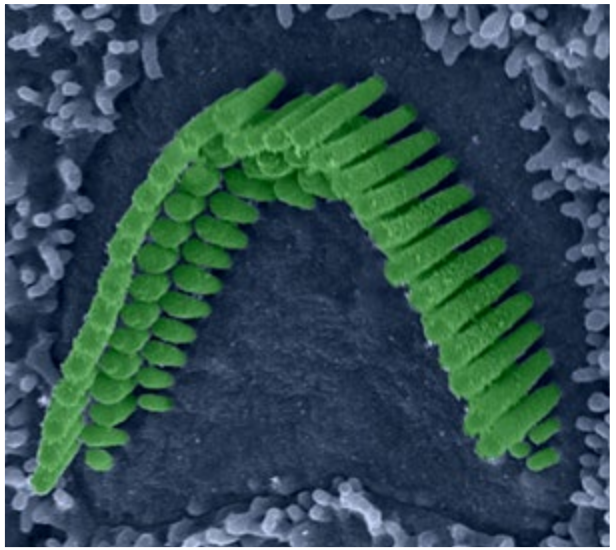


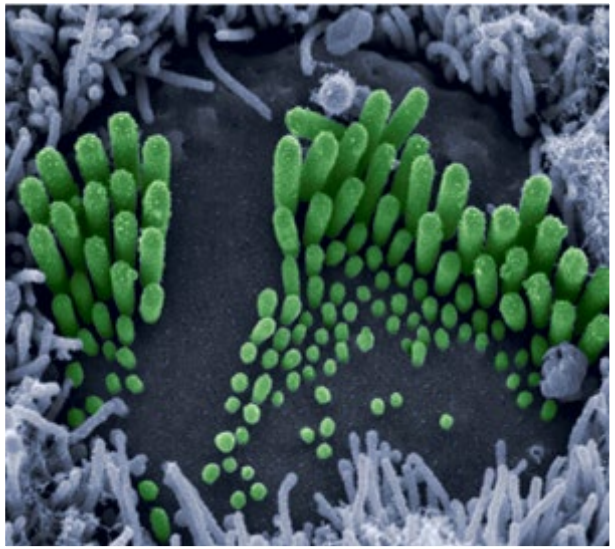
Inner ear abnormalities in shaker-1 mice (defective myosin VIIa)

control



Ush1





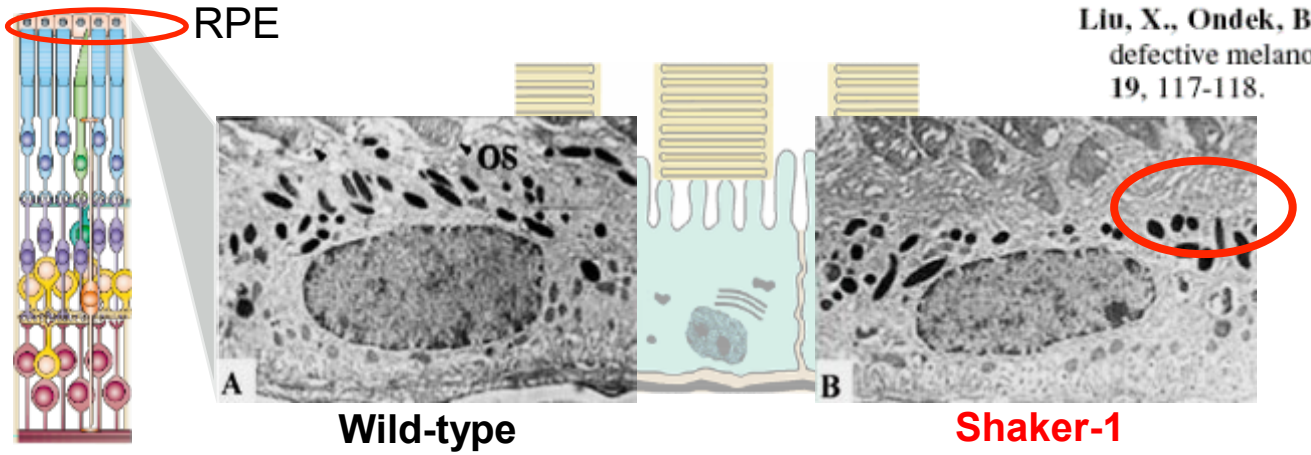
Splayed and fragmented hair bundles are observed in the absence of a functional myosin VIIa, already at embryonic stage (E17 in shaker-1 mice)

Self T *et al. Development* (1996); Lefèvre G *et al. Development* (2008)

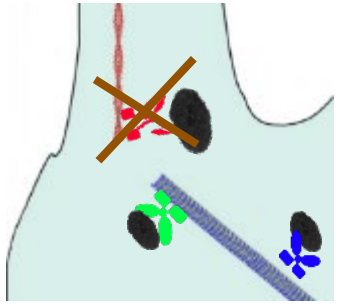
Retinal abnormalities in shaker-1 mice (defective myosin VIIa)

❖ **Decreased outer segment phagocytosis in RPE cells** *Gibbs D et al, …> Williams DS, PNAS 2003*

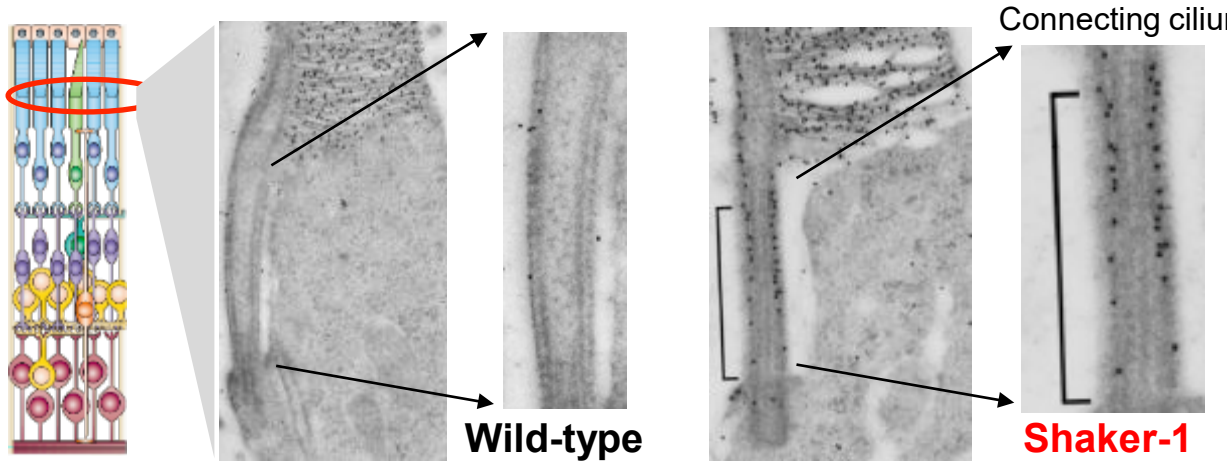
❖ **Melanosome mislocalization in RPE cells**



Liu, X., Ondek, B. and Williams, D. S. (1998). Mutant myosin VIIa causes defective melanosome distribution in the RPE of shaker-1 mice. *Nat. Genet.* 19, 117-118.



❖ **Opsin transport delay in photoreceptor cells** *Liu X et al, …> Williams DS, 1999, Wolfrum U & Schmitt A, 2000*



Myosin VIIa Participates in Opsin Transport through The Photoreceptor Cilium

The Journal of Neuroscience, August 1, 1999, *19*(15):6267–6274

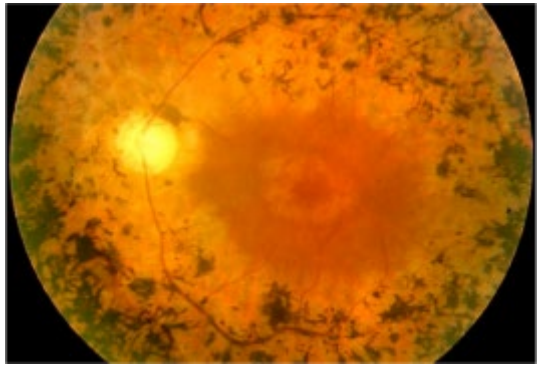
Xinran Liu,[1] Igor P. Udovichenko,[1] Stephen D.M. Brown,[2] Karen P. Steel,[3] and David S. Williams[1]

Phenotype discrepancy between USH1 patients and related mouse models ?

❖ **Whilst USH1 mutant mice do reproduce the inner ear-related symptoms, differences exist as to expressivity of retinal dysfunction?**

Human

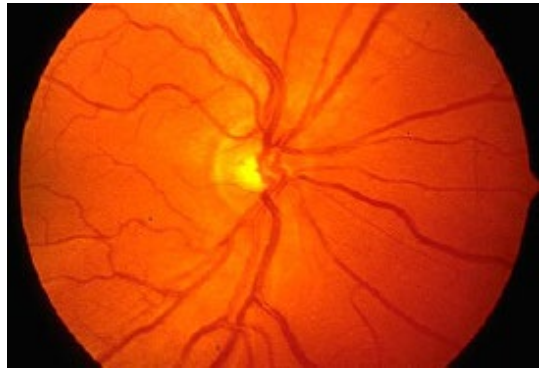
- Congenital deafness
- Circling behavior



- Retinitis pigmentosa

Mouse

- Congenital deafness
- Circling behavior

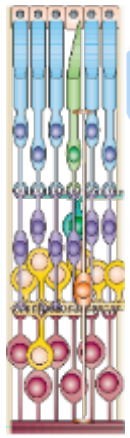


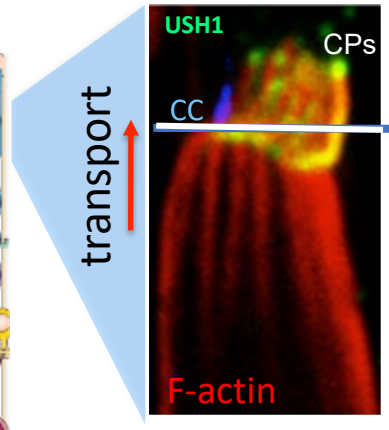
- No retinitis pigmentosa

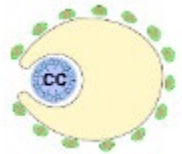
USH1 mouse models display no visual defects

Molecular and structural differences between mouse and primate photoreceptors

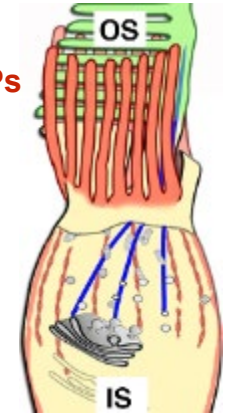
Primate

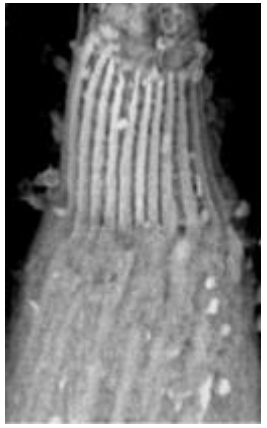






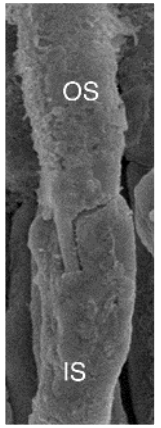
ring of
F-actin-labelled
calyceal processes





Sahly et al. *J. Cell Biol.* (2012)

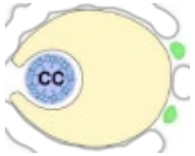
Mouse



The outer segment
(OS)

Connecting cilium
(CC)

The inner segment
(IS)



No ring of calyceal processes (CPs) in mouse photoreceptor cells

❖ Loss of USH1 function leads to defective calyceal processes & impaired outer segment disks morphogenesis

Morpholino-Based approach in Xenopus to study USH1 role in the retina

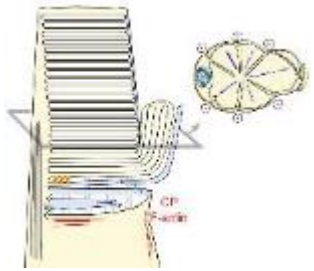
wild-type

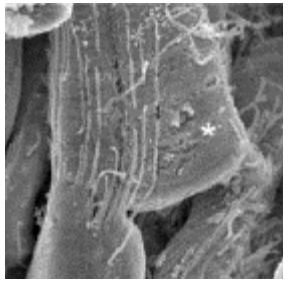
rod photoreceptor

Schietroma C *et al. J. Cell Biol.* (2017)

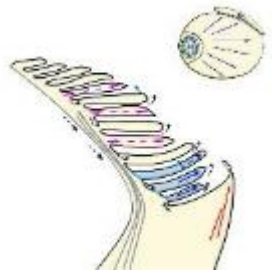
***X. tropicalis pcdh15* morphant**

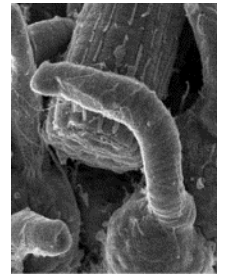
rod photoreceptor





cone photoreceptor





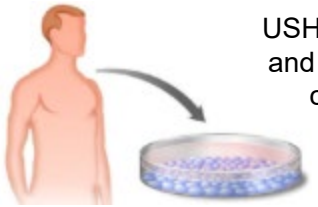
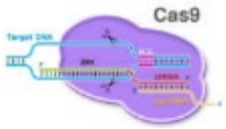
❖ Unmet fundamental and medical needs:

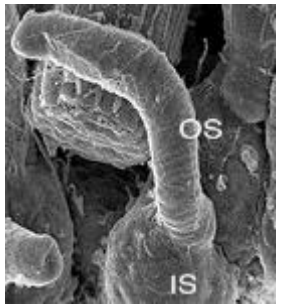
Identify for each USH gene the defective primary subcellular compartment(s)

- Apart from already available Usher 1 mice, production and characterization of additional mutants, either for new USH genes or harbouring specific human USH mutations.

Production and characterization of reliable USH preclinical animal models

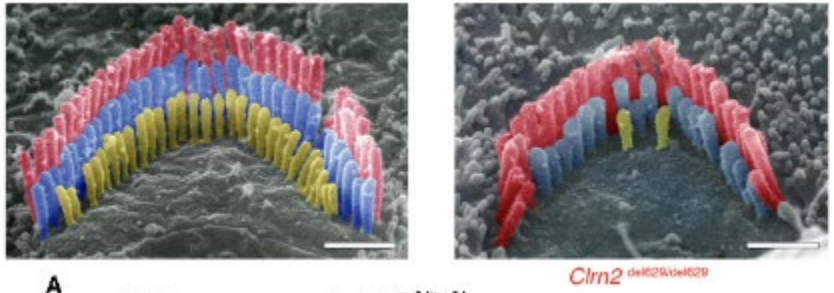
- In addition to mouse models, new cellular and pre-clinical USH non-murine models, suitable for the understanding of the disease pathogenesis and the preclinical validation of therapeutic interventions.

mouse	iPS cells	Macaque (NHP)	Pig
	 USH patient and control cells	 *shRNAs* AAV-mediated delivery 	CRISPR/ Cas9  
> 35 mutated USH alleles available			
Challenging conditions" in USH mice	**Develop and validate iPSCs**	**Develop and fully characterize USH macaque models.**	**Develop and fully characterize USH pig models.**



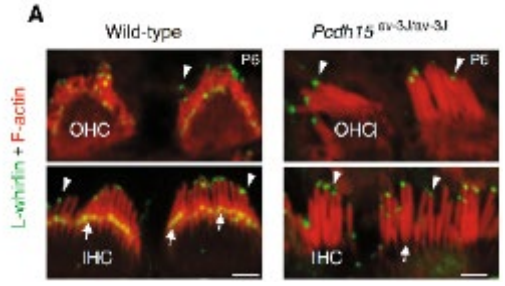
A series of functional, morphological and molecular analyses enabled us to show that, in the absence of Usher proteins, the calyceal processes were not correctly maintained around the external segments of the photoreceptors, leading to defects in the organization and layout of the membrane discs. This disruption of the normal course of photoreceptor outer segment morphogenesis is the cause of Usher retinopathy.

Shietroma et al. J. Cell Biol. 2017



Identification of new genes involved in deafness, clarin-2, a tetraspan-like protein, from the same family as clarin-1, involved in Usher syndrome type IIIa (USH3A) in mice, then also in humans, with the additional characterization of new models in mice and zebrafish

Vona B et al. Hum Genet, 2021

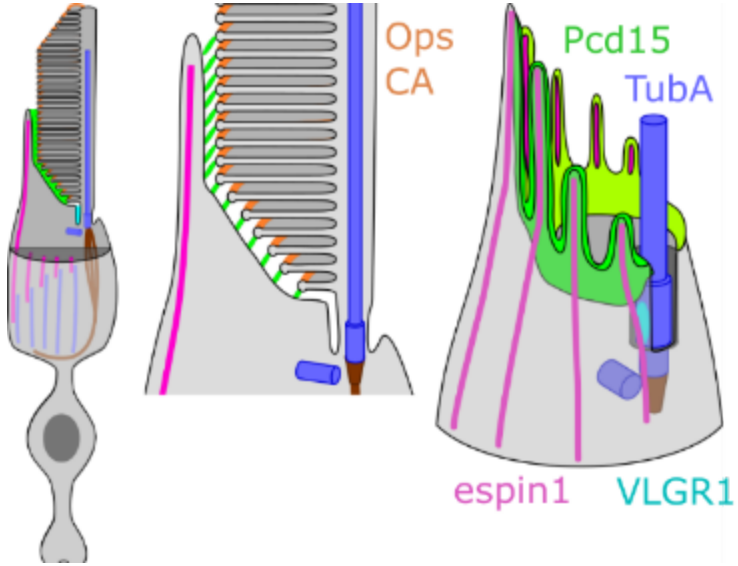


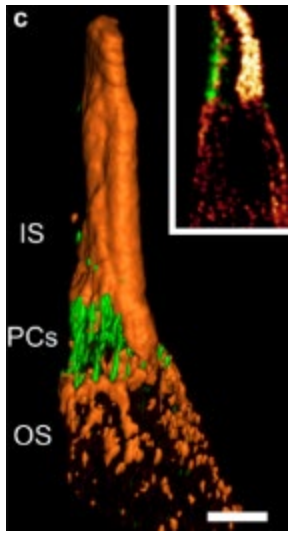
Interdependence between Usher 2 protein, whirlin, and Usher 1 proteins, in particular cadherin-23 (USH1D)

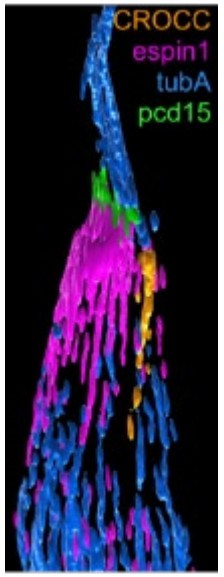
Michel V et al. Sci. Report, 2020

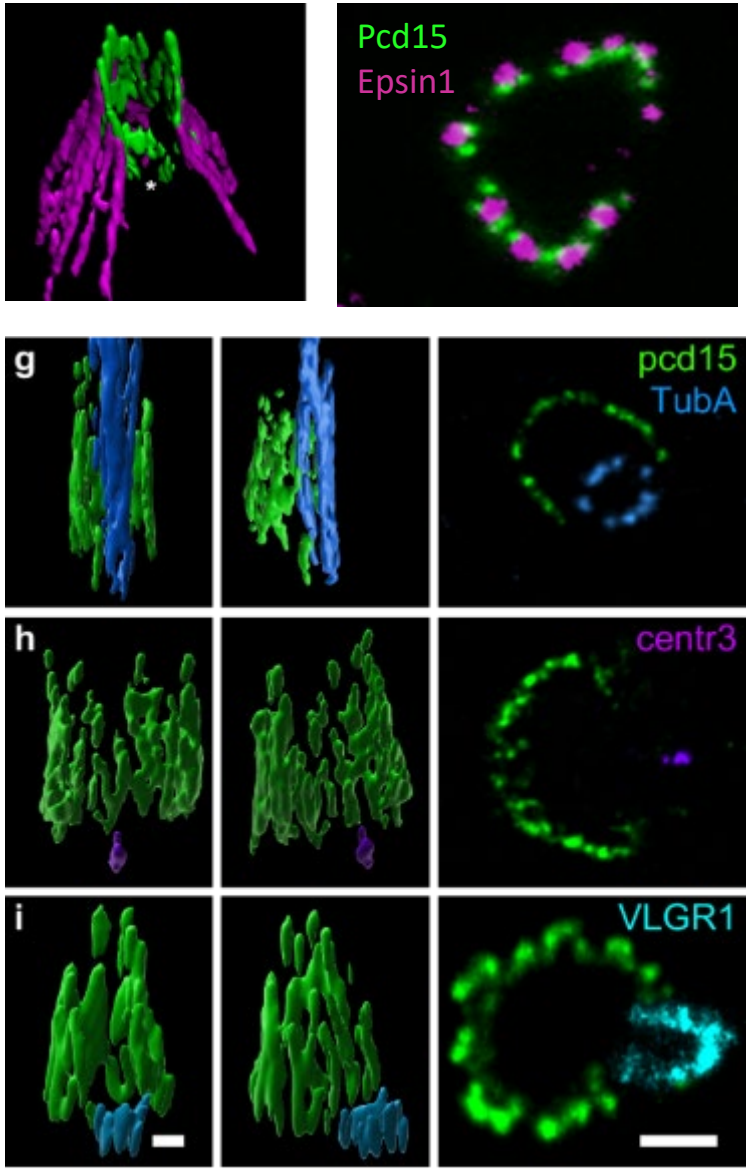
we created 12 various animal models for Usher hearing and vision: namely Ush1F and Ush1D xenopus morphants (vision), Ush1C and Ush1G albino mice (vision), CIB2/Ush1J defective mice (hearing and vision), Ush3a total and conditional knock-out mice (audition, $Clrn1^{-/-}$ et $Clrn1^{fl/fl}$, Myo15-$Cre^{+/-}$), Clrn2 deficient mice (mutation pW4*(stop), $Clrn2^{del629/del629}$, $Clrn1^{-/-}Clrn2^{-/-}$ mice, $USH1C^{\triangle PDZ}$.

Primate cone photoreceptor assymetry



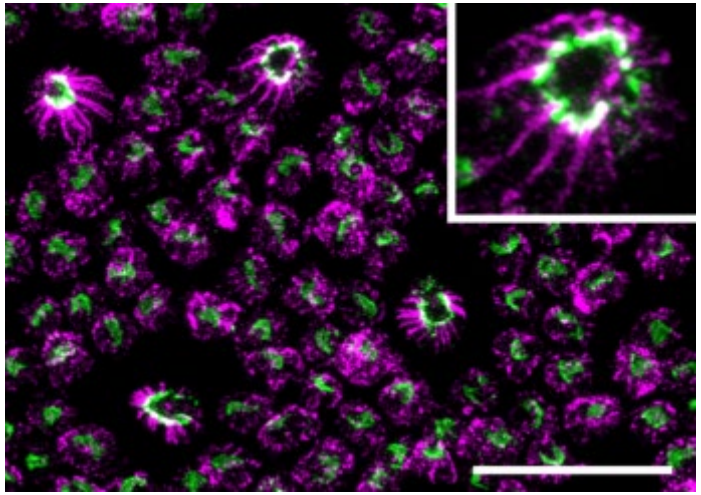


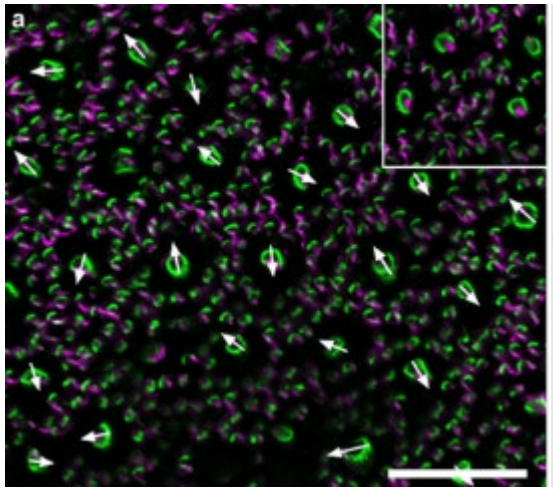


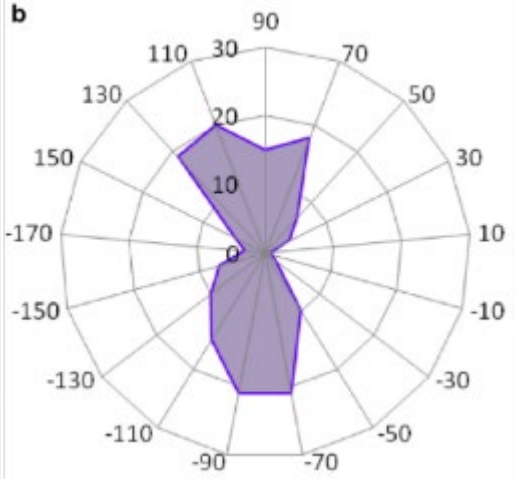


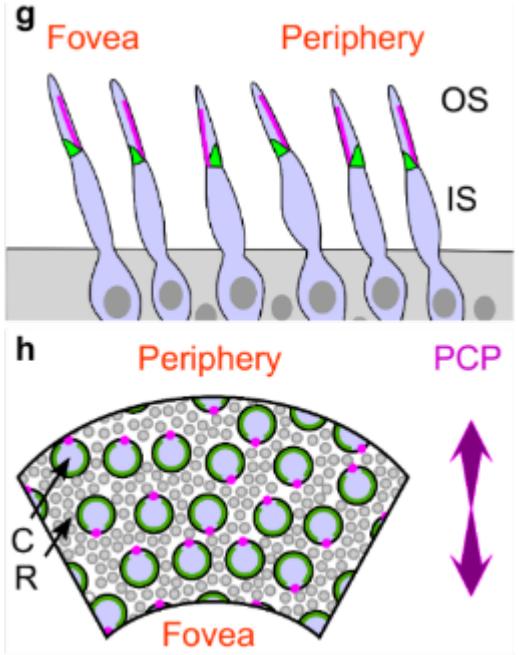
(Verschueren et al. Submitted)

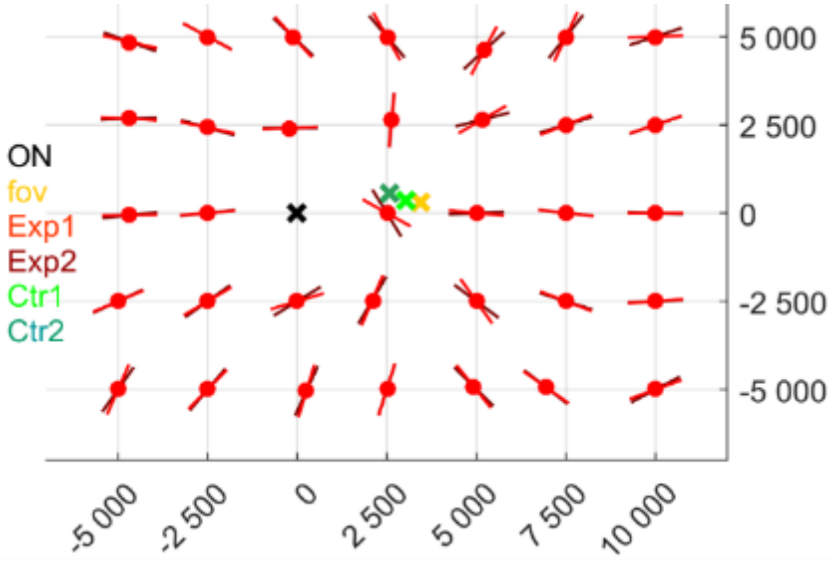
Primate cone photoreceptor planar polarity





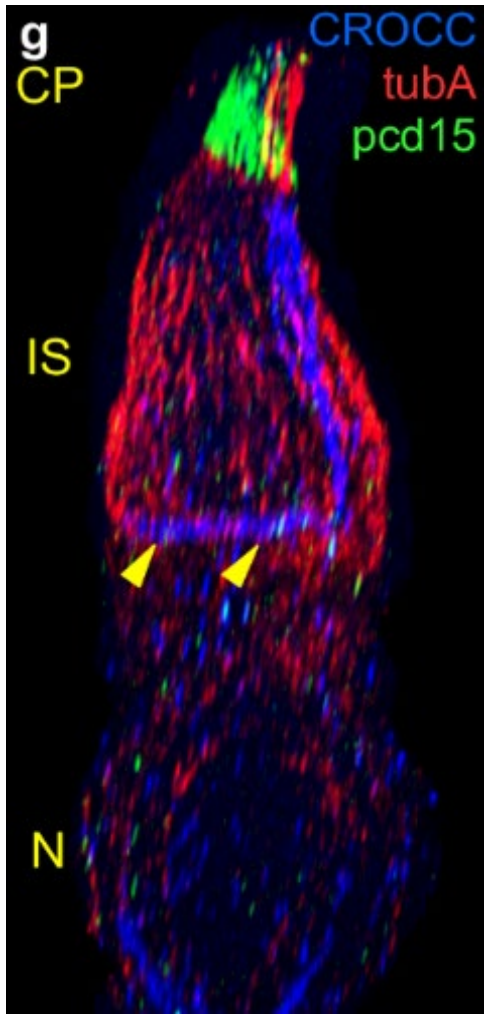


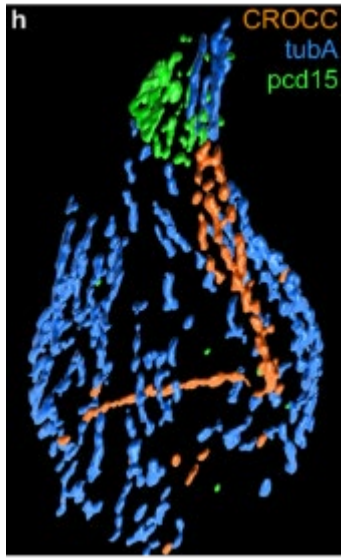


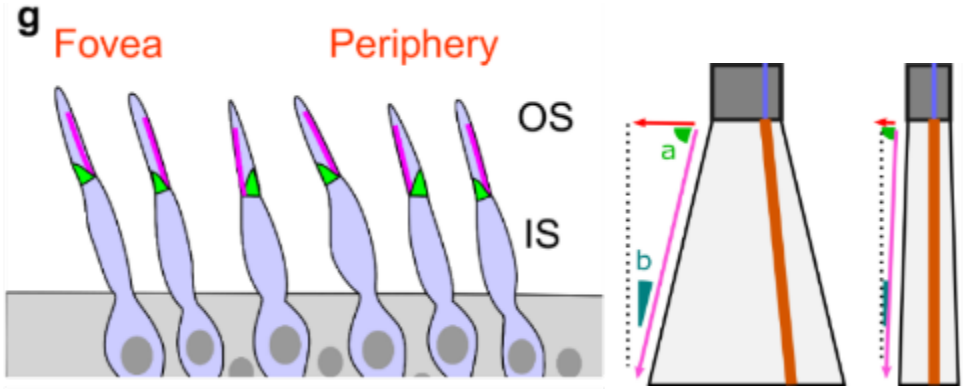


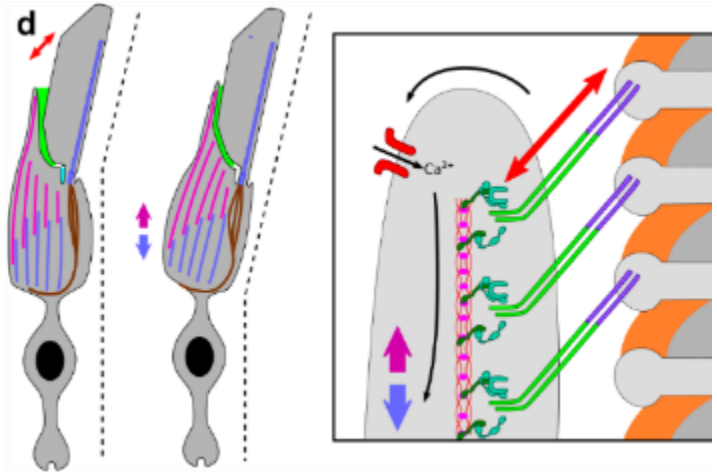
(Verschueren et al. Submitted)

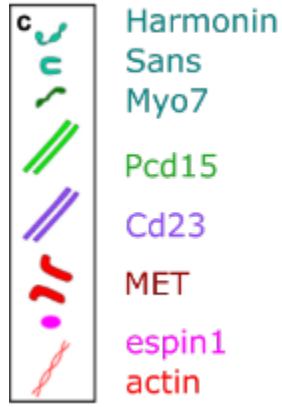
A mechanotransduction machinery to orient the OS-IS supporting the Stiles-Crawford effect ?











(Verschueren et al. Submitted)

Objective: performing precise phenotyping, genotype/phenotype correlation and longitudinal disease follow-up in patients affected with Usher syndromes regardless the type (i.e. type 1, 2 and 3). The precise phenotyping is concentrating on 4 aspects: retinal, auditory, vestibular and neurocognition

✓Multicentric longitudinal study with deep phenotyping of Usher syndromes on 4 aspects:

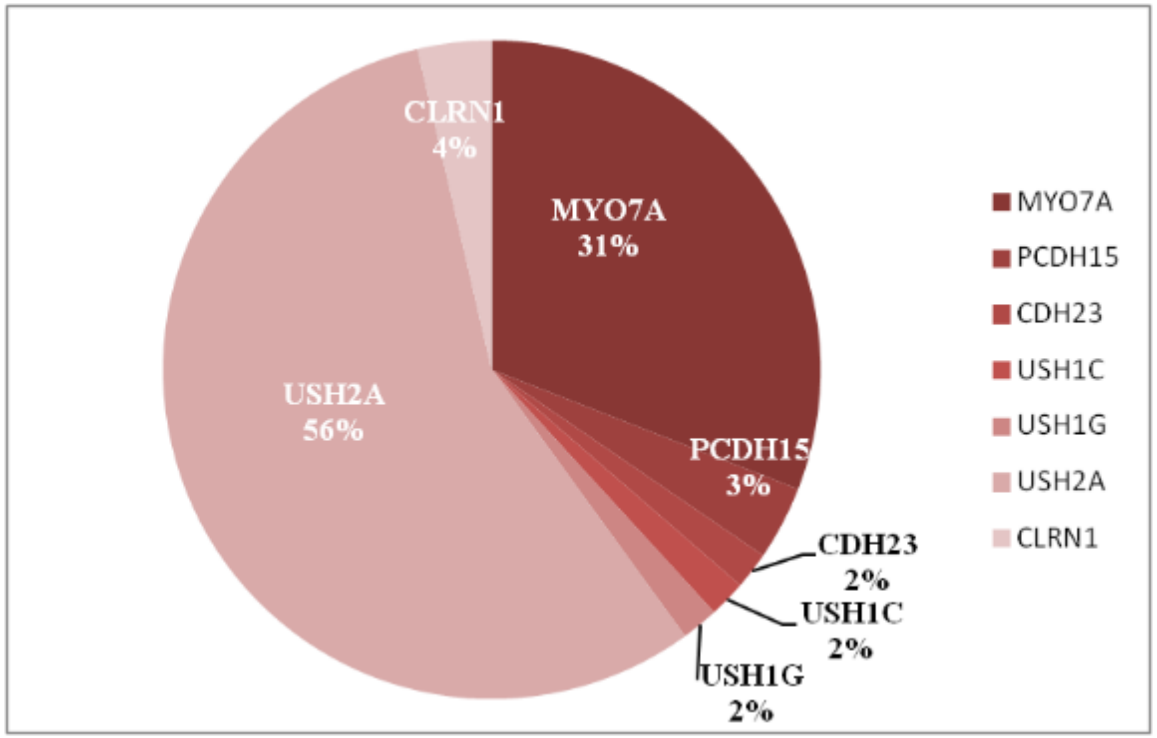
- retinal, auditory, vestibular and neuro-cognition

✓ Across 8 centers

- CIC1423 *CHNO des Quinze-Vingts*
- *Ophthalmology, ENT and the neurocognitive departments of Pitié Salpétrière* Hospital
- ENT department and genetic department of Necker hospital
- ENT department of Robert Debré hospital
- Fondation Hospitalière Sainte Marie

INFORMATION AND INCLUSIONS

More than 200 patients were informed about the study
March 2021: **152 patients included**



Difficulties encountered

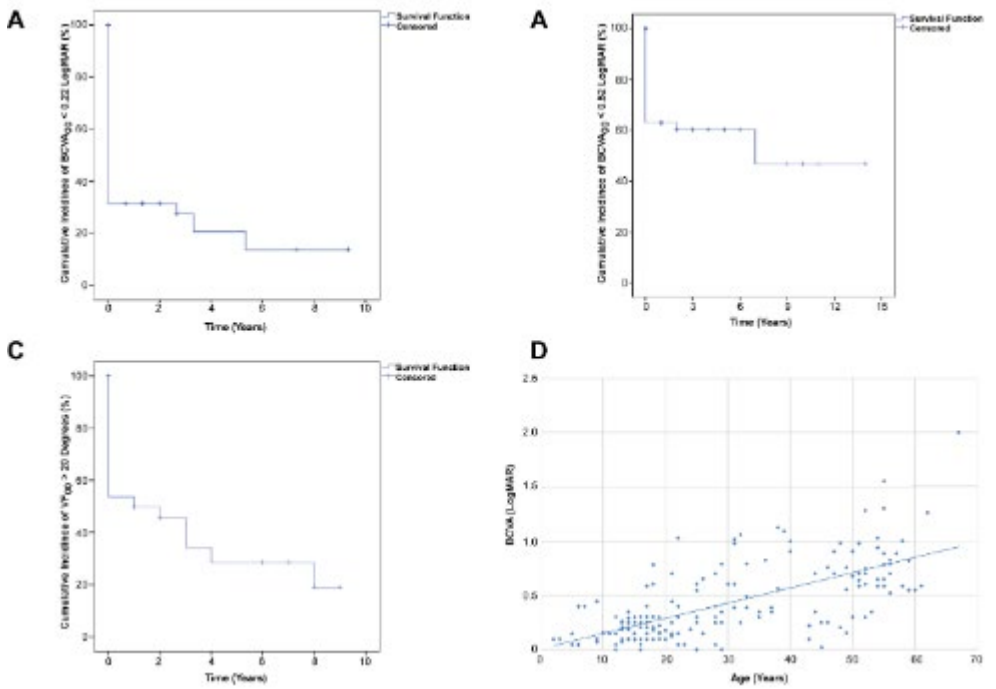
- Difficulties with communication and mobility with subjects experiencing double handicap (hearing and visual impairment)
- Refusal (no treatment involved)
- Burden of the protocol for the patient but also the sites involved
- March 2020 and the sanitary crisis put a temporary stop in the recruitment of new subjects and the follow-up of others as priority from the health authorities were put to only urgent and covid-19 care

RETROSPECTIVE STUDY FOR PATIENTS WITH MYO7A MUTATIONS (USH1B)

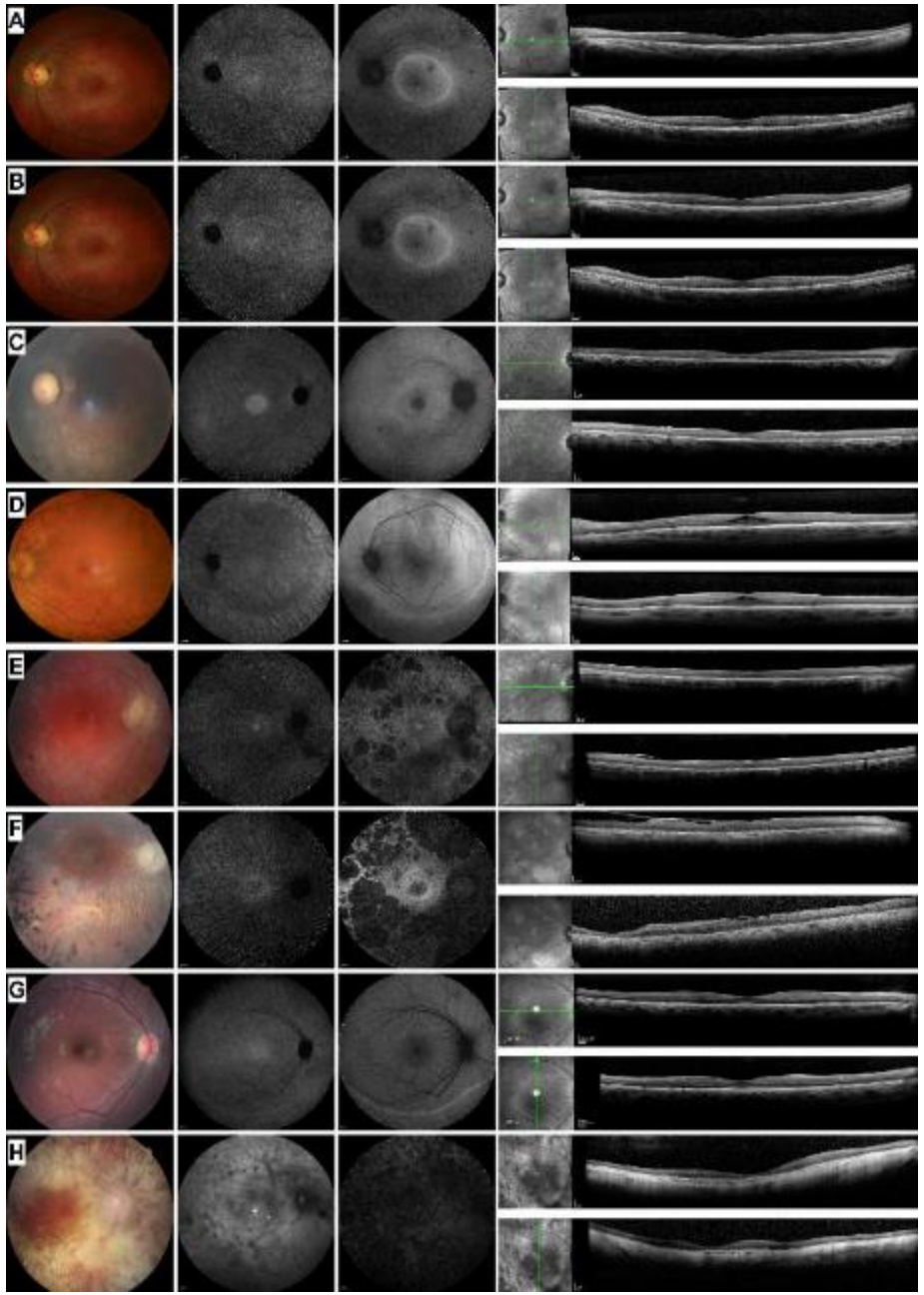
	Myo7A
Female (%)	27/53 (51%)
Mean age at diagnosis ± SD [range; number of subjects] (years)	12.33±11.84 [1-48;33]
Mean age at first visit available ± SD [range; number of subjects] (years)	29.01±17.43 [2-67; 53]
Follow-up time for BCVA Mean ± SD [range] (years) Only one visit Range 1-5 Range 6-10 Range 11-15	Total number = 53 4.09±4.34 [0-15] n=16 n=23 n=8 n=7
Follow-up time for VF Mean ± SD [range] (years) Only one visit Range 1-5 Range 6-10 Range 11-16	Total number = 46 2.46±3.58 [0-16] n=24 n=13 n=7 n=2
Night blindness as presenting symptom	16/20 (80%)
$BCVA_{OU}$(LogMAR) at first visit available	0.54±0.70 [n= 53]
Annual rate of BCVA decline (LogMAR/year)	0.025±0.54 [n=38]
VF (degrees) at first visit available	42.74±46.7 [n=43]
Annual rate decline of VF (%/year)	10.2 ± 15.9 [n=22]
binocular normal color vision	18/39 (46.1%)
Cataract and/or previous cataract surgery in at least one eye	21/40 (52.5%)
Bilateral undetectable ffERG	39/44 (88.6%)
Preserved EZ and ONL	28/53 (52.8%)
Mono- or bilateral SD-OCT evidence based CME	13/53 (24.5%)
Mono- or bilateral ERM	30/53 (56.6%)

Medical records of 53 patients (42 families) harboring mutations in *MYO7A* followed in one center (CHNO)

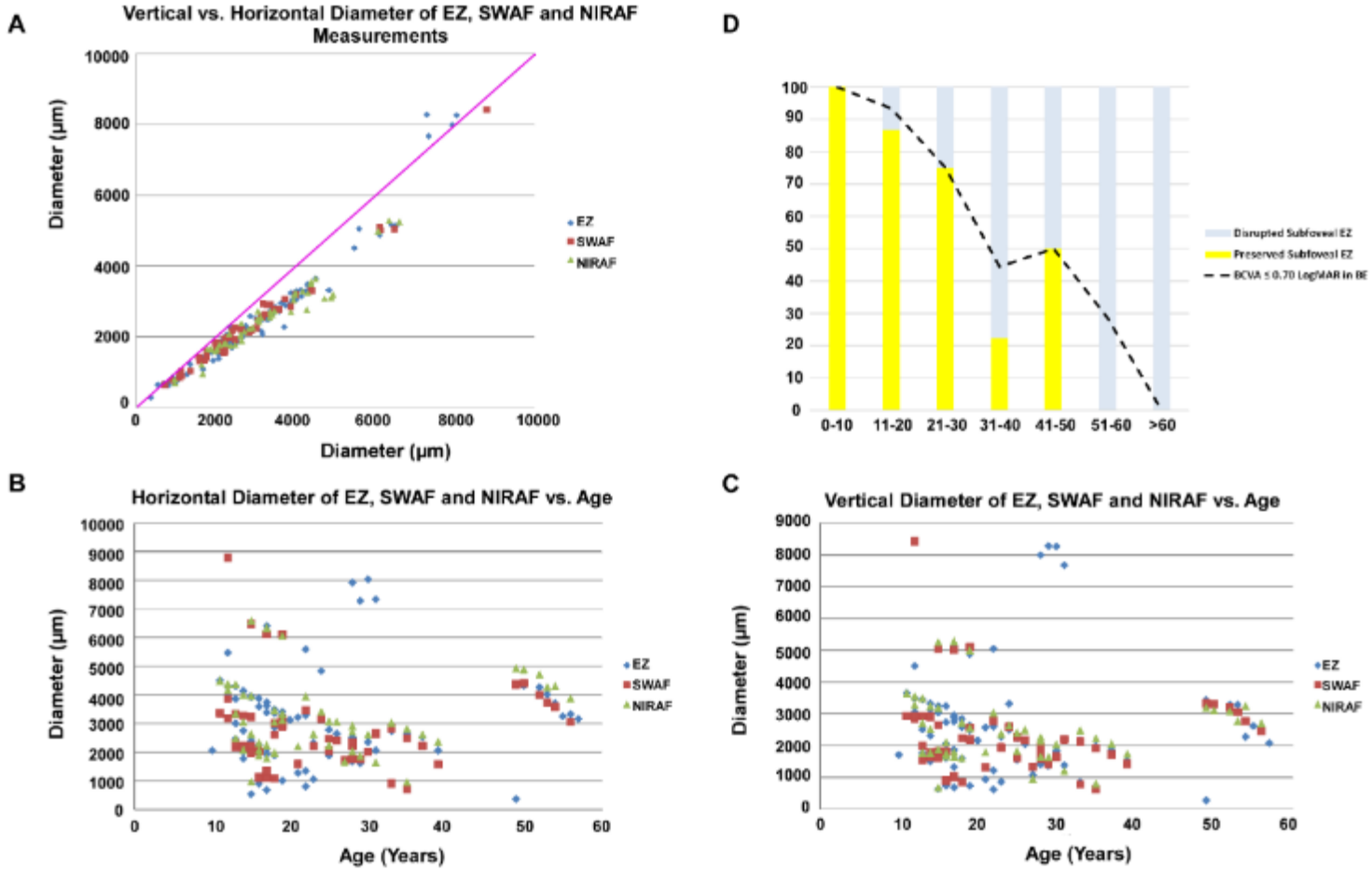
Visual acuity and visual field regression with age



Katheb et al, RETINA, 2020



Structural parameter alterations do not correlate with age

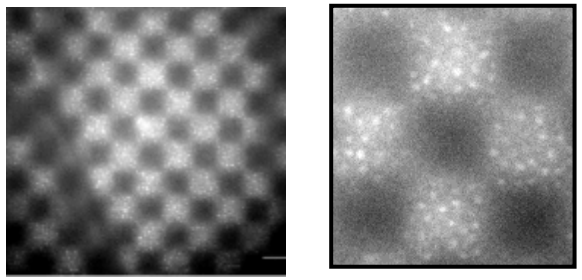


Katheb et al, RETINA, 2020

Retinal imaging

High speed Adaptive Optics platform with high performance innovative instruments.

1-Implementation of **structured illumination imager**



2-**multiangle AO**

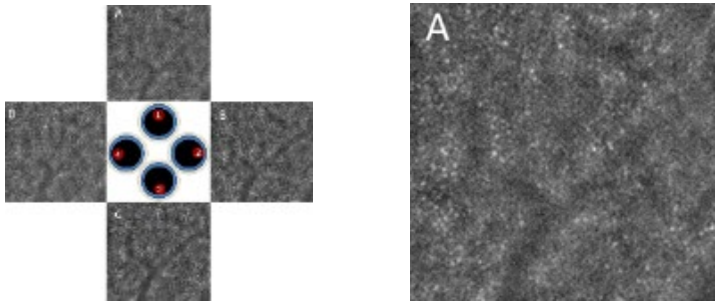
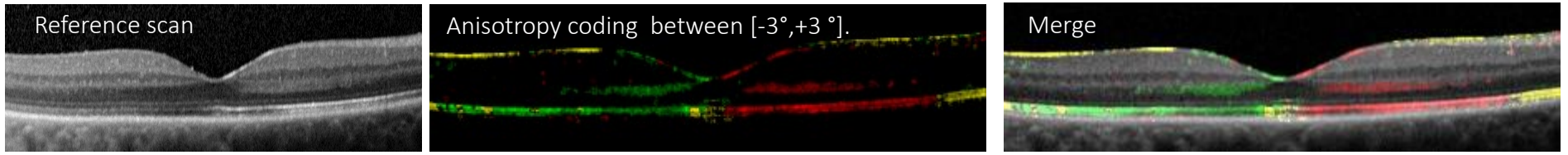


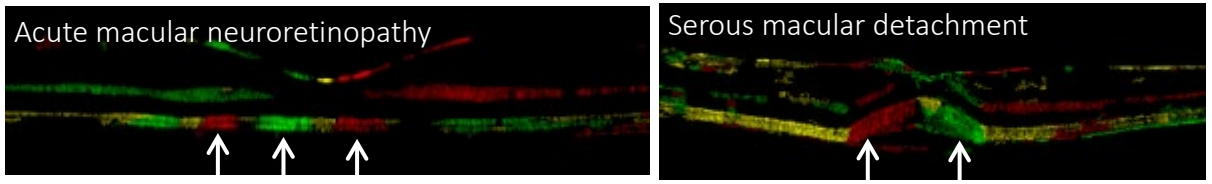
Image processing and analysis softwares

A software for multiangle processing of OCT scans (Rossant et al, in revision) enables color display of photoreceptor anisotropy

Control

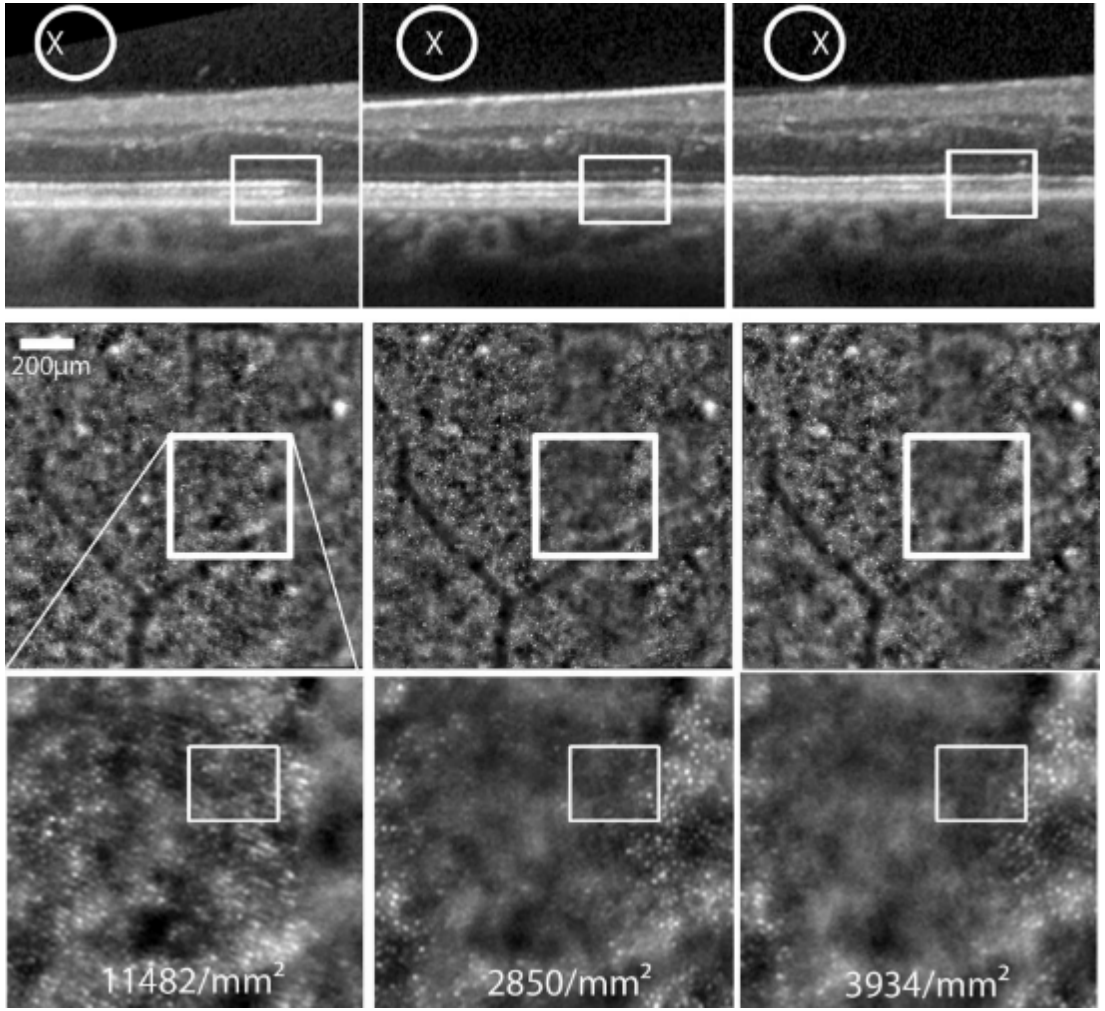


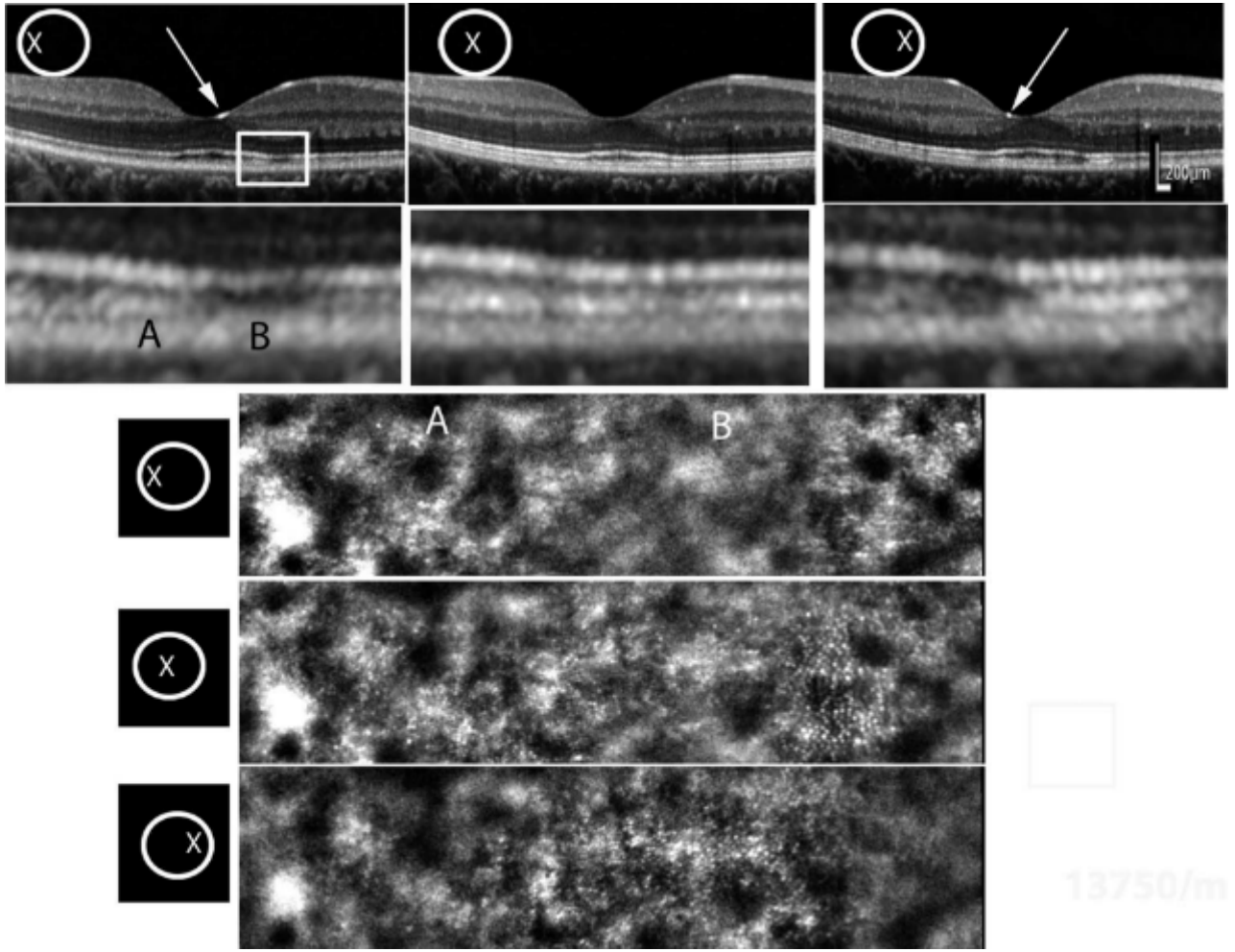
Diseased eyes



Results of clinical evaluation

Identification of directional and positional variability of photoreceptors in rare and common diseases (Bottin et al, CABR 2018; Paques et al, RETINA, 2020)





Progressing toward extensive clinical exploitation

-Clinical research:

Agreement with ANSM for the high speed imagers and its declinations

Multiangle OCT of RP

Angiography

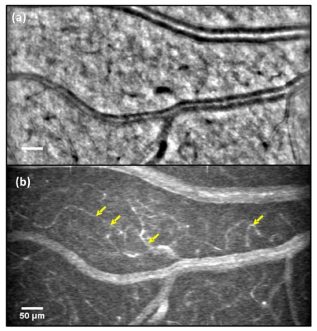
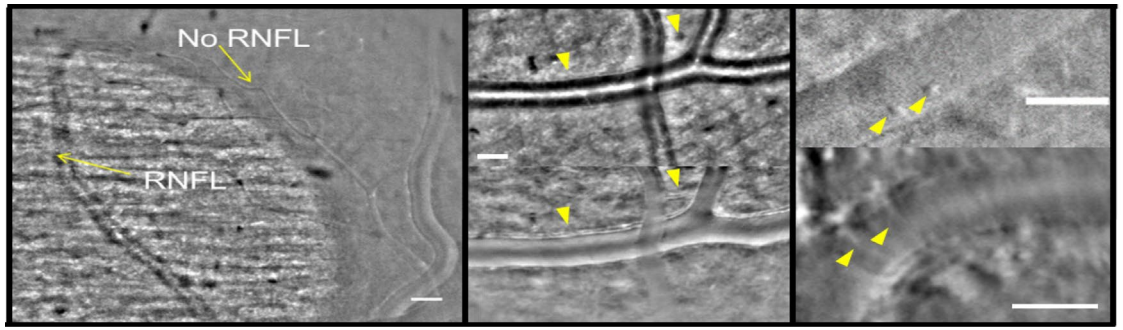


Fig.1 (a)Average image (b)NIR AOFA angiography image, arrows show revealed capillaries

Dark field imaging

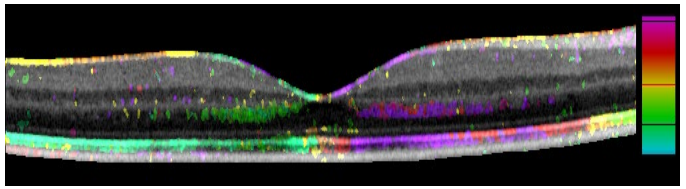


Gofas-Salas et al, *Biomedical optics express, 2019*

-Software

New version of multiangle OCT analysis to increase the angle span (up to 14°)

Design of a software for multiangle AO

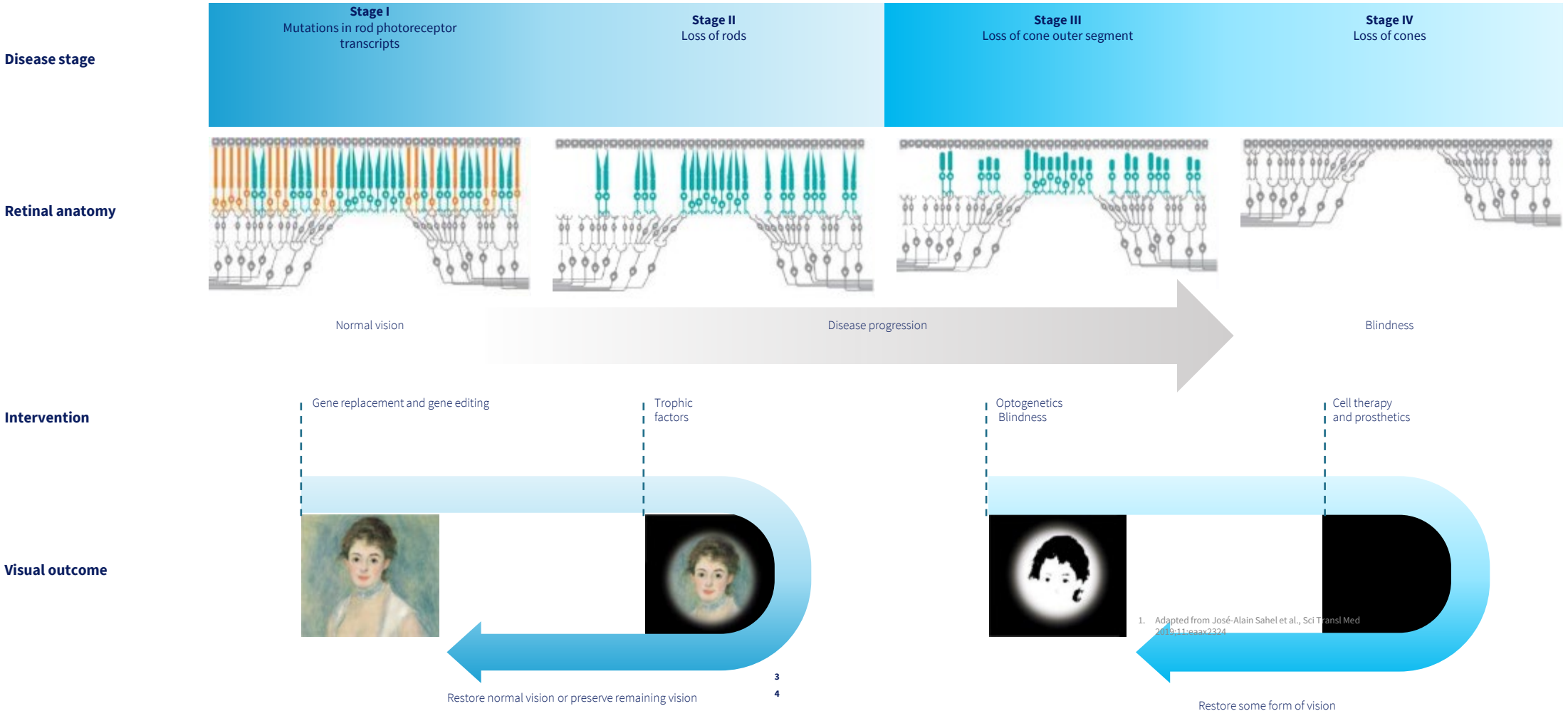


Color coding of multiangle OCT over -7° to +7°

Therapies in development

- **The development of efficient gene therapies**
  - What vectors (size, tissue diffusion)
  - What promoters
  - When is it too late ?
- **The development of gene independent approaches**
  - Neuroprotection
  - Optogenetics
  - Prosthetics
  - Cell replacement

GENE THERAPY FOR VISION RESTORATION IN ROD-CONE DYSTROPHIES



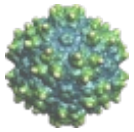
1. Adapted from José-Alain Sahel et al., Sci Transl Med 2019;11:eaaw2324

The Usher syndrome & potential treatment solutions ?

Several approaches:

Gene and/or mutation-specific therapies

Adeno Associated Virus
(**AAV**)



- ✓ Gene replacement therapies
- ✓ Mutation specific therapies

Anti-Sense Oligonucleotide (ASO)-based RNA interference (RNAi)

Genre editing-based: e.g. ZFNs, CRISPR/Cas9

Gene-independent" approaches, as a common strategy for several forms of deafness

- ✓ Sensory restoration: Cochlear implants, retinal prostheses, optogenetics, …
- ✓ Local protective therapies (RDCVF, Taurin, Trophic factors: e.g. NT3, BDNF, …)
- ✓ Sensory cells regeneration

… new auditory hair cells, or trans-differentiation from support cells

Gene therapy for Usher syndrome: The inner ear

	MOUSE MODEL	THERAPEUTIC APPROACH	DELIVERY	REFERENCE
Usher syndrome type I				
USH 1C	*Ush1c c.216G>A Knockin* mice (Acadian mutation)	Gene replacement (AAV-Anc80L65)	RWM injection (P1, P10)	Pan et al. 2017
		Antisense Oligonucleotides (ASO-29)	Intra-peritoneal injection (P3, P5, P10, P13, P16)	Lentz et al. 2013
			Intra-amniotic injection (E13)	Depreux et al. 2016
	p.R31X HEK293 cells	ZFNs	Lipofectamine	Overlack et al. 2012
USH 1G	*Ush1g* $^{-/-}$ mice	Gene replacement (AAV-1, -2, -5, -8)	RWM injection (P2.5)	Emptoz et al. 2017
Usher syndrome type II				
USH 2A	*USH2A c.2299delG* patient dermal fibroblasts	CRISPR/Cas9 RNP	Lipofectamine	Fuster-Garcia et al. 2017
USH 2D	*Whirler* mice	Gene replacement (AAV-8)	RWM injection (P1-P5)	Chien et al. 2015
			Posterior semicircular canal injection (P4)	Isgrig et al. 2017
Usher syndrome type III				
USH 3A	*Clrn1*$^{N48K/N48K}$ mice *x Atoh1-enhancer-Clrn1*	Small molecule (BF844)	Intra-peritoneal injection (P10 to P45)	Alagramam et al. 2016
	Clrn1$^{-/-}$ & KO-TgAC1 mice	Gene replacement (AAV-2,-8)	RWM injection (P1-P3)	Geng et al. 2017
	Clrn1$^{ex4fl/fl}$ *Myo15-Cre*$^{+/-}$ mice	Gene replacement (AAV-8)	RWM injection (P1-P3)	Dulon et al. 2018
	Clrn1$^{-/-}$ mice	Gene replacement (AAV-9 PHP.B)	RWM injection (P0-P1; P30)	György et al. 2019

e.g. example of USH1G

AAV8-mediated gene replacement in *sans/Usher type 1G* mutant mice

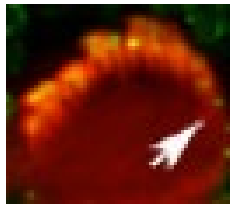
USH1G (*USH1G*, 17q25.1 - OMIM 607696) : Sans

ORF = *1383 bp*

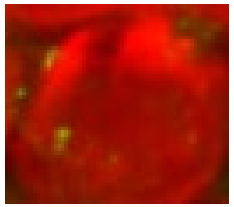
Emptoz A *et al. PNAS* 2017

AAV8-Sans-IRES-GFP **restores SANS/Ush1g** expression and targeting in ***Ush1g*$^{-/-}$** auditory hair cells

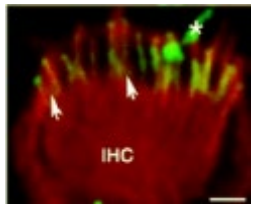
Control



Ush1g -/-



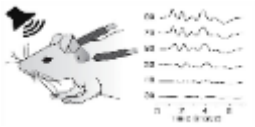
***Ush1g-/-* injected**

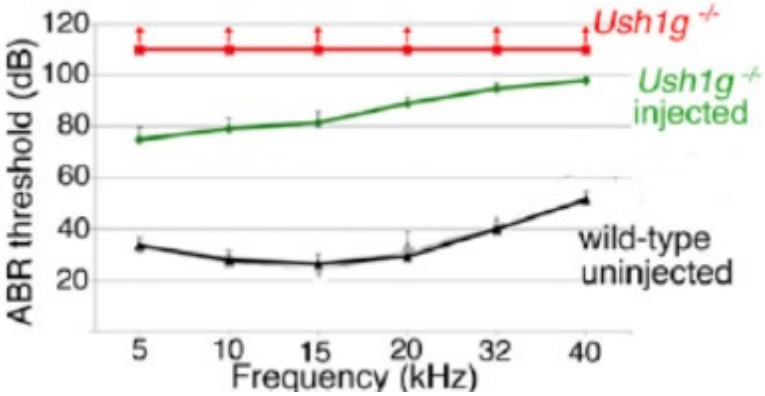


A single local injection of *USH1G* enabled the mice to recover, in a durable way, partially the hearing and completely the balance functions

Hearing sensitivity: Auditory Brainstem **R**esponses (ABR)s

Auditory **B**rainstem **R**esponses (ABRs)





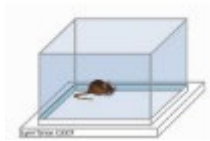
Partial recovery of hearing sensitivity

Exploratory behavior: Video-tracking in an open-field chamber

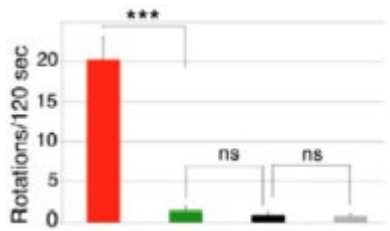
Wild type (non injected)

***Ush1g* -/- (non injected)**

Open Field Test



***Ush1g* -/- (injected)**



Full recovery of balance behavior

The Usher syndrome (USH) genes & AAV-mediated therapy

USH1

USH1B (*MYO7A*, 11q13.5 - OMIM 276903) : **myosin VIIa**

***ORF** = 6645 bp*
2215 aa, 254 kDa

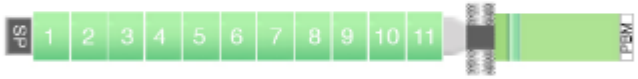
USH1C (*USH1C*, 11p15.1 - OMIM 605242) : **harmonin**

***ORF** = 2697 bp*
899 aa, 98 kDa

USH1D (*CDH23*, 10q22.1 - OMIM 605516) : **cadherin-23**

***ORF** = 10 062 bp*
3354 aa, 369 kDa

USH1F (*PCDH15*,10q21.1 - OMIM 605514) : **protocadherin-15**



***ORF** = 5865 bp*
1955 aa, 216 kDa

USH1G (*USH1G*, 17q25.1 - OMIM 607696) : **Sans**

***ORF** = 1383 bp*
461 aa, 51 kDa

Atypical form

DFNB48/USH1J (*CIB2*, 15q25.1 - OMIM 605564) :
calcium integrin binding protein 2

***ORF** = 561 bp*
187 aa, 21 kDa

USH2

USH2A (*USH2A*, 1q41 - OMIM 608400) : **usherin**

«transmembrane form»

***ORF** = 15 606 bp*
5202 aa, 575 kDa

USH2C (*GPR98*, 5q14.3 - OMIM 602851) : **ADGVR1**
(adhesion G-protein coupled receptor V1)

***ORF** = 18 918 bp*
6306 aa, 693 kDa

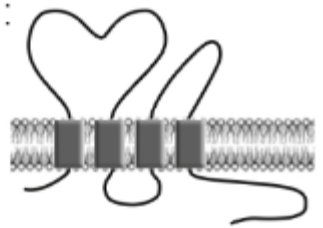
USH2D (WHRN, 9q32 - OMIM 607928) : **whirlin**

Long isoform (L)

***ORF** = 2721 bp*
907 aa, 96 kDa

USH3

USH3A (*CLRN1*, 3q25.1 - OMIM 606397) :
clarin-1

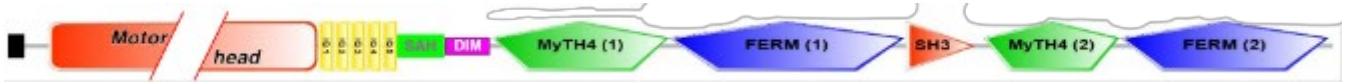


***ORF** = 696 bp*
232 aa, 25 kDa

Only 5 USH genes
fit into a single AAV

The Usher syndrome type IB & viral-mediated therapy

USH1B/Myosin VIIa/MYO7A: actin based motor protein



MYO7A ORF: 6645 bp

Too big for a single AAV (max packaging capcity: 4.7 kb)

Alternatives:

- ✓ *Oversized AAVs ?*
- ✓ *Dual/Hybrid AAVs ?*
- ✓ *Other vectors ?*

Virus	Expression	Genome	Packaging Capacity	Virus Size (nm)	Cells Infected	Target Cell Genome Integration	Immune Response
Lentivirus	Stable	RNA	<8 Kb	80-130	Dividing/Non-dividing	Yes	Low
AAV	Transient or Stable*	single stranded linear DNA	~4.5 Kb	18-26	Dividing/Non-dividing	No*	Very Low
Adenovirus	Transient	double stranded linear DNA	>8 Kb	105	Dividing/Non-dividing	No	High
γ-Retrovirus	Stable	RNA	<8 Kb	80-130	Dividing	Yes	Moderate

https://www.addgene.org/viral-vectors/

Gene therapy for Usher syndrome: The retina

Comparison of different strategies for viral delivery of MYO7A

	Lentivirus		Adeno-associated virus			
	HIV-based	EIAV-based	AAV2 AAV5	AAV2 AAV8	AAV8	AAV8
Myo7a cDNA encapsulation	Single	Single	Single[a]	Dual overlapping	Dual trans-splicing	Dual hybrid
Genome integration	Yes	Yes	No	No	No	No
Retinal cell layer targeted	RPE mainly	RPE PR	RPE PR	RPE PR	RPE PR	RPE PR
Phenotype correction mouse						
RPE	Mosaic[b]	Unknown	Yes[c,d]	Mosaic[c,e]	Mosaic[e]	Mosaic[e]
PR	Yes[b]	Yes[f]	Yes[c,d]	Yes[c,e]	Unknown	Unknown

[c]Lopes et al. (2013).
[d]Colella et al. (2013).
[e]Trapani et al. (2014).
[f]Zallocchi et al. (2014).

Lentiviral- and Equine Infectious Anemia Virus (EIAV)-MYO7A expression in the retina

Hashimoto T, Gibbs D, Lillo C, Azarian SM, Legacki E, Zhang XM, Yang XJ, Williams DS. 2007. Lentiviral gene replacement therapy of retinas in a mouse model for Usher syndrome type 1B. *Gene Ther* **14:** 584–594.

Zallocchi M, Binley K, Lad Y, Ellis S, Widdowson P, Iqball S, Scripps V, Kelleher M, Loader J, Miskin JP, et al. 2014. EIAV-based retinal gene therapy in the *shaker1* mouse model for Usher syndrome type 1B: Development of UshStat. *PLoS ONE* **9:** e94272.

Ushstat clinical trial

Oversized and/or dual/hybrid AAV vectors

Lopes VS, Boye SE, Louie CM, Boye S, Dyka F, Chiodo V, Fofo H, Hauswirth WW, Williams DS. 2013. Retinal gene therapy with a large MYO7A cDNA using adeno-associated virus. *Gene Ther* **20:** 824–833.

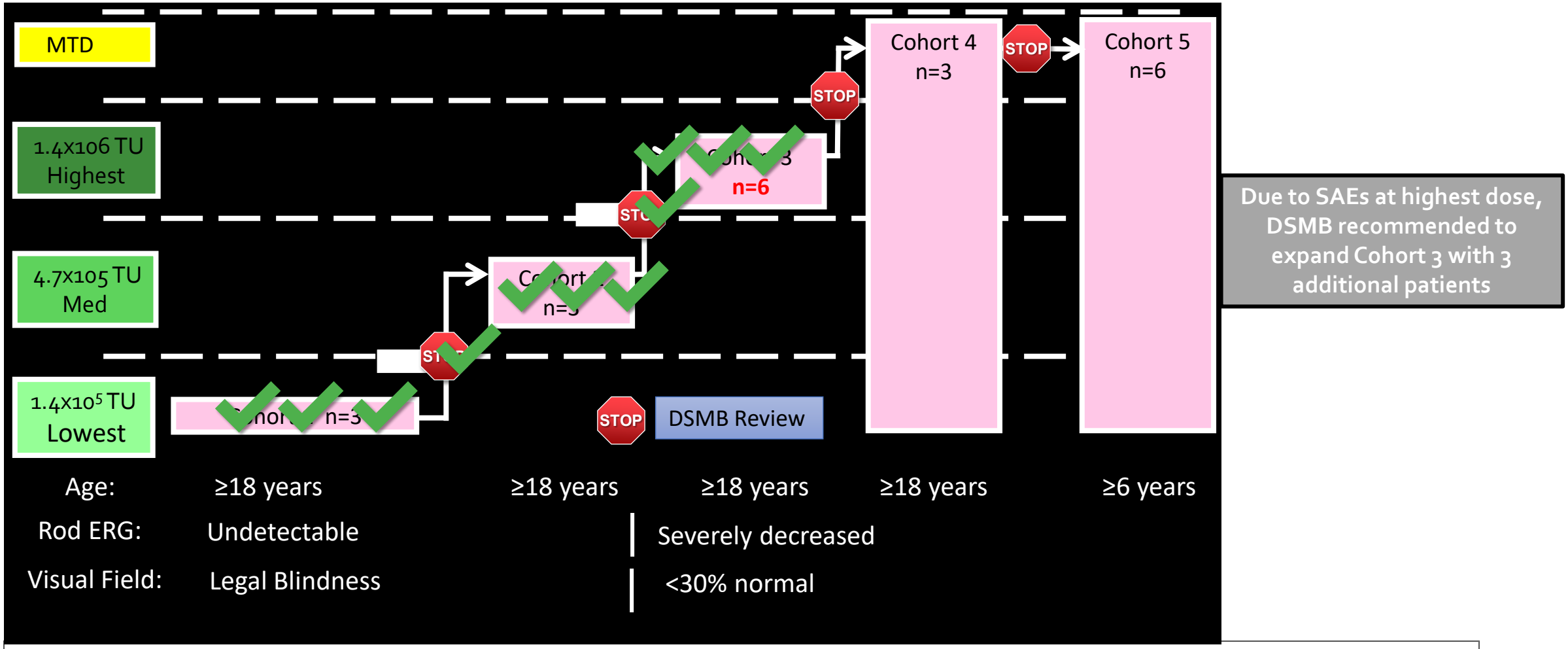
Trapani I, Colella P, Sommella A, Iodice C, Cesi G, de Simone S, Marrocco E, Rossi S, Giunti M, Palfi A, et al. 2014. Effective delivery of large genes to the retina by dual AAV vectors. *EMBO Mol Med* **6:** 194–211.

A Phase I/IIa Dose Escalation Safety Study of Subretinally Injected SAR421869 (UshStat) Administered to Patients with Retinitis Pigmentosa Associated with Usher Syndrome Type 1B

NCT01505062

- **Objectives:**
  - Primary: To evaluate the safety and tolerability of SAR421869 in USH1B patients
  - Secondary: To evaluate for possible biological activity of SAR421869
- **Design:**
  - Phase I/IIa dose escalation study
- **Vector:**
  - SAR421869, a non-primate *MYO7A* lentiviral vector based on EIAV
- **Delivery:**
  - Subretinal injection
- **Sites (Primary Investigator):**
  - Casey Eye Institute, Portland, Oregon (Richard Weleber, MD)
  - Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, Paris, France (José-Alain Sahel, MD)
- **Sponsor:**
  - Sanofi

UshStat (SAR421869) – Study Design



Following the subretinal injection of SAR421869 patients are assessed on Day 1, and weeks 1, 2, 4, 8, 12, 16, 20, 24, 36 and 48 post-treatment. Subjects then enter long term follow up study (LTS13619) for 15 years.

Safety Summary: SAR421869 Program (TDU13600 & LTS13619)

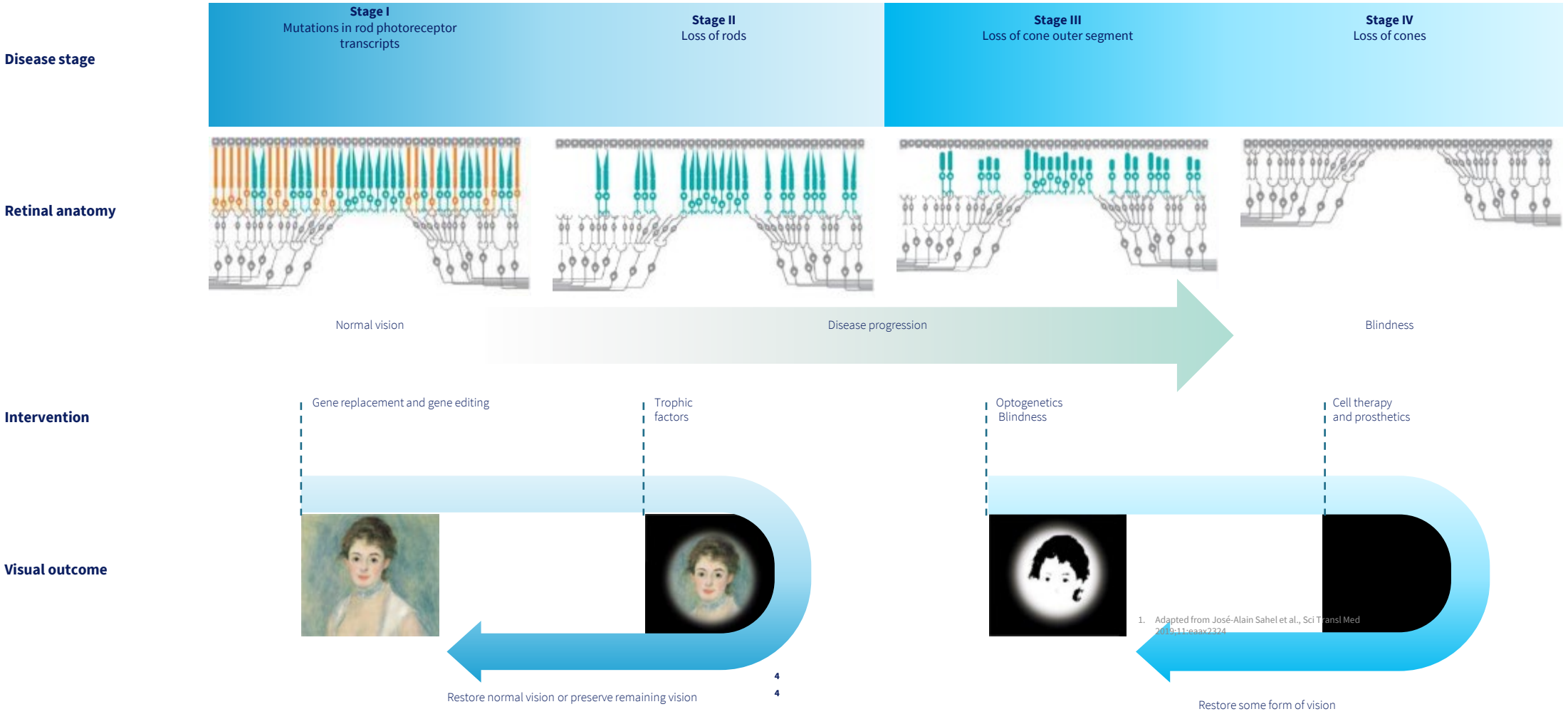
- To date, **9 patients** have been treated with SAR421869. A pooled analysis of the AEs reported in the studies TDU13600 and LTS13619 showed a total of 67 AEs, of which 4 were SAEs and 63 were non-serious.

- **4 SAEs** have been reported in 3 patients treated with SAR421869
  - *2 SAEs reported in 2 patients (Severe Panuveitis and Visual acuity reduced) both related to IMP and surgical procedures*
  - *2 SAE reported in 1 patient (Road traffic accident and ligment rupture) were unrelated to IMP or surgical procedure.*

- **The AE profile** for the eye was common to any intraocular surgery and no significant systemic reactions were observed
  - *A total of 63 non-serious AEs were reported in both the TDU13600 and the LTS13619 studies*
  - *Majority of the AEs (84%) were mild in severity and 3 AEs were severe and 8 AEs were moderate in severity.*
  - ***Two of single events were related to IMP only by the investigators***

Note: No safety concern was identified so far in the long term follow-up of patients treated with SAR421869

GENE THERAPY FOR VISION RESTORATION IN ROD-CONE DYSTROPHIES



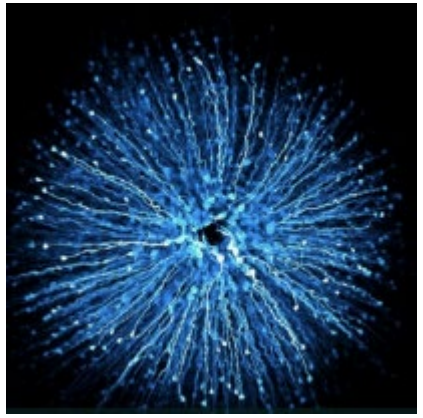
1. Adapted from José-Alain Sahel et al., Sci Transl Med 2019;11:eaaw2324

2- Gene-dependent and gene-independent therapies to restore normal vision

After photoreceptor degeneration, light responses can be restored using optogenetics in the remaining other cell types of the retina.

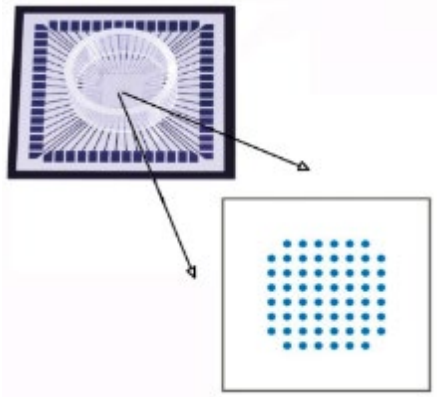
2.2: Optogenetics to restore vision in gene-independent manner:

Chaffiol et al. Mol. Therapy 2017
Khabou et al. JCI Insight 2018
Garita-Hernandez et al., Int J Mol Sci. 2020



- ✓ Using AAVs in mouse models, organoids derived from induced pluripotent human stem cells, post-mortem human retinal explants and live monkeys, **new vector-promoter combinations were identified** to overcome the limitations associated with the transduction of foveal cones.

These vectors allow expression of microbial opsins at levels compatible with restoration of vision by optogenetics.

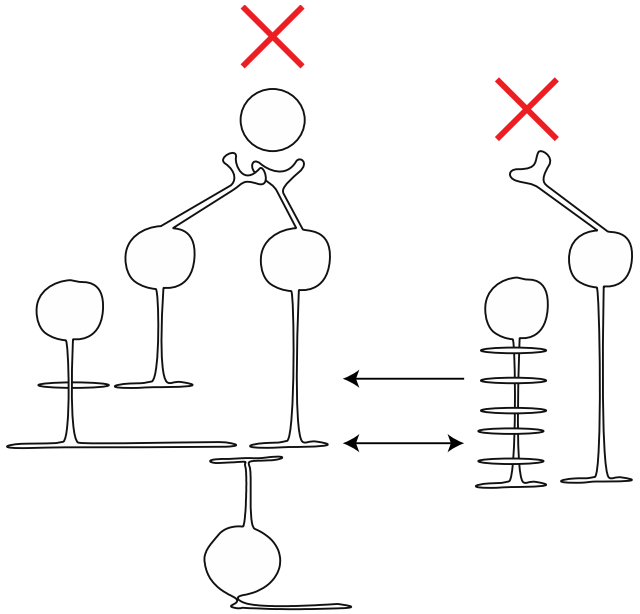


- ✓ To overcome the risk of light toxicity using a blue-sensitive microbial opsin, we have targeted retinal ganglion with the red-sensitive microbial opsin, ChrimsonR.

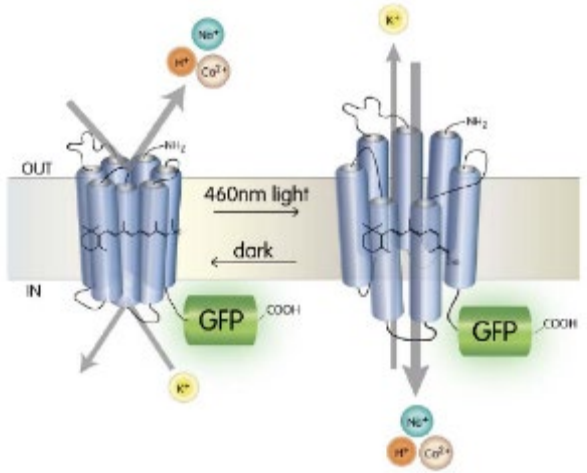
Ferrari et al., PLoS Comput Biol. 2020
Gauvain et al., Commun. Biol., 2021

Data obtained in rodents and non-human primates have allowed Gensight biologics to file for clinical trials in France, England and USA. **The first patient has been injected in 2019** (NCT03326336).

Make artificial photoreceptors from specific cell types within the retina using optogenetic tools



Blind retina

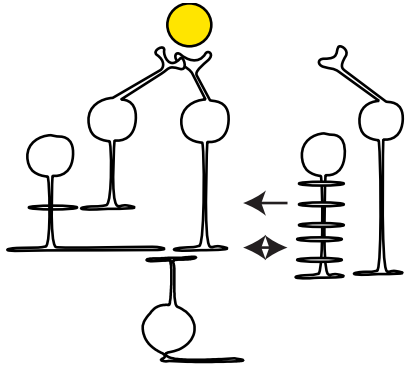


Light sensitive channel

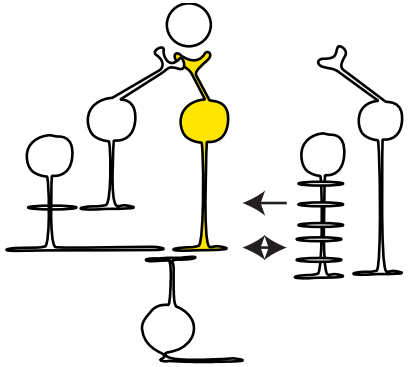
Four different kinds of optogenetic therapy

Sahel et al, Nature Medicine, 2021

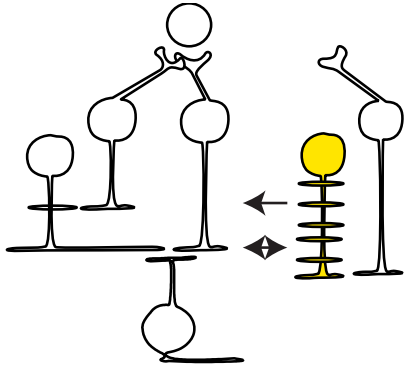
Cones



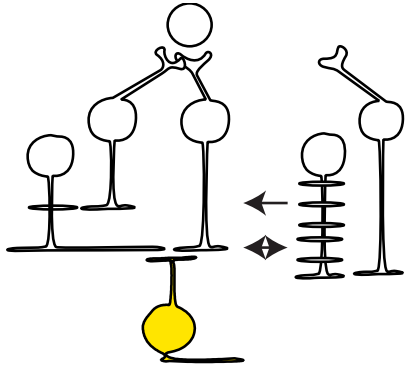
Bipolar cells



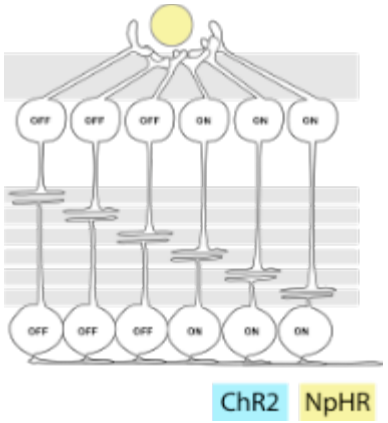
AII amacrine cells



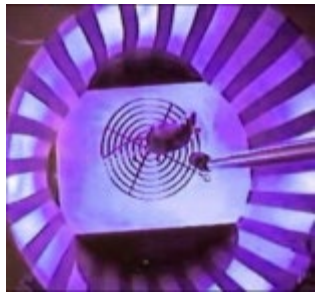
Ganglion cells



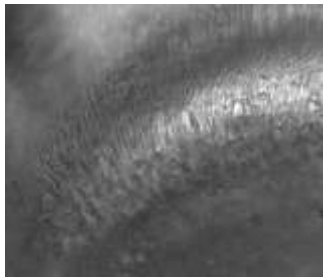
Translational path



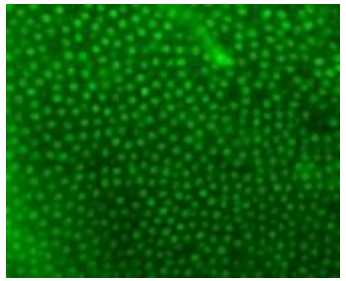
1. Restoration of retinal and cortical function in mice



2. Restoration of visual behavior in mice



3. Restoration of function ex vivo in human retina



4. Primate studies: specificity, efficacy and safety

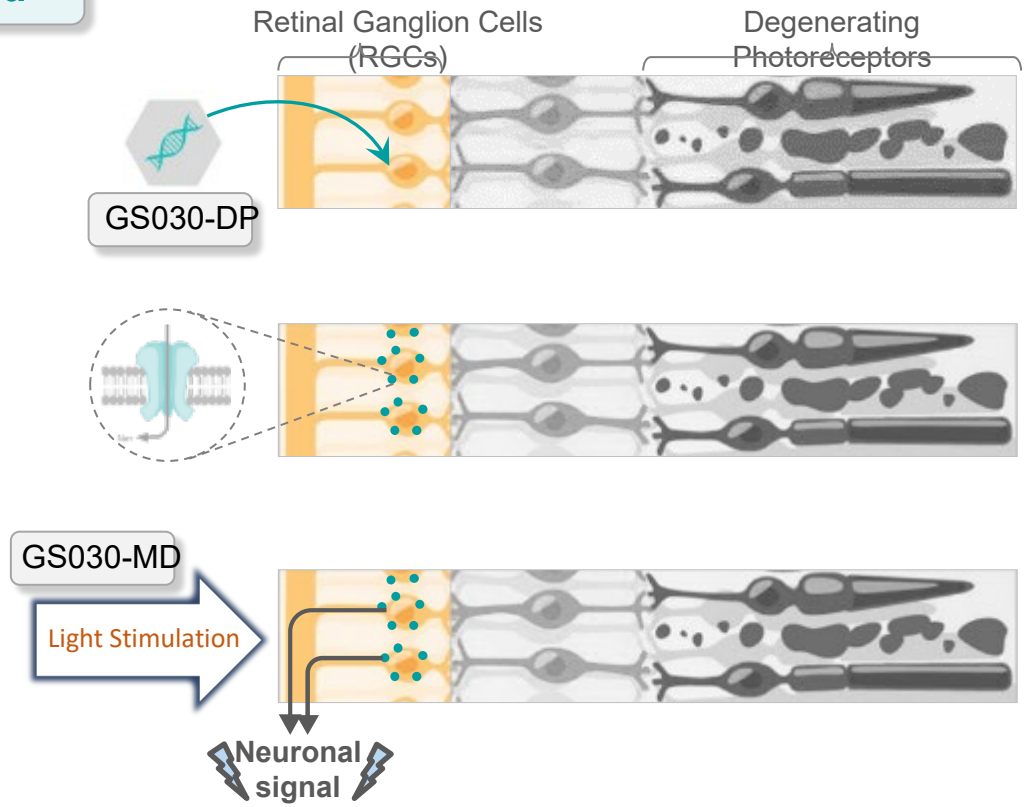
5. Clinical trial

GS030 optogenetic therapy:

Combined gene therapy and medical device to restore retinal light sensitivity

Mechanism of Action of GS030 Combined Therapy

1. Intravitreal injection of viral vector and RGC transfection
2. Expression of light-sensitive ChrimsonR on RGC surface
3. Induction of neuronal signal by photostimulation of bioengineered RGCs



➢ **Restore light sensitivity of the retina by modifying and training RGCs to act as photoreceptors**

GS030 optogenetic therapy:

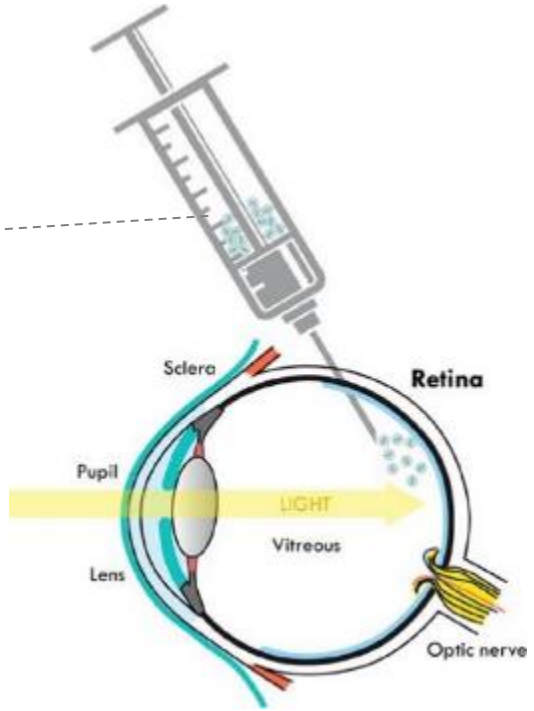
Combined gene therapy and medical device to restore retinal light sensitivity

Drug Product

GS030-DP

ChrimsonR gene

AAV2.7m8 vector



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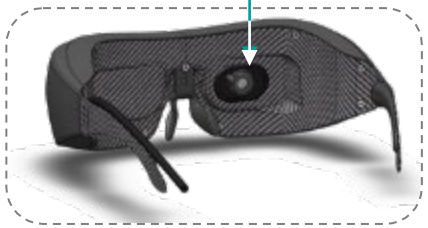
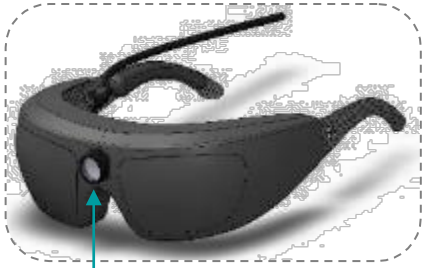
Light Projector



GS030-MD Medical Device



Event-based camera

The product of research collaboration with

Massachusetts Institute of Technology

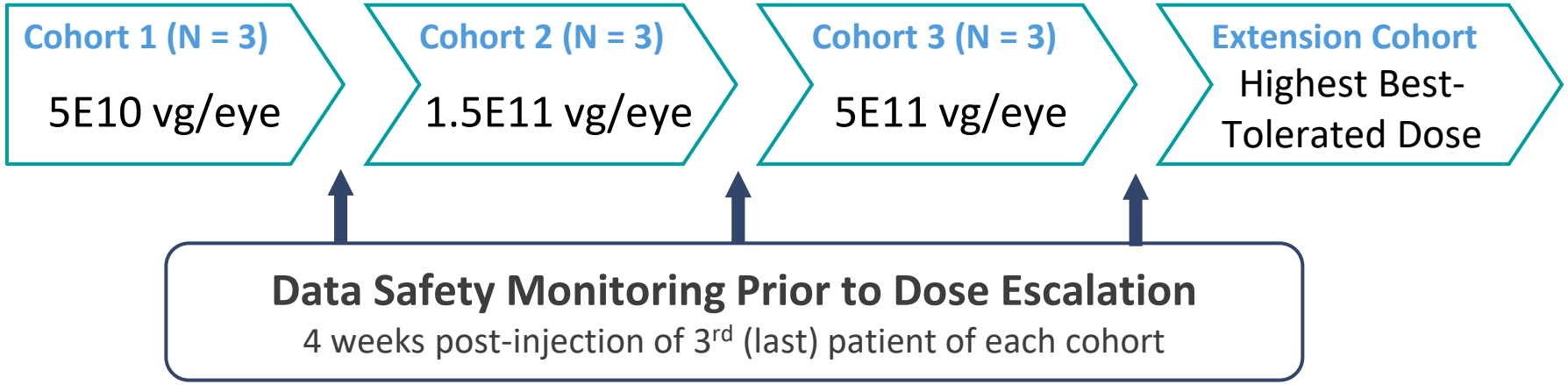
ADVERUM BIOTECHNOLOGIES

UPMC

PIONEER: First-in-human clinical trial of GS030 optogenetic therapy

- Phase I/IIa, open label, unmasked, non-randomized, dose-escalation study (NCT03326336)
- 3 sites: UK (Moorfields Eye Hospital, London), France (Hôpital des XV-XX, Paris), USA (University of Pittsburgh Medical Center)
- Study population: end-stage non-syndromic RP
- **Single intravitreal injection in the worst-affected eye**
- Primary endpoint: SAFETY and TOLERABILITY at Year 1
- Secondary endpoints: visual function, orientation and mobility, OCT, quality of life, immune response

Dose Escalation



vg: viral genomes

PIONEER: Nine patients treated with combined therapy GS030

Recruitment update:

- First cohort of 3 patients was injected with lowest dose (5E10 vg/eye) as of March 2019.
- Second cohort of 3 patients was injected with medium dose (1.5E11 vg/eye) as of February 2020.
- Third cohort of 3 patients was injected with highest dose (5E11 vg/eye) as of June 2021.
  - ➢ Completion of extension cohort planned before end of 2021.

First use of GS030 goggles post-injection was performed 8 weeks later, at hospital under medical supervision.

Combined therapy is well tolerated up to 2.5 years after IVT:

- No adverse events leading to study discontinuation
- Most common ocular adverse event : anterior chamber or intermediate intraocular inflammation responsive to corticosteroid treatment (5/9 subjects)
- No systemic issue

Case report published in *Nature Medicine* :
Partial recovery of visual function in a blind RP patient after optogenetic treatment

Credits: Sahel *et al., Nature Medicine*

Following optogenetic therapy, a 58-year-old patient with a genetic form of blindness was able to detect cups on a table.

A 58-year-old blind patient:

- Diagnosed with RP 40 years ago
- Had light perception when enrolled in the study
- Partially regained vision after GS030 optogenetic therapy:
  - » Could **locate and count objects** on a table
  - » Could **identify crosswalks** in the street

Available on www.gensight-biologics.com:

✓ Video of the patient performing the tests

✓ Interview of the patient

Credits: Sahel *et al., Nature Medicine*

The experimental set-up where the patient was asked to say whether the cup was present on the table. Behavioral responses and brain activity were recorded simultaneously during this test.

➢ Key milestone on the path to restore vision

Sahel J.A. *et al.*, ***Nature Medicine*, May 2021**

https://www.nature.com/articles/s41591-021-01351-4

IOB Institute of Molecular and Clinical Ophthalmology Basel

GenSight BIOLOGICS

University of Pittsburgh

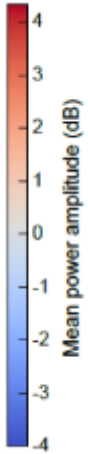
INSTITUT DE LA VISION

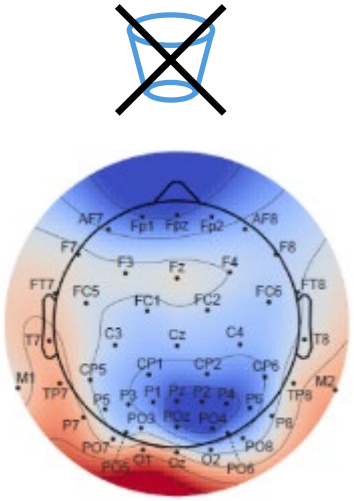
Case report published in *Nature Medicine* :

Partial recovery of visual function in a blind RP patient after optogenetic treatment

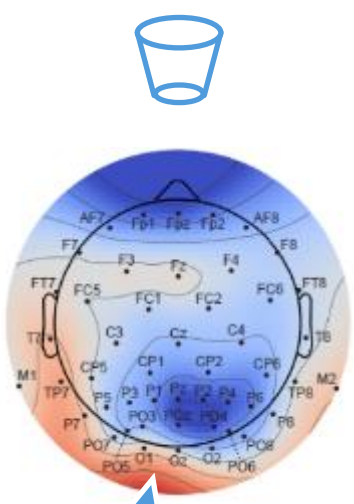
Brain activity was recorded during behavioral test:

- Eyes open
- Stimulation with goggles
- **No object** on table

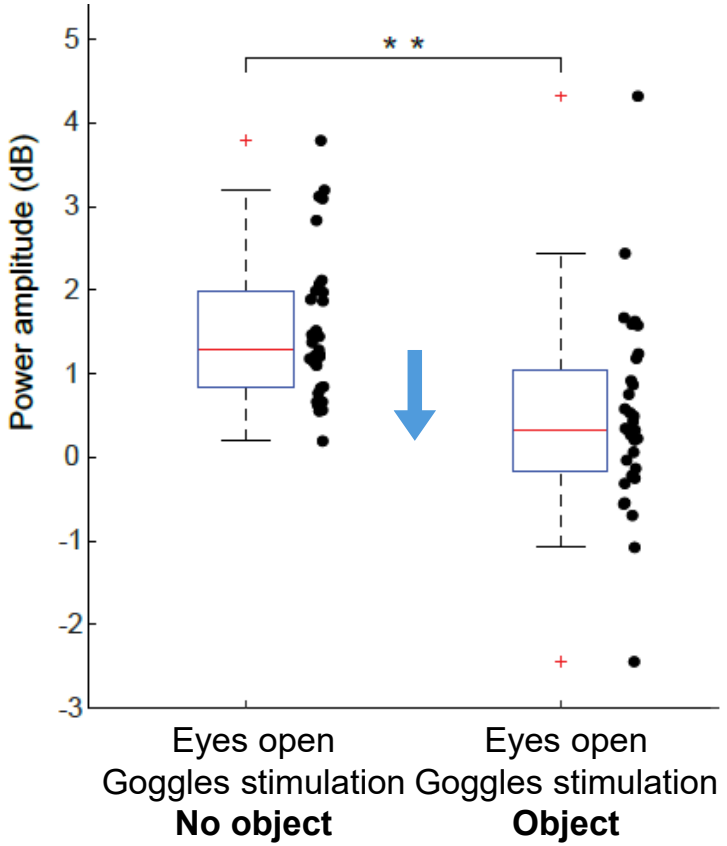




- Eyes open
- Stimulation with goggles
- **Object** on table



Significant **power decrease / desynchronization** of occipital 14-Hz alpha oscillations



Credits: Sahel *et al.*, *Nature Medicine*

https://www.nature.com/articles/s41591-021-01351-4

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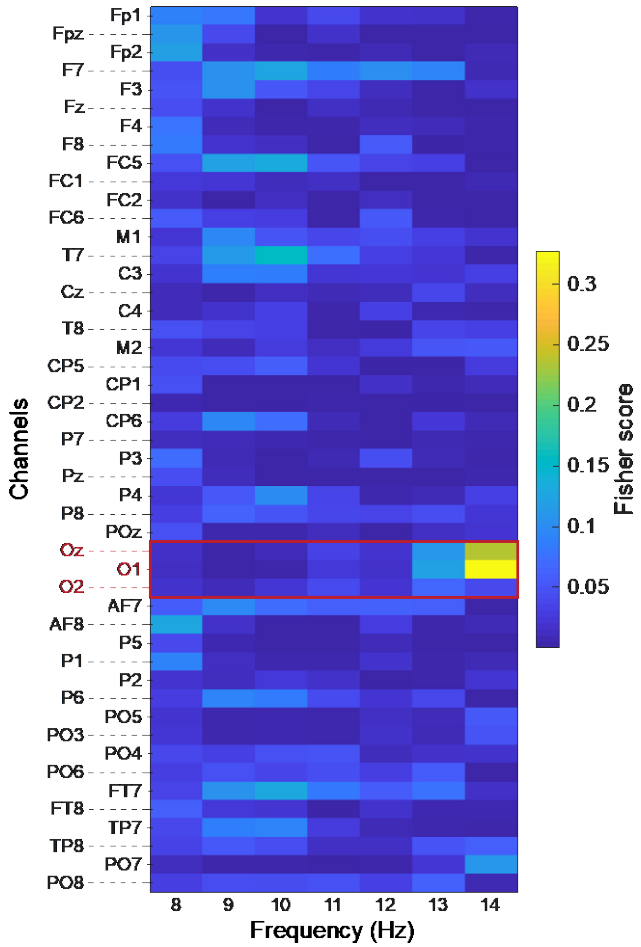
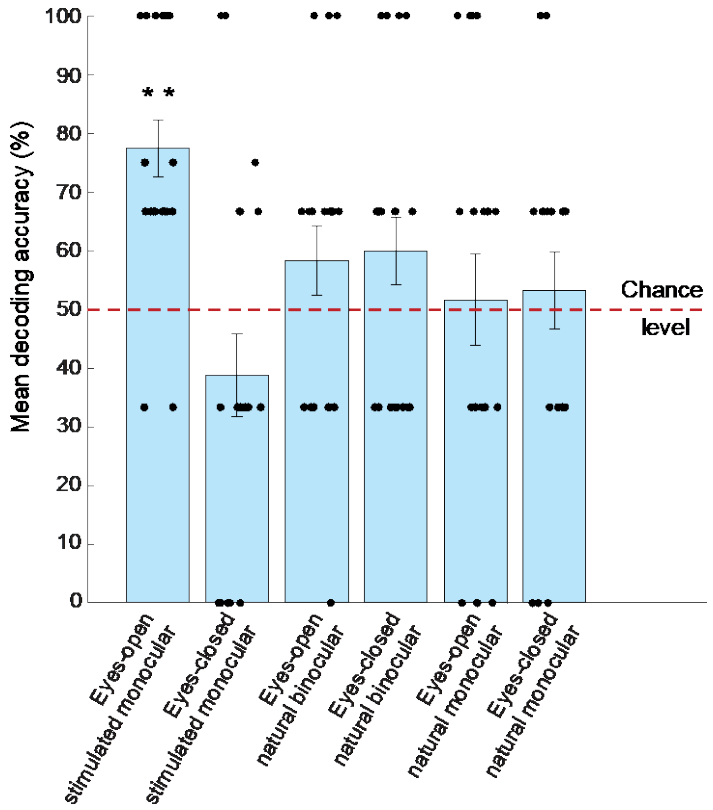
Activity in the visual cortex predicts the presence of visual objects





Interim results of PIONEER trial

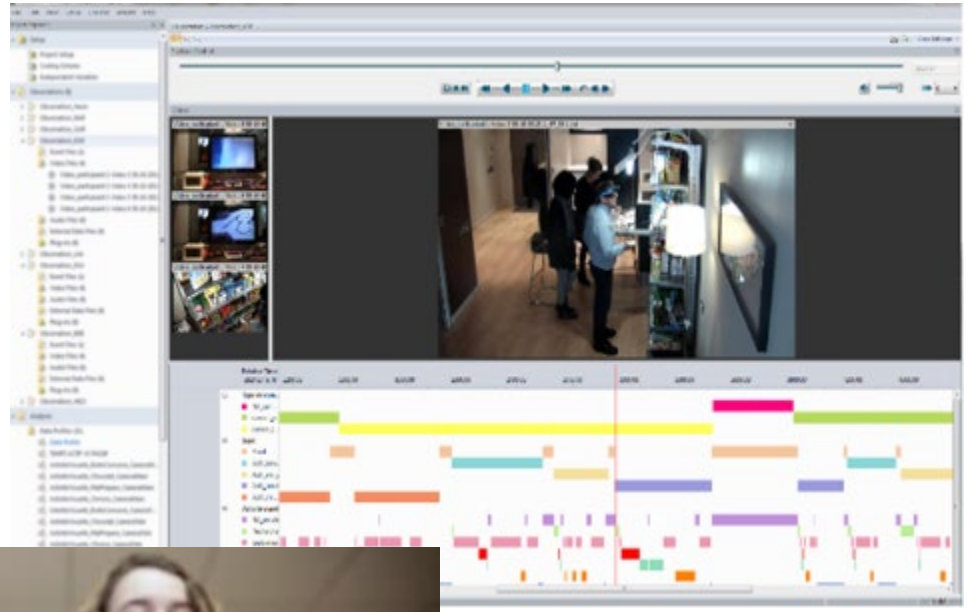
- Patients generally tolerate the light projected by the goggles, most patients tolerate high intensities well
- Clinical site in France reports visual improvement after training in real-life conditions (Sahel *et al.* 2021, *Nature Medicine*)
- Some patients in France and US are now able to come for follow-up and training
- New tests have been implemented and existing tests have been modified to avoid ceiling/flooring effects, and to detect improvements observed in real-world scenarios.
- Cohort 3 (highest dose of gene therapy):
  - First patient treated 1 year ago
  - The other 2 patients treated in June 2021 have not been evaluated after injection yet.

The implications of multisensory impairment

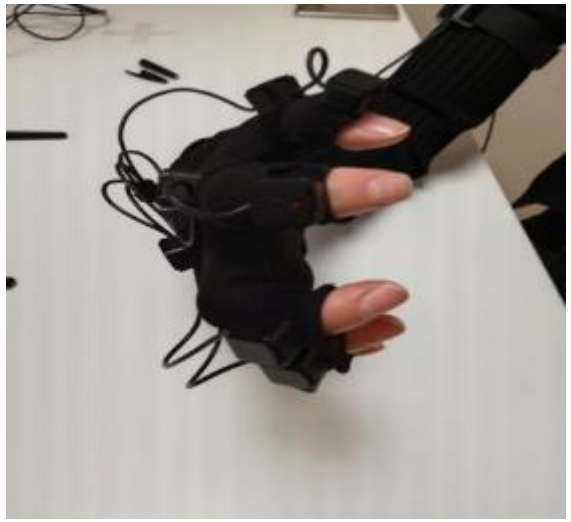
- Communication issues
- Impact of visual loss on balance
- Holistic care

Homelab

- Laboratory apartment of 45 m² which reproduces a real residential environment
- Equipped with various monitoring and recording systems



Example : Oculo-manual coordination



• Choice of task => the loss of the central visual field due to AMD reduces the ability to plan the trajectory of the hand and the anticipation of the pinch movement (oculo-manual coordination).

• Instructions : Locate and grasp the pen corresponding to the provided lid, put the lid on the pen and then place it in the pot.

• 8 trials
• Photopic condition (500 lux)
• Use of a glove equipped with inertial units
• Measurement of the kinematic parameters of the grasping phase (grasping speed, accuracy of the « pinch » movement, number of trajectory corrections,...)
• Observation of implemented strategies (sensory compensations)
• Subjective participant feedback for each trial

Artificial Street / Streetlab (1)

Indoor platform simulating urban environment

- ✓ Realistic street elements and dimensions (60 m^2)
- ✓ Controlled environment / reproducible experimental conditions
- ✓ Integrated measurement tools

Auditive and visual immersion

- ✓ Adjustable scenery
- ✓ 3-D sound system
- ✓ Light control (intensity, color)

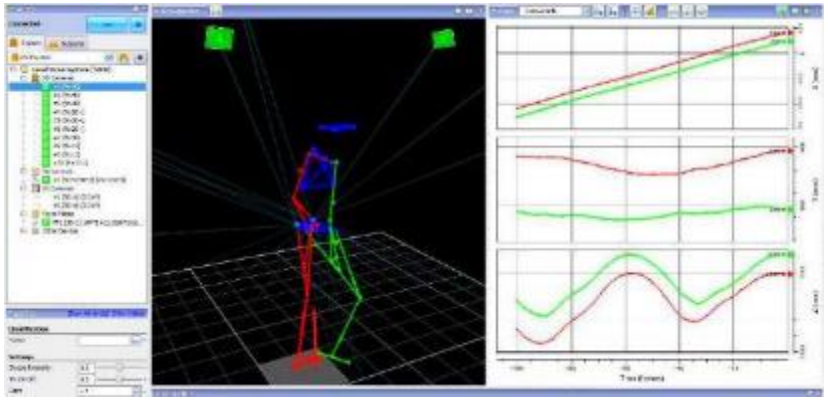
Artificial Street / Streetlab (2)

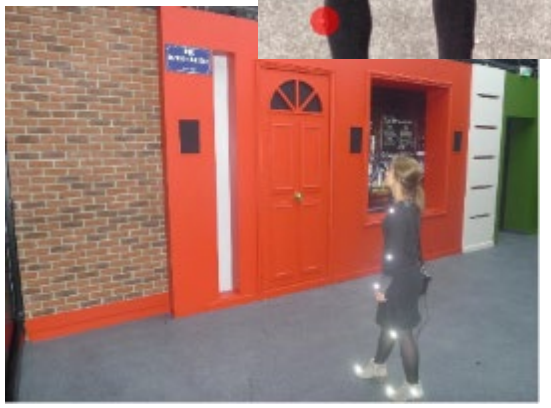
Behavioral recording

- ✓ Motion capture system (Vicon©) with passive markers
- ✓ Inertial sensors
- ✓ Eye-tracker
- ✓ Surveillance cameras

Control room

- ✓ Monitoring and recording
- ✓ Post-processing

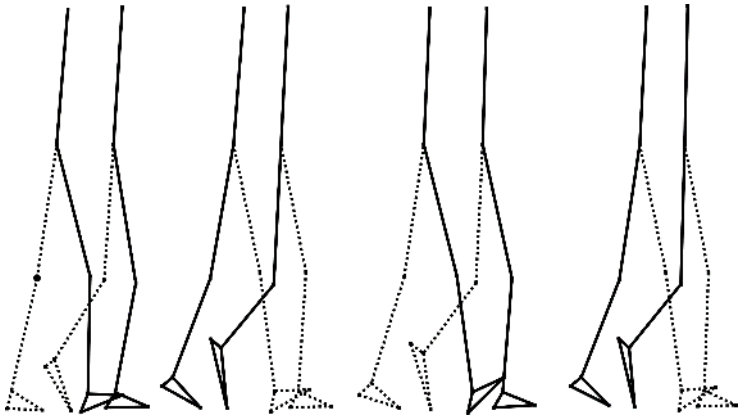




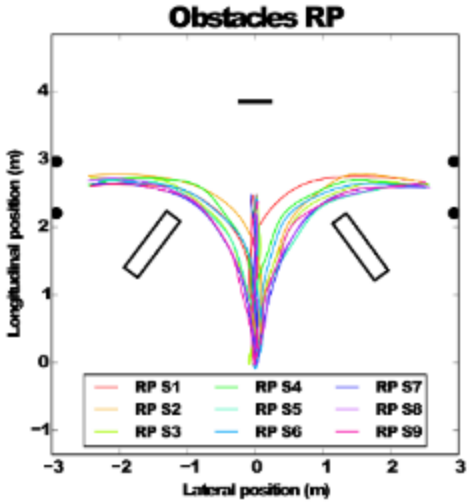
Objective behavioral measurements

Gait analysis allows measure and analysis

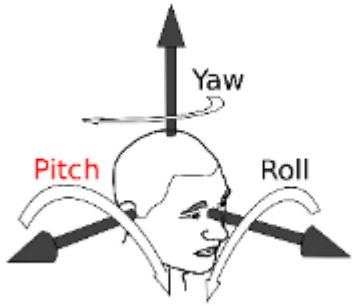
- ✓Movement patterns
- ✓Kinematics and kinetics
- ✓Forces produced by movements

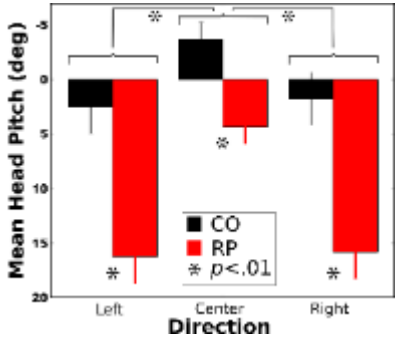


Ex.1: **Walking cycle** affected by:
- aging (*e.g.* shorter stride length)
- low-vision (*e.g.* longer stance duration)



Ex.2: **Trajectory** variability modified in « tunnel vision » RP patients



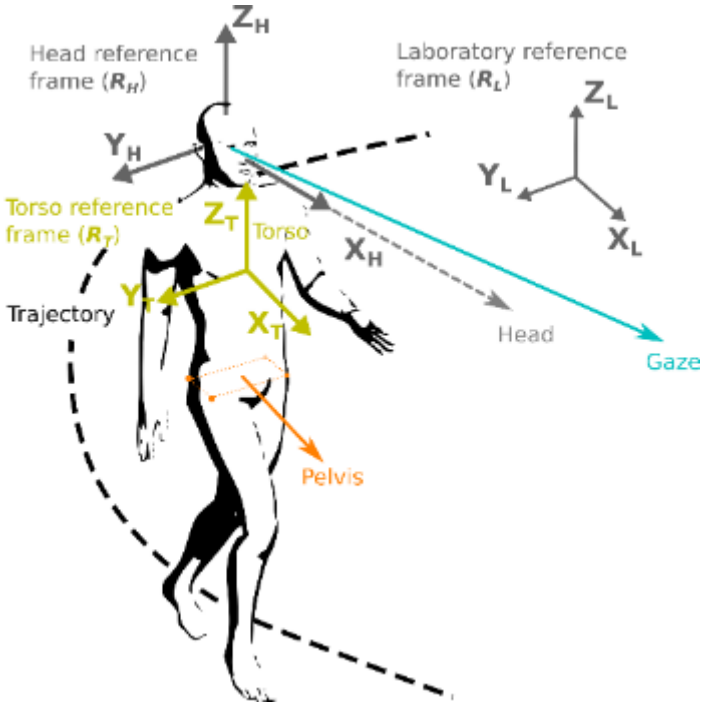


Ex.3: **Head direction** modified in RP patients

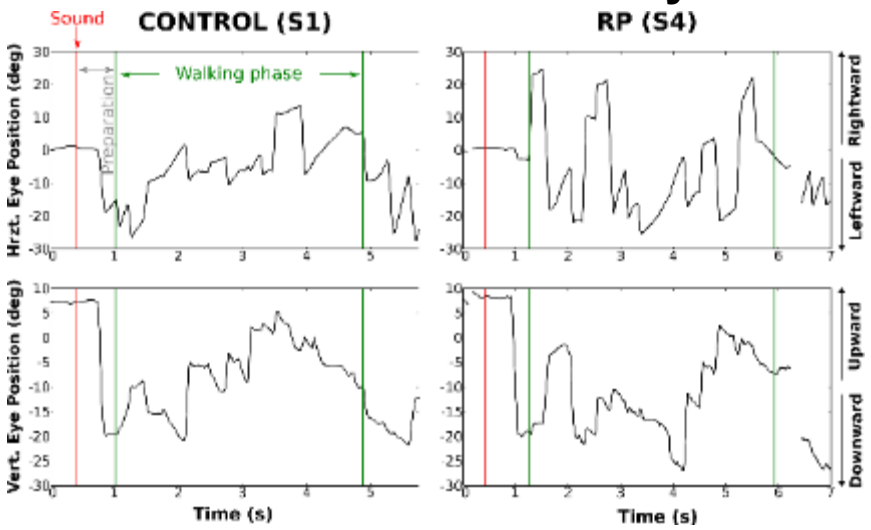
Objective behavioral measurements

Gaze behavior (head + eye orientation)

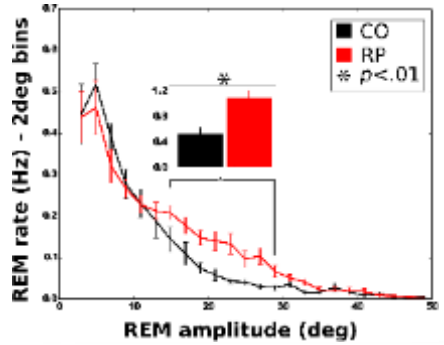
- ✓fixations / saccades (#, amplitude...)
- ✓Eye-head coordination (*e.g.* VOR gain)
- ✓Fixation location
- ✓Gaze sampling strategy (adaptation)



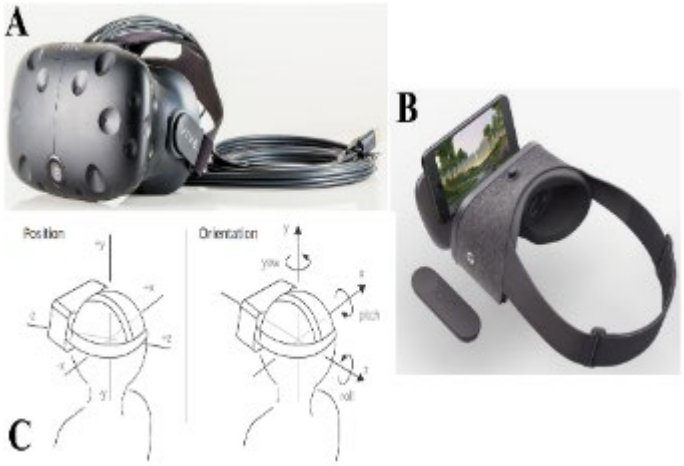
***Ex.1:* Rotations of the eye**



***Ex.2:* Saccade amplitude**



Our approach



Develop:

- Set of standardised tasks inspired by daily life situations
- In controlled **real and virtual environments**
  - ⇾ immersive head mounted display (immersion in a complex controlled world)
  - ⇾ cutting edge motion capture tools (measure sensorimotor abilities)

Advantages:

- Reliable, robust, ergonomic, and can be rapidly deployed on a large scale
- Coupled with standardized tasks, ensure same experimental constraints for each patient and investigation center
- With virtual reality, possible to quantify the behaviour of patients in circumstances that are very difficult to evaluate in the real world

MOST VR MOST IRL

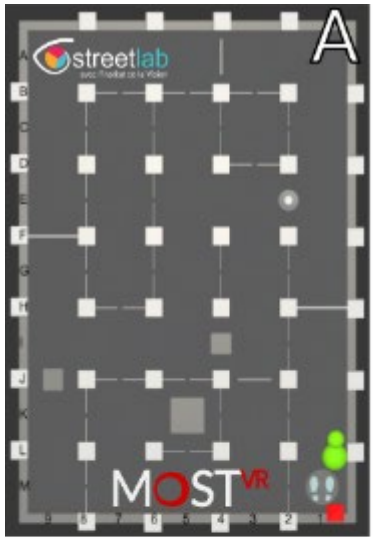
Mobility Standardized Test in Virtual Reality

A behavioral endpoint to assess the performance of patients with visual deficit in daily-life

(1) Task: natural walking in a maze

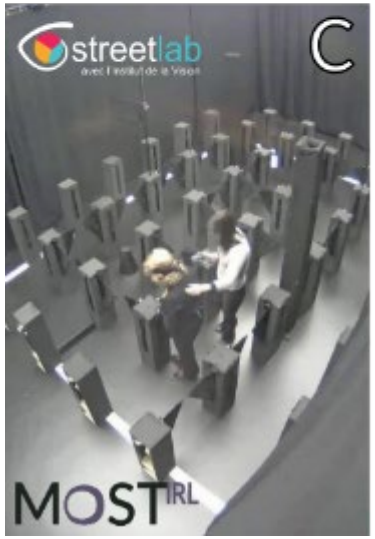
- No arrow to guide the path
- **Standardised routes** (difficulty, length...)
- **6 normalized light conditions**
- Custom VR contrast sensitivity (CS) test

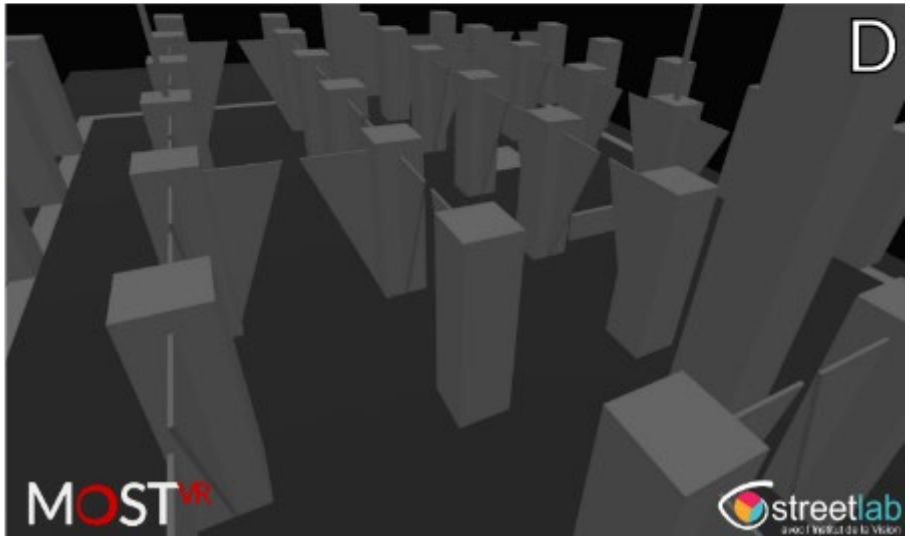
Exact same mobility test in **Virtual Reality** (actual walking) and IRL



(2) Multiple performance measurements

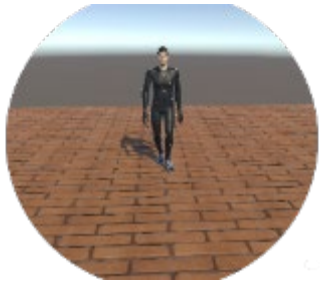
- Trial duration / walking speed
- Errors (collisions, interventions, obstacle avoidance)
- Head and feet movements
- Eye-tracking



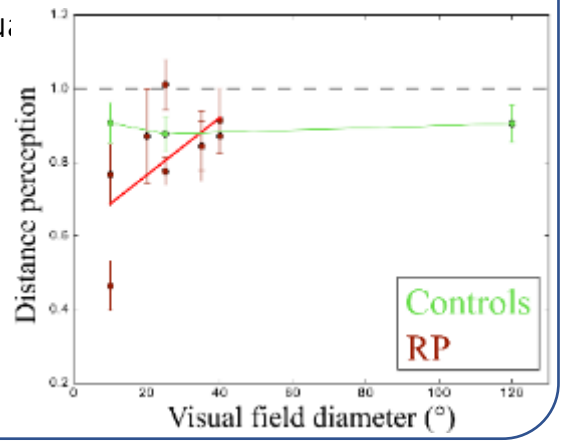


Development and Validation of Integrative Behavioral Tasks to Assess Visual Loss Impact on Daily Life of Usher Patients

Distance perception in virtual reality (VR)
10 RP, 4 Usher 1, 12 controls (simulated visu constriction)



Preliminary results



Movement perception in VR
10 RP, 4 Usher 1, 8 controls (with simulated VF constriction)

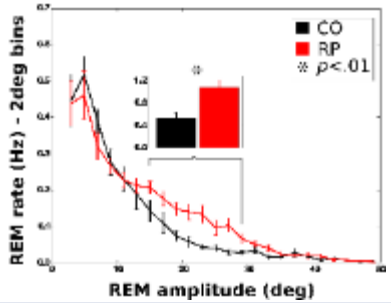
Time to collision with a pedestrian

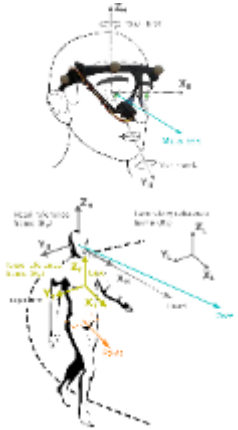
Time to collision with a car

Posture and mobility in real situations to identify **adaptive gaze strategies**

- 9 RP, 8 controls, with full body motion capture + eye movements
- **Goal directed locomotion and trajectory reproduction**

-> larger visual exploration
-> floor fixation to enhance spatial localisation
-> adaptive exploratory strategy





équilibrio

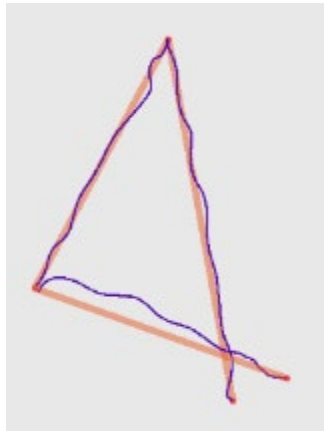
Development of serious mini-games for patients with vestibular disorder

- vestibulo-ocular reflex
- saccades
- inter-segmental coordination

Study with Institut Départemental Gustave Baguer (12 patients)

Reproducing paths with closed eyes

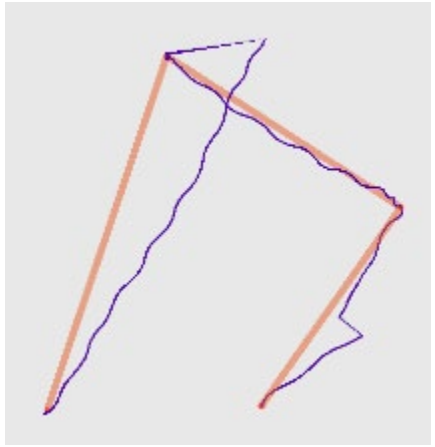
Usher type 2
Vestibule normal



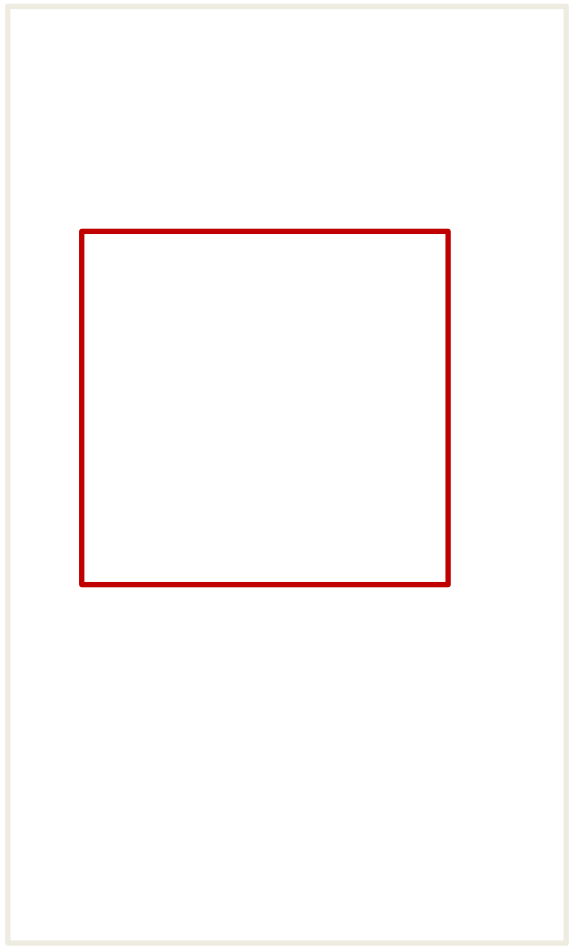
Open eyes

Closed eyes

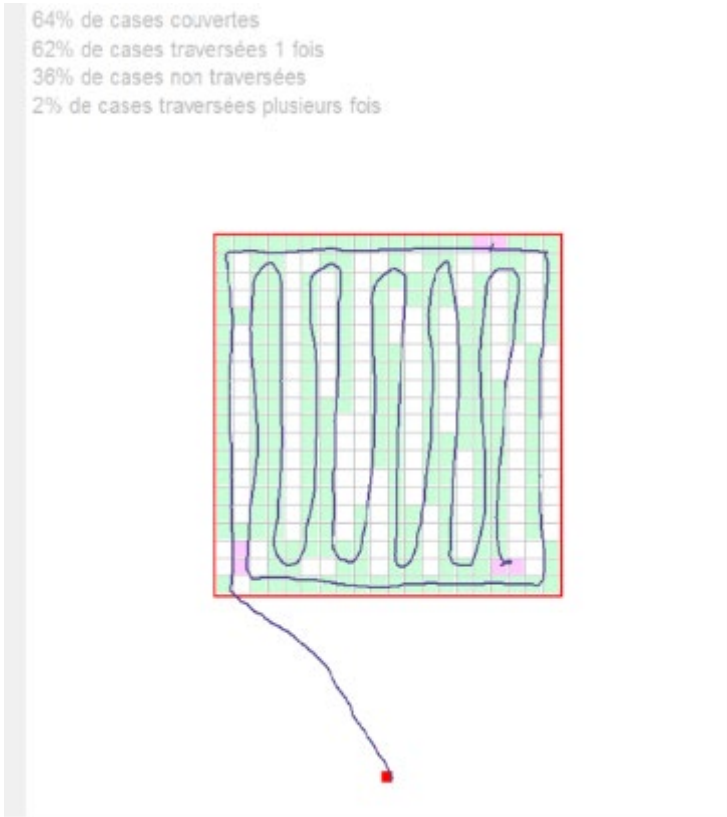
Usher type 1
Vestibule areflexia



Finding your keys : pathfinding (Subtest BADS)



Usher type 1

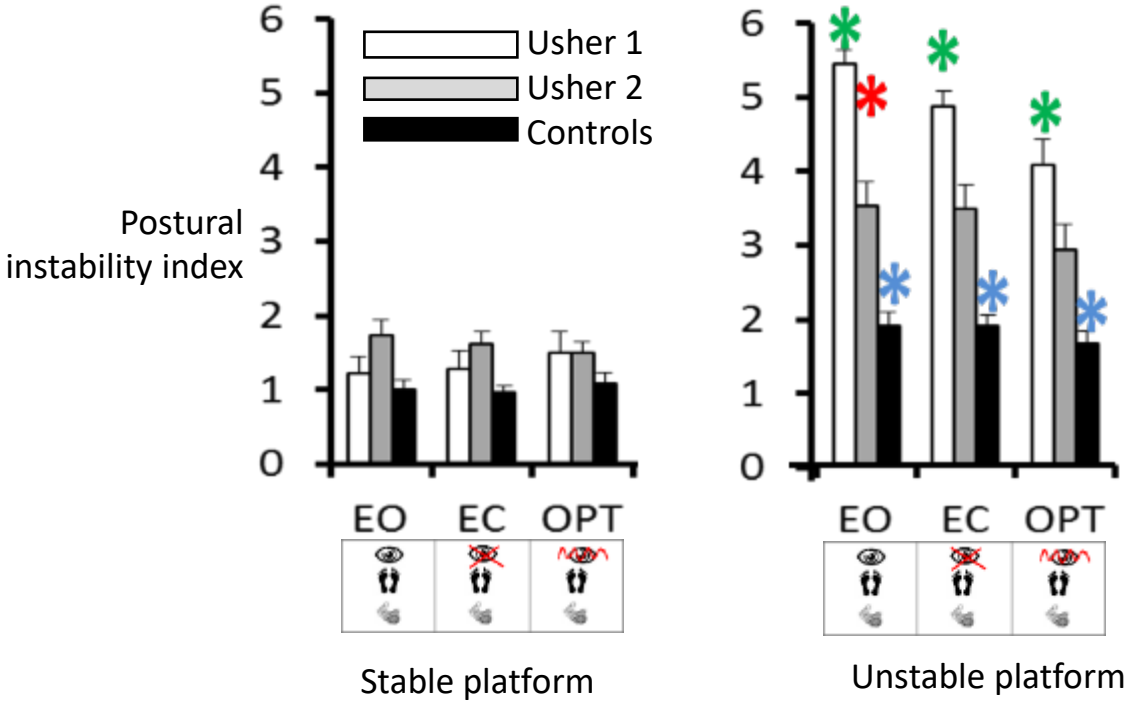


Usher type 2

Vestibular rehabilitation for Complete Bilateral Vestibular Loss (CBVL) for Usher patients (vibrotactile belts)

- Protocol under study to prove the effect of the belt by a double-masked trial before proposing the prolonged wearing of the prosthesis (Department of Epidemiology R Debré).

- Establishment of a database of Usher patients without vestibular deficit and with visual deficit to distinguish the effects of visual and vestibular deficits on responses with:
  - ✓ Multisensory Framiral Platform



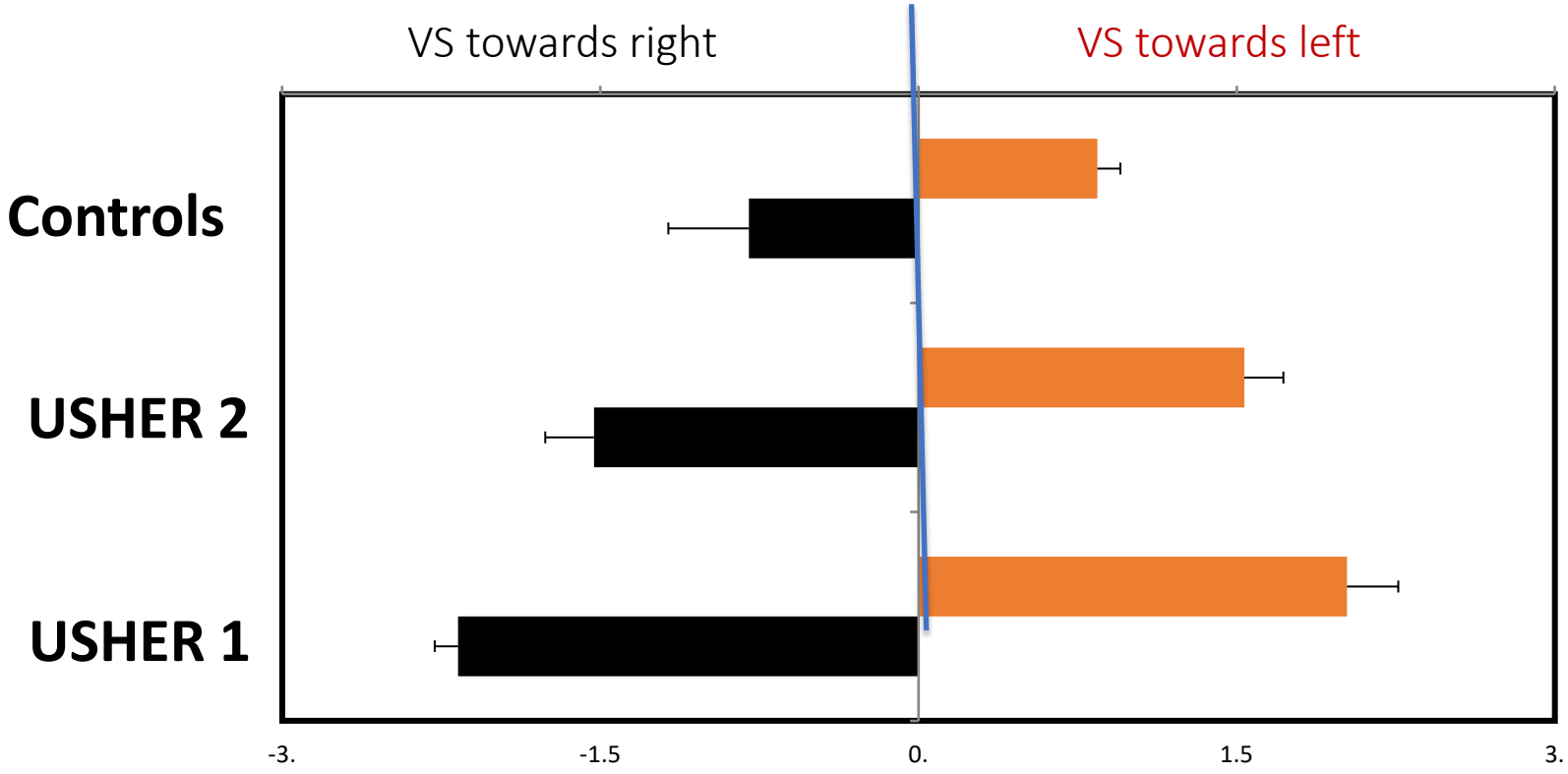
✱ USHER 1/USHER 2 significative difference
✱ USHER 1/Control significative difference
✱ USHER 2/Control significative difference

→ The PII can discriminate USHER 1, USHER 2 patients and controls

EO: Eyes opened; EC: Eyes closed; OPT: Optokinetic

Subjective visual vertical (VVS)

(Mesurée avec MTT Framiral)



Psychological, anthropological and sociological approaches

WP leaders : R. POTIER, S. MARLIN

Social science' research on deaf-blindness is an emerging field. The literature shows that deafblind people constitute a population at risk for mental health and emotional difficulties. This would be related to deafblindness' consequences on communication, access to information and mobility conditions. These difficulties lead to a social isolation's risk (or, conversely, over-protection) and loss of control (or fear of losing control) over the environment and events. Those consequences could be exacerbated by communication difficulties in care relationships, the fear that those relationships create misunderstandings or lead to interventions that do not correspond to patients' care or life choices.

Those studies generally focus on a "deaf-blind" population that is not well defined. They seldom articulate quantitative and qualitative approaches; and they often covers only a dozen individuals. There are also methodological pitfalls concerning interviews' accessibility. The literature also focuses, too often, on the negative aspects and does not explore enough resources and processes of resilience as well as new technologies' place or collective initiatives place. Moreover there is no social science study on Usher syndrome in France.

This human science research on Usher Syndrome focuses on the perception and self-presentation of Usher People, and the exploration of the links between identity processes and their life course, their professional choices, their communication practices, the social networks they invest as well as their displacement strategies, the use (or non-use) of the diversity of available technical aids (cane, braille, equipment, digital tools, etc.), their psychological coping strategies, and so one. This research crosses the analysis of the daily lives of patients, children and adults, with the analysis of the daily life of their loved ones and of the diversity of professionals interacting with them. **This research crosses sociological, psychological and medical perspectives and uses both qualitative and quantitative methods** (deep interviews, observations / summaries data sheets, questionnaire, medical data)

- ✓ **The work on the study design and on a psycho-social questionnaire, and on their accessibility for Usher Patients** (available in text contrast and in French Sign Language, conditions of an interview related to the diversity of patients profiles) are part of the research results. What is at stake is not only methodological, but ethical and theoretical issues.
- ✓ **The most advanced analysis** concerns data sheets and interviews with adult Usher patients, and with professionals.

There is a need to improve the conditions of diagnosis and medical monitoring with better information for non-specialists, teachers, occupational therapists, and medical staff on :

- Usher syndrome, and for non-specialist about the long-terme evolution and the great diversity of situations
- the concept of blindness from medical, legal and patient perspectives
- talking about genetics and syndrome transmission in a more neutral way (less negative)
- the fact that from patient perspectives there is not one but several diagnosis (evolution steps)
- discrimination and psychologic violence as a result of inaccurate anticipation of vision evolution by teachers, parents etc.
- the living conditions of these patients, in the diversity of their strategies
- the fact that French Sign Language and Tactile FSL are full national languages
- the profession of “intermediator” (deaf professionals of socio-linguistic mediation)
- the variability of what one defines as “autonomy” or “social integration”, and “quality of life”

Regarding the expectations of Usher patients about genetic research :

- ***A great majority want to halt the degenerative process and visual field loss***. Only a minority hope to restore the lost vision.
- ***The conditions, reliability and eligibility of therapies are not clear.*** *Information is not always available in FSL.*
- ***Restoring hearing is out of place for the overwhelming majority of people we met***. 1/2 are opposed. ¼ can't consider it without an "on/off" function and ¼ would accept it if associated with an intervention on the vision.

This first analysis also shows general needs for :

- ***More sharing of clinical knowledge between the professionals*** of different specialties (related to limits and recommendations criteria for cochlear implant, to sporting practices in prevention of patients balance disorders, etc.)
- ***Specialized psychological support of patients, in the long term, but also for their spouses or parents and siblings.*** Help is needed about the management of emotions and verbal aggression, the limits of a caregiver's posture, the way of expressing or taking into account difficulties which are not visible.
- ***Information on social aids and the facilitators the daily life related to deaf blindness***, in a neutral, complete and understandable comprehensive way (rights, help for commuting to work, trained daily activities support staff, etc.).
- ***Contacts with Usher peers-referrers*** to share common feelings, to project themselves on the evolution of their situation and identify the solutions associated for daily life and work.
- ***The need to support the use of the cane, braille, tactile FSL and haptic coordination when Usher people want to do it and not according to the level of visual complexity.*** Indeed, these usages are context-dependent (urban, social, lightening and familial context).

What is at stake is positive anticipation. It consists of exploring different benchmarks (including tactile ones), places and activities, gaining experience, becoming familiar with a variety of approaches, that can be used alternately, depending of location, time, fatigue or environment and not exclusively in extreme situations "last resort" (e.g. very complex environments, blindness).

Major gaps

- Relevant large animal models
- Large capacity vectors
- Better understanding of natural history and outcome measures
- Integrating the multisensory dimension
- Integrating patient perspectives at all stages