

# USHER 1b

## Works in progress and knowledge gaps

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# 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**

- natural history data
- Outcome measures
- PROs, PBTs

# 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¶**

```
1  ACGTATACGGGCTCCATCCTGGTGGCTGTGAACCCCTACCAGCTGCTCTC
   T Y T G S I L V A V N P Y Q L L S

51  CATCTACTCGCCAGAGCACATCCGCCAGTATACCAACAAGAAGATTGGGG
   I Y S P E H I R Q Y T N K K I G E

101 AGATGCCCCCCCACATCTTTGCCATTGCTGACAACCTGCTACTTCAACATG
    M P P H I F A I A D N C Y F N M

151 AAACGCAACAGCCGAGACCAGTGCTGCATCATCAG
    K R N S R D Q C C I I S
           ↑
           T
           ↓
        STOP
```

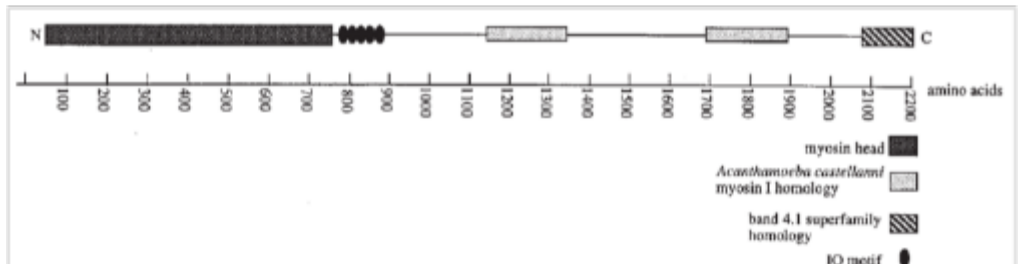
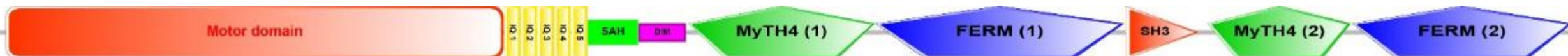


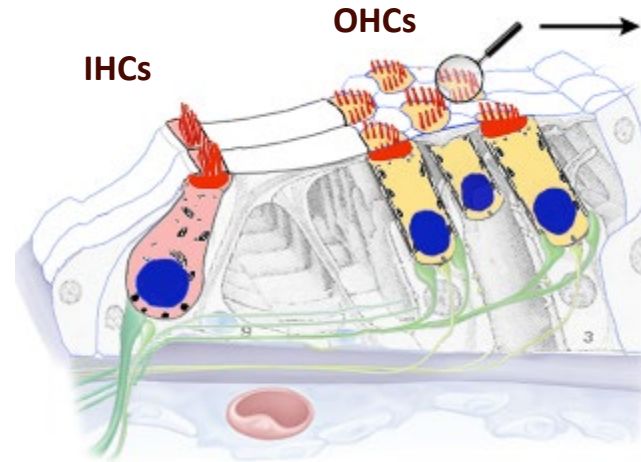
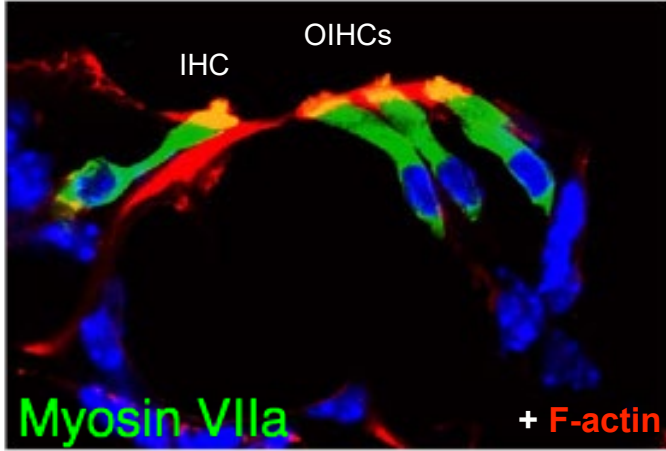
Fig. 3. Schematic representation of the myosin VIIA molecule.



# Cellular and subcellular targets of USH1B protein ?

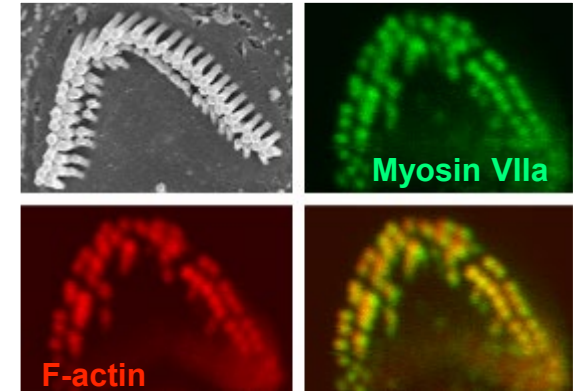
## ❖ Inner ear: the sensory hair cells & the mechano-sensitive hair bundles

Auditory hair cells



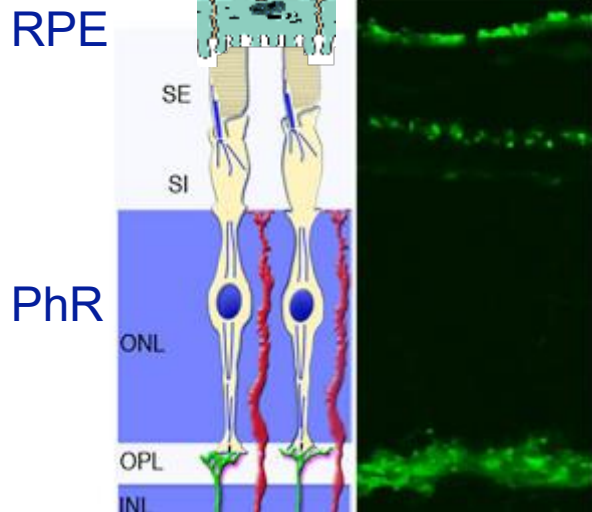
Auditory sensory organ: organ of Corti

Sound receptive-hair bundle

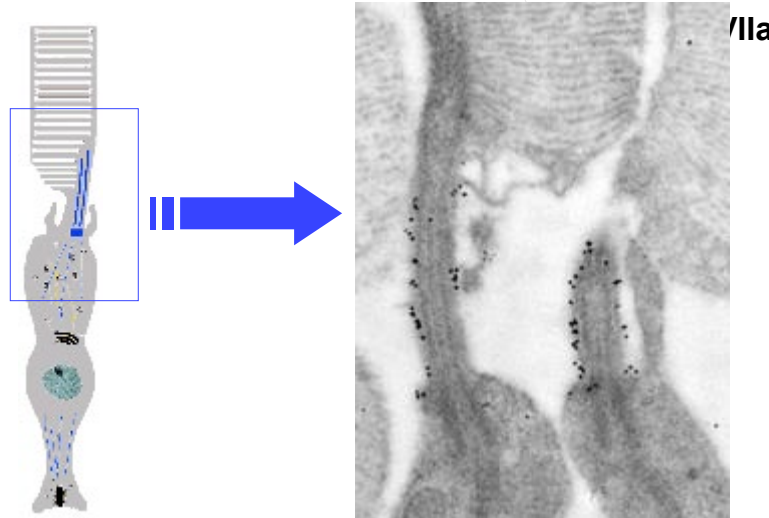


El-Amraoui A, et al. -> Petit C, HMG 1996

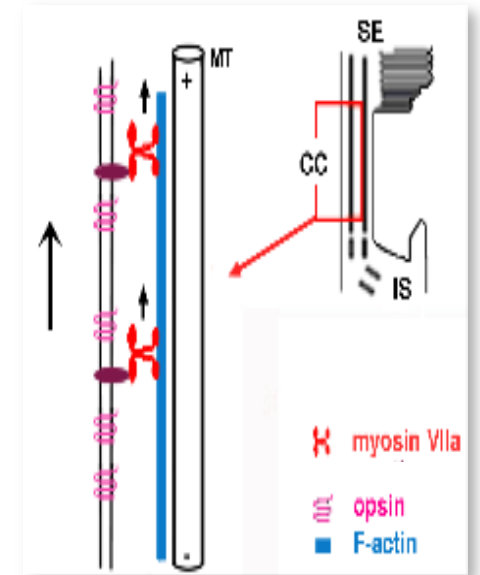
## ❖ Retina: Photoreceptors (PhR) & retinal pigment epithelial cells (RPE)



Reiners et al. 2003  
Liu X et al. 1997



Source:  
U. Wolfrum 2000

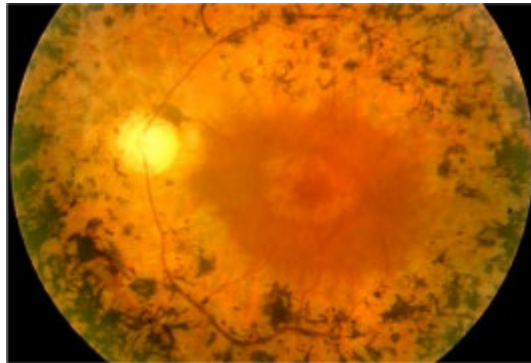


# Phenotype discrepancy between USH1 patients and related mouse models ?

- ❖ 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

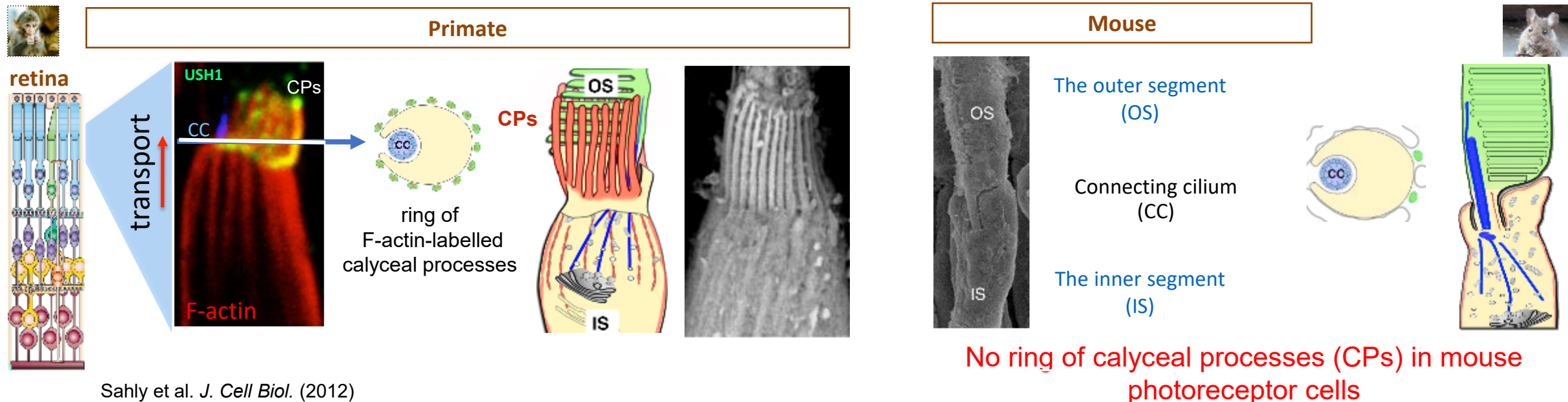


- ☀ No retinitis pigmentosa



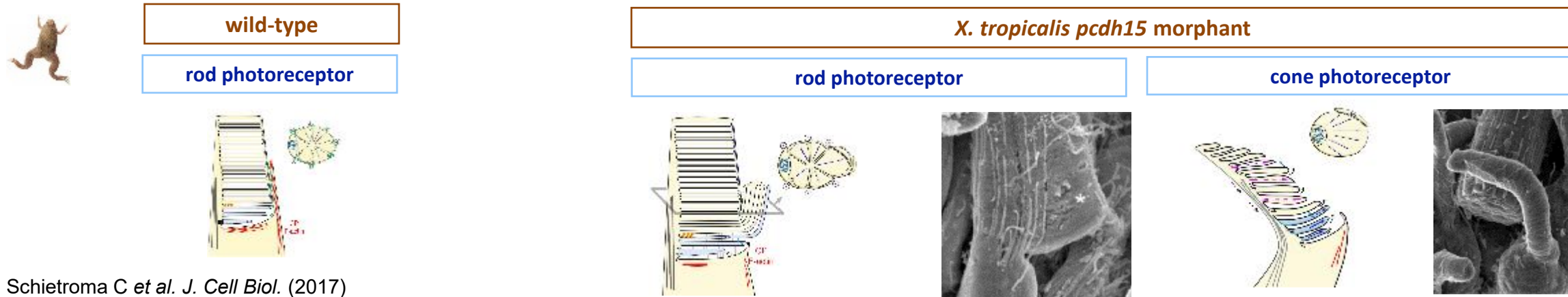
USH1 mouse models display no visual defects

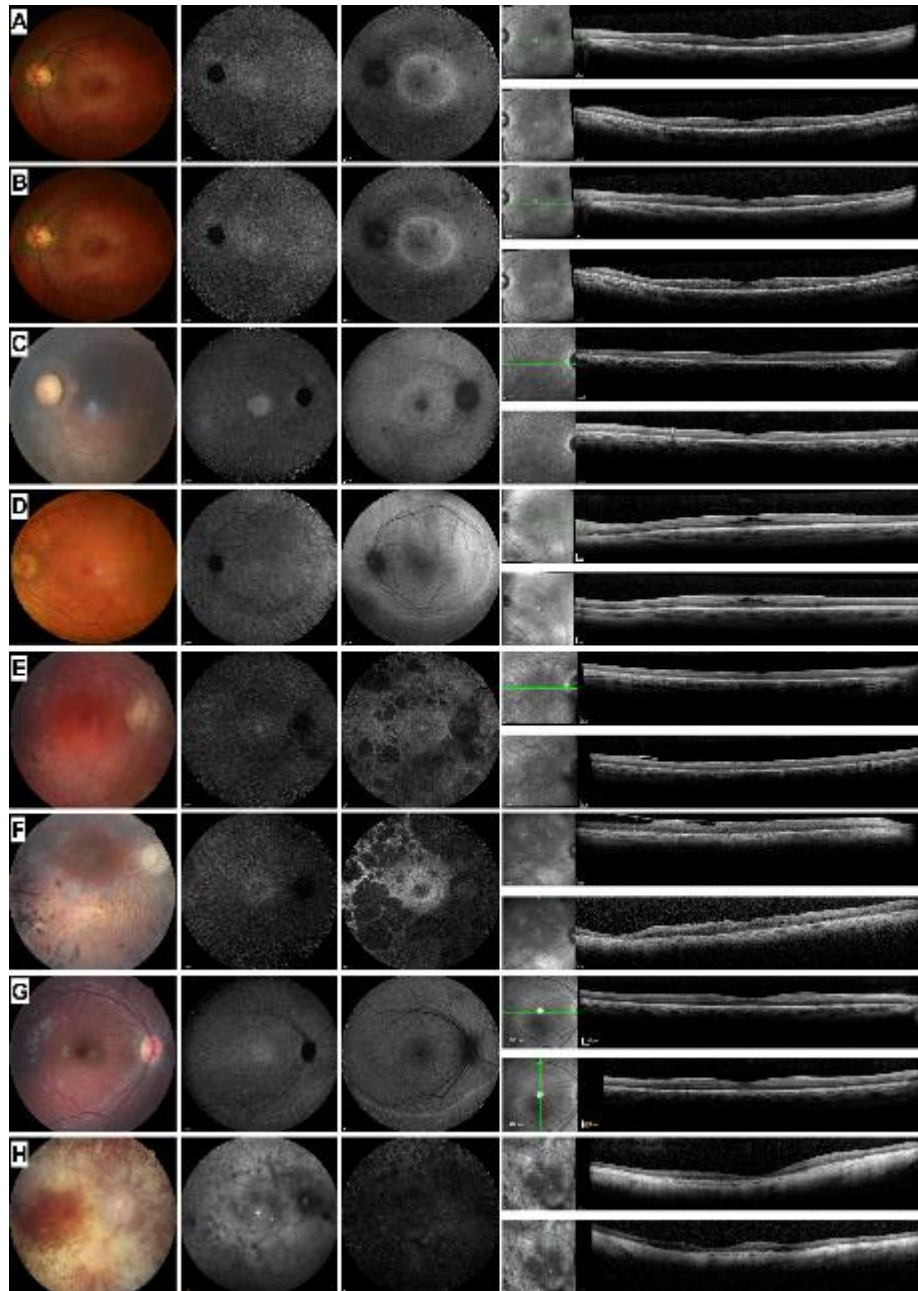
# Molecular and structural differences between mouse and primate photoreceptors



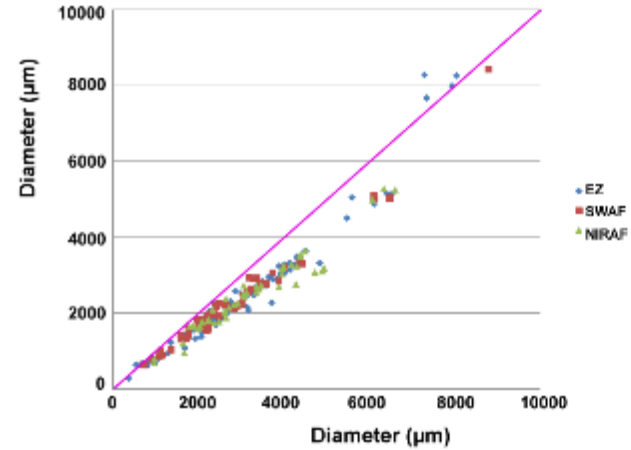
## ❖ Loss of USH1 function leads to defective calyceal processes & impaired outer segment disks morphogenesis

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

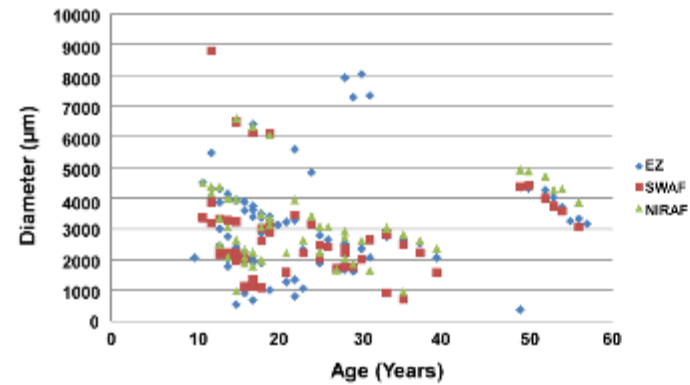




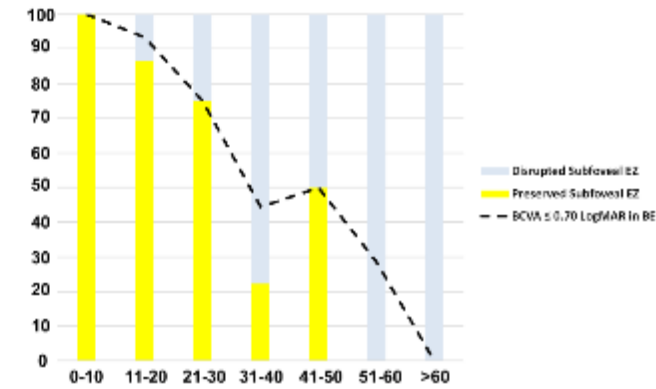
**A** Vertical vs. Horizontal Diameter of EZ, SWAF and NIRAF Measurements



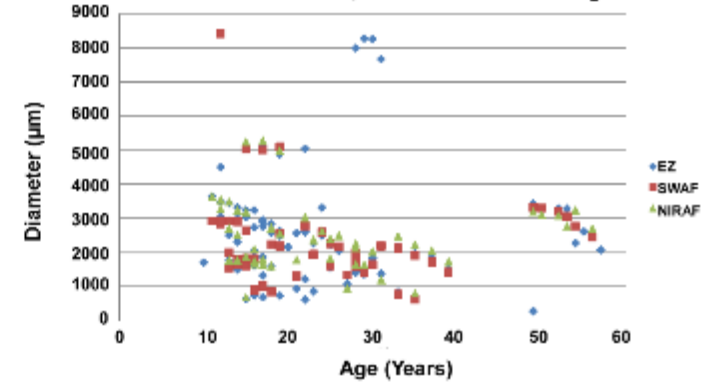
**B** Horizontal Diameter of EZ, SWAF and NIRAF vs. Age



**D**



**C** Vertical Diameter of EZ, SWAF and NIRAF vs. Age

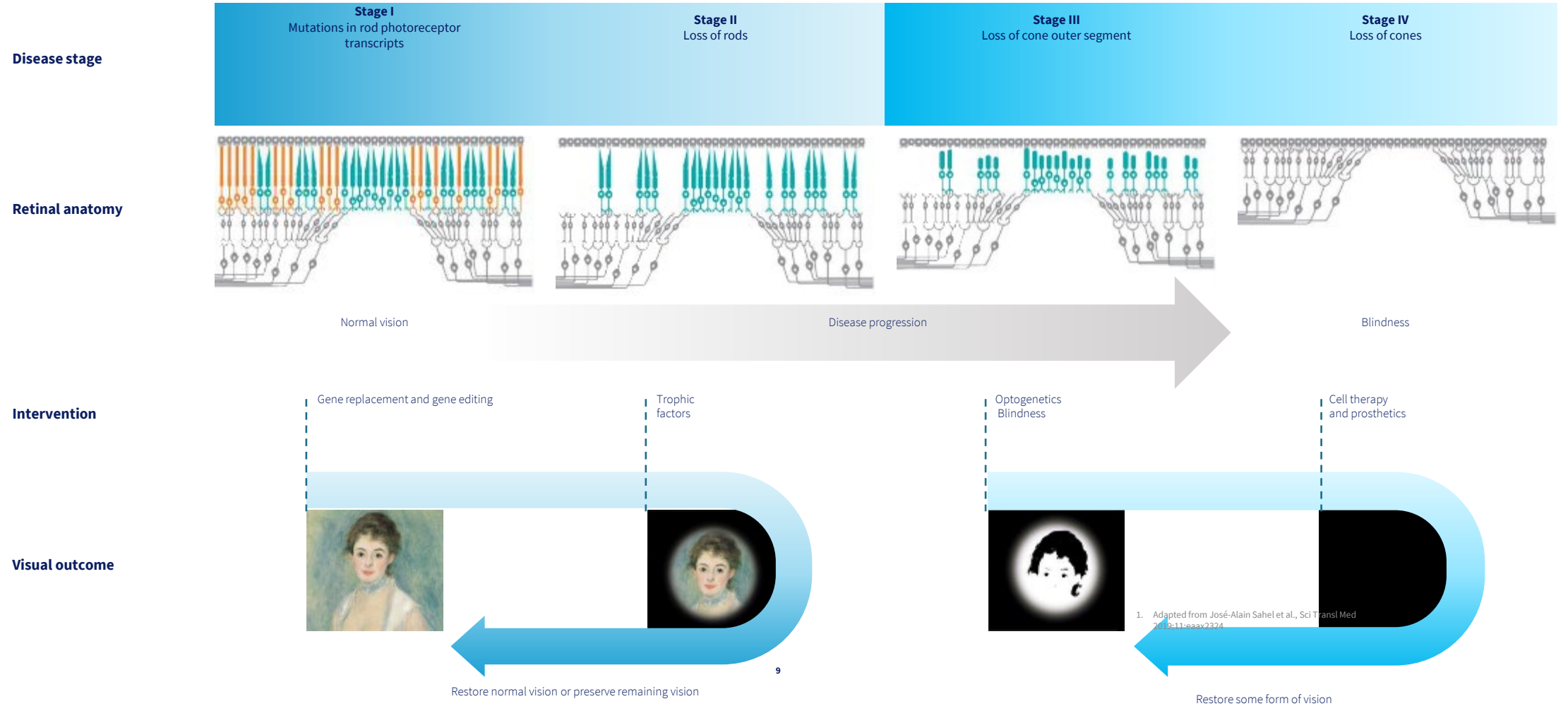


# Therapies in development

- **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



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

## USH1

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



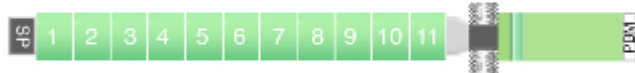
USH1C (*USH1C*, 11p15.1 - OMIM 605242) : harmonin



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



ORF = 6645 bp  
2215 aa, 254 kDa

ORF = 2697 bp  
899 aa, 98 kDa

ORF = 10 062 bp  
3354 aa, 369 kDa

ORF = 5865 bp  
1955 aa, 216 kDa

ORF = 1383 bp  
461 aa, 51 kDa

ORF = 561 bp  
187 aa, 21 kDa

## 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

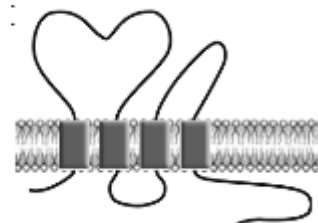
Long isoform (L)



ORF = 2721 bp  
907 aa, 96 kDa

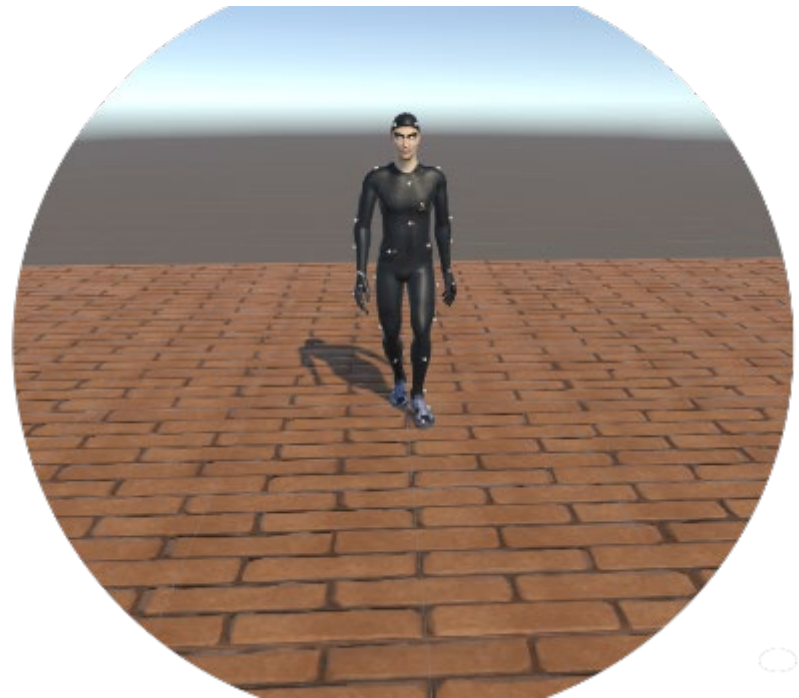
## USH3

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



Only 5 USH genes  
fit into a single AAV

- **The implications of multisensory impairment**
- Communication issues
- Impact of visual loss on balance
- Holistic care



# 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