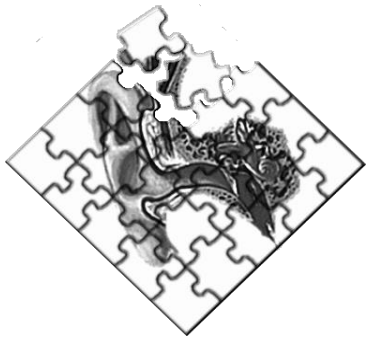
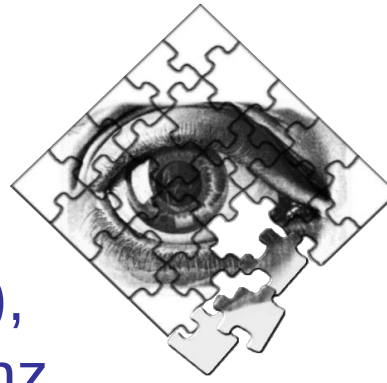
# Summary: Cell and Molecular Biology of the Usher Syndrome




**Uwe Wolfrum**

Molecular Cell Biology,
Institute of Molecular Physiology (IMP),
Johannes Gutenberg University of Mainz
wolfrum@uni-mainz.de

**USH2018**

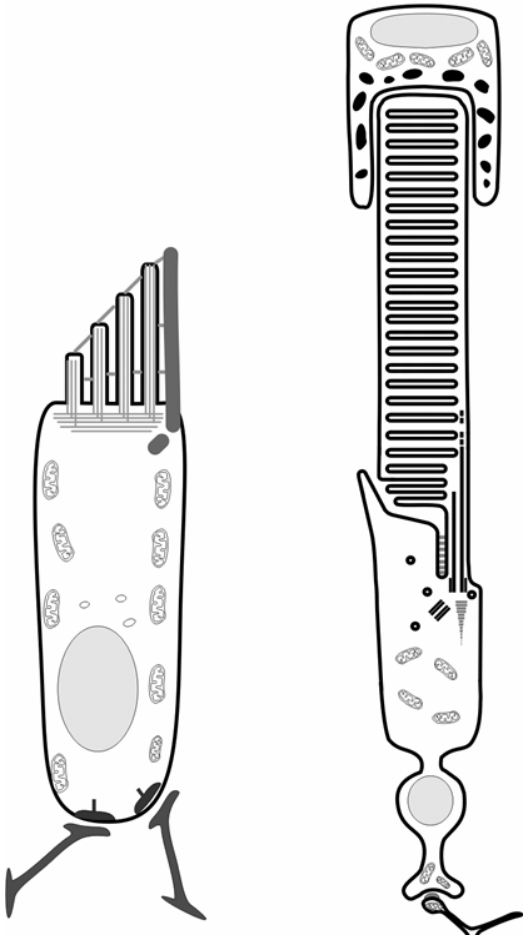
July 21, 2018

4th International Symposium on Usher Syndrome
USH 2018 – July 19-21, 2018 in Mainz, Germany

JG|U

# Human Usher syndrome (USH)

- **USH is the most common form of combined hereditary deaf-blindness.**
  **~ 1:10,000 to 1:6,000**
  - **Hearing impairment**
  - **Vestibular dysfunction**
  - **Vision loss – *Retinitis pigmentosa***
  - **Olfactory impairment ?**
- **USH is a complex disease:**
  **- 3 clinical types (USH1, USH2, USH3);**
  **- > 15 genetic subtypes.**
- **10 USH causing genes are identified, so far.**
- **USH proteins belong to diverse protein families**
  **molecular motors, cell adhesion &**
  **transmembrane molecules, scaffold proteins …**

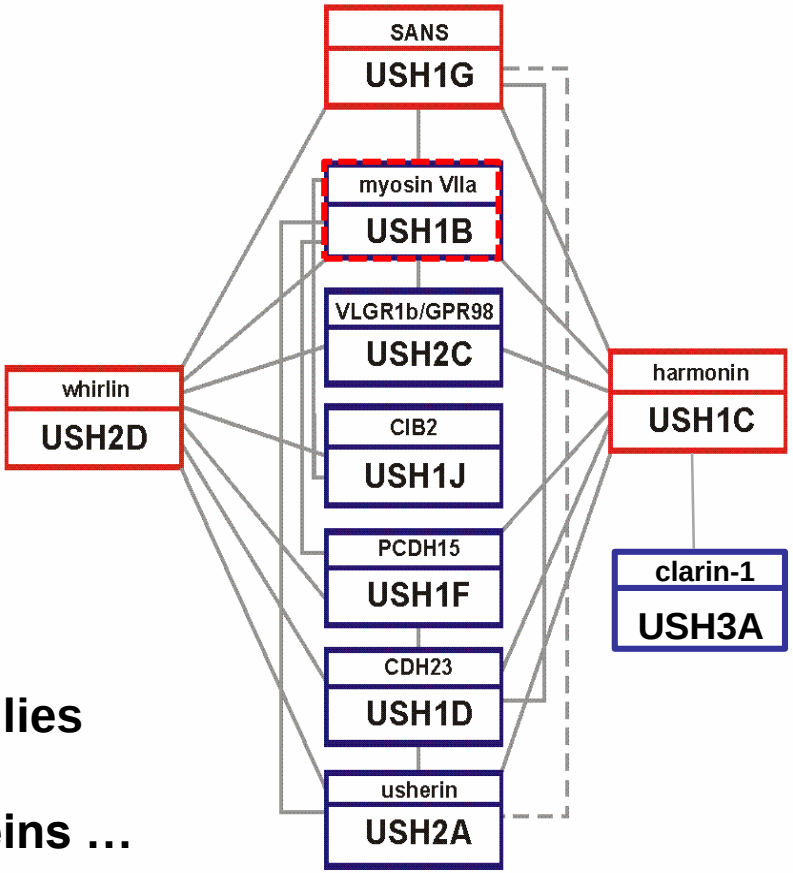


**Deciphering the molecular and cellular function of disease/USH molecules is essential for the development of an effective therapy.**

# Human Usher syndrome (USH)

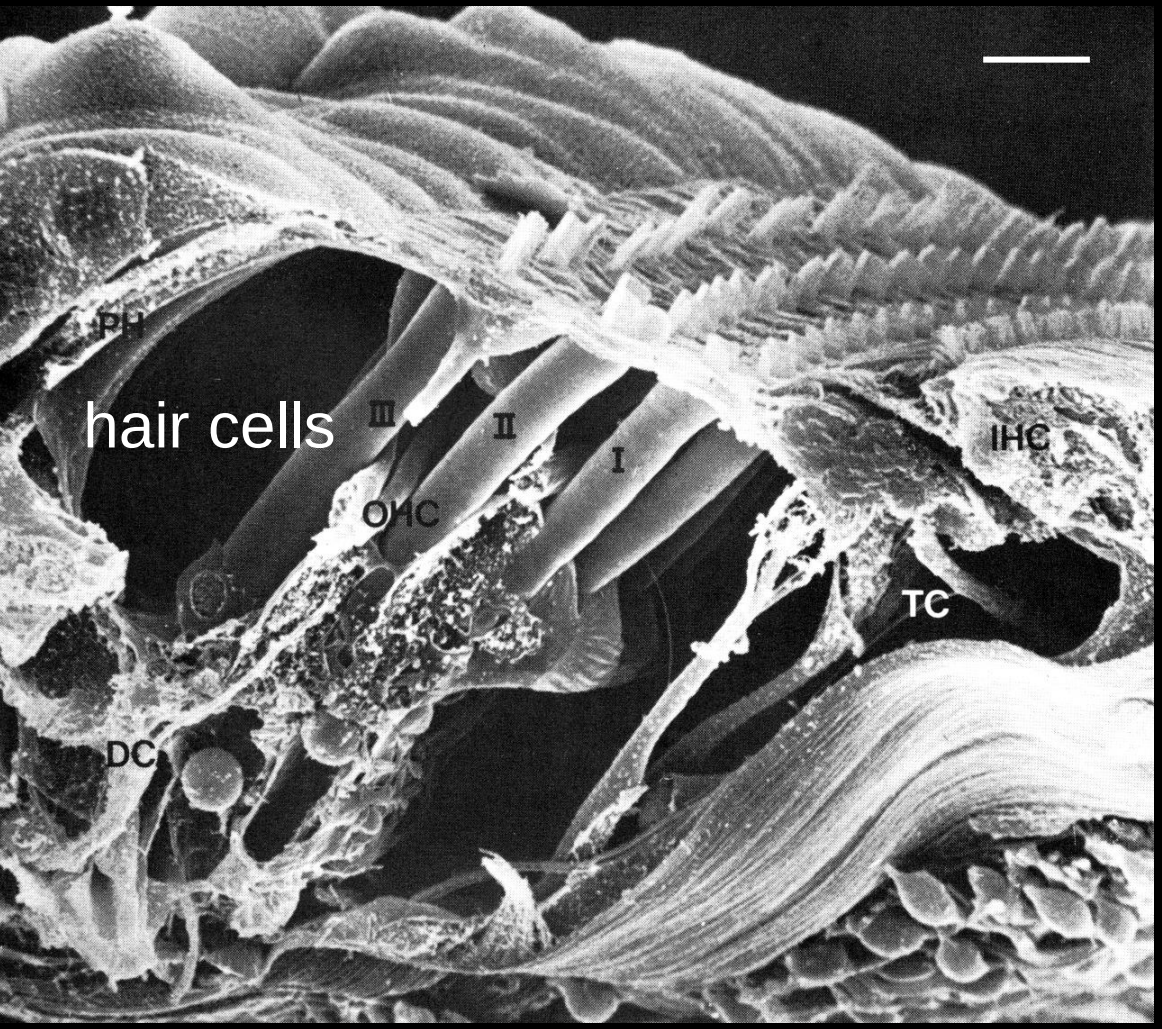
- **USH is the most common form of combined hereditary deaf-blindness.**
  **~ 1:10,000 to 1:6,000**
  - **Hearing impairment**
  - **Vestibular dysfunction**
  - **Vision loss – *Retinitis pigmentosa***
  - **Olfactory impairment ?**
- **USH is a complex disease:**
  **- 3 clinical types (USH1, USH2, USH3);**
  **- > 15 genetic subtypes.**
- **10 USH causing genes are identified, so far.**
- **USH proteins belong to diverse protein families**
  **molecular motors, cell adhesion &**
  **transmembrane molecules, scaffold proteins …**

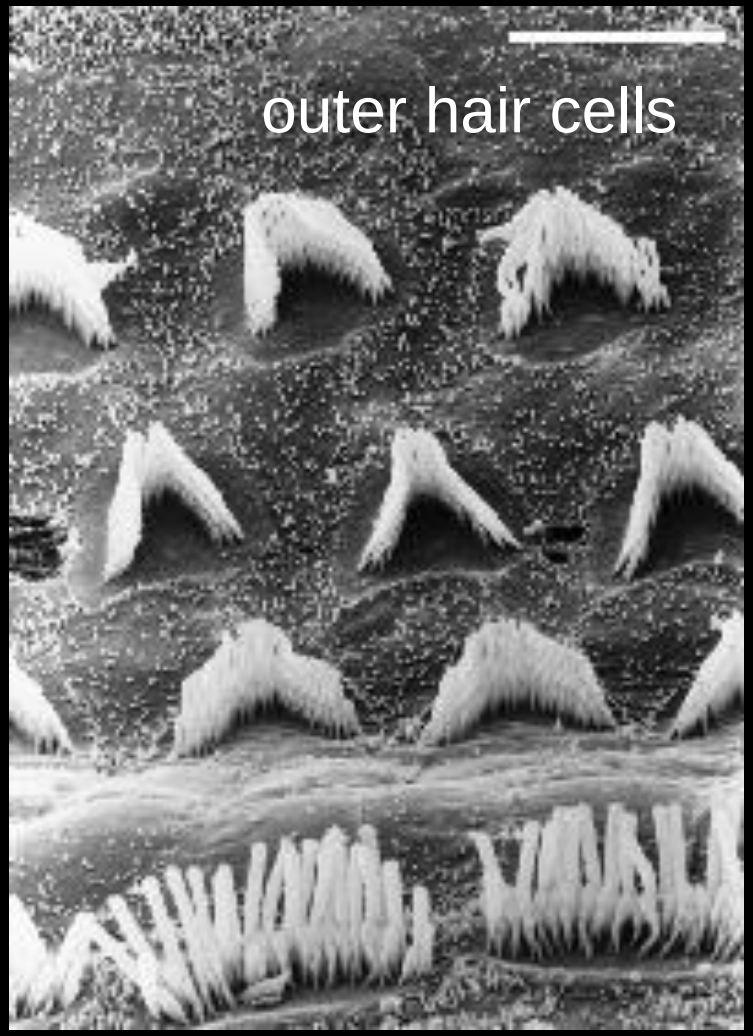
## USH protein network




All USH proteins are integrated into protein networks - the USH interactome.

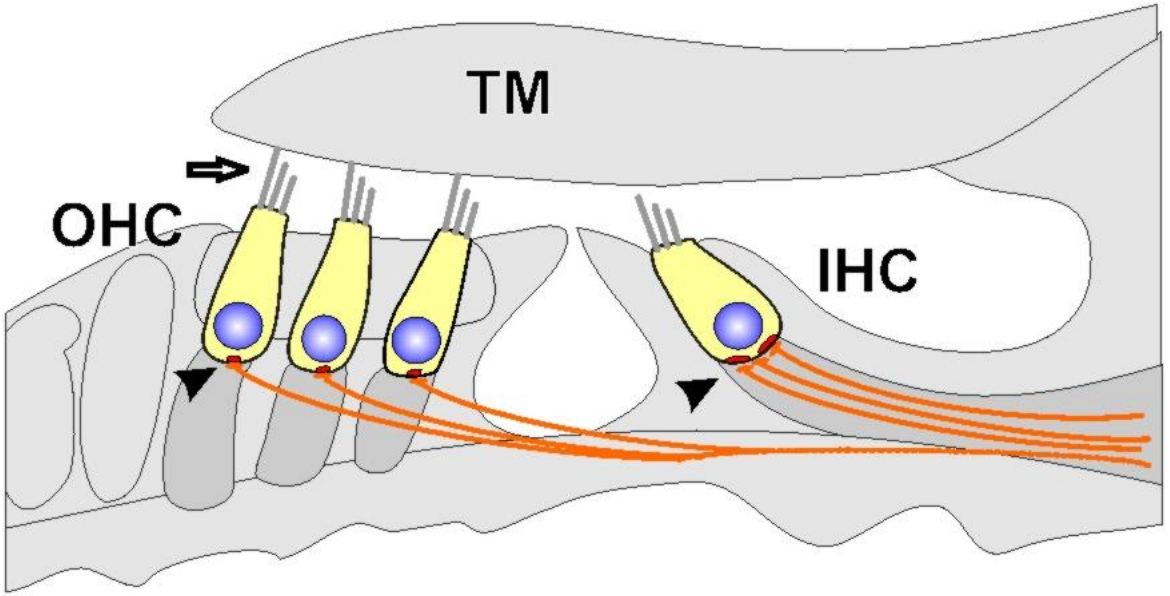
# Scanning electron microscopy of cochlear hair cells



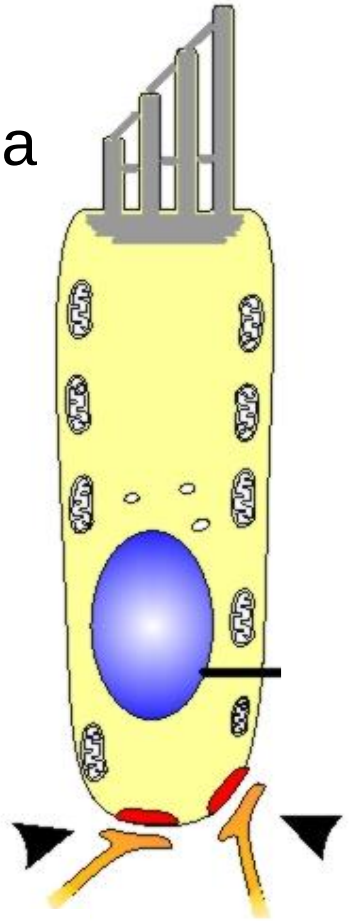
# Hair cells of the inner ear

## Organ of Corti




## Hair cell

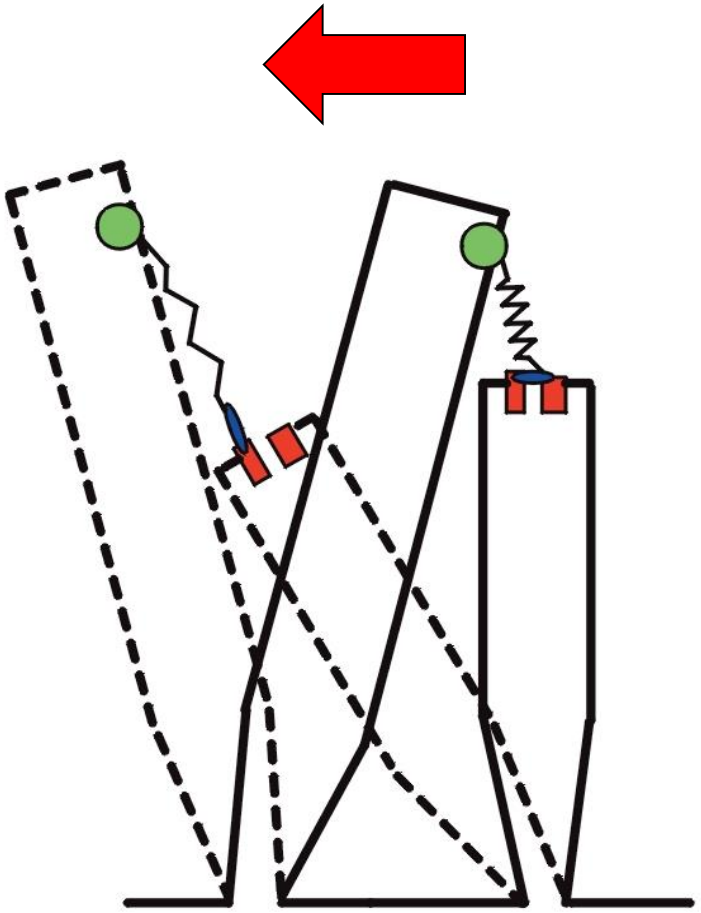
Stereocilia



Synapses

Reiners et al. HMG 2005

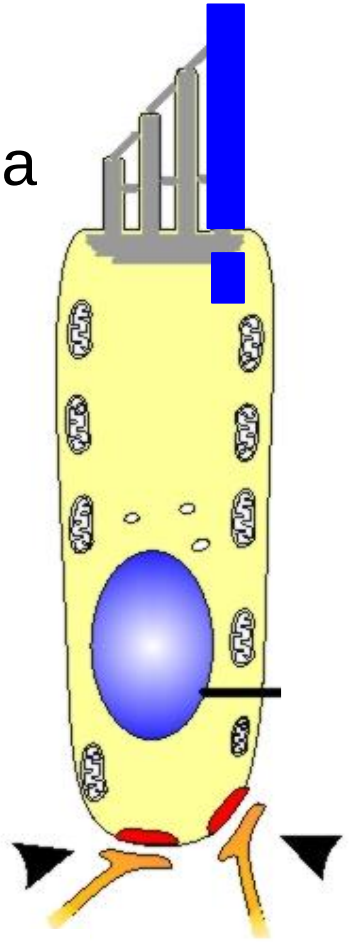
# Auditory hair cell function



Depolarization of hair cell

Hair cell

Stereocilia



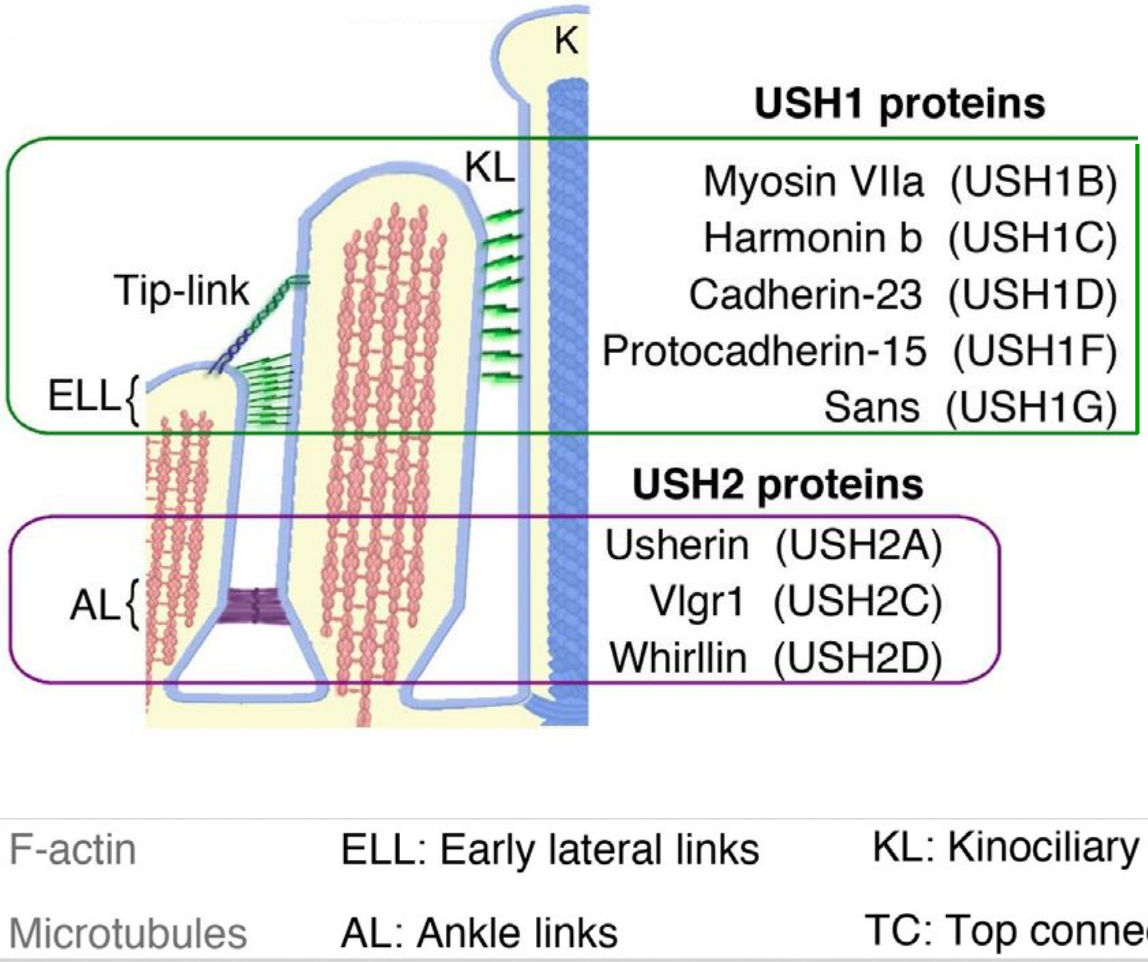
Synapses

Hearing

Reiners et al. HMG 2005

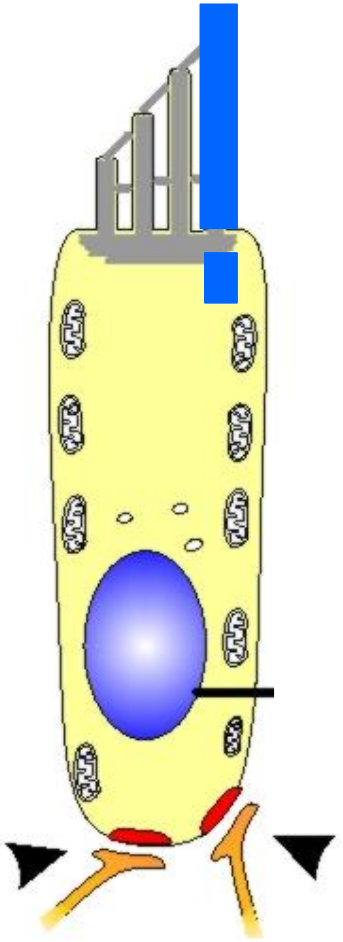
# Usher protein expression in hair cells

## Kinocilium




F-actin
Microtubules
ELL: Early lateral links
AL: Ankle links
KL: Kinociliary links
TC: Top connectors

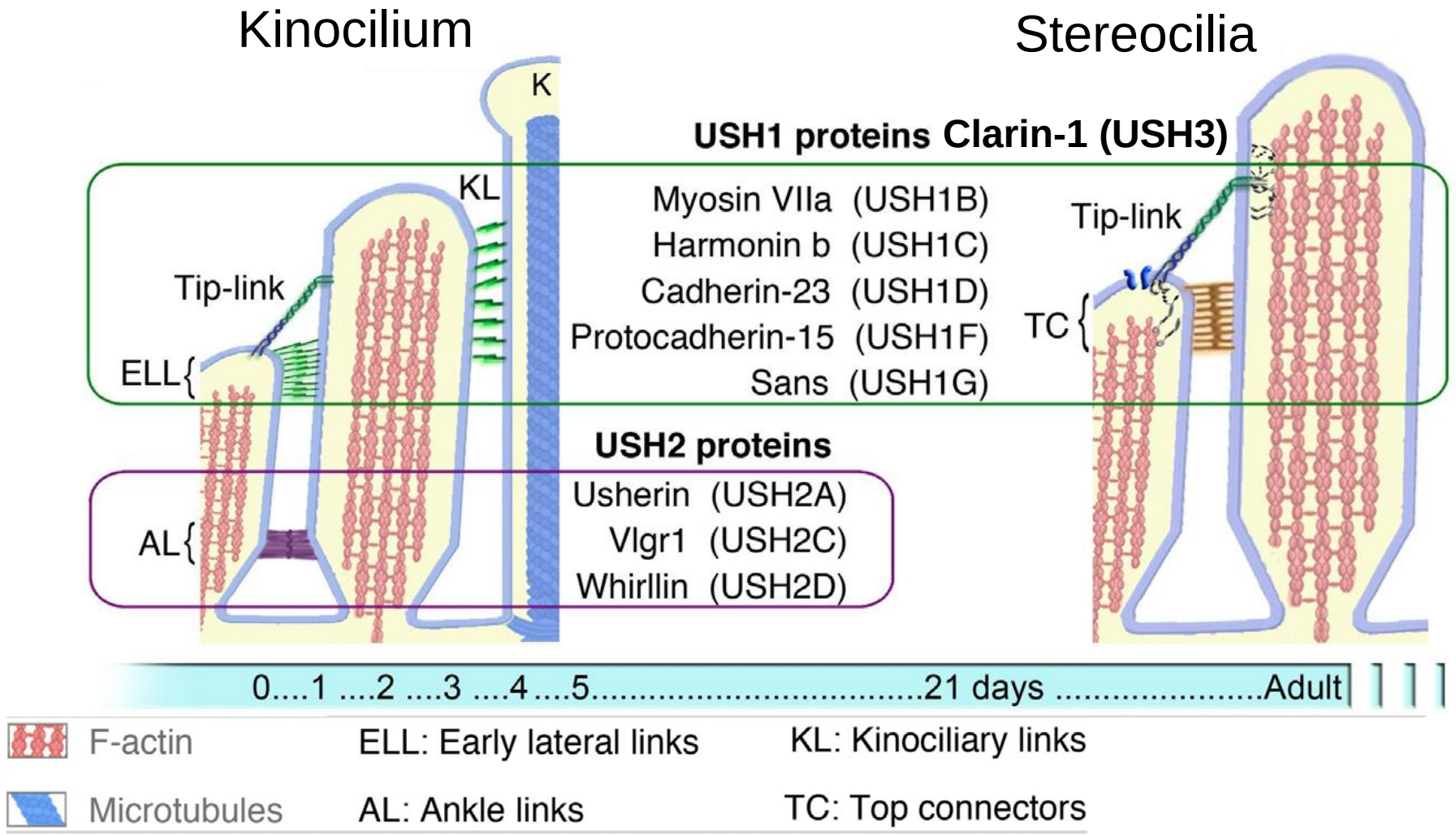
## Stereocilia



El-Amraoui and Petit 2014

Wolfrum 2011

# Usher protein expression in hair cells



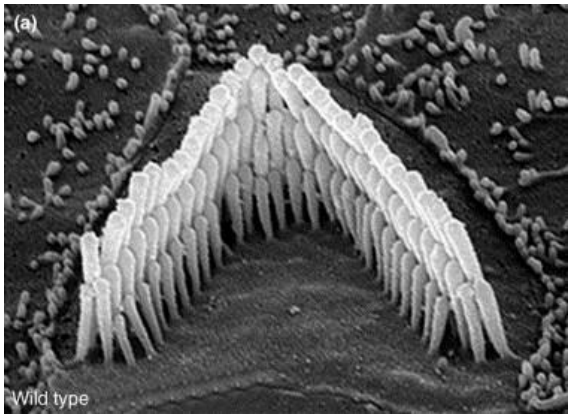

El-Amraoui and Petit 2014

# Auditory hair cell function

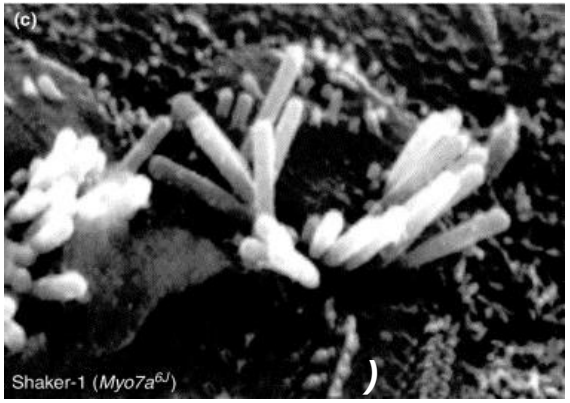
Differentiation:

Defective organization
hair bundles (sterocilia)

Wild type



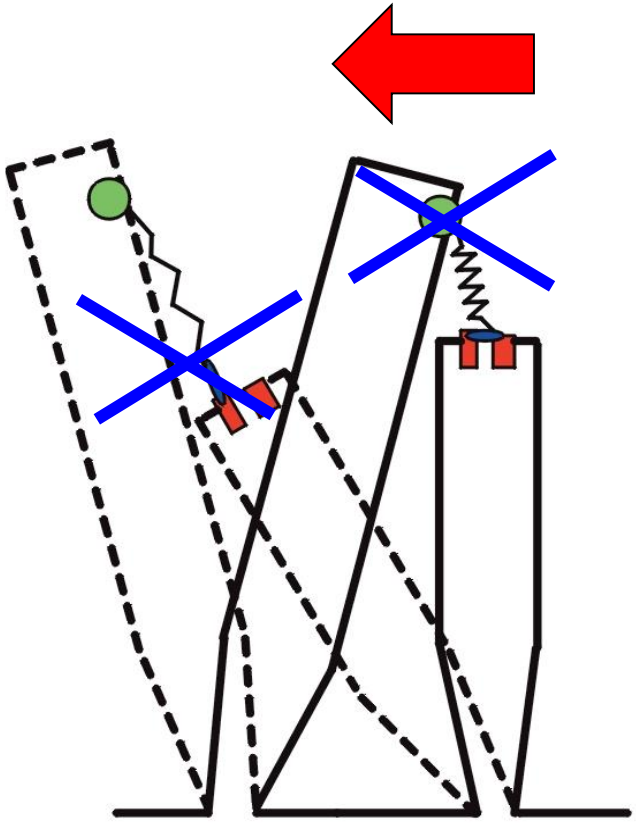

Myo7a
deficient




Disordered stereo cilia

Mature hair cells:

Defective signal transduction

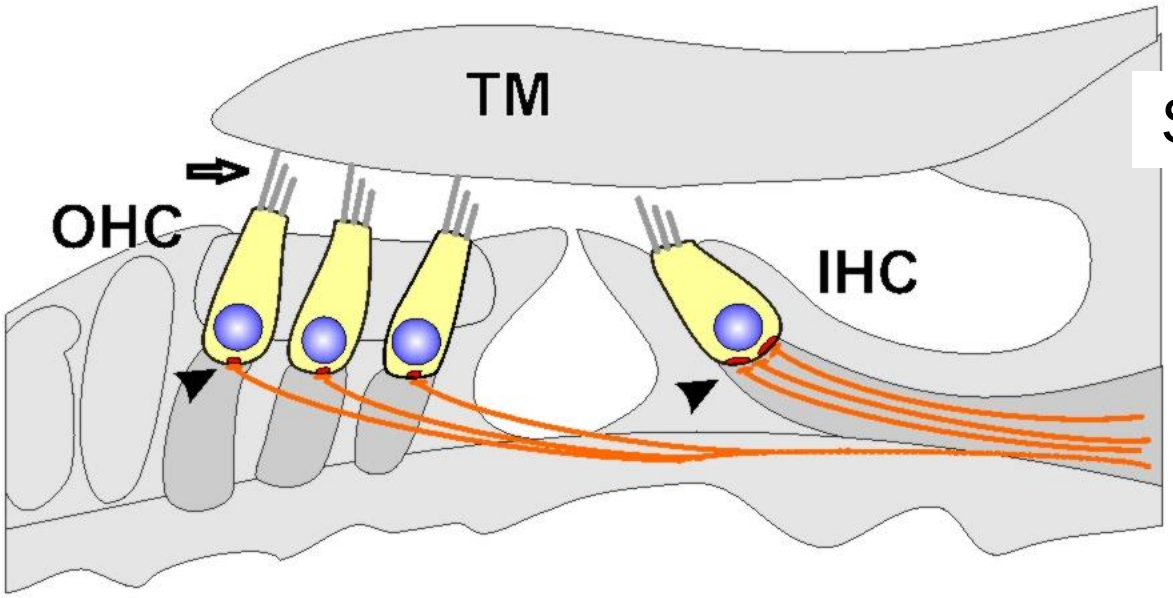


~~Depolarization of hair cell~~

~~Hearing~~

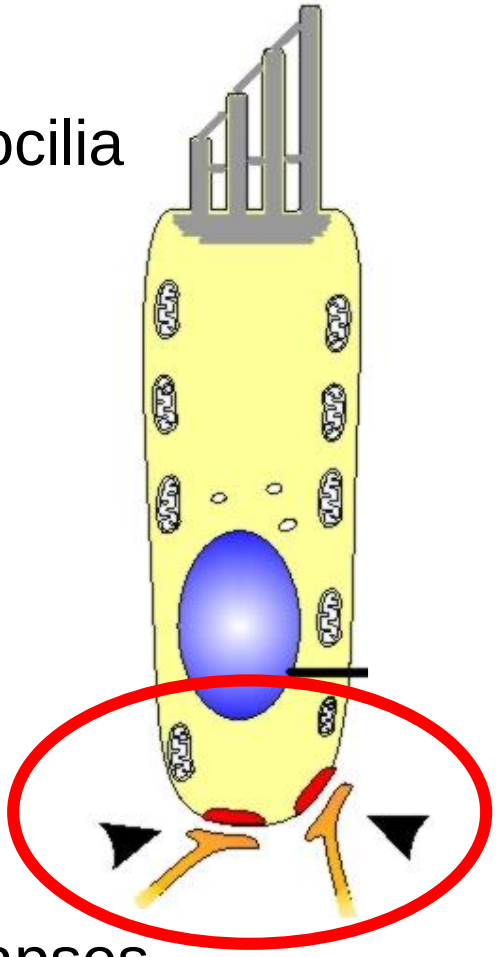
# Hair cells of the inner ear

## Organ of Corti




## Hair cell

Stereocilia



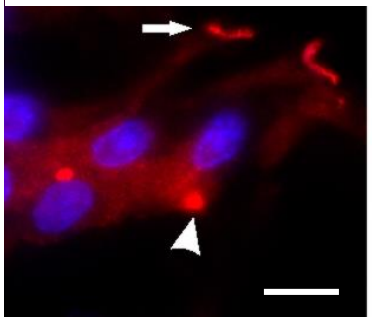
Synapses

Clarin-1
(USH3A)

Aziz El-Amraoui

Dulon et al. J Clin Invest 2018

**VLGR1 (USH2C)**



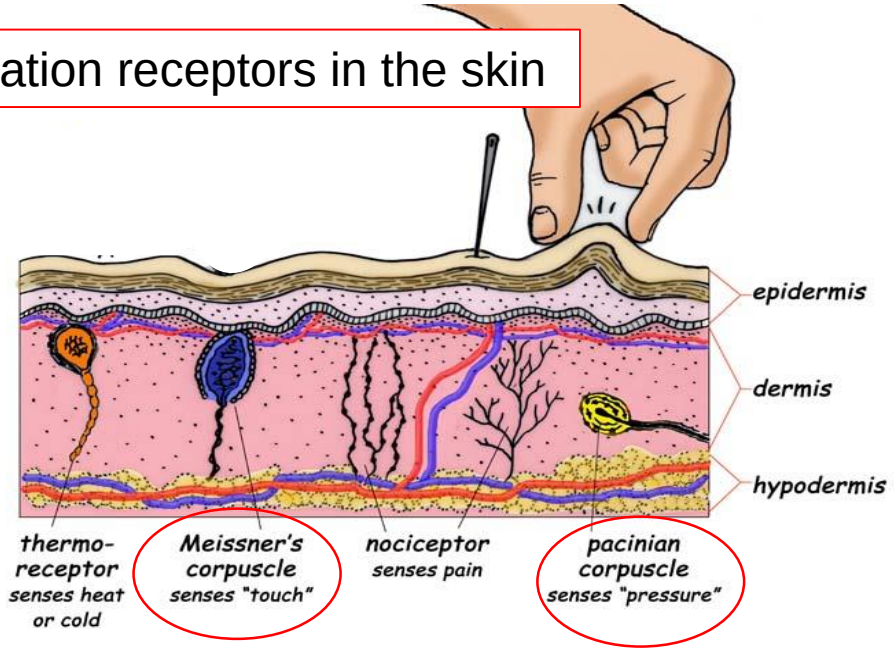
Reiners et al. HMG 2005

# Impact of the Usher syndrome on touch

Touch deficits in USH2A patients.

- Higher finger vibration detection thresholds

Touch and vibration receptors in the skin




https://www.exploringnature.org/db/view/Touch-and-the-Sensory-Receptors-of-the-Skin

- USH2A protein is expressed in glabrous and hairy skin terminal Schwann cells, associated with Aβ-low threshold mechanoreceptors (Meissner´s corpuscles).
- Ush2a knock out mice show reduced vibration sensitivity.

USH2A/Usherin is involved in vibration and gentle touch in the skin.

Fred Schaller

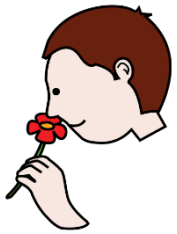
Max-Delbrück Centre for Mol. Med. Berlin

Abstract # 26

# Impact of the Usher syndrome on olfaction

Expression of USH molecules in olfactory epithelium/cells

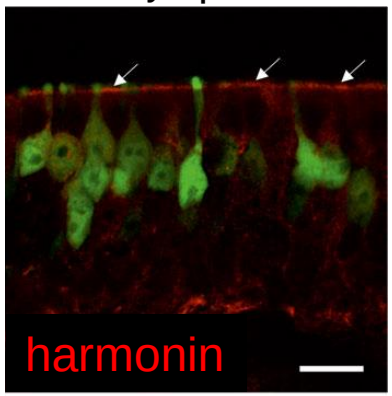
e.g. Wolfrum et al. 1998

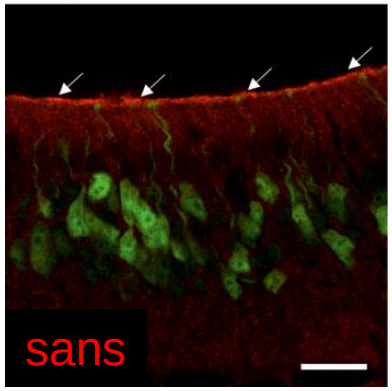


Controversy on olfaction deficiency in Usher syndrome patients:

Zrada et al. 1996 - Seeliger et al. 1999

olfactory epithelium



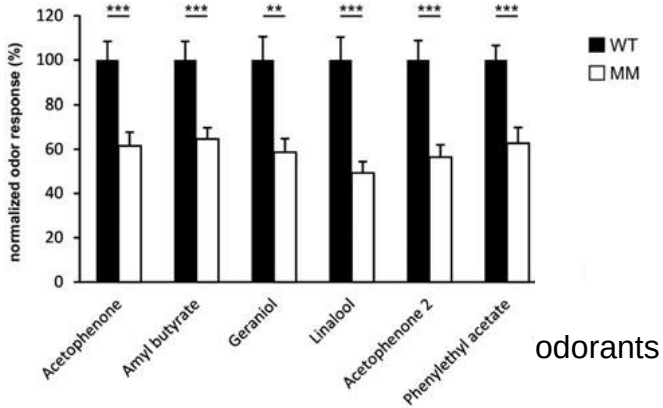




Analyses of olfaction in USH mice

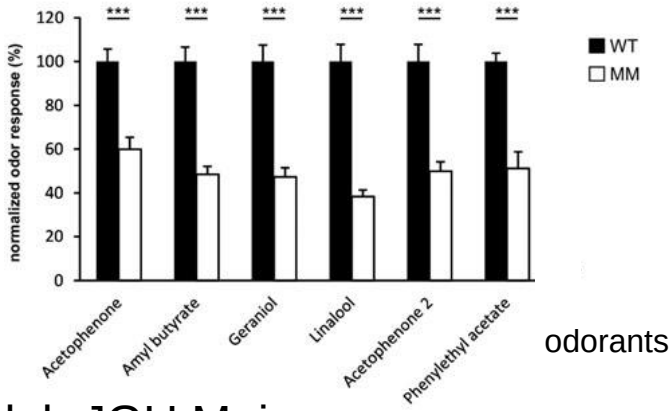
… reveal olfactory deficiency.

Jansen et al. 2016

harmonin/Ush1C deficient mice

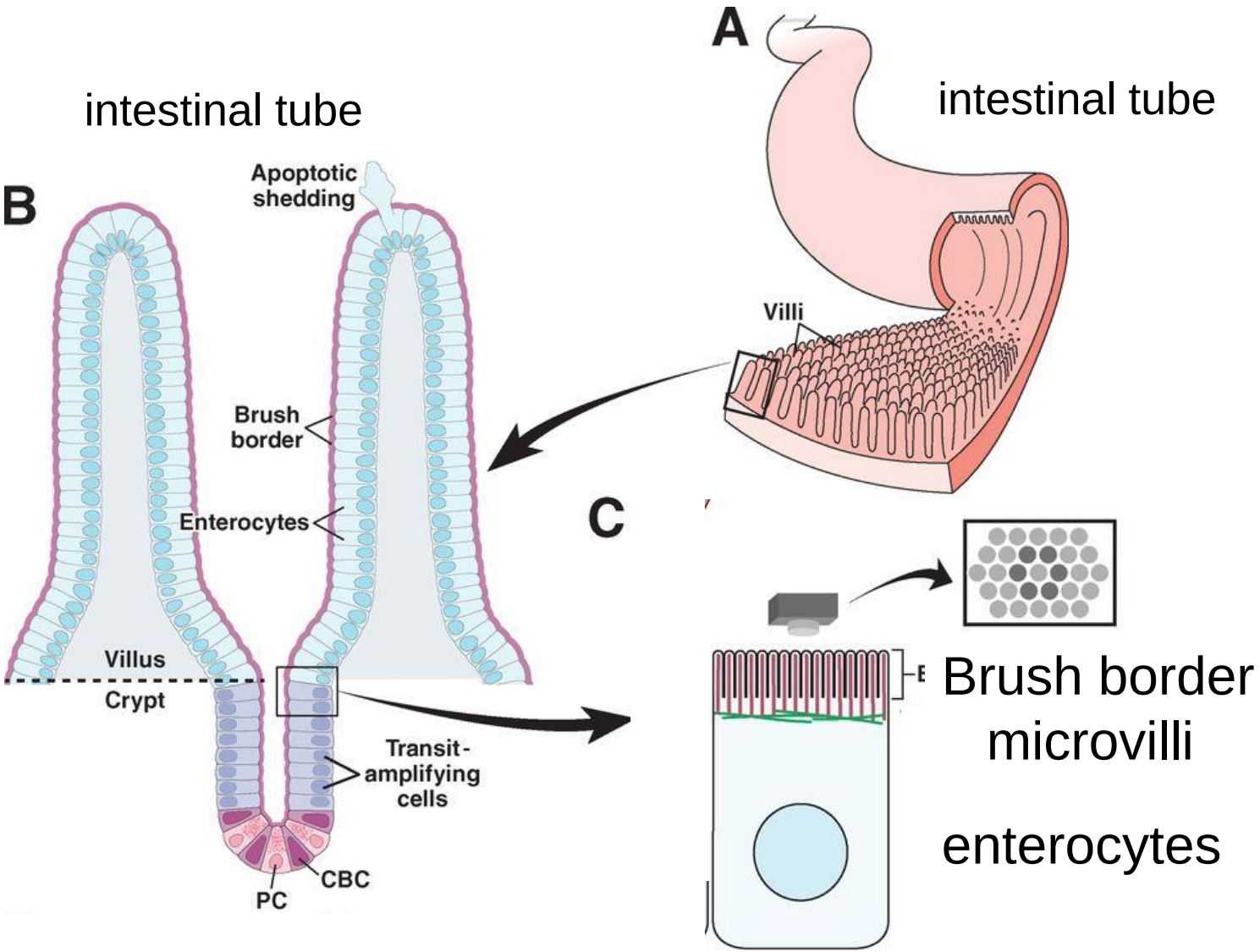



sans/Ush1G deficient mice




Collaboration: H. Hatt lab/RU Bochum & U. Wolfrum lab JGU Mainz

# USH proteins in the intestine

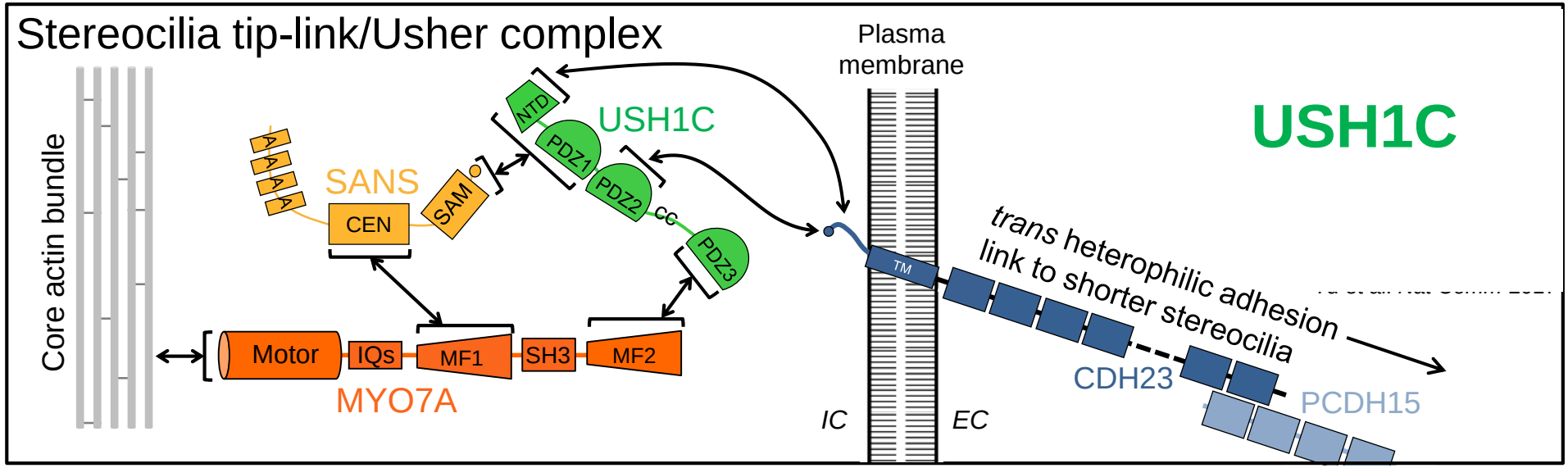


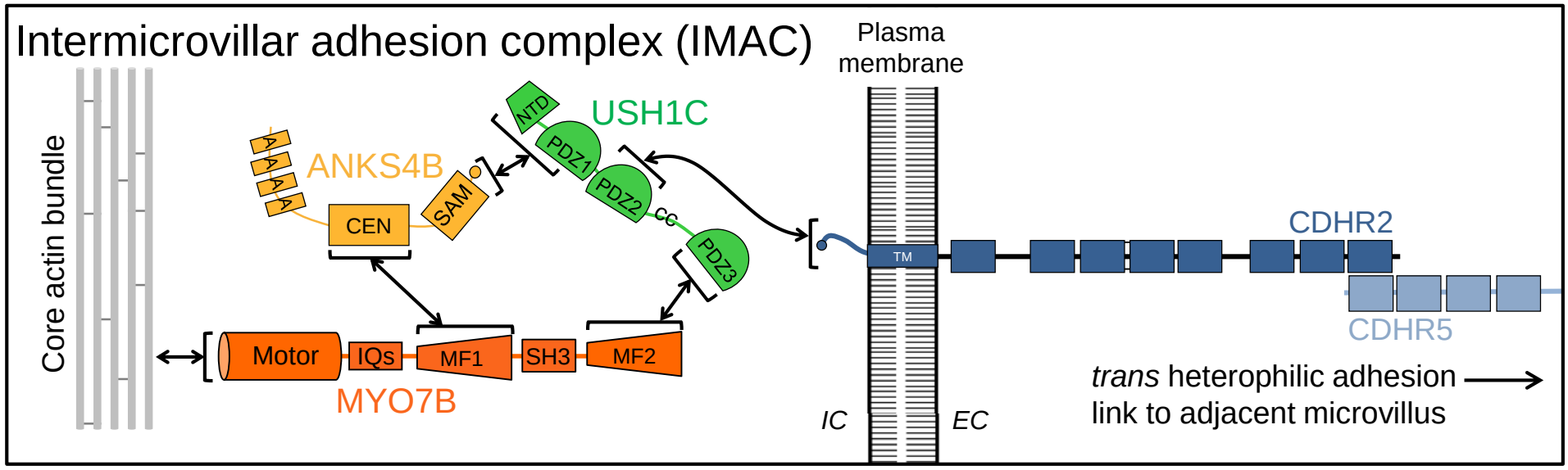

Matt Tyska

Mingjie Zhang

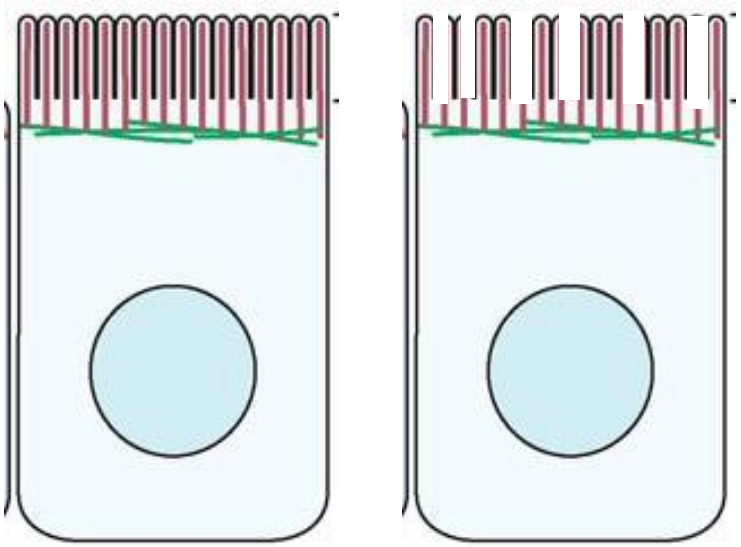
Scott W. Crawley et al. J Cell Biol 2014

# The distal tips of stereocilia and microvilli are linked by a conserved adhesion complex



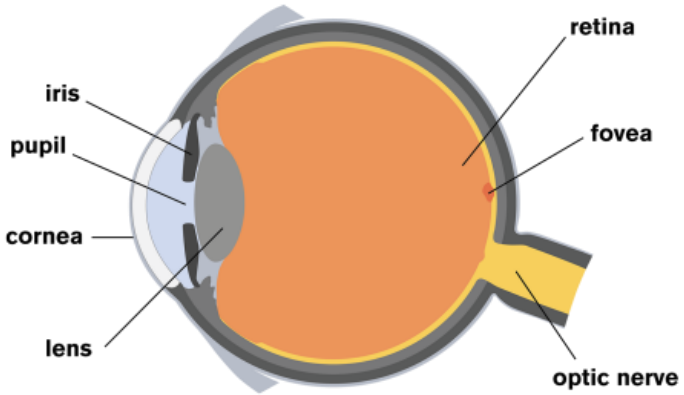
# Intermicrovillar adhesion complex defects cause reduced microvillar packing & decreased growth rate




Decreased growth due to nutritional deficiency.

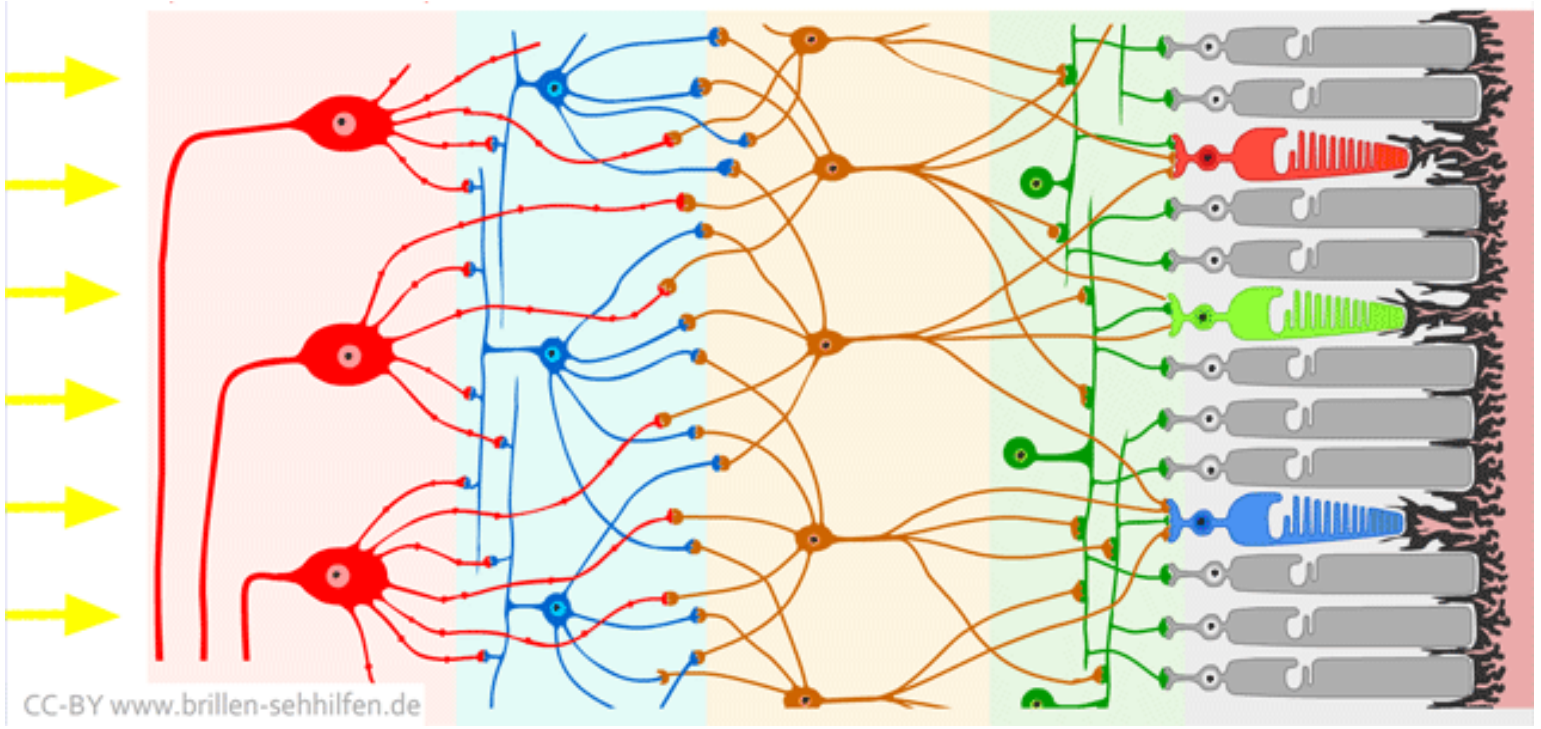
Matthew J. Tyska

# The vertebrate eye and retina

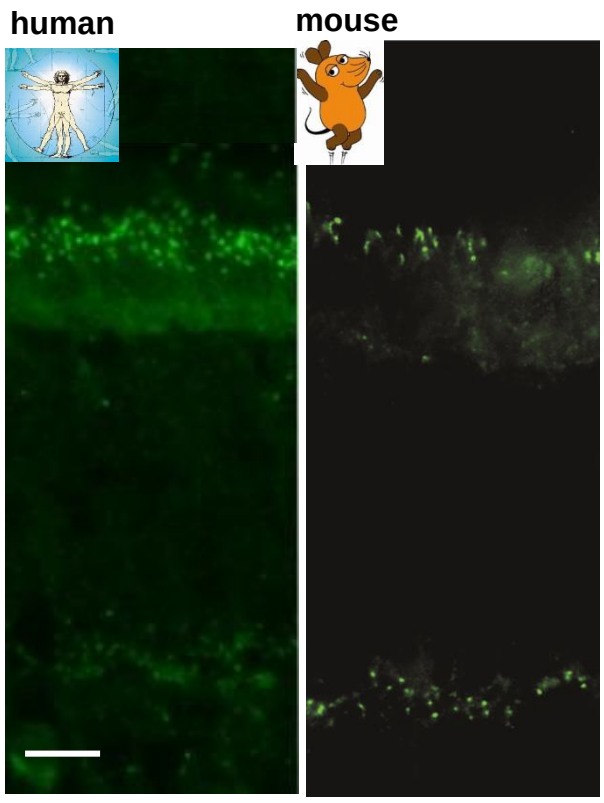



Photoreceptors:

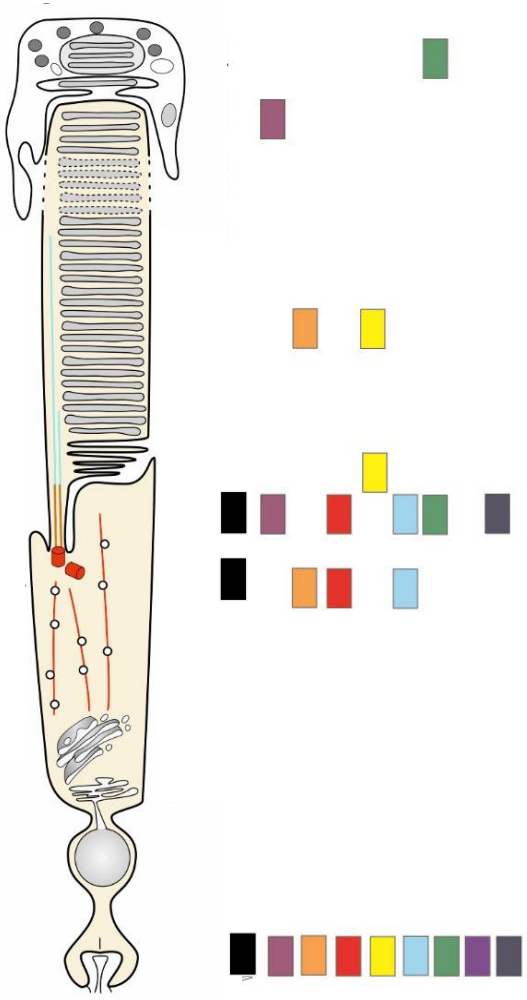
cones & rods



# USH protein expression




VLGR1/GPR98 (USH2C)



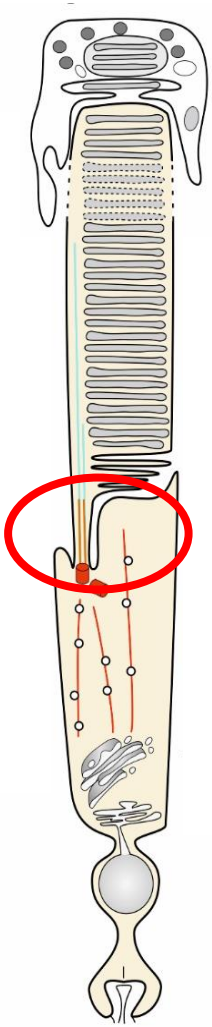
**USH1:** myosin VIIa | harmonin | Cdh23 | Pcdh15 | SANS

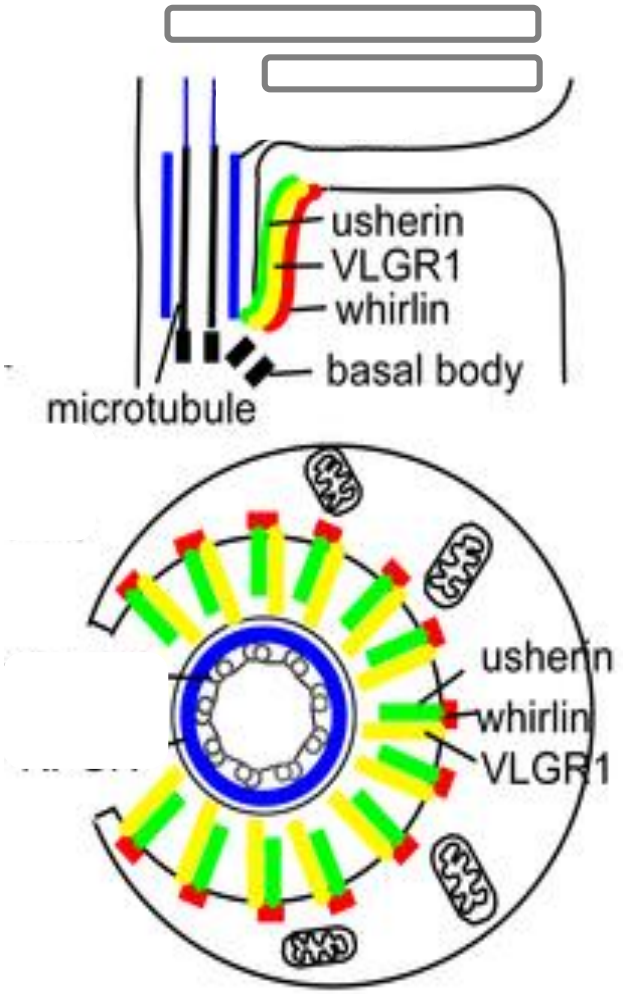
**USH2:** USH2A (usherin) | NBC3 ("USH2B") | VLGR1b (USH2C) | whirlin (USH2D)



Wolfrum (2011)

# USH protein expression

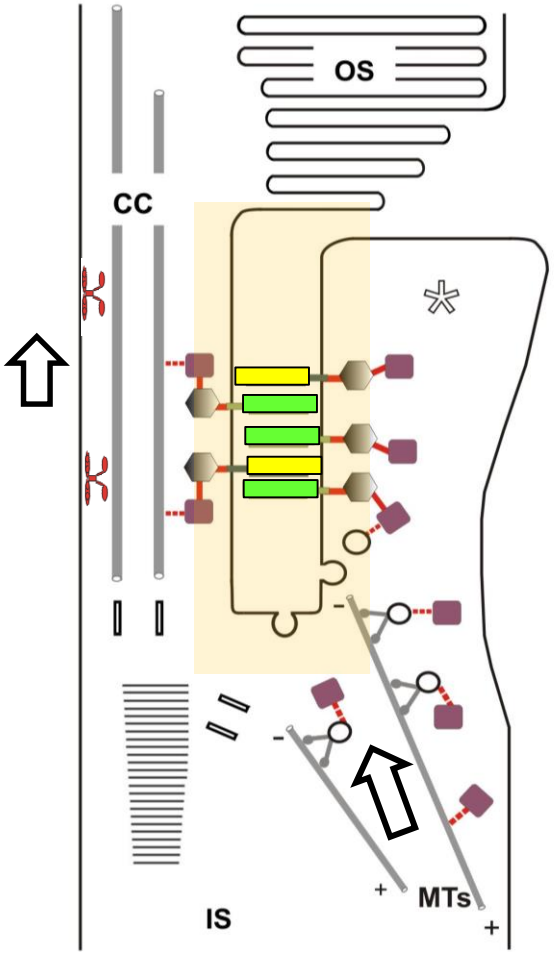




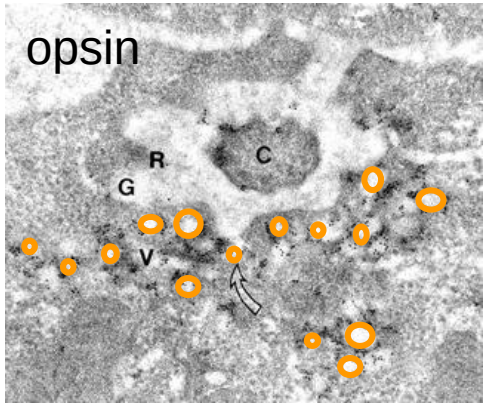

Jun Yang

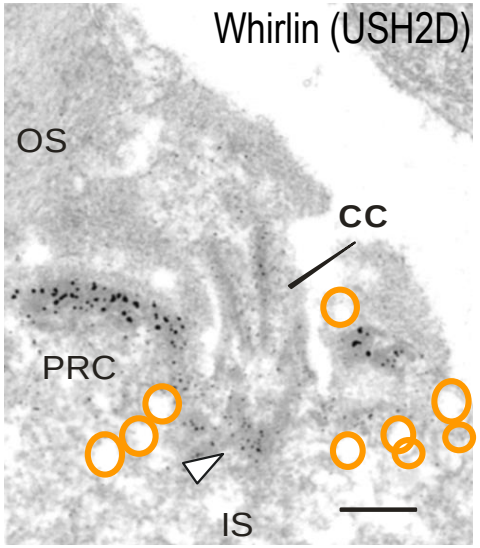
Yang et al. 2010

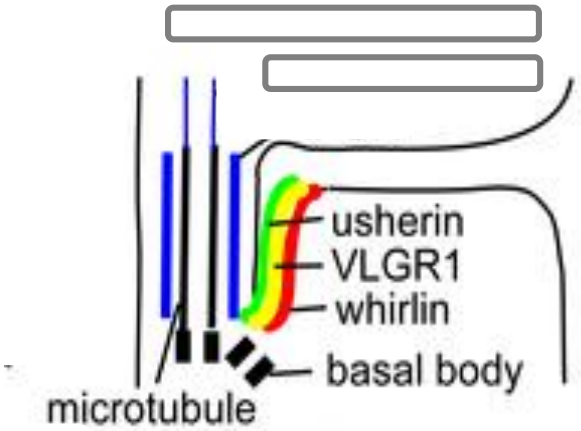
# USH adhesion complex defines the docking membrane for transport vesicles

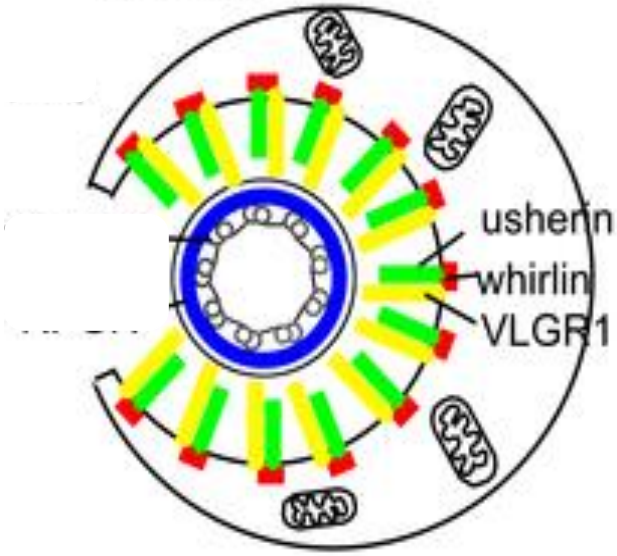



Papermaster 2000




USH2A Isoform b
VLGR1b (USH2C)
SANS (USH1G)
whirlin (USH2D)

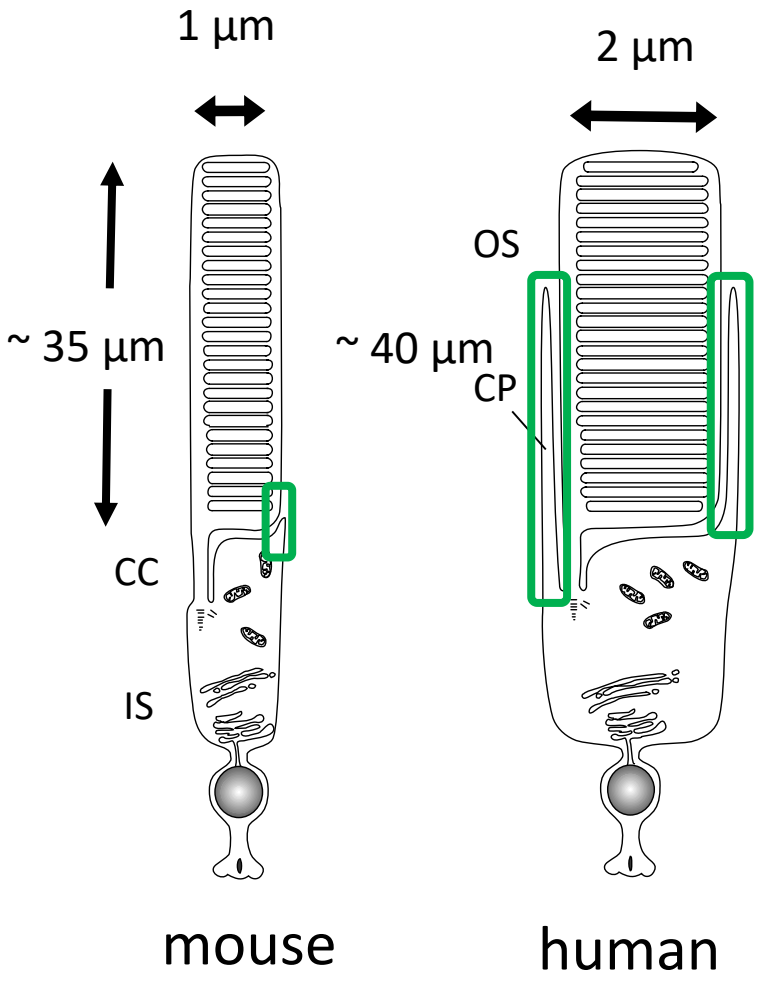
Maerker et al. 2008

Yang et al. 2010

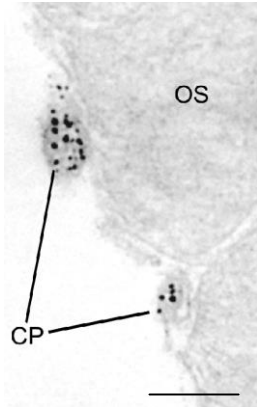
USH1 mouse retinas do not degenerate.

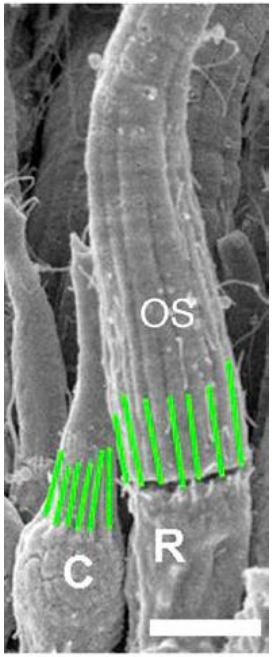
≠

# Calyceal processes are abscent in mouse




USH proteins in calyceal processes



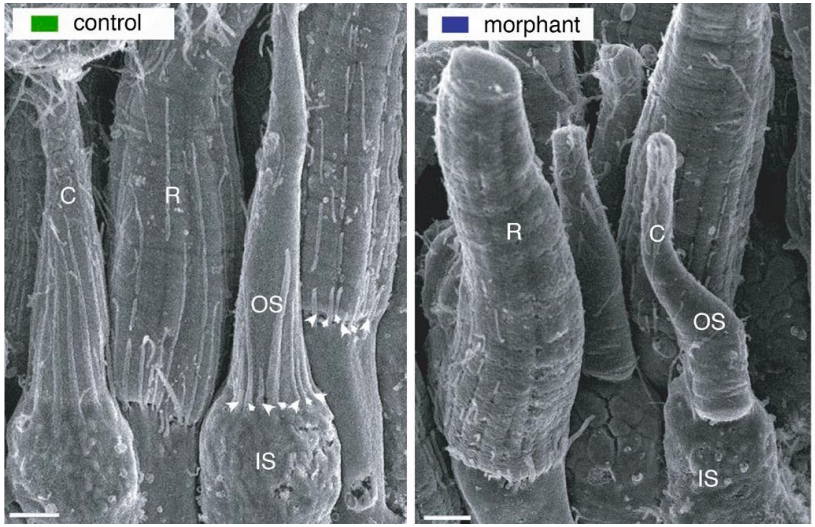




Sahly et al. 2012, JCB
Wolfrum 2010, ARVO

RNAseq data and qPCR revealed very low expression of USH genes in murine retinas.

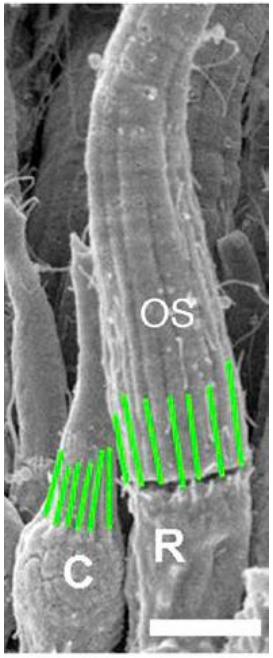
# Absence of calyceal processes in a Pcdh15 (USH1F) frogs

Xenepus



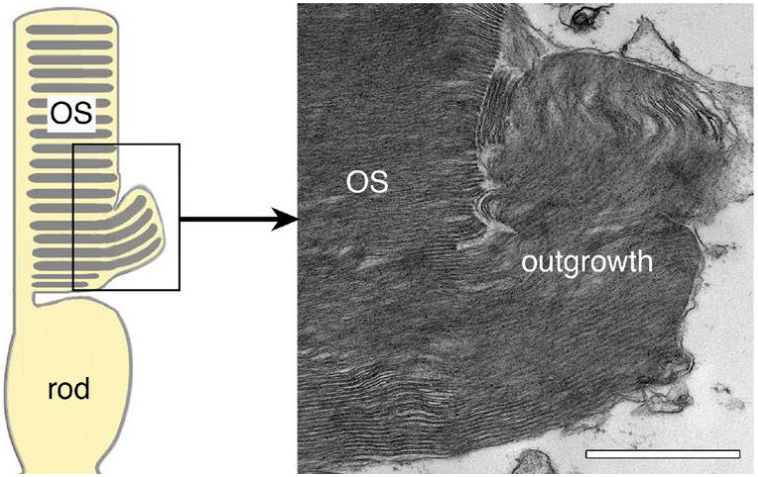

no calycael processes:

bend outer segments




Pcdh15

Over growth of basal outer segment disks

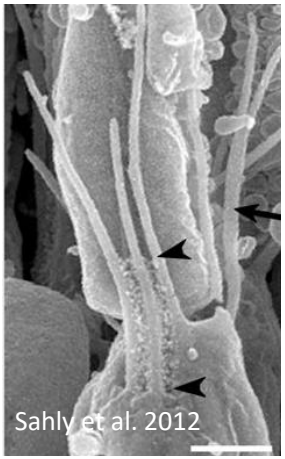


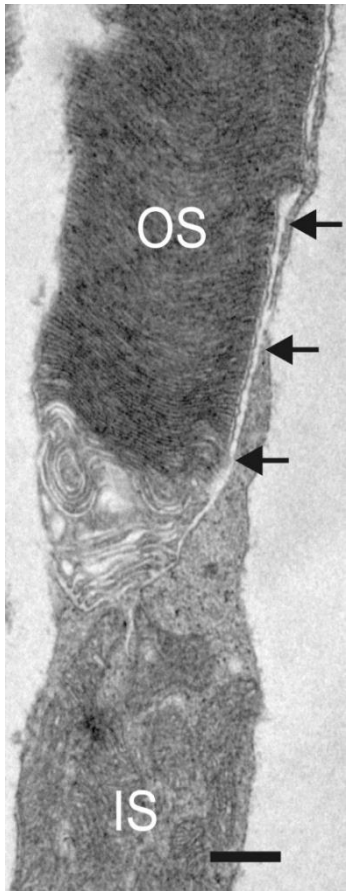

Aziz El-Amraoui



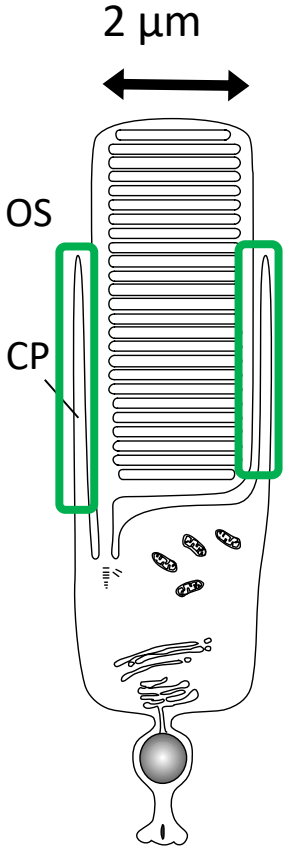
Schietroma et al. 2017

# Porcine eyes/photoreceptors are similar to human …



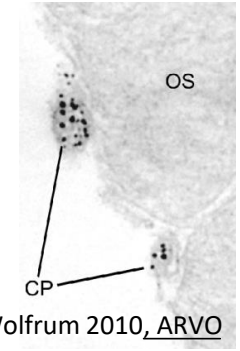

pig




human

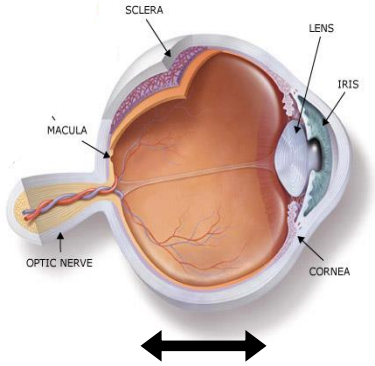
more cones
macula

**USH proteins in CP**




Wolfrum 2010, ARVO
Sahly et al. 2012, JCB

**Eye ball size**



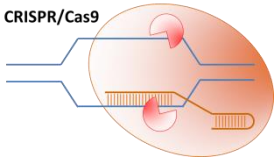

Human: 25 mm
Pig: 24 mm
Mouse: 3.5 mm

calyceal processes: several numerous

# Design of a transgenic pig as a valuable model for USH

**Designe and generation of a humanized USH1C mutation for evaluating treatment options**

- Gene therapy
- Read-through treatments
- Gene repair approaches
- Cellular and tissue replacement




Nikolai Klymiuk

Eckhard Wolf

Uwe Wolfrum

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

FAUN-STIFTUNG

USHER2020 FOUNDATION

FOUNDATION FIGHTING BLINDNESS

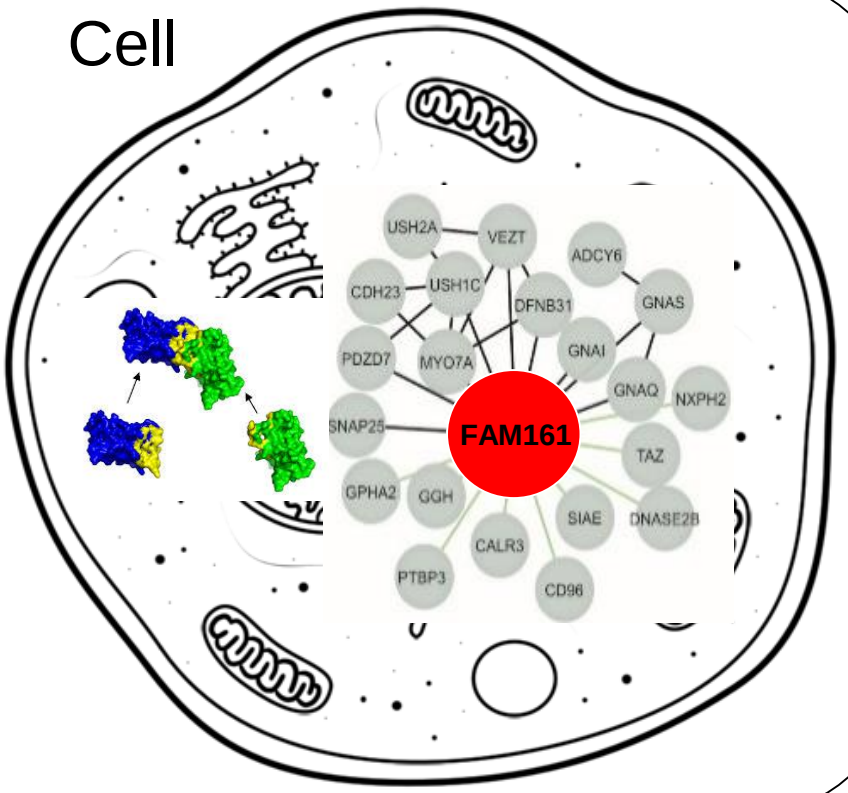
JG|U JOHANNES GUTENBERG UNIVERSITÄT MAINZ

# Design of a transgenic pig as a valuable model for USH

Wolfrum lab

Society

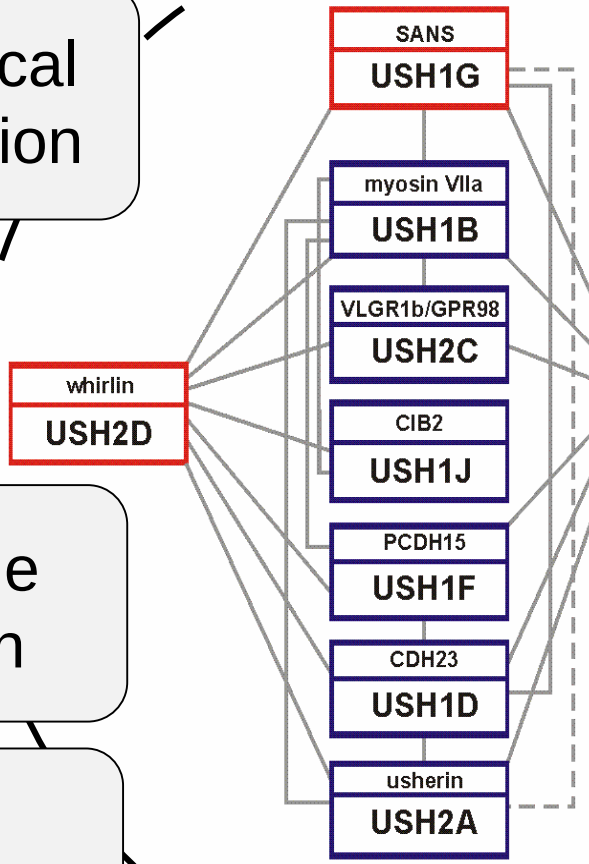
Cell




Tell me who your friends are and
I´ll tell you who you are.

⇛ Proteomics

# USH protein network - functions




# 24 mechanical stabilization

channel regulation

Gregory et al. 2011, Dulon et al. 2018

# 24 membrane adhesion

endocytosis

Bauss et al. 2014

# 18 ciliary transport

ciliogenesis / deciliation

# 21, 23

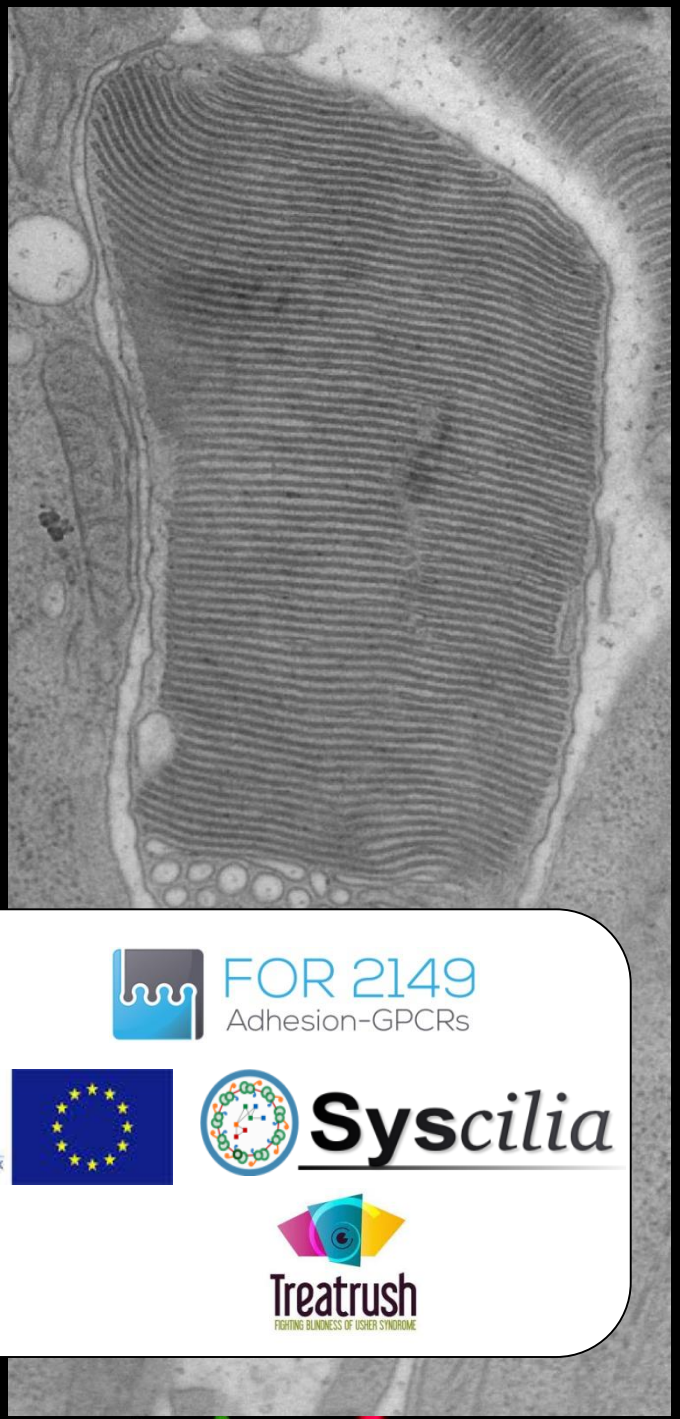
gene regulation splicing

# 19

# Abstracts from Wolfrum lab

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

# Thank you!



FAUN

PRO RETINA

FcB

DFG

FOR 2149
Adhesion-GPCRs

FOUNDATION FIGHTING BLINDNESS

GeneRED

USHER2020 FOUNDATION

SEVENTH FRAMEWORK PROGRAMME

Syscilia

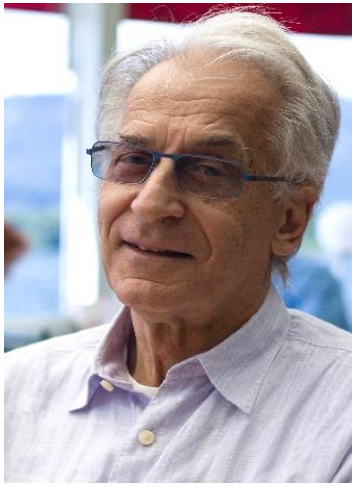
Bundesministerium für Bildung und Forschung

E-Rare

ur-USH

Treatrush
FIGHTING BLINDNESS OF USHER SYNDROME

# In memory of:



H. Steffen Suchert

1945 - 2015

"Ted", Elaine, and Thomas Welp

- 2015