

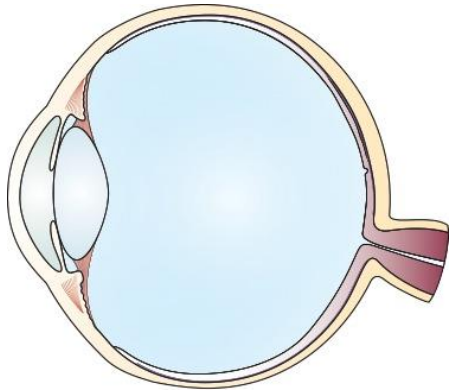
# Thérapie génique indépendante des mutations

Deniz Dalkara  
& José-Alain Sahel

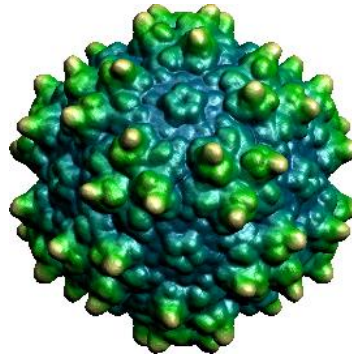


16 Mai 2018

# Thérapie génique oculaire



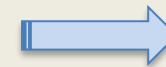
Virus Adéno-associé (AAV)  
ou  
Lentivirus



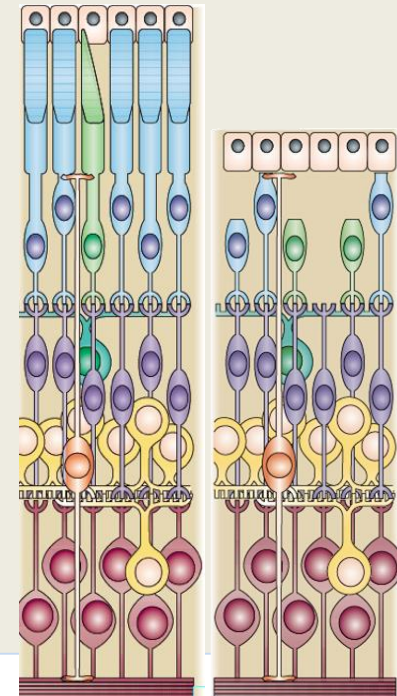
- Utilisation du matériel génétique pour ralentir ou guérir la dégénérescence rétinienne

## Dégénérescence Rétinienne

- Maladies Héritaires
- Maladies Complexes



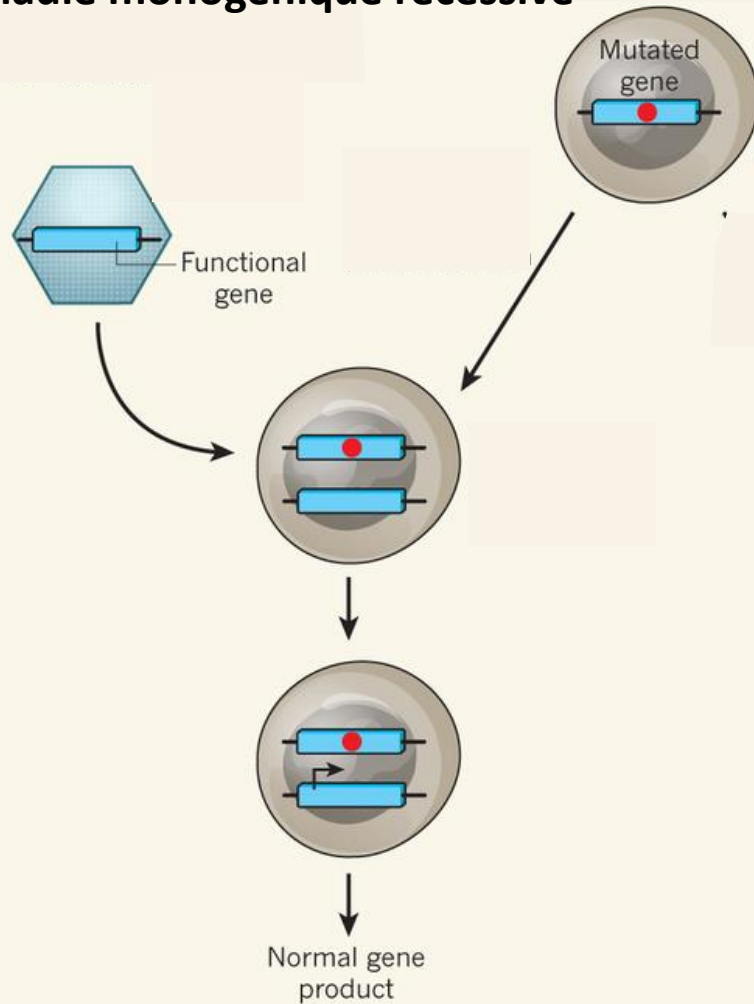
Cécité



# Thérapie génique : différents possibilités

## 1- Addition de gènes (remplacement ou supplémentation de gènes)

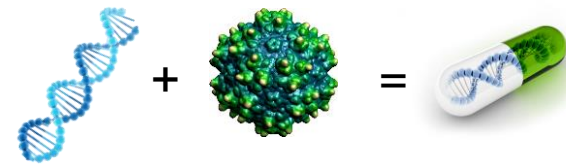
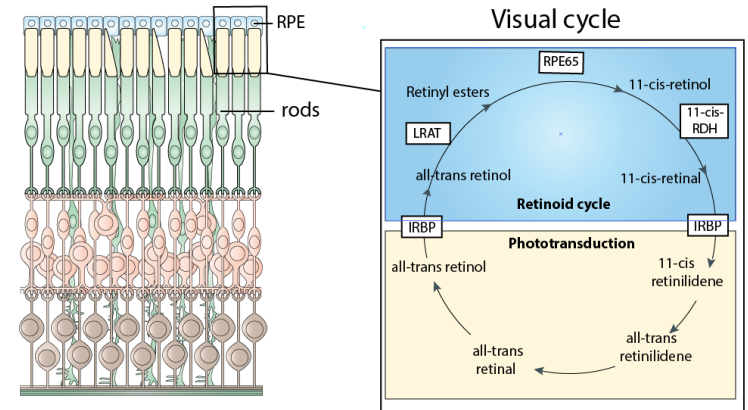
### Maladie monogénique récessive



Maguire and Bennett, **N Engl J Med**, 2008

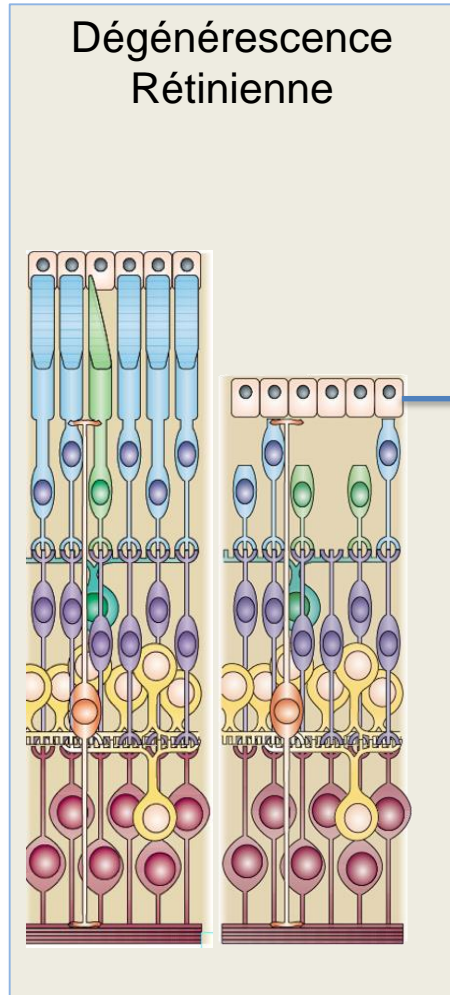
Bainbridge and Ali, **N Engl J Med**, 2008

Cideciyan and Hauswirth, **PNAS**, 2008

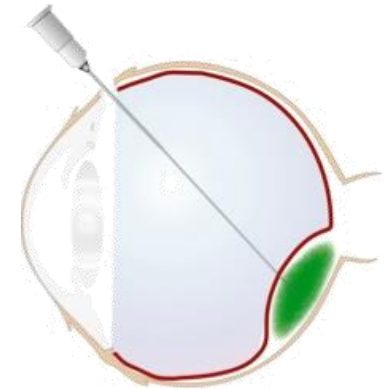
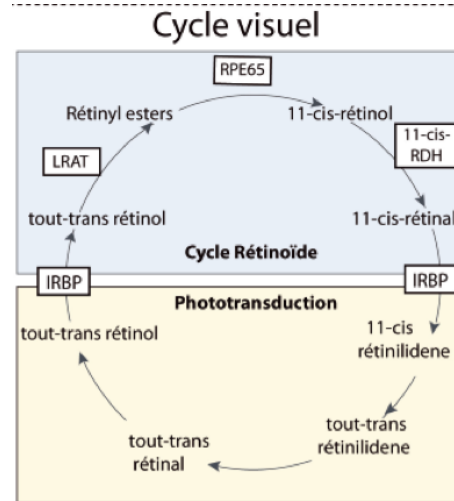
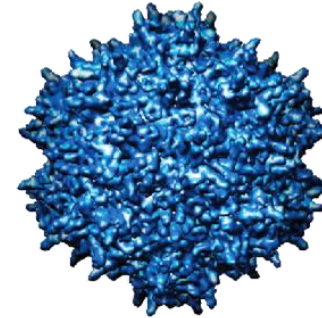


- ✓ Sans effet adverse
- ✓ Bénéfique

# Amaurose congénitale de Leber

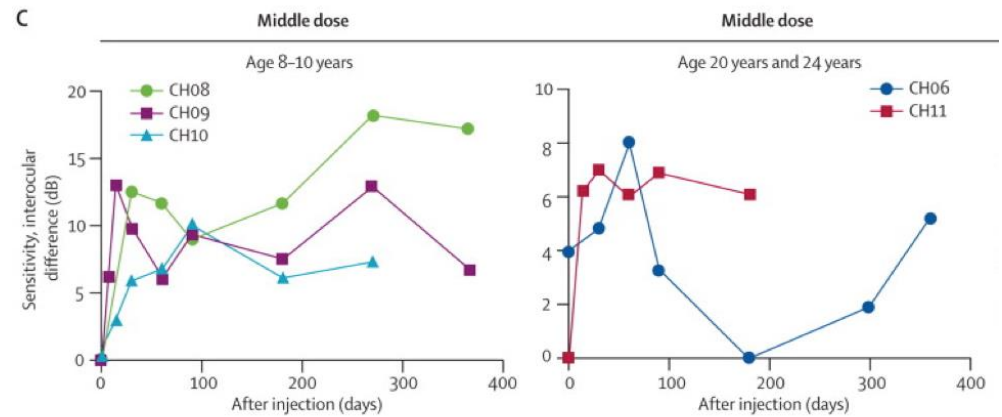


RPE65



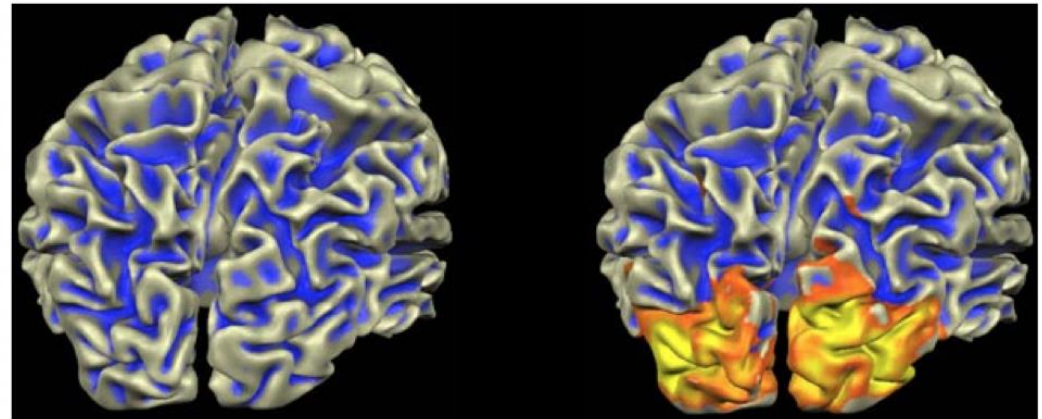
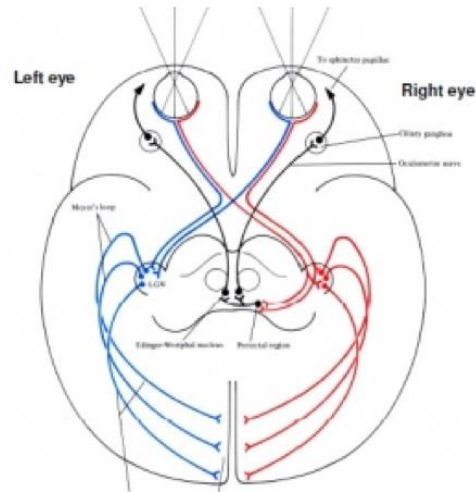
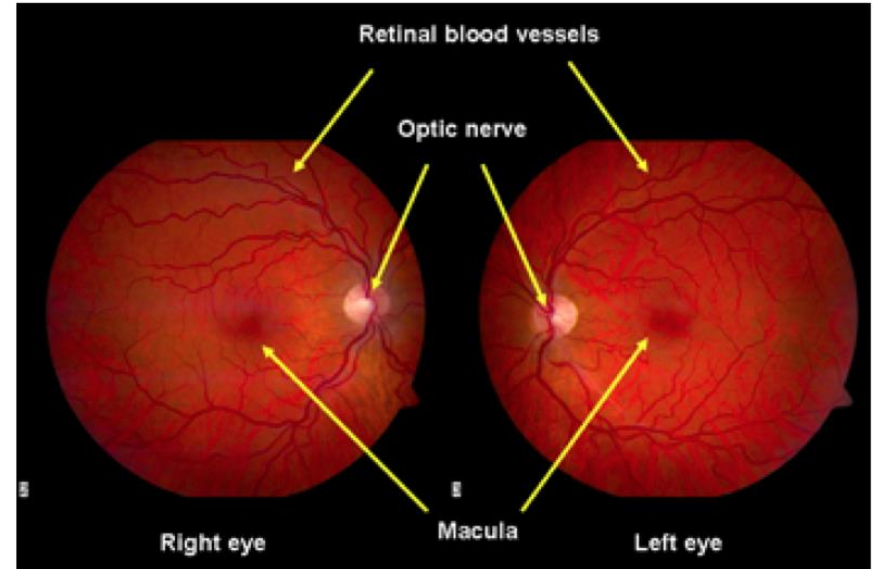
Déficiéncie d'une enzyme =  
cécité des l'enfance

# Une meilleure efficacité chez les enfants..



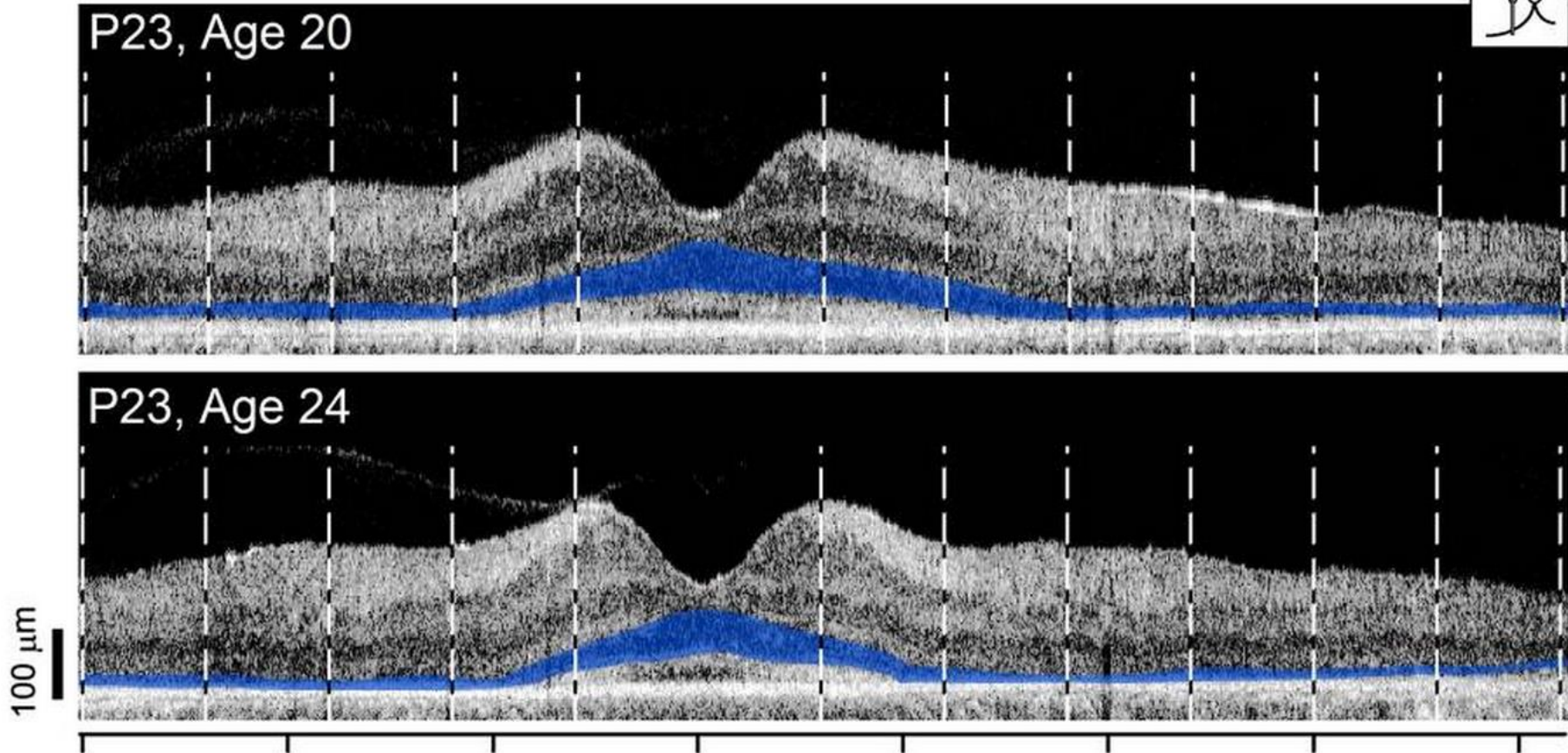
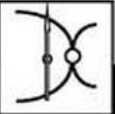
Maguire et al., *Lancet*. 2009

# Ré-administration dans l'œil contralatéral

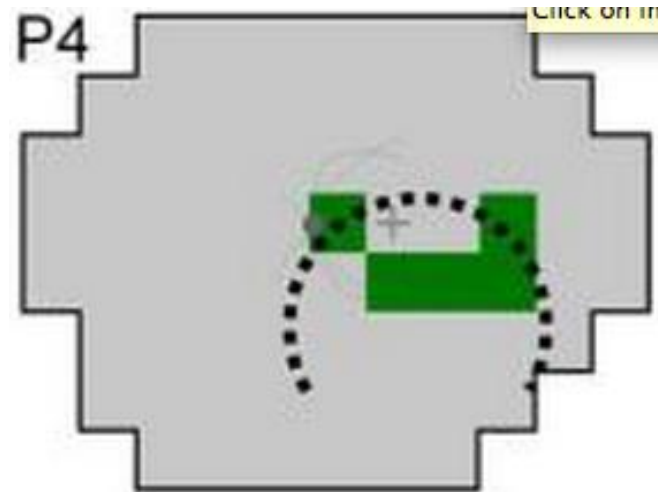
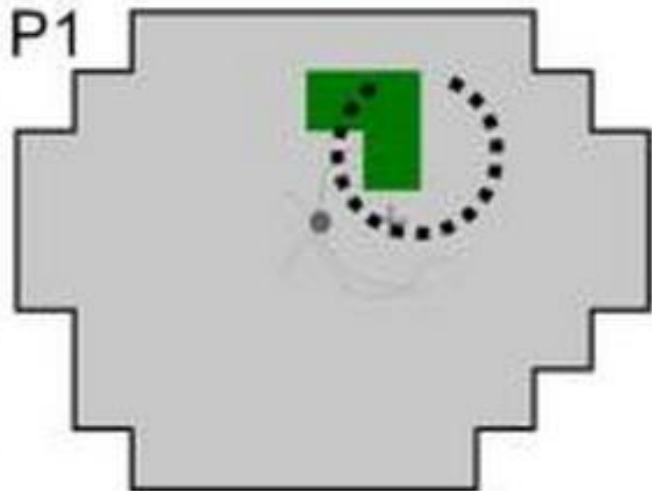
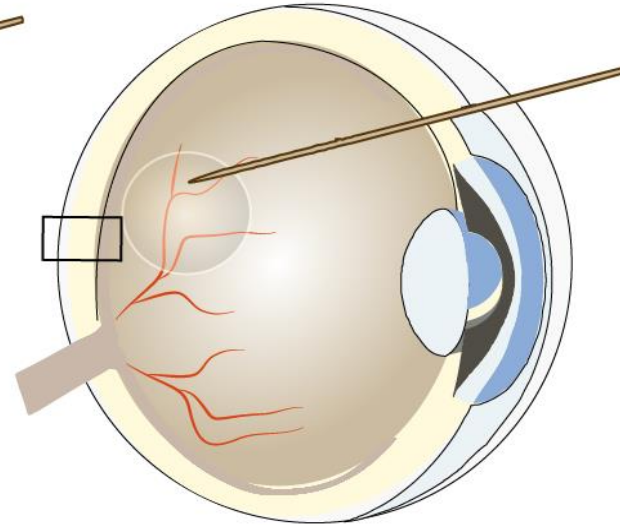
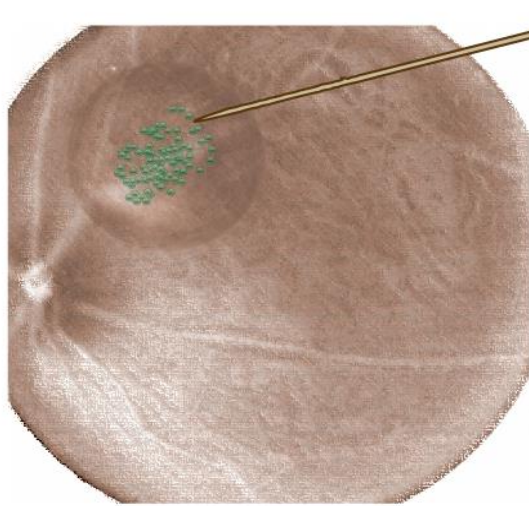


**Jean Bennett et al.,** Sci Transl Med 8 February 2012: Vol. 4, Issue 120, p. 120ra15  
AAV2 Gene Therapy Readministration in Three Adults with Congenital Blindness

# La dégénérescence continue malgré le traitement



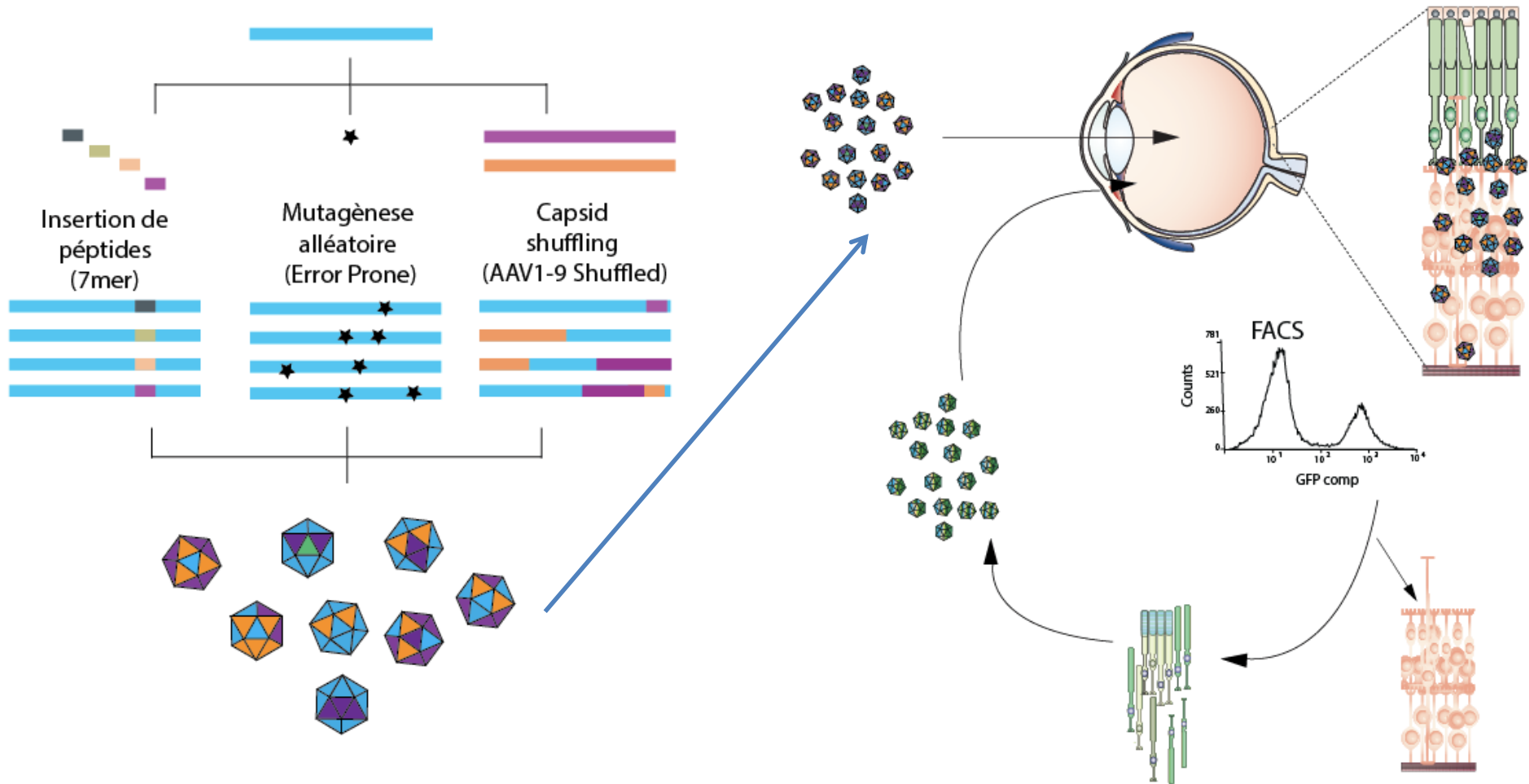
# Le traitement n'est pas efficace en dessous de la fovéa





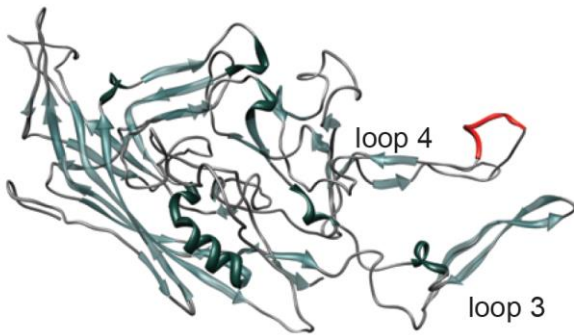
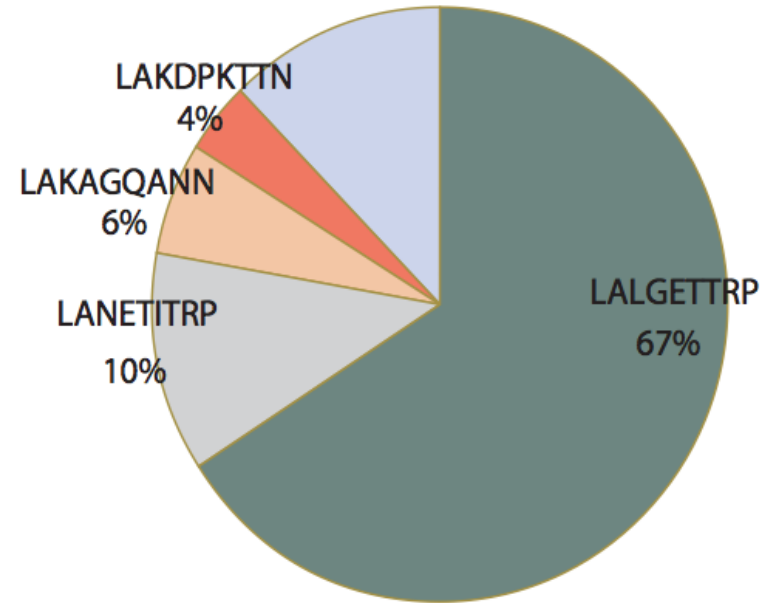
# Conception des meilleurs AAVs pour éviter une chirurgie complexe

Input: gène codant le capsid d'AAV

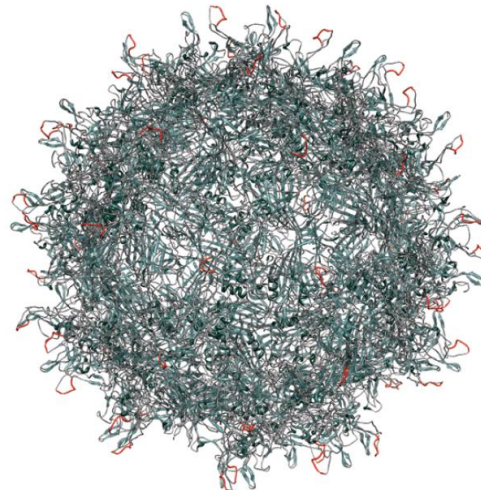


# Convergence vers une capside de pointe

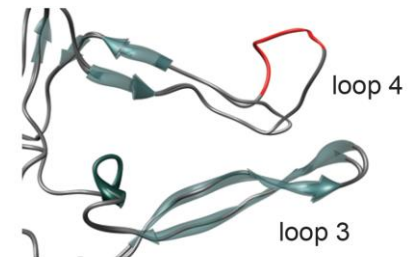
Clone	Percentage
AAV2 588~ LALGETTRP	67
AAV2 588~ LANETITRP	10
AAV2 588~ LAKAGQANN	6
AAV2 588~ LAKDPKTTN	4



VP1 monomer: AAV2-7M8

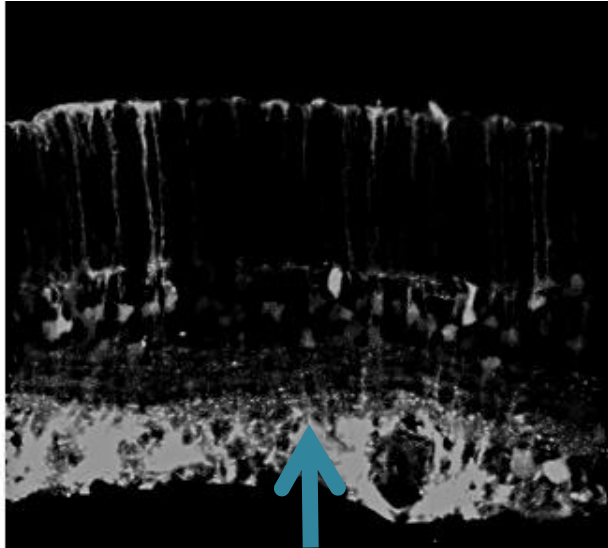
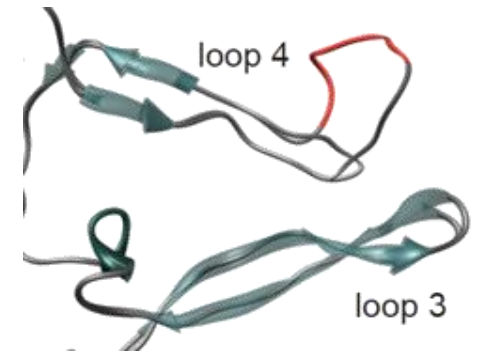
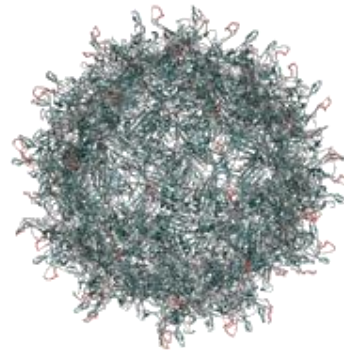
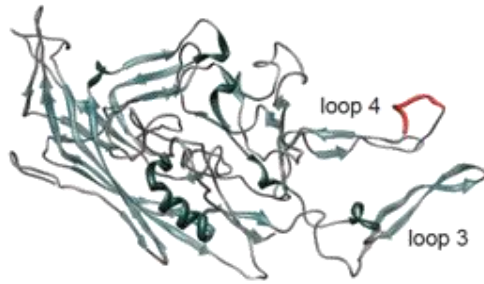


Capside entier composé de 60 monomeres

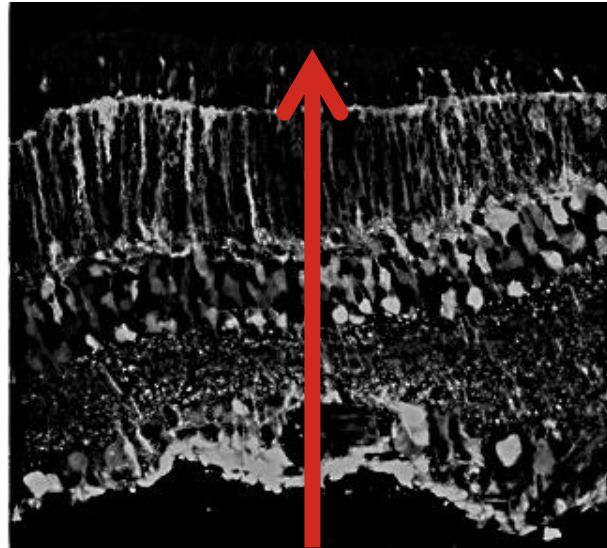


Zoom sur le monomer: AAV2-7M8

# Vecteur avec des capacités de transduction et infiltration améliorées

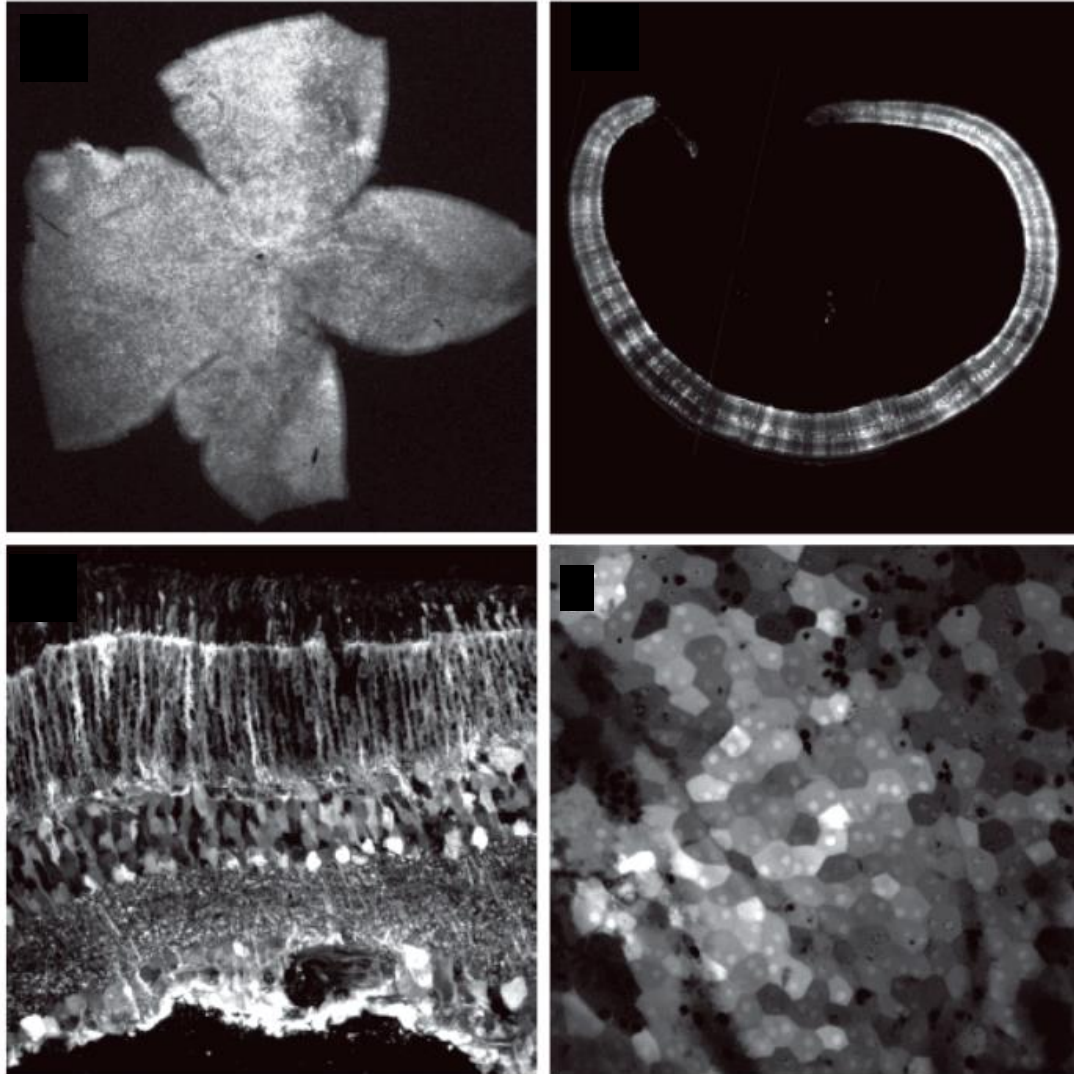


**AAV2.CAG.GFP**  
Parental  
serotype



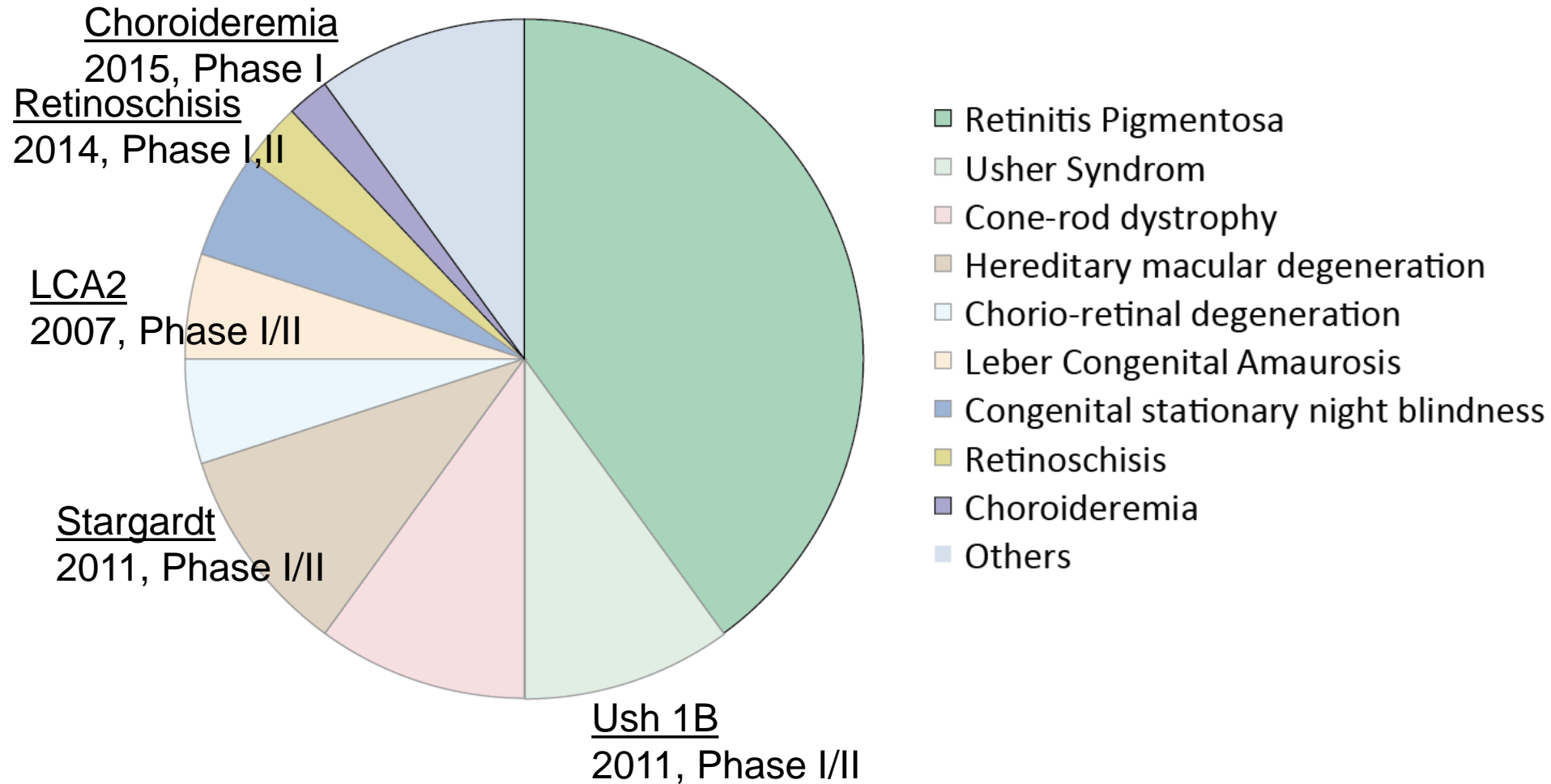
**7m8.CAG.GFP**  
Enhanced variant for PR  
transduction

# Une expression pan-rétinienne et trans-rétinienne : jusqu'à l'EPR



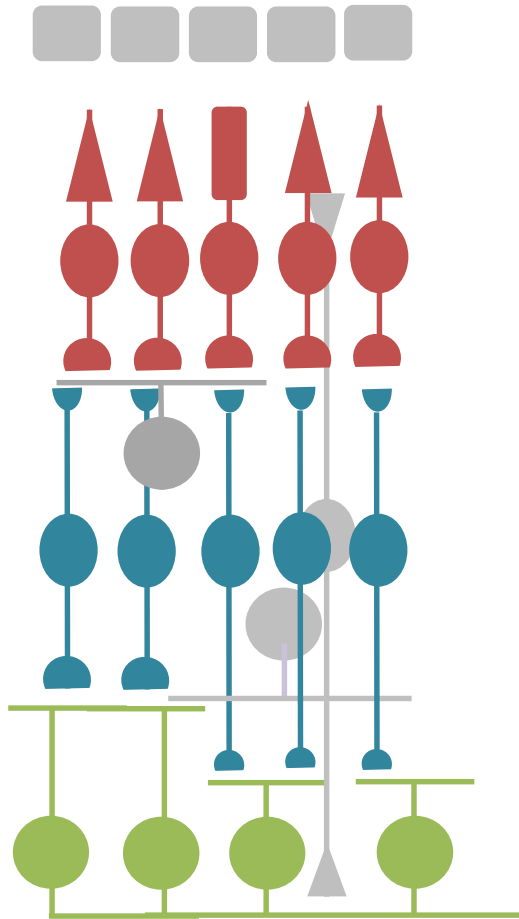
# Thérapie génique : différents possibilités

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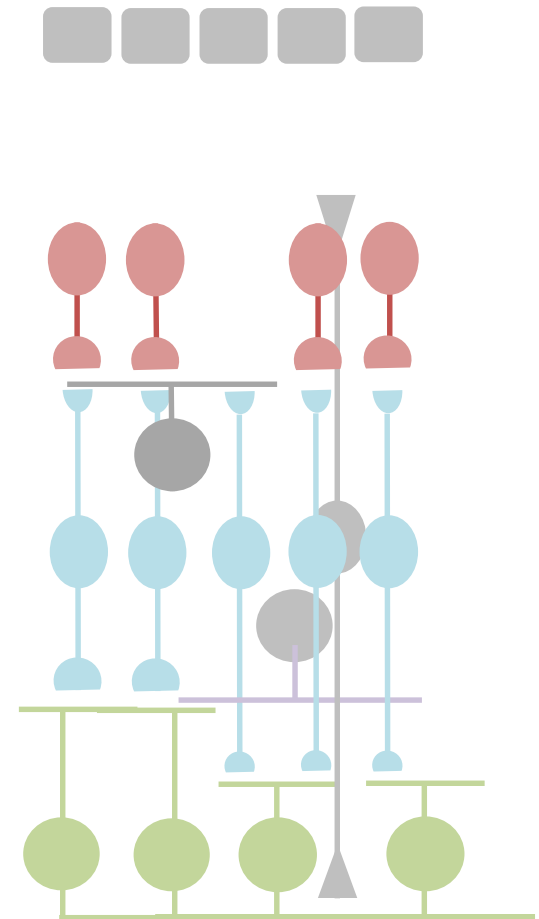


# Thérapie génique indépendante des mutations

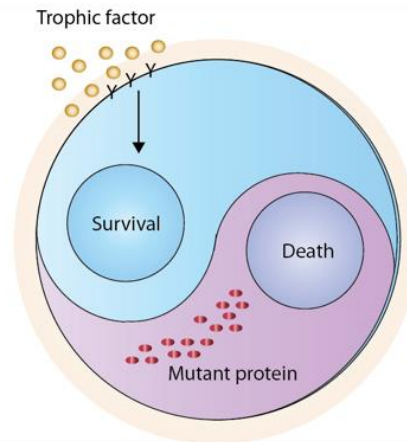
Rétine normale



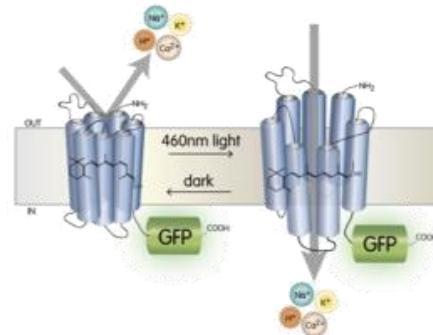
Rétine aveugle



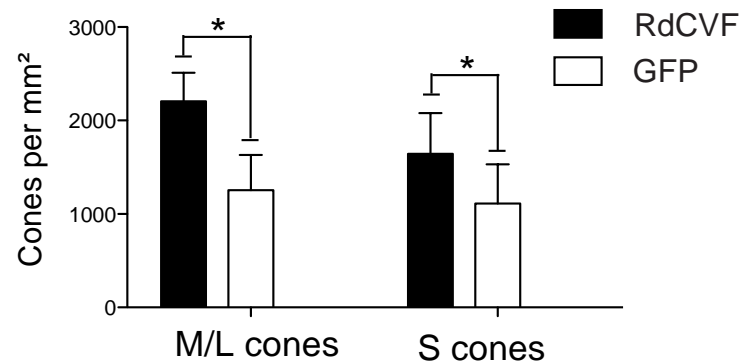
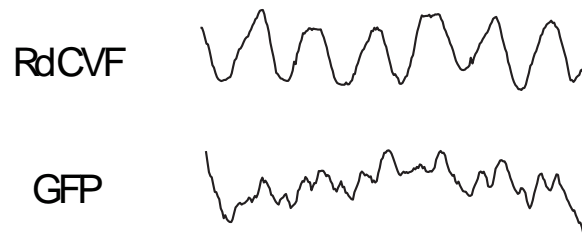
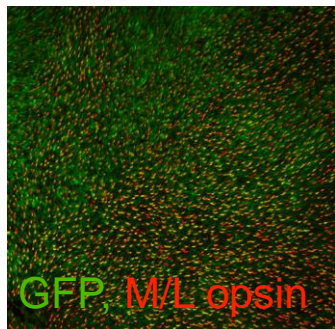
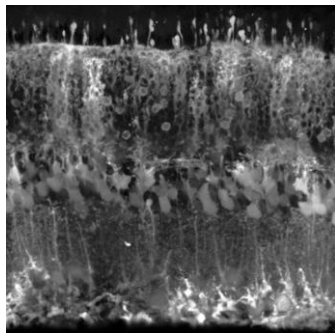
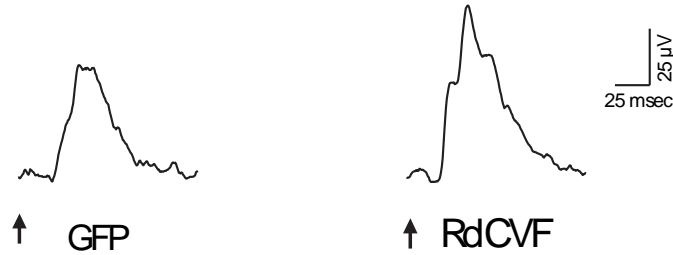
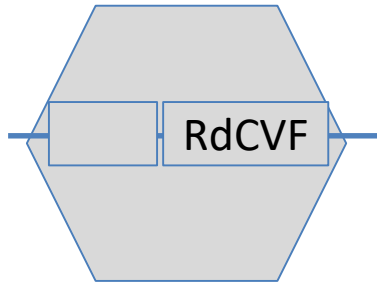
## Sécrétion de facteurs trophiques



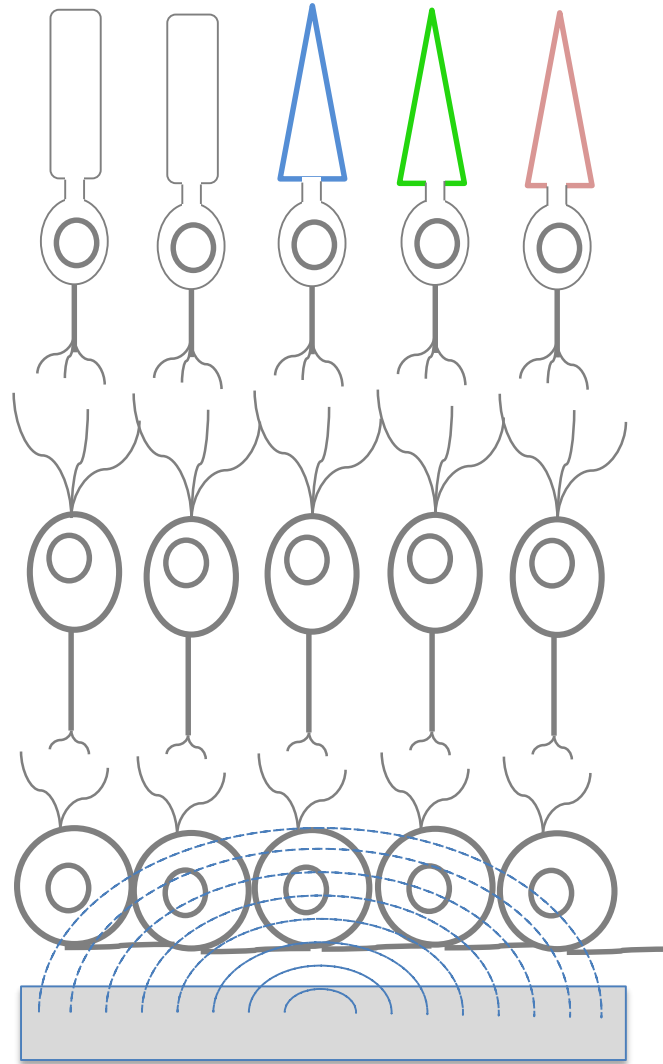
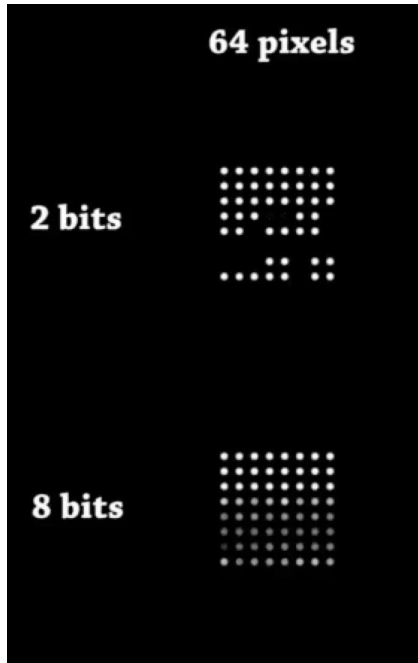
## Optogénétique



# Administration intravitéenne d'AAV2-7m8 codant RdCVF relenti la dégénérescence des cônes



# Restauration visuelle par implants versus l'optogénétique

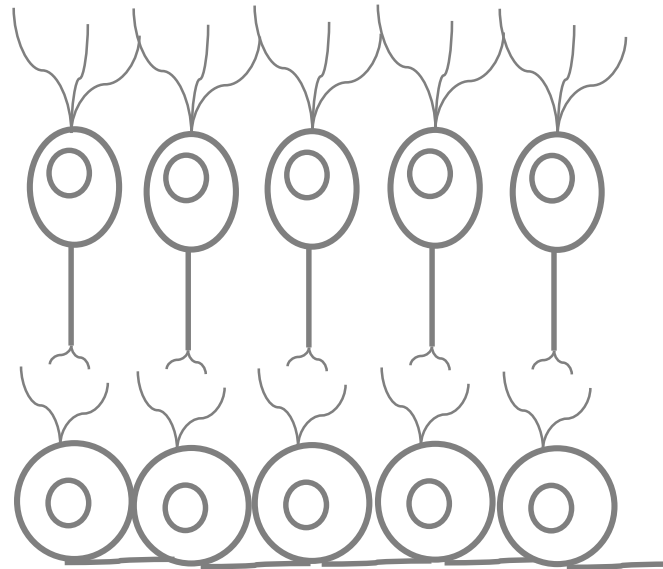
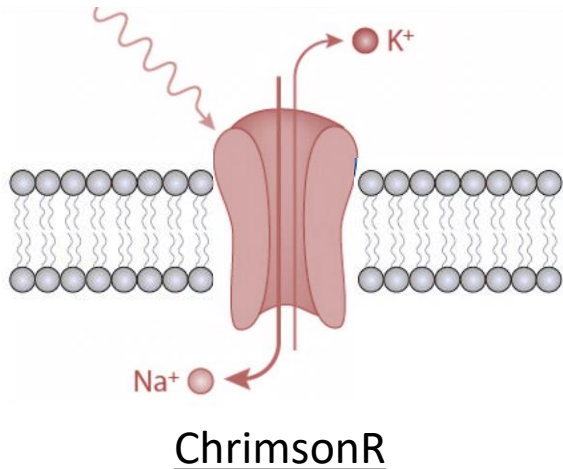
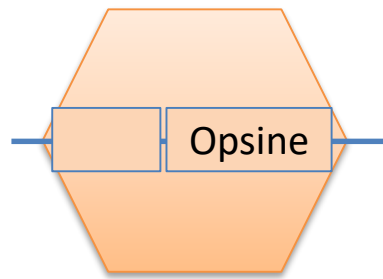




# L'optogénétique transforme chaque neurone en cellule photoréceptrice

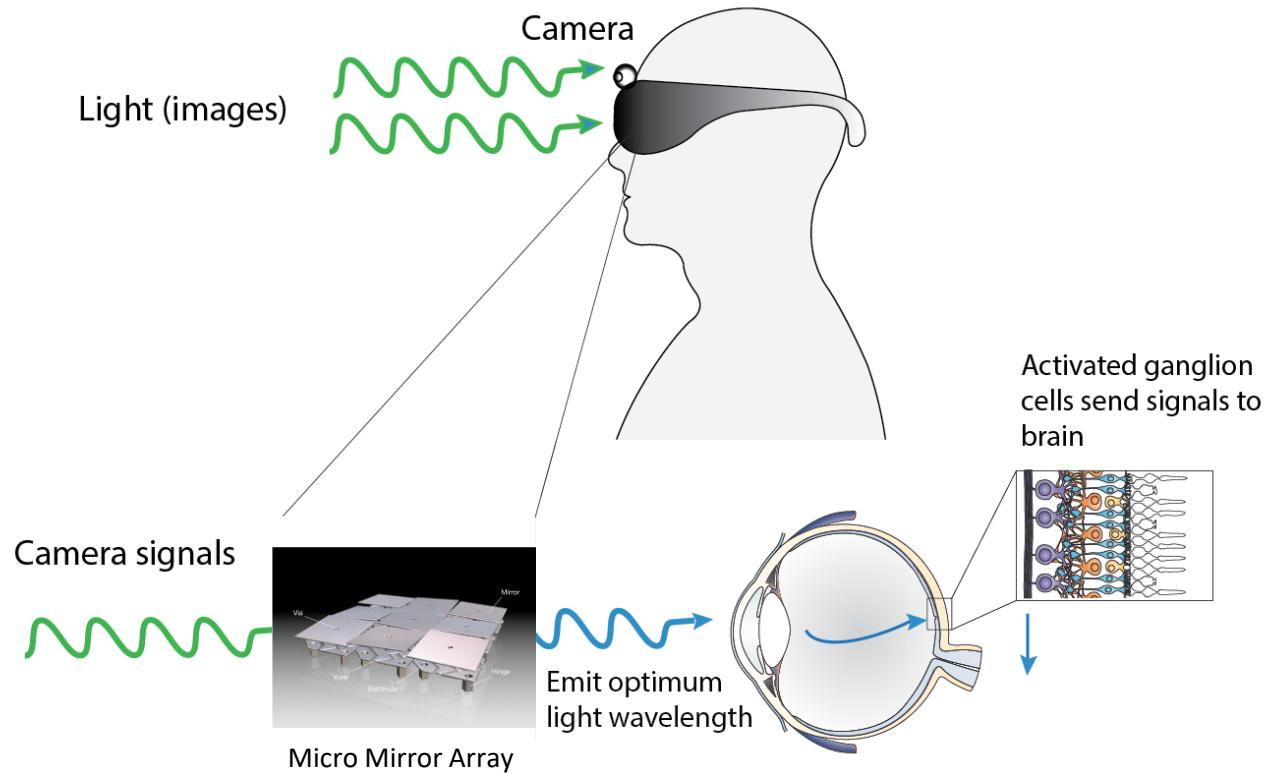
GS030

AAV2-7m8



# Development des lunettes de stimulation

- The big picture: product development (vector technology and glasses)





Mélissa Desrosiers  
 Hanen Khabou  
 Arthur Planul  
 Marcela Garita  
 Céline Winckler  
 Cardillia-Joe Simon

Céline Nouvel-Jaillard  
**Stéphane Bertin**  
 Elena Brazhnikova

**José-Alain Sahel**  
**Thierry Leveillard**  
**Serge Picaud**  
**Jens Duebel**  
 Emilie Macé  
 Olivier Marre  
 Antoine Chaffiol  
 Romain Caplette  
 Elisabeth Dubus

Botond Roska  
 Ernst Bamberg  
 John Flannery  
 David Schaffer  
 Ed Boyden  
 Karl Deisseroth



Max-Planck-Innovation

