

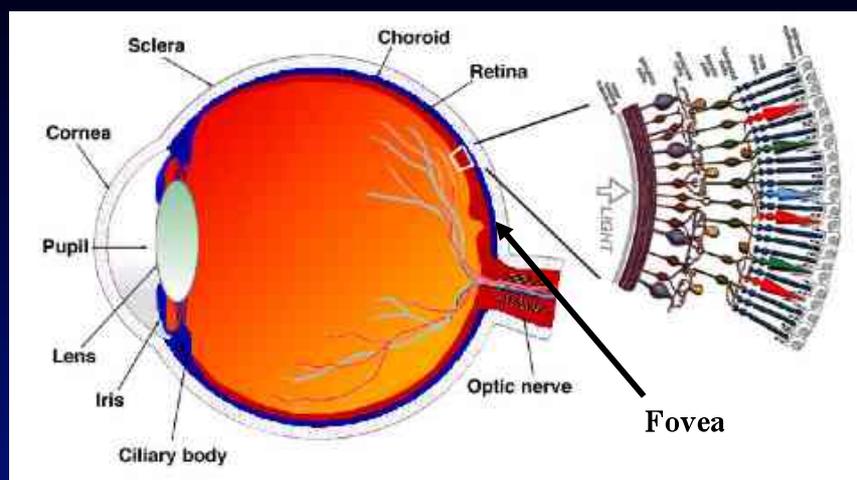
# Maladies Rétiniennes: Stratégies thérapeutiques et nouvelles perspectives

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*Serge.picaud@inserm.fr*

## La structure de l'oeil

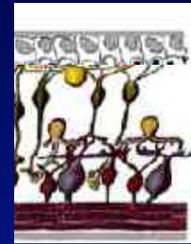


## Pathologies avec dégénérescence des photorécepteurs

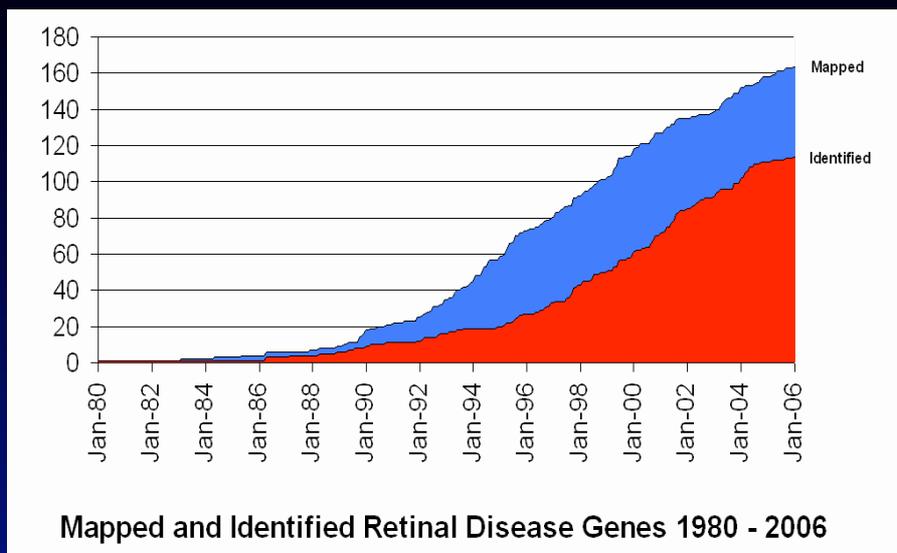
- Dégénérescence maculaire liée à l'âge en France plus de 1,5 M dont 10-20% malvoyants



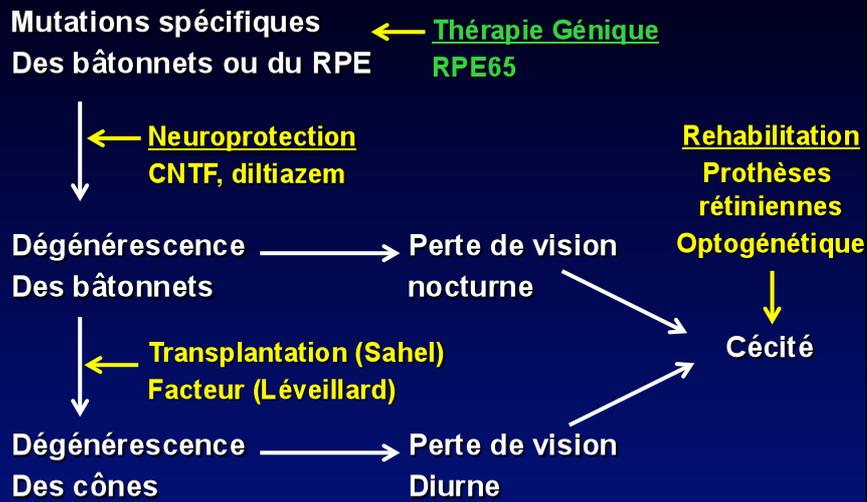
- Rétinopathies pigmentaires 1/4000 naissances



## Hétérogénéité génétique



## Approches thérapeutiques et réparatrices

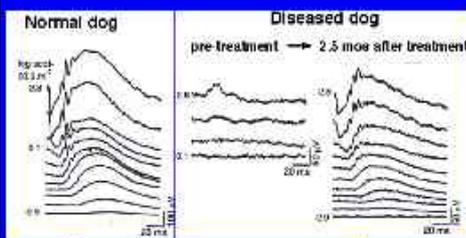


## Gene Therapy

Acland G. M *et al.* (2001) Gene therapy restores vision in a canine model of childhood blindness. *Nat Genet* **28**, 92-95.

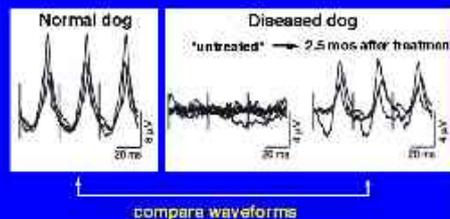


RESULTS: Treatment allows the retina to develop an electrical response (electroretinogram, ERG)



ERG data after dark adaptation collected by B. Janssen, A. G. Davidson & T. Aleman

RESULTS: Treatment allows the retina to develop a cone-mediated electrical response (electroretinogram, ERG)



ERG data pre-treatment performed by S. J. Cottrell, A. G. Davidson & T. Aleman

## Essais cliniques par thérapie génique

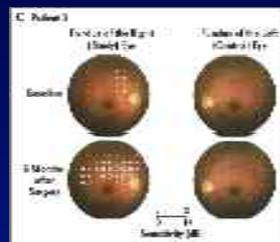
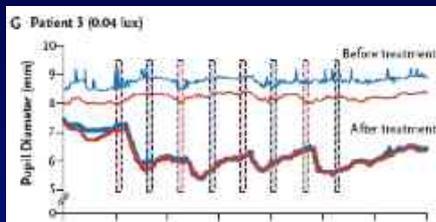
### Effect of Gene Therapy on Visual Function in Leber's Congenital Amaurosis

James W.B. Bainbridge, Ph.D., F.R.C.Ophth., Alexander J. Smith, Ph.D.

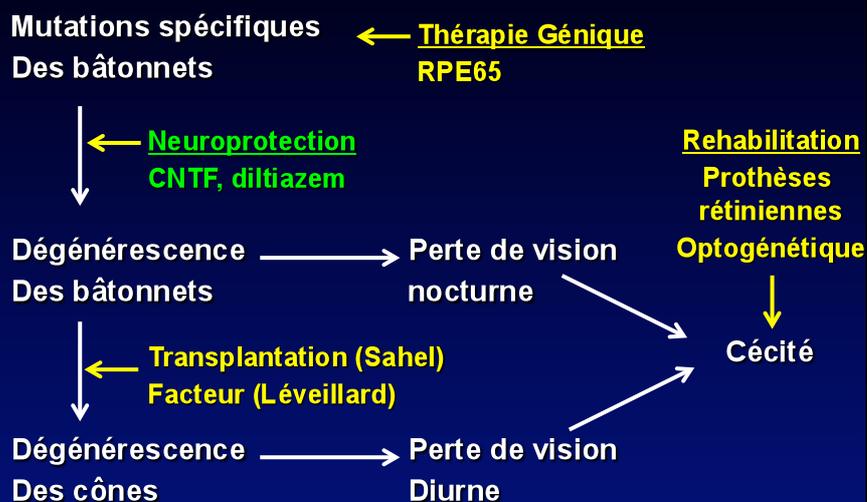
### Safety and Efficacy of Gene Transfer for Leber's Congenital Amaurosis

Albert M. Maguire, M.D., Francesca Simonelli, M.D., Eric A. Pierce, M.D., Ph.D.

N ENGL J MED 358;21 WWW.NEJM.ORG MAY 22, 2008

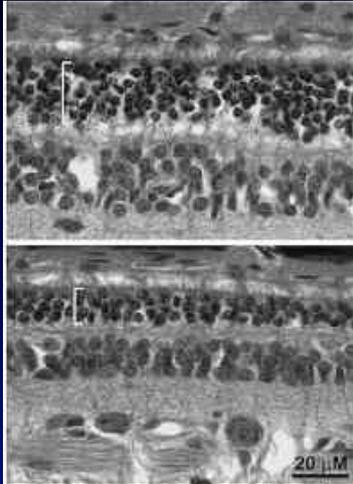


## Approches thérapeutiques et réparatrices

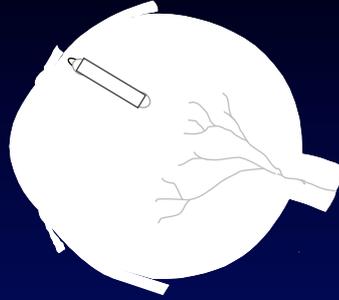


## Le CNTF protège les photorécepteurs des chiens rcd

CNTF



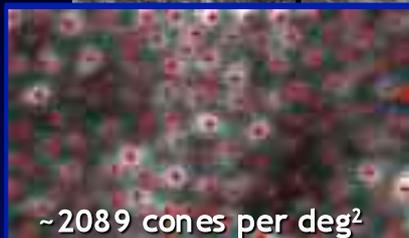
Contrôle



Tao W. *et al.* (2002) Encapsulated cell-based delivery of CNTF reduces photoreceptor degeneration in animal models of retinitis pigmentosa. *Invest Ophthalmol Vis Sci* **43**, 3292-3298.

Baseline

21 months later



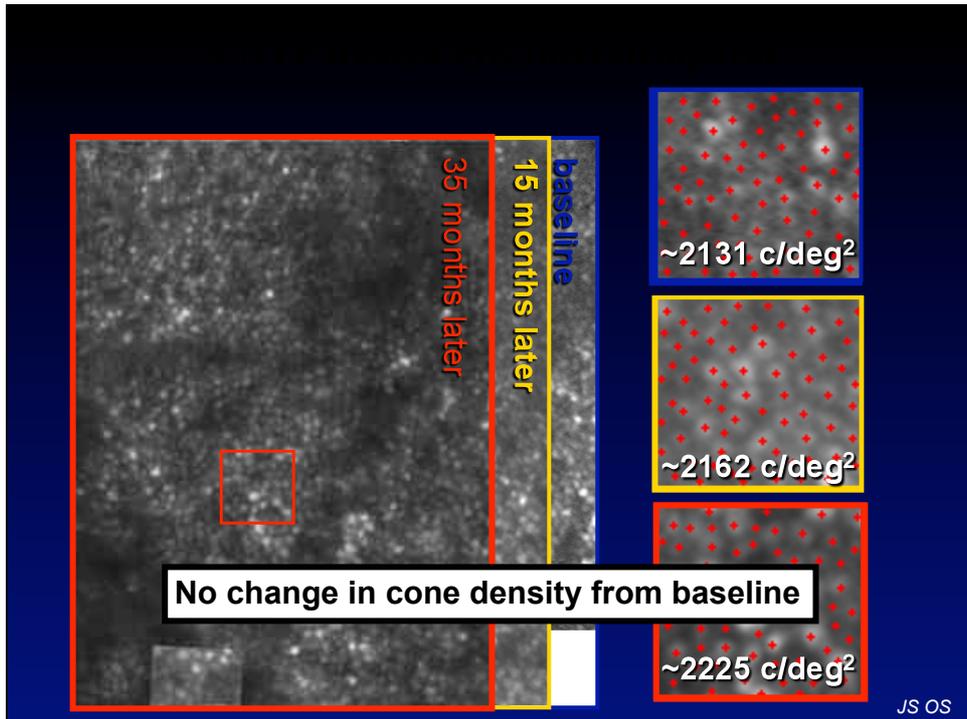
~2089 cones per deg<sup>2</sup>



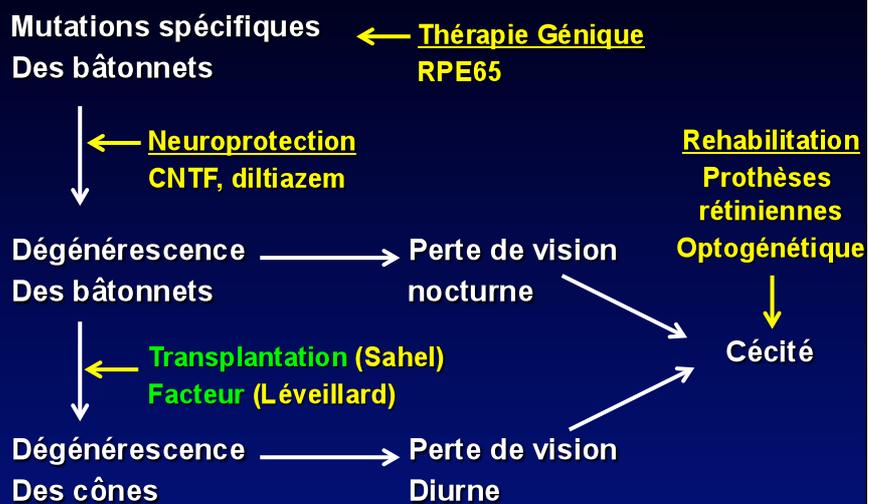
~1593 cones per deg<sup>2</sup>

~24% drop in cone density from baseline

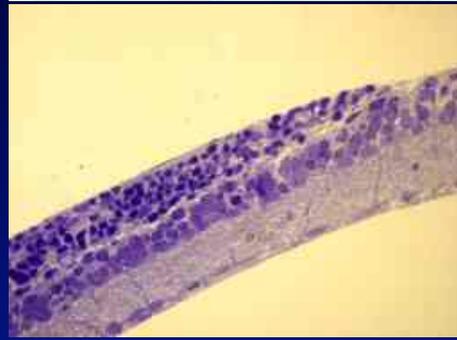
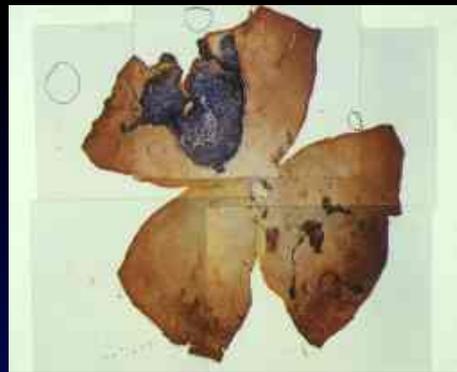
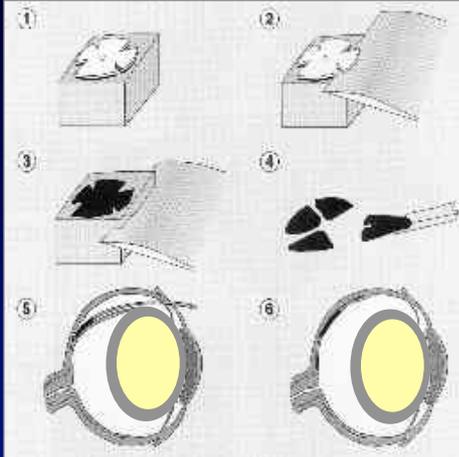
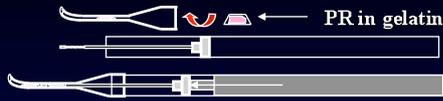
JS OD



## Approches thérapeutiques et réparatrices



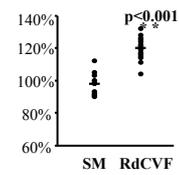
## PR transplantation



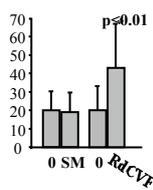
## RdCVF protein increases cone survival and preserves cone function

### RdCVF protein injections

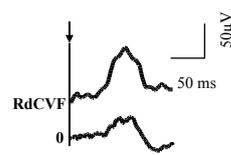
A Cone density



B Photopic b-wave amplitude ( $\mu\text{V}$ )

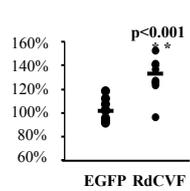


C Photopic ERG

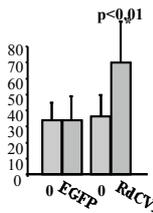


### AAV2.5-RdCVF injection

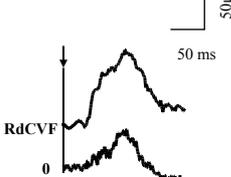
D Cone density



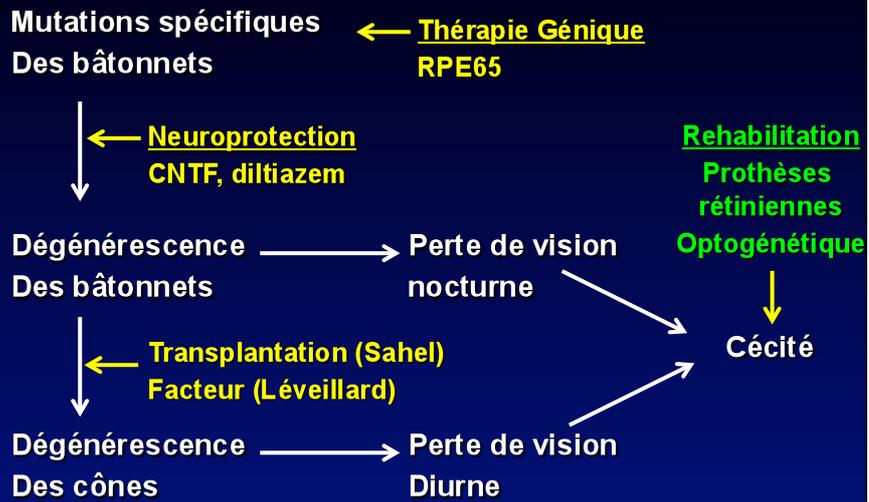
E Photopic b-wave amplitude ( $\mu\text{V}$ )



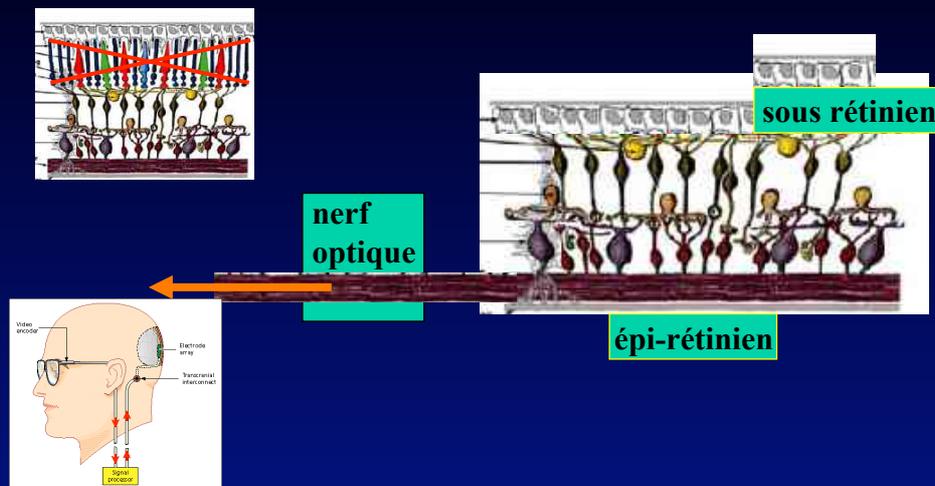
F Photopic ERG



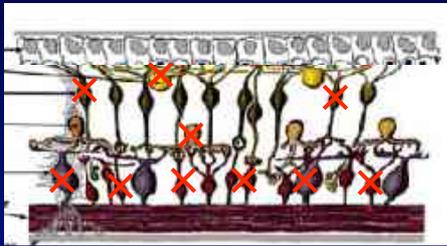
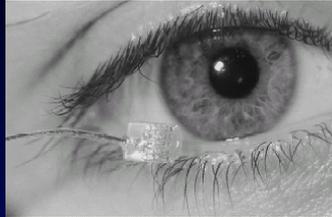
## Approches thérapeutiques et réparatrices



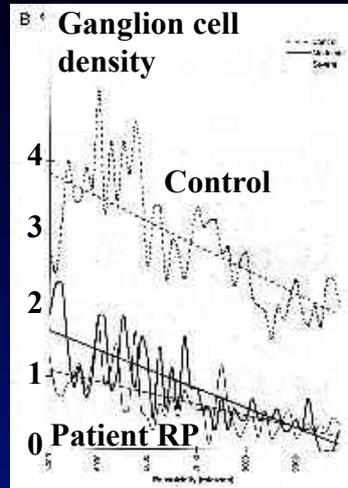
## Le concept de la rétine artificielle: Stimulation électrique des neurones rétiniens



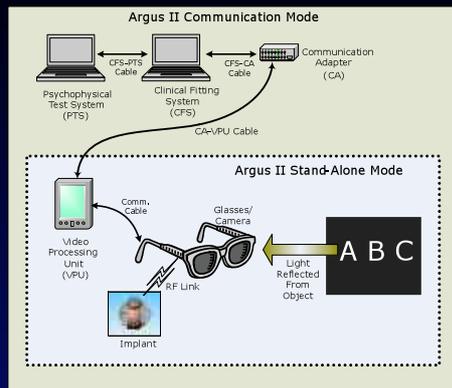
## Dégénérescence des cellules ganglionnaires



(Humayun et al., 1999a,b)



## Implant rétinien ARGUS II : 60 électrodes



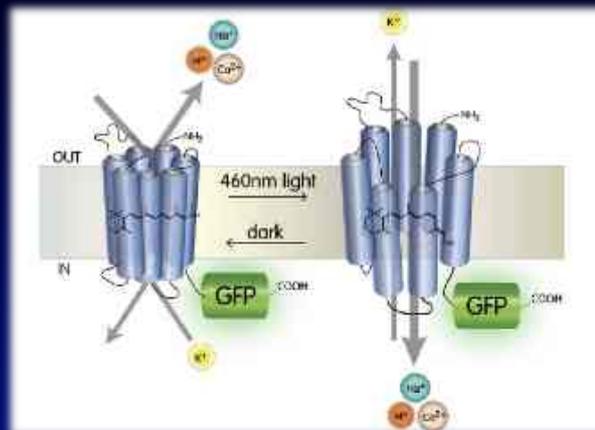
Durée de l'étude : 3 ans  
 Visites de contrôles trimestrielles  
**Entraînement et Stimulations rétiniennes hebdomadaires**  
 A la fin de l'étude, le sujet peut garder et utiliser l'implant

## Quel est notre objectif ?



## Thérapie génique avec les rhodopsine-canaux, des canaux ioniques ouverts par la stimulation lumineuse

Nagel et al. PNAS 2003, 100:13940



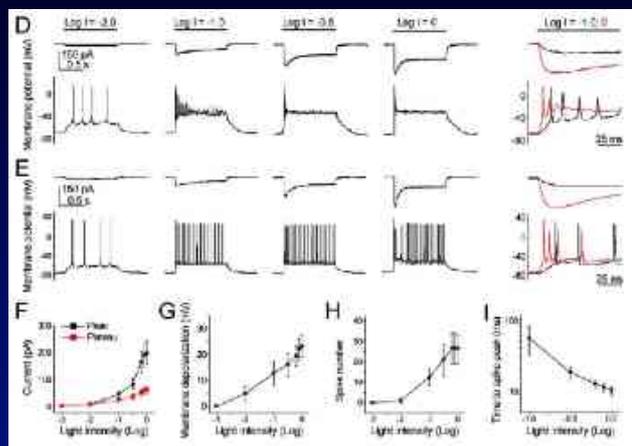
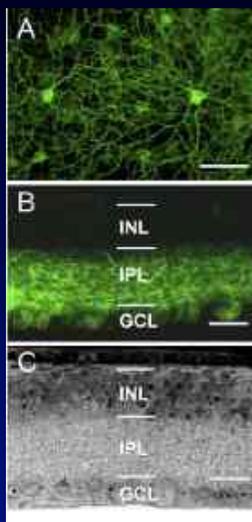
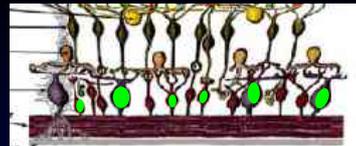
Flannery & Greenberg, Neuron 2006

# Performances visuelles



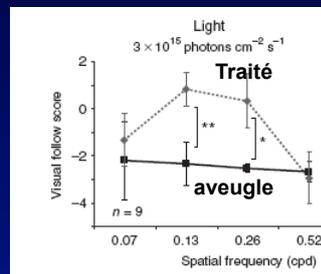
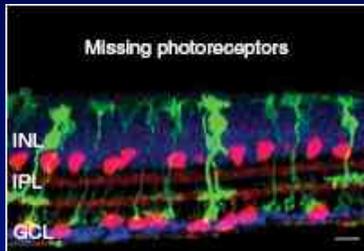
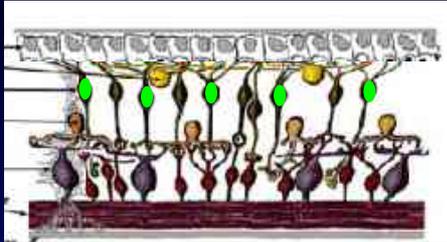
# Introduction dans les cellules ganglionnaires

Bi et al. Neuron 2006, 50:23-33



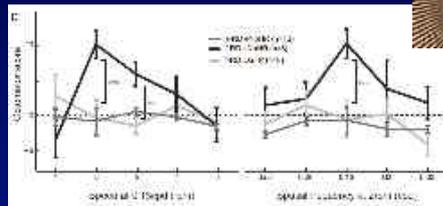
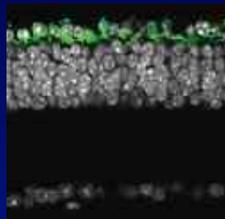
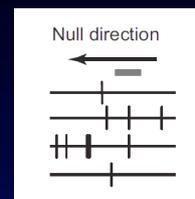
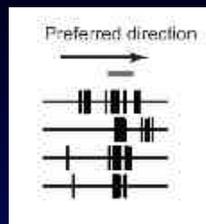
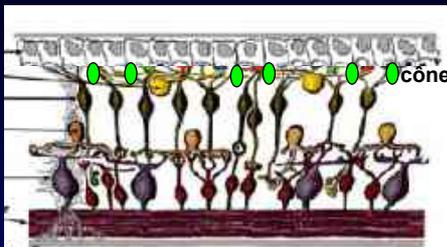
## Introduction dans les cellules bipolaires: réhabilitation visuelle

- Protéine sensible à la lumière introduite par thérapie génique



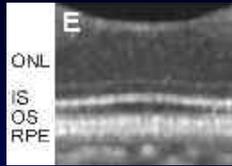
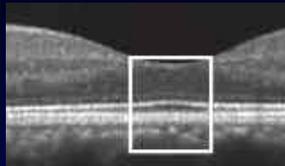
## Introduction dans des photorécepteurs insensibles à la lumière

- Protéine sensible à la lumière introduite par thérapie génique

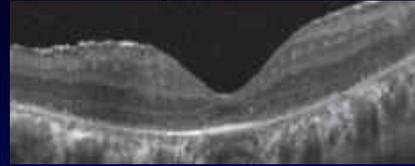


## Application aux patients atteints de rétinopathie pigmentaire

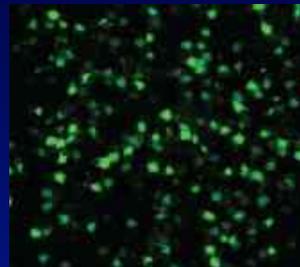
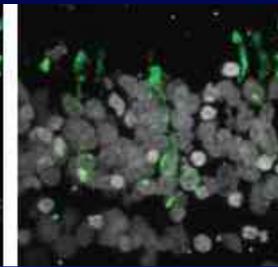
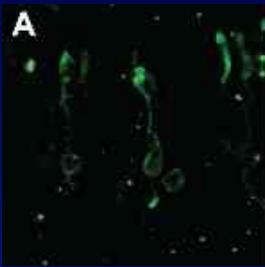
Personne sans pathologie



Patient aveugle par rétinopathie pigmentaire



Expression dans des Photorécepteurs humains postmortem



## L'Institut Vision : Janvier 2008

**L'Institut de la Vision**  
(6000 m<sup>2</sup>)

- Laboratoire Académiques
- Entreprises
- Plateformes communes

**Centre d'Investigation Clinique en ophtalmologie**

- 400 m<sup>2</sup>

**Strasbourg (1992)**

150m<sup>2</sup>

(2002 transfert de 20 personnes à Paris)

