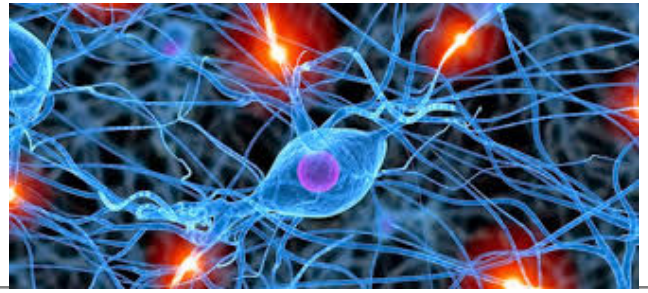
El Futuro de la Neuro-Oftalmología.



Ane Pérez Sarriegui

Hospital Universitario Ramón y Cajal

Discutidor Senior: Dr. Julio González Martín-Moro

"El mejor modo de predecir el futuro es inventándolo"

OCT

TERAPIA GÉNICA

TTO INTRAVITREO

CÉLULAS MADRE

NEUROPROTECCIÓN

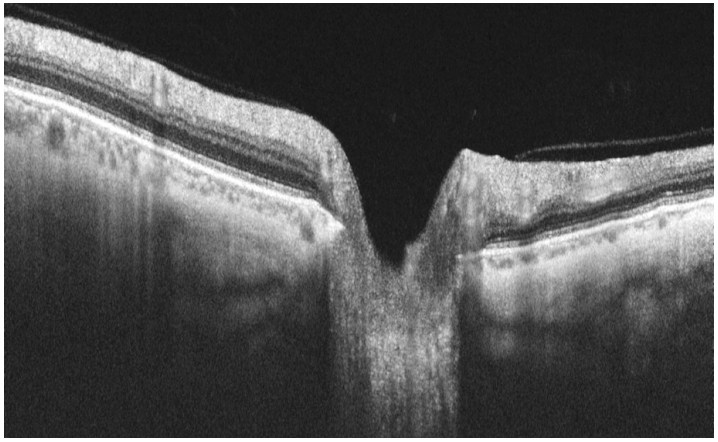
NEUROREGENERACIÓN

BIOMARCADORES

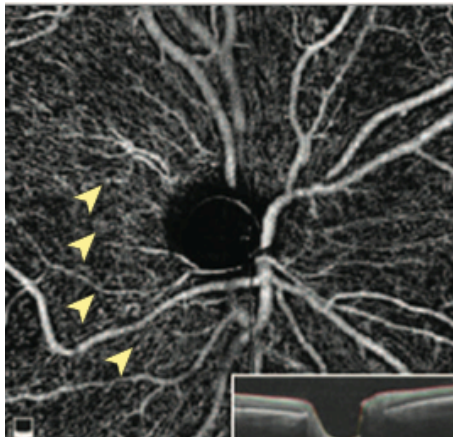
MODELOS ANIMALES

DIAGNÓSTICO

OCT



PROFUNDIDAD

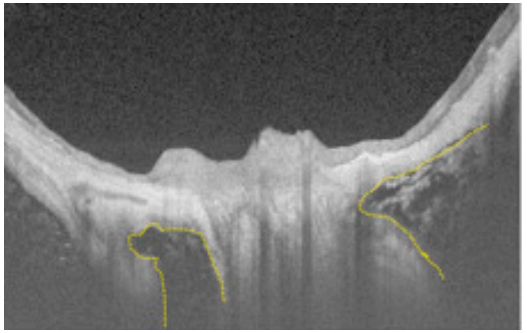


ESTUDIO VASCULAR ONH

OCT

Diagnóstico
Follow-Up
Pronóstico

1. Estudio individual de las 10 capas de la retina
   - Ej: Importancia de las células ganglionares: daño estructural precoz.
2. Biomarcardores de enfermedad
   - Ej: Enf Parkinson, Enf Alzheimer
3. Diagnostico Diferencial
   - Ej: Esclerosis Múltiple vs Nueromielitis Óptica
4. Profundidad:
   1. Lámina cribosa
   2. Espacio Subaracnoideo perióptico



ANGIO-OCT

Vacularización cabeza del nervio óptico

- Densidad y Flujo vascular.
- Red capilar peripapilar.
- 3D.
- Estudio de la vascularización peripapilar por capas.

YA ESTUDIADO EN
- Glaucoma
- Esclerosis Múltiple
- NOHL

¿Qué se me ocurre?

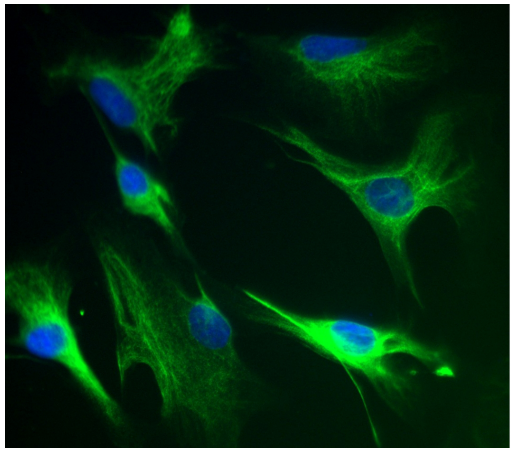
1. Correlacionar déficit vascular con alteración campimétrica.
2. Estudiarlo en
   - Enfermedades Neurodenerativas.
   - NOIANA: Etiopatogénia
   - Edema NO: Px visual?

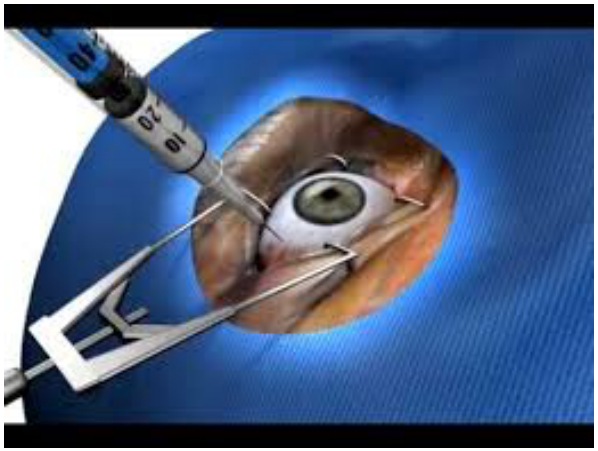
TRATAMIENTO

NEUROPROTECCIÓN

NEUROREGENERACIÓN

TERAPIA GÉNICA

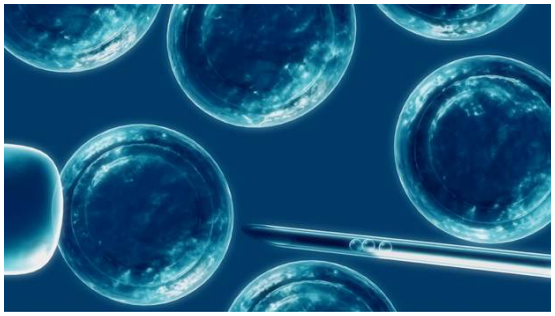




1. NEUROPROTECCIÓN NEUROREGENERACIÓN

Células ganglionares de la retina

1. Células madre
   - Neurales
   - Mesenquimales
2. Factores neurotróficos
3. Antioxidantes



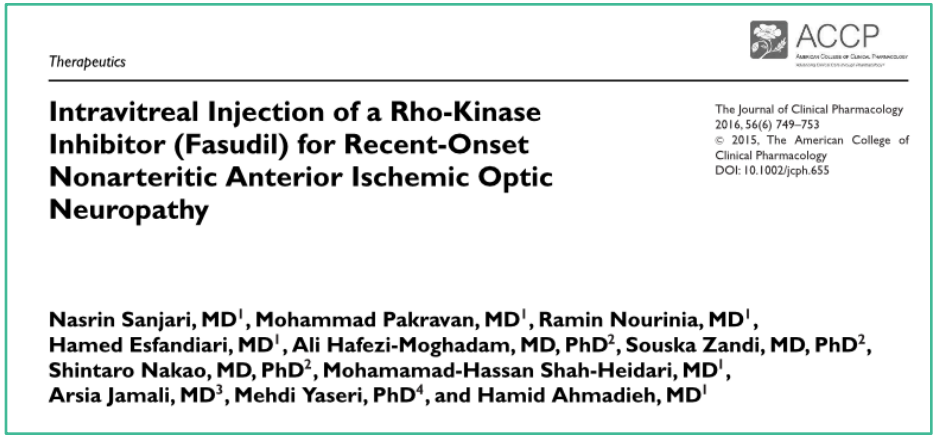
NOIANA

QPI-1007
(Inhibe expresión caspasa 2)

Inhibe apoptosis celular

FASUDIL
(Inhibidor Rho-Kinasa)

Inhibe inflamación
Aumenta el flujo vascular



Therapeutics

ACCP

Intravitreal Injection of a Rho-Kinase Inhibitor (Fasudil) for Recent-Onset Nonarteritic Anterior Ischemic Optic Neuropathy

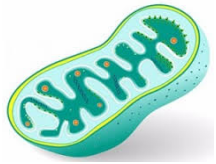
The Journal of Clinical Pharmacology
2016, 56(6) 749–753

DOI: 10.1002/jcph.655

Nasrin Sanjari, MD[1], Mohammad Pakravan, MD[1], Ramin Nourinia, MD[1], Hamed Esfandiari, MD[1], Ali Hafezi-Moghadam, MD, PhD[2], Souska Zandi, MD, PhD[2], Shintaro Nakao, MD, PhD[2], Mohamamad-Hassan Shah-Heidari, MD[1], Arsia Jamali, MD[3], Mehdi Yaseri, PhD[4], and Hamid Ahmadieh, MD[1]

¿Etiopatogénia?
¿ Ensayos Clínicos Controlados, Aleatorizados?
¿Prevención de afectación contralateral?

NOHL



1. IDEBENONA

2. EPI-743

A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy

Thomas Klopstock,[1] Patrick Yu-Wai-Man,[2,3,4] Konstantinos Dimitriadis,[1] Jacinthe Rouleau,[5] Suzette Heck,[1] Maura Bailie,[2,3,4] Alaa Atawan,[2,3,4] Sandip Chattopadhyay,[2,3,4] Marion Schubert,[1] Aylin Garip,[6] Marcus Kernt,[6] Diana Petraki,[7] Christian Rummey,[7] Mika Leinonen,[8] Günther Metz,[7] Philip G. Griffiths,[2,3,4] Thomas Meier[7] and Patrick F. Chinnery[2,3,4]

¿?

ORIGINAL CONTRIBUTION

Effect of EPI-743 on the Clinical Course of the Mitochondrial Disease Leber Hereditary Optic Neuropathy

Alfredo A. Sadun, MD, PhD; Carlos Filipe Chicani, MD, PhD; Fred N. Ross-Cisneros, BA; Piero Barboni, MD; Martin Thoolen, PhD; William D. Shrader, PhD; Kenneth Kubis, MD; Valerio Carelli, MD, PhD; Guy Miller, MD, PhD

Objective: To evaluate the safety and efficacy of a new therapeutic agent, EPI-743, in Leber hereditary optic neuropathy (LHON) using standard clinical, anatomic, and functional visual outcome measures.

Design: Open-label clinical trial.

Setting: University medical center.

Patients: Five patients with genetically confirmed LHON with acute loss of vision were consecutively enrolled and treated with the experimental therapeutic agent EPI-743 within 90 days of conversion.

Intervention: During the course of the study, 5 consecutive patients received EPI-743, by mouth, 3 times daily (100-400 mg per dose).

Main Outcome Measures: Treatment effect was assessed by serial measurements of anatomic and functional visual indices over 6 to 18 months, including Snellen visual acuity, retinal nerve fiber layer thickness measured by optical coherence tomography, Humphrey visual fields (mean decibels and area with 1–log unit depression), and color vision. Treatment effect in this clinical proof of principle study was assessed by comparison of the prospective open-label treatment group with historical controls.

Results: Of 5 subjects treated with EPI-743, 4 demonstrated arrest of disease progression and reversal of visual loss. Two patients exhibited a total recovery of visual acuity. No drug-related adverse events were recorded.

Conclusions: In a small open-label trial, EPI-743 arrested disease progression and reversed vision loss in all but 1 of the 5 consecutively treated patients with LHON. Given the known natural history of acute and rapid progression of LHON resulting in chronic and persistent bilateral blindness, these data suggest that the previously described irreversible priming to retinal ganglion cell loss may be reversed.

Arch Neurol. 2012;69(3):331-338

2. TERAPIA GÉNICA

1. Manipular la información genética de células con mutación para corregir un defecto genético.
2. Dotar a las células de una nueva función que les permita superar una alteración.

Vectores → Virus Adeno Asociados (AAV)

Neuropatía Óptica de Leber (NOHL)

1. Genes y mutaciones conocidas.
2. Diana conocida (CGR).
3. Inoculación directa (intravitrea).
4. Privilegio Inmune
5. Periodo ventana.

NOHL

TERAPIA GÉNICA

(Expresión alotópica)

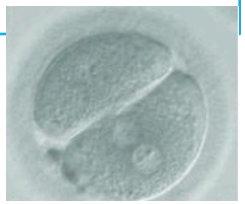
Efficacy and Safety of rAAV2-ND4 Treatment for Leber's Hereditary Optic Neuropathy

Xing Wan[1,*], Han Pei[1,*], Min-jian Zhao[2,*], Shuo Yang[1,*], Wei-kun Hu[1], Heng He[1], Si-qi Ma[1], Ge Zhang[3], Xiao-yan Dong[4], Chen Chen[5], Dao-wen Wang[5] & Bin Li[1]

Leber's hereditary optic neuropathy (LHON) is a mitochondrially inherited disease leading to blindness. A mitochondrial DNA point mutation at the 11778 nucleotide site of the NADH dehydrogenase subunit 4 (*ND4*) gene is the most common cause. The aim of this study was to evaluate the efficacy and safety of a recombinant adeno-associated virus 2 (AAV2) carrying *ND4* (rAAV2-ND4) in LHON patients carrying the G11778A mutation. Nine patients were administered rAAV2-ND4 by intravitreal injection to one eye and then followed for 9 months. Ophthalmologic examinations of visual acuity, visual field, and optical coherence tomography were performed. Physical examinations included routine blood and urine. The visual acuity of the injected eyes of six patients improved by at least 0.3 log MAR after 9 months of follow-up. In these six patients, the visual field was enlarged but the retinal nerve fibre layer remained relatively stable. No other outcome measure was significantly changed. None of the nine patients had local or systemic adverse events related to the vector during the 9-month follow-up period. These findings support the feasible use of gene therapy for LHON.

¿Qué se me ocurre?

1. Vectores con acceso directo a la mitocondria.
2. Estudios multicentricos a nivel mundial.
3. "Prevenir es mejor que curar"
   - Reemplazar mtDNA en oocitos.



CONCLUSIONES