17 de noviembre de 2021

LIM21, a treatment for retinitis pigmentosa (RP) and age-related macular degeneration (AMD)

limnopharma

Dr. Elena Puerta-Fernández, CEO

Content

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2. The Product: LIM21

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b) Innovative mechanisms of action
c) Differential features facing the market
d) Current status of development
e) IPR protection
f) Pitfalls & Risks to be considered

3. Partnering Opportunities

Novel treatments for ocular diseases

Elena Puerta-Fernández, CEO

November 2021

New molecules

Mouse models

WO2018/096196

WO2018/100219

limnopharma

Founded 2019

Team

Dr. Elena Puerta
CEO

Dr. Juan C. Morales
Sci. Advisor & Founder

Dr. Francisco Díaz
Sci. Advisor & Founder

Dr. Natalia Pérez
Founder

Dr. David Alcántara
BD & Founder

Team

5 PhD's (Chemistry, Biochemistry, Medical Sciences)

UNIVERSIDAD DE GRANADA

CSIC Consejo Superior de Investigaciones Científicas

UAM Universidad Autónoma de Madrid

Universidad de Sevilla

Universidad de los Andes

95 years accumulated Research experience

University of East Anglia

University of Rochester

Okayama University

Harvard Medical School

Yale University

Stanford University

Université Bordeaux Segalen

Freie Universität Berlin

Uppsala Universitet

AIST National Institute of Advanced Industrial Science and Technology (AIST)

25 years accumulated Business experience

ABENGOA

BIOSEARCH LIFE

SACSIS Sociedad para el Avance Científico

Scientific Advisory Board

Prof. Claudio Punzo

- ✓ Professor of Ophthalmology **UMass Medical School**
- ✓ Animal models of retinal diseases
- ✓ **International expert in Retinitis Pigmentosa.**

Prof. Shomi Bhattacharya

- ✓ Emeritus Professor of Ophthalmology at **UCL**.
- ✓ Director of CABIMER from 2008 to 2016.
- ✓ **International expert in Retinitis Pigmentosa.**

Dr. Francisco Gómez-Ulla

- ✓ Founder and Director - **Gómez-Ulla Ophthalmological Institute**.
- ✓ Head of the Ophthalmology Hospital Universitario de Santiago.
- ✓ Over 40 years of **experience in macular degeneration.**

Dr. Javier Galán

- ✓ Director Pharmaceutical Development at ***Avizorex***.
- ✓ 20 years at *Alcon* as Director Pharm. Dev.
- ✓ Expert in **Ophthalmic Drug Delivery Technologies**.

Dr. Diego del Río

- ✓ Director of Strategic Planning & Business Analytics at ***Grifols***.
- ✓ MBA in General Management UC Berkeley
- ✓ Expert in **Business Development**

Awards

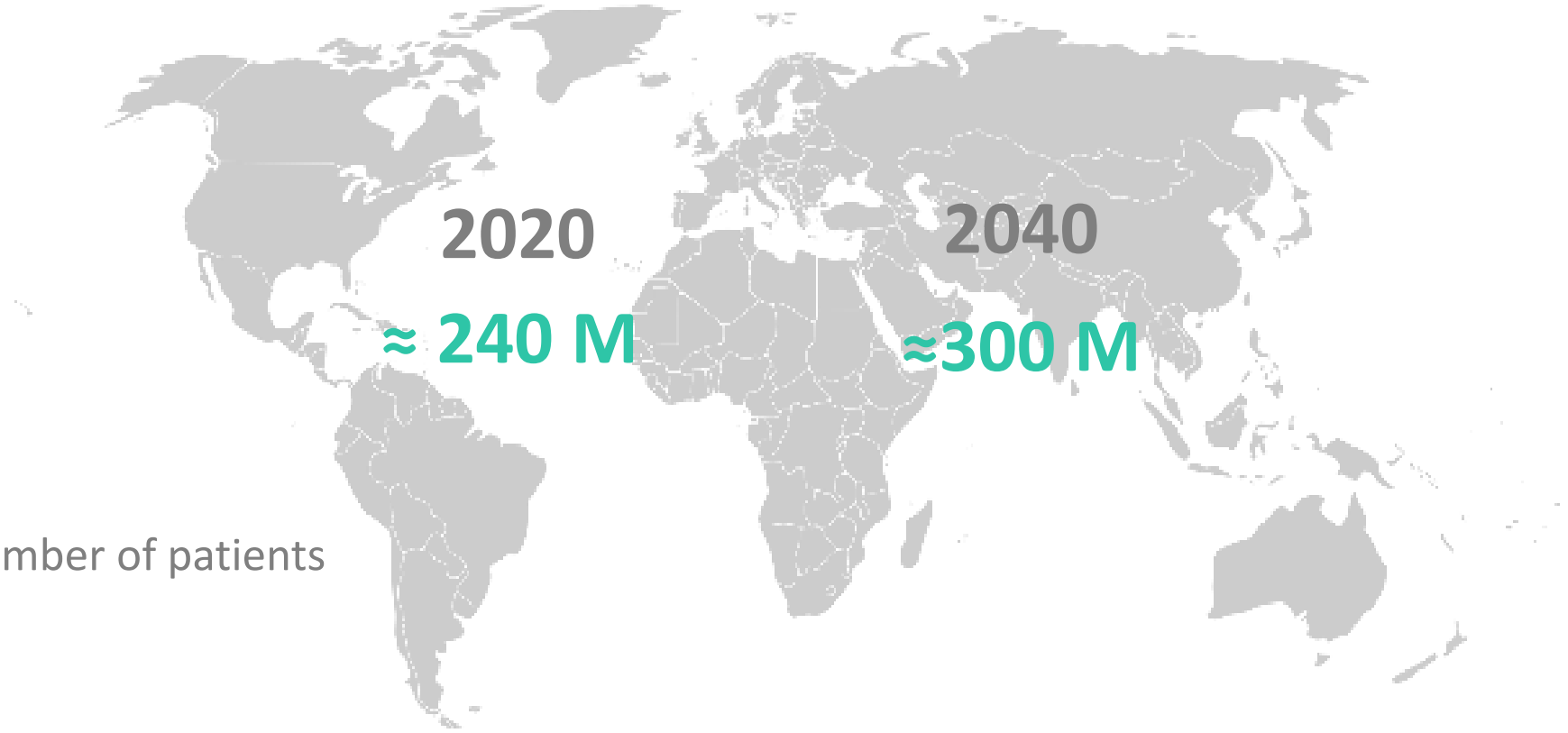
Avenir Matmut Start-Up Prize
Awarded 2019

Premio Everis España
Finalist 2020
(Top 5 out of 700 companies)

Startup Andalucía Roadshow
Awarded 2021

2.a. Target indications

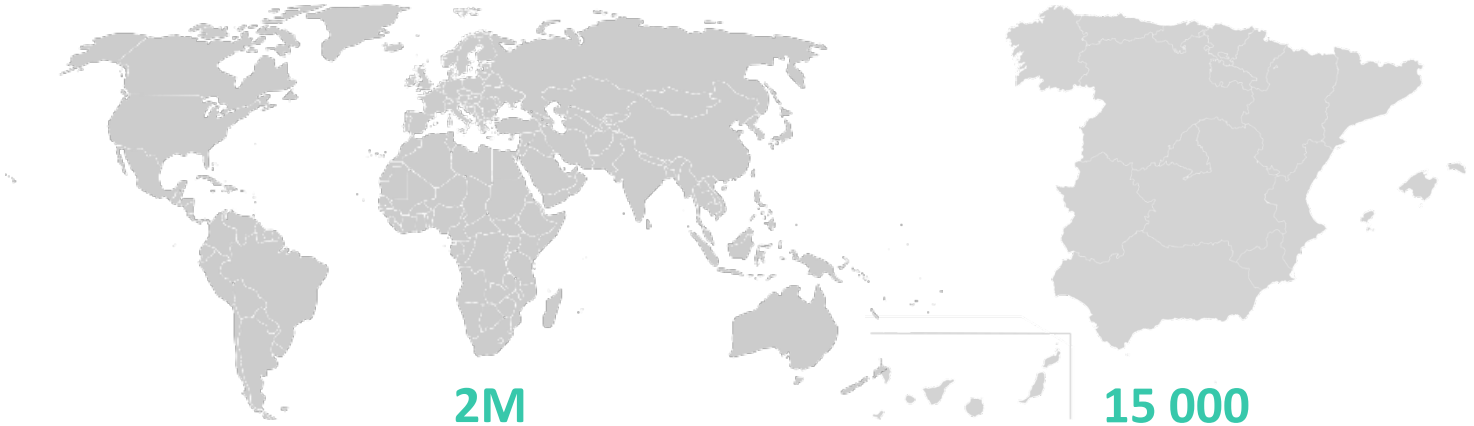
Retinal degenerative diseases leading to blindness



Estimated number of patients

Retinitis Pigmentosa,

a rare disease



Disease Prevalence

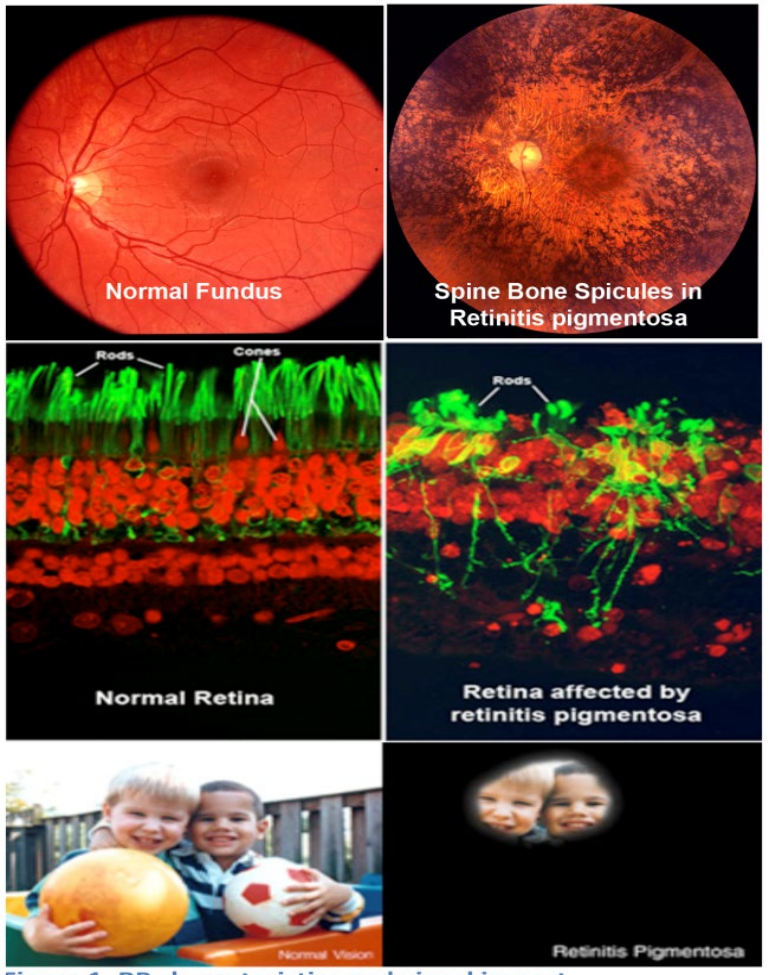


Figure 1. RP characteristics and visual impact

Current treatment

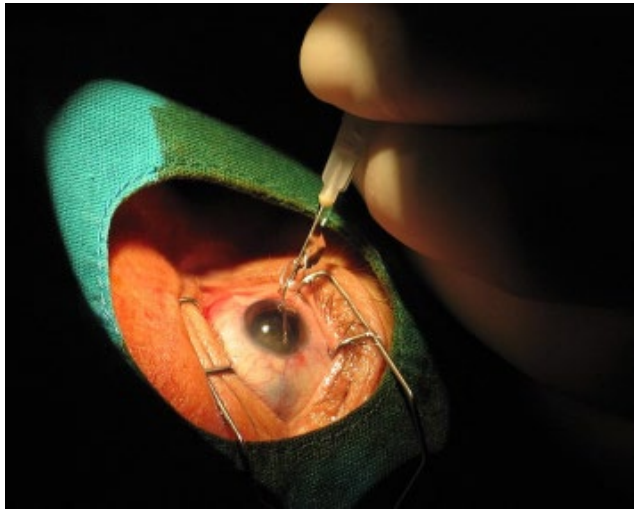
The only available treatment:

- Only for RPE65 (more than 80 genes)
- 98% of patients without treatment
- Treatment cost: $425.000/eye
- Subretinal injection (surgery room)

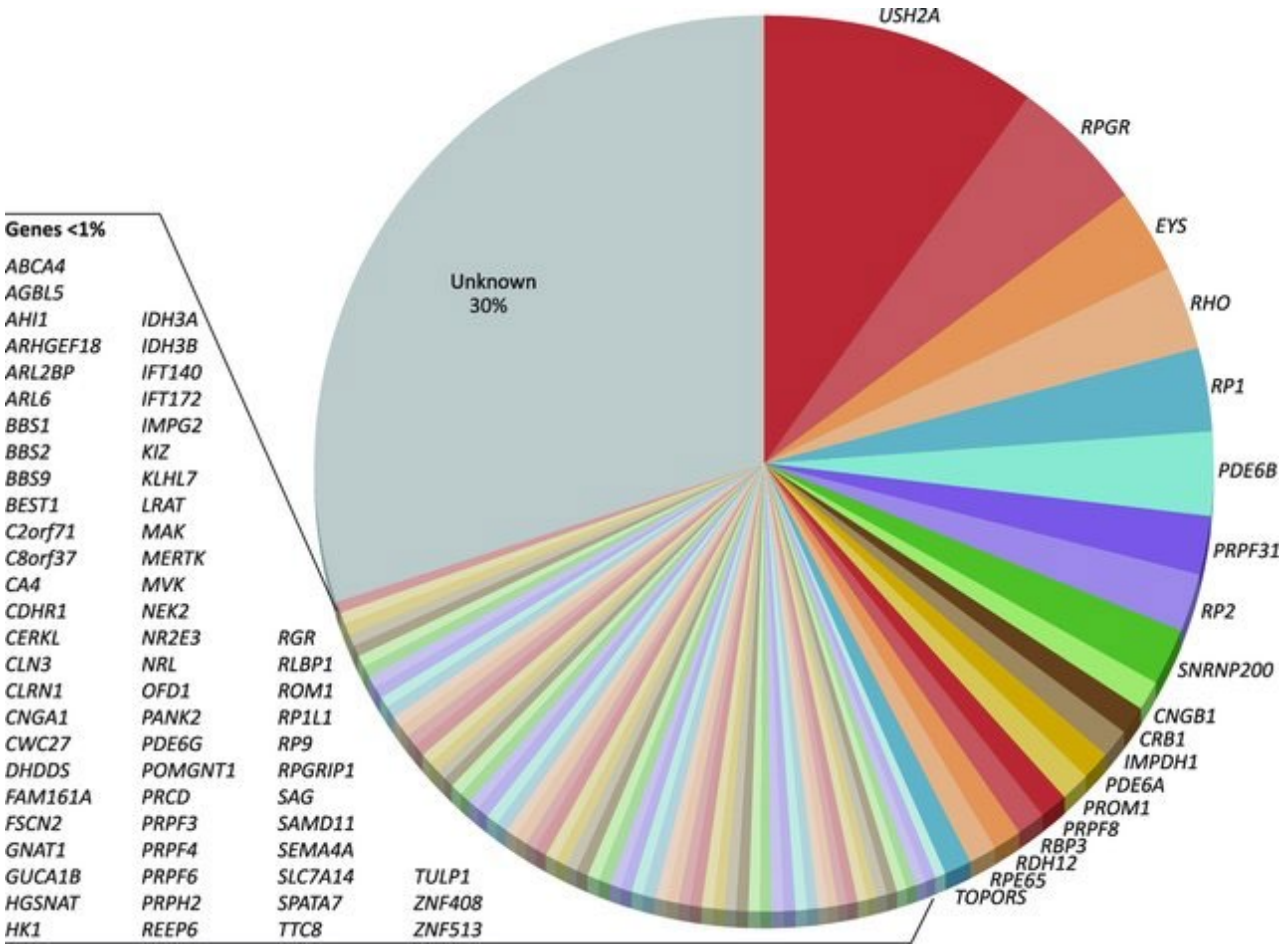
LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

NOVARTIS

Spark™ THERAPEUTICS

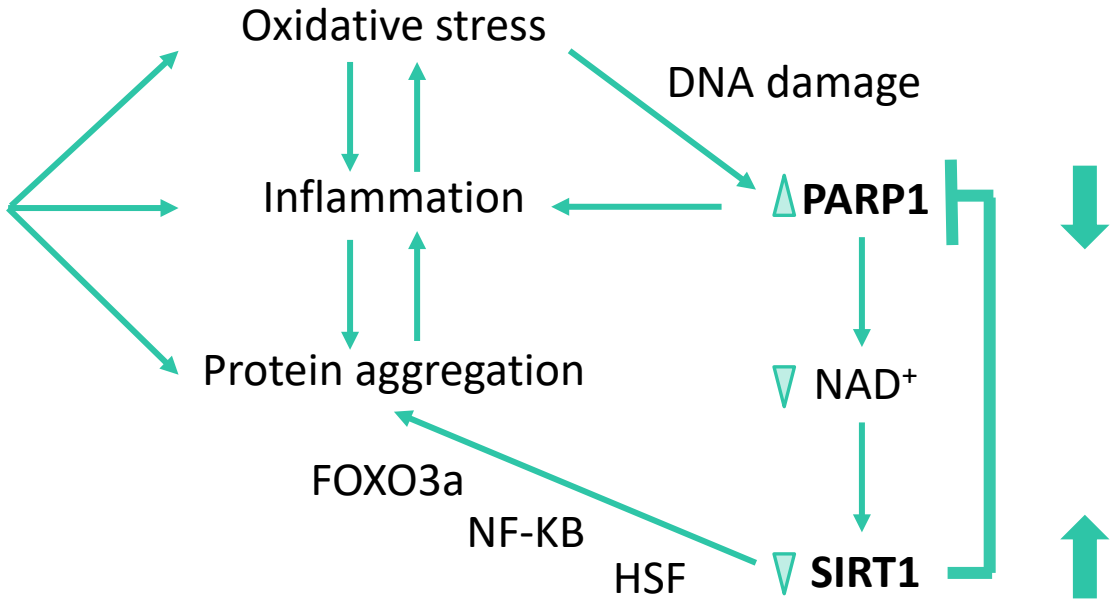


Retinitis Pigmentosa



Estimated relative contribution of genes to non-syndromic retinitis pigmentosa. (Verbakel, et al. 2018)

SIRT1/PARP1 balance and RP



Arango-Gonzalez B, et al. PLoS One. 2014 Nov 13;9(11):e112142.

SIRT1 as a therapeutic target

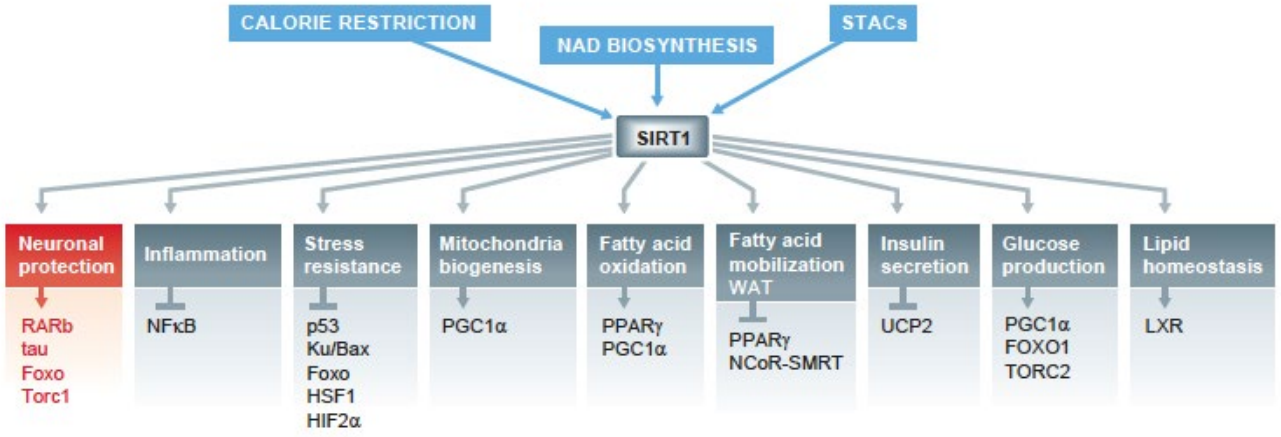
Sirtuins Expression and Their Role in Retinal Diseases

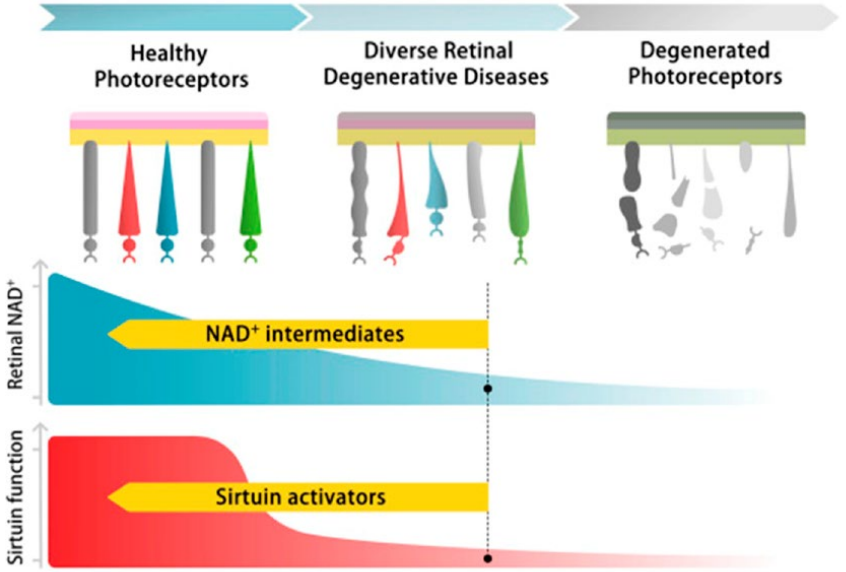
Sankarathi Balaiya,[1,2] Khaled K. Abu-Amero,[1,3] Altaf A. Kondkar,[3] and Kakarla V. Chalam[1]

Oxidative Medicine and Cellular Longevity 2017:3187594

NAD+ and sirtuins in retinal degenerative diseases: a look at future therapies

Jonathan B. Lin[1,2] and Rajendra S. Apte[1,2,3,4,*] *Prog Retin Eye Res.* 2018 November ; 67: 118–129.





Donmez, Outeriro, EMBO Mol Med, 2013 Mar;5(3):344-52

PARP-1 inhibition

Excessive Activation of Poly(ADP-Ribose) Polymerase Contributes to Inherited Photoreceptor Degeneration in the Retinal Degeneration 1 Mouse

François Paquet-Durand,[1]* José Silva,[1]* Tanuja Talukdar,[1] Leif E. Johnson,[1] Seifollah Azadi,[1] Theo van Veen,[1] Marius Ueffing,[2,3] Stefanie M. Hauck,[2] and Per A. R. Ekström[1]

The Journal of Neuroscience, September 19, 2007 • 27(38):10311–10319 • **10311**

Olaparib significantly delays photoreceptor loss in a model for hereditary retinal degeneration

Ayse Sahaboglu[1,*], Melanie Barth[1,2,*], Enver Secer[1,3], Eva M. del Amo[4], Arto Urtti[4,5], Yvan Arsenijevic[6], Eberhart Zrenner[1] & François Paquet-Durand[1]

SCIENTIFIC REPORTS | 6:39537 | DOI: 10.1038/srep39537

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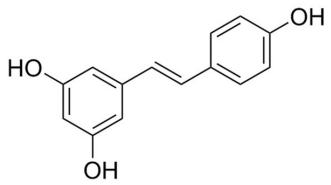
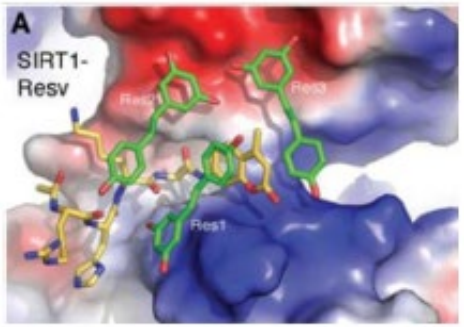
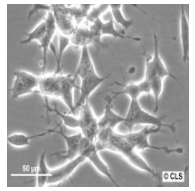
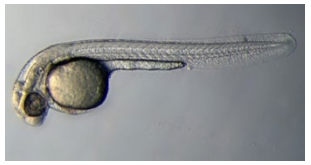
Our approach

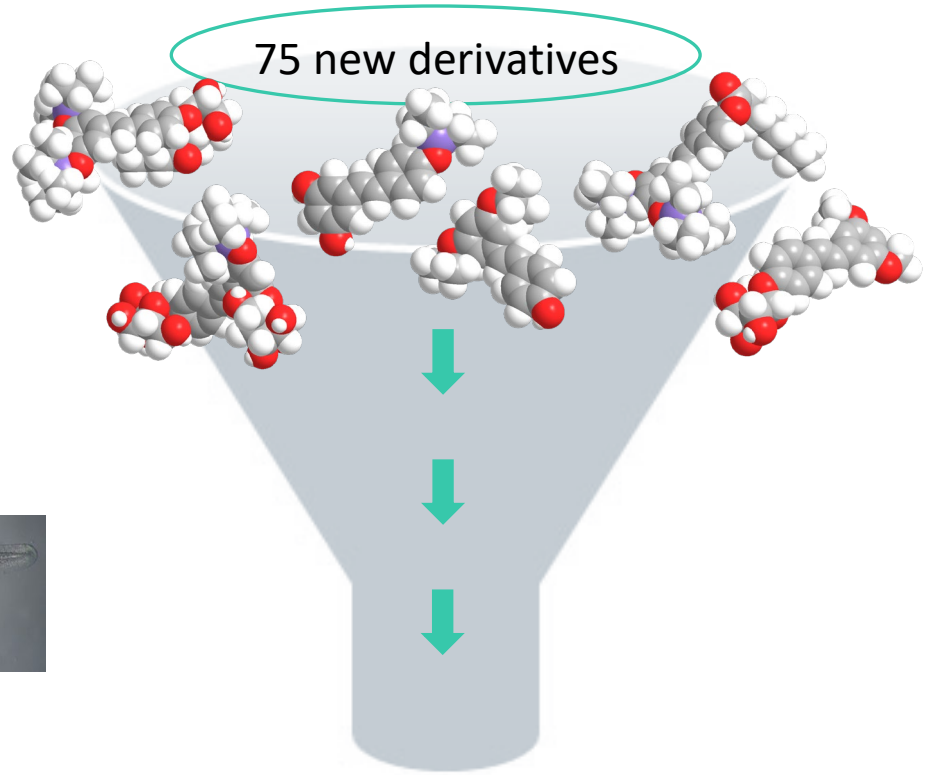




- Natural product as HIT
- Rational design of derivatives & chemical synthesis







LIM21

LIM24

LIM109

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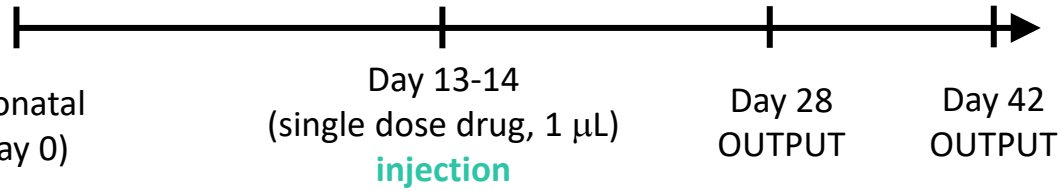
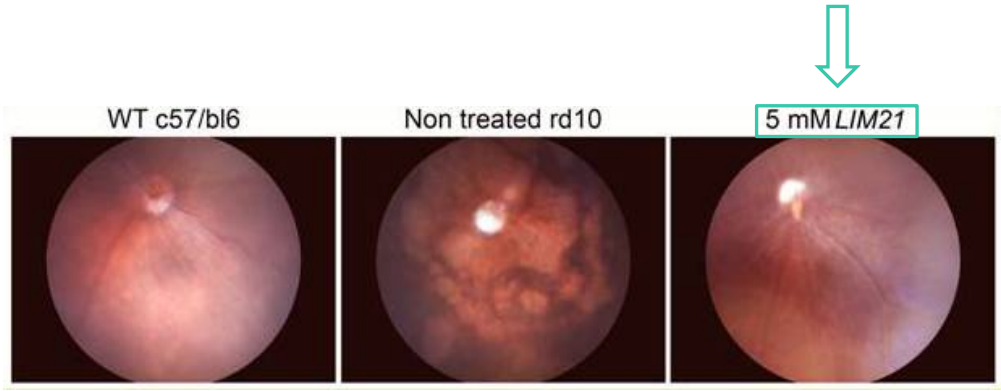
Junta de Andalucía
Fundación Progreso y Salud
Consejería de Salud

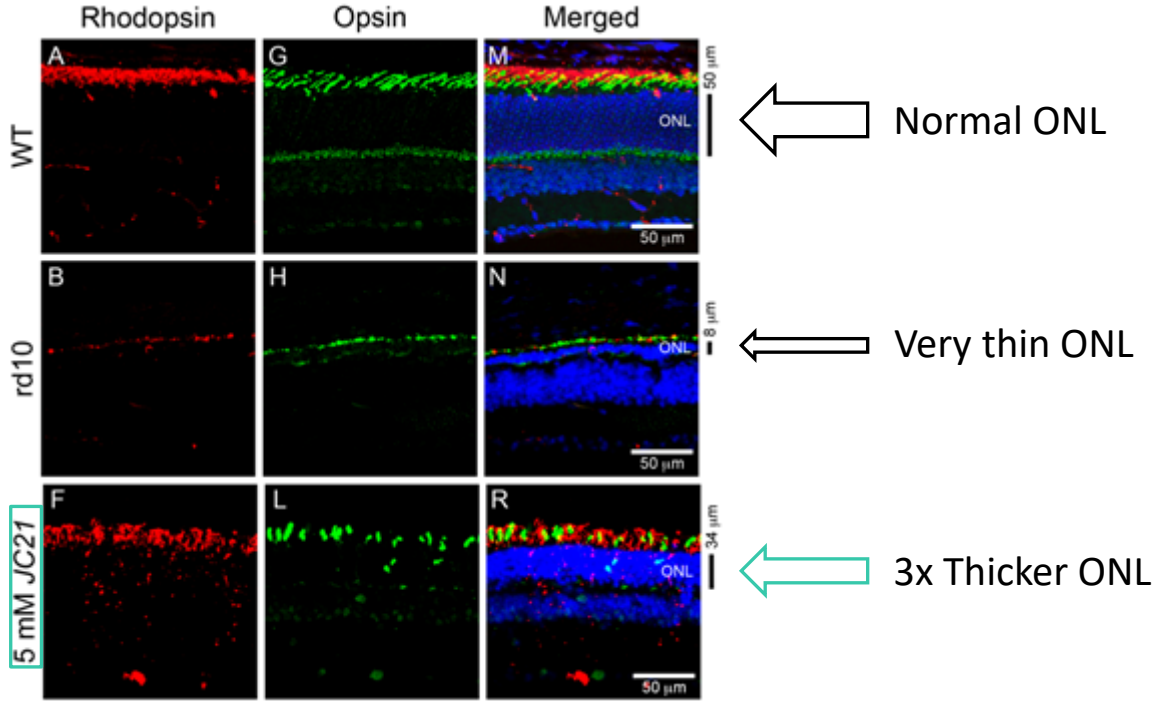
rd10 mice assays

Experimental design





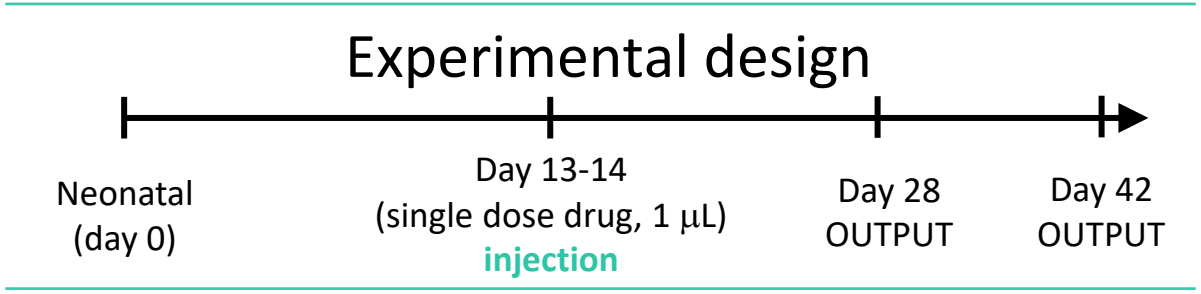
Fundus of rd10 mice retina displayed less amount of bone spicule pigments in the LIM21 treated group



Immunostaining of rd10 mice retina showed thicker retinas and preservation of rhodopsin and opsin signal in the LIM21 treated group

2b. Innovative Mode of Action:

PARP-1 inhibition
Sirt1 activation



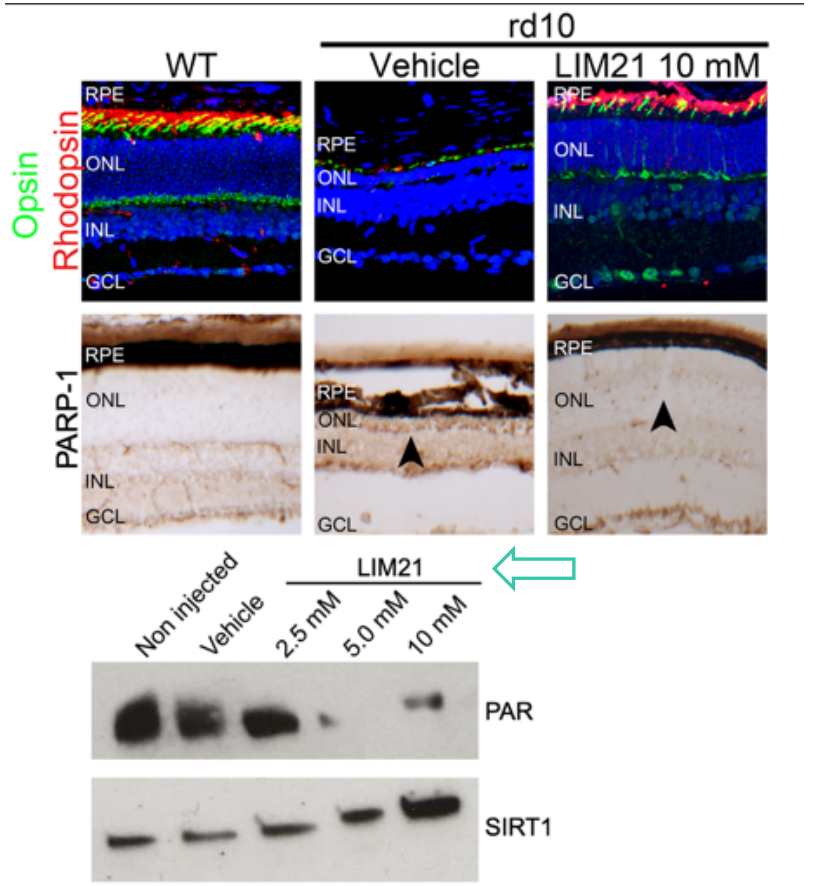
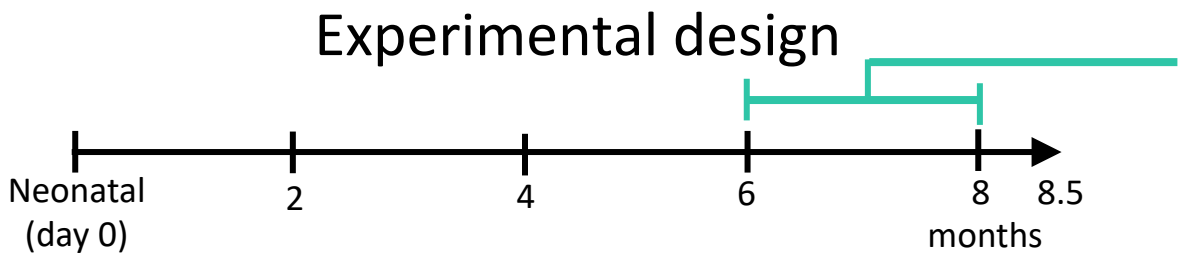
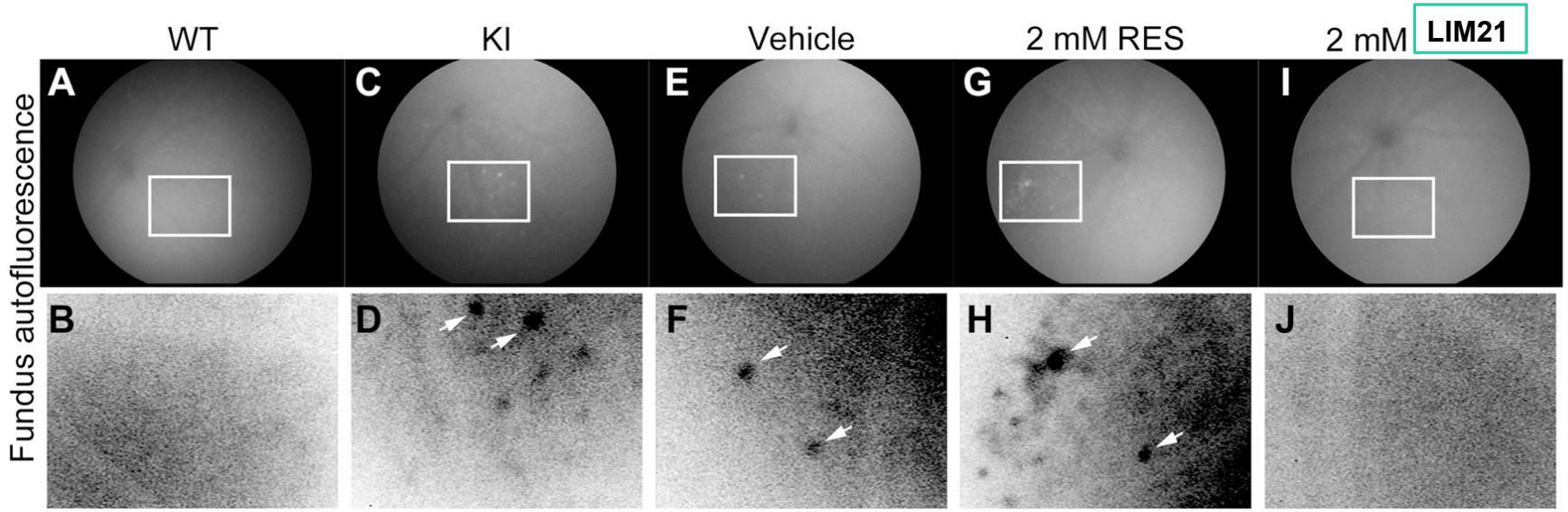


Figure 4: *Immunostaining of rd10 mouse retinas treated with LIM21 showing Rhodopsin, Opsin and PARP-1 expression. Wester blotting of SIRT1 and PAR polymers.*

prpf31 mice assay

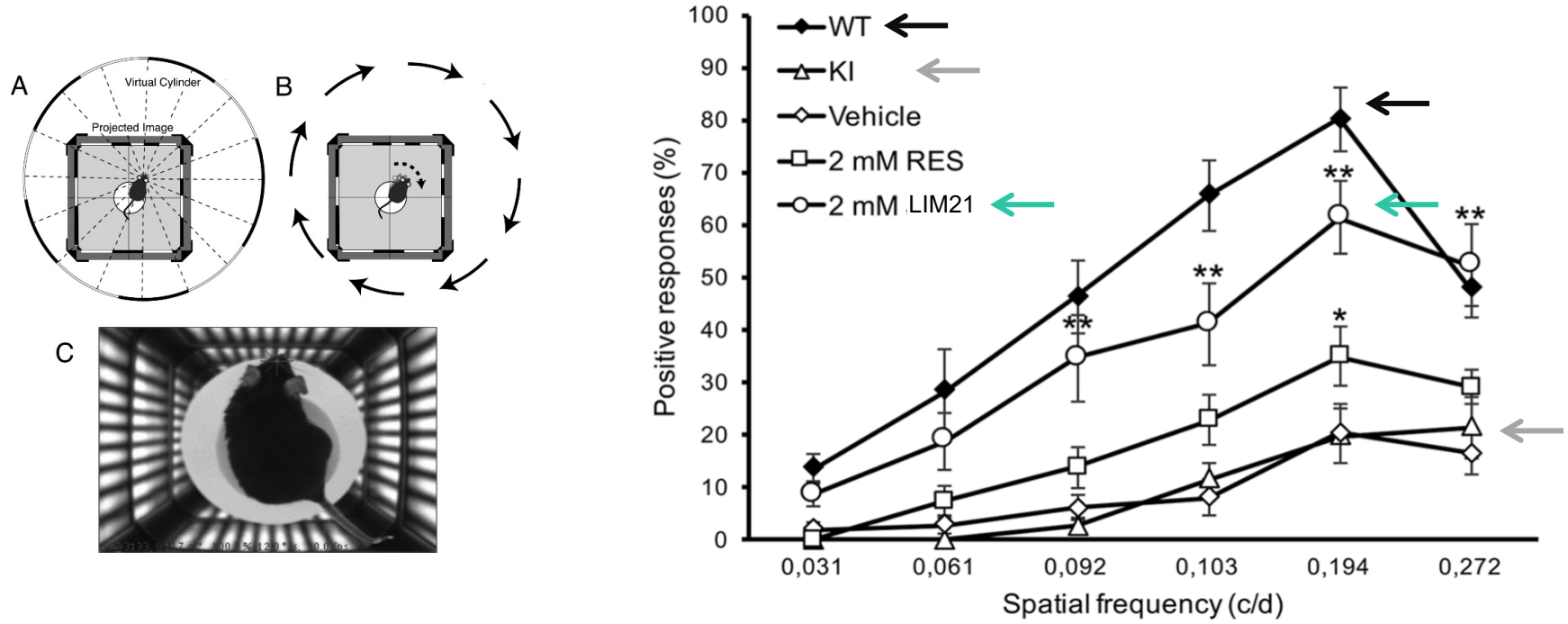


Treatment months 6-8
5 doses/week, 20 µL, 2mM (0.1%)
EYE DROPS Administration



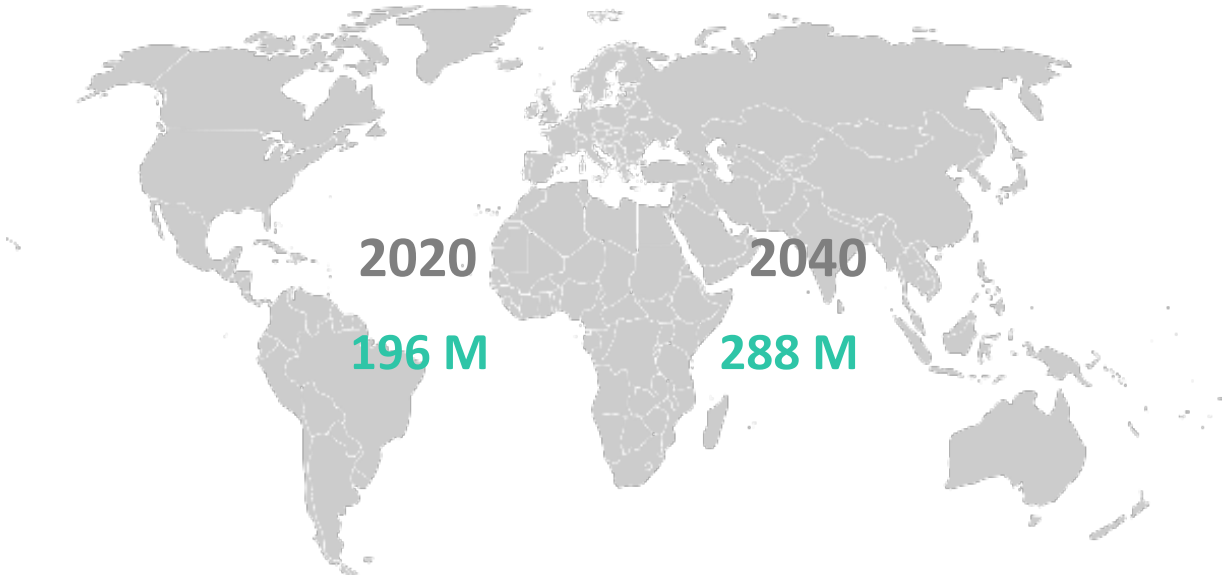
Fundus of Prpf31 mice retina

prpf31 mice assay

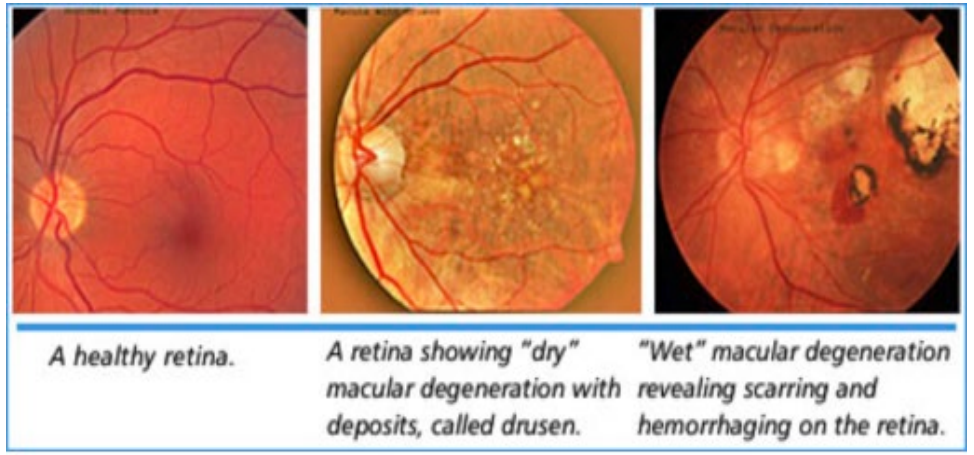


Left: optomotor test. Right: Representation of visual acuity

Age related macular disease



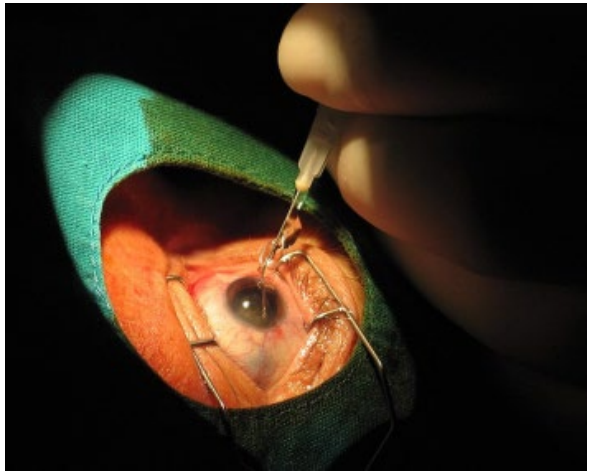
Disease Prevalence



Dry AMD, 90 %
Wet AMD 10 % (in the majority leads to blindness)

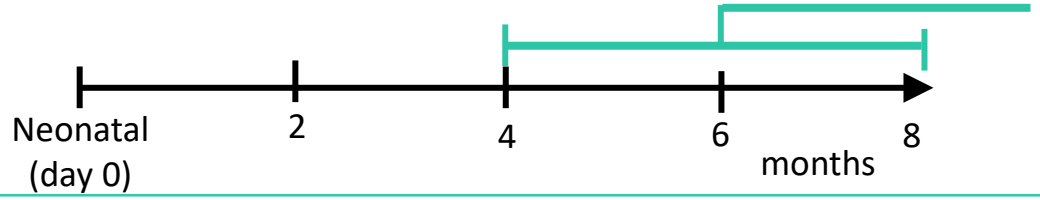
Treatments available

- Wet AMD Treatment cost: 12.000€/year
- Dry AMD: No treatment

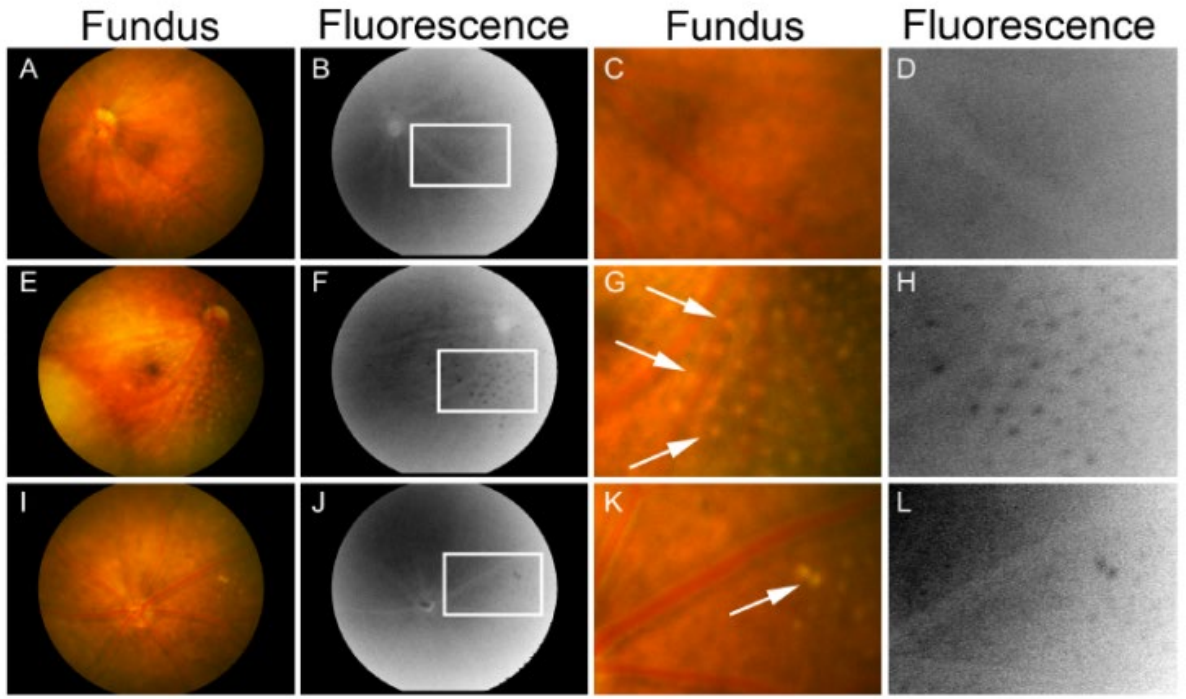


NRF2$^{-/-}$ mice assay

Experimental design



Treatment months 4-8
5 doses/week, 20 µL, 5mM (0.25%)
EYE DROPS Administration



healthy mouse

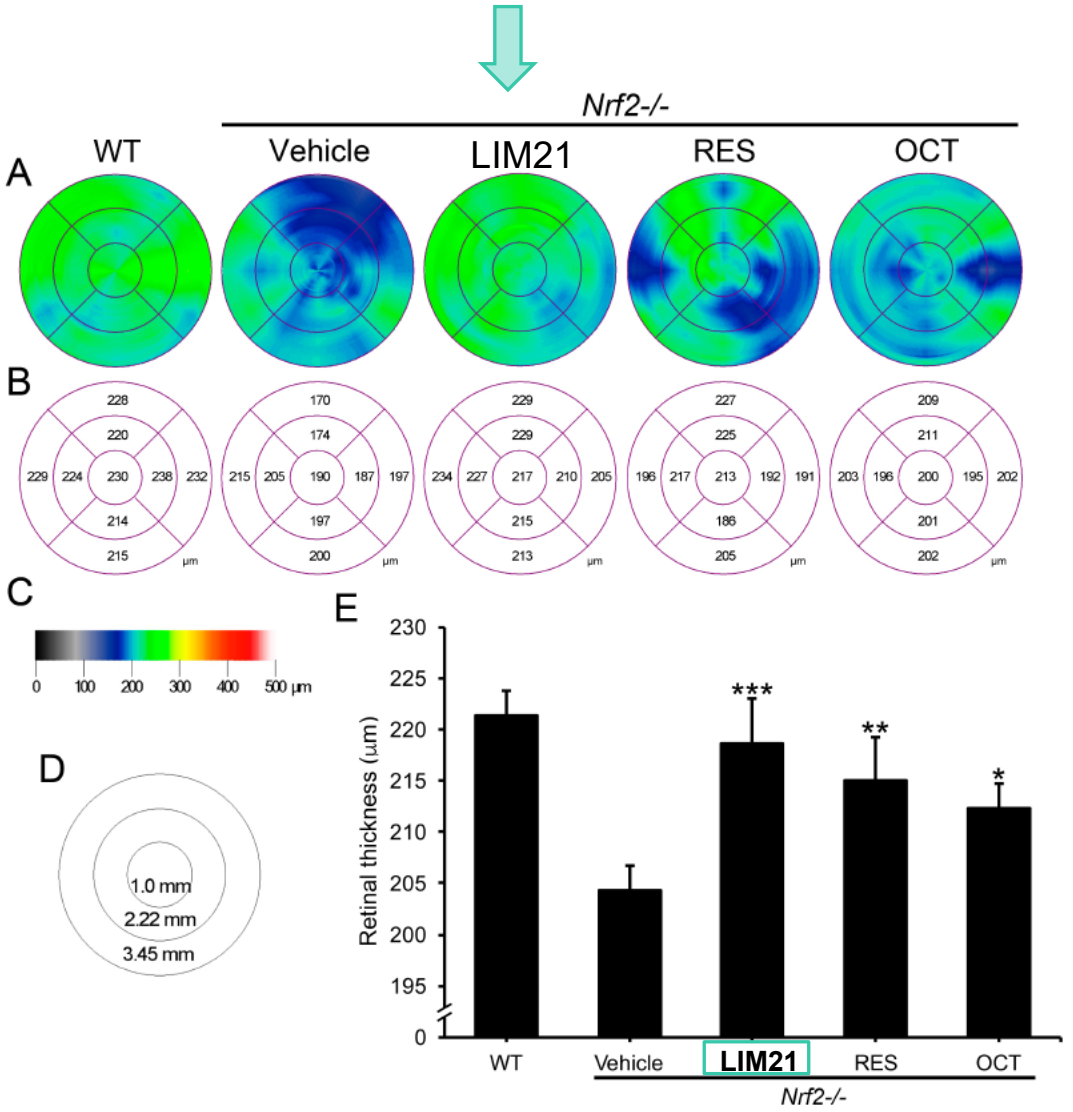
NRF2^{-} (mouse with dry AMD)

NRF2^{-} treated with LIM21

NRF2$^{-/-}$ mice assay

LIM21 treatment increases considerably retinal thickness on NRF2^{-} mice.

In fact, retinal thickness is similar to that observed in healthy control mice (WT)



Retinal thickness

The Solution: LIM21

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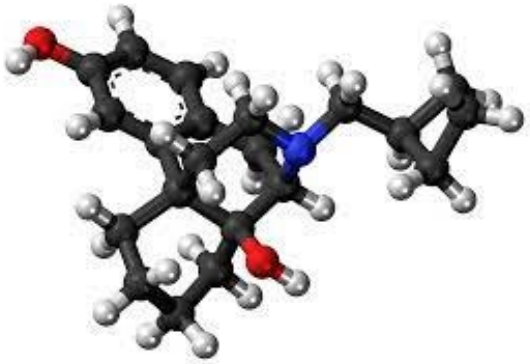
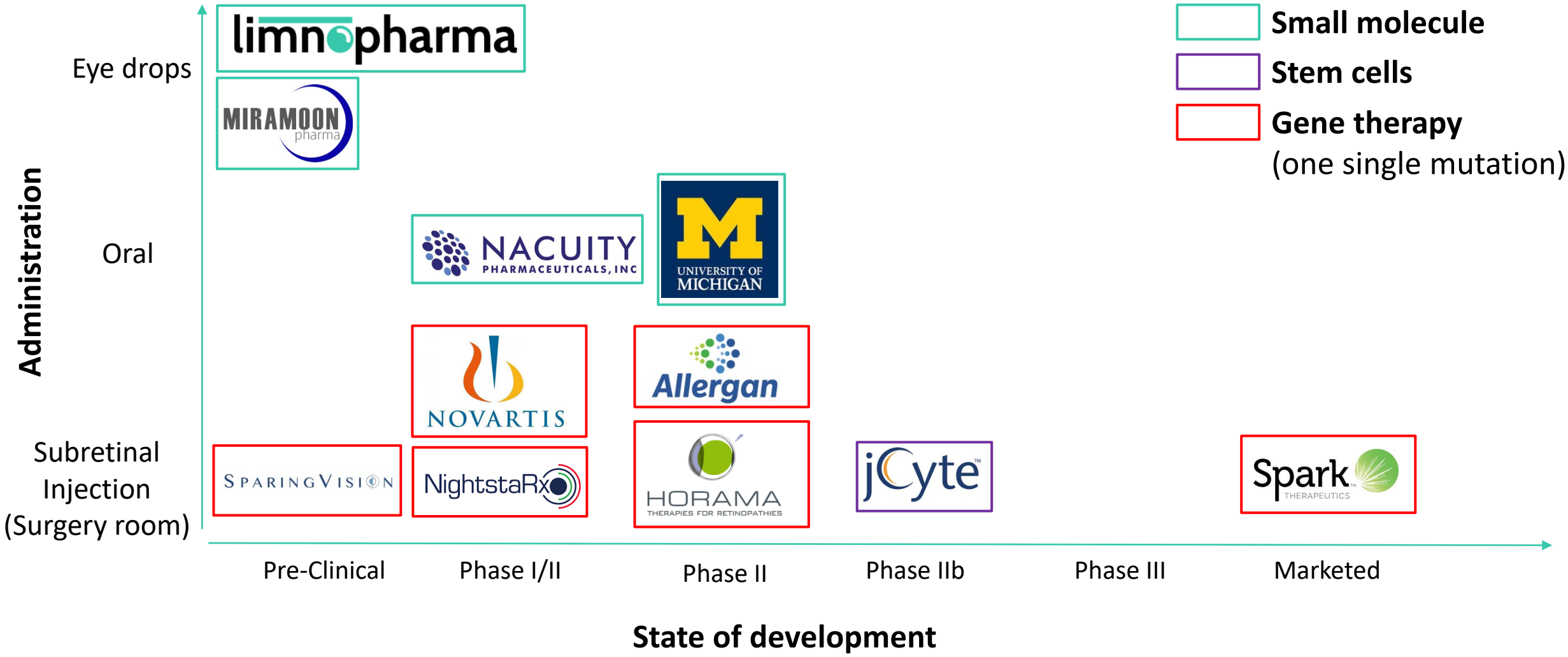
- Administration

- Small molecule

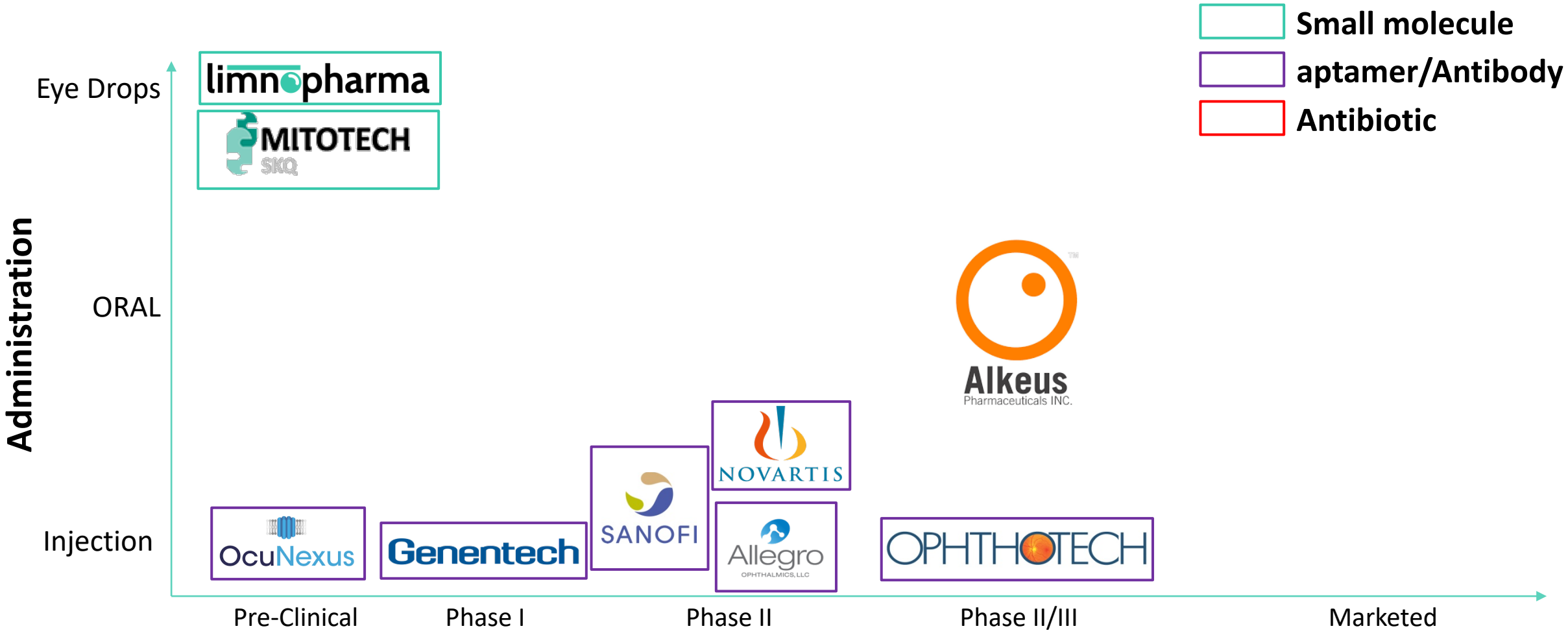


- Efficacy

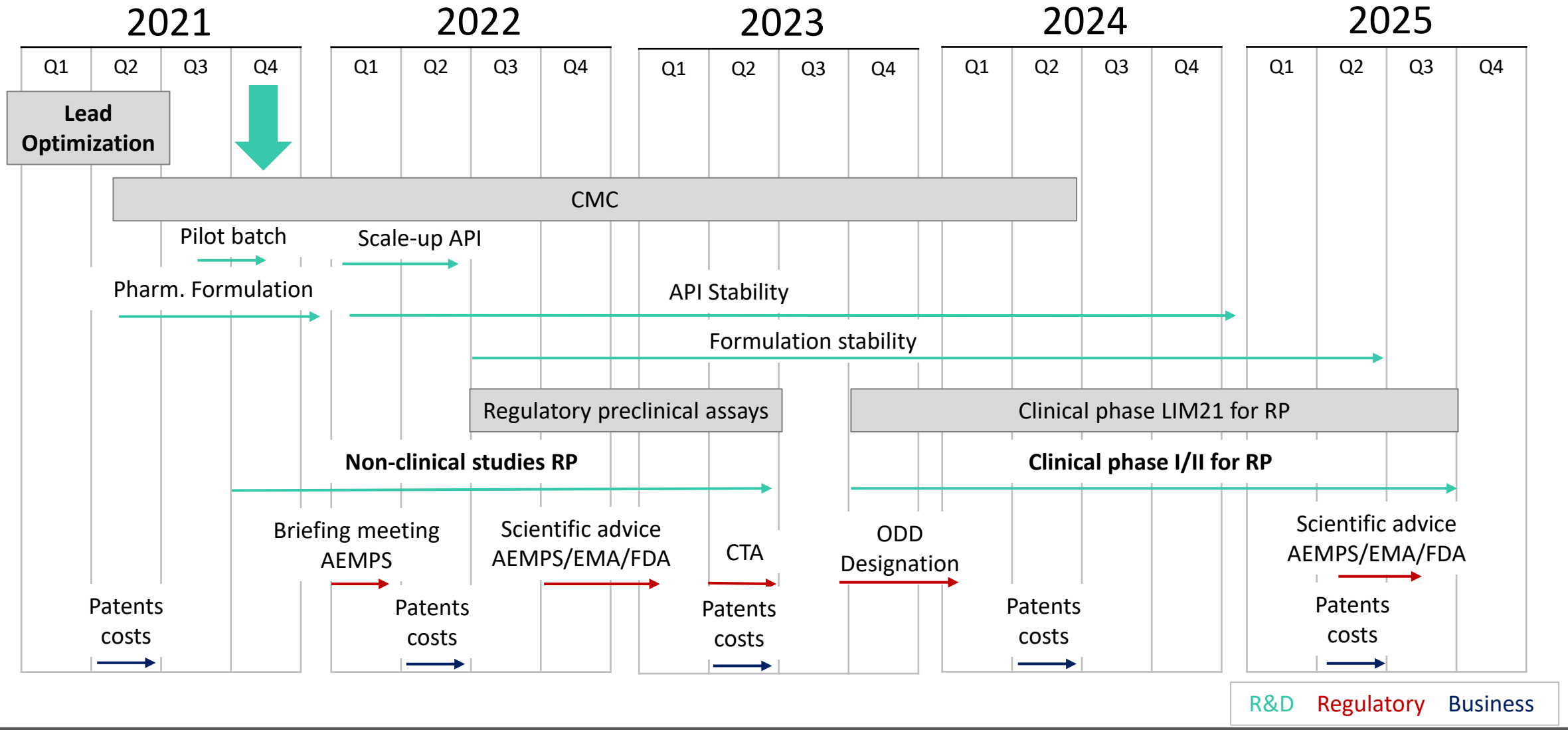
Competitors RP:



Competitors dry-AMD:

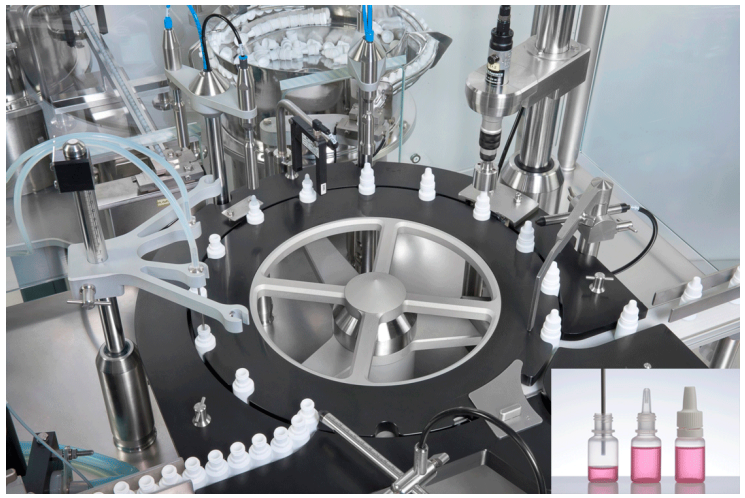


2d. Current Status of Development



LIM21 CMC

- **LIM21** has been prepared in 80 g scale



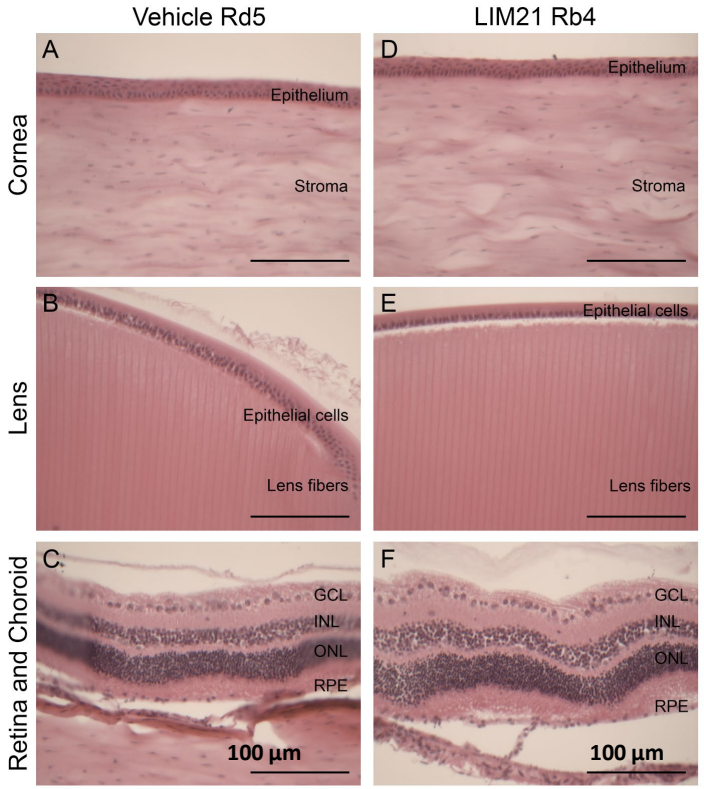
GalChimia

FAMAR

- **LIM21** preliminary formulation (13% HP-β-cyclodextrin, 2% tyloxapol)

LIM21 ocular tolerability

- Rabbits. Administration of LIM21 or vehicle. Eye drops 15 days, three times per day
- Outcomes: Clinical observations (mortality/morbidity and general clinical observations), Ocular observations (Draize score; McDonald-Shadducks score (corneal damage) and Schimer strips (tear secretion)



Under these experimental conditions, LIM21 is well tolerated

No toxicity signals were observed.

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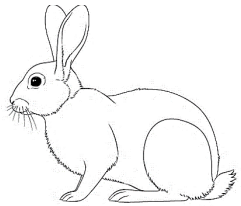
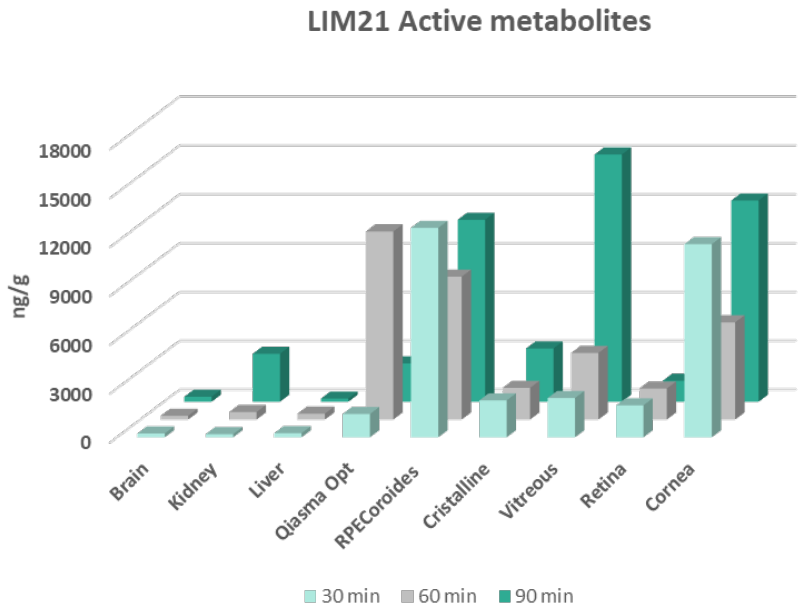
LIM21 biodistribution

- LIM21 eye drops
- Experimental conditions: **SD rats**
  * samples at 30, 60 or 90 min
  * UPLC-MS-MS
- Experimental conditions: **Rabbits**, those for the tolerability study
  * sample collection at 20 h
  * UPLC-MS-MS





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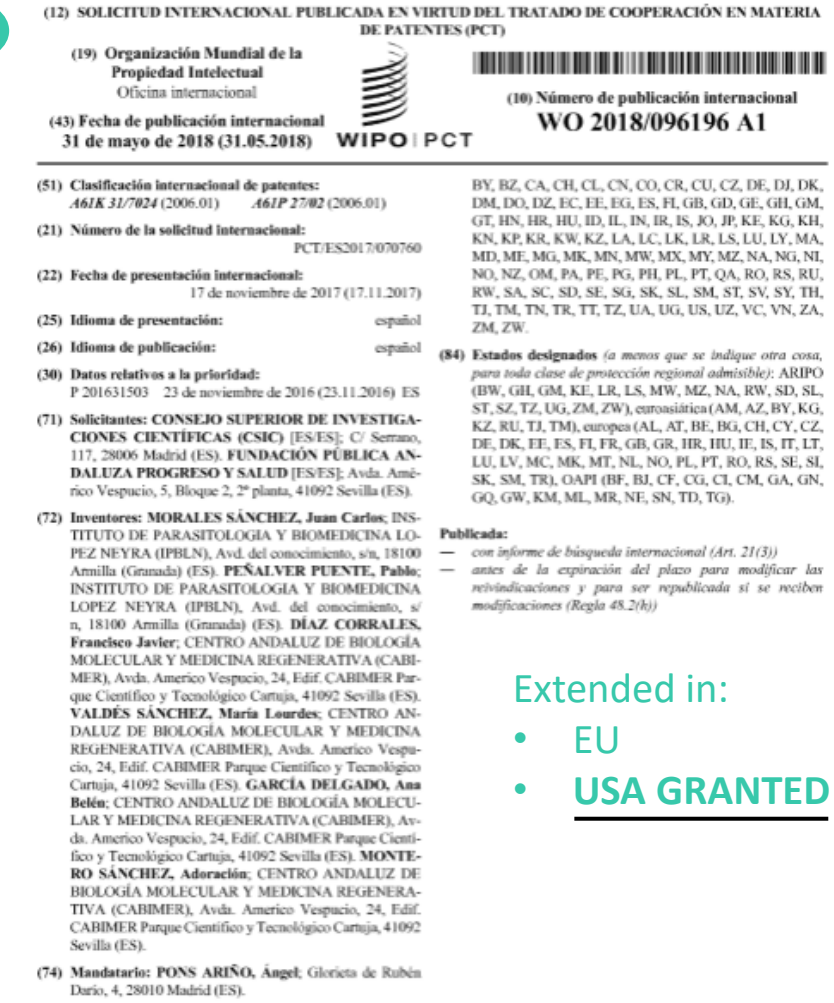
LIM21 active metabolites detected in the back of the eye for both, rats and rabbits

2.e. Intellectual Property

1



(12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual
Oficina internacional

(43) Fecha de publicación internacional
31 de mayo de 2018 (31.05.2018)

WIPO | PCT

(10) Número de publicación internacional
WO 2018/096196 A1

(51) Clasificación internacional de patentes:
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(22) Fecha de presentación internacional:
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(26) Idioma de publicación: español

(30) Datos relativos a la prioridad:
P 201631503 23 de noviembre de 2016 (23.11.2016) ES

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(74) Mandatario: **PONS ARIÑO, Ángel**; Glorieta de Rubén Darío, 4, 28010 Madrid (ES).

BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Estados designados *(a menos que se indique otra cosa, para toda clase de protección regional admisible)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), euroasiática (AM, AZ, BY, KG, KZ, RU, TJ, TM), europea (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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— *con informe de búsqueda internacional (Art. 21(3))*
— *antes de la expiración del plazo para modificar las reivindicaciones y para ser republicada si se reciben modificaciones (Regla 48.2(h))*

Extended in:

- EU
- **USA GRANTED**

2

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Publicada:
— *con informe de búsqueda internacional (Art. 21(3))*

Extended in:

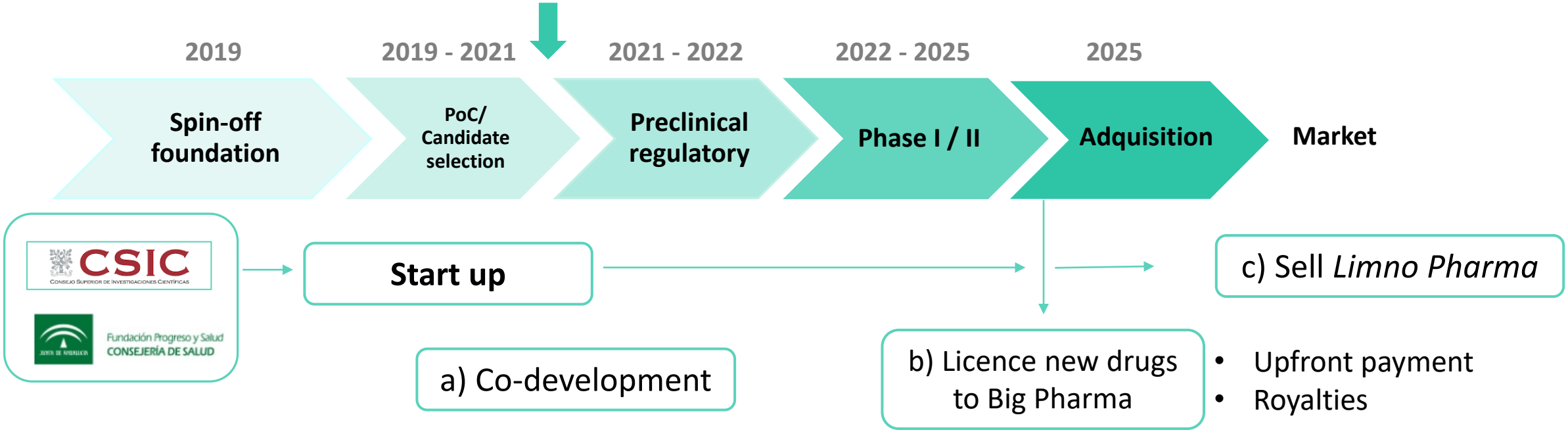
- EU
- **USA GRANTED**
- Japan
- China
- Canada
- Australia
- Mexico

2.f. Pitfalls & Risks to be considered

- Preclinical:
  - CMC: Low risk
  - Biodistribution (Back of the eye): Low risk
  - Toxicity: Low risk
    - Clinical:
      - Safety: Low risk
      - Efficacy: Medium risk. Difficulty in RP clinical trial design

Oculis
Next Generation Topical Ophthalmics

3. Partnering Opportunities



Seed round (2019-20)	Series A (2021-23)	Series B (2023-25)
€ 0,5 M	**€ 4 M**	**€ 6 M**
Closed	CMC & Preclinical studies	Clinical Phase I/IIa

Market analysis

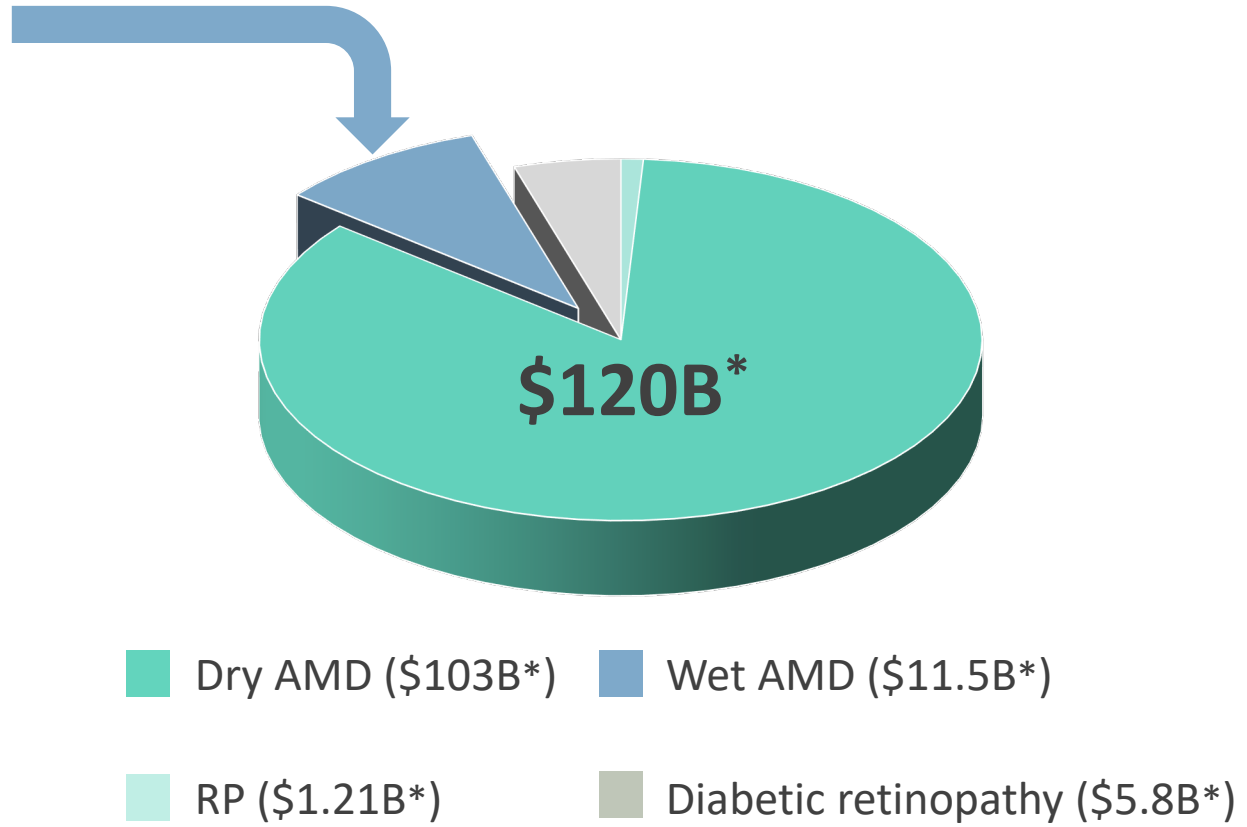
Wet AMD market will increase from **$4.9B** (2016) to **$11.5B** (2026) in the **7MM§**

BAYER

Wet AMD treatment

$6551 M, sales in 2018

(Among the 10 top-selling drugs)



7MM§: USA, France, Germany, Italy, Spain, United Kingdom and Japan

* Estimated from wet AMD market in 2026

World Health Organization:

2200 M People with low vision or blindness

1000M could be treated

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