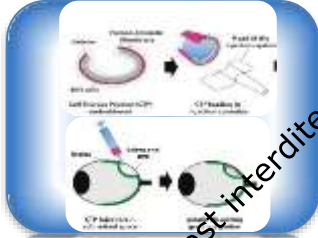
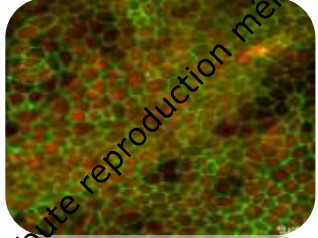


DU 21 AU 23
NOVEMBRE
2018

18^e
CONGRÈS
DE LA
SFGM-TC
Corum de Montpellier



Preclinical validation of a tissue engineered product consisting in RPE derived from human embryonic stem cells disposed on human amniotic membrane

Christelle Monville, PhD



Indications: Retinitis Pigmentosa and AMD

The **RPE layer** has multiple critical roles in the health function of photoreceptors and the retina as a whole.

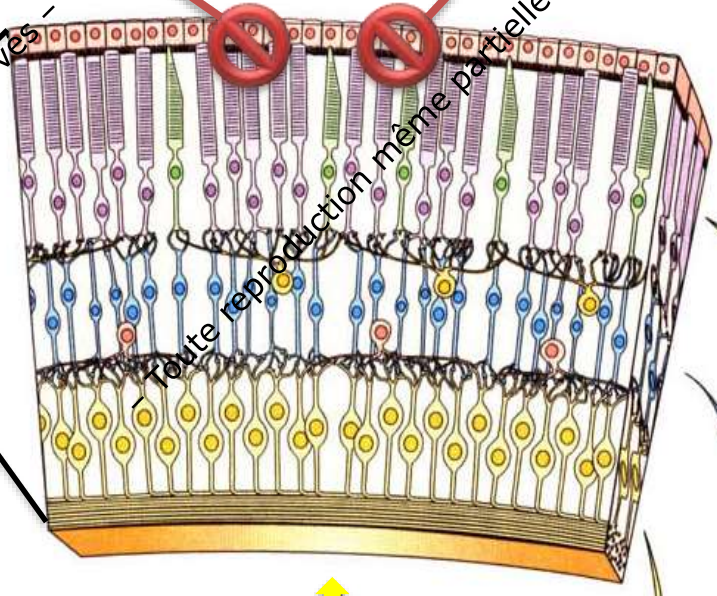
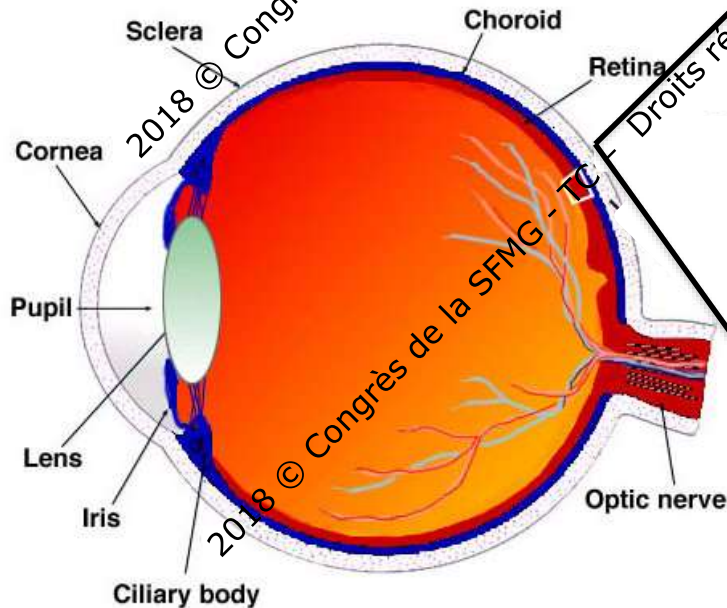
Provides nutrients and growth factors| photoreceptors see no blood

Recycles Vitamin A maintains photoreceptor excitability

Detoxifies photoreceptor layer

Maintains Bruch's Membrane
• natural antiangiogenic barrier
• immune privilege of retina

Absorbs stray light/protects from UV



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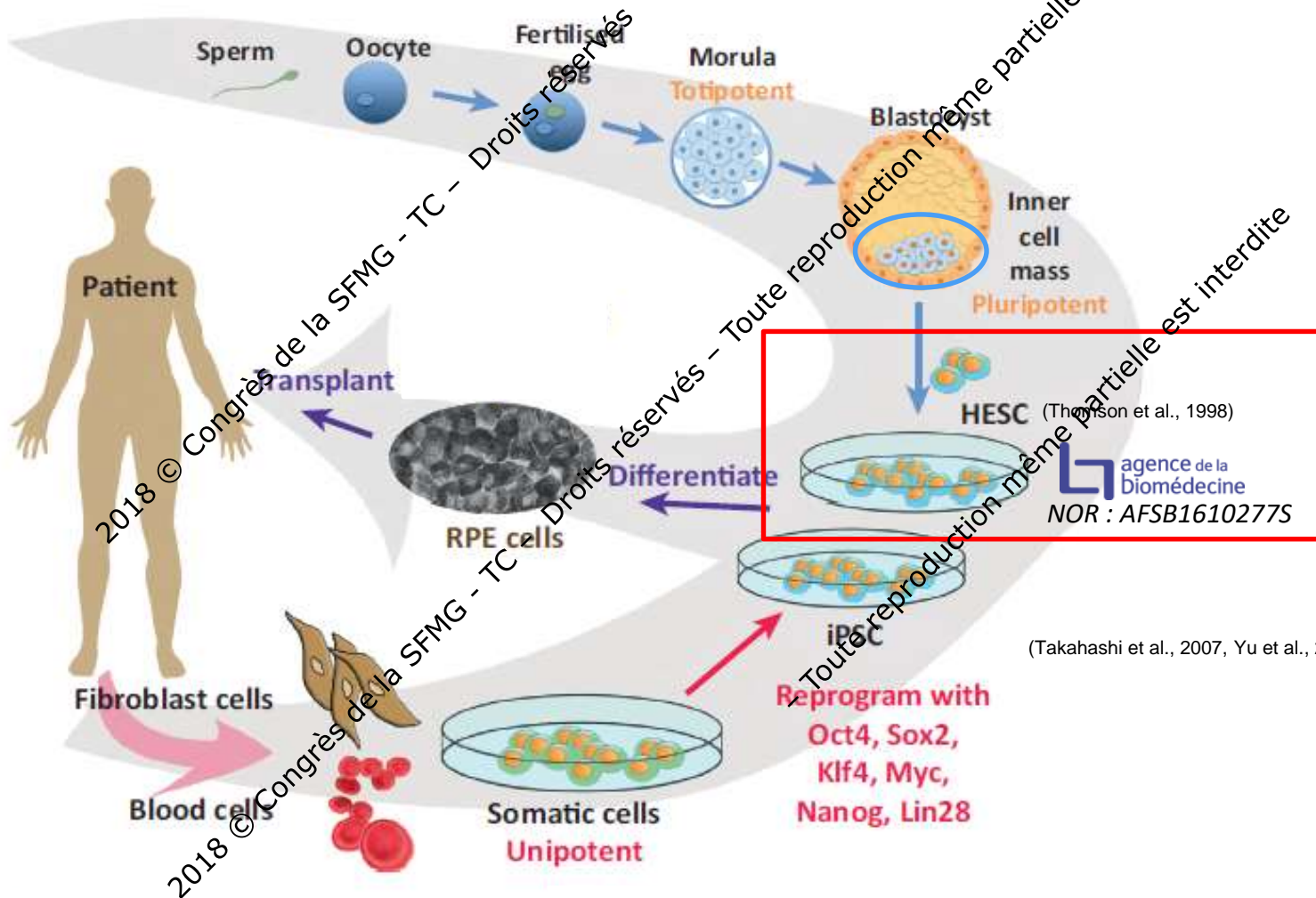
2018 © Congrès de la SFMG - TC

Droits réservés - Toute reproduction même partielle est interdite.

Toute reproduction même partielle est interdite.

Toute reproduction même partielle est interdite.

Human pluripotent stem cells



2012 Nobel Prize



John Gurdon

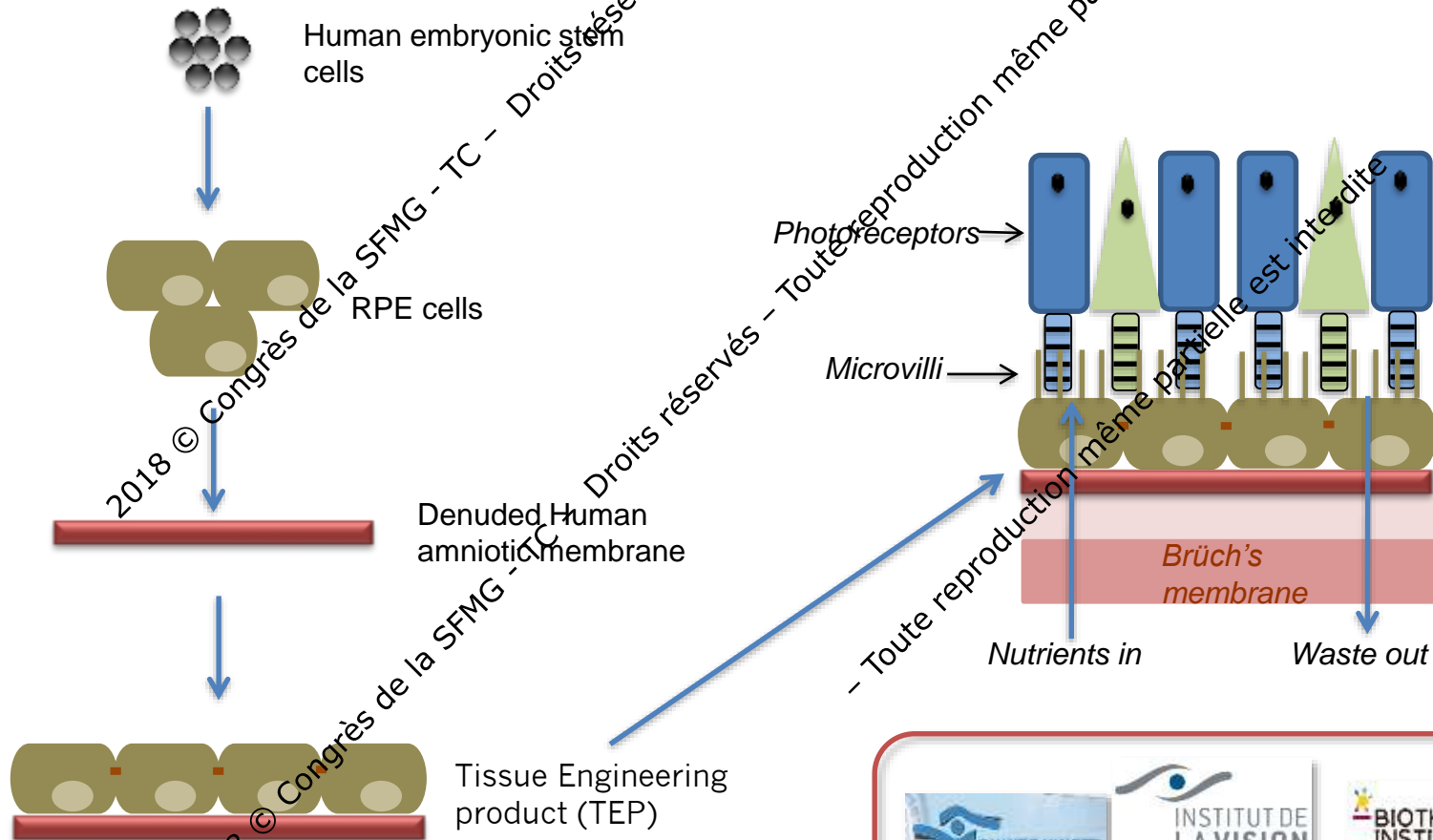
(Takahashi et al., 2007, Yu et al., 2007)



Shinya Yamanaka

Objectives

- Cell replacement of the degenerated RPE layer with a RPE layer generated from human embryonic stem cells (hESCs)

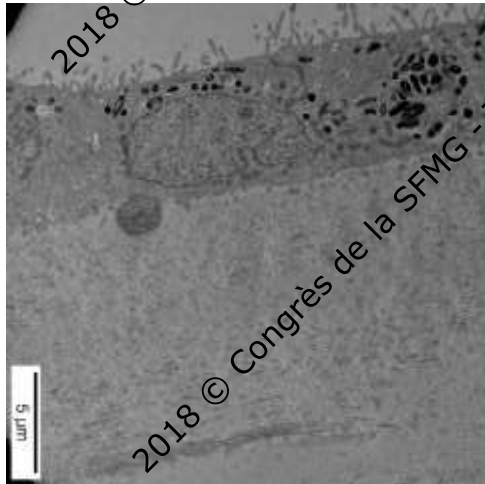


RPE layer Advantages

Polarized RPE cells



- ◇ Non-proliferative
- ◇ Better survival in advanced stages of disease
- ◇ Do not migrate
- ◇ Increased growth factor secretion
- ◇ Better integration



Membrane support

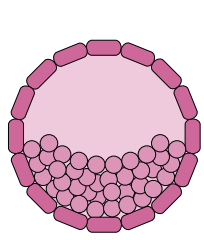


- ◇ Biological Substrate for RPE to attach & polarize
- ◇ 50-100 μm thickness
- ◇ Non immunogen
- ◇ Anti-inflammatory properties
- ◇ Already used for corneal implantations (ANSM PPT44)
- ◇ Not a limiting source (200-300 cesarean/year at AP-HP)



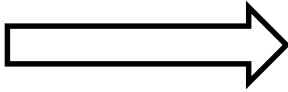


Manufacturing process



Embryo

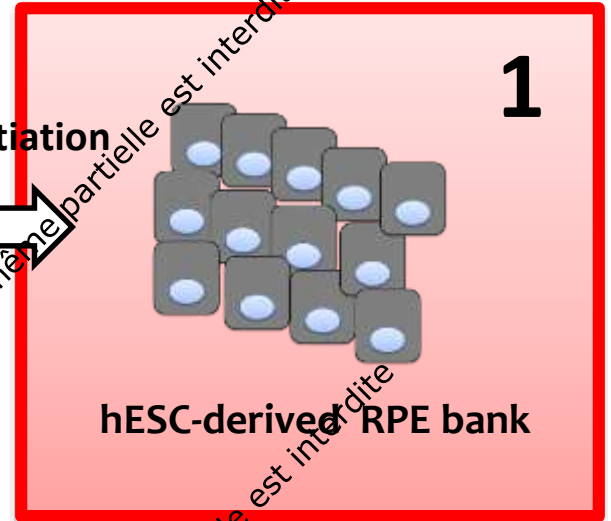
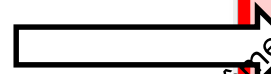
hESCs derivation and amplification



Droits réservés

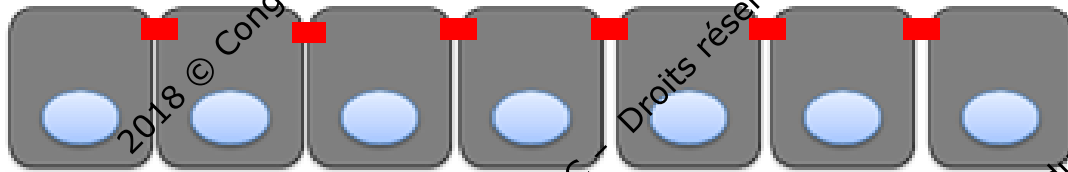
hESCs bank

hESCs differentiation



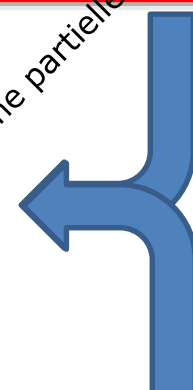
hESC-derived RPE bank

Tissue Engineered Product



Human Amniotic Membrane

Tissue engineering



Human amniotic membrane bank

Dr Jarraya, Tissue Bank, St Louis, Paris



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Clinical RPE-bank



A. Plancheron W. Habeler

J0

J21

J0₊₂₁

J54₊₂₁

J94₊₂₁

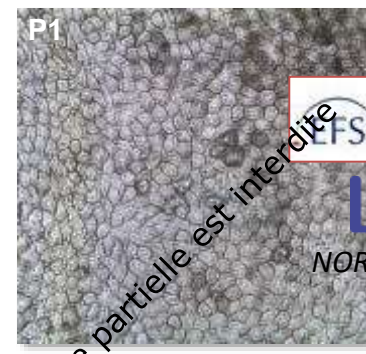
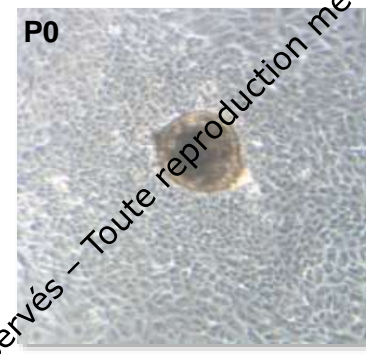
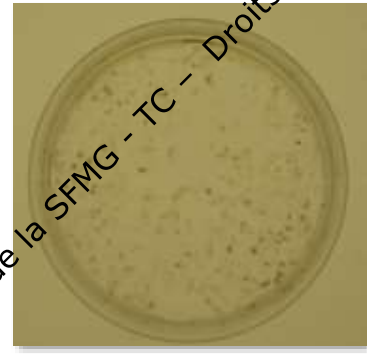
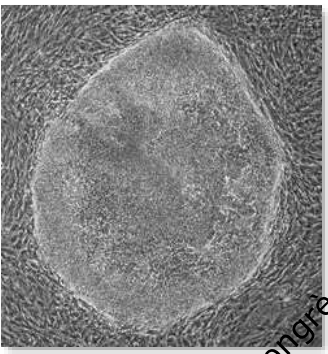
J117₊₂₁

hES-RC9 ampli

RPE Diff

RPE Ampli

RPE Ampli



RPE-BANK



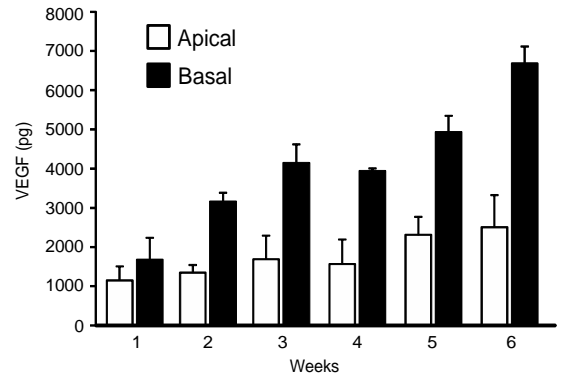
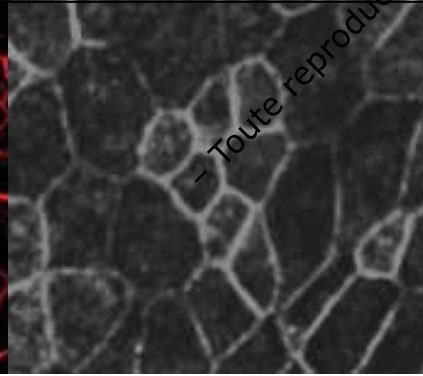
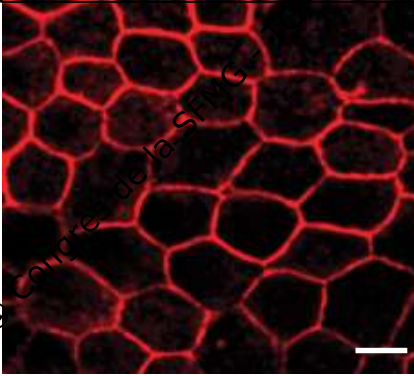
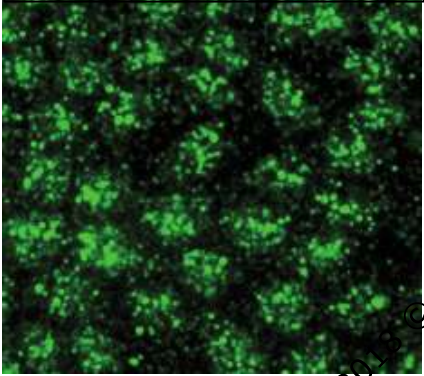
Agence de la Biomédecine

NOR : AFSB1530503S

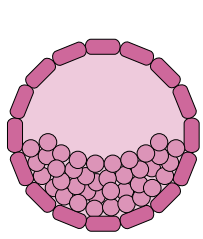
Pax6

Ezrin

MERTK

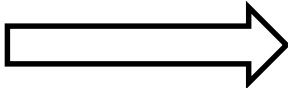


Manufacturing process



Embryo

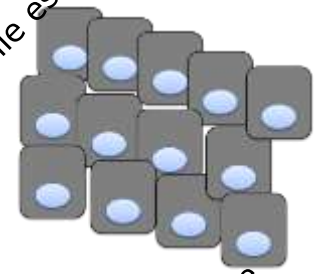
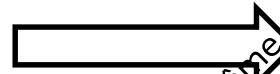
hESCs derivation and amplification



Droits réservés


hESCs bank

hESCs differentiation

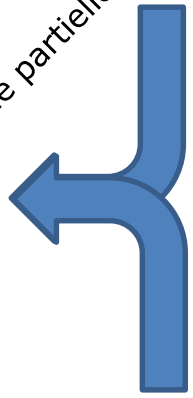


hESC-derived RPE bank

Tissue Engineered Product 2



Human Amniotic Membrane



Tissue engineering

Human amniotic membrane bank

Dr Jarraya, Tissue Bank, St Louis, Paris

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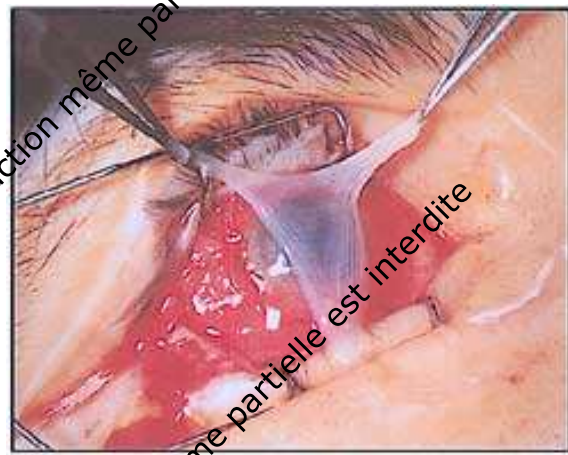
Biological support: Human Amniotic Membrane



Amniotic Membrane



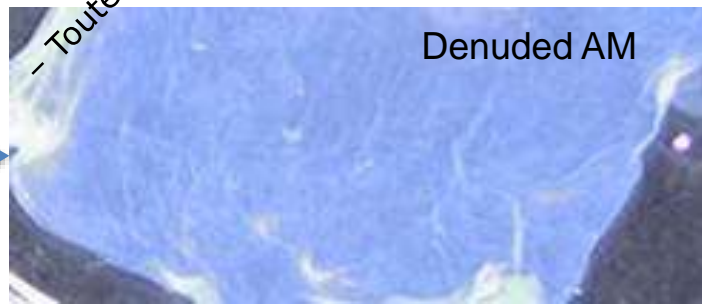
Cryopreserved AM



Already used in clinic

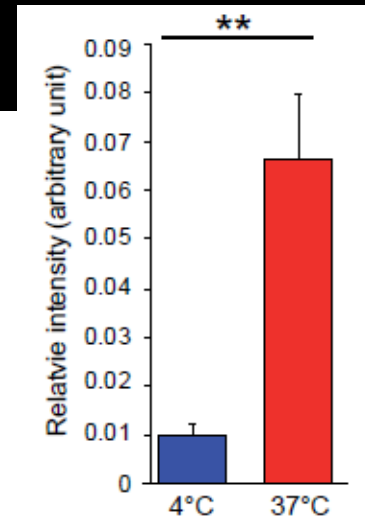
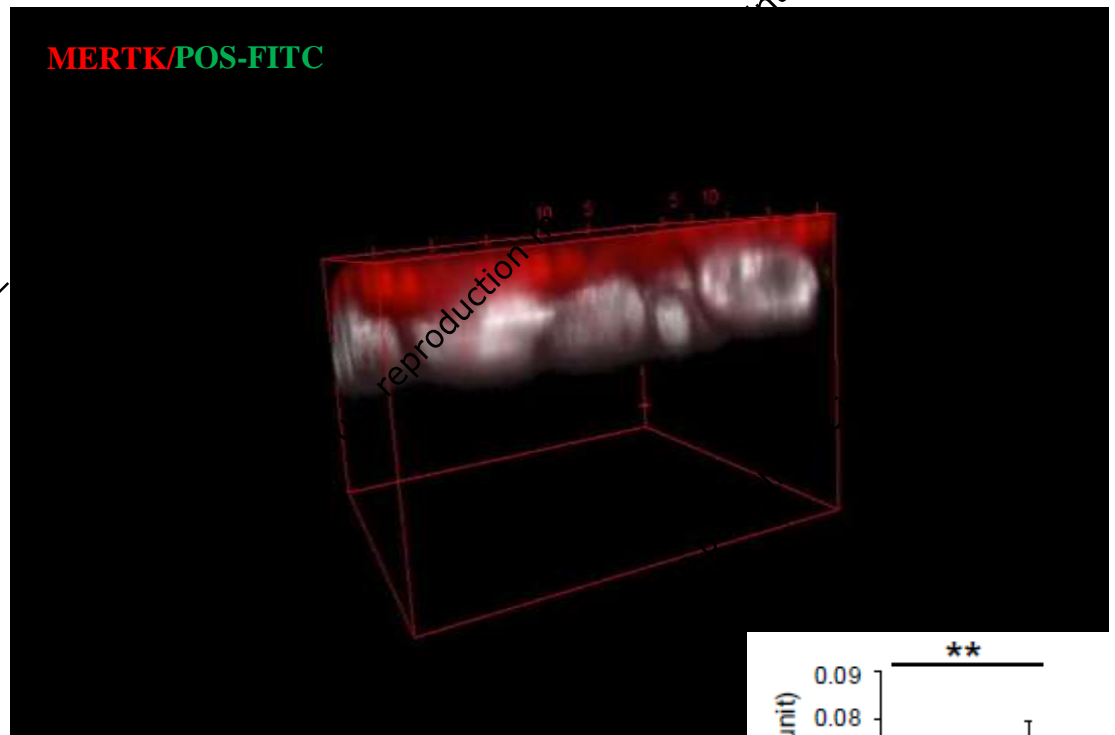
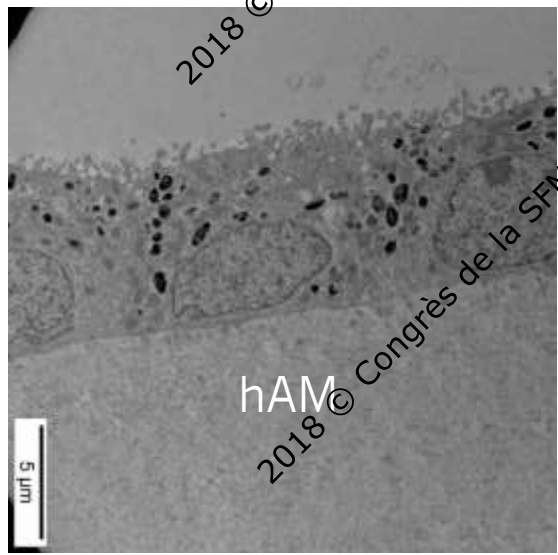


Thermolysin



Denuded AM

Polarized and functional RPE on hAM



- Toute reproducti

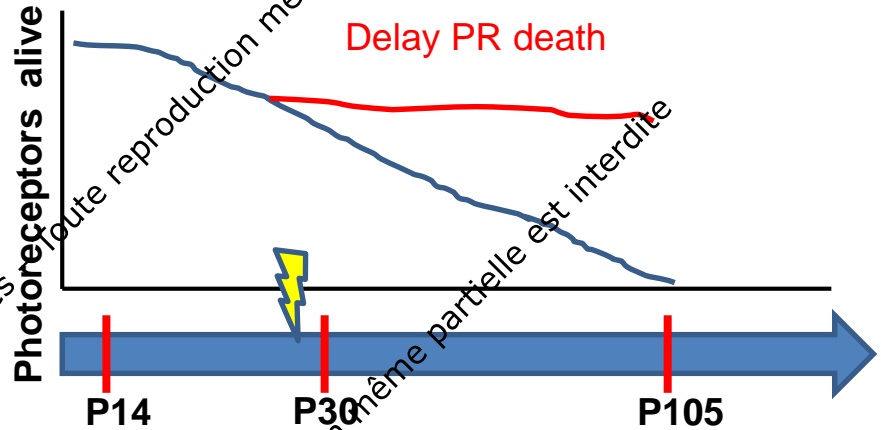
Proof of concept in rodents

Royal college of surgeons (RCS) rat model

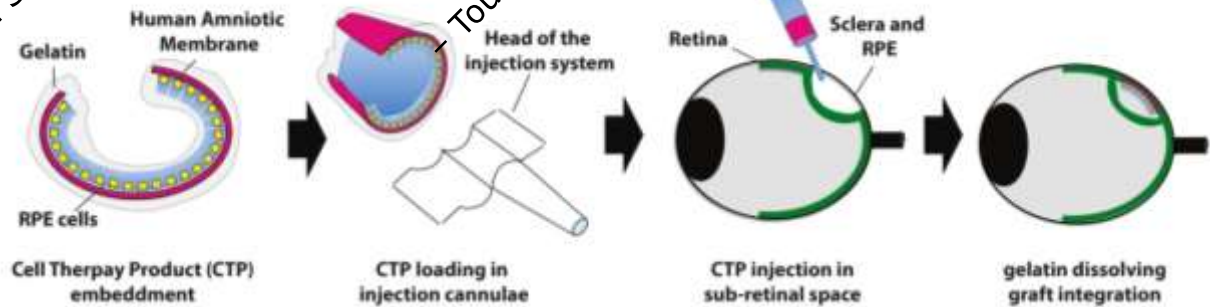


K. Ben M'Barek

- Functional defect of RPE (phagocytosis)
- Photoreceptor death from 21d
- At 60 days postnatal: no ERG response

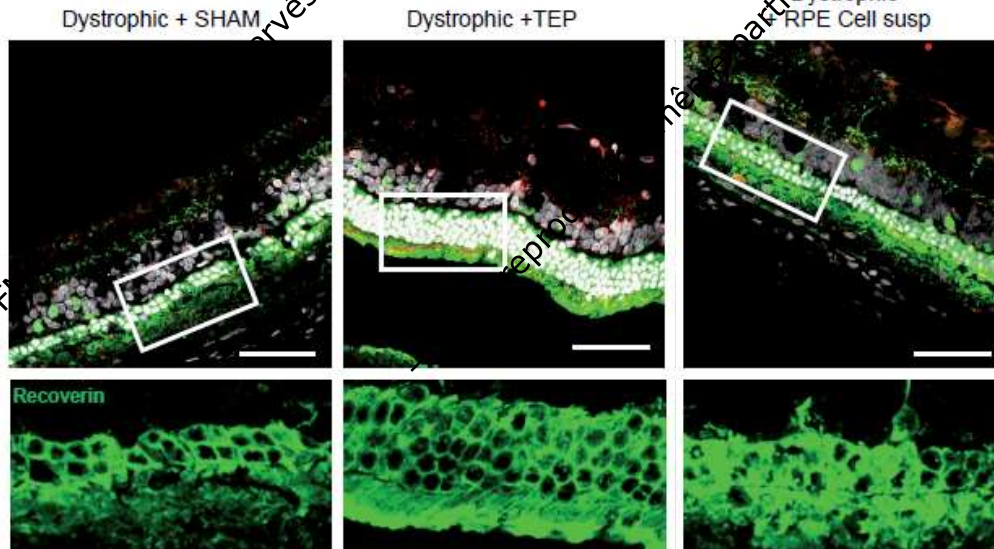
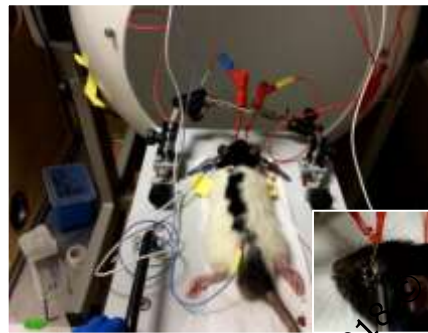
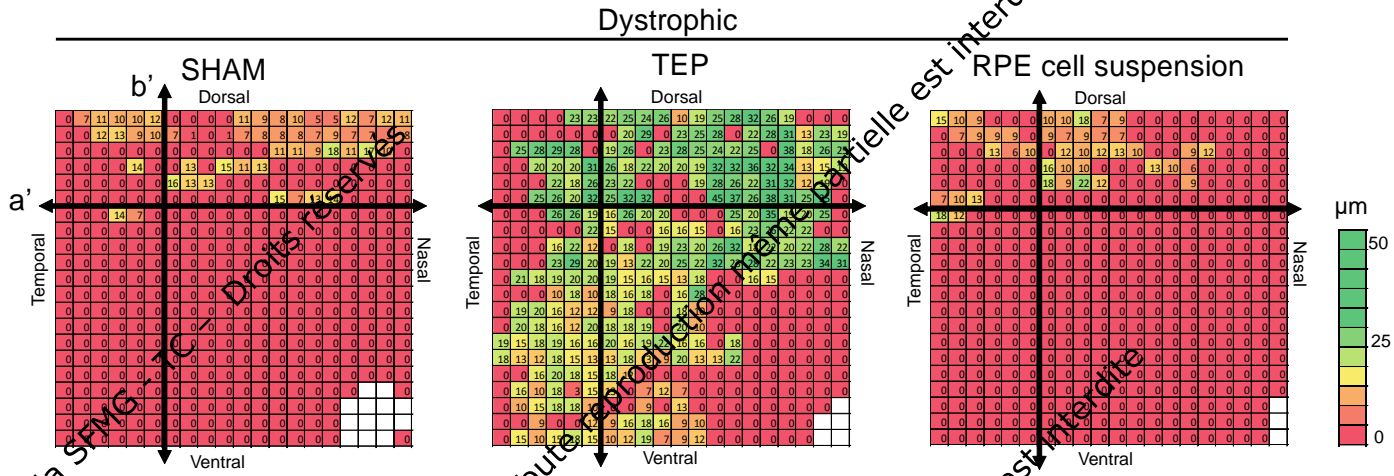
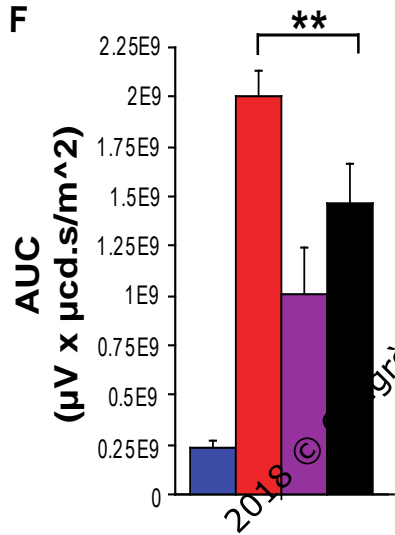


Use of IOL injectors



Functional analysis in RCS rats

- Dystrophic
- TEP-STREAM
- RPE suspension
- SHAM

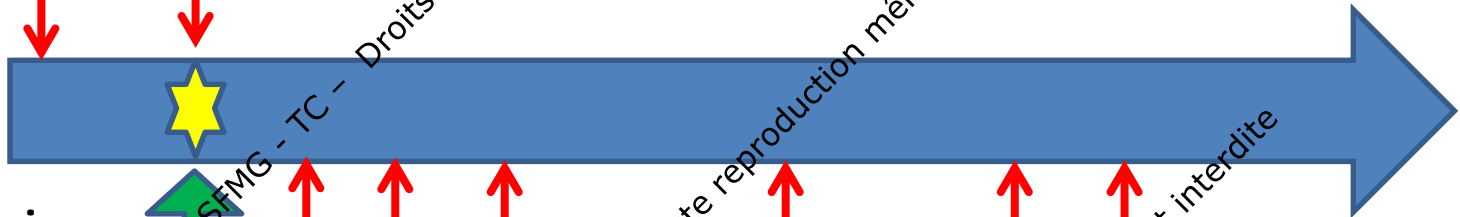


Non human primate study

Baseline:
ERG, OCT
fundus

Surgery

6 primates
Females
5/8 years old;
immunosuppression



D1/2

W1

W2

W4

W6

W7

Slit lamp, fundus, OCT

Baseline:
ERG, necropsy,
Histology of the
retina

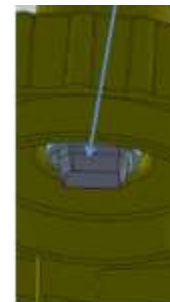
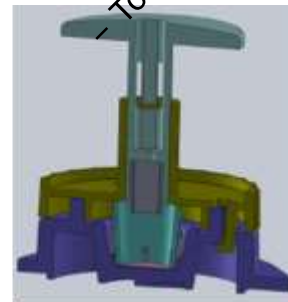
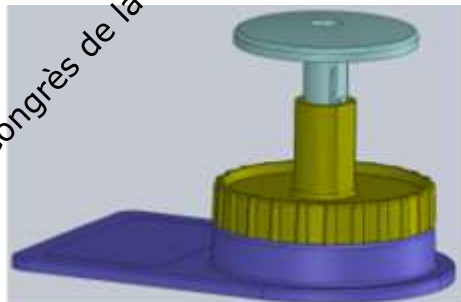
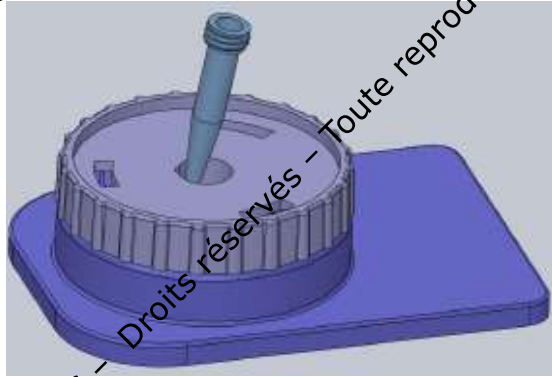
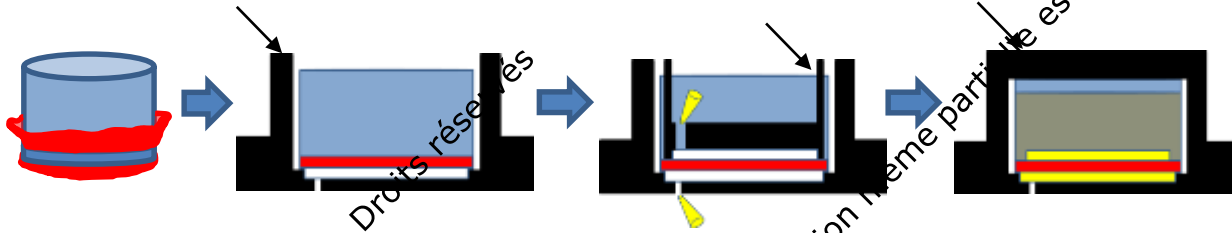
GMP facility

12
therapeutic
units

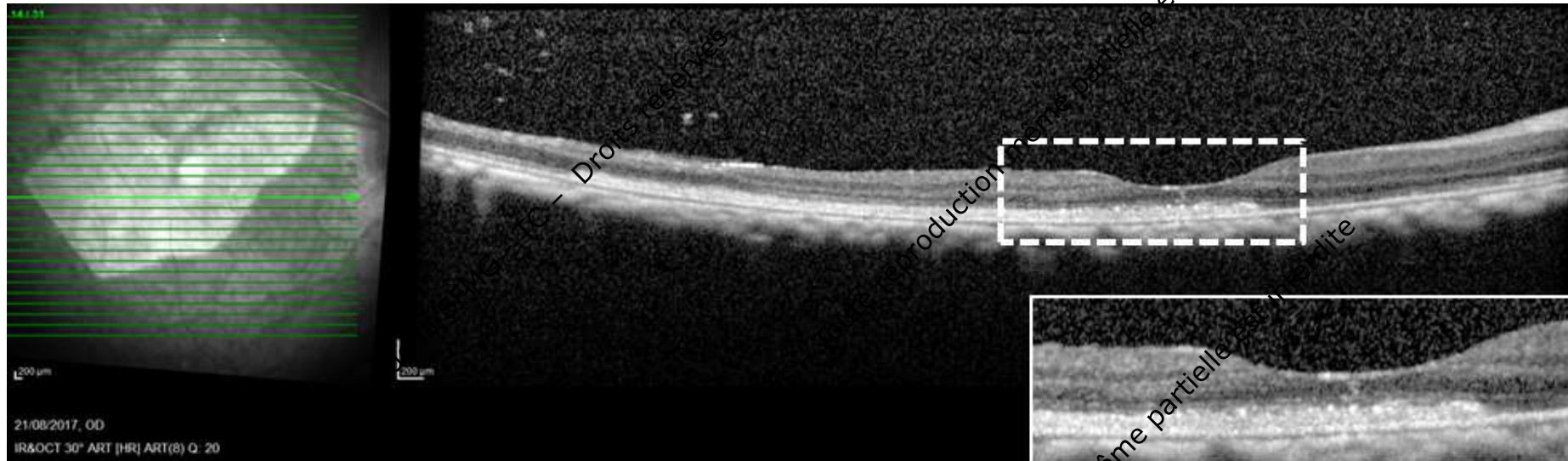


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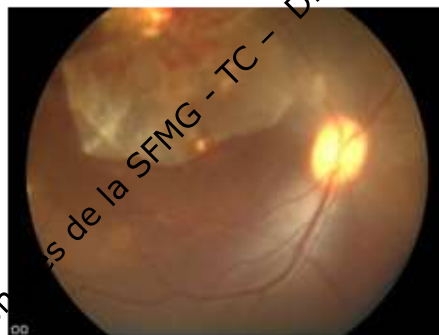
Graft preparation: Specific medical device development



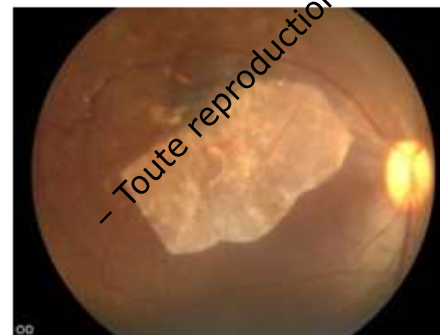
Implantation in nonhuman primates: stability of the graft



D0



D7



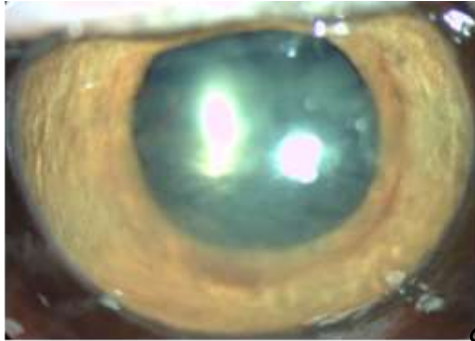
W5



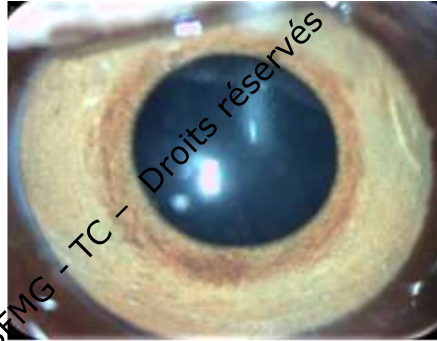
W7

Transitory Inflammation following surgery

No major function alteration

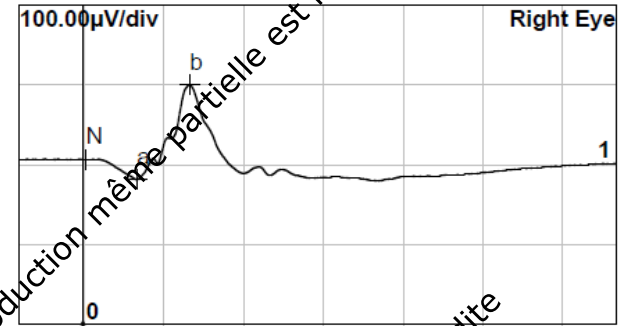


Day 1

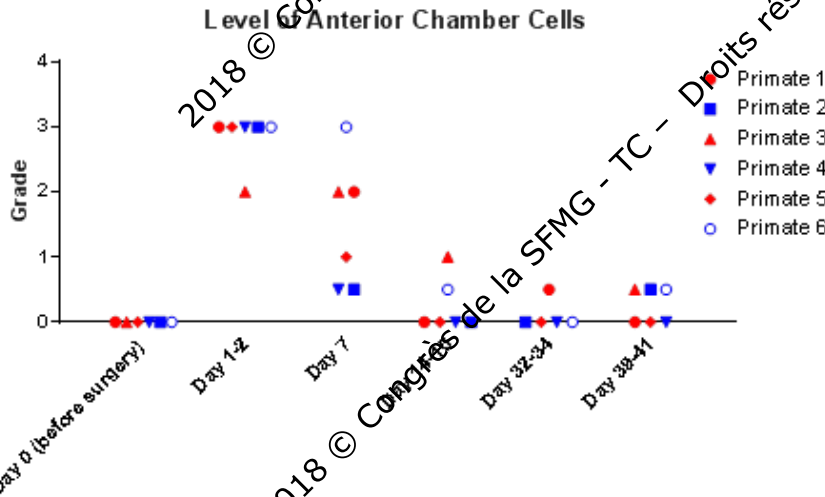
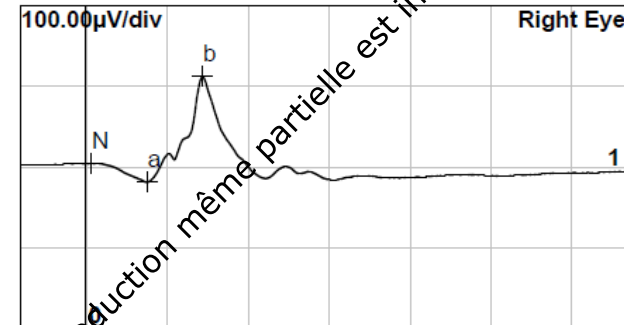


Day 7

Photopic 3.0 ERG MGF

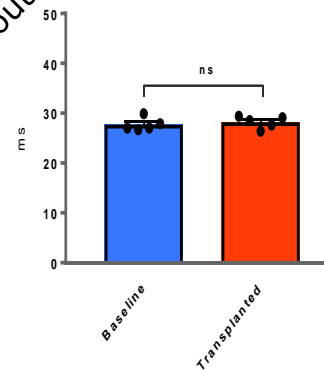


Photopic 3.0 ERG MGF

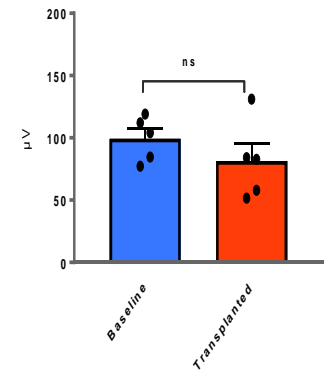


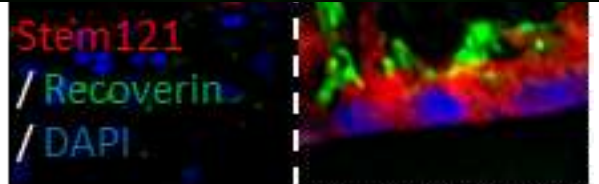
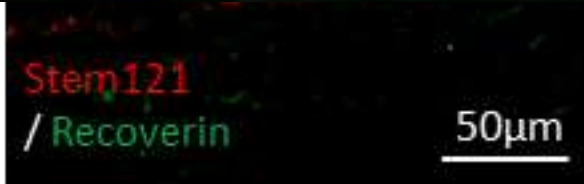
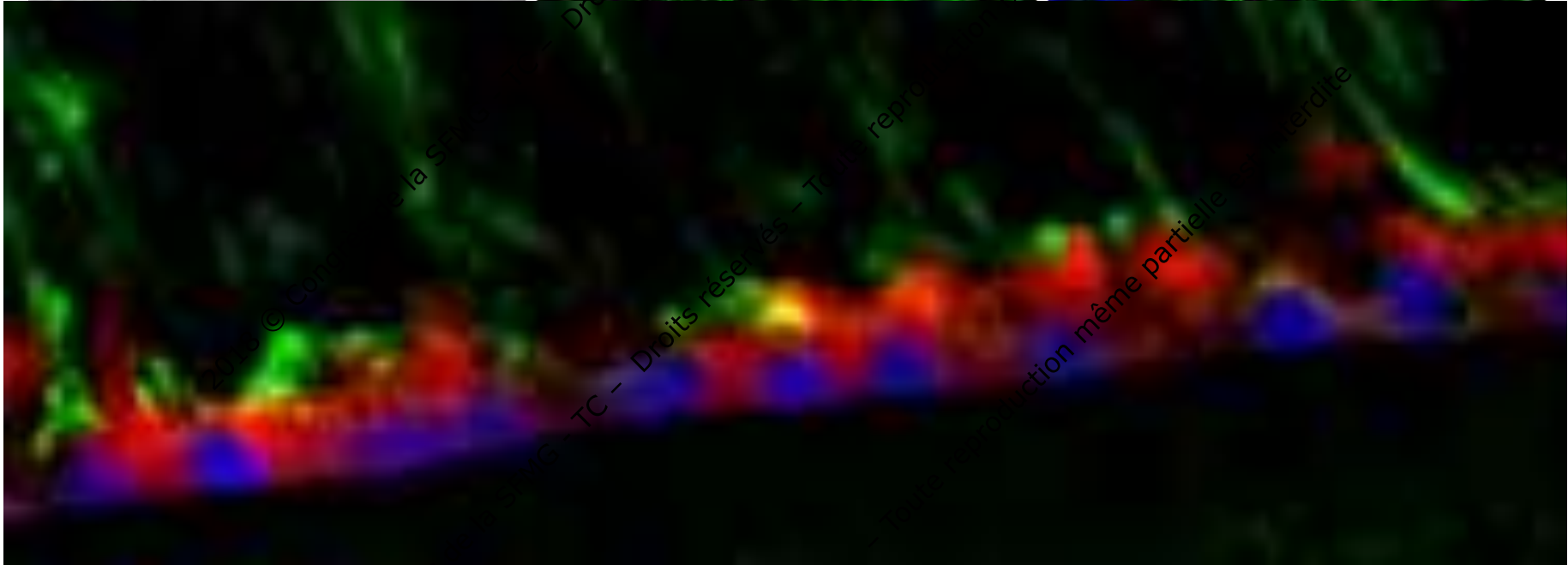
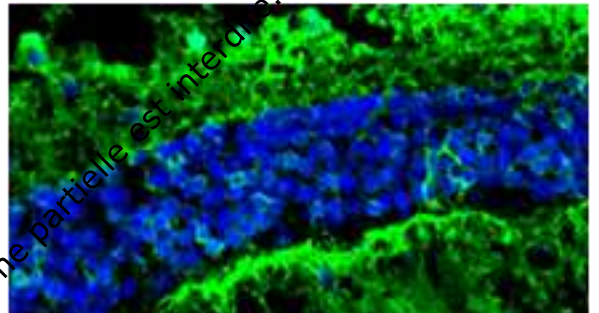
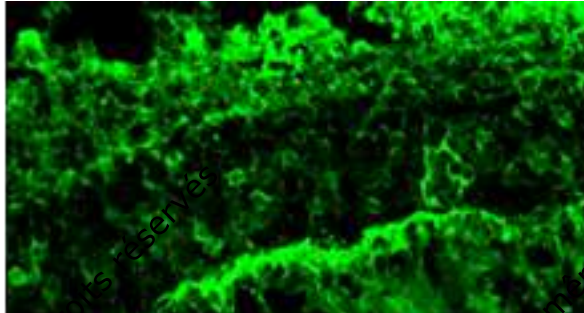
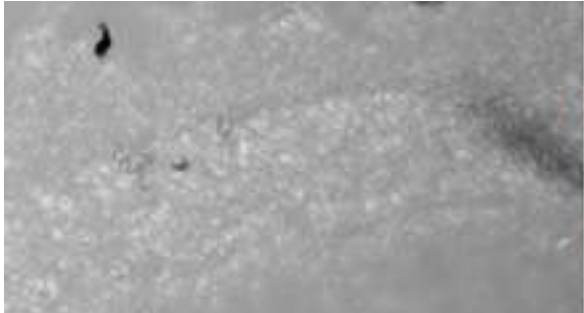
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B wave_implicit time BL vs TR



B wave amplitude BL vs TR

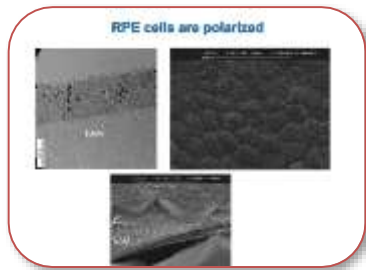




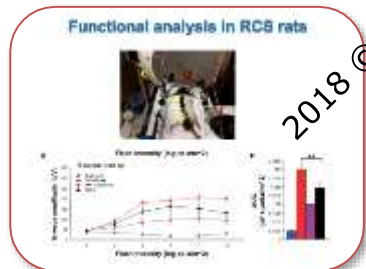
Conclusions



- We have developed a protocol to generate an unlimited number of clinical grade RPE from hESCs (GMP bank ready).



- In vitro validation of hAM as a support allowing the formation of an epithelial sheet of RPE suitable for clinical application.

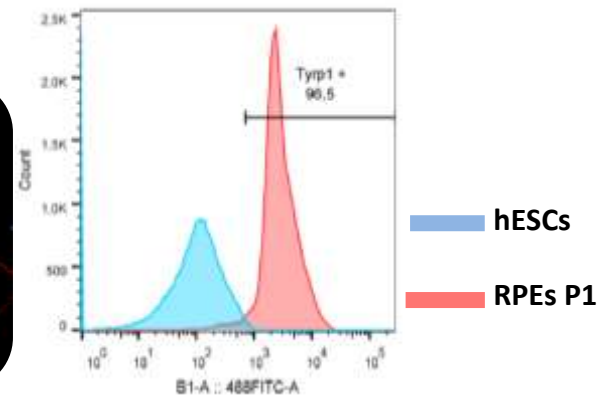
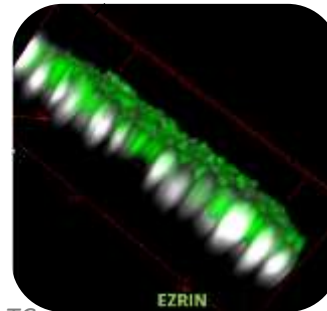
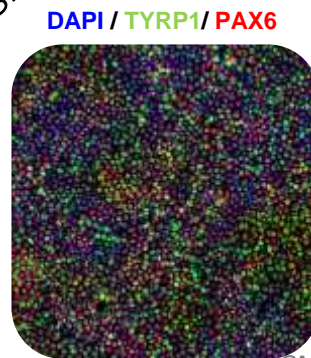
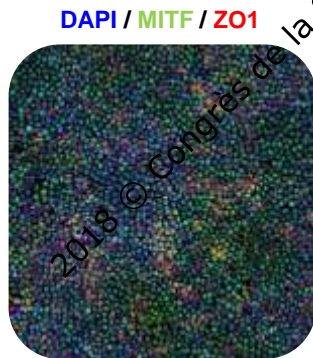
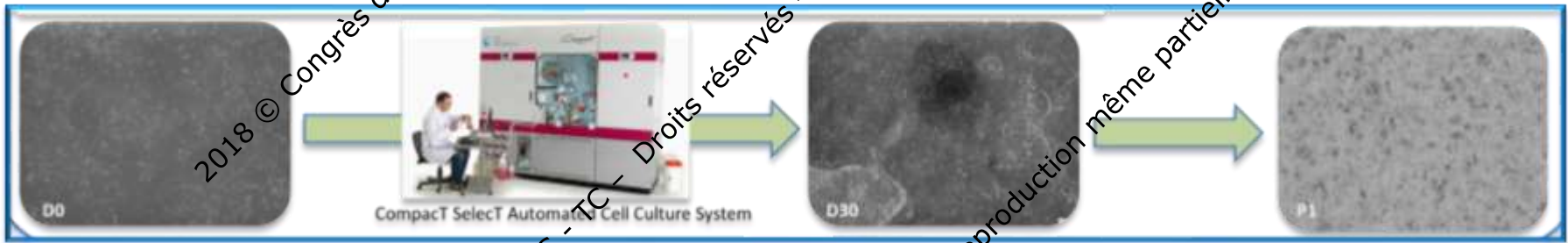


- Functionality/Safety (preclinical) of the Tissue engineered product (TEP) in animal models (mouse, rats and Monkeys)



- Clinical trial planned in 2019 in patients with MERTK, RPE65, LRAT mutations

Transposing bench-scale practices to automated and robotized systems



Acknowledgements



- Karim Ben M'Barek
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- Florence Ganne

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- Helene Lafolly



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- Saddek Mohand Said

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- Valérie Vanneaux



- Claire-Maëlle Fovet



- Paul de Sousa
- Janet Downie

