DES « MINI-CERVEAUX » POUR MODÉLISER LES MALADIES NEURODÉGÉNÉRATIVES ?

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Recherche sur les Cellules Souches (FSSCR)

ORGANISMES MULTICELLULAIRES

Organes et fonctions

ORGANISMES MULTICELLULAIRES

Organes et fonctions

ORGANISMES MULTICELLULAIRES

Organes et fonctions

100 ORGANES

ORGANISMES MULTICELLULAIRES

Organes et fonctions

SUP biotech

100 ORGANES

cerveau

poumons

coeur

estomac

moelle osseuse

muscles

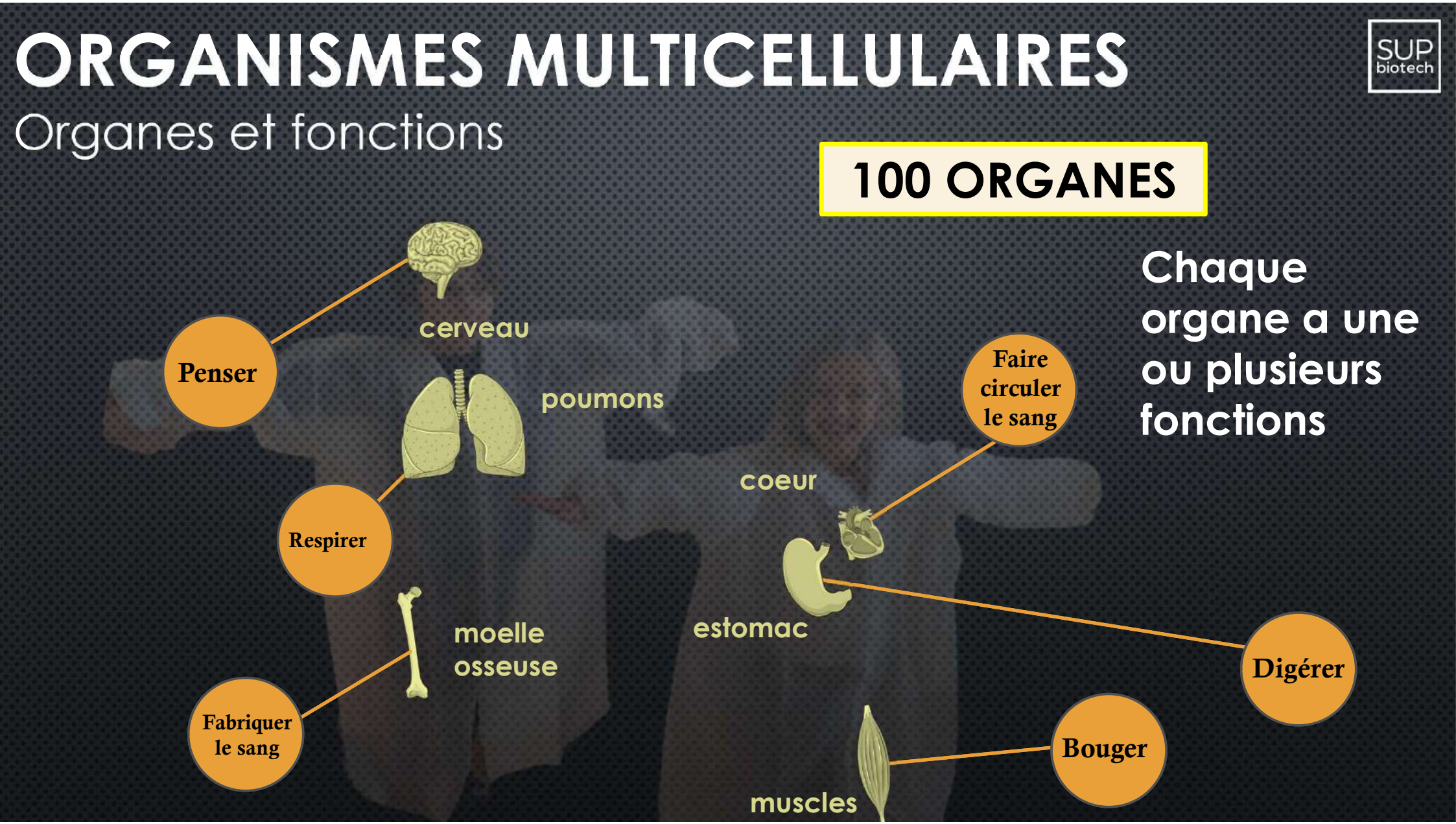
ORGANISMES MULTICELLULAIRES

Organes et fonctions

SUP biotech

100 ORGANES

Chaque organe a une ou plusieurs fonctions



ORGANISMES MULTICELLULAIRES

Organes et fonctions

37 000 000 000 000 000 000 CELLULES
($37x10^{18}$)

cerveau

poumons

coeur

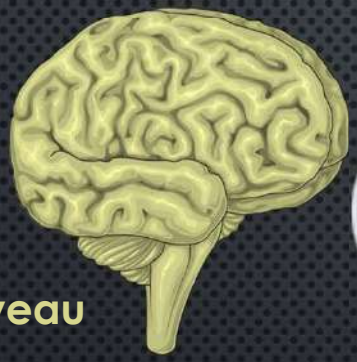
estomac

moelle
osseuse

muscles

LES CELLULES, BRIQUES INDISPENSABLES

cerveau



Neurones

Circulation sanguine

Lymphocytes Mémoire

estomac

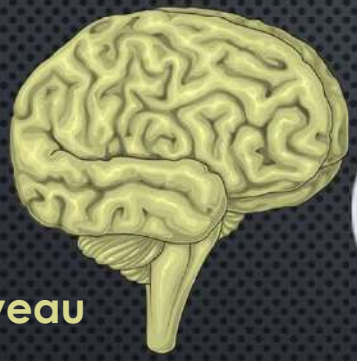
Muqueuse Estomac

Globules Rouges

LES CELLULES, BRIQUES INDISPENSABLES

Durée de vie des cellules

cerveau



Neurones
(vie)

Circulation sanguine

Lymphocytes Mémoire
(20-50ans)

estomac

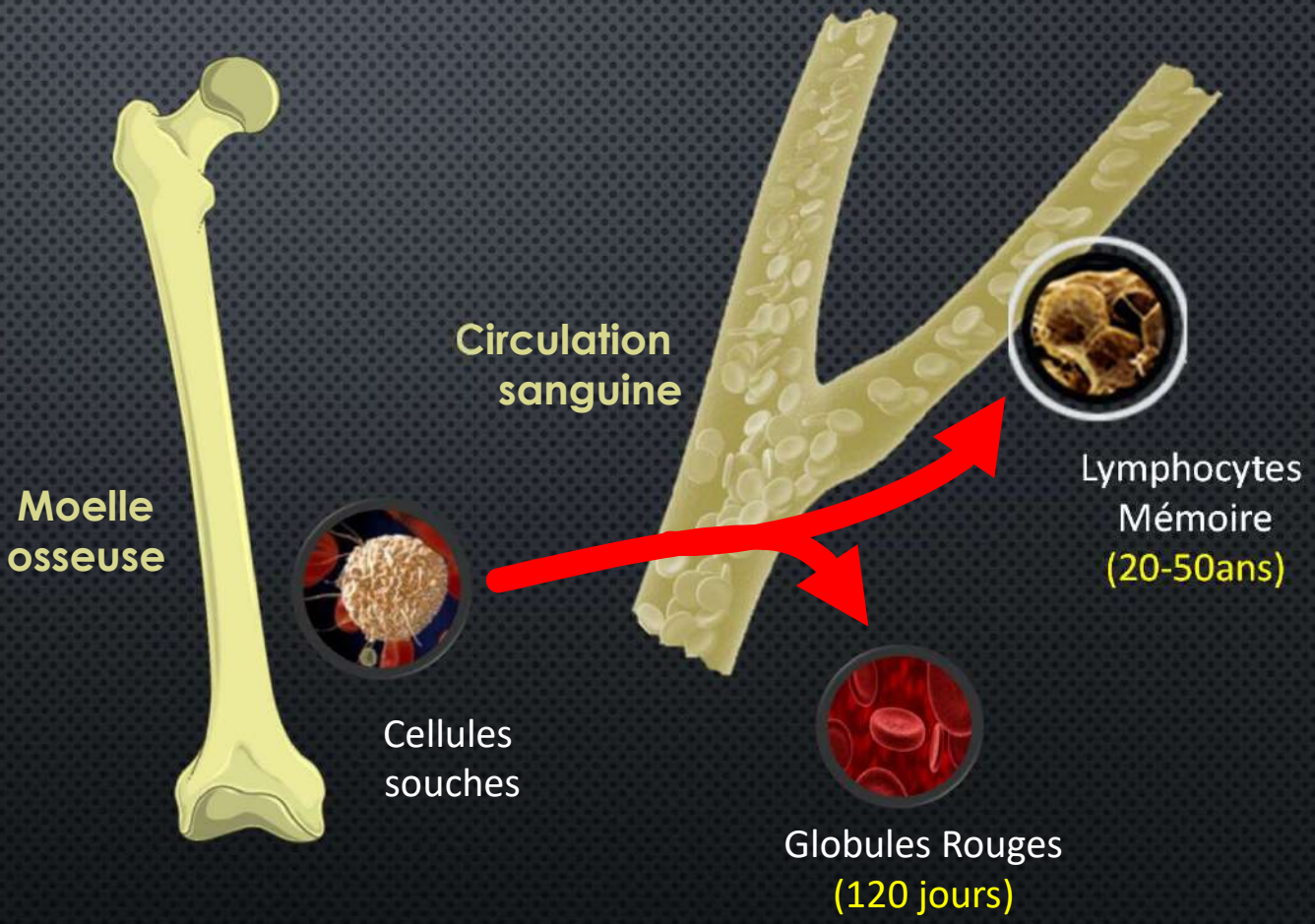
Muqueuse Estomac
(3 jours)

Globules Rouges
(120 jours)

LES CELLULES SOUCHES

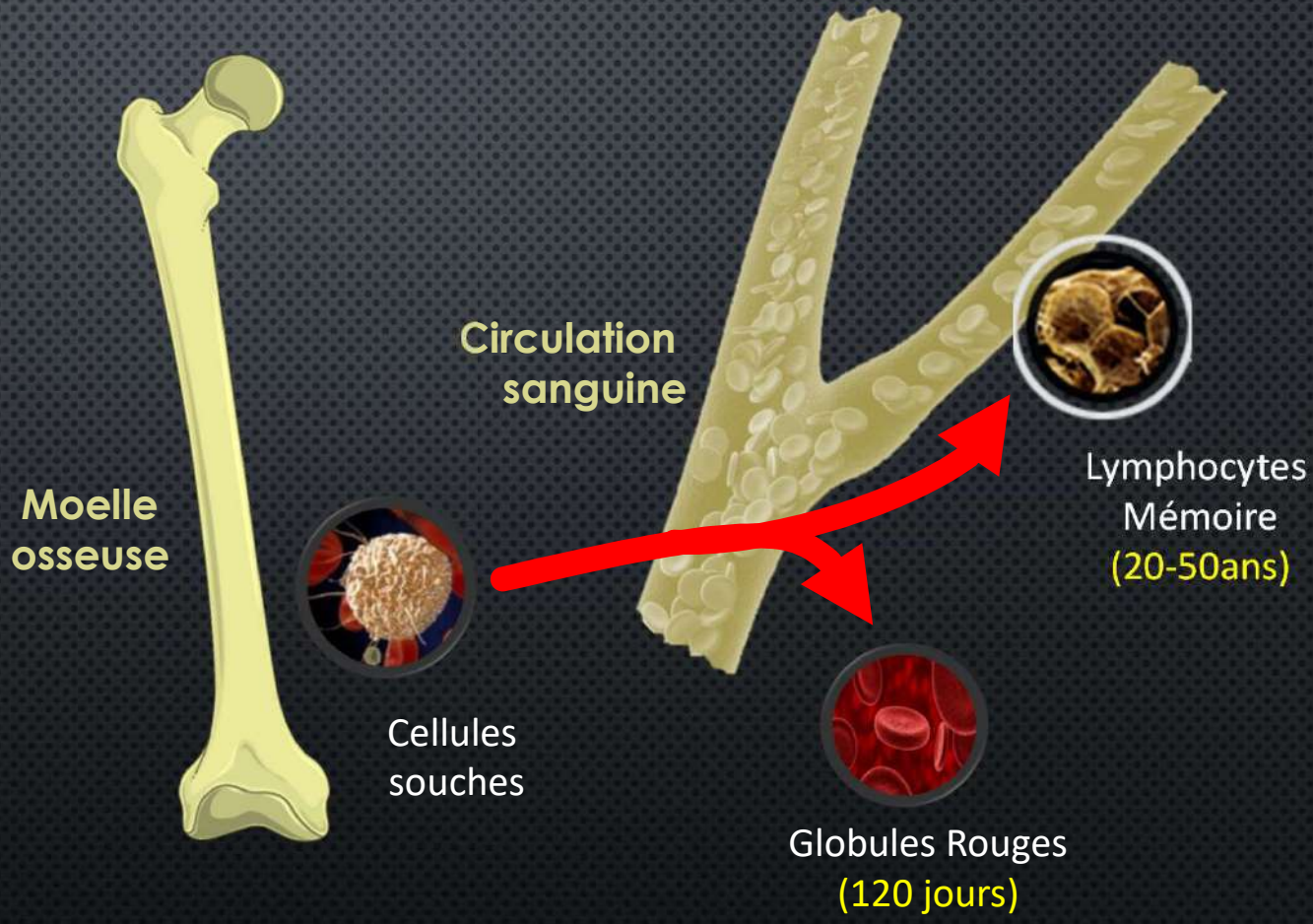
Source cellulaire au sein des organes

LES CELLULES SOUCHES



LES CELLULES SOUCHES

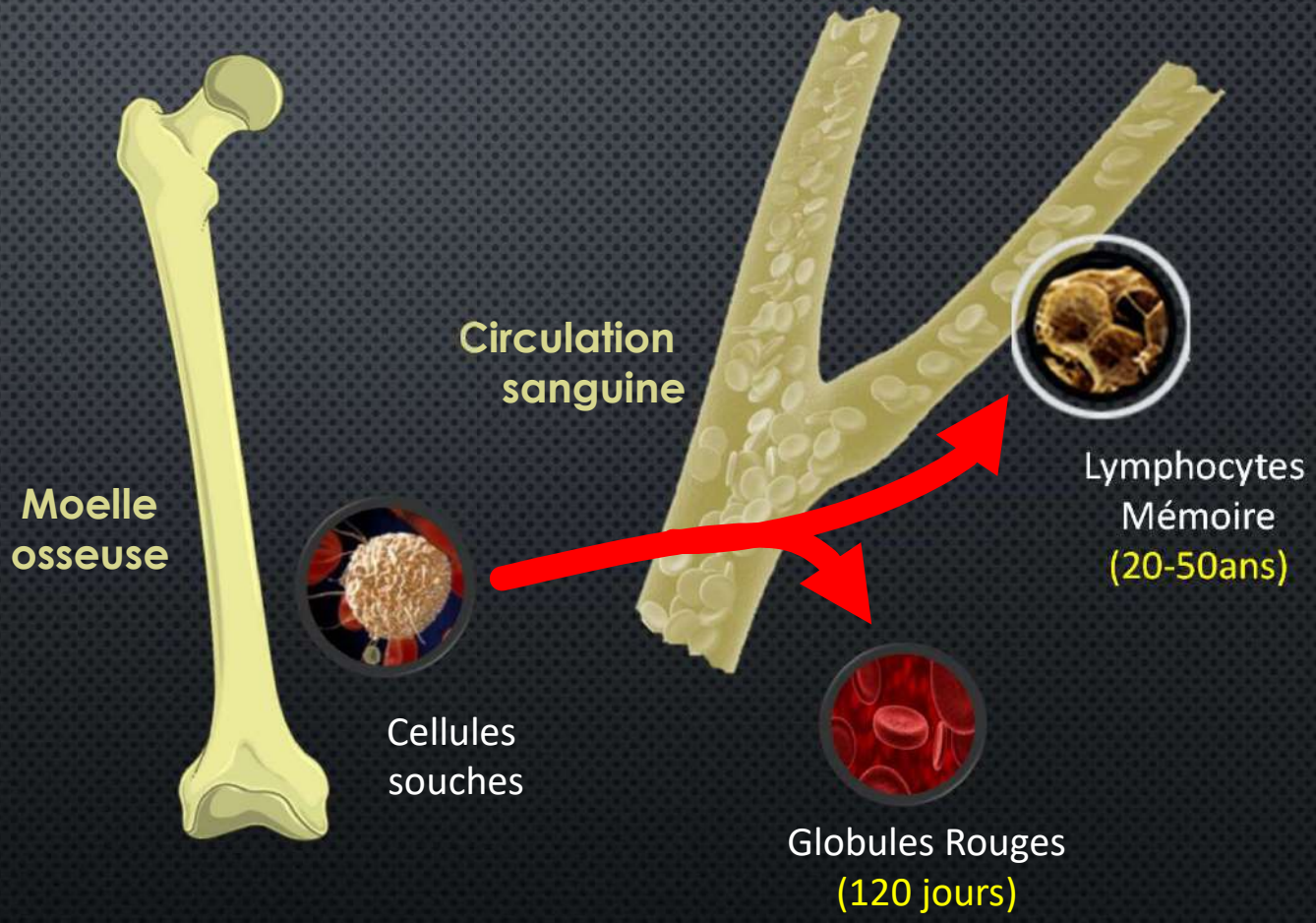
Les Cellules Souches sont là pendant toute la vie pour approvisionner l'organisme en cellules



LES CELLULES SOUCHES

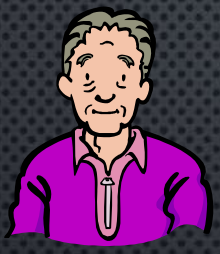
Les Cellules Souches

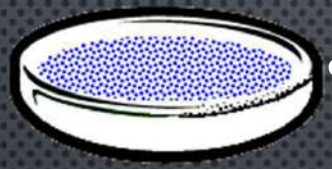
- Rares
- Difficiles à identifier
- Difficile à cultiver



LES CELLULES SOUCHES PLURIPOTENTES

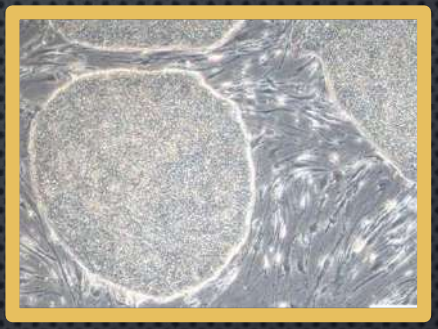
Obtenues à partir de n'importe quel patient.....





Cellules du patient
(par exemple cellules de peau)

Reprogrammation cellulaire



Cellules IPS

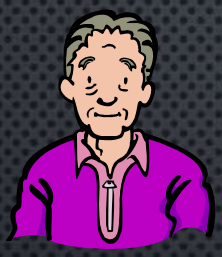
(Souches Pluripotentes Induites)

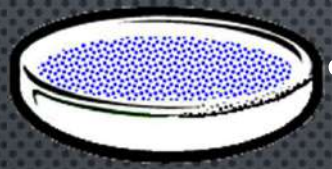
Pr Shinya Yamanaka

Nobel 2012

LES CELLULES SOUCHES PLURIPOTENTES

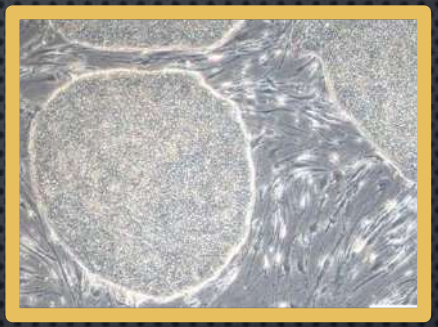
Capables de se différencier en n'importe quelle cellule….





Cellules du patient
(par exemple cellules de peau)

Reprogrammation cellulaire



Cellules IPS
(Souches Pluripotentes Induites)

Neurones

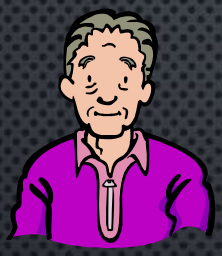
Cellules intestinales

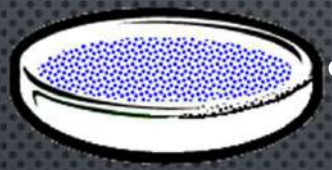
Cellules Musculaires

DIFFERENCIATION

LES CELLULES SOUCHES PLURIPOTENTES

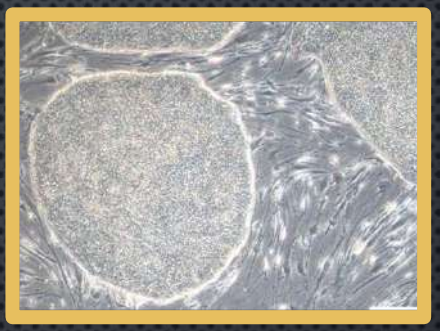
Capables de se différencier en n'importe quelle cellule….





Cellules du patient
(par exemple cellules de peau)

Reprogrammation cellulaire



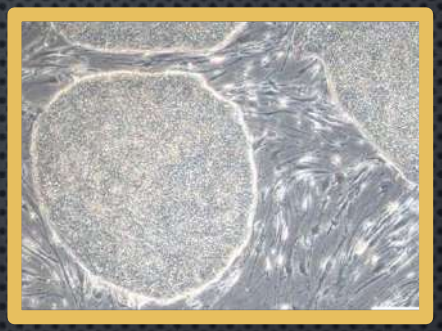
Cellules IPS
(Souches Pluripotentes Induites)

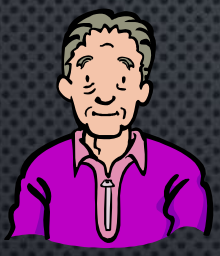
DIFFERENCIATION

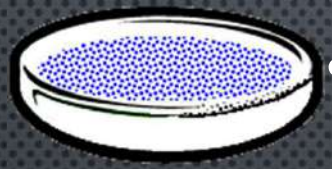
Modélisation in vitro
Criblage pharmacologique

LES CELLULES SOUCHES PLURIPOTENTES

Capables de se différencier en n'importe quelle cellule….







Cellules du patient
(par exemple cellules de peau)

Reprogrammation cellulaire

Cellules IPS
(Souches Pluripotentes Induites)

DIFFERENCIATION

Modélisation in vitro
Criblage pharmacologique

Thérapie cellulaire

CELLULES SOUCHES PLURIPOTENTES : CAPABLES DE S'AUTO-ORGANISER

THE BRAINMAKER

BY DAVID CYRANOSKI

With his knack for knowing what stem cells want, Yoshiki Sasai has grown an eye and parts of a brain in a dish.

In December 2010, Robin Ali became suddenly excited by the usually mundane task of reviewing a scientific paper. "I was running around my room, waving the manuscript," he recalls. The paper described how a clump of embryonic stem cells had grown into a rounded goblet of retinal tissue. The structure, called an optic cup, forms the back of the eye in a growing embryo. But this one was in a dish, and videos accompanying the paper showed the structure slowly sprouting and blossoming. For Ali, an ophthalmologist at University College London who has devoted two decades to repairing vision, the implications were immediate. "It was clear to me it was a landmark paper," he says. "He has transformed the field."

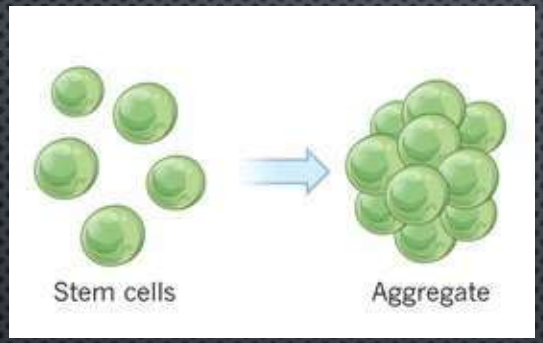
'He' is Yoshiki Sasai, a stem-cell biologist at the RIKEN Center for Developmental Biology in Kobe, Japan. Sasai has impressed many researchers with his green-fingered talent for coaxing neural stem cells to grow into elaborate structures. As well as the optic cup[1], he has cultivated the delicate tissue layers of the cerebral cortex[2] and a rudimentary, hormone-making pituitary gland[3]. He is now well on the way to growing a cerebellum[4] — the brain structure that coordinates movement and balance. "These papers make for the most addictive series of stem-cell papers in recent years," says Luc Leyns, a stem-cell scientist at the Free University of Brussels.

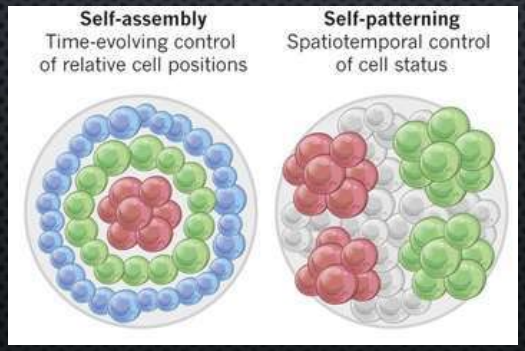
Sasai's work is more than tissue engineering. It tackles questions that have puzzled developmental biologists for decades. How do the proliferating stem cells of an embryo organize themselves seamlessly into the complex structures of the body and brain? And is tissue formation driven by a genetic program intrinsic to cells, or shaped by external cues from neighbouring tissues? By combining intuition with patient trial and error, Sasai has found that it takes a delicate

444 | NATURE | VOL 488 | 23 AUGUST 2012

Pr Yoskiki Sasaï

Nature, 2012



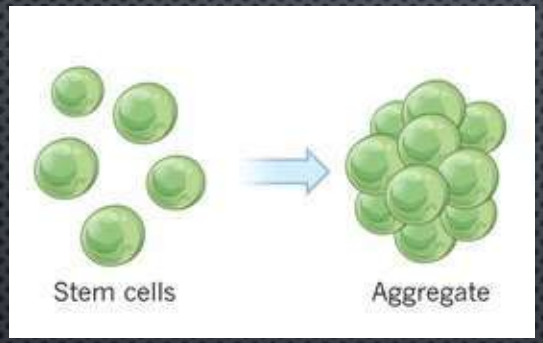


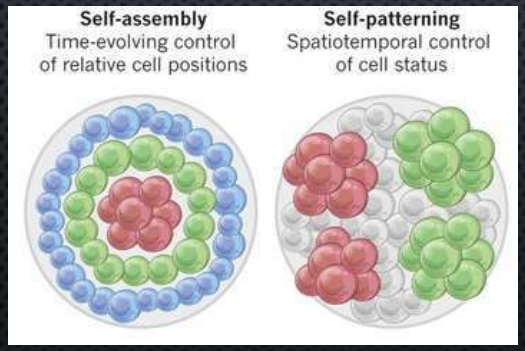
Auto-assemblage

Auto-modelage

CELLULES SOUCHES PLURIPOTENTES : CAPABLES DE S'AUTO-ORGANISER

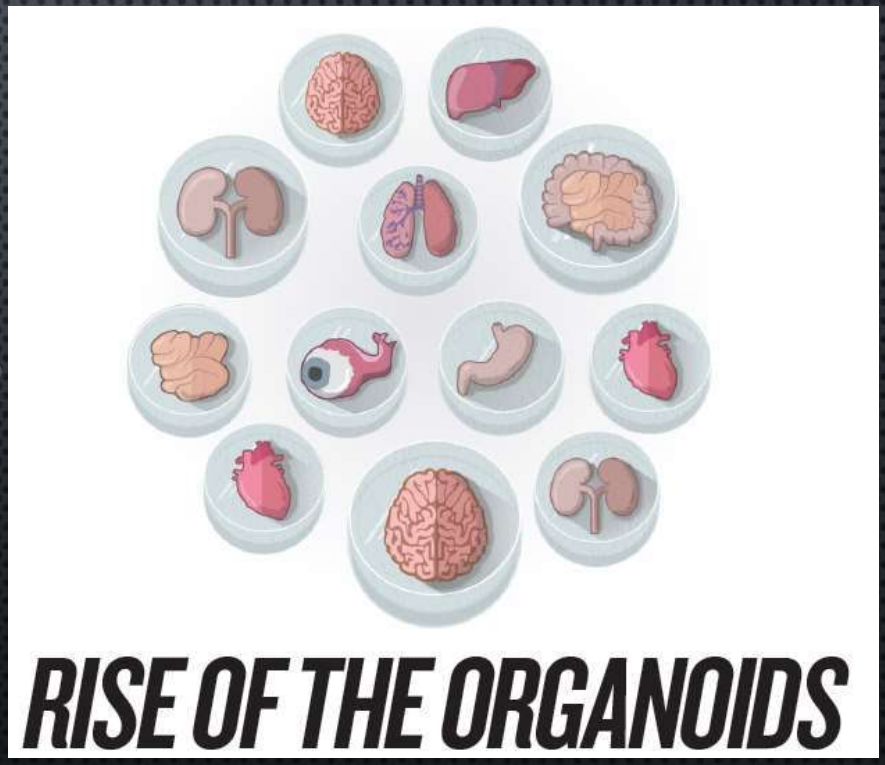
Nature, 2012





Auto-assemblage

Auto-modelage

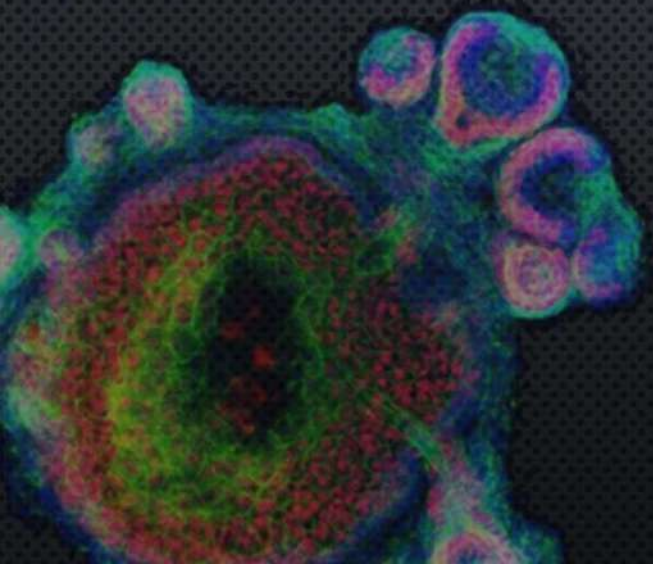


Nature, 2015

ORGANOIDE

Définition

"Organoids are three-dimensional tissue structures, which self-organise and recapitulate complex aspects of their organ counterparts, ranging from physiological processes to regeneration and disease. "

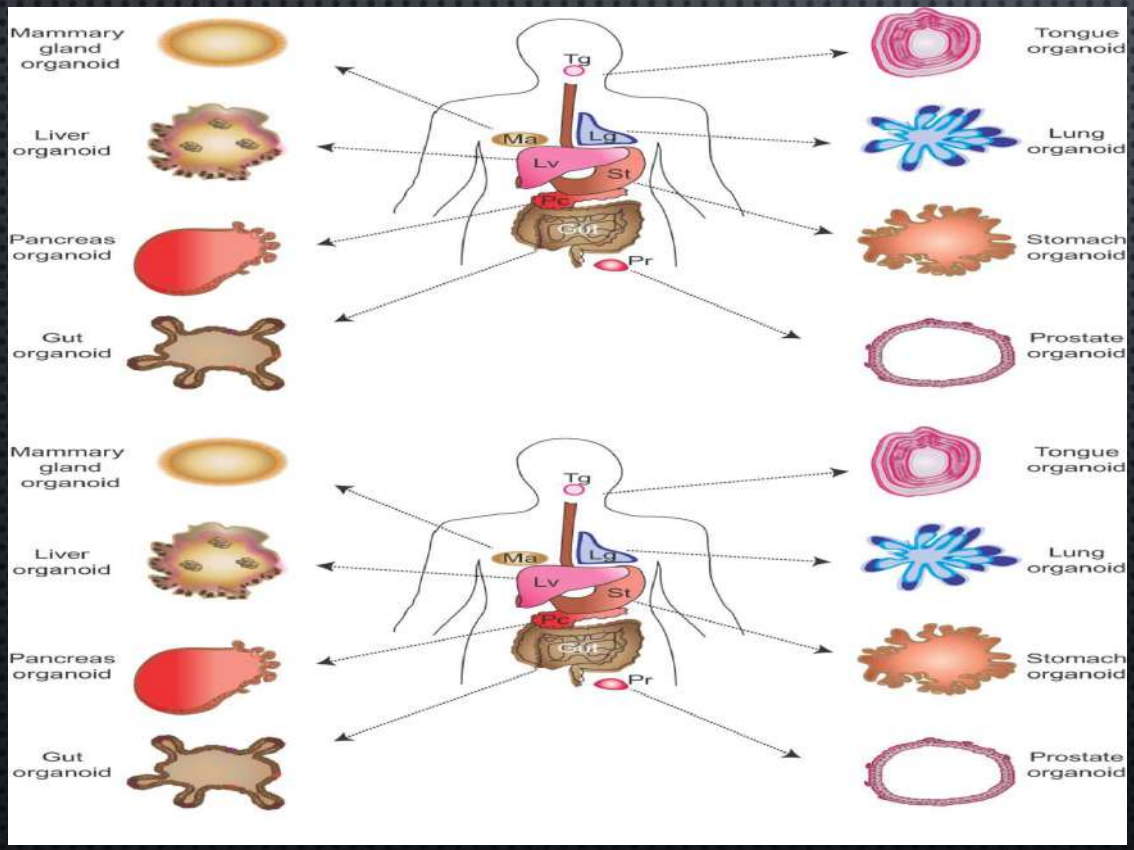


"Les organoïdes sont des **structures tissulaires tridimensionnelles** qui s'**auto-organisent** et **récapitulent certains aspects complexes** des organes modélisés, allant des processus physiologiques à la régénération et aux maladies. "

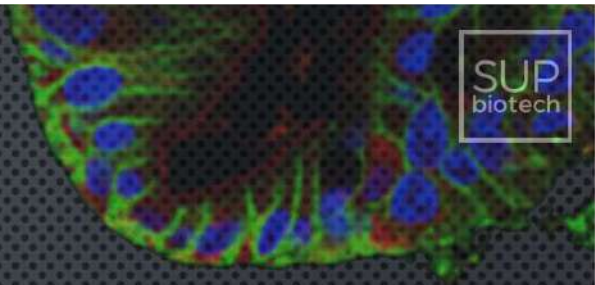
Nature Cell Biology ***v.20***, p. 633 (2018)

ORGANOIDES

Source



Huch et al., Development, 2015



Organoïdes dérivés de cellules "adultes"

- Intestin (Sato et al., 2009)
- Glande mammaire(Dontu et al., 2003)
- Os (Kale et al., 2000)
- Estomac (Barker et al., 2010b)
- Côlon (Jung et al., 2011)
- Foie (Huch et al., 2013)
- Pancréas (Boj et al., 2015)
- Poumon (Lee et al., 2014)
- Prostate (Gao et al., 2014)
- Glande salivaire (Nanduri et al., 2014)
- Langue (Hisha et al., 2013)

Exemple

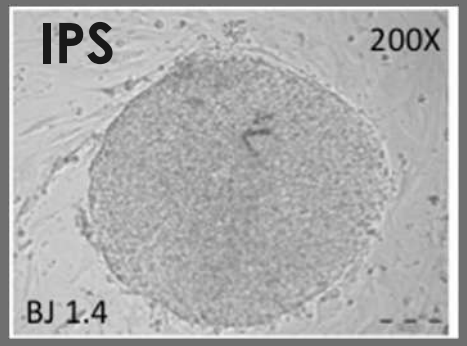
ORGANOIDES CEREBRAUX

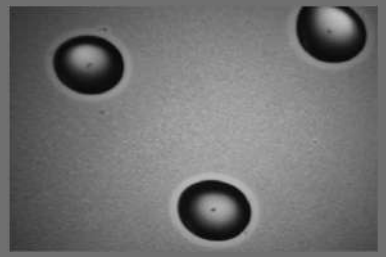
ORGANOIDES CEREBRAUX

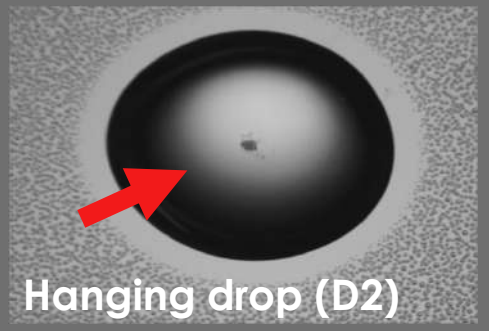
Au laboratoire [Nassor (..) Yates, Front Cell Neur, 2020]

day 2

day 5

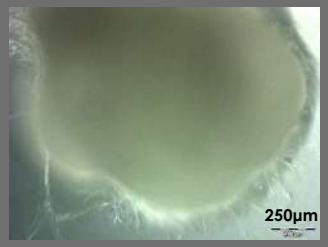


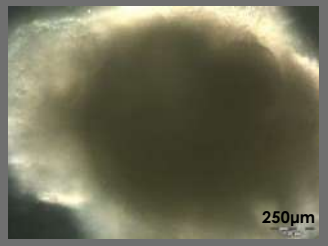


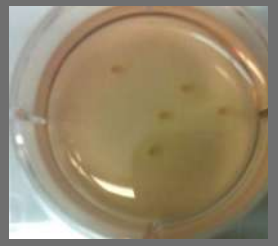


DIFFERENTIATION DES CELLULES SOUCHES

day
30+



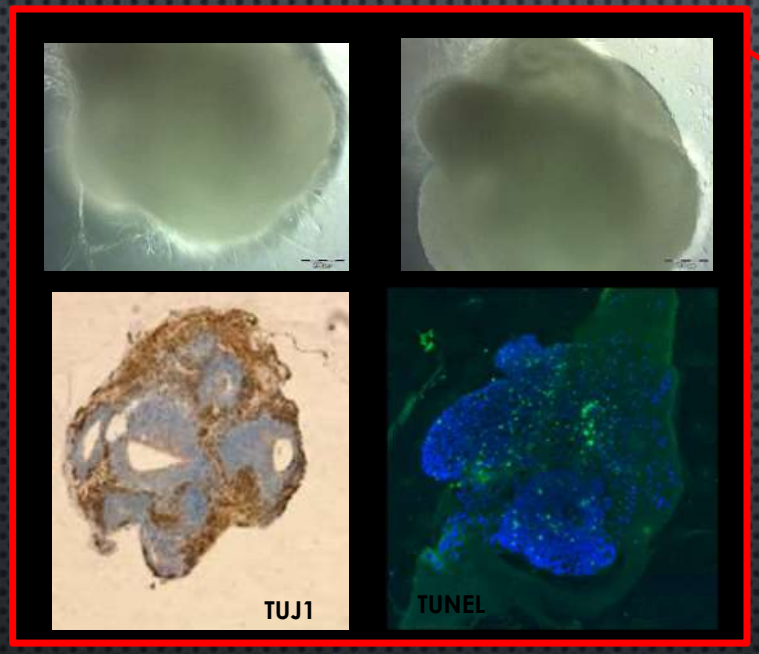




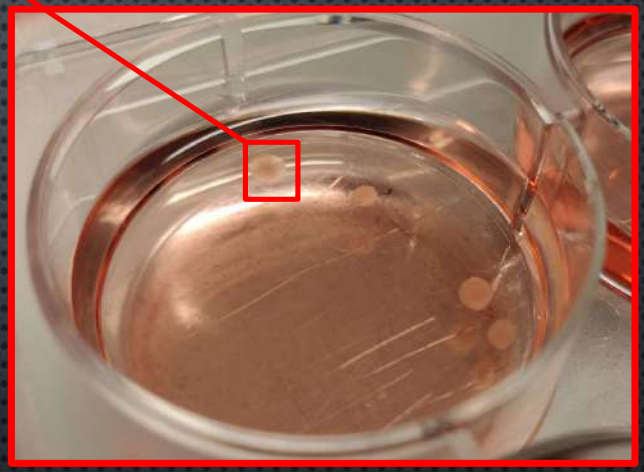
« Mini-Brains »
up to
2,2 mm
x 1,4
mm
in size

ORGANOIDES CEREBRAUX

Les challenges



Organoïdes cérébraux
1-12 mois



Les organoïdes contiennent :

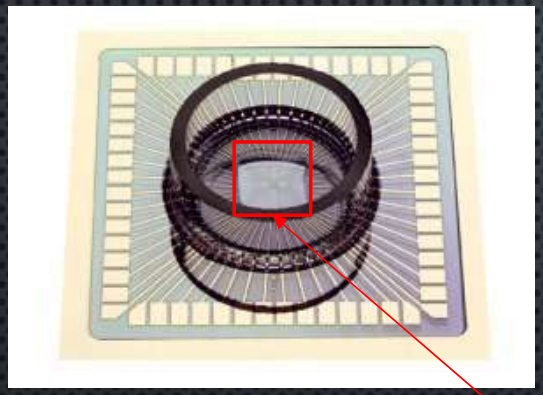
☑
- Des neurones
- Des cellules gliales

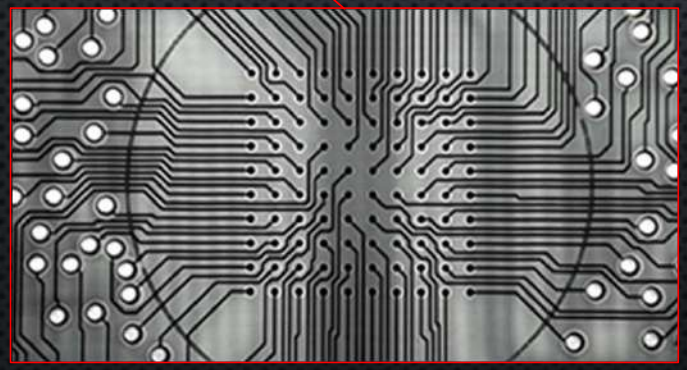
Les organoïdes ne contiennent pas :

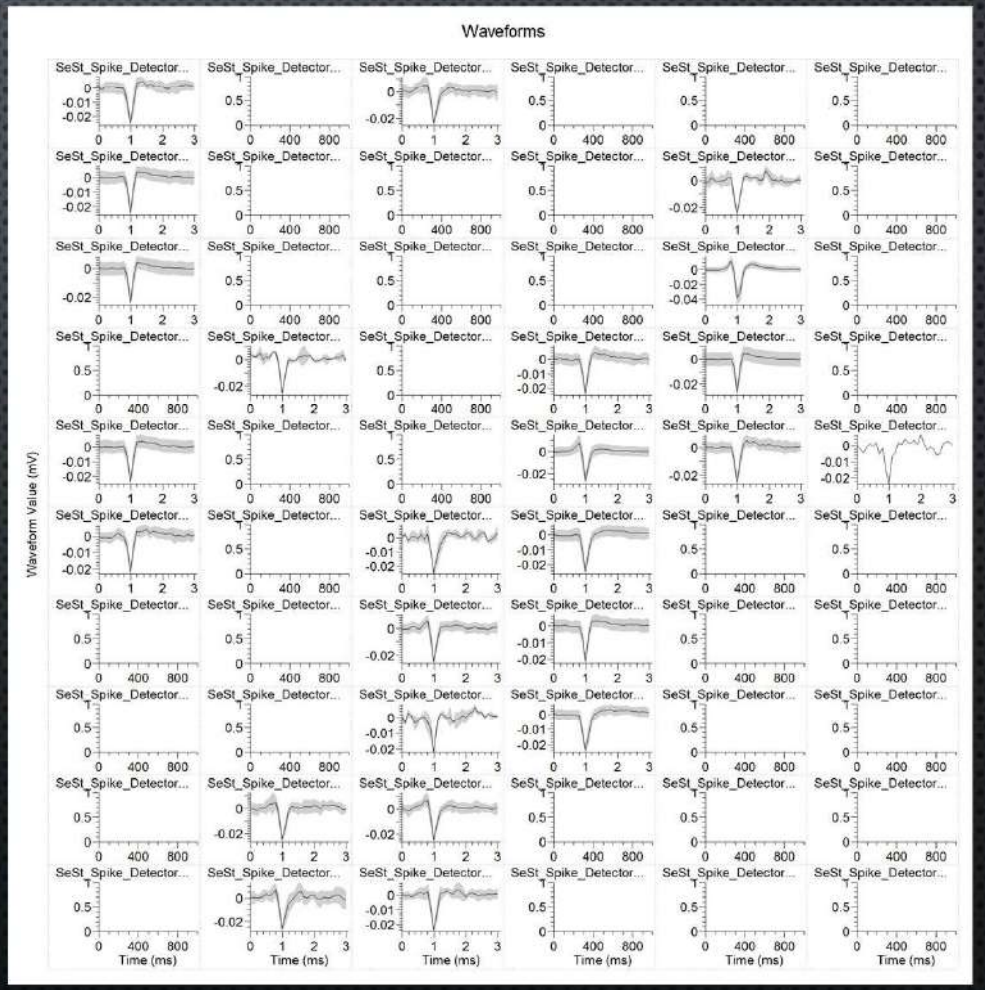
☒
- D'oligodendrocytes
- De vascularisation
- De cellules immunitaires

ORGANOIDES CEREBRAUX

Caractérisation fonctionnelle : activité électrophysiologique



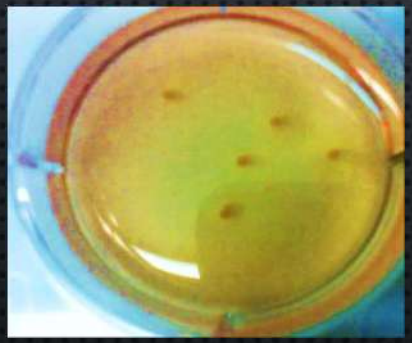




Collab JL BUEE/S HALLIEZ, INSERM

LES ORGANOIDES SONT DES MODELES

LES ORGANOIDES SONT DES MODELES



≠

ORGANOIDES CEREBRAUX

Les challenges

Les organoïdes peuvent-ils être utilisés pour modéliser les maladies neurodégénératives ?

Variabilité

10% EB deviennent des MB

Différences entre MB

Nature embryonnaire

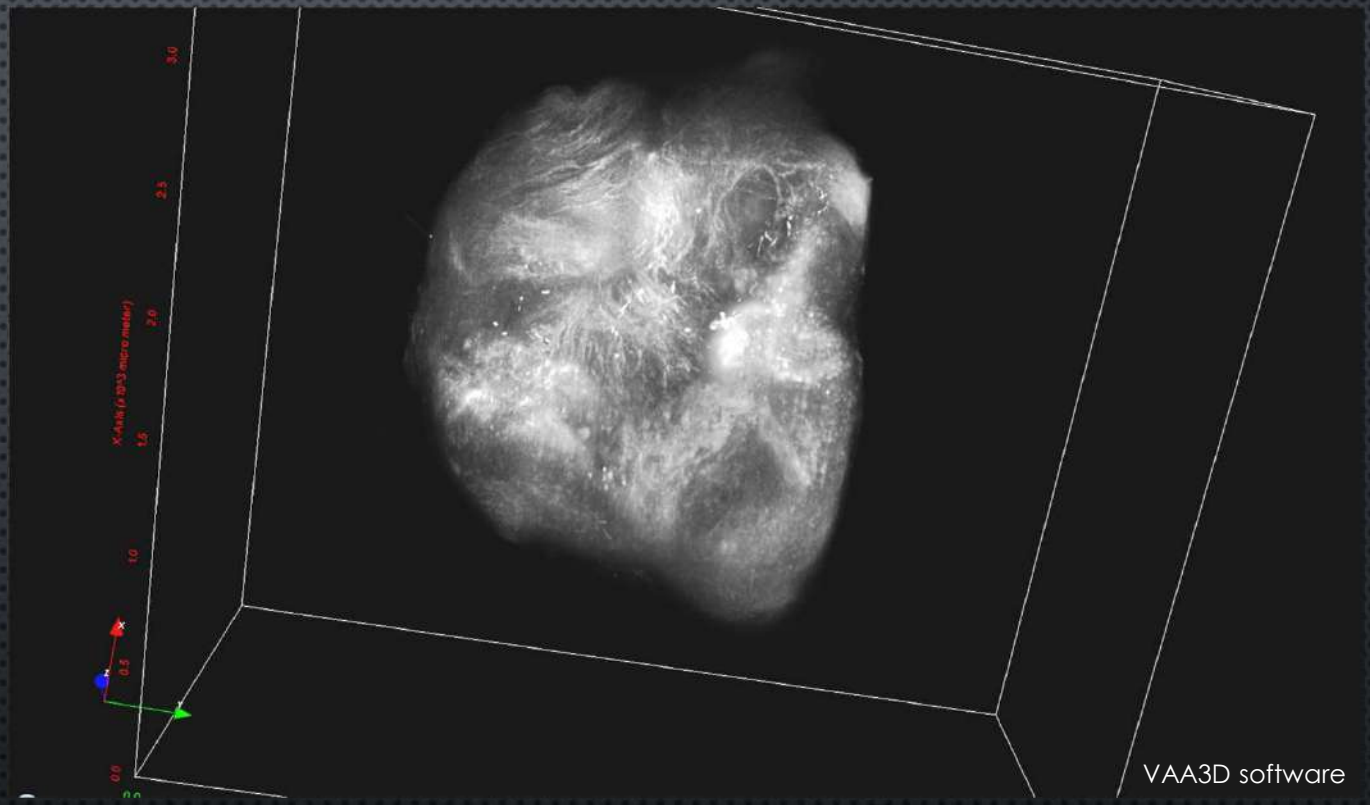
Taille et culture

Difficultés inhérentes à la 3D

Marquages, imagerie

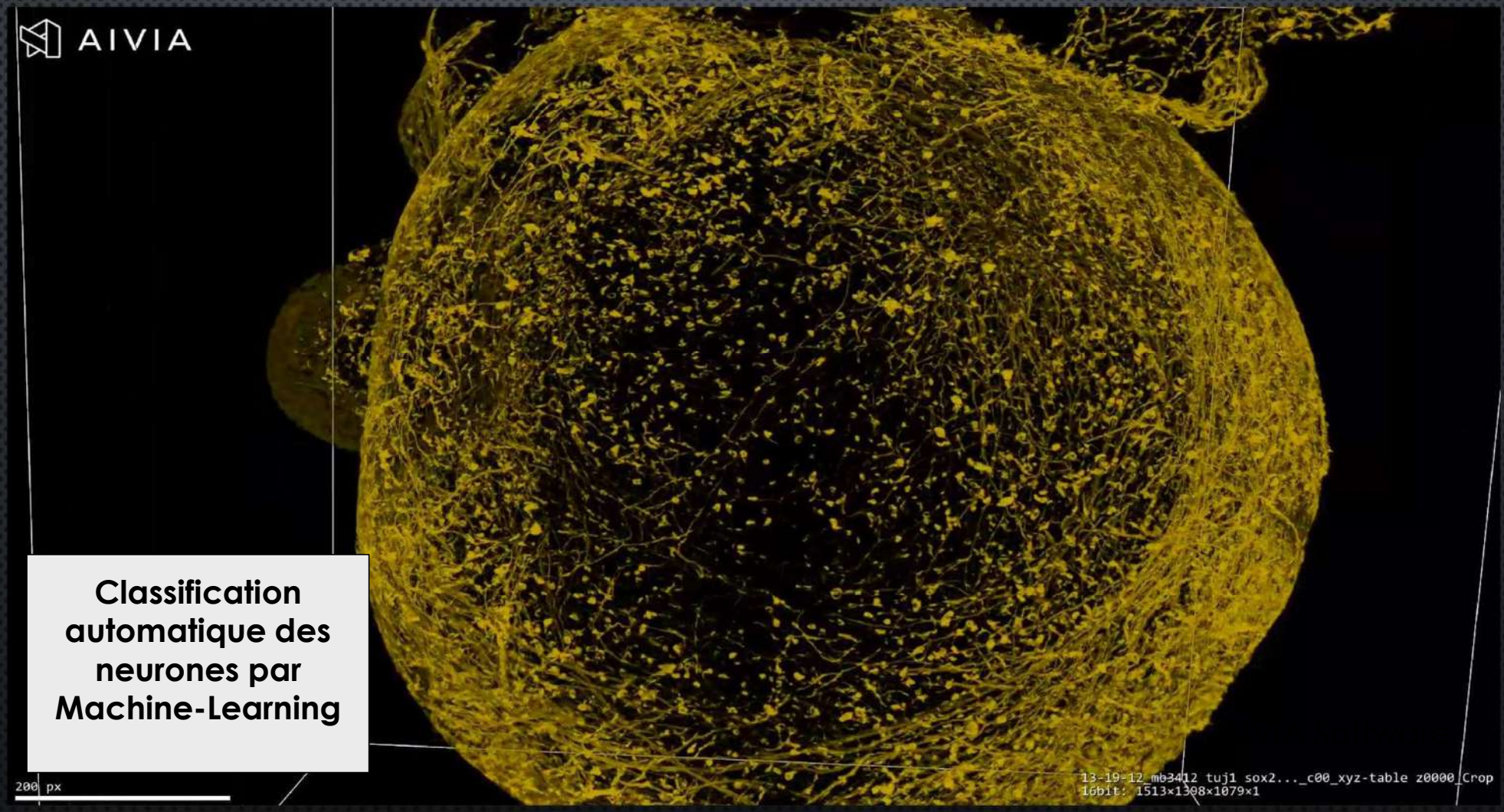
CHALLENGES : IMAGERIE

CHALLENGES : IMAGERIE



Cellules IPS exprimant une fusion Tau-GFP

CHALLENGES : IMAGERIE ET ANALYSE



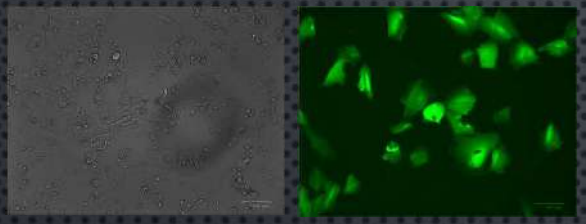
Classification automatique des neurones par Machine-Learning

NOUVEAU MODELE : CELLULES TRISOMIE 21

REPROGRAMMATION DE CELLULES TRISOMIE 21

SUP biotech

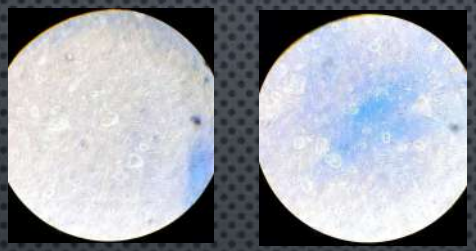
→ **T21.2 – Sendai-GFP:**



Observation of T21.2 AF cells infected with Sendai-GFP – after 12 days – left: brightfield ; right: GFP filter – magnification: 20X – (Thomas Lemonnier)

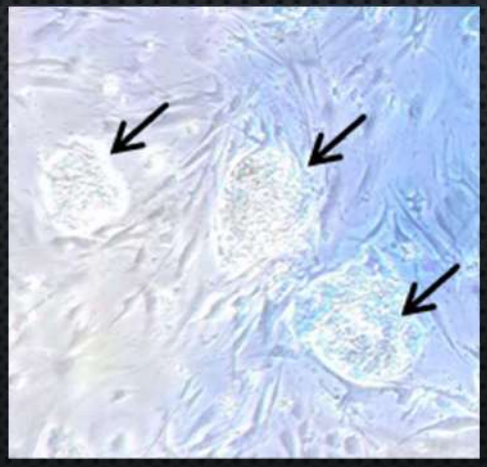
→ **T21.2 – Sendai:**

50K 100K



7 colonies 20 colonies

Observation of T21.2 AF cells infected with normal Sendai virus – after 12 days – magnification: 4X – (Thomas Lemonnier)



En cours au labo:

- Caractérisation
- Organoïdes

Pour une nouvelle approche dans le cadre du développement d'un traitement anténatal de la trisomie 21 : la reprogrammation de cellules amniotiques en cellules souches pluripotentes induites spécifiques

Professeur François Vialard, Université UVSQ

Nouvelles du Chromosome 21

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CONCLUSION (?)

Les organoïdes peuvent-ils être utilisés pour modéliser les maladies neurodégénératives ?

- Complexité du tissu = high content
- Variabilité entre organoïdes
- Nature embryonnaire
- Convergence des technologies :
  - IPS / Genome editing
  - Imagerie
  - Data analysis

Maladie d'Alzheimer
> IPS patients
> Induction pathologique

Vieillissement in vitro
> Maladies progéroïdes

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Hans Clevers, 7 avril