

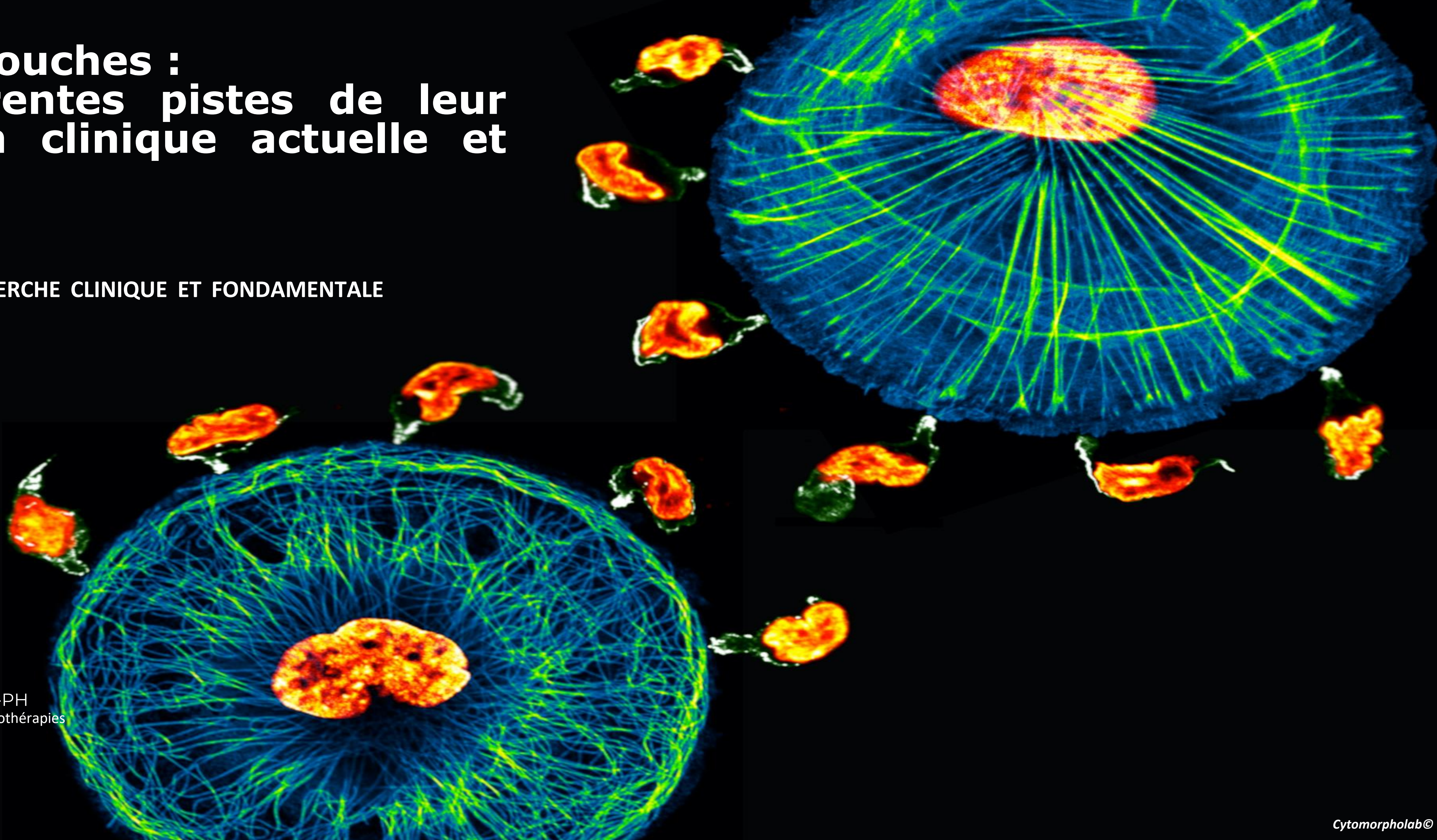
Cellules souches : les différentes pistes de leur utilisation clinique actuelle et future

SEMINAIRE DE RECHERCHE CLINIQUE ET FONDAMENTALE
GETAID-REMININD

02/12/2022

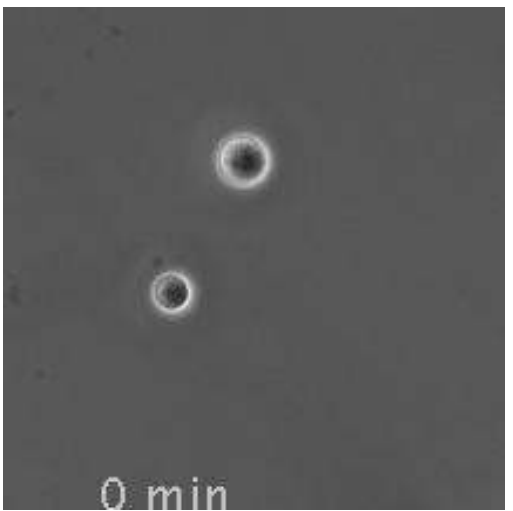
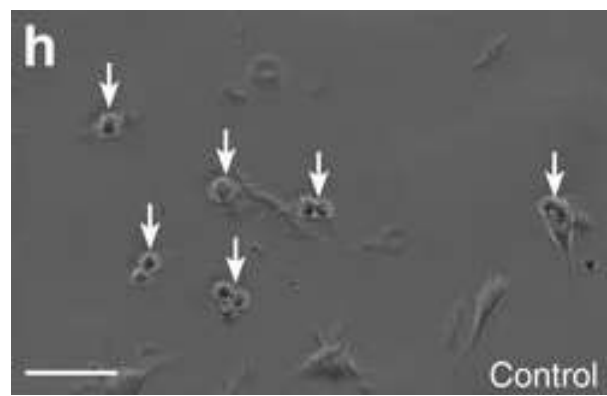
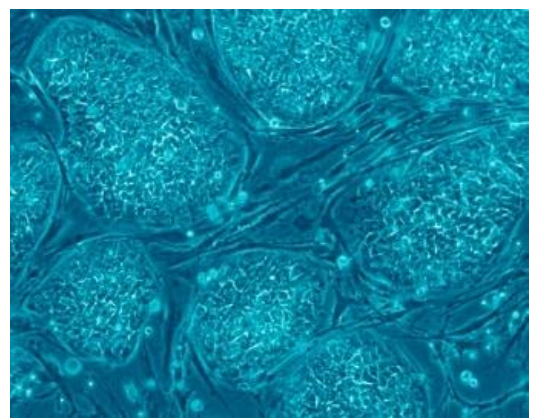
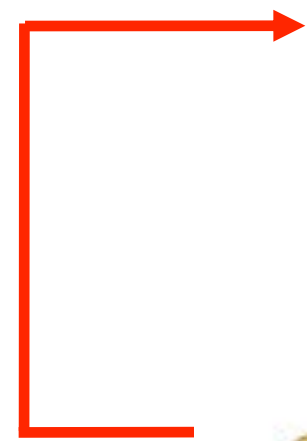
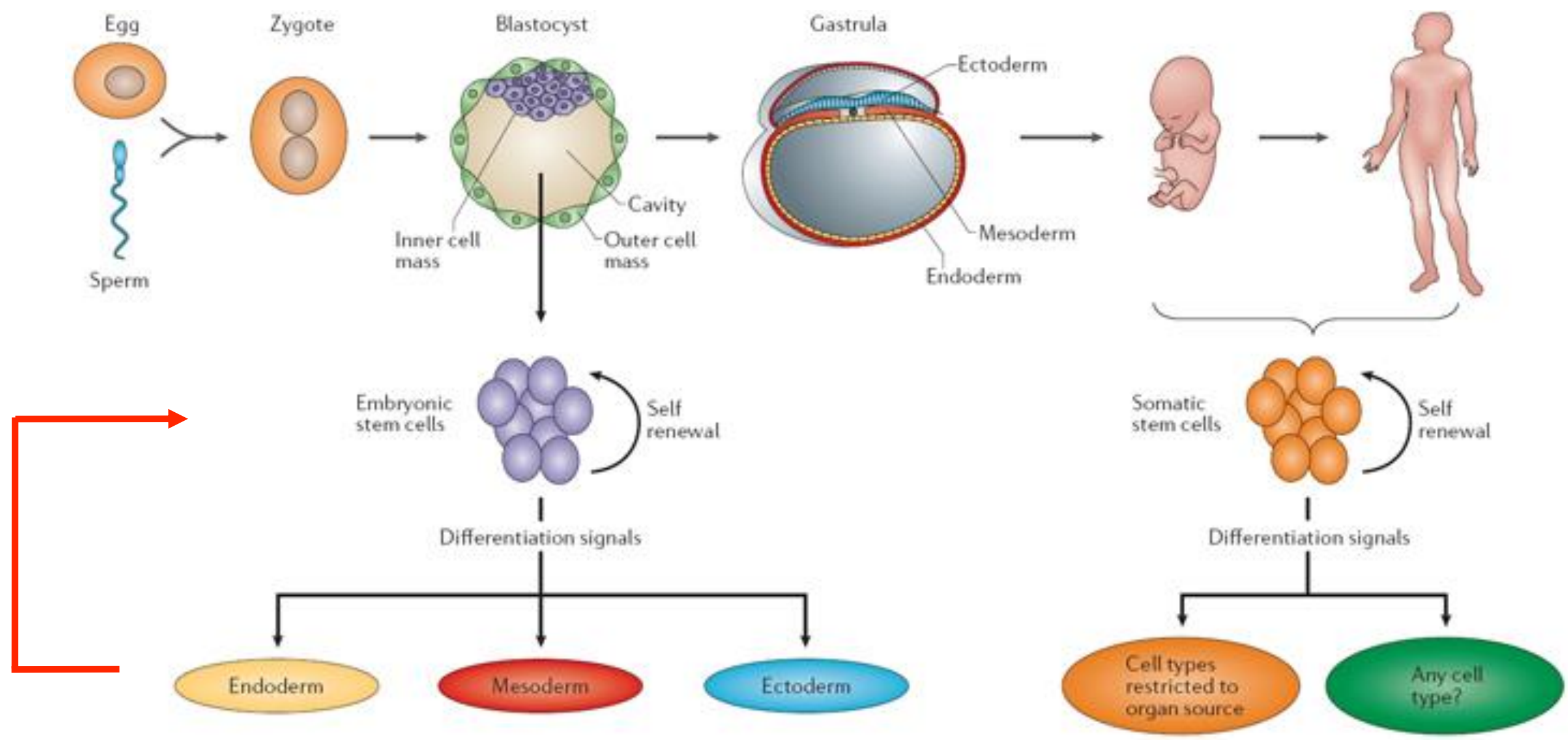
Dr Miryam Mebarki, MCU-PH
Unité de Thérapie Cellulaire, CIC Biothérapies
INSERM U976
Hôpital Saint-Louis

.....
Faculté de Pharmacie
Université Paris Cité
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Cytomorpholab®

Origine des cellules souches



Reprogrammation cellulaire

The Nobel Prize in Physiology or Medicine 2012

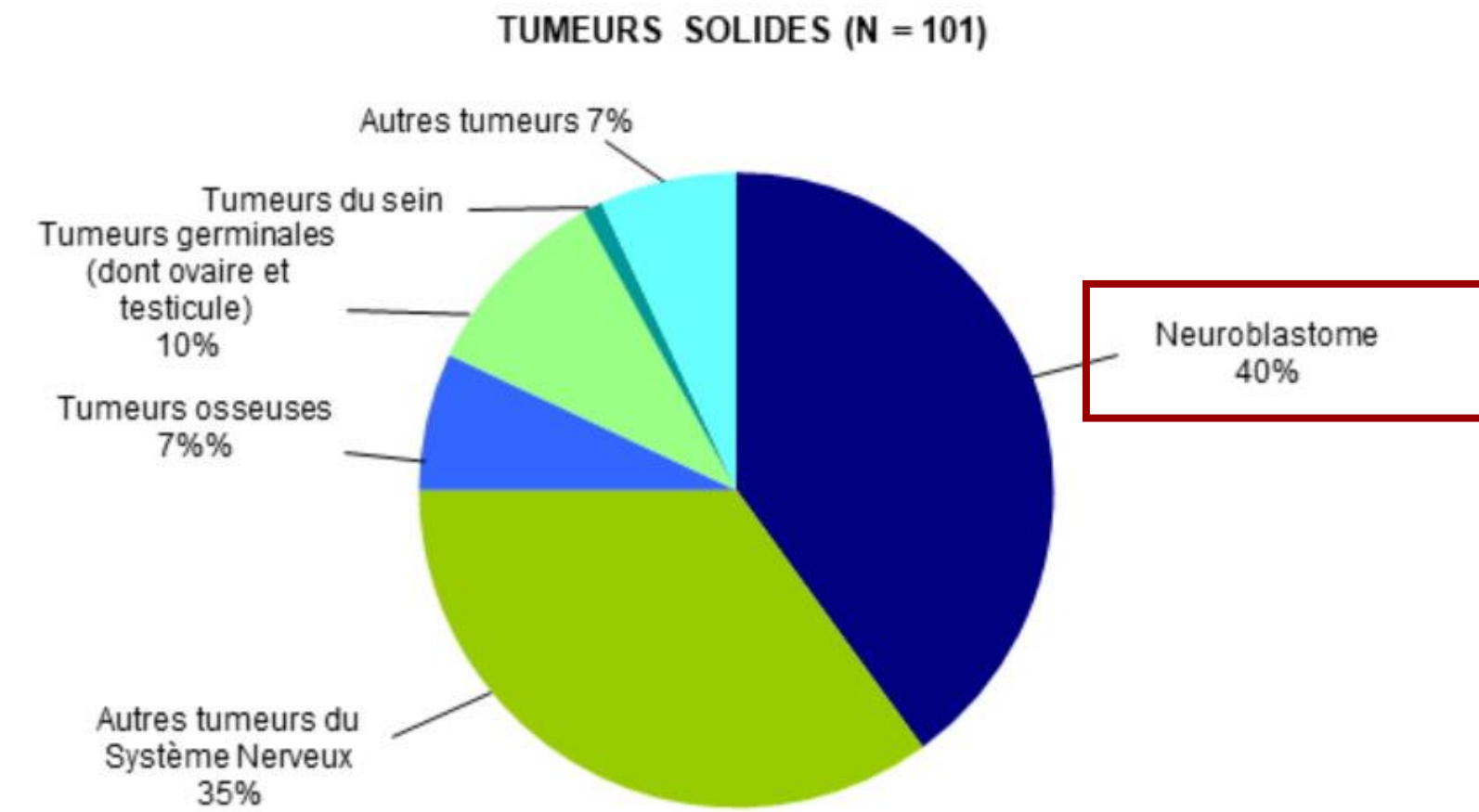
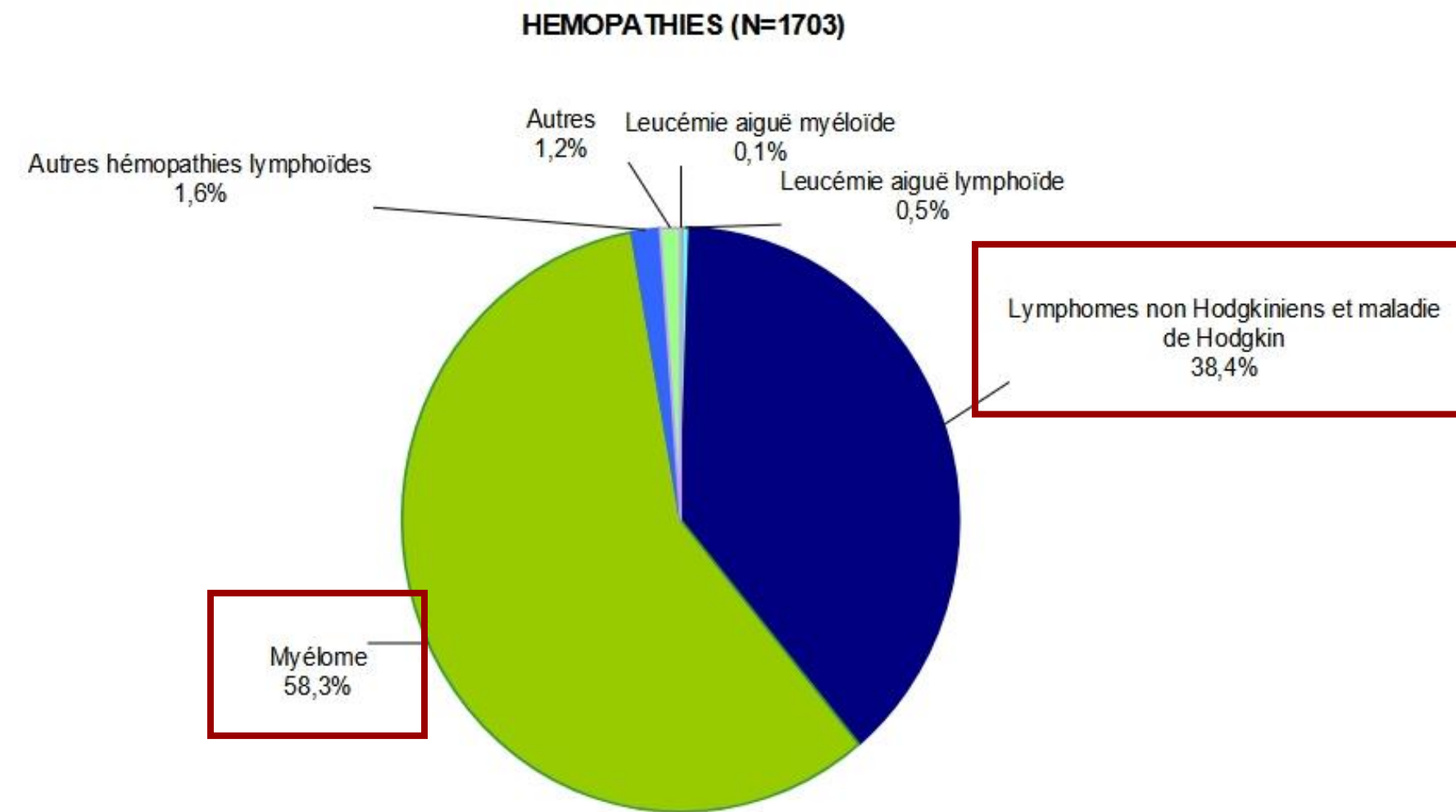
Photo: U. Montan
Sir John B. Gurdon

Photo: U. Montan
Shinya Yamanaka

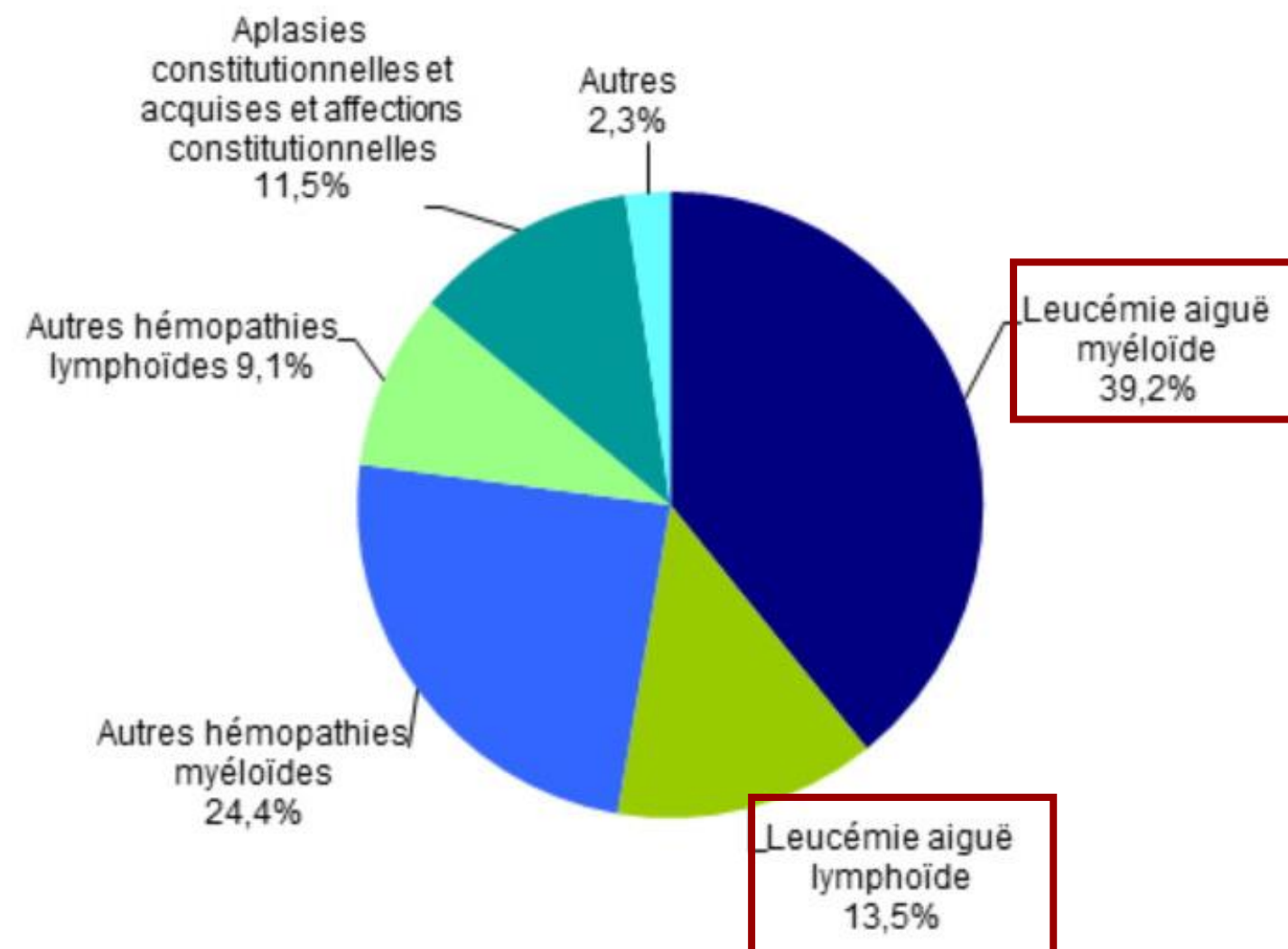
iPS-MEF24-1-9

Chial, H. Nature Education 2008
 Rocheteau et al, Nature com 2015
 K Takahashi, S Yamanaka, Cell 2006

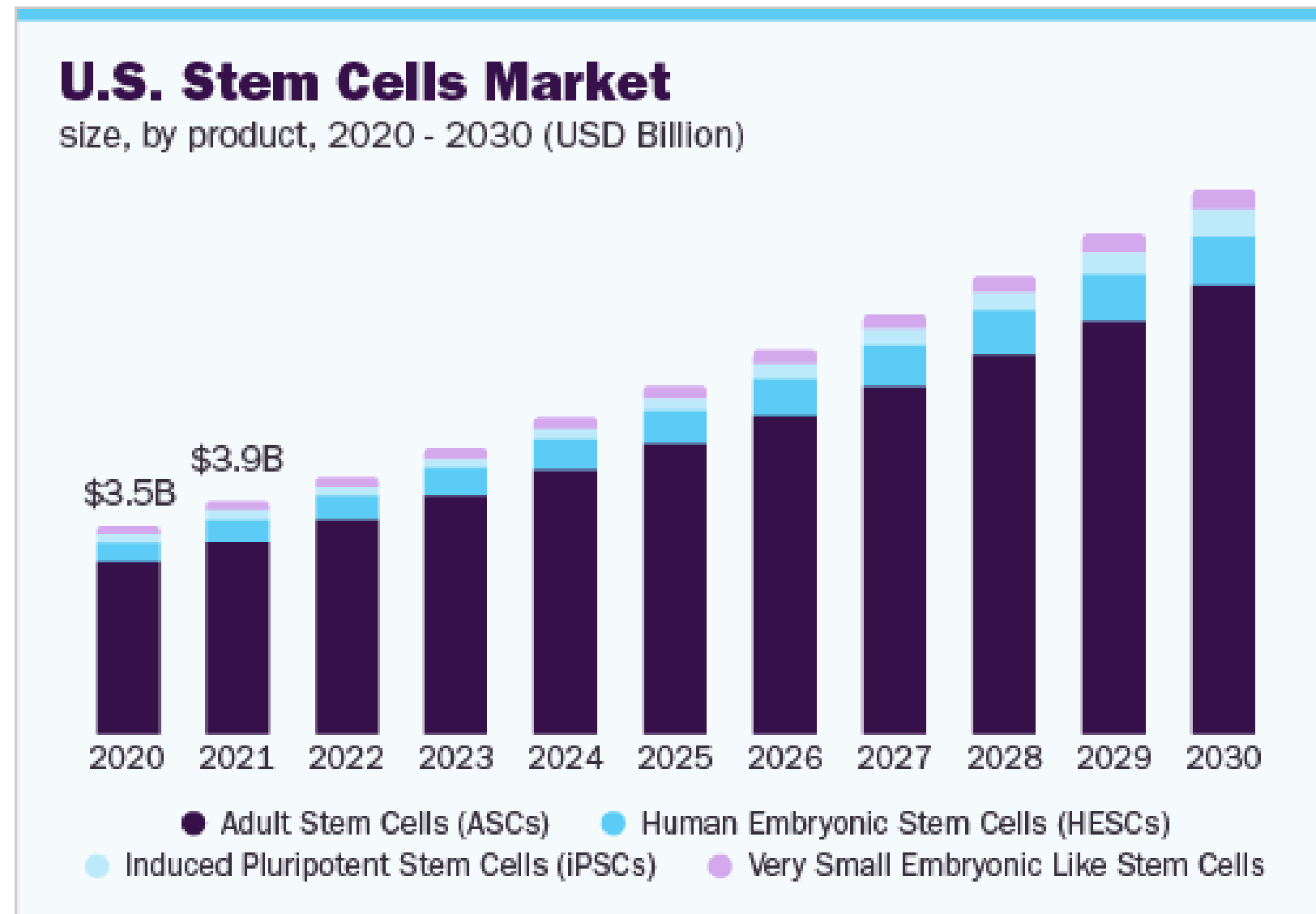
Autogreffe



Allogreffe



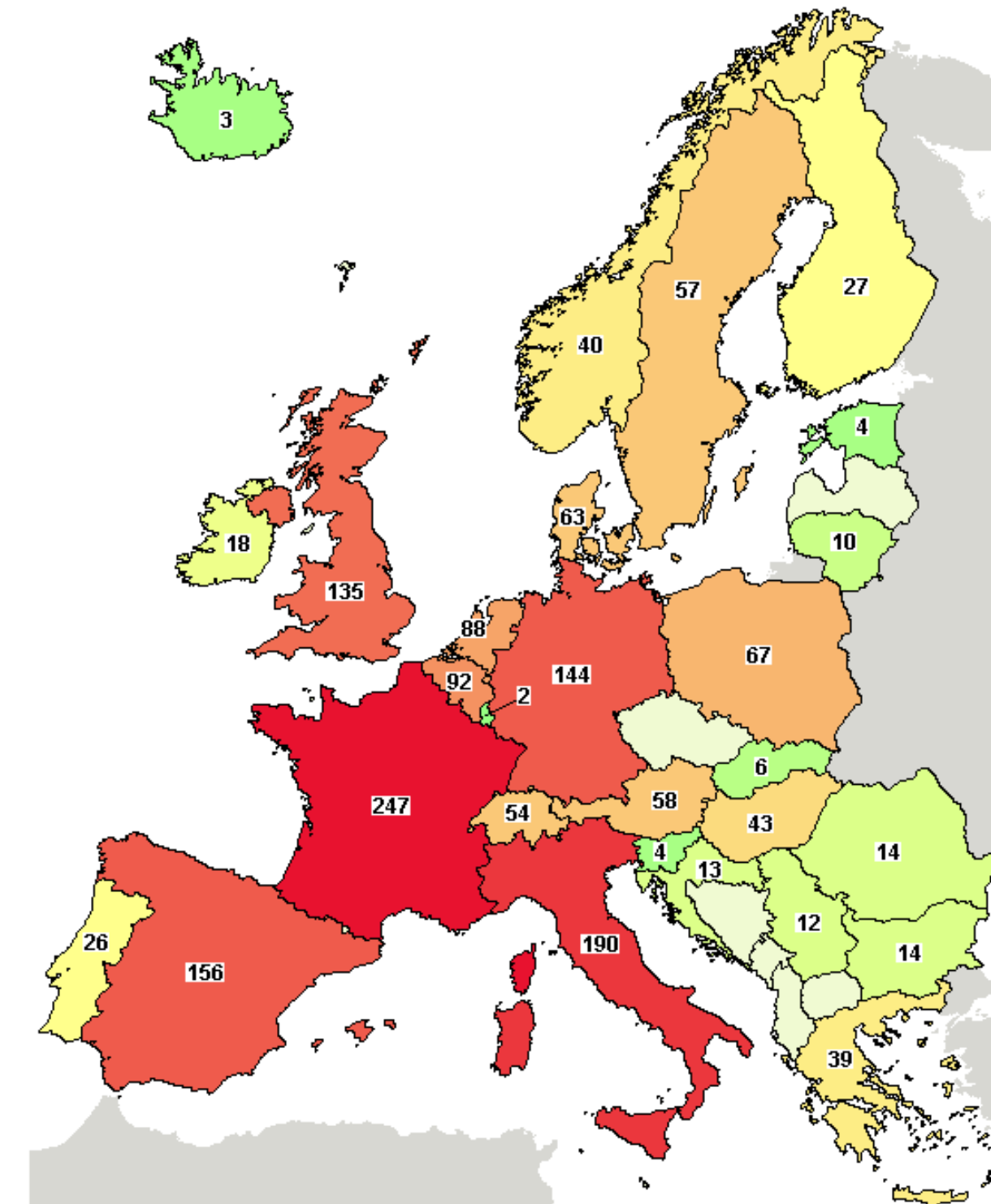
Greffe mais pas que...



Adult Stem Cells (ASCs)

- Hematopoietic
- Mesenchymal
- Neural
- Epithelial/Skin
- Others

Clinical trials in Europe > 600



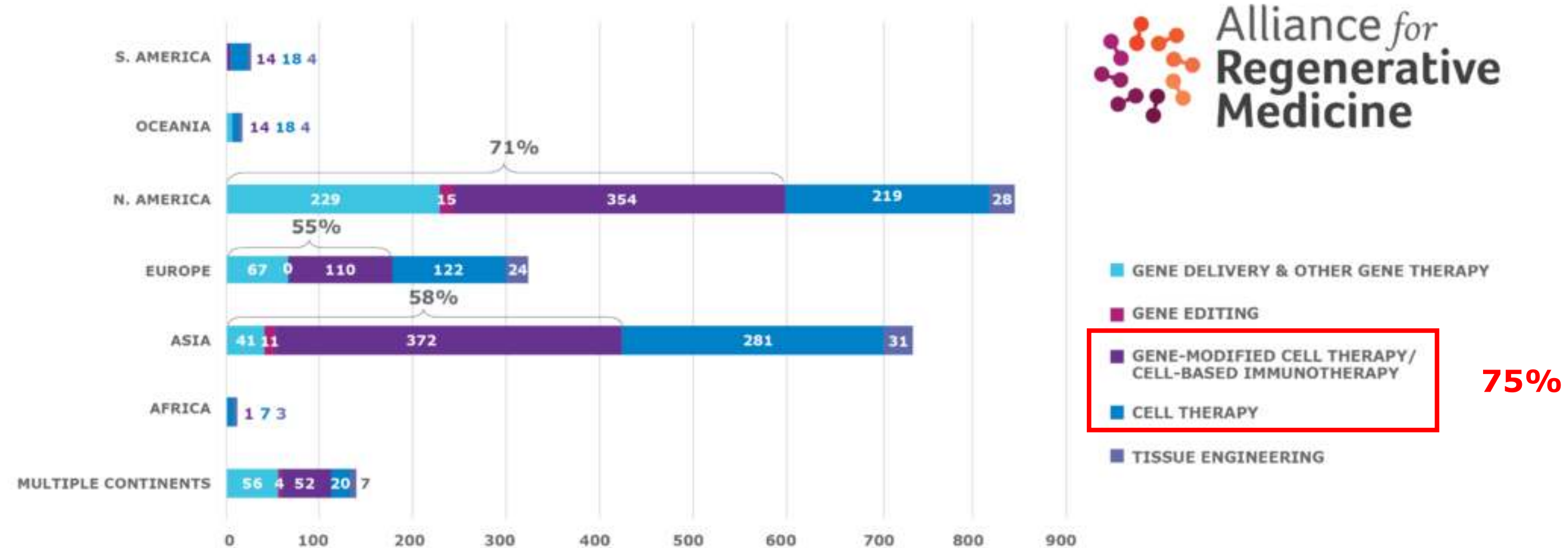
Perspectives : les MTI

Cellules souches : matière de départ pour fabriquer des médicaments de thérapie innovante (MTI)

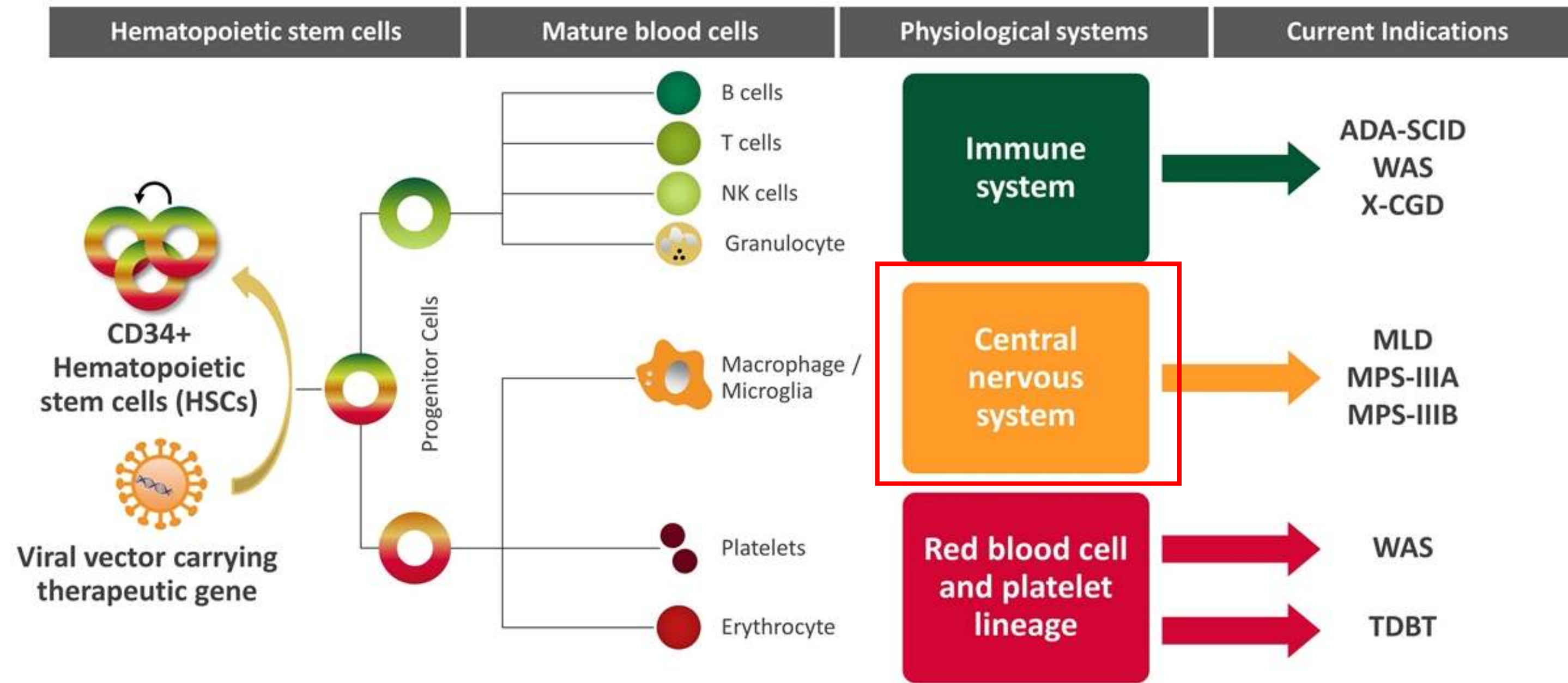
Advanced Therapy Medicinal Products (ATMPs) are medicines for human use that are based on genes, tissues or cells



- a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a tissue engineered product as defined in point (b).



Médicaments de thérapie génique à composante cellulaire



Atidarsagène autotemcel

Thérapie génique contenant une population autologue enrichie en cellules CD34+ transduites ex vivo avec un vecteur lentiviral codant le gène de l'arylsulfatase A (ARSA) humaine

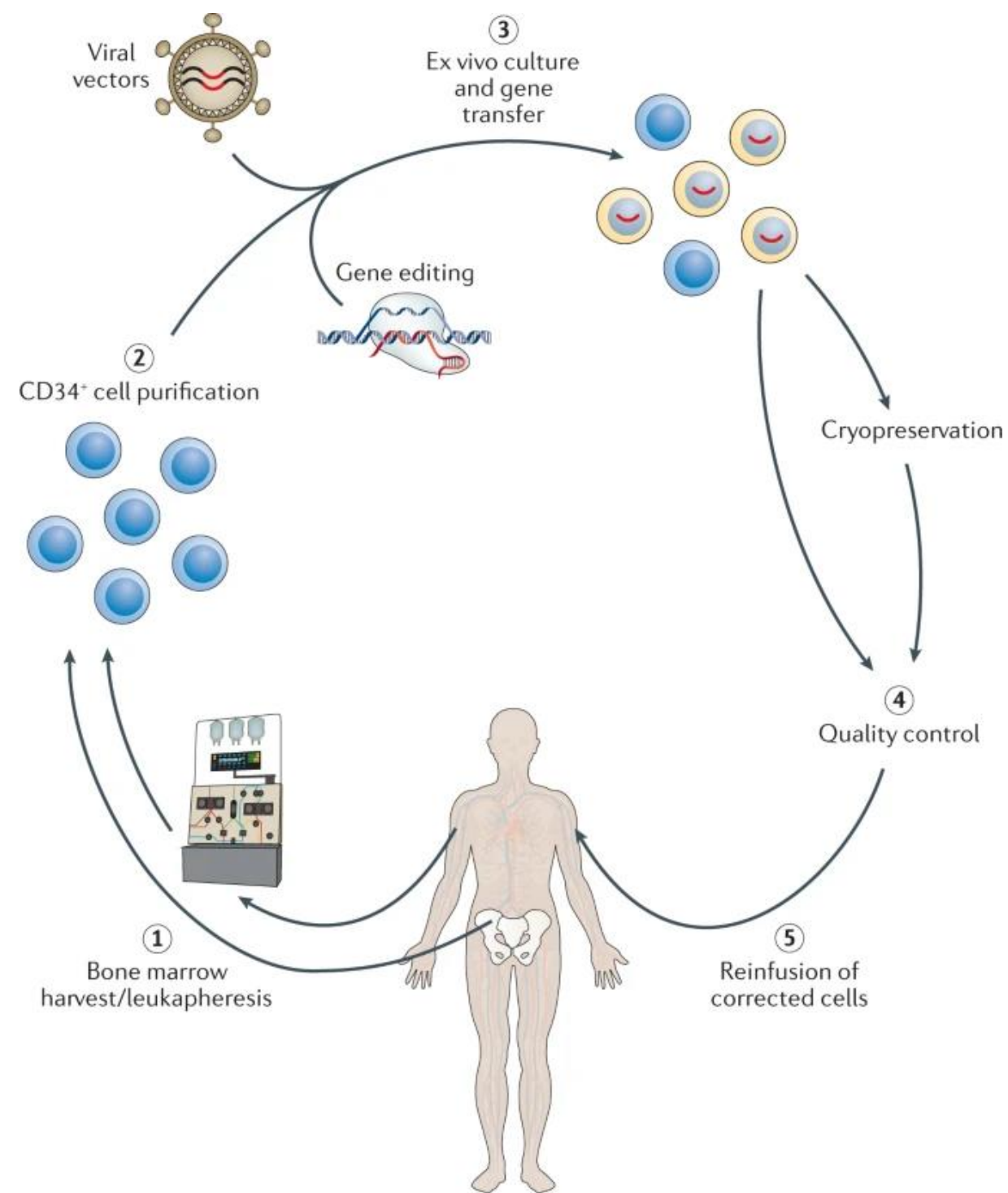
Traitement de la leucodystrophie métachromatique caractérisée par des mutations bialléliques du gène de l'arylsulfatase A (ARSA)



Médicaments de thérapie génique à composante cellulaire

Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access

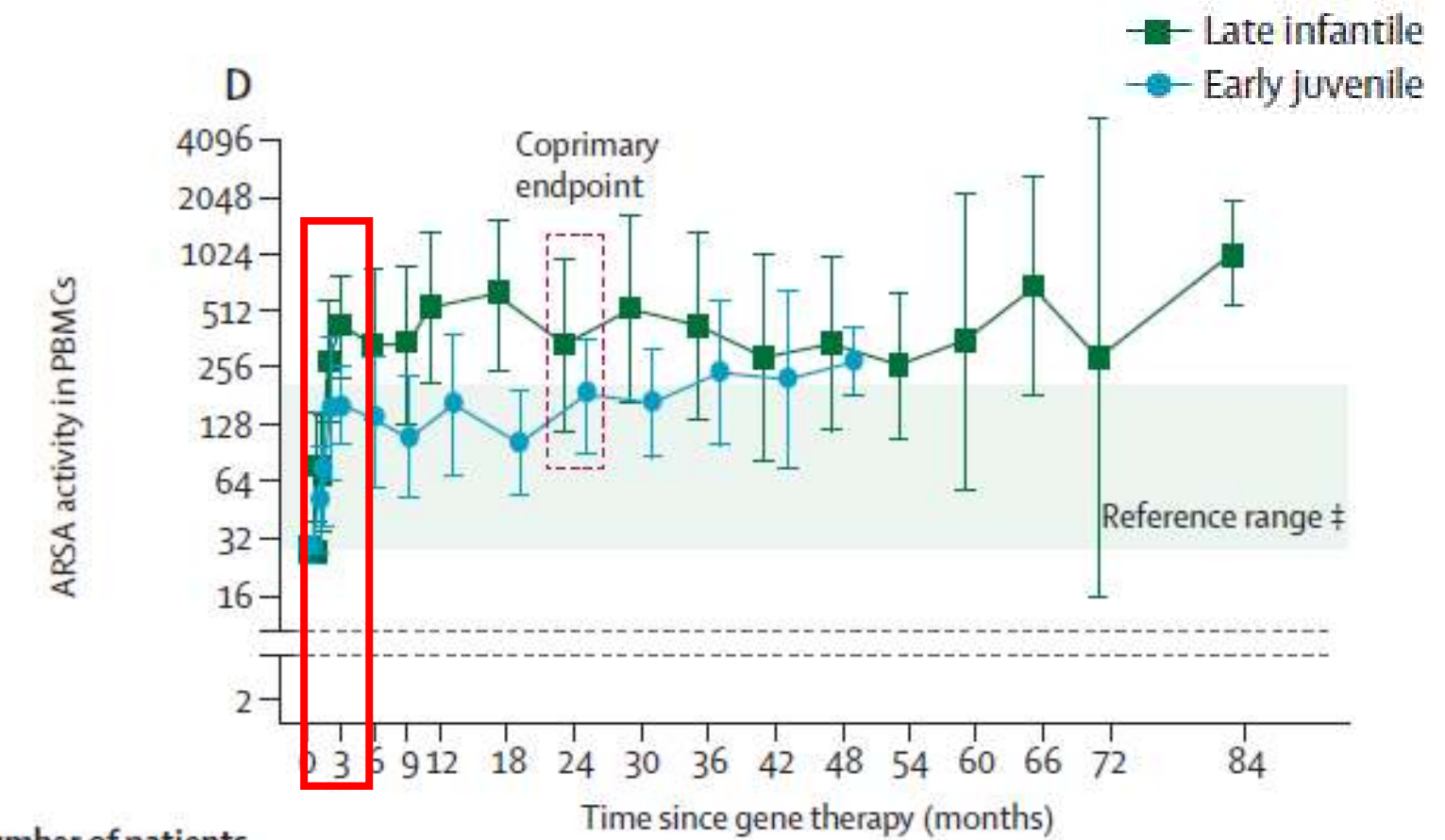
Francesca Fumagalli*, Valeria Calbi*, Maria Grazia Natali Sora, Maria Sessa, Cristina Baldoli, Paola Maria V Rancoita, Francesca Ciotti, Marina Sarzana, Maddalena Fraschini, Alberto Andrea Zambon, Serena Acquati, Daniela Redaelli, Vanessa Attanasio, Simona Miglietta, Fabiola De Mattia, Federica Barzaghi, Francesca Ferrua, Maddalena Migliavacca, Francesca Tucci, Vera Gallo, Ubaldo Del Carro, Sabrina Canale, Ivana Spiga, Laura Lorioli, Salvatore Recupero, Elena Sophia Fratini, Francesco Morena, Paolo Silvani, Maria Rosa Calvi, Marcella Facchini, Sara Locatelli, Ambra Corti, Stefano Zancan, Gigliola Antonioli, Giada Farinelli, Michela Gabaldo, Jesus Garcia-Segovia, Laetitia C Schwab, Gerald F Downey, Massimo Filippi, Maria Pia Cicalese, Sabata Martino, Clelia Di Serio, Fabio Ciceri, Maria Ester Bernardo, Luigi Naldini, Alessandra Biffi†, Alessandro Aiuti†



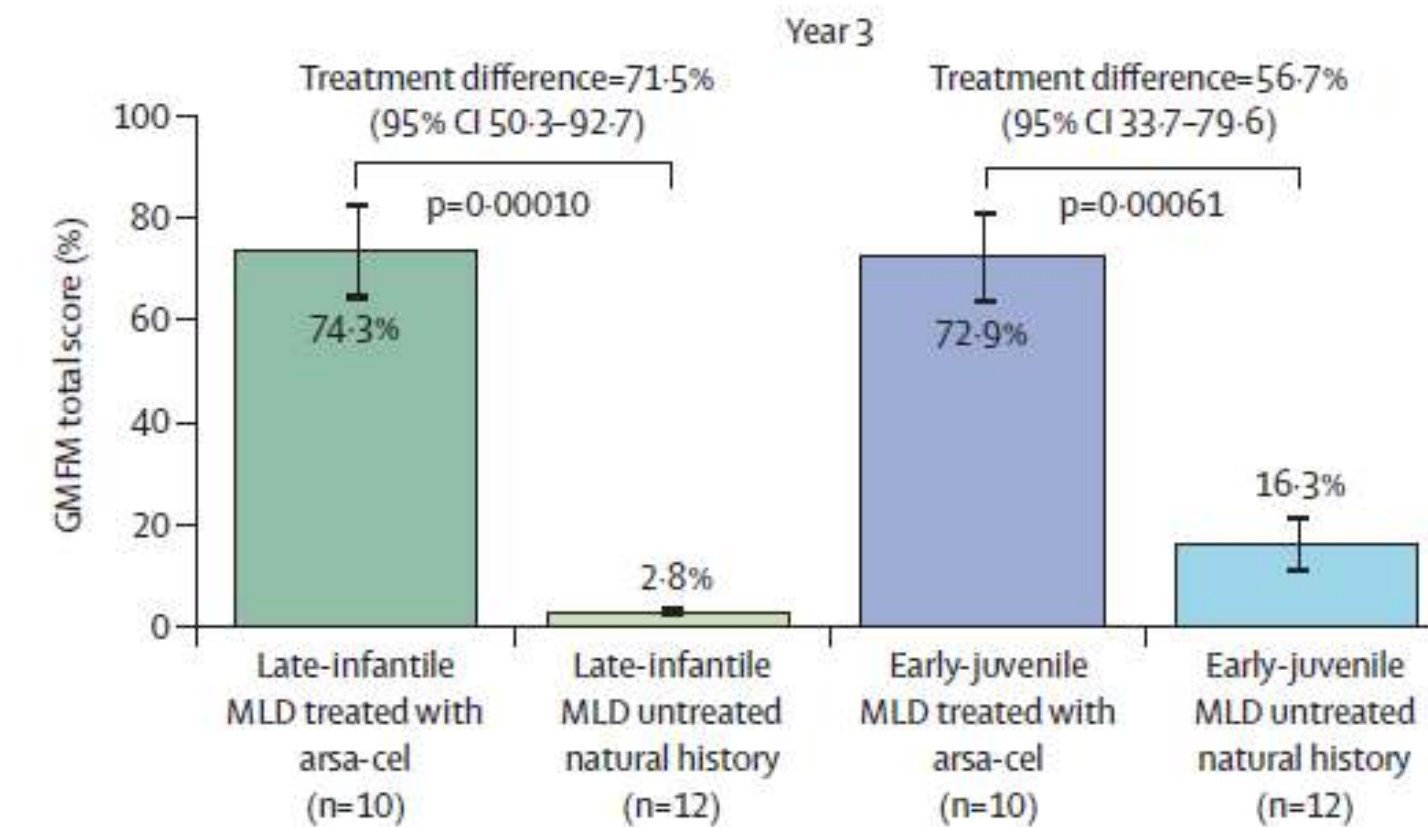
Ferrari, G., Thrasher, A.J. & Aiuti, A. Nat Rev Genet 2021

Sécurité à long terme ?

Prix > 2M €

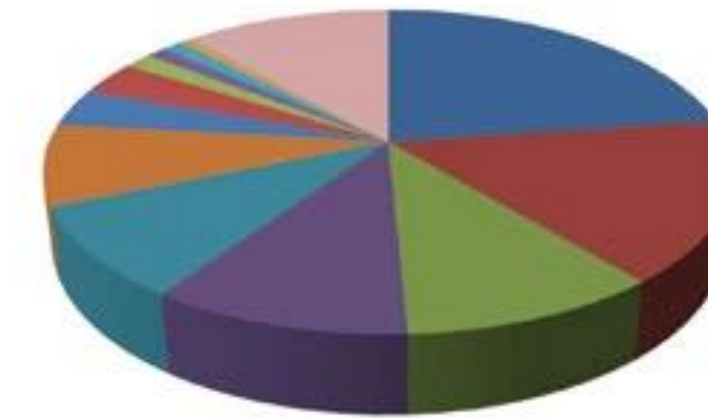
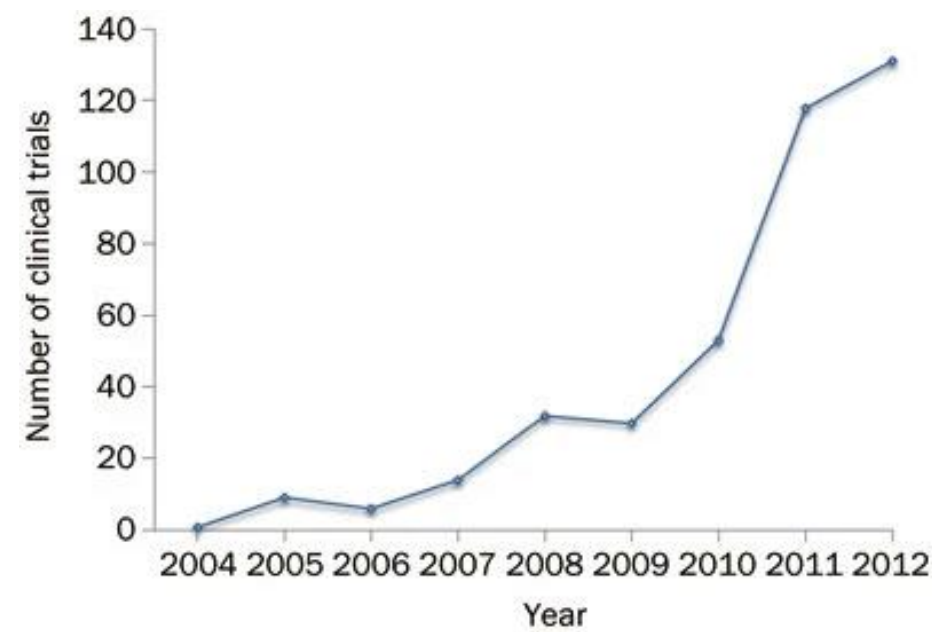


Number of patients	0	3	6	9	12	18	24	30	36	42	48	54	60	66	72	84	
Late infantile	15	15	11	11	12	16	11	11	9	10	5	7	6	5	4	3	3
Early juvenile	13	12	10	10	10	10	10	9	9	9	6	4

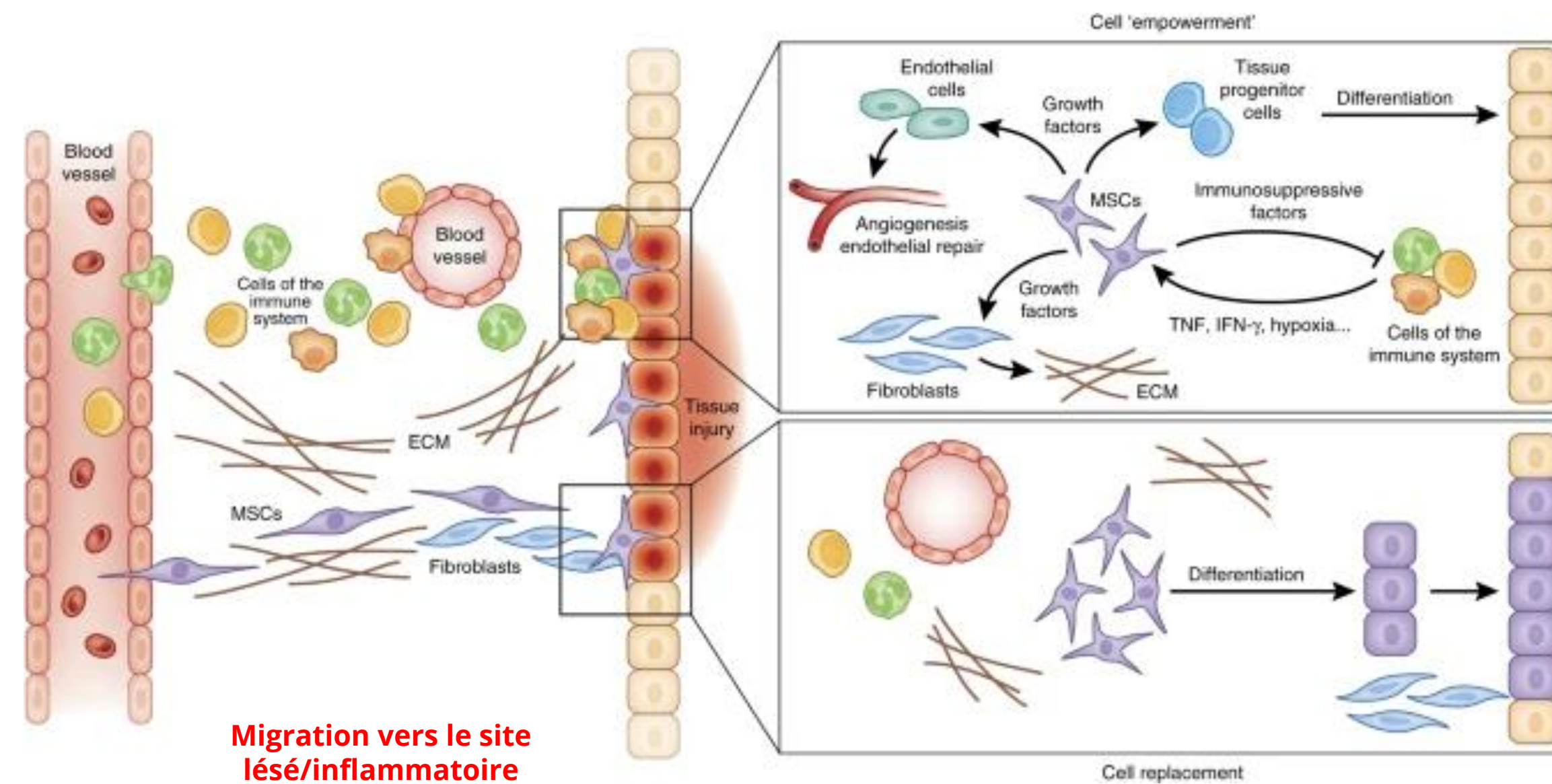


Médicaments de thérapie cellulaire

Cellules stromales mésenchymateuses



- | | |
|---------------------------------|-------------------------------------|
| ■ Myocardial infarction (22.9%) | ■ Graft versus host disease (16.0%) |
| ■ Diabetes (10.3%) | ■ Liver cirrhosis (10.3%) |
| ■ Spinal cord injury (9.2%) | ■ Osteoarthritis (8.0%) |
| ■ Crohn's disease (3.8%) | ■ Multiple sclerosis (3.4%) |
| ■ Aplastic anemia (1.5%) | ■ Systemic lupus (1.1%) |
| ■ Rheumatoid arthritis (1.1%) | ■ Parkinson's disease (0.8%) |
| ■ Brain injury (0.4%) | ■ Others (11.0%) |



Propriétés paracrines

Différenciation

Migration vers le site lésé/inflammatoire

Katie Vicari/Nature Publishing Group

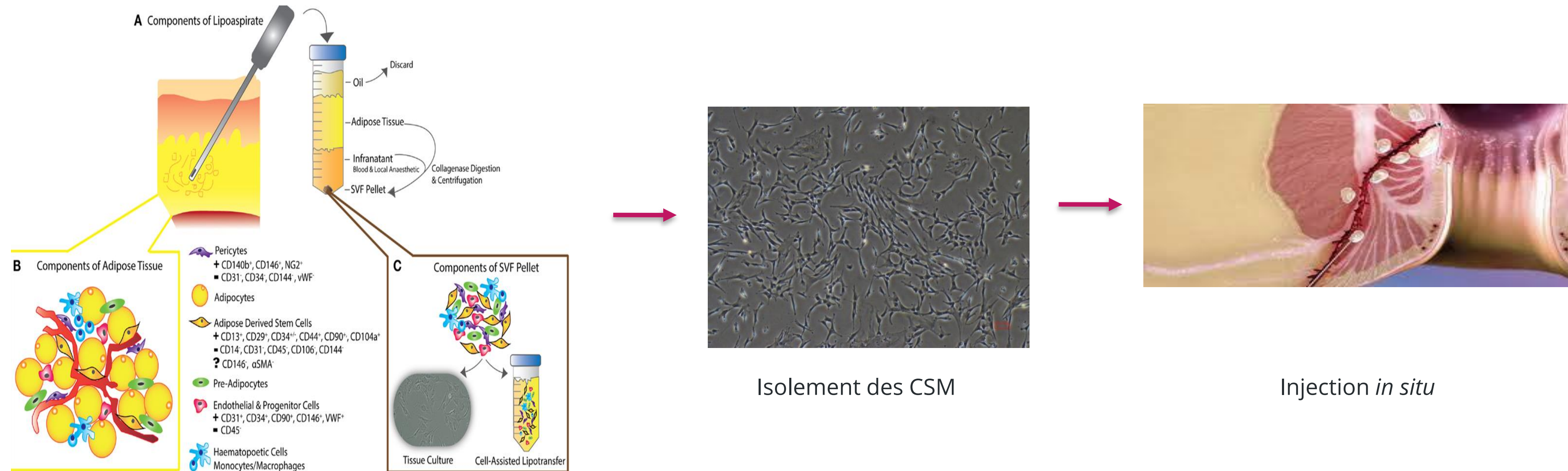
Médicaments de Thérapie Cellulaire

Darvadstrocel (Alofisel®) : cellules « souches » mésenchymateuses (CSM) allogéniques isolées du tissu adipeux et amplifiées *in vitro*

Traitement des fistules anales complexes de la maladie de Crohn grâce aux propriétés immunomodulatrices des CSM -> action immunologique



51 300 €



Tissu adipeux subdermal

Médicaments de Thérapie Cellulaire

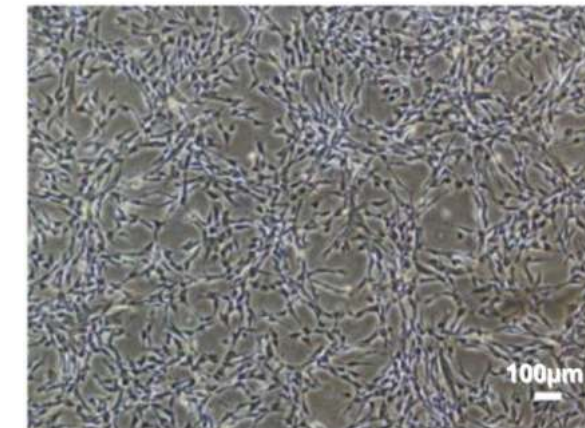
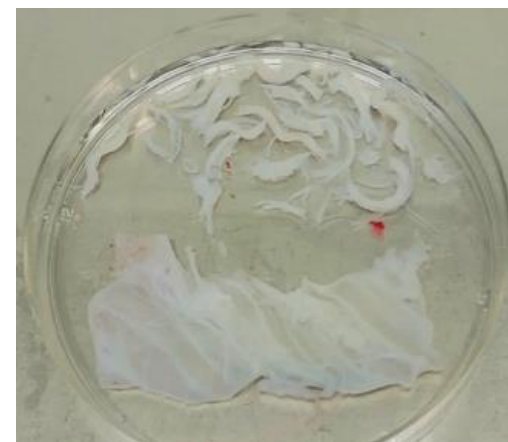
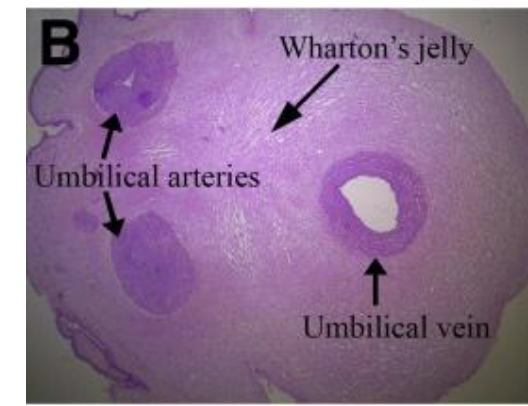
RESEARCH

Open Access

Development of a human umbilical cord-derived mesenchymal stromal cell-based advanced therapy medicinal product to treat immune and/or inflammatory diseases

Miryam Mebarki^{1,2,5*}, Nathan Iglicki², Céline Marigny¹, Camille Abadie¹, Claire Nicolet¹, Guillaume Churlaud³, Camille Maheux³, Hélène Boucher³, Antoine Monselet^{6,7}, Philippe Menasché⁸, Jérôme Larghero^{1,2,3}, Lionel Faivre^{1,2} and Audrey Cras^{1,4,5*}

Explant Method



Monselet et al. *Critical Care* (2022) 26:48
<https://doi.org/10.1186/s13054-022-03930-4>

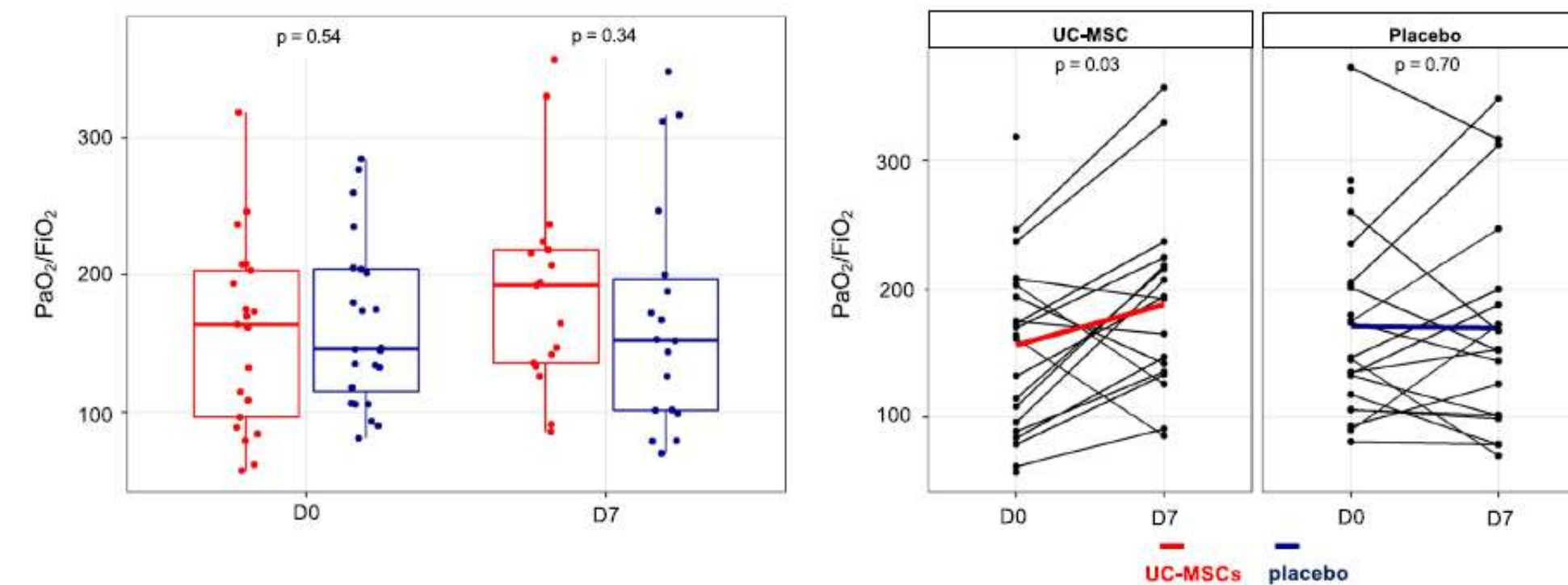
Critical Care

Treatment of COVID-19-associated ARDS with mesenchymal stromal cells: a multicenter randomized double-blind trial

Antoine Monselet^{1,2,3,23*}, Caroline Hauw-Berlemont^{4†}, Miryam Mebarki^{5†}, Nicholas Heming⁶, Julien Mayaux⁷, Otriv Nguekap Tchoumba^{2,3}, Jean-Luc Diehl^{4,8}, Alexandre Demoule⁷, Djillali Annane⁹, Clémence Marois^{9,10}, Sophie Demeret^{9,10}, Emmanuel Weiss^{11,12}, Guillaume Voiriot¹³, Muriel Fartoukh¹³, Jean-Michel Constantin¹, Bruno Mégarbane¹⁴, Gaëtan Plantefève¹⁵, Stéphanie Malard-Castagnet¹⁶, Sonia Burrel¹⁷, Michelle Rosenzweig^{2,3}, Nicolas Tchitchek^{2,3}, Hélène Boucher-Pillet¹⁸, Guillaume Churlaud¹⁸, Audrey Cras^{5,19}, Camille Maheux¹⁸, Chloé Pezzana²⁰, Mamadou Hassimiou Diallo²¹, Jacques Ropers²¹, Philippe Menasché^{22†}, Jérôme Larghero^{5,18†} and AHPH STROMA-CoV-2 Collaborative Research Group

Phase IIb, Multicenter, double-blind, randomized & placebo-controlled (21 vs 24)

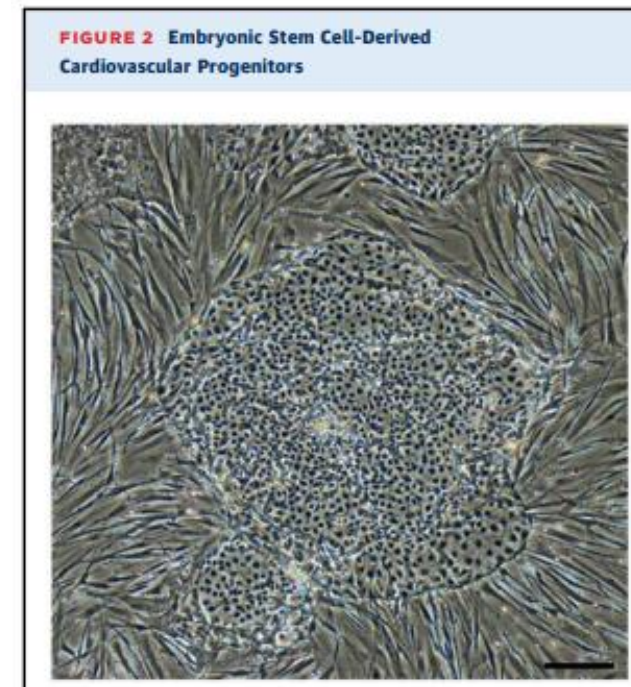
3 IV infusions of 1×10^6 UC-MSCs/kg



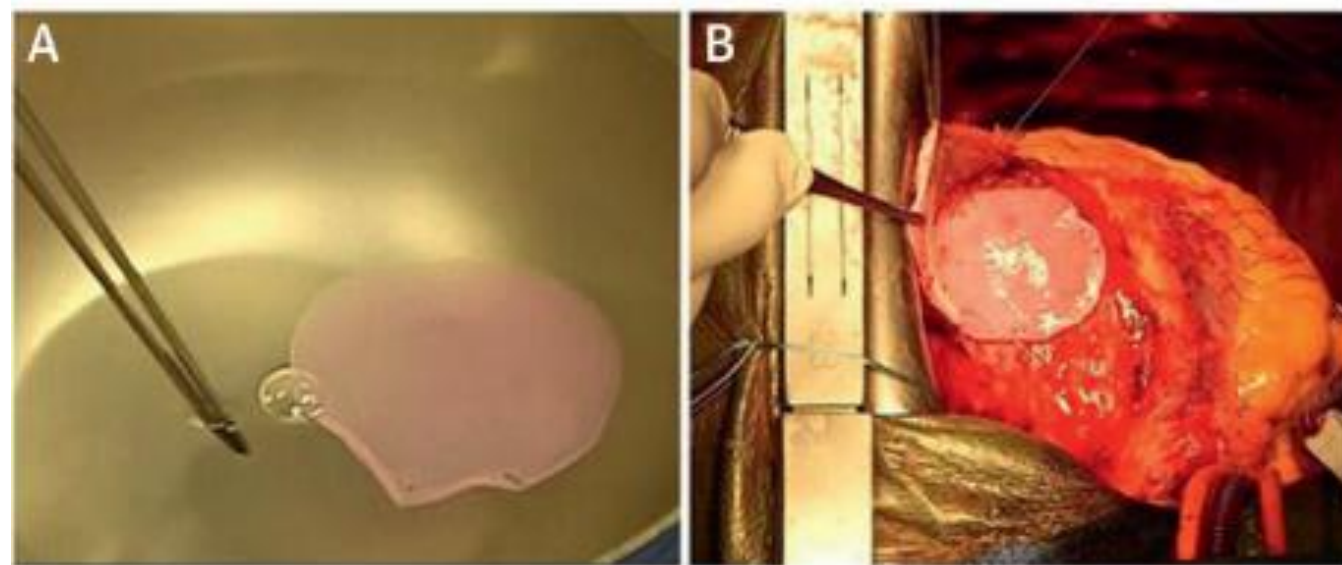
PaO₂/FiO₂: partial pressure of oxygen to fractional inspired oxygen ratio

Médicaments de Thérapie Cellulaire

Cellules souches embryonnaires



Différenciation des CSE en progéniteurs myocardiaques

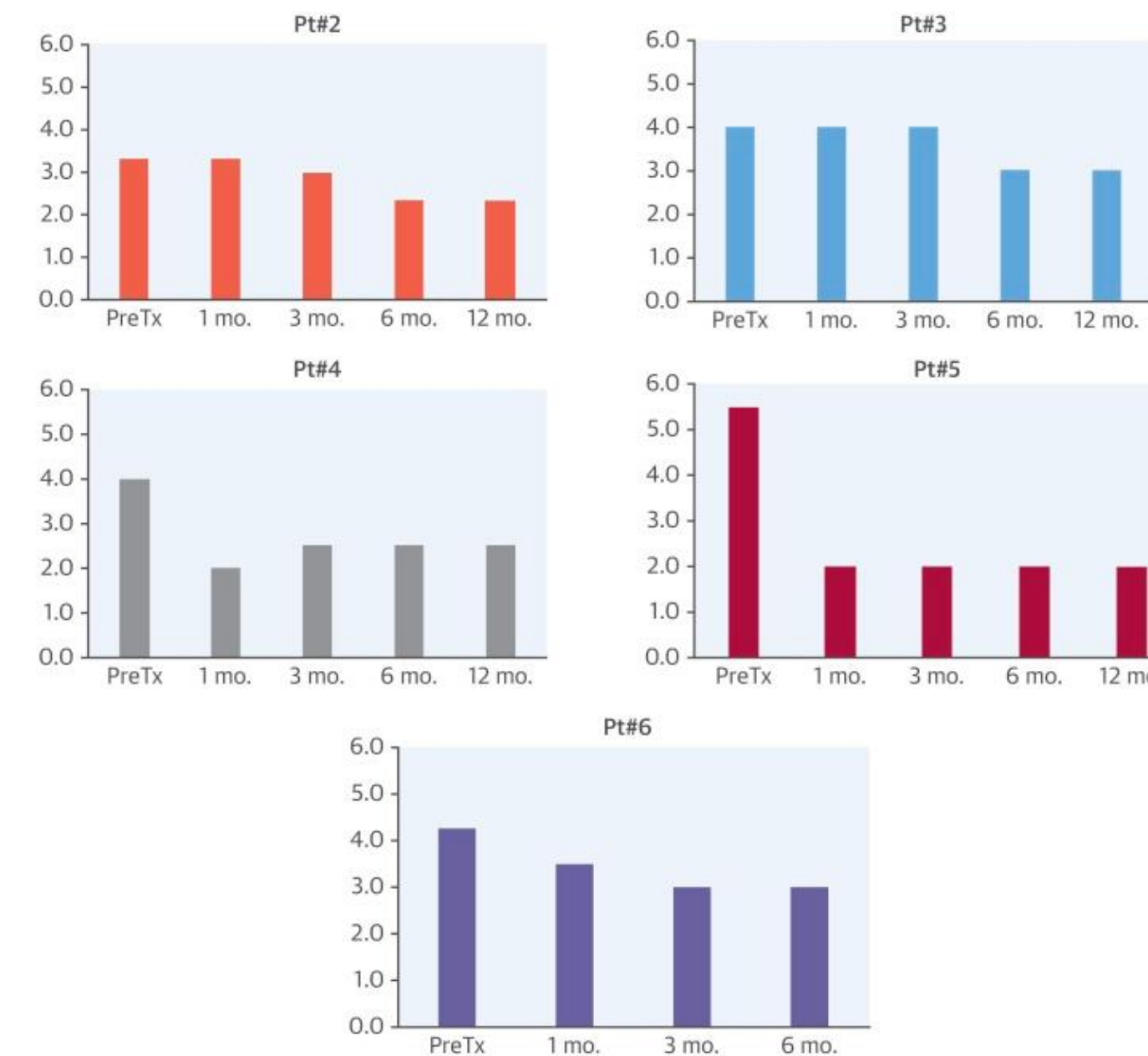


Ensemencement des cellules sur un patch de fibrine des Transplantation du patch *in situ*

Transplantation of Human Embryonic Stem Cell-Derived Cardiovascular Progenitors for Severe Ischemic Left Ventricular Dysfunction

Philippe Menasché, MD,^{a,b,c} Valérie Vanneaux, PHARM.D,^{d,e} Albert Hagège, MD,^{b,c,f} Alain Bel, MD,^a Bernard Cholley, MD,^{b,g} Alexandre Parouchev, PhD,^{d,e} Isabelle Cacciapuoti, MSc,^{d,e} Reem Al-Daccak, PhD,^h Nadine Benhamouda, MSc,ⁱ Hélène Blons, PhD,^j Onnik Agbulut, PhD,^k Lucie Tosca, PhD,^l Jean-Hugues Trouvin, PHARM.D,^{m,n} Jean-Roch Fabreguettes, PHARM.D,^o Valérie Bellamy, BASC,^c Dominique Charron, MD,^{p,q} Eric Tartour, MD,^{b,c,j} Gérard Tachdjian, MD,^l Michel Desnos, MD,^{b,c,f} Jérôme Larghero, PhD^{d,e,q}

CENTRAL ILLUSTRATION: Individual Changes in the Wall Motion Score of the Cell/Patch-Treated Segments Over Time



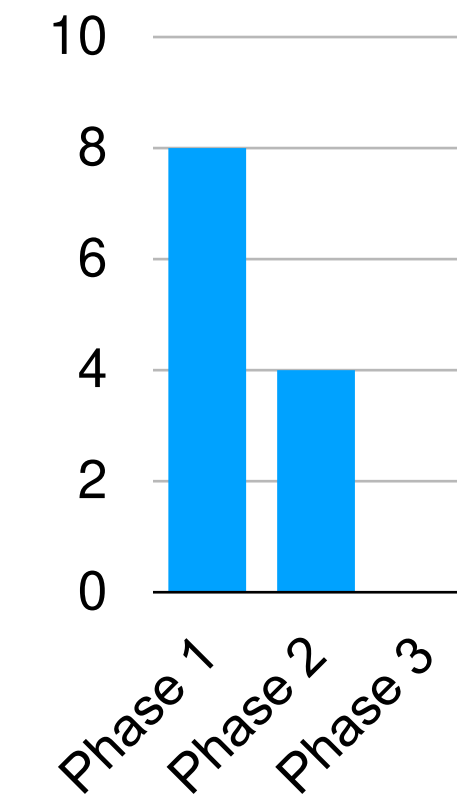
Médicaments de Thérapie Cellulaire

iPS cells

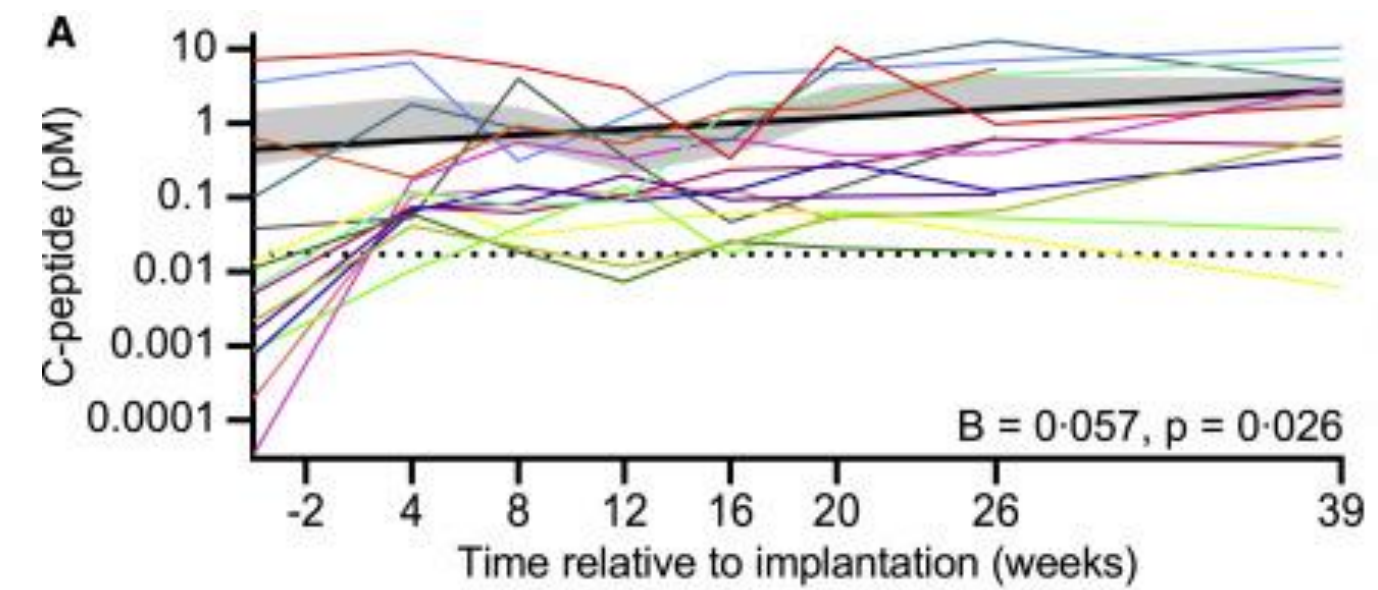
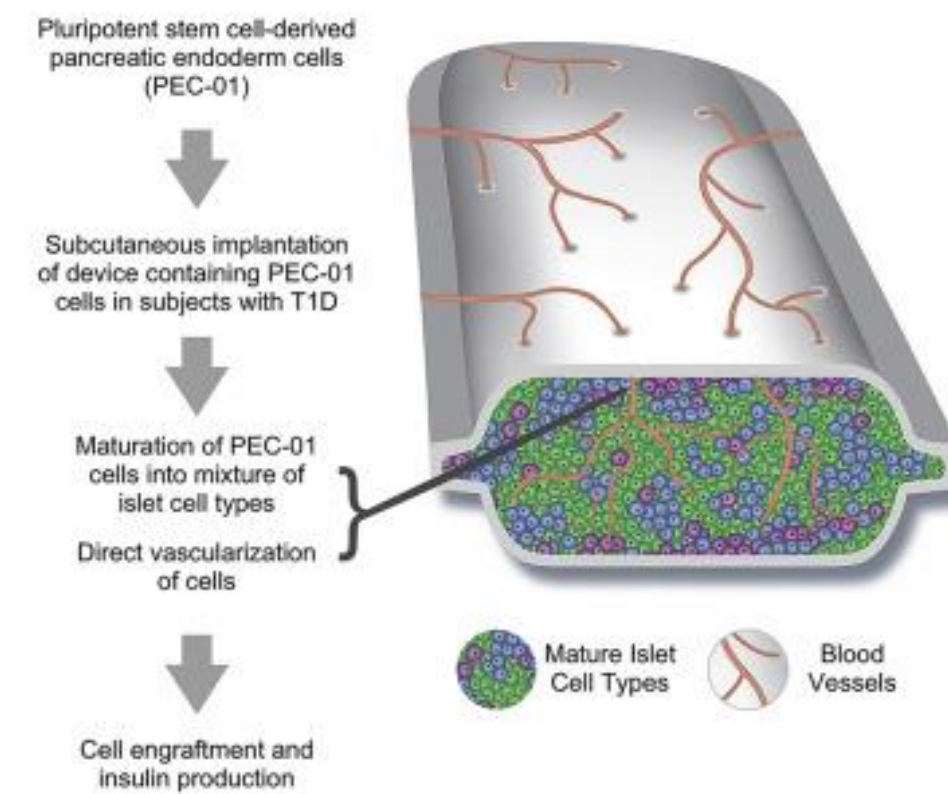
Clinical and Translational Report

Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes

Adam Ramzy,¹ David M. Thompson,² Kirsten A. Ward-Hartstonge,^{3,4} Sabine Ivison,^{3,4} Laura Cook,^{3,4} Rosa V. Garcia,^{3,4} Jackson Loyal,² Peter T.W. Kim,³ Garth L. Warnock,³ Megan K. Levings,^{3,4,5} and Timothy J. Kieffer^{1,3,5,6,*}



VC-02 Macroencapsulation Device



Home take messages

- Recherche clinique active avec différentes cellules souches
 - Autologues *versus* allogéniques
 - Perspectives : MTI -> thérapies de rupture
 - Médicaments de thérapie génique avec une composante cellulaire
 - Médicaments de thérapie cellulaire
 - Médicaments d'ingénierie tissulaire
 - Questions médico-économiques +++
 - Nouveaux circuits hospitaliers et pharmaceutiques
-

Merci de votre attention

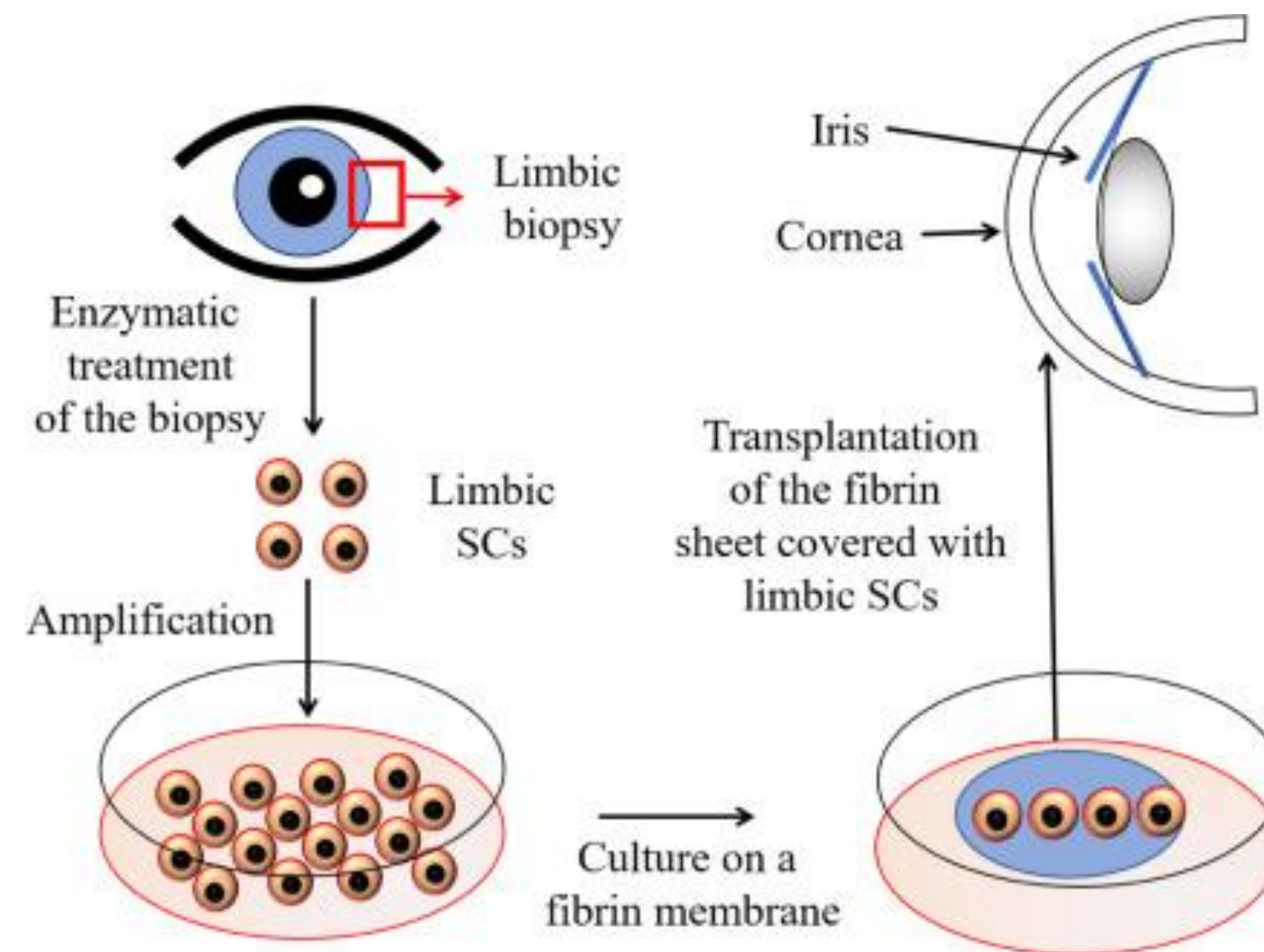
Médicaments d'ingénierie tissulaire

Holoclar® : cellules épithéliales de la cornée, autologues, amplifiées *ex vivo* et contenant des cellules souches *limbiques*

Traitement des déficits en cellules souches limbiques causés par une brûlure.



A minimum of 1 - 2 mm² of undamaged limbus is required for biopsy



Recommended dose:
79,000 - 316,000 cells/ cm²

1cm² product/cm² defect