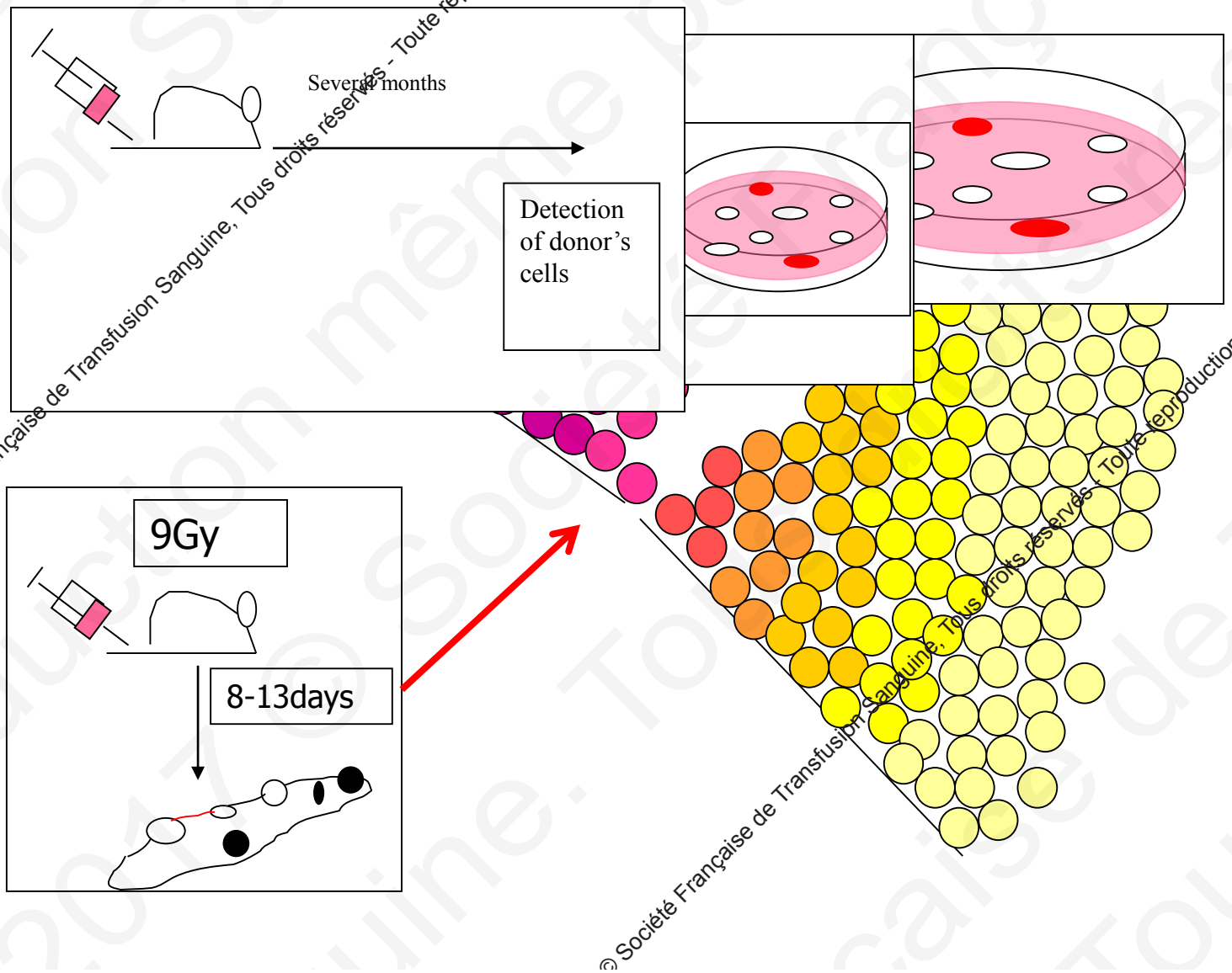
Paradigme évolutionnaire de la cellule souche et ingénierie cellulaire

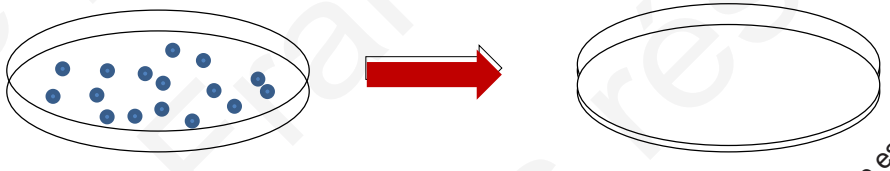
Zoran IVANOVIC
EFS AQUITAINE-LImousin
(U1035 INSERM/Université de Bordeaux):

HEMATOPOIESIS: A PARADIGMATIC CASE

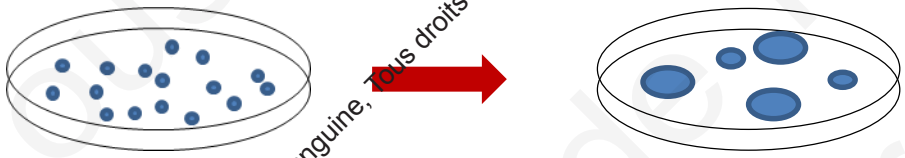


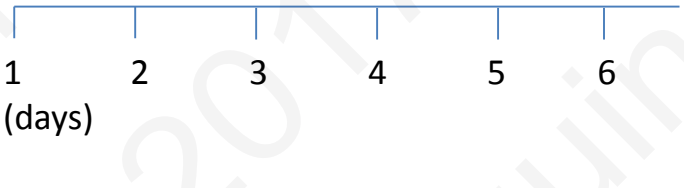
Dello Sbarba et al.
Exp Hematol 15:137-42,1987

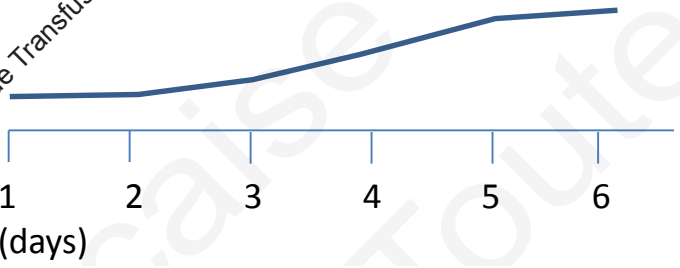
Saturation of respiratory chain by excess of pyruvate



Saturation of respiratory chain by excess of pyruvate







HEMATOPOIESIS: A PARADIGMATIC CASE

SRC (greffe à long terme)

MRA, pré-CFC, LTC-IC

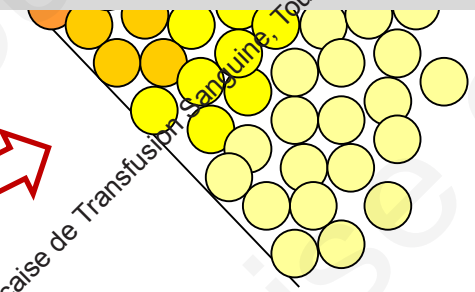
CFC

SINCE PROLIFERATING IN PARALLEL WITH INHIBITION OF OXIDATIVE PHOSPHORILATION THE AUTHORS CONCLUDED THAT THE STEM CELLS (pre-CFCs), UNLIKE THE COMMITTED PROGENITORS (CFC), EXHIBIT SOME ANAEROBIC FEATURES

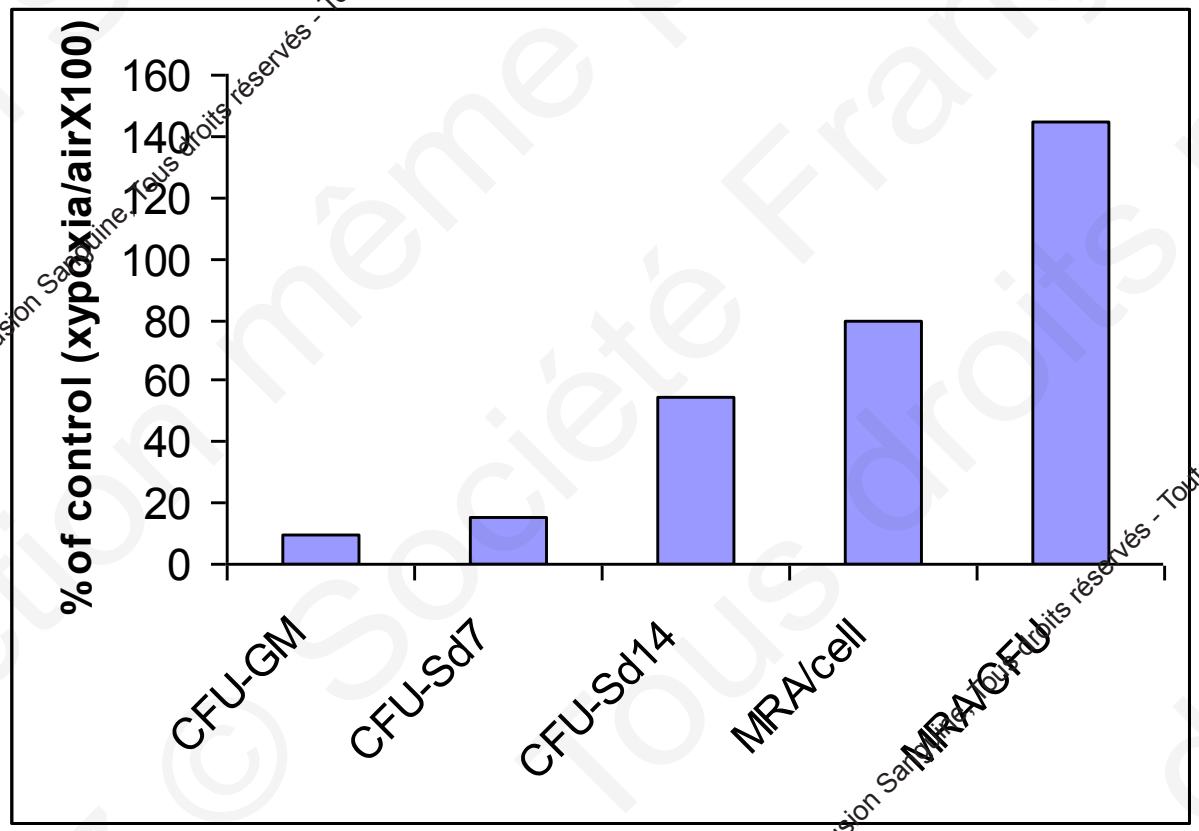
PROLIFERATION

INHIBITION OF CELL RESPIRATION

A REVERSIBLE CYTOSTATIC EFFECT



Cipolleschi et al. Blood 1993



Hypothesis: **HSC are resistant to hypoxia due to their quiescence and low en energetic demands.**

L'EXPANSION DES CFU-GM, HPP-CFC et MRA à 20% d'O_2 et 1% d'O_2

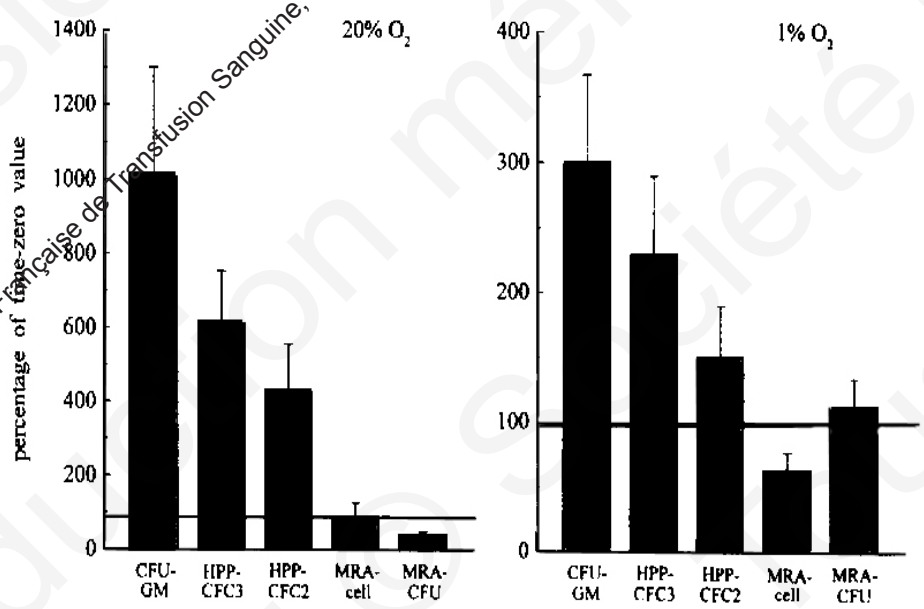


Fig 2. Effects of hypoxia on the expansion or maintenance of progenitors in culture. The figure summarizes the data reported in Tables I and III. Histograms represent the total numbers of progenitors in culture expressed as percentages of the corresponding time zero values (horizontal lines) and are means ± SEM of the numbers of independent experiments indicated in the legends to Tables I and III. The statistical significance of the differences are given in the legends to Tables I and III.

Ivanovic et al, Br J Haematol 108: 424-9, 2000

L'HYPOXIE MAINTIENT LA CAPACITE PROLIFERATIVE DE L'HPP-CFC

Table II. Effects of hypoxia on the secondary clonogenic ability of HPP-CFC2.

	Number of day 7 secondary colonies per HPP-CFC2 recovered from			
	Day 5		Day 8	
	liquid cultures at			
Expt no.	20% O_2	1% O_2	20% O_2	1% O_2
1	0	3·0	0	35·0
2	0·5	69·5	0	8·0
3	1·0	25·0	0·5	113·0

The values represent the number of secondary colonies per primary colony generated from HPP-CFC2 recovered from day 5 or day 8, hypoxic or control, liquid cultures in three independent experiments. Cells from four primary colonies were pooled, counted and replated at identical numbers across individual experiments and experimental conditions. The count of secondary colonies (at day 7 only, to determine the total replating potential) enabled the estimation of the average number of progenitors per

Ivanovic et al, Br J Haematol 108:424-9, 2000

British Journal of Haematology, 2000, 108, 424–429

Incubation of murine bone marrow cells in hypoxia ensures the maintenance of marrow-repopulating ability together with the expansion of committed progenitors

ZORAN IVANOVIĆ,[1] BENEDETTA BARTOLOZZI,[2] PIETRO ANTONIO BERNABEI,[2] MARIA GRAZIA CIPOLLESCHI,[1] ELISABETTA ROVIDA,[1] PAVLE MILENKOVIĆ,[3] VINCENT PRALORAN[4] AND PERSIO DELLO SBARBA[1]

[1]*Department of Experimental Pathology and Oncology, and* [2]*Haematology Unit, A. O. Careggi, University of Florence, Florence, Italy,* [3]*Institute for Medical Research, Belgrade, Yugoslavia, and* [4]*Laboratory of Experimental Haematology, University of Limoges, Limoges, France*

Received 28 July 1999; accepted for publication 18 October 1999

« **Hypoxia might act directly on haematopoietic stem cells by shifting the balance between self-renewal and commitment towards self-renewal.** »

Maintenance of stem cells is paralleled by their proliferation, showed on murine and human cells:

- *Cipolleschi et al, Leukemia 14:735-9, 2000*
- *Ivanovic et al, Transfusion 40:1482-8,2000*
- *Ivanovic et al, Exp Hematol 30: 67-73, 2002*

Maintenance of stem cells is paralleled by their proliferation, showed on murine and human cells:

- *Danet et al, J Clin Invest 2003;112:126–135.*

Adjusting ex vivo cytokine-stimulation and appropriately low O2 concentration it is possible to amplify, simultaneously, committed progenitors and stem cells:

- *Ivanovic et al, Stem Cells 22: 716-24, 2004*

Extremely low O2 concentration (0,1%): re-entering in G0 of 50% actively proliferating CD34+ cells while others are continuing to proliferate

- Hermitte et al, Stem Cells 24: 65-73, 2006

Extremely low O2 concentration (0,1%): re-entering in G0 of actively proliferating more mature FDCP-Mix cells while the minority of primitive FDCP-Mix culture-initiating cells continue to proliferate slowly

- Guitart et al, Cell Death Differ 18: 174-82, 2011

A subpopulation of Mesenchymal Stem Cells proliferates actively in anaerobic conditions (0% O2)

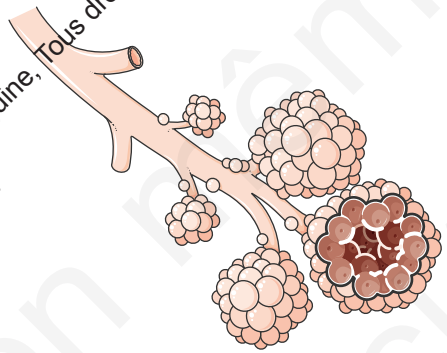
- Our unpublished data, work in progress

ATMOSPHERE
20% O_2

HYPEROXIA

Cells exposed to atmosphere O_2 concentration

ALVEOLI
13,1% O_2

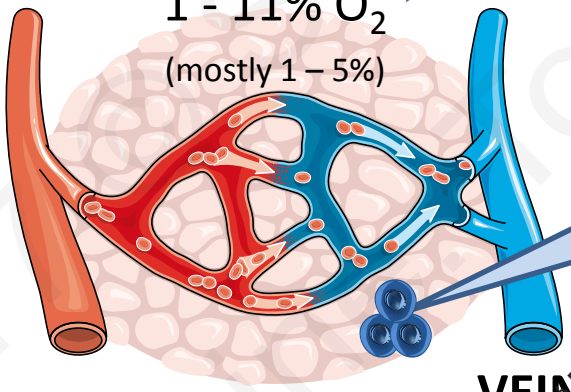


NORMOXEMIA

TISSUES
1 - 11% O_2
(mostly 1 – 5%)

Cellular O_2 level
(in general)
< 1 - 2,5%

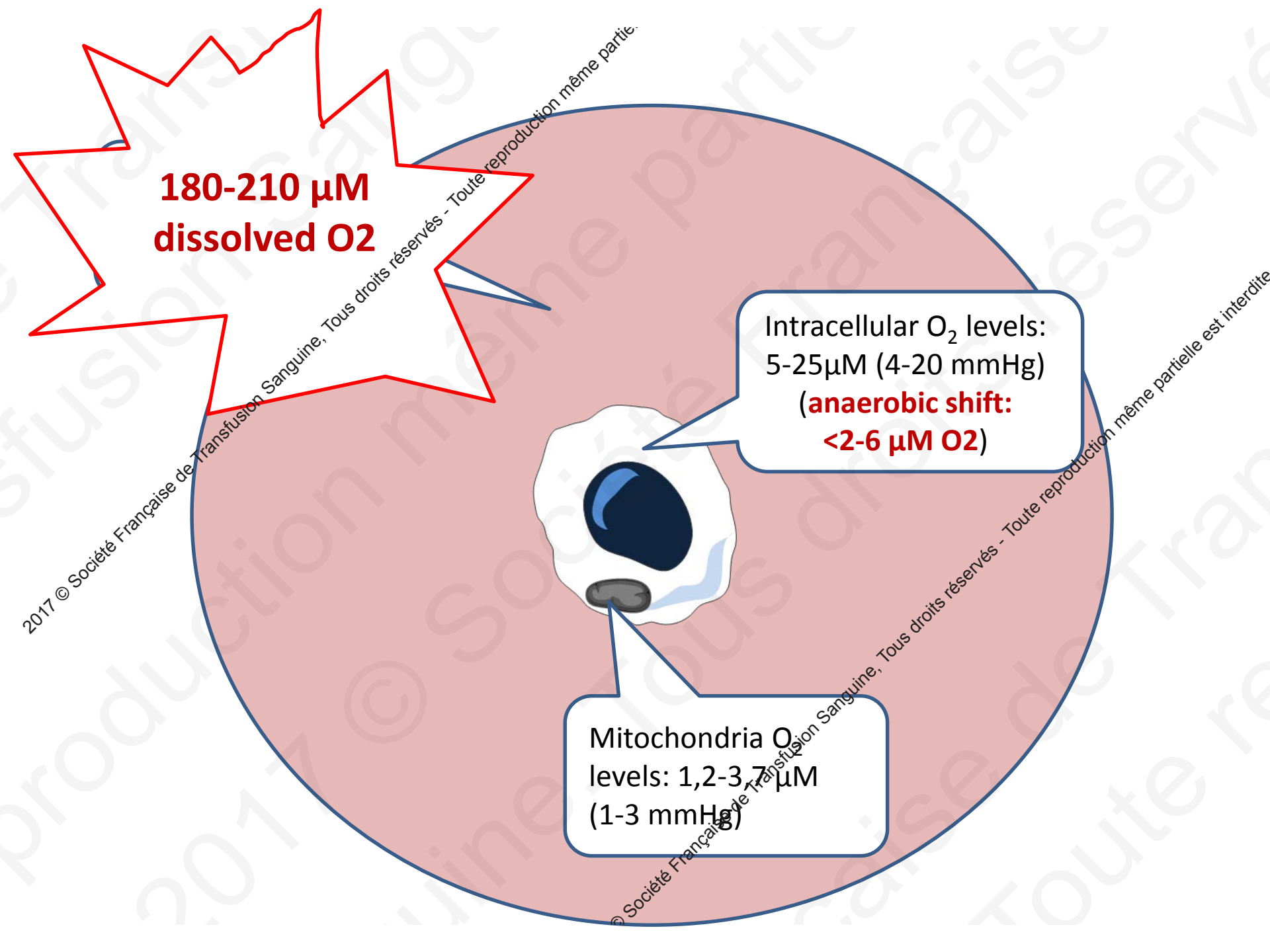
ARTERIAL BLOOD
13% O_2

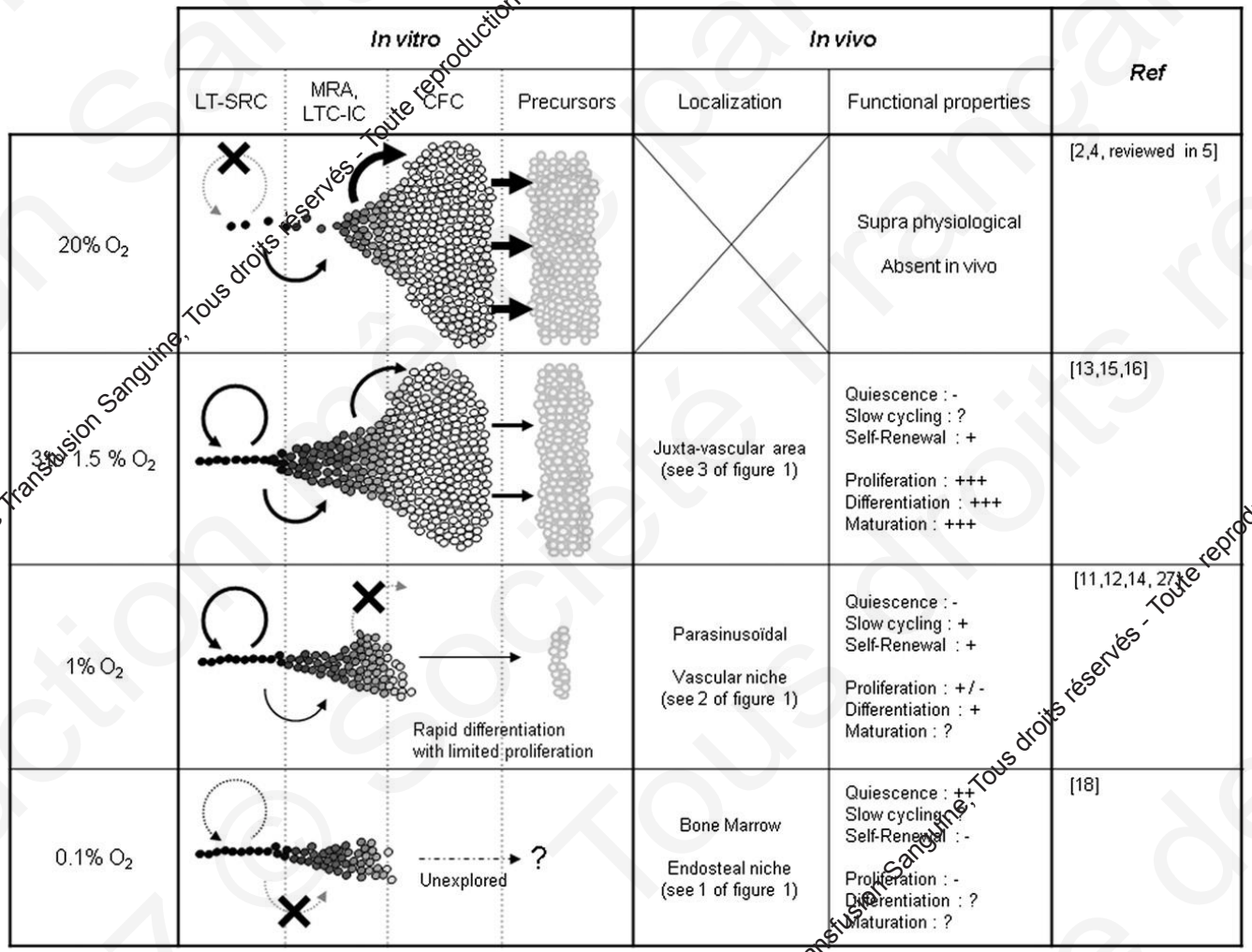


STEM CELL NICHE
< 1,3%
(pimonidazole positive)

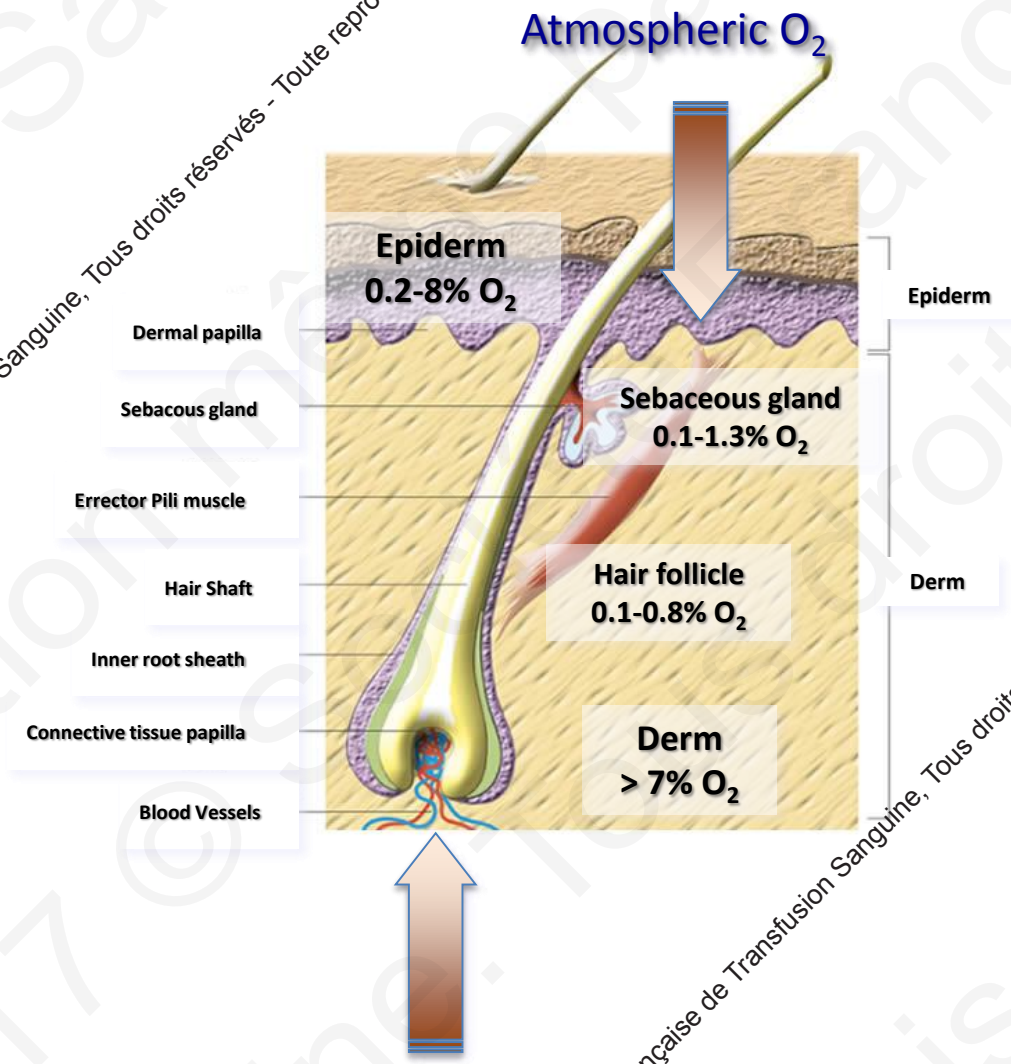
PHYSIOXIA

VEIN BLOOD
5,3% O_2





Skin oxygenation: dermis vs epidermis



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STEM CELLS DURING DEVELOPMENT

zygote

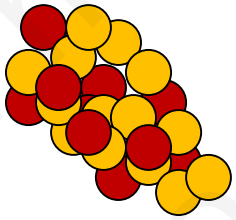
embryo

Fetal tissue

Neonatal tissue

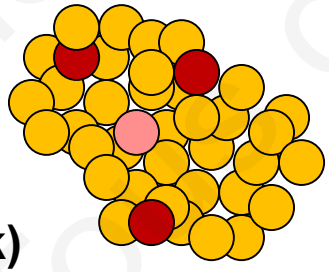
Adult Tissue

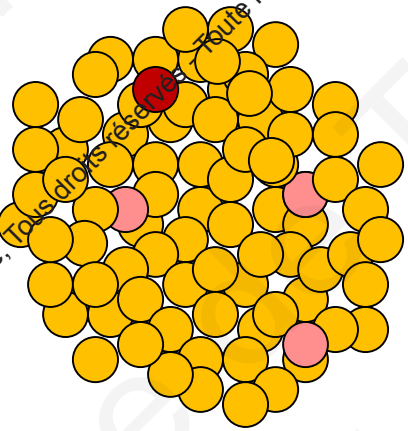
1.5% O2



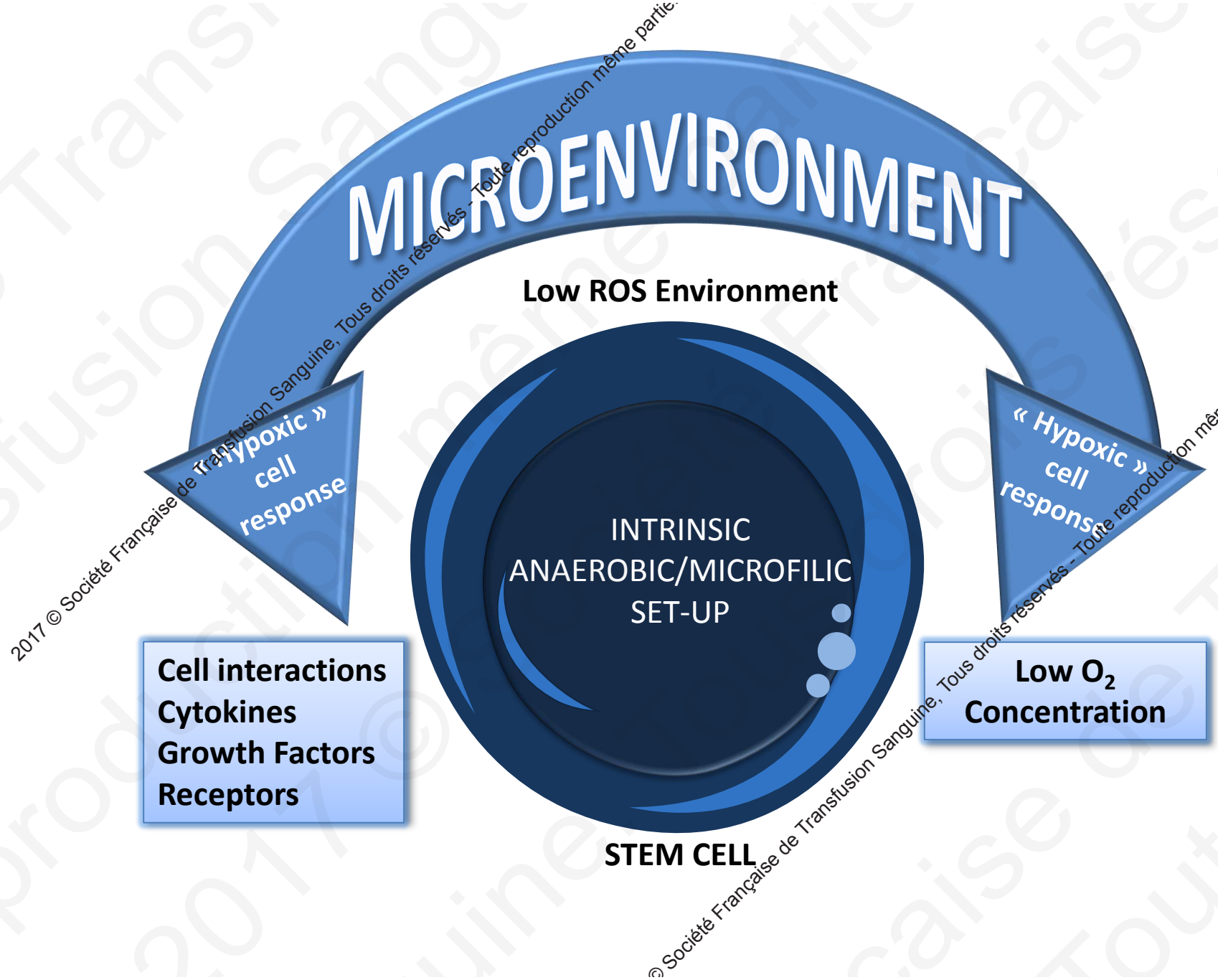
2.3% O2 (8-10 gest. Wk)

1.15-4%
Placental (« Cord »)
Blood: (*Kotaska et al 2010*)





Estimated in BM endoosteal niches to be 0 to 1% (*Chow et al, Biophys J 81: 685-96, 2001*)



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Mechanisms of Ageing and Development 124 (2003) 857–863

mechanisms of ageing and development

www.elsevier.com/locate/mechagedev

Mini-review

Primitive, and protective, our cellular oxygenation status?

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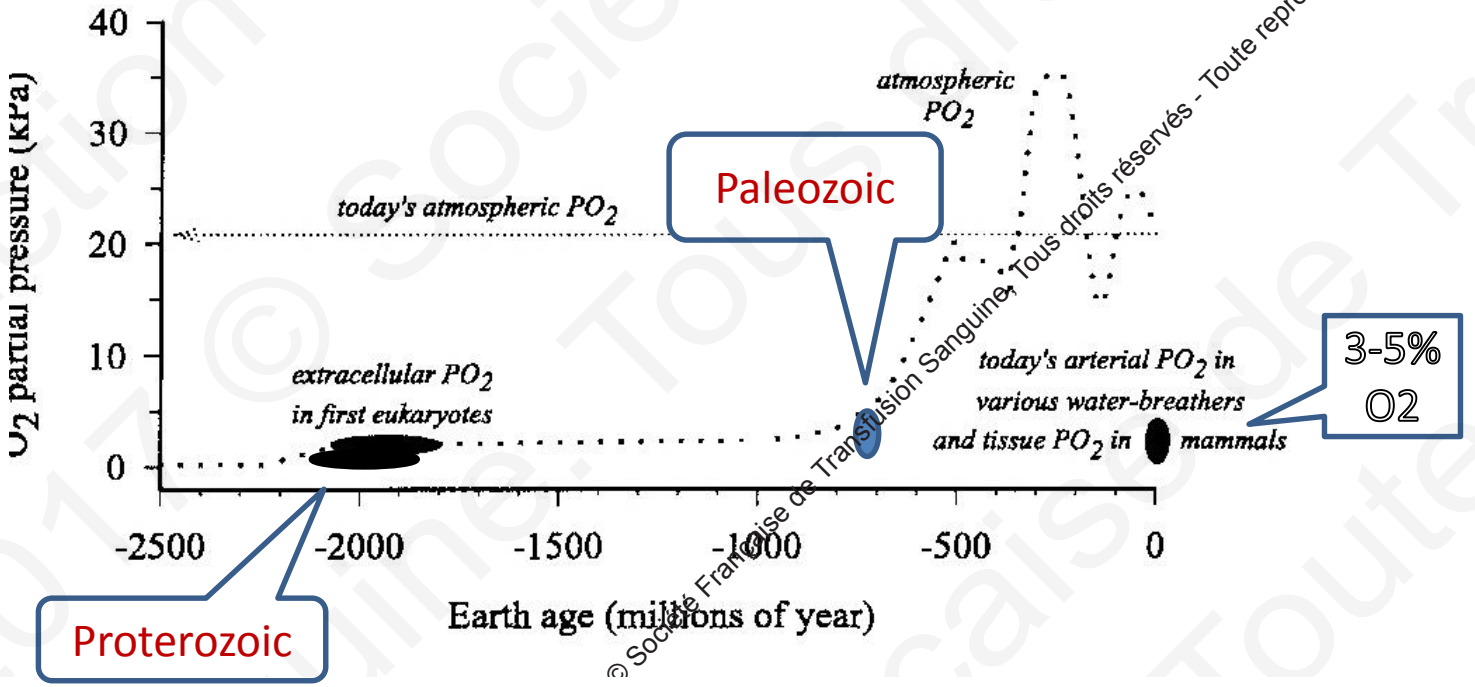
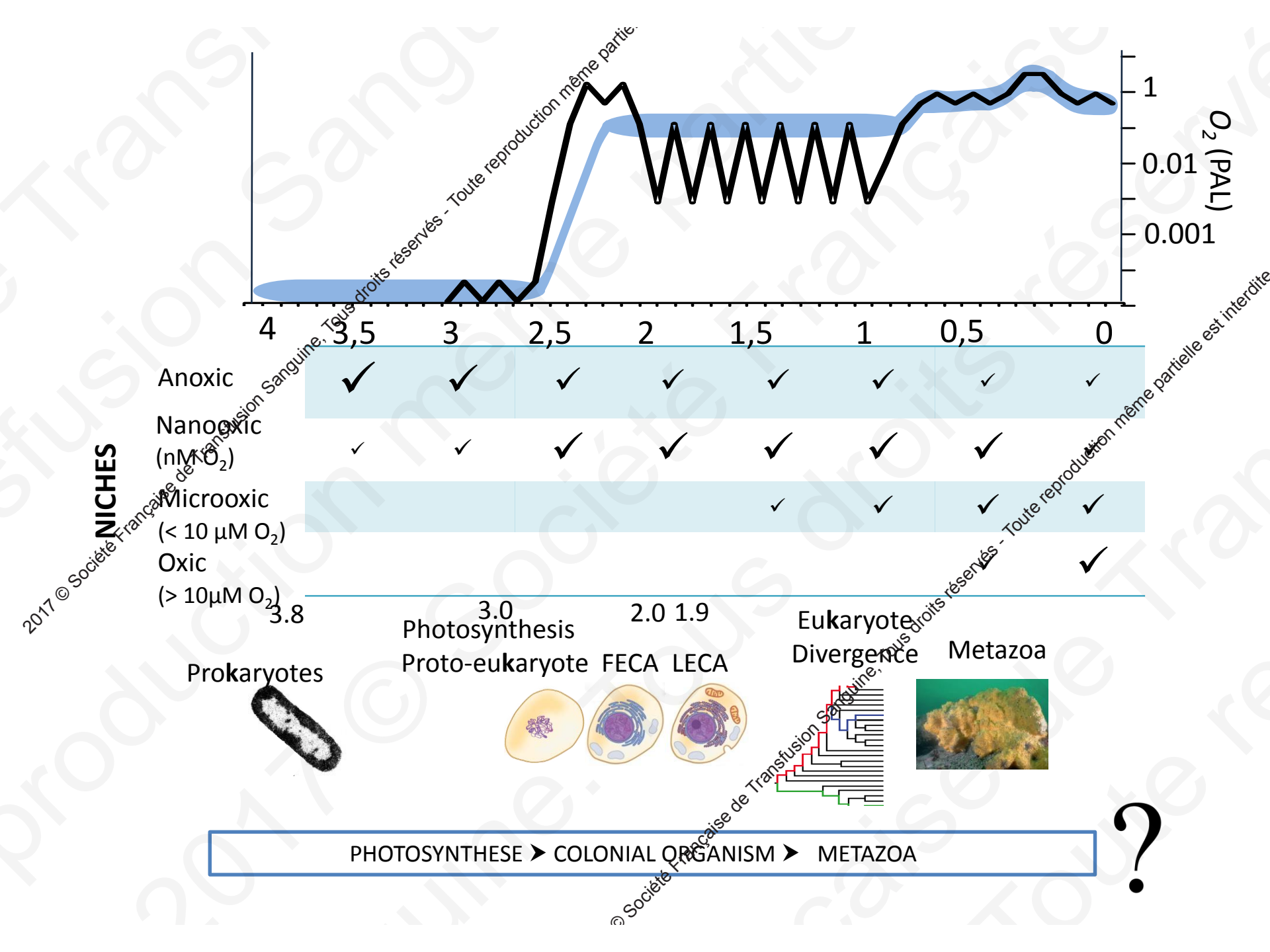
Received 9 May 2003; accepted 22 May 2003





This concept , named “OXYGEN STEM CELL PARADIGM” was explained in details in a review article:

Journal of Cellular Physiology

Hypoxia or In Situ Normoxia: The Stem Cell Paradigm

ZORAN IVANOVIC*

Aquitaine-Limousin Branch of French Blood Institute, Bordeaux, France

Although O_2 concentrations are considerably lowered in vivo, depending on the tissue and cell population in question (some cells need almost anoxic environment for their maintenance) the cell and tissue cultures are usually performed at atmospheric O_2 concentration (20–21%). As an instructive example, the relationship between stem cells and micro-environmental/culture oxygenation has been recapitulated. The basic principle of stem cell biology, “the generation-age hypothesis,” and hypoxic metabolic properties of stem cells are considered in the context of the oxygen-dependent evolution of life and its transposition to ontogenesis and development. A hypothesis relating the self-renewal with the anaerobic and hypoxic metabolic properties of stem cells and the actual O_2 availability is elaborated (“oxygen stem cell paradigm”). Many examples demonstrated that the cellular response is substantially different at atmospheric O_2 concentration when compared to lower O_2 concentrations which better approximate the physiologic situation. These lower O_2 concentrations, traditionally called “hypoxia” represent, in fact, an in situ normoxia, and should be used in experimentation to get an insight of the real cell/cytokine physiology. The revision of our knowledge on cell/cytokine physiology, which has been acquired ex vivo at non physiological atmospheric (20–21%) O_2 concentrations representing a hyperoxic state for most primate cells, has thus become imperious.

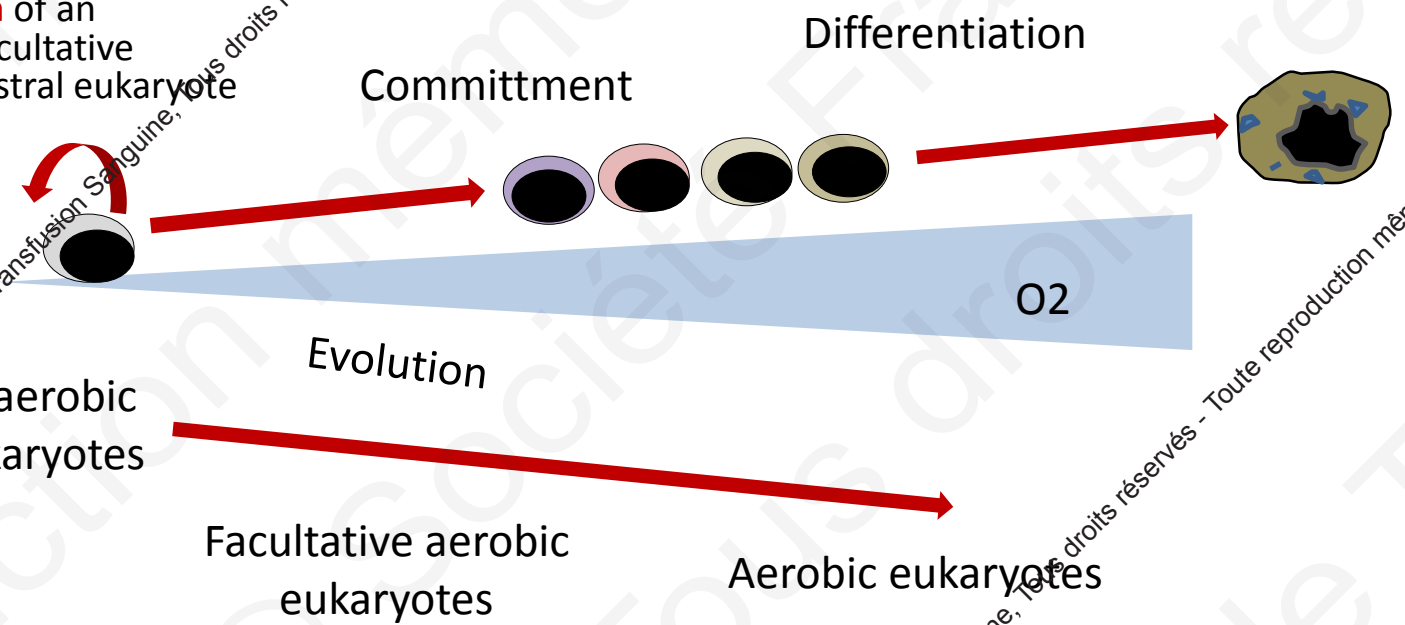
J. Cell. Physiol. 219: 271–275, 2009.

AS A MATTER OF FACT, STEM CELLS MIMIC AN EARLY EVOLUTIONNARY STAGE CHARACTERIZED WITH VERY LIMITED O_2 AVAILABILITIES

(REMINDING THOSE UNICELLULAR ORGANISMS STILL NOT COMPLETELY ADAPTED TO OXYGEN, EXHIBITING THE "HYPOXIC" METABOLIC TYPE)

Self-renewal
nothing but simple proliferation without differentiation

Self-renewing divisions of stem cells look like **basic reproduction** of an anaerobic/facultative aerobic ancestral eukaryote



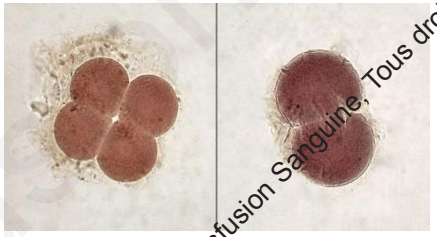
Inhibition of oxidative phosphorylation and stimulation of anaerobic glycolysis enhance the stemness regardless of how this action is operated

- Takubo et al Cell Stem Cell 12: 49-61, 2013
- Forristal et al Blood 121: 759-69, 2013

Commitment and differentiation are paralleled by intensification of oxidative phosphorylation, resulting in loss of the self-renewal capacity

- Takubo et al Cell Stem Cell 12: 49-61, 2013

The most primitive stem cells – blastomeres from mammalian pre-implantation embryo as well as embryonic stem cells:



Loss of pluripotency – Committment - Differentiation

- Limited oxidative capacities;
- Rely greatly on anaerobic glycolysis;
- Low number of small and immature mitochondria located around the nucleus.

- Shift towards oxidative phosphorylation;
- The number of mitochondria and mitochondrial copies per cell increase;
- Mitochondria acquire more mature morphology.

Facucho-Oliveira & St John. Stem Cell Rev 5: 140-158, 2009

Induction of Pluripotent Stem Sells from Mature Somatic Cells (iPSCs):

- **Somatic mitochondria revert to an immature ESC-like state with respect to organelle morphology, expression of nuclear factors involved in mitochondrial biogenesis and distribution and content of mitochondrial DNA** (*Prigione et al, Int J Dve Biol 54: 1729-41, 2010*);

- **Is proceeded by transition from an oxidative to an anaerobic metabolic state** (*Folmes et al, Cell Stem Cell 11: 596-606, 2012*)

Conversely, upon differentiation in both iPSC and ESCs:

- **Maturation of mitochondria and anaerobic to anaerobic metabolic transition** (*Facucho-Oliveira & St John. Stem Cell Rev 5: 140-158, 2009; Prigione et al, Int J Dve Biol 54: 1729-41, 2010)*

Finally, inhibition of the mitochondrial respiratory chain of HSC and ESCs:

- **Enhancement of stemness** (PTPMT1 - a mitochondrial phosphatase - depletion: *Yu et al Cell Stem cell 12, 67-74, 2013;* antimycin A or myxothiazol blockade of complex III: *Varum et al Stem Cell Res 3, 142-156, 2009*).

These data confirm the features revealed a quarter of a century ago by Dello Sbarba et al (*Exp Hematol 15:137-42, 1987*)

(lack of citation of Dello Sbarba's work in recent papers)

In addition to the metabolism of glucose, HIF system (including HIF2)controls cell proliferation, survival and apoptosis and more than 200 genes including:

- WNT,
- Notch
- Foxo
- Nanog
- Pax
- GATA
- Stat…

"Pluripotency factors"

"Regulators of stemnees"

Takahashi K, Yamanaka S
Cell, 126: 663– 676, 2006.
(+ Klf4 and c-Myc)

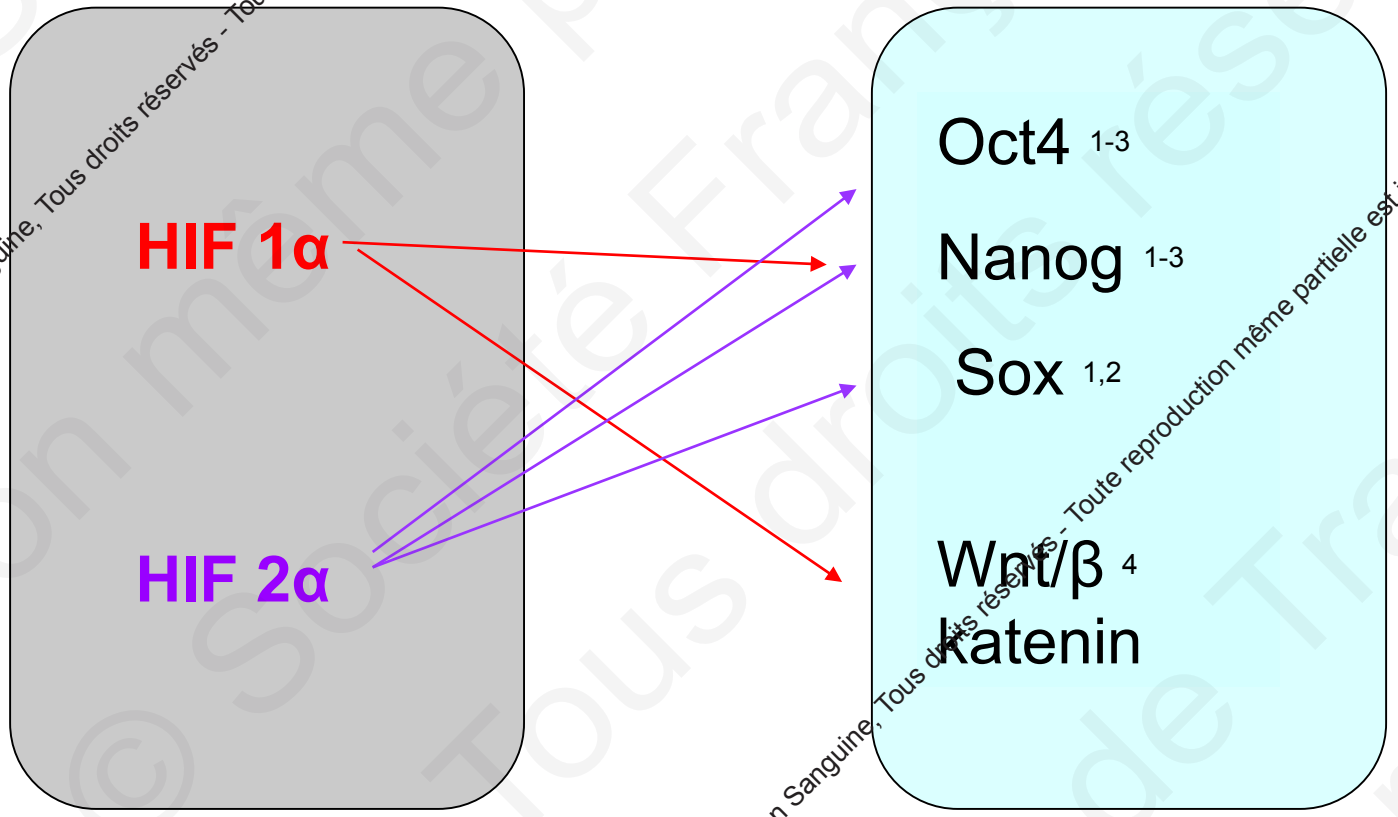
Re-programmation is enhanced by the low O2 concentrations:
Yoshida et al, Cell Stem Cell 5: 237-241, 2009.

FACTOR HIF AND EXPRESSION OF « PLURIPOTENCY REGULATORS »

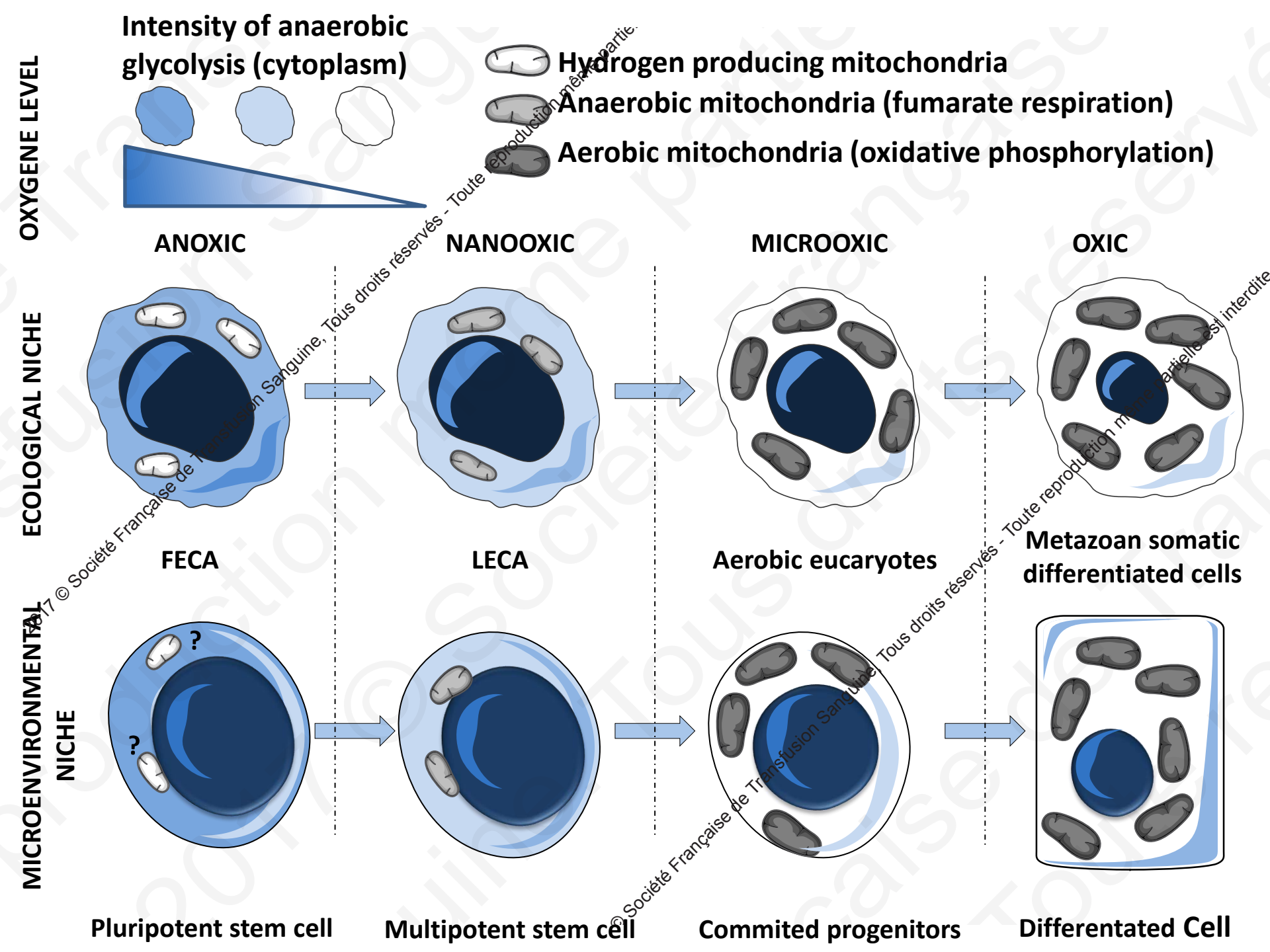
Stem Cell. 2009
Sep 4;5(3):237-41.
Epub 2009 Aug 27.

Hypoxia enhances the generation of induced pluripotent stem cells.

Yoshida Y, Takahashi K, Okita K, Ichisaka T, Yamanaka S.



1. Covello KL, Kehler J, Yu H, Gordan JD, Arsham AM, Hu CJ, Labosky PA, Simon MC, Keith B (2006) HIF-2 regulates Oct-4: effects of hypoxia on stem cell function, embryonic development, and tumor growth. Genes Dev 20: 557–570
2. Forristal CE, Wright KL, Hanley NA, Oreffo RO, Houghton FD (2010) Hypoxia inducible factors regulate pluripotency and proliferation in human embryonic stem cells cultured at reduced oxygen tensions. Reproduction 139: 85–97.
3. Ji L, Liu YX, Yang C, Yue W, Shi SS, Bai CX, Xi JF, Nan X, Pei XT. Self-renewal and pluripotency is maintained in human embryonic stem cells by co-culture with human fetal liver stromal cells expressing hypoxia inducible factor 1alpha. J Cell Physiol. 2009 Oct;221(1):54-66
4. Mazumdar J, O'Brien WT, Johnson RS, LaManna JC, Chavez JC, Klein PS, Simon MC. O2 regulates stem cells through Wnt/β-catenin signalling. Nat Cell Biol. 2010 Oct;12(10):1007-13.

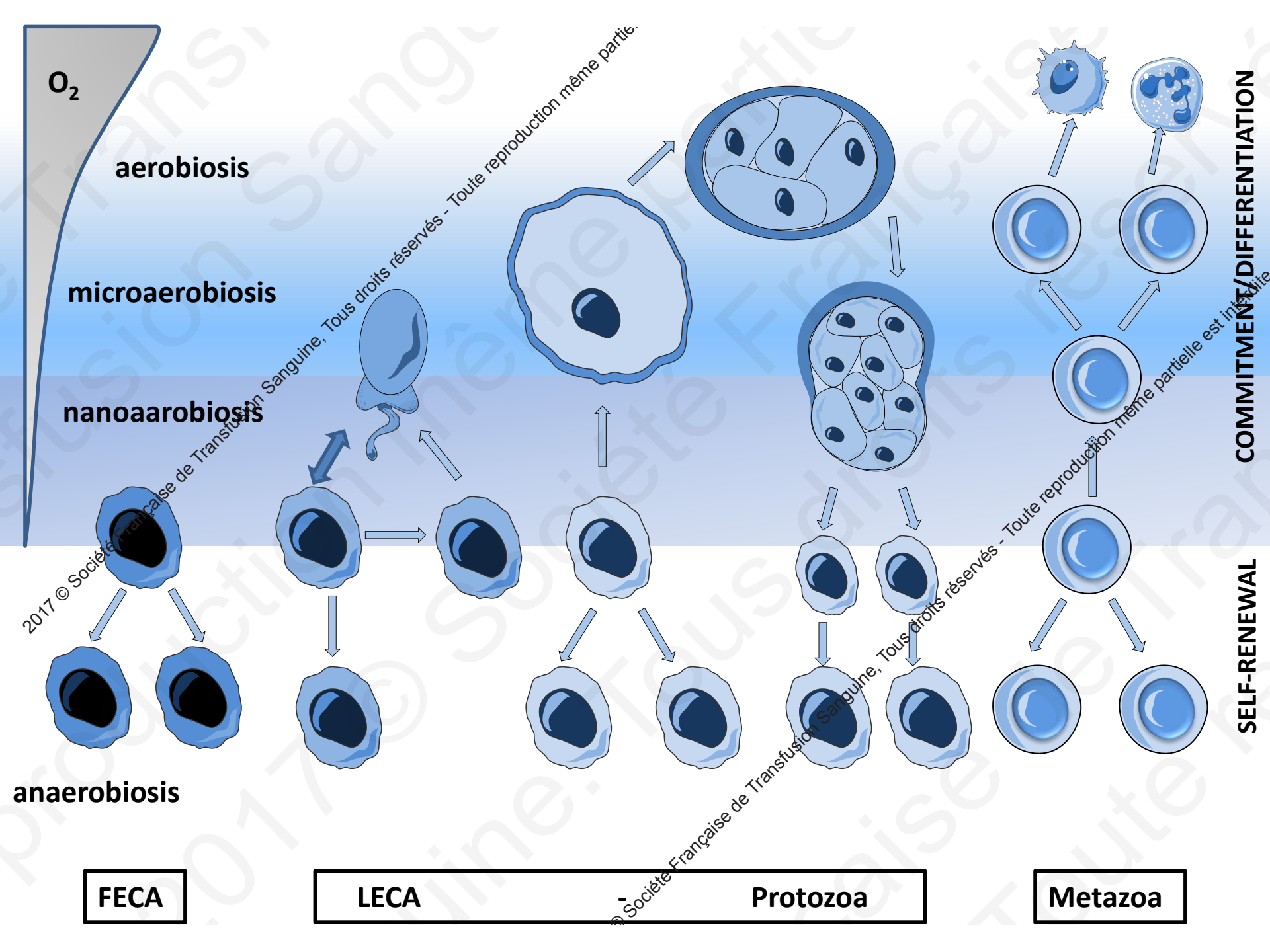


"**Evolutionary Paradigm of Stem Cell**" considers that the "stemness" looks like a cellular state where functions are limited by activation of a **"minimal essential genome"** i.e. of genes corresponding to those expressed in primitive anaerobic unicellular eukaryotes acquiring the first extensions for adaptation to moderate (low) oxygen concentrations.

Thus, a limited energy supply would allow the realization of the programs strictly necessary for survival and division of cells unlike activation of differentiation programs (energy consuming).

The low energy availability should also allow the expression of primary signalling pathways operating in survival and proliferation. These pathways are, in general highly evolutionary conserved.

The simple division into two identical cells represents, in fact, the phenomenon called "self-renewal".



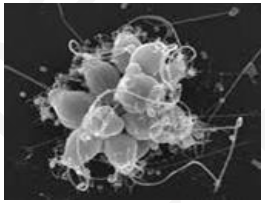
ToolKit FECA (Minimal Essential Eukaryote Genome)

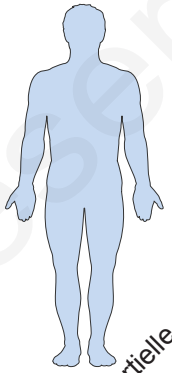
ToolKit LECA addition

ToolKit Colonial Prometazoa addition

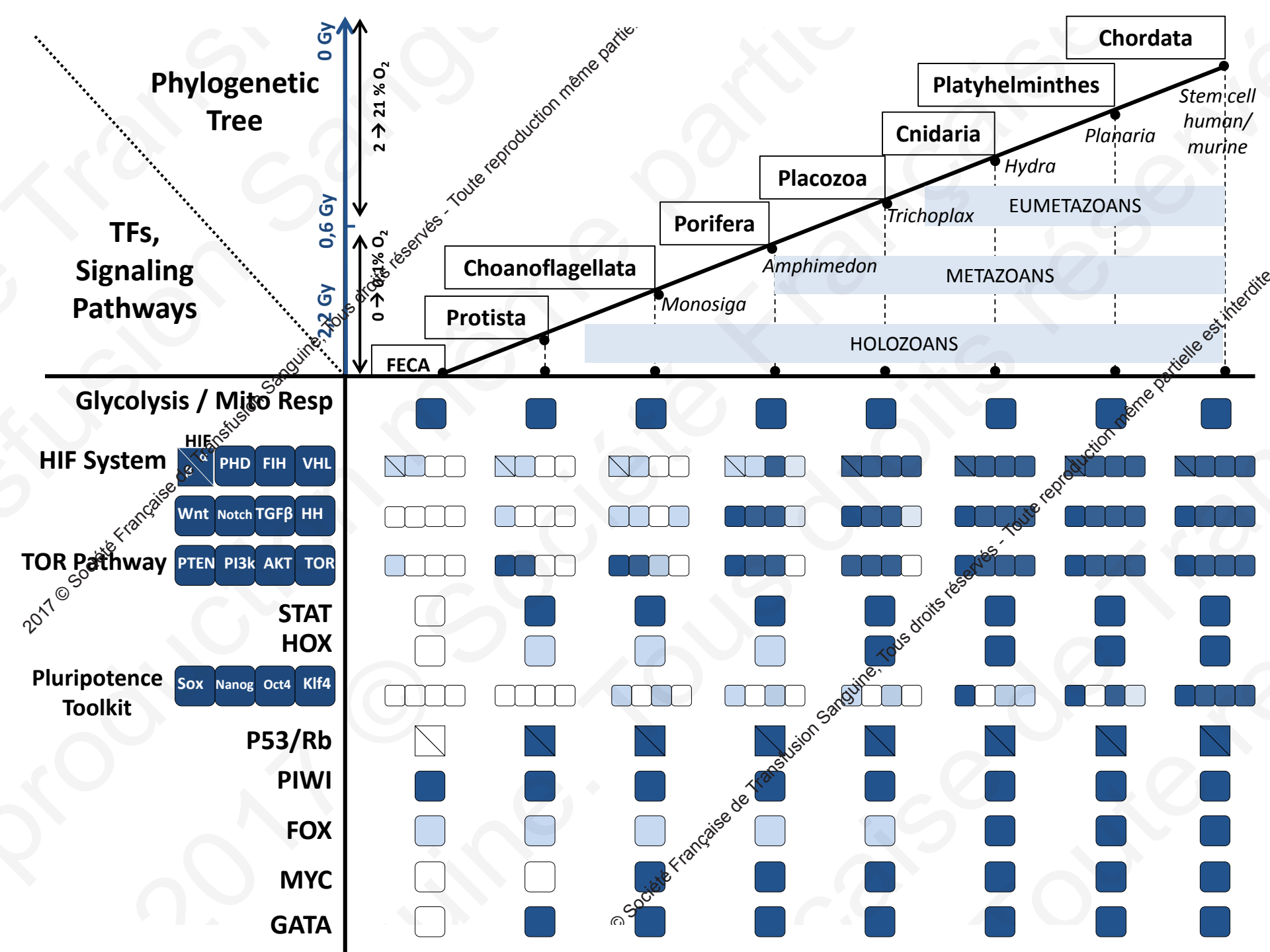
ToolKit Metazoa addition



	Procaryotes	FECA	LECA	Colonial Prometazoa	Metazoa (stem cells)	Mammals (stem cells)	
						Normal	Cancer
Anaerobiosis	✓	✓	✓	✓	✓		✓
Simple Division	✓	✓	✓	✓	✓		✓
Migration	✓	✓	✓	✓	✓		✓
Differentiation	-	✓	✓	✓	✓		✓
Colony forming ability	-	-	✓	✓	✓		✓
Multicellular Regulation	-	-	-	✓	✓		✓


Phylogenetic Tree
TFs, Signaling Pathways
0 Gy
0,6 Gy
2 Gy
2 → 21 % O2
0 → 0,1 % O2
Chordata
Platyhelminthes
Cnidaria
Placozoa
Porifera
Choanoflagellata
Protista
FECA
Stem cell human/ murine
Planaria
Hydra
Trichoplax
Amphimedon
Monosiga
EUMETAZOANS
METAZOANS
HOLOZOANS
Glycolysis / Mito Resp
HIF System
HIF
α
β
PHD
FIH
VHL
Wnt
Notch
TGFβ
HH
TOR Pathway
PTEN
PI3k
AKT
TOR
STAT
HOX
Pluripotence Toolkit
Sox
Nanog
Oct4
Klf4
P53/Rb
PIWI
FOX
MYC
GATA
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Anaerobiosis and Stemness

An evolutionary paradigm

By Zoran Ivanovic & Marija Vlaski-Lafarge

Etablissement Français du Sang Aquitaine-Limousin/UMR 5164
CNRS-University of Bordeaux, France

A complete first-to-market review and analysis of the relevant literature in the field of hypoxia, hypoxic regulation and stem cell maintenance to assist in the progression toward clinical application.

Anaerobiosis and Stemness: An evolutionary paradigm provides a context for understanding the many complexities and evolutionary features of stem cells and the clinical implications of anaerobiosis in stem cells. Combining theoretical and experimental knowledge, the authors provide a broad understanding of how the absence or low concentrations of oxygen can play an influential role in the maintenance and self-renewal of stem cells and stem cell differentiation. This understanding has clinical implications for the fields of regenerative medicine, cancer biology and transplantation, as well as cell engineering and cell therapy. ***Anaerobiosis and Stemness*** is an important resource for stem cell and developmental biologists alike, as well as oncologists, cancer biologists, and researchers using stem cells for regeneration.

KEY FEATURES

- Highlights the molecular and evolutionary features of stem cells which make them so important to all biological research
- Explores methods of isolation, characterization, activation, and maintenance of stem cells
- Includes models for clinical application in regenerative medicine, cancer therapy and transplantation

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ISBN 978-0-12-800540-8

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Anaerobiosis and Stemness
An evolutionary paradigm

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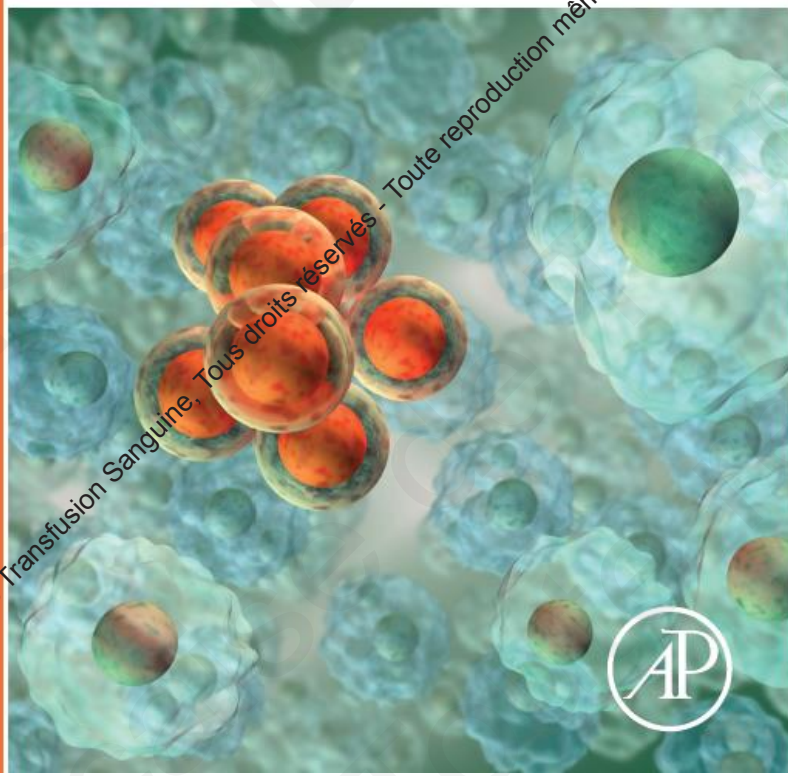
Anaerobiosis and Stemness

An evolutionary paradigm

Zoran Ivanovic & Marija Vlaski-Lafarge



Thus, manipulation of energetic metabolism of stem cells should allow mastering their self-renewal/commitment/differentiation ratio, which is the major imperative for engineering of appropriate cell products for regenerative medicine.

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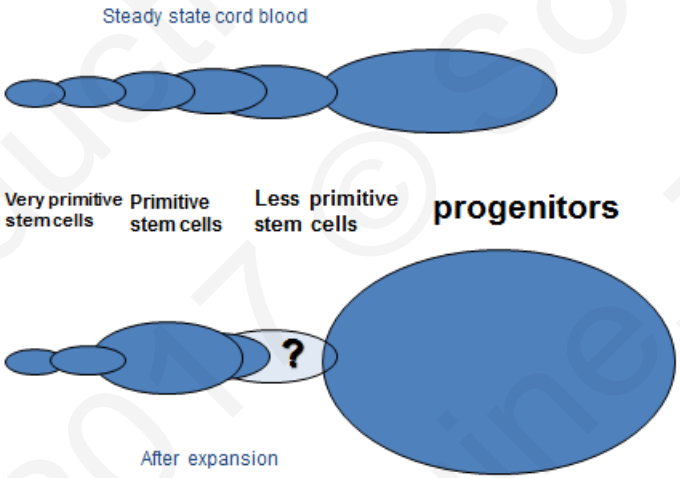
Application on ex vivo expansion of Hematopoietic stem and progenitor cells

The first attempts : mimicking of the low O2 concentration by combining the anti-oxidants-supplemented medium and the cytokines stabilizing HIF-1α (SCF, MGDF (Tpo)) which enabled preservation of primitive stem cells in course of ex vivo expansion of committed progenitors

- HP01 medium;
- "Cobary" cocktail: SCF,G-CSF,Flt-3L, MGDF;
- Two-step culture in "bags".

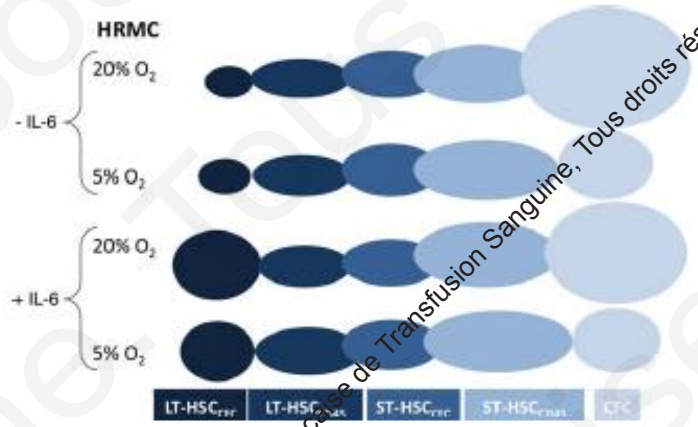


- ***Ivanovic et al, Cell Transplant 20:1453-63, 2011***
- ***Duchez et al, Cell Transplant 21: 2517–21, 2012.***

Interleukin-6 enhances the activity of in vivo long-term reconstituting hematopoietic stem cells in "hypoxic-like" expansion cultures ex vivo

Pascaline Duchez, Laura Rodriguez, Jean Chevaleyre, Veronique Lapostolle, Marija Vlaski, Philippe Brunet de la Grange, and Zoran Ivanovic

TRANSFUSION 2015;55;2684–2691



In fact, the main advances in the clinical-scale ex-vivo expansion procedures are related to "hypoxic response" (i.e. "primitive" or "ancestral" modality of cellular functioning) leading to the maintenance of stemness

They refer also to:

- Signaling via Notch [Delaney et al Nat Med 16: 232-6, 2010];
- Signaling via: HOXB4, Wnt and Hedgehog [Campbell et al Curr Opin Hematol 15: 319-25, 2008],
- pharmacologic stabilization of HIF-α [Forristal et al Blood 151, 759-769, 2013],
- activation of anaerobic glycolysis/attenuation of oxidative phosphorylation in mitochondria [Takubo et al Cell Stem Cell 12: 49-61, 2013].

Application on improvement of ex-vivo Red Blood Cell Production

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ELSEVIER

Experimental Hematology

Experimental Hematology 2009;37:573–584

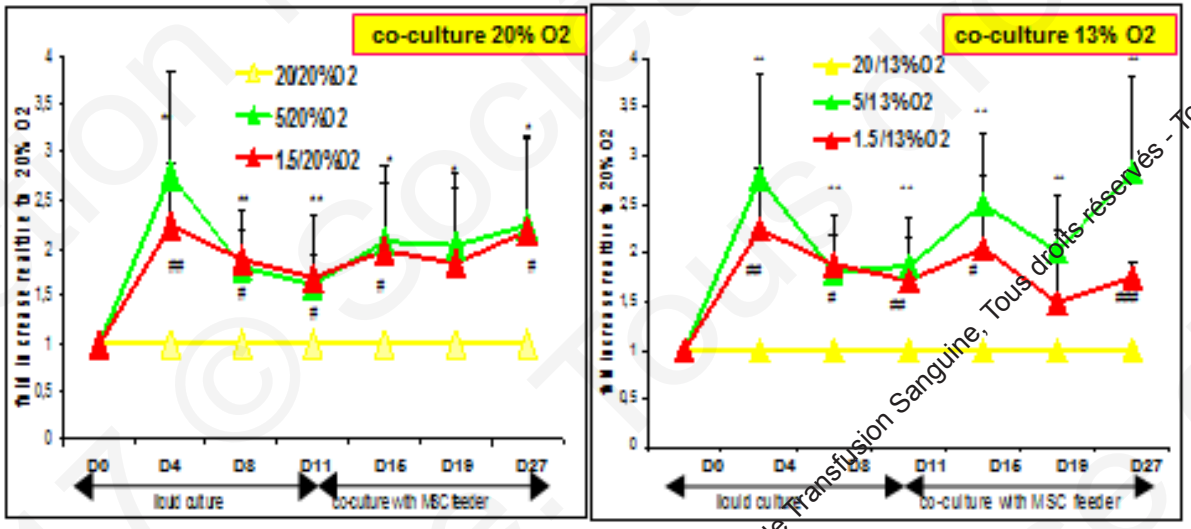
Low oxygen concentration as a general physiologic regulator of erythropoiesis beyond the EPO-related downstream tuning and a tool for the optimization of red blood cell production ex vivo

Marija Vlaski[a], Xavier Lafarge[a], Jean Chevaleyre[a], Pascale Duchez[a], Jean-Michel Boiron[a,b], and Zoran Ivanovic[a]

[a]Aquitaine-Limousin Branch of French Blood Institute, Bordeaux, France; [b]University Victor Segalen Bordeaux, Bordeaux, France

(Received 24 October 2008; revised 19 January 2009; accepted 20 January 2009)

Cell expansion



1.5% O_2 (#p<0.05, ##p<0.01, ###p<0.001), 5% O_2 (p<0.05, **p<0.01, ***p<0.001) *vs* 20% O_2, n=6

Application on conditioning of MSC for transplantation in anoxic/ischemic area

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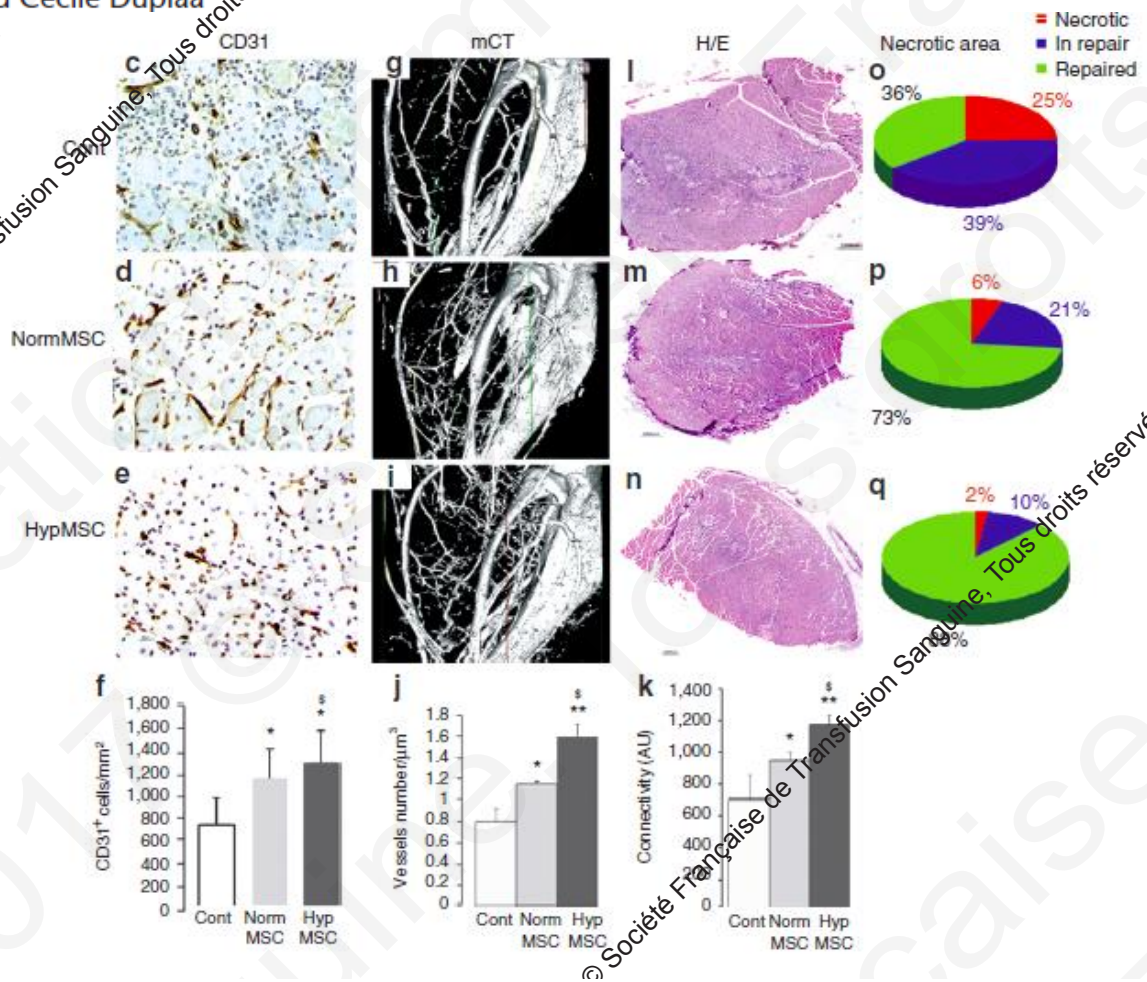
Hypoxia Preconditioned Mesenchymal Stem Cells Improve Vascular and Skeletal Muscle Fiber Regeneration After Ischemia Through a Wnt4-dependent Pathway

Molecular Therapy
18:1545-52, 2010.

Lionel Leroux[1,2], Betty Descamps[1], Nancy F Tojais[1], Benjamin Séguy[2], Pierre Oses[2], Catherine Moreau[1], Danièle Daret[1], Zoran Ivanovic[3], Jean-Michel Boiron[3], Jean-Marie D Lamazière[1], Pascale Dufourcq[1,4], Thierry Couffinhal[1,2] and Cécile Duplàa[1]

Mouse model of hindlimb ishemia



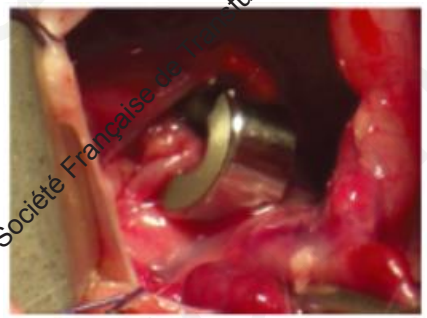
European Journal of Cardio-Thoracic Surgery 0 (2012) 1–8
doi:10.1093/ejcts/ezs549

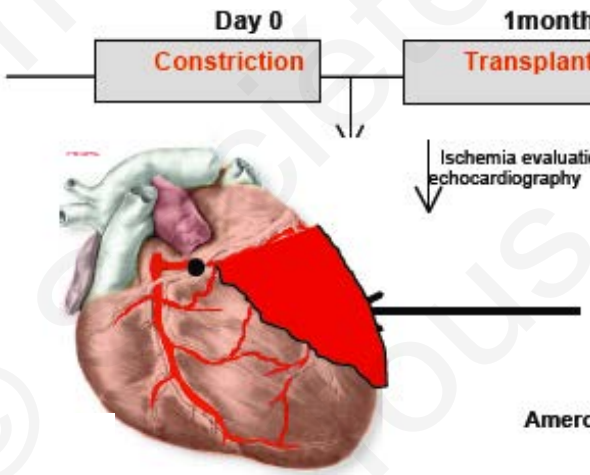
ORIGINAL ARTICLE

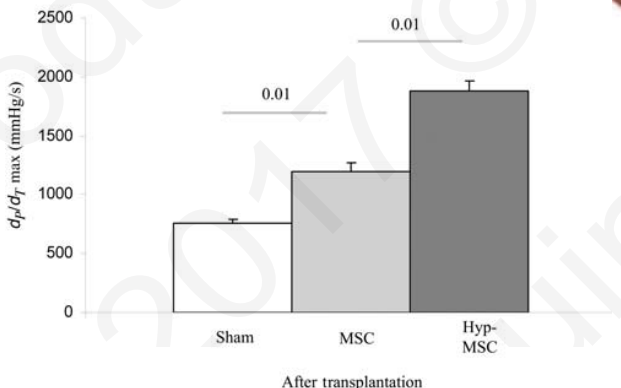
EXPERIMENTAL

Hypoxia-preconditioned mesenchymal stromal cells improve cardiac function in a swine model of chronic myocardial ischaemia

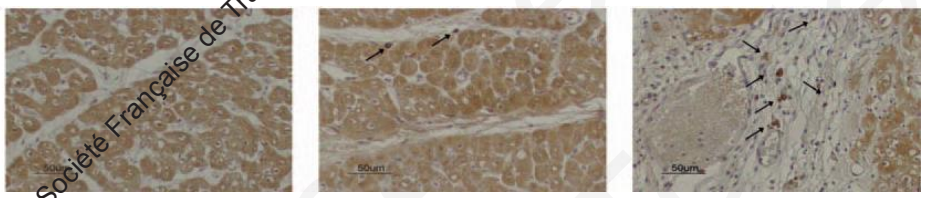
Jeremie Jaussaud[a], Matthieu Biais[a,b,c], Joachim Calderon[a,b], Jean Chevaleyre[d,e], Pascale Duchez[d,e], Zoran Ivanovic[d,e], Thierry Couffinhal[a,c] and Laurent Barandon[a,c,f,*]







Sham MSC Hypo-MSC

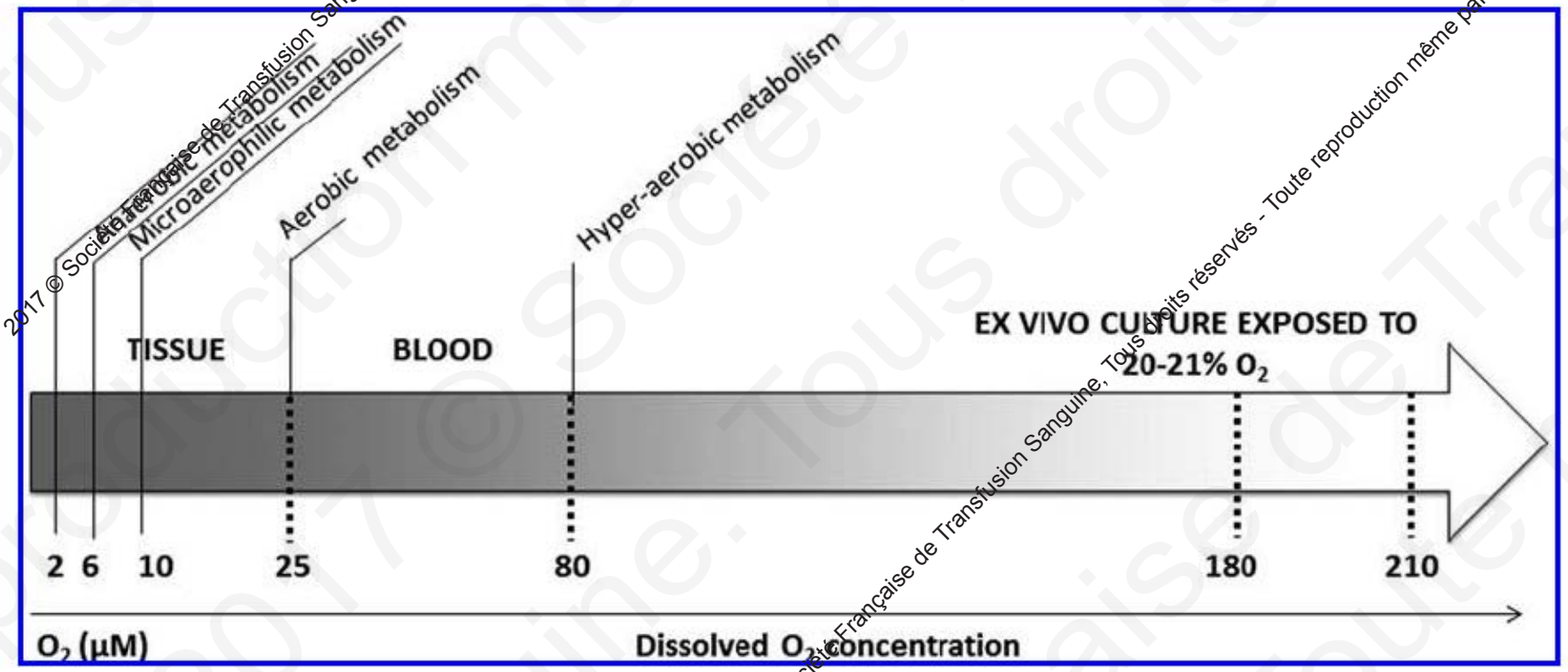


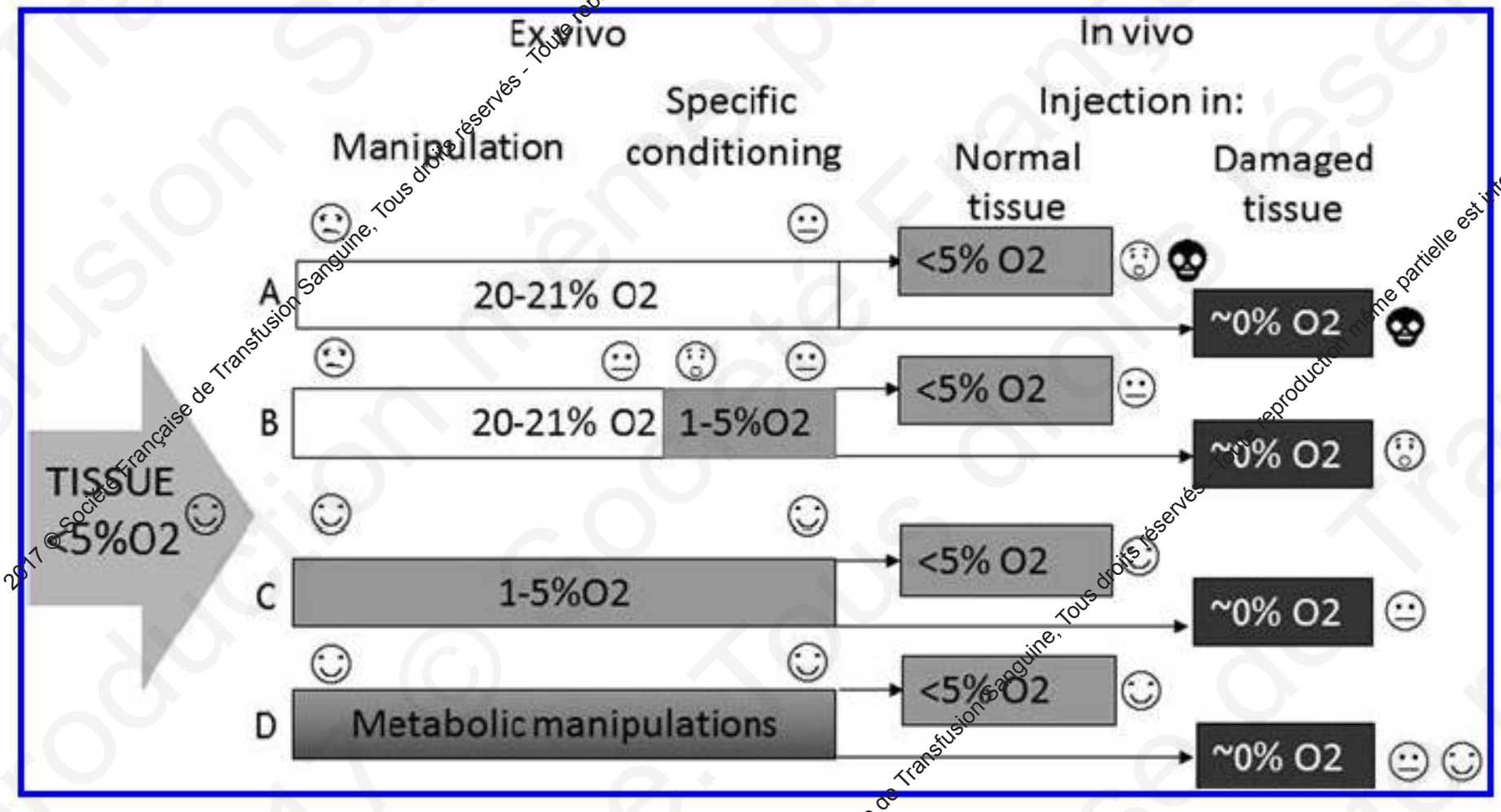
STEM CELLS AND DEVELOPMENT
Volume 26, Number 8, 2017

DOI: 10.1089/scd.2016.0268

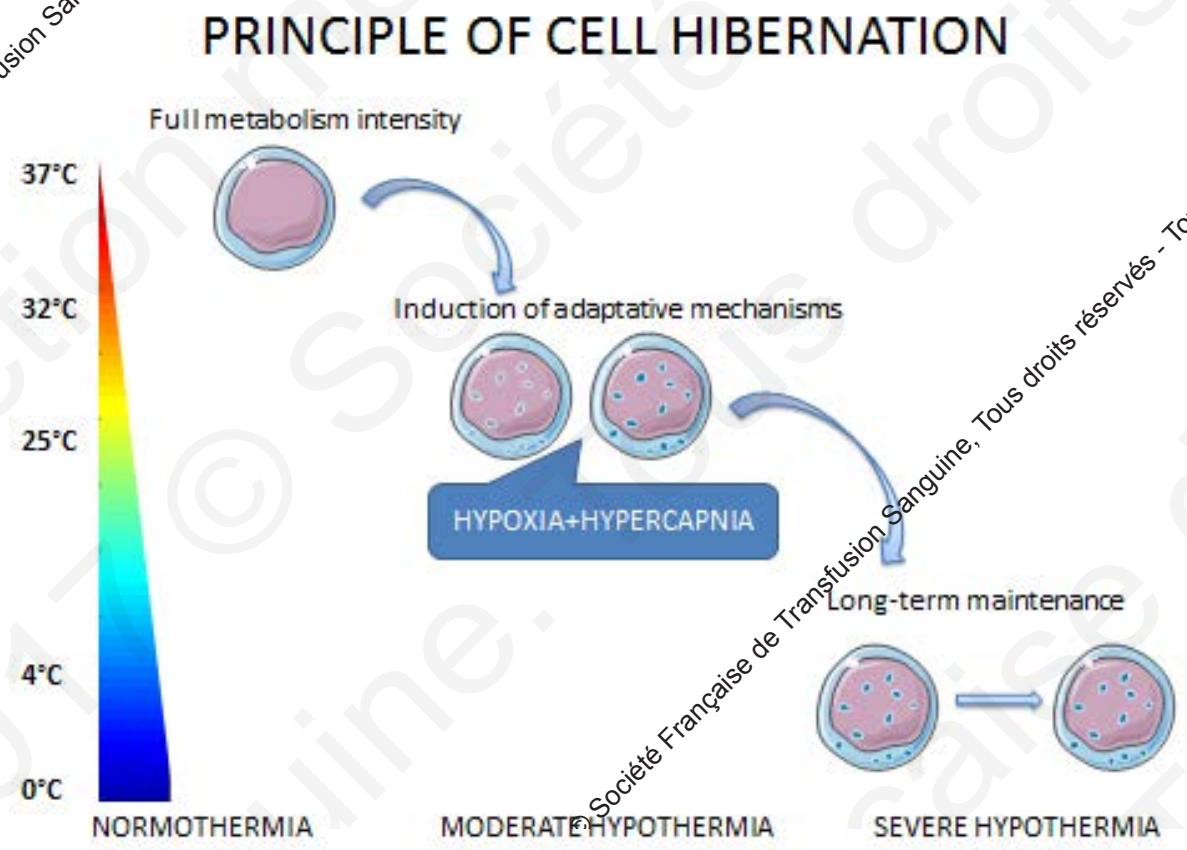
Strategies to Enhance Implantation and Survival of Stem Cells After Their Injection in Ischemic Neural Tissue

Ioanna Sandvig,[1] Ivana Gadjanski,[2,3] Marija Vlaski-Lafarge,[4,5] Leonora Buzanska,[6] Darija Loncaric,[4,5] Ana Sarnowska,[6] Laura Rodriguez,[4,5] Axel Sandvig,[1,7] and Zoran Ivanovic[4,5]





New principle: Cell Hibernation and its Application on Cell Conservation in hypothermia



Journal of Cellular Physiology

Hypoxia/Hypercapnia-Induced Adaptation Maintains Functional Capacity of Cord Blood Stem and Progenitor Cells at 4°C

MARIJA VLASKI,[1,2] LUC NEGRONI,[3] MILICA KOVACEVIC-FILIPOVIC,[4] CHRISTELLE GUIBERT,[5] PHILIPPE BRUNET DE LA GRANGE,[1,2] RODRIGUE ROSSIGNOL,[6] JEAN CHEVALEYRE,[1,2] PASCALE DUCHEZ,[1,2] XAVIER LAFARGE,[1] VINCENT PRALORAN,[2] JEAN-MARIE SCHMITTER,[3] AND ZORAN IVANOVIC[1,2]*

J. Cell. Physiol. 229: 2153–2165, 2014.

A Novel Procedure to Improve Functional Preservation of Hematopoietic Stem and Progenitor Cells in Cord Blood Stored at +4°C Before Cryopreservation

Jean Chevaleyre,[1,2,*] Laura Rodriguez,[1,3,*] Pascale Duchez,[1,2] Marie Plainfossé,[3,†] Bernard Dazey,[1] Véronique Lapostolle,[1,2] Marija Vlaski,[1,2] Philippe Brunet de la Grange,[1,2] Bruno Delorme,[3] and Zoran Ivanovic[1,2]

STEM CELLS AND DEVELOPMENT
Volume 23, Number 15, 2014

DOI: 10.1089/scd.2014.0046

TRANSFUSION 2009;49:1738-1746.

Low-oxygen and high-carbon-dioxide atmosphere improves the conservation of hematopoietic progenitors in hypothermia

Michel Jeanne, Milica Kovacevic-Filipovic, Milène Szyporta, Marija Vlaski, Francis Hermitte, Xavier Lafarge, Pascale Duchez, Jean-Michel Boiron, Vincent Praloran, and Zoran Ivanovic

TRANSPLANTATION AND CELLULAR ENGINEERING

TRANSFUSION 2010;50:120-127.

CD34+ cells obtained from "good mobilizers" are more activated and exhibit lower ex vivo expansion efficiency than their counterparts from "poor mobilizers"

Zoran Ivanovic, Milica Kovacevic-Filipovic, Michel Jeanne, Leslie Ardilouze, Anne Bertot, Milène Szyporta, Francis Hermitte, Xavier Lafarge, Pascale Duchez, Marija Vlaski, Noel Milpied, Mirjana Pavlovic, Vincent Praloran, and Jean-Michel Boiron

Application on improvement of procedures of hematopoietic stem and progenitor cells cryopreservation

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TRANSPLANTATION AND CELLULAR ENGINEERING

TRANSFUSION 2013;53:2012-2019.

Cryopreservation of hematopoietic stem and progenitor cells amplified ex vivo from cord blood CD34+ cells

Pascale Duchez, Jean Chevaleyre, Philippe Brunet de la Grange, Marija Vlaski, Jean-Michel Boiron, Guy Wouters, and Zoran Ivanovic

Cytotherapy, 2016; 18: 1543–1547

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STEM CELL CRYOPRESERVATION

Clinical-scale validation of a new efficient procedure for cryopreservation of *ex vivo* expanded cord blood hematopoietic stem and progenitor cells

PASCALE DUCHEZ[1,2], LAURA RODRIGUEZ[1,2], JEAN CHEVALEYRE[1,2], PHILIPPE BRUNET DE LA GRANGE[1,2] & ZORAN IVANOVIC[1,2]

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