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Project leader

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Research Interests:

- Embryonic, induced pluripotent stem cells and teeth-derived adult stem cells [ESC, iPSC, SCAPs (Stem Cells from Apical Papillae)]: Mechanisms of maintenance and exit of cell pluripotency or multipotency/ differentiation/ apoptosis/ autophagy/ cell metabolism/ 3D culture in biomaterials.
- Impact of pleiotropic LIF (Leukemia Inhibitory Factor) cytokine, ECM (extra cellular matrix) and environmental paradigms on stem cell fates (oxygen concentration, biomaterials).
- Cancer stem cells (glioblastoma and gastric cancer)
- Regenerative medecine

Stem cells have the specific dual property to either self-renew or differentiate in specialized cells, depending upon environmental stimuli. The understanding of self- renewal mechanisms and of those triggering differentiation is of major importance for the control of stem cell plasticity and therefore for its potential application in cellular therapy. **Murine ES cells (mESC),** derived from the inner cell mass of blastocysts, are maintained pluripotent *in vitro*, in the naïve state, in the presence of LIF (Leukemia Inhibitory Factor). This cytokine, from the IL6 family, displays pleiotropic effects depending upon cell types and cell maturity. LIF is conserved in the non-eutherian vertebrate species, and has evolved as being the "nidation hormone" in mammals.

During this last decade, my work was dedicated to the identification and the understanding of targets of LIF involved in the maintenance of mESC pluripotency and in differentiation processes. In addition, we have investigated the mechanisms of pluripotency/differentiation cell switches and characterized plasticity windows in which cells could revert from a committed to a more immature fate in a LIF-dependent way. Environmental parameters (like oxygen concentration or regulators of the Extra Cellular Matrix) have also been investigated in these processes. Our work highlights the fact that genetic programs activated in pluripotent cells grown under physioxic concentration of O2 (3%, which mimics O2 concentration in embryos) are different than those operating under 21% O2, the hyperoxic condition more classically used for cell culture and in which, so far, most transcriptome and proteome analyses have been performed.

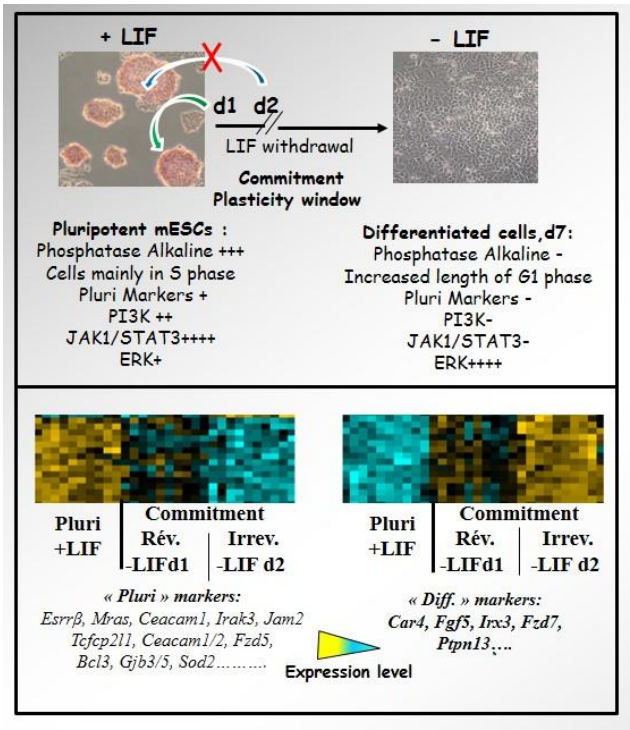
We are further exploring these new genetic programs at work under physioxia. We are investigating these mechanisms in **mESC, hiPSC** and more recently in **hSCAPs**.

We have also investigated the impact of LIF in **cancer stem cells** and have characterized expression profiles of LIF targets and of "stemness" genes in a collection of **glioma-derived cancer stem cells**, obtained under collaboration with the laboratory of MP Junier/H. Chneiweiss,U1130 Inserm, Neuroscience Paris Seine, UPMC and in **gastric cancer-derived stem cells** (in collaboration with Dr. C. Varon and C. Staedel,

University of Bordeaux). In addition we have set up a “stemness sensor test” which allows to evaluate the impact of the tumor-derived conditioned medium to maintain pluripotency of mESC cells. **Our aim** is now to evaluate whether this test could help to score tumor specimen with a “stemness index” helping to better make a diagnosis and a relevant treatment. In that context we are also characterizing the link of LIF with the Hippo pathway, recently shown to display anti-metastatic effect in breast cancer.

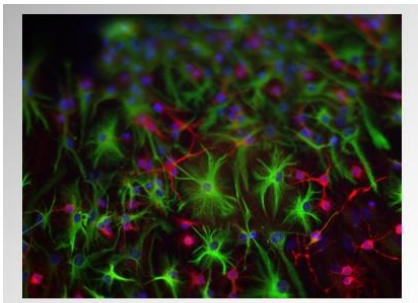
Keywords/expertise:

- Embryonic Stem cells (ESCs and iPSCs)
- Adult stem cells (MSCs, SCAPs)
- Cancer stem cells (glioma and gastric cancer)
- Pluripotency
- Cell plasticity
- Reprogrammation
- Differentiation
- Neurons
- Apoptosis
- metabolism
- LIF/gp130 signaling
- MAPK/ PI3K signaling
- Hypoxia/ Physioxia
- Extracellular matrix
- Biomaterials (hydrogels)
- Regenerative Medicine
- Cell-based therapies
- Translational medicine



The mESC model : To study mESCs and their derivatives in pluripotent, committed and differentiated states, by molecular, biochemical and functionnal approaches.

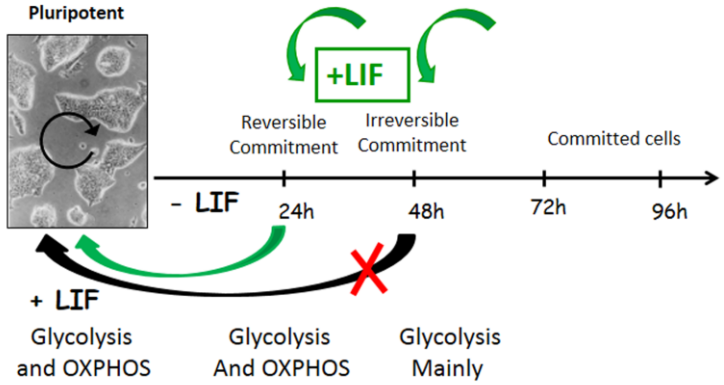
Cell cultures labelled with Alkaline Phosphatase (AP) kit (which reveals AP activity by a pink color) and transcriptomic tree view representations of gene expression are shown in the upper and lower parts of the figure respectively (from Trouillas et al, 2009, BMC genomics)



Neuronal differentiation:
mESCs in embryoid bodies for 8 days and plated for 13 days. GFAP, green/ MAP2, red. From the BIC imagerie center in Bordeaux (H.B. and Camille Genuer, Choquet's Lab.)

An example of **ES-derived** neuron (MAP2+) and glial cells (GFAP+) obtained after a simple differentiation procedure with mESCs . Around 50% of cell culture are neuronal/glial-like cells.

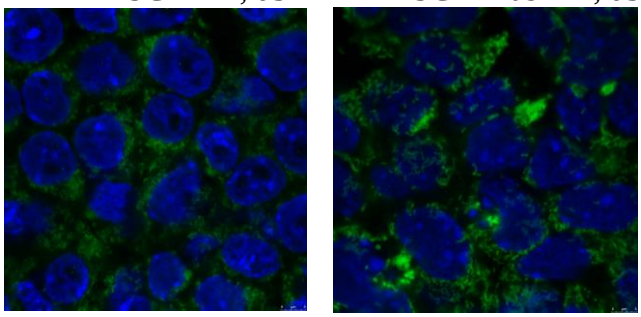
(Boeuf H. et al, Unpublished results)



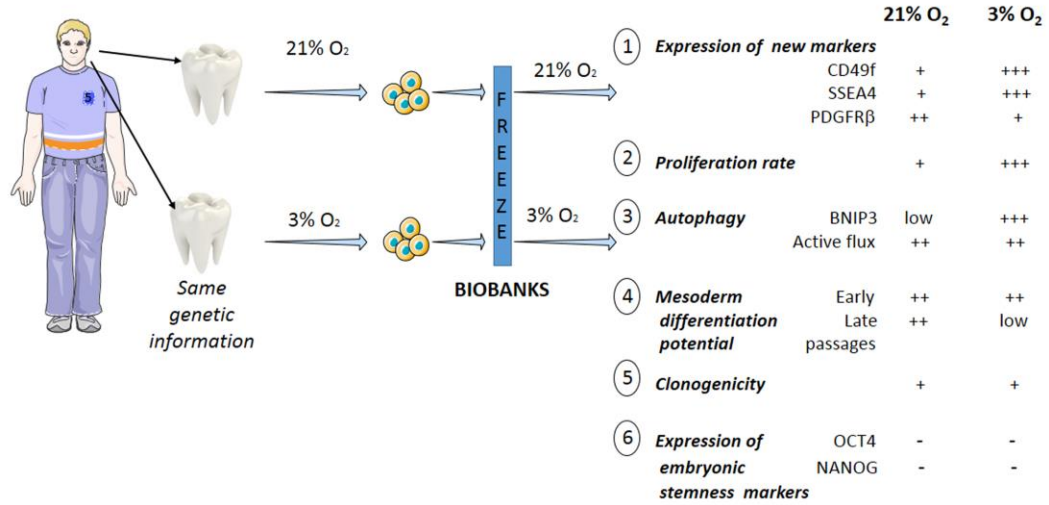
Graphical abstract: mESCs, pluripotent with LIF, are induced to differentiate by removing LIF for the times indicated in hours (h). Metabolic status of cells, along with their properties, are indicated. The switch towards "glycolysis mainly" status is associated with irreversible LIF-dependent reversion of cells and lost of plasticity at this early time frame window.

(From Vlaski et al, Stem cells, 2019)

mESC +LIF, d3 mESC minus LIF, d3



Murine ESC grown for 3 days with or without LIF have been immunolabelled with **TOMM20**, a mitochondrial outer membrane protein. Mitochondrial morphology is different with and without LIF attesting a metabolic change along cell commitment (from Vlaski et al, Stem Cells, 2019).



Graphical abstract

Legend : We have developed a unique new model of adult teeth-derived stem cells (SCAPs) and characterized their stemness properties under physiological cell growth conditions towards potential applications in regenerative medicine. The salient features of SCAPs derived under low O2 concentration are summarized.

(From Rémy et al, Cells, 2019)

Selected publications:

Seeneevassen L., Zaafour A., Sifré E., Genevois C., Nguyen T.L., Pobiedonoscew Y., Giese A., Guignard J., Tiffon C., Rousseau B., Raymond AA, Belleannée G., Boeuf H., Gronnier C., Martin O., Giraud J., Lehours P., Dubus P. and C. Varon (2022). Leukaemia Inhibitory Factor inhibits invasion and metastasis in gastric adenocarcinoma, submitted.

Mavinga M., Palmier M., Rémy M., Jeannière C., Lenoir S., Rey S., Saint-Marc M., Alonso F., Genot E., Thébaud N., Chevret E., Mournetas V., Rousseau B., Boiziau C. and H. Bœuf (2022): The journey of SCAPs (stem cells from apical papilla), from their native tissue to grafting: impact of oxygen concentration. Submitted.

Seeneevassen L., Giraud J., Molina-Castro S., Sifré E., Tiffon C., Beauvois C., Staedel C., Mégraud F., Lehours P., Martin O., Boeuf H., Dubus P. and C. Varon (2020): Leukaemia Inhibitory Factor (LIF) inhibits Cancer Stem Cells tumorigenic properties through Hippo kinases activation in Gastric Cancer. Cancers, Jul 22; 12 (8)/E2011. Doi: 10.3390/cancers 12082011.

Rémy M., Ferraro F. , Le Salver P. , Rey S., Genot E., Djavaheri-Mergny M., Thébaud N., Boiziau C. and H. Boeuf (2019): Isolation and Culture of Human Stem Cells from Apical Papilla under Low Oxygen Concentration Highlight Original Properties. Cells, 8, 1485.

Acharya A., Brungs S., Lichterfeld Y., Hescheler J., Hemmersbach R., Boeuf H. and A. Sachinidis (2019) : Parabolic flight-induced acute hypergravity and microgravity modulates the beating contractile rate of human cardiomyocytes. Cells. 8(4), 352-366.

Vlaski-Lafarge M, Loncaric D., Perez L., Labat V., Debeissat, C., Brunet de la Grange P., Ivanovic Z. and H. Bœuf (2019) : Bioenergetic changes underline plasticity of murine embryonic stem cells. Stem Cells,37(4):463-475.

Acharya A., Brungs S., Henry M., Rotshteyn T., Singh Yaduvanshi N., Wegener L., Jentzsch S., Hescheler J., Hemmersbach R., Boeuf H. and A. Sachinidis (2018) Modulation of differentiation processes in murine embryonic stem cells exposed to parabolic flight-induced acute hypergravity and microgravity", Stem cells and Development,15;27(12):838-847.

Hammoud AA, Kirstein N, Mournetas V, Darracq A, Broc S, Blanchard C, Zeinedine D, Mortada M and H. Boeuf (2016) Murine Embryonic Stem Cell Plasticity Is Regulated through Klf5 and Maintained by Metalloproteinase MMP1 and Hypoxia. *PloS ONE*. 11(1): e0146281.

Zeineddine D., Abou-Hammoud A., Mortada M. and H. Bœuf (2014) The oct4 protein: more than a magic stemness marker. *Am J Stem Cells*, 3 (2), 74-82.

Mathieu, ME, Faucheux, C., Saucourt, C., Soulet, F., Gauthereau, X., Fédou, S., Trouillas, M., Thézé, N., Thiébaud, P. and H. Boeuf (2013) Mras GTPase is a novel stemness marker that impacts mouse embryonic stem cell plasticity and Xenopus embryonic cell fate. *Development*, 140, 3311-3322.

Mathieu M.E., Saucourt C., Mournetas V., Gauthereau X., Thézé N., Praloran V., Thiébaud P and H. Bœuf (2012) LIF-dependent signaling: new pieces in the Lego. *Stem cell Reviews and Reports*, Mar;8(1):1-15.

Schulz, H., Kolde, R., Adler, P., Aksoy, I., Anastassiadis, K., Bader, M., Billon, N., Boeuf, H., et al, and A. K. Hatzopoulos (2009) The FunGenES database: a genomics ressource for mouse embryonic stem cell differentiation. *PloS ONE*. 4, e6804. 1-14.

Trouillas, M., C. Saucourt, B. Guillotin, X. Gauthereau, L. Ding, F. Buchholz, M.X. Doss, A. Sachinidis, J. Hescheler, O. Hummel, N. Huebner, R. Kolde, J. Vilo, H. Schultz, and H. Boeuf (2009) Three LIF-dependent signatures and gene clusters with atypical expression profiles, identified by transcriptome studies in mouse ES cells and early derivatives. *BMC Genomics.* 10(1): 73-84.

Trouillas M, Saucourt C, Guillotin B, Gauthereau X, Taupin JL, Moreau JF and Boeuf H. (2009) The LIF cytokine : towards adulthood . *European Cytokine Network*, 20, 51-62.

Teaching Activities:

UE stem cells, Master BCPP, Bordeaux (4 to 8h/ year)
UE Biotherapies, for the Physicians, Bordeaux (2 h/ year)
Master Cancer Biology (4h/ year)
Intervention in Lycées of Bordeaux for Pre-graduate students

Clinical Activities:

None

Fundings:

Fondation Gueules Cassées, (2021-2023): 65 000 Euros
AAP département STS, UBx, (2020): 15 000 Euros
ATT University of Bordeaux (2016-2018): Hypoxcell Program: 68 000 Euros
INCA, 2015-2017 : Consommables and salary : 67 000 Euros
Contrat Région Aquitaine, 2013-2015 : Equipment, : 68 000 Euros
Préciput ANR, 2013, Equipment : 35 000 Euros
Subvention FR Transbiomed, 2011-2012 : 12 000 Euros

Subvention ARC, 2009-2010 : 50 000 Euros
European program FUNGENES : 2004-2007 : 180 000 Euros

Memberships: French Society for Stem Cell Research (FSSCR), BIOMAT association

Education:

May 2000: **H**abilitation à **D**iriger des **R**echerches, University of Strasbourg, France

1989/1992: Post-doctoral internship, Professor H. Varmus, University of California, San Francisco, San Francisco, U.S.A. NIH/ CNRS fellowship.

1988 CNRS position, Research associate (CR2).

1983/1987: PhD, University of Strasbourg, Professor Claude Kedinger, IGBMC laboratory, Strasbourg, France. Strasbourg university fellowship.

1978-1982 : Engineer in Biology, Genetics, Biochemistry: C.U.S.T./ POLYTECH, University Blaise Pascal, Clermont-Ferrand, France.

Links:

Research Gate: https://www.researchgate.net/profile/Helene_Boeuf/stats/reads?date=2016-02-21