



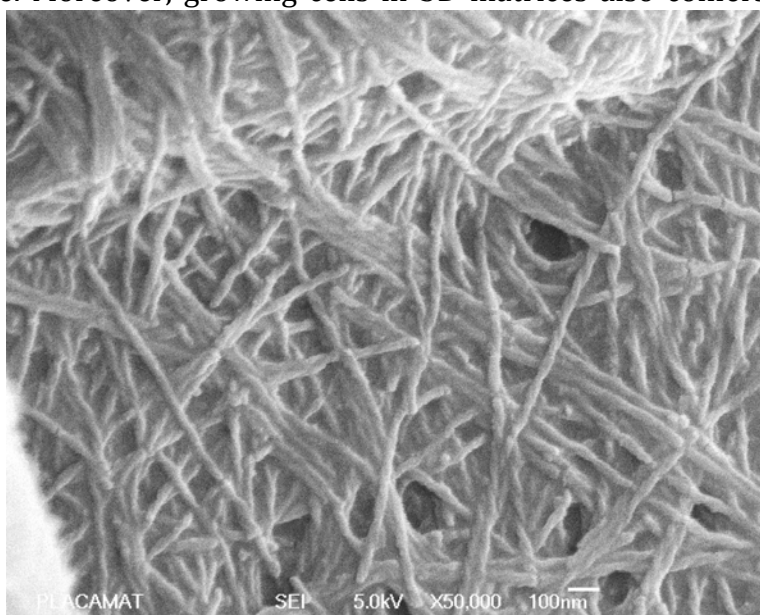
**Olivier Chassande, Ph.D.**  
Charged of Research (CR1 – CNRS)



## Research Interests:

### *Control of stem cell fate by 3D culture in hydrogel matrix*

Controlling cell fate is usually achieved by the use of cytokines, growth factors or other biochemical agents. It has become clear over the last decade that cells are exquisitely sensitive to the support on which they grow. The availability, density and pattern of cell adherence sites, the stiffness of the support are key factors determining cell fate. Moreover, growing cells in 3D matrices also confers them different properties as compared to conventional 2D culture. Hydrogels offer versatile scaffolds for cells, and their potential application for regenerative medicine stimulate the interest of researchers. Hydrogels can be obtained either from natural organisms (alginate, agarose, chitosan...) or by chemical synthesis. Whereas the majority of studies address polymers, a new generation of gels are appearing, which are obtained from small amphiphilic molecules capable of self-assembling into supra-molecular structures by tuning physical parameters such as temperature. According to the compound used as building block, a variety of structures can be obtained, characterized, at the microscopic scale, by fiber size and connectivity and, at the macroscopic scale, by elastic



moduli. These parameters, together with chemical structure and the presence of cell binding sites, determine cell behavior. The aim of this project is to determine: how the compound's chemical formula determines gel structure; 2) how the gel structure parameters control cell behavior; how gel structure modifies host tissue reactions (inflammation, angiogenesis, fibrosis) and determines gel stability. These studies are based on the collaboration between the Chembiomed group (INSERM U869), which has developed these new low molecular weight gelators, and the BIOTIS group. Our work is focused on the study of cell-gel interactions and on subcutaneous implantations in mice for the investigation of tissue reactions.

### ***Improving material compatibility using gels, molecules and cells.***

Implanting a material in a tissue generates a foreign body reaction. This reaction of the tissue is complex and occurs in several steps: as some blood is likely to be released from broken capillaries or vessels in the implantation site, platelet and complement activation are the very first events that occur, followed by clotting. Macrophages are then rapidly recruited and activated, and if they cannot resorb the foreign body, they will form giant cells. These giant cells will, in turn, stimulate the recruitment of fibroblasts and their activation towards myofibroblasts, which will deposit a thick dense matrix, forming together the fibrotic capsule. Each material elicits a different tissue response, according to its size, shape, stiffness, surface roughness, porosity, and to the molecular motifs exposed at the surface. In addition, each tissue and precise site of implantation, and the protocol used to perform this implantation, will strongly influence the cellular and molecular reactions. Therefore each new material should be assessed for the tissue reaction it triggers, choosing the appropriate model or different models, depending of the future application. Since tissue reactions will determine the success, or the failure of the material to fulfill its function, a challenge for future applications is to modify, or modulate, the tissue reaction to optimize it in order to obtain the optimal function. This usually requires modification of the material characteristics, or its association with other materials, molecules or cells which will promote a more favorable environment for the material. My favorite approach to improve biocompatibility is to coat materials with smart hydrogels, which provide protection from the immune system, but which can also bring bioactive molecules or cells to create a more favorable environment. I focus on physical gels, produced by the self-assembly of low molecular weight amphiphilic glycol-nucleo-lipids into supramolecular structures resulting in interconnected fibrillary miscelles. These gels show unusual physical properties, and are biocompatible. Furthermore, they are cell-compatible and can be used as a reservoir for large molecules such as growth factors. We use these gels to coat gold electrodes, with the aim of designing implantable biosensors for diabetic patients. We plan to include angiogenic growth factors to promote vascularization around the implanted device, and aggregated mesenchymal stem cells to hinder immunological reactions of the host.

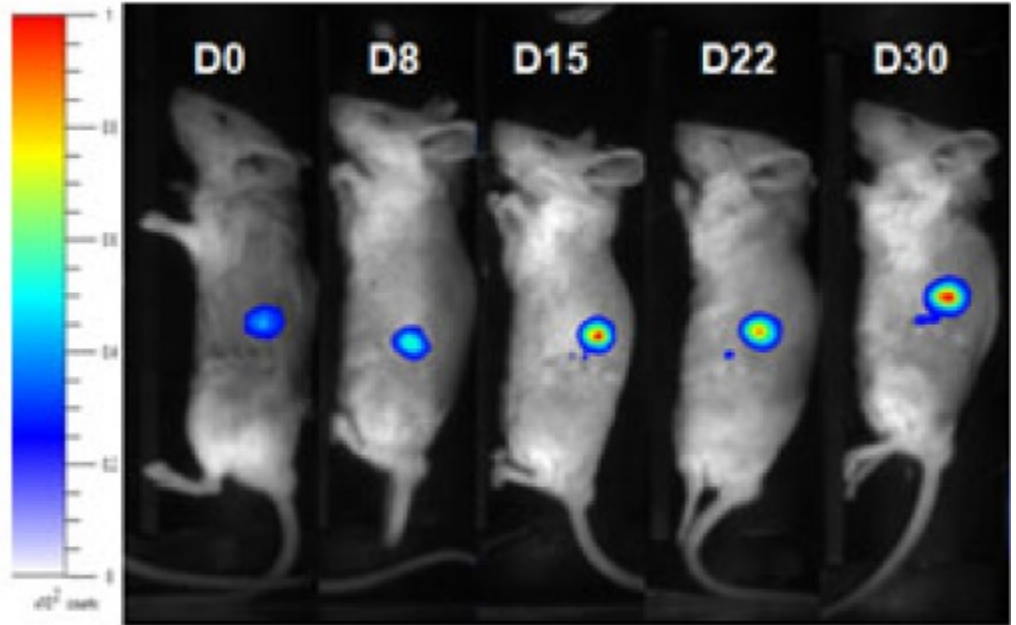


A thread of human CAM can be spooled and used as a suture or can be assembled in a complex tridimensional tissue using classic textile technologies (weaving, braiding, knitting) to create human textiles.

## *In vivo imaging of cells, bone, materials and physiopathological processes*

Designing new products for regenerative medicine implies challenging them in tissues before taking them to clinical trials. Many pre-clinical animal models can be set up to provide evidence for the functionality or efficiency of our favorite new products. However most of the procedures used to evaluate these products are based on histology. This means long, tedious experiments, this requires that you determine at what age you are going to kill the animals, and if you want to investigate several time points you will need a large number of animals, a lot of money, and a lot of “hands”. An

alternative to analyses at discrete time points is longitudinal follow-up, using imaging techniques. Imaging devices and tools are expanding in biology and medicine. In the past, our laboratory has experienced MRI as a useful tool to follow material integration, degradation, and inflammatory reaction, taking advantage of the strong experience, skills and involvement of the



CNRS UMR 5536. I wish to set up more tools and methods to get more information on tissue reaction and on the fate of implanted materials and cells, taking advantage of other another local strong expertise in the field of bioluminescence and tomo-fluorescence. It is indeed possible to label the cells you implant with either a cell labeling fluorescent agent, or by genetically inserting the gene coding for a fluorescent protein or for the luciferase enzyme, using lentiviruses. You can then track those cells both in vitro in complex 3D scaffolds, and in vivo provided your cells are implanted in a superficial site. We have used the genetically labeling method in several studies. The next step will be to use available chemical fluorescent probes which can provide quantitative assessment of several important physio-pathological processes: inflammation, vascularization, apoptosis, hypoxia, bone formation. All these processes can be revealed by specific probes coupled to fluorochromes. These probes can be visualized using tomo-fluorescence devices, which allow precise localization and quantification of the signal. Such equipment is available at the VIVOPTIC platform (IBIO, UMS 3428). Since probes are commercially available, the next step is the implementation of these tools and application to our biomaterials.

### **Keywords/expertise:**

- Animal experimentation
- Mouse genetics models
- In vitro/in vivo bioluminescence,
- In vitro/in vivo fluorescence
- Hydrogels
- Molecular biology

## Selected publications:

- 1- Wystrychowski, W., McAllister, T.N., Zagalski, K., Dusserre, N., Cierpka, L., and L'Heureux, N. First human use of an allogeneic tissue-engineered vascular graft for hemodialysis access. *J Vasc Surg*, (60), 1353-1357 (2014).
- 2- Peck, M., Gebhart, D., Dusserre, N., McAllister, T.N., and L'Heureux, N. The evolution of vascular tissue engineering and current state of the art. *Cells Tissues Organs*, (195), 144-158 (2012).
- 3- Wystrychowski, W., Cierpka, L., Zagalski, K., Garrido, S., Dusserre, N., Radochonski, S., McAllister, T.N., and L'Heureux, N. Case study: first implantation of a frozen, devitalized tissue-engineered vascular graft for urgent hemodialysis access. *J Vasc Access*, (12), 67-70 (2011).
- 4- Peck, M., Dusserre, N., McAllister, T.N., and L'Heureux, N. Tissue engineering by self-assembly. *Materials Today*, (14), 218-224 (2011).
- 5- McAllister, T., Iyican, C., Dusserre, N., and L'Heureux, N. Regulatory Challenges for Cell-Based Therapeutics. In *Stem Cell and Tissue Engineering*, S. Li, N. L'Heureux, and J. Elisseeff, eds. (World Scientific Publishing Co.), pp. 423-440 (2011).
- 6- Li, S., L'Heureux, N., and Elisseeff, J., eds. *Stem Cell and Tissue Engineering*. (World Scientific Publishing Co.) (2011).
- 7- Kellar, R.S., Lancaster, J.J., Goldman, S., McAllister, T., and L'Heureux, N. Cardiovascular Tissue Engineering. In *Comprehensive Biomaterials*, P. Ducheyne, K.E. Healy, D.W. Hutmacher, D.W. Grainger, and C.J. Kirkpatrick, eds. (Elsevier), pp. 361-376 (2011).
- 8- Dusserre, N., McAllister, T., and L'Heureux, N. Quality Control of Autologous Cell- and Tissue-Based Therapies. In *Stem Cell and Tissue Engineering*, S. Li, N. L'Heureux, and J. Elisseeff, eds. (World Scientific Publishing Co.), pp. 397-422 (2011).
- 9- McAllister, T.N., Maruszewski, M., Garrido, S.A., Wystrychowski, W., Dusserre, N., Marini, A., Zagalski, K., Fiorillo, A., Avila, H., Mangano, X., Antonelli, J., Kocher, A., Zembala, M., Cierpka, L., de la Fuente, L.M., and L'Heureux, N. Effectiveness of haemodialysis access with an autologous tissue-engineered vascular graft: a multicentre cohort study. *Lancet*, (373), 1440-1446 (2009).
- 10- Konig, G., McAllister, T.N., Dusserre, N., Garrido, S.A., Iyican, C., Marini, A., Fiorillo, A., Avila, H., Wystrychowski, W., Zagalski, K., Maruszewski, M., Jones, A.L., Cierpka, L., de la Fuente, L.M., and L'Heureux, N. Mechanical properties of completely autologous human tissue engineered blood vessels compared to human saphenous vein and mammary artery. *Biomaterials*, (30), 1542-1550 (2009).
- 11- L'Heureux, N., McAllister, T.N., and de la Fuente, L.M. Tissue-engineered blood vessel for adult arterial revascularization. *N Engl J Med*, (357), 1451-1453 (2007).
- 12- L'Heureux, N., Dusserre, N., Konig, G., Victor, B., Keire, P., Wight, T.N., Chronos, N.A., Kyles, A.E., Gregory, C.R., Hoyt, G., Robbins, R.C., and McAllister, T.N. Human tissue-engineered blood vessels for adult arterial revascularization. *Nat Med*, (12), 361-365 (2006).
- 13- L'Heureux, N., Paquet, S., Labbe, R., Germain, L., and Auger, F.A. A completely biological tissue-engineered human blood vessel. *FASEB J*, (12), 47-56 (1998).

## Patents:

- 1- McAllister, T., and L'Heureux, N. Tissue engineered cellular sheets, and methods of making same. USPTO Patent No. 8,076,137 (December 13, 2011).
- 2- McAllister, T., and L'Heureux, N. Bioreactor for the manufacture of tissue engineered blood vessels. USPTO Patent No. 7,744,526 (June 29, 2010).
- 3- McAllister, T., and L'Heureux, N. Tissue engineered cellular sheets, methods of making and use thereof. USPTO Patent No. 7,504,258 (March 17, 2009).
- 4- McAllister, T., and L'Heureux, N. Method of culturing cells to produce a tissue sheet. USPTO Patent No. 7,166,464 (January 23, 2007).
- 5- McAllister, T., and L'Heureux, N. Tissue engineered blood vessels and apparatus for their manufacture. USPTO Patent No. 7,112,218 (September 26, 2006).
- 6- McAllister, T., and L'Heureux, N. Tissue engineered blood vessels and methods and apparatus for their manufacture. USPTO Patent No. 6,503,273 (January 7, 2003).
- 7- L'Heureux, N., Auger, F.A., and Germain, L. Production of a contractile smooth muscle. USPTO Patent No. 5,618,718 (April 8, 1997).

## Education:

1991-96	Ph.D. in Molecular & Cell Biology	Université Laval, Québec, Canada Laboratoire d'Angiogenèse Expérimentale / LOEX
1994	Internship (3 months)	Université Louis Pasteur de Strasbourg, France UMR CNRS 7034 (Pr. J-C Stoclet)
1989-91	M.Sc. in Immunol. & Cell Biology	Université Laval, Québec, Canada Laboratoire d'Angiogenèse Expérimentale / LOEX
1990	Internship (3 months)	Université Claude Bernard, Lyon, France INSERM U209 (Pr. J. Thivolet)
1986-89	B.Sc. in Biochemistry	Université Laval, Québec, Canada

## Links:

Linkedin: [https://www.linkedin.com/in/nicolas-l-heureux-199554b?trk=nav\\_responsive\\_tab\\_profile](https://www.linkedin.com/in/nicolas-l-heureux-199554b?trk=nav_responsive_tab_profile)

ResearchGate: [https://www.researchgate.net/profile/Nicolas\\_LHeureux](https://www.researchgate.net/profile/Nicolas_LHeureux)

BxCR: Bordeaux Consortium for Tissue Engineering: <https://bcm.u-bordeaux.fr>

BIOMAT : The French association for the development of biomaterials, Tissue Engineering and Regenerative Medicine: <http://www.biomat.fr>