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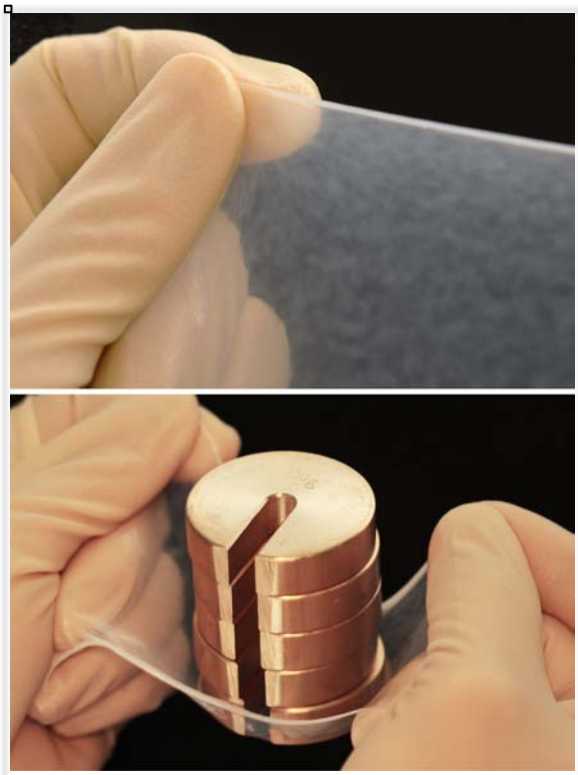
Research Interests:

Cell-assembled extracellular matrix (CAM)

My interests have always been centered on the use of human cells to produce tissue-engineered constructs for therapeutic applications. My experience has been focused on the field of cardiovascular tissue engineering but I like to also dabble in other areas. For over 20 years, I have worked on using the extracellular matrix produced by normal human cells in culture. This cell-assembled matrix (CAM) is a unique material that can have remarkable mechanical strength when produced in the right culture conditions. I have used this CAM to produce small-diameter, tissue-engineered blood vessels (TEBV) that display burst pressures similar to the of native human blood vessels, but without the need for any exogenous scaffolding such a synthetic polymers or animal/cadaveric tissues(see below "selected publication" #10 and 13). Because they do not include foreign materials, because the CAM is not chemically or otherwise denatured, and because the CAM is of human origin, we would not expect constructs build following this approach to trigger a response from neither the adaptive nor the innate immune system (1). I spent 15 years as the co-founder and Chief Scientific Officer of Cytograft Tissue Engineering (San

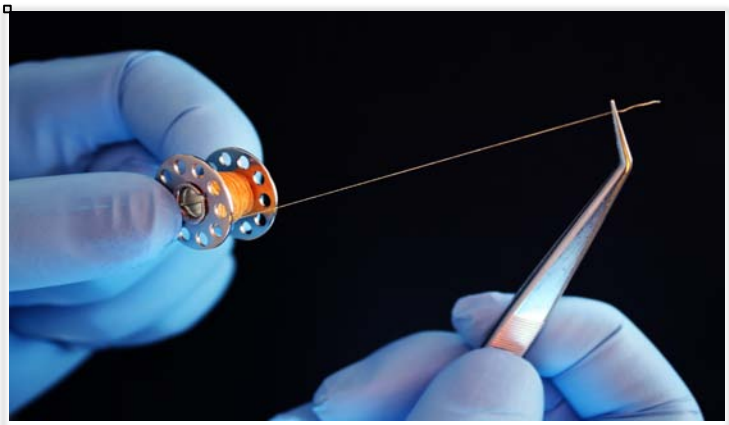


A sheet of human CAM is a true bio-material that can have remarkable mechanical properties while avoiding immune and inflammatory reactions. (from review: *Cells Tissues Organs* 195, 144-158, 2012)

Francisco, California) driving the R&D effort to bring these TEBVs to the clinic. These CAM-based TEBVs were the first completely biological TEBVs to be implanted in humans and the first TEBVs to be implanted in the high-pressure arterial system (11). These TEBVs have shown remarkable patency as arteriovenous shunt for hemodialysis of end stage renal disease patients with durability of up to 3 years (11).

Thread-Based Tissue Engineering: or how to make Human Textiles.

The CAM is produced at the bottom of culture flasks as sheets of various shapes and sizes. The sheets can be cut, stacked, folded or, like in the case of the above-mentioned blood vessel, rolled to create a variety of tissues. In the specific case of TEBVs, the sheet-based approach has a significant drawback: the need for a long culture period (maturation) to allow the cells to fuse the different layers of sheets together. In addition, fusion is limited to a certain depth because of transport issues, which entails a two-layer strategy to create thicker tissues. At BioTis (U1026), I am now developing a new production method based on the use of threads of CAM instead of sheets. Taking advantage of various textile technologies (weaving, knitting, braiding), we can literally produce human textiles with a wide range of geometries, porosities, (anisotropic) mechanical properties, and all that with regional tunability. In addition, because threads can be connected to each other, the size of the constructs is no longer limited to the size of culture flasks. But the most interesting advantage of this thread-based approach is the fact that the cohesion of the constructs does not rely on a maturation phase and is not hindered by transport limitations. Indeed, the textiles are ready for use as soon as they are assembled, which takes the production time of the TEBV from roughly 6 months to about 2 months (or even less). The development of a thread-based TEBV is one of the main research projects in my group. However, because this approach can provide near-native conjunctive tissue in a wide range of configurations, we are also exploring other applications in Regenerative Medicine.

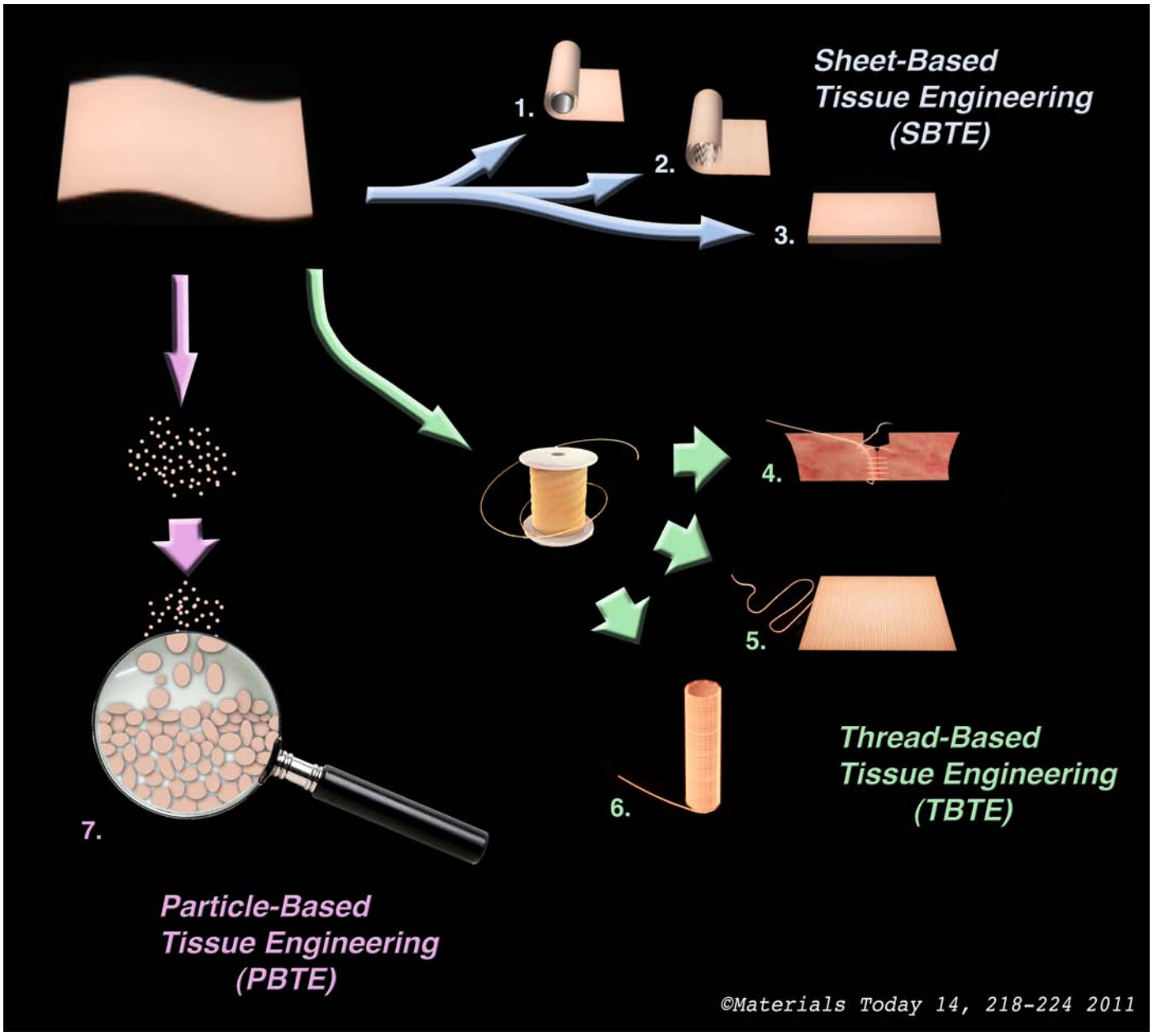


A thread of human CAM can be spooled and used as a suture or can be assembled in a complex tridimensional tissue using classic textile technologies (weaving, braiding, knitting) to create human textiles.

Particle-Based Tissue Engineering: moldable and injectable.

Human CAM can also be produced in the form of particles that can be molded or injected. This particle-based approach can be used to produce porous structures for tissue engineering or can even be injected directly *in vivo* to create new tissues. This has obvious aesthetic applications but also tissue reconstruction and cell-delivery applications.

Below is schematic representation of the various building strategies we have developed using CAM:



Keywords/expertise:

- Human cell culture
- Bioreactors
- Cardiovascular biology
- Endothelium
- Fibroblasts
- Smooth muscle cells
- Tissue-engineering
- Bioengineering
- Regenerative Medicine
- Cell-based therapies
- Vascular graft
- Extracellular matrix
- Collagen
- Histology
- Immunofluorescence
- Electron microscopy
- Mechanical properties
- Mechanical stimulation
- Pre-clinical studies
- Clinical trials
- Translational medicine
- Entrepreneurship
- Startup
- Patents
- Technology transfert

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).

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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:

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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'Angiogénèse 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'Angiogénèse 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

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ReaserchGate: https://www.researchgate.net/profile/Nicolas_LHeureux

BxCR: Bordeaux Consortium for Tissue Engineering: https://bcrm.u-bordeaux.fr

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