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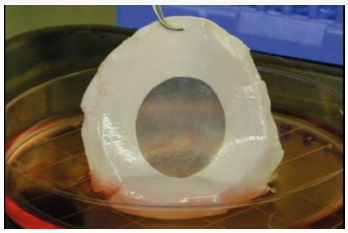


A CGMP FACILITY FOR PERSONALIZED TISSUE ENGINEERING: HEALING PATIENTS' WOUNDS WITH TISSUES PRODUCED IN THE LAB

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ABSTRACT

Patients who are severely burned over 80% of their total body surface area require autologous grafts to cover their wounds with their own cells. Patients with a visual deficit due to limbal stem cell deficiency need an autologous corneal epithelial graft to restore their sight. Other individuals suffer from damaged tissues (adipose tissue, bladder, sectioned nerve, etc.) that must be replaced in order to restore their health. The LOEX/*CHU de Québec-Université Laval* has developed methods to reconstruct tissues in the laboratory. However, the Health Canada regulatory agency requires that tissues grafted on patients be produced in specialized laboratories following the Good Manufacturing Practices (**GMP**) standard and practices. Therefore, in order to continue our innovative development of personalized tissue engineering and assess the breakthrough potential of tissues engineered by our internationally dominant technology, the self-assembly approach, our overall objective is to build specialized GMP laboratories that will allow us to advance our clinical research in order to concretize the translation of discoveries for the benefit of patients.

PROJECT

For more than 30 years, researchers at the LOEX/*CHU de Québec-Université Laval* (CHU-UL) have been working to reconstruct tissues in the laboratory in order to transplant them in patients to heal tissue deficits. The first tissue to be replaced was the epidermis, which allowed severe burn victims to heal more quickly. Over time, other tissues have been developed and are being evaluated in clinical trials.

The CHU-UL is the only facility in Canada currently producing autologous tissues reconstructed by tissue engineering *in vitro* that are transplanted in humans. The treatments we develop permit us to replace failing or inexistent tissues with new laboratory-cultured tissues whose properties are similar to those of the native tissue. This unique expertise means that we can transplant tissues whose cells are already organized in a three-dimensional structure, which favors the retention of stem cells and thus the long-term maintenance and renewal of the tissue once grafted in the patient. In addition, since the cells used in the graft come from the patient, the tissues will not be rejected and will remain in place over the long term. The treatments are therefore both personal and permanent.

The reconstructed tissues are currently produced in clean rooms on the site of the *Hôpital de l'Enfant-Jésus*. These clean rooms have the proper infrastructure (high ventilation, sterility) and are used according to very strict operating specifications [standard operating procedures (**SOP**)] but they have not been validated, due to a lack of funding at the time of construction. These rooms are used for Phase I/II clinical research in Canada. However, for Phase III clinical trials or once clinical trials are completed, Health Canada requires higher standards. At this level, tissues must be produced in rooms validated according to GMP standards.

Ensuring the safety and efficacy of therapeutic products intended for human use requires compliance with quality standards. These measures to ensure quality should cover all aspects and stages of production in order to ensure the proper design, monitoring and control of manufacturing processes and facilities. GMP regulations are the international benchmark for quality management, and compliance with these regulations requires that proper procedures have been consistently followed at every stage of the manufacturing process.

This infrastructure project will include three GMP rooms as well as the equipment necessary for the production, quality assurance and quality control of human tissues reconstructed in the laboratory. The equipment and the validation of the rooms are already being subsidized by the Canada Foundation for Innovation for the amount of $11.775M. The facility will be close to the clean room of the LOEX that is located on the site of the *Hôpital de l'Enfant-Jésus du CHU de Québec.* In collaboration with the CHU Foundation, we are looking for 20% of the building cost. **The total cost of the construction is $20 M. The grant requires that 20% of the cost ($4 M) be provided by one or several partners.**

WHAT WILL THESE ROOMS BE USED FOR?

In the past years, several patients burned over more than 50% of their body have been treated with skin reconstructed in our laboratory. When a large surface area is burned, the classical method of treatment, the autograft, is not sufficient to cure these patients. LOEX researchers then intervene by producing reconstructed skin in the laboratory from the patient's own cells cultured from a small skin biopsy. It is currently possible to produce this skin for patients as a phase I/II clinical trial is underway to assess its effectiveness. The preliminary results obtained show that the treatment is effective and allows burn closure without generating pain (donor sites used to harvest autografts are very painful), nor pathological scars (often leading to corrective surgery). However, this pan-Canadian clinical trial will soon come to an end and, following the presentation of the results obtained to Health Canada, the researchers will have to carry out a phase III clinical trial. Tissues will then have to be produced in GMP rooms.

The eye is covered by the transparent cornea, and stem cells are necessary for its regeneration. In the event of stem cell loss (burn, disease), the cornea loses its transparency, which compromises vision and causes pain for patients. This rare condition (10/10,000) is called limbal stem cell deficiency. Researchers have developed a corneal epithelial culture autograft (CECA) which, after transplantation, can restore stem cells in these patients and improve, or even restore, sight. This first in Canada is being evaluated in a phase I/II clinical trial. About 25 CHU-UL patients have already benefited from this innovative treatment and others are being treated as part of a clinical trial whose patients are recruited not only in Quebec City but also in Montreal and Toronto. In the near future, we

expect to have Health Canada approval to evaluate the effectiveness of CECA on a larger number of patients in a phase III clinical trial which will require production of the tissue in GMP rooms.

Dystrophic epidermolysis bullosa is a rare genetic disease in which a protein mutation prevents proper adhesion between the dermis and epidermis. The skin becomes fragile and peels off easily following friction. Children affected by this syndrome are called butterfly children, their skin being fragile like the wings of a butterfly. They suffer from permanent sores and there is no treatment for this disease. Our strategy aims to use gene therapy to correct the patient's skin cells. These corrected cells will be used to reconstruct genetically modified skin that will then be grafted in patients to provide them with permanent recovery. The research work is very promising, and the LOEX researchers are almost ready to start a phase I/II clinical trial. One of the 3 GMP rooms of the current infrastructure project will be for gene therapy.

Other projects are currently being evaluated in order to better treat patients (ulcers, bladder replacement, prolapsed bladder, urethra, tissues for filling deficits created by cancer resection, repair of peripheral nerve lesions, etc.). These projects are still at the preclinical level but phase I/II clinical trials could begin in the coming years.

In conclusion, the LOEX at the CHU-UL is a pioneer in the production of tissues in the laboratory. It develops innovative treatments through personalized tissue engineering. These GMP rooms are essential for these clinical applications to become available in Quebec and Canada. Help us heal severe burns, and people suffering from problems that affect their vision or from genetic skin diseases.

FINANCIAL NEEDS

For this project, the budget is divided in 2 parts. The first part has been secured following a highly selective Canadian competition. The Canada Foundation for Innovation (CFI) with its partners (the Quebec Government and the private sector) approved a $11.775 M grant for acquiring the specialized equipment necessary to produce personalized tissue-engineered substitutes in the GMP facility.

The second part ($20 M) is required for building the facility in which the equipment bought through the CFI grant will be located. **The grant requires that 20 % of the cost be provided by one or several partners. Thus, we are seeking sponsors/donors to participate in providing the 20 % ($4 M).**

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