Michael A. Laflamme: “Sooner or later we will manage to regenerate the heart”

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Michael A. Laflamme's research at Toronto University's McEwen Stem Cell Institute (Canada) focusses on the development of new therapies for heart failure after a heart attack, based on human pluripotent stem cells (hPSC) as hPSC are the only stem cell type capable of differentiating into large quantities of phenotypically unambiguous cardiomyocytes. His aim is to restore the electrical and contractile function of injured hearts by "remuscularizing" the infarct scar with hPSC-derived cardiomyocytes.

His laboratory has already made a number of important advances in this area, including the development of efficient protocols to guide hPSCs into cardiomyocytes and specialized cardiac subtypes, proof-of-concept transplantation studies with hPSC-derived cardiomyocytes in rodent myocardial infarction models, and the first direct demonstration that hPSC-derived cardiomyocytes can become electrically integrated and activate synchronously with host myocardium in injured hearts. His current work is based on these successes and is bringing us closer to feasible cell therapy.

- **How near or far are we from being able to regenerate the heart?**

I think we are going to manage it sooner or later. It is a challenge but there is a lot of very promising research underway. Our laboratory focusses on administering endogenous cells, heart muscle cells, to treat myocardial infarction. There are other groups following other, more endogenous, lines of work, which are attempting make cardiomyocytes recover their capacity to divide. All of these approaches have their challenges, but I am convinced that we are close. In my opinion, there is no fundamental reason why we can't achieve.

- **What exactly is your approach?**

We work with heart muscle cells that we are generating from pluripotent stem cells, which are special because they can differentiate into any type of cell found in an adult. There are two types of pluripotent stem cells: embryonic stem cells, derived from surplus in vitro fertilization embryos, and induced pluripotent stem cells (iPS cells), which can reprogramme themselves from ordinary somatic cells, such as skin or blood cells, to become the equivalent of embryonic stem cells.

We have had great success guiding these cells to become useful ones, such as cardiomyocytes. I was one of the first to work on these cells, in 2002. At that time, even obtaining a small percentage of heart muscle cells was an enormous achievement. Now, we can reach a purity higher than 95% and produce thousands of millions of these cells in a month. The challenge facing us now is to transfer these cells to animal myocardial infarction models, ensuring delivery and proper integration into the heart.

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- **Are these cells the same as the ones in the heart?**

Not exactly the same ones as in an adult heart, but similar to the cells found in early foetal development. One challenge is their immature phenotype. We have been working on ways to mature these cells. In addition, the heart is made up of various types of cell, not only cardiomyocytes. There are other types of cell that carry out important functions, such as immune cells, fibroblasts and vascular cells. We can generate all of these cells from iPS or embryonic cells. This allows us to start contemplating co-administration of these cells. During the first 10-15 years in the laboratory, we focussed on obtaining a population of cardiomyocytes that was as pure as possible. Now we are going in the opposite direction, we want to control what types of non-cardiomyocyte cell are present.

- **Will future transplants include all of these types of cell?**

That is the aim. Although cardiomyocytes naturally attract other types of cell, co-delivery could accelerate the process.

- **What results have you had in experimental models?**

The outcomes are promising. Cells can form new myocardium in infarction areas and electrically integrate with the heart, improving contractile function. However, our main challenge are arrhythmias, particularly in large animal models..

- **How are you approaching the problem of arrhythmias?**

We have tried many solutions. An effective approach is to mature the cells before transplantation. This reduces the arrhythmias and improves the general results. We also use conventional antiarrhythmic drugs, which significantly help.

- **What about long-term risks, like cancer?**

Tumorigenesis is always a concern when using products based on pluripotent stem cells, but it isn't our main worry. We have seen tumours in our extensive studies with animals. Our efforts focus on efficiently guiding these cells towards the desired ones, minimising risk.

- **Does cell transplant the only solution for heart disease?**

There are other approaches, such as heart transplant, xenotransplantation, ventricular assistance devices and stimulation of endogenous repair. Different clinical scenarios may require different solutions.

- **¿When did your interest in medical science and heart diseases begin?**

I've always loved science. At university I followed a combined course of medicine and postgraduate studies at Emory. During that period, you visit different laboratories and do rotations in them. To be quite honest, the reason I probably ended up in heart research is because, when you spend time in those labs, you can be working with neurons, which obviously have important functions, or with epithelial cells, or whatever, in a laboratory that works with cardiomyocytes I discovered what cardiomyocytes do that other types of cell don't: they contract. I remember having felt captivated by the instant gratification, by seeing something in action before my eyes. It grabbed my imagination.

And the same thing happened when I finished medical school and postgraduate studies. I did a residency in anatomical pathology, and I became a pathologist specialized in cardiac pathology. I was working in a laboratory, and I remember the first time we had a plate of beating cardiomyocytes obtained from stem cells. To this day I never tire of seeing them beat. If I have a bad day, I like to go to the lab and look through the microscope to see a beating culture.

The real motivation is that heart disease is obviously very serious. There is an urgent need for therapies. I don't see patients in my clinical role, but in my role as cardiac pathologist, I see the worst results. I see the hearts of people who have had to undergo a heart transplant or, worse yet, I perform autopsies. Many of these people die of heart failure. As I observe these sick hearts, I hope to contribute in some way.

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