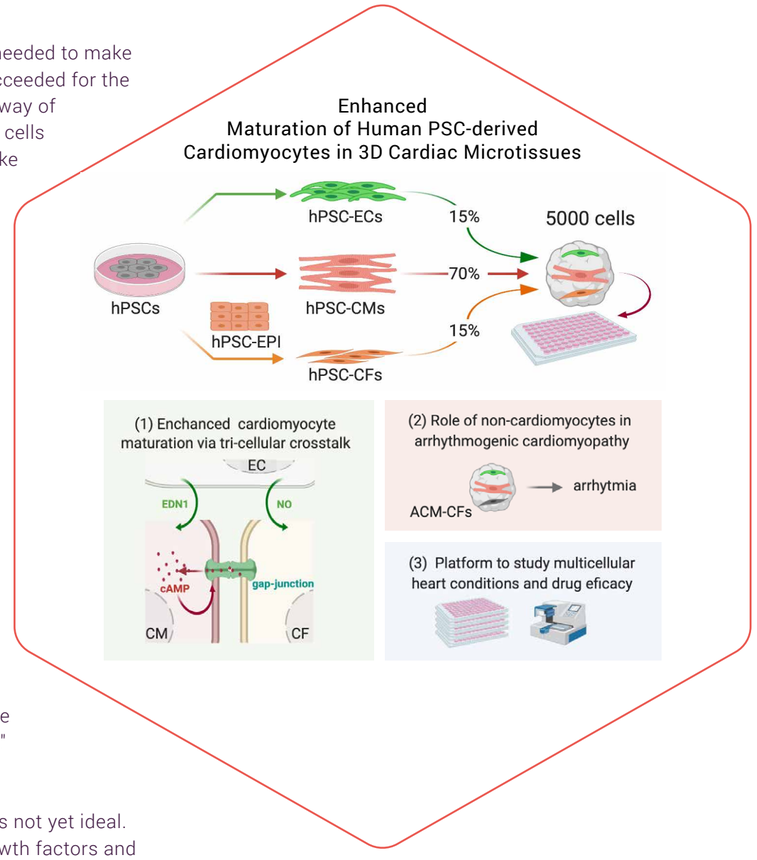
Mini-hearts from human stem cells: towards future disease models and drug discovery

The 14th of February 2001 was an extraordinary Valentine's Day. On that day, Professor of Developmental Biology Christine Mummery (LUMC) and her team succeeded in developing embryonic stem cells into beating heart cells. "The efficiency was still low; only 5% of the heart cells were beating, but it was an essential first step. The big surprise came in 2018: we then succeeded in growing the cardiomyocytes themselves - the beating heart cells - and the blood vessels and connective tissue cells. With this, we had our mini hearts that allow us to control diseases in great detail, discover new drugs and take steps towards personalised medicines."

In 2000, Mummery introduced human embryonic stem cells in the Netherlands and received the first licence to develop new cell lines from surplus IVF embryos. Four cell lines were developed; much of the work on these cell lines involved their differentiation into cardiomyocytes. She then went on to improve the process with defined reagents, and increased efficiency and reproducibility resulting in a reasonable success in transplanting cells into the hearts of mice in 2007. The aim was to repair the heart after myocardial infarction. Mummery: "Unfortunately, the results were disappointing. We did manage to place the cells in the hearts of the mice, and we also saw some improvement in heart function, but ultimately after one month, there was no significant difference in the natural recovery process after myocardial infarction."

New perspectives for cell therapy

Nevertheless, the team persevered. After her sabbatical at the Harvard Stem Cell Institute, Mummery decided to stop focusing on embryonic stem cells and to continue developing human induced pluripotent stem cells (hiPS cells). This was partly in response to the publication of Shinya Yamanaka with promising study results with hiPS cells (https://pubmed.ncbi.nlm.nih.gov/33007237/). "George Daley of the Harvard Stem Cell Institute gave me all the 'ingredients' needed to make hiPS cells. Back in the Netherlands, we succeeded for the first time: we were able to apply the same way of differentiation as with the embryonic stem cells and thus take over everything 1-to-1 to make cardiomyocytes from hiPS cells. This offered new perspectives for cell therapy and, especially in the short term, new insights into diseases because we could now also make hiPS cells from patients with, for example, heart disease. We published about this for the first time in 2009 (https://pubmed.ncbi.nlm.nih.gov/19449339/). Soon after, I wanted to see to what extent we could study genetic diseases and possibly discover new medicines. We took hiPS cells from patients who had mutations in important heart genes such as ion channels and then went on to repair the mutation genetically. The results showed that we saw almost the same defect in the hiPS cells derived from cardiomyocytes as in the patient. This was a brilliant observation! We knew we could use hiPS cells for much research from then on."



Adult cardiomyocytes

It was a significant step, but the model was not yet ideal. Mummery: "We were still using natural growth factors and supplements to grow the cells, so every new batch had to be re-optimised. This took a lot of time. Also, the cells were still very immature; they corresponded to foetal heart cells of 16-18 weeks old, whereas most heart diseases develop after birth or at an older age. Because the heart cells did match, an entire complement ion channel was present in the heart cell. Therefore, they could be used to study the side effects of drugs on the heart, for example. We have done several publications on cardiotoxicity studies. These successes have convinced regulatory authorities in some countries that using a human model system of the heart is better than other models. The FDA, for example, has changed its regulations based on that robust data."

"Fundamental research is fantastic: you have all the freedom - your only limitation is your imagination - and it is fantastic to make this journey of discovery together"

Christine Mummery *is a Professor of Developmental Biology, Founding Editor in Chief of Stem Cell Reports, and she serves on the Editorial (Advisory) Boards of Stem Cell, Stem Cells, Circulation Research among others. She also holds board positions at the Hubrecht and Gurdon Institutes and several foundations. This year, she has been nominated for the Ariens Award.*