From cells to organ... in a dish!

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What is the problem?

The immune system protects our body against infections and diseases. To do so, the immune system relies on a small, often overlooked organ, called the thymus (see Figure 1). The thymus makes T cells, the defence cells that our body needs to fight off infections caused by bacteria, viruses and parasites.

The thymus makes a lot of T cells during childhood to help build our immune system.

However, as we get older our thymus slowly shrinks and becomes filled with fat cells. This means that less T cells are made, making it harder to fight off new infections and illnesses (see Figure 2). This natural aging of the thymus greatly affects immunocompromised patients, who need to boost their impaired immune system by making a lot of new T cells. Unfortunately, there is currently no therapy to help the aging thymus make more T cells.

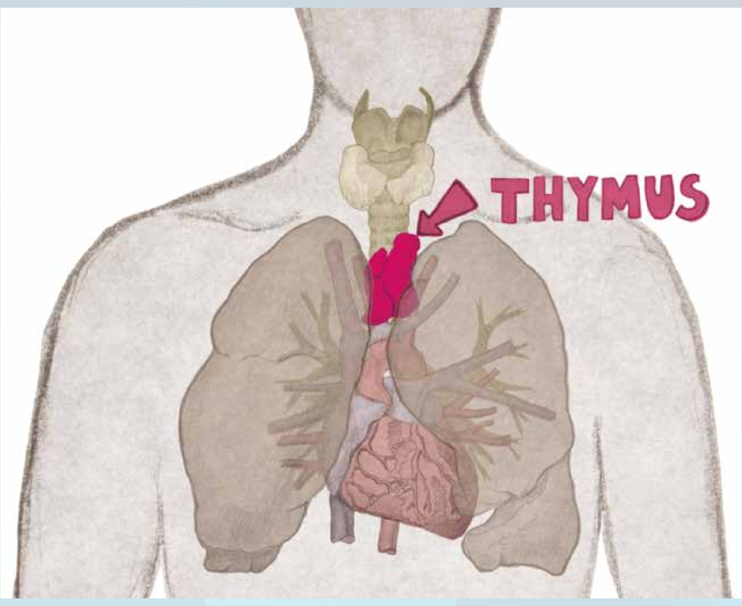

Figure 1 The thymus.

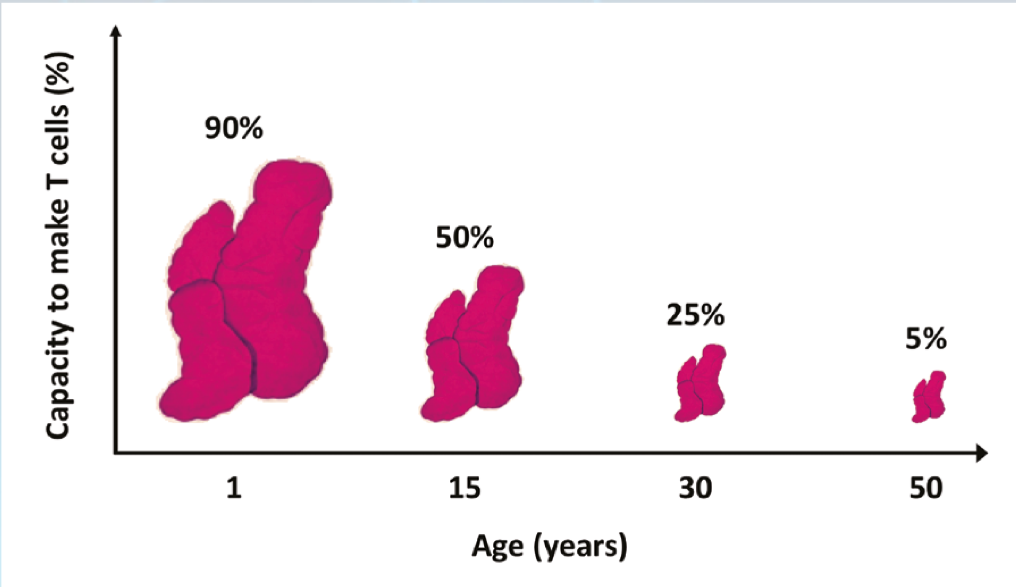

Figure 2 Natural aging of the thymus.

What are we interested in?

We want to develop strategies to repair or replace the aging thymus in immunocompromised patients.

The thymus is made up of a type of cells called thymic epithelial cells. We know that thymic epithelial cells are needed to make T cells. We also know that a protein called FOXN1 is needed to make thymic epithelial cells (see Figure 3).

A few year ago, scientists from our group made a groundbreaking discovery: they found that they could use cellular reprogramming to change a type of cells called fibroblasts into engineered thymic epithelial cells in a dish, and that these engineered cells could grow into a new thymus in a mouse (see Figure 4)!

We now want to build on these exciting findings to develop an efficient way to make a thymus in a mouse using cells that could be used to treat patients in the future.

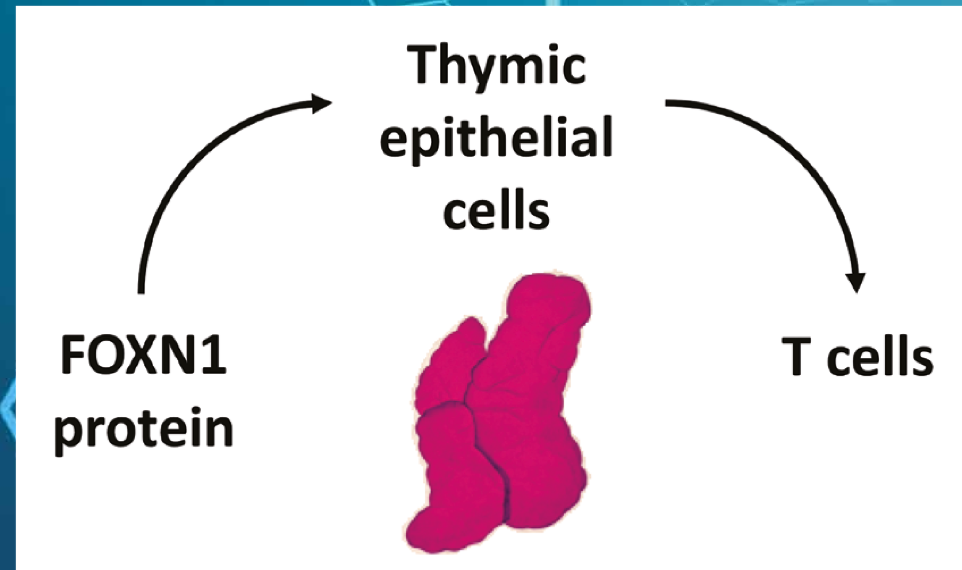

Figure 3 Key components of a healthy thymus.

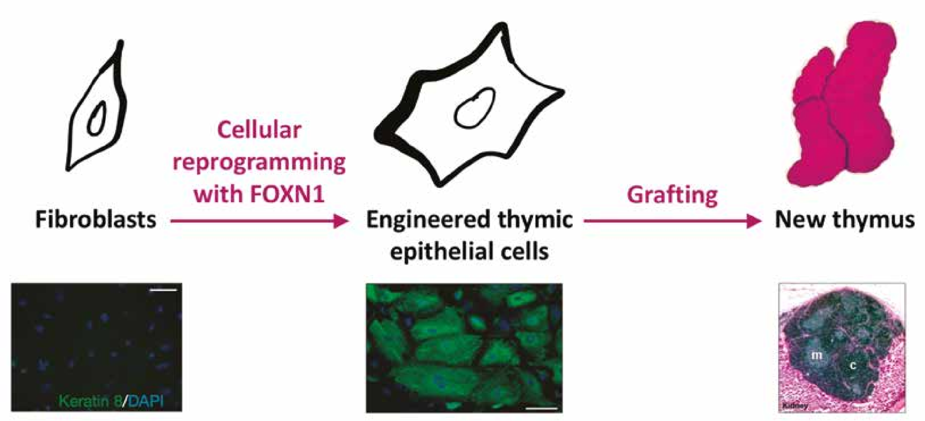

Figure 4 Growing a thymus in a mouse using engineered (reprogrammed) thymic epithelial cells (image adapted from Bredenkamp et al., 2014, Nature Cell Biology).

What did we do?

We tested whether it was possible to use pluripotent stem cells to create a new thymus in a mouse. Pluripotent stem cells can develop into any type of cells in our body, so they are a good starting material for our experiments (see Figure 5).

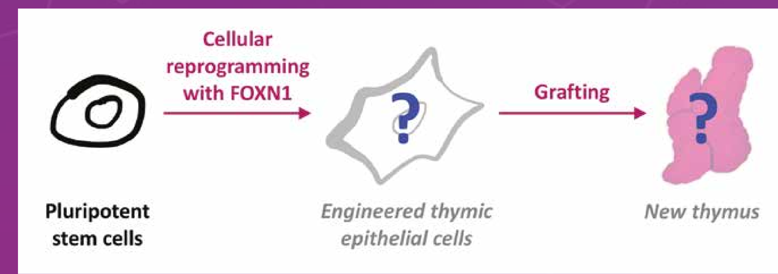

Figure 5 Can pluripotent stem cells be used to grow a new thymus in a mouse?

What did we find?

We first found that cellular reprogramming with the FOXN1 protein could transform mouse pluripotent stem cells into engineered thymic epithelial cells in a dish (see Figure 6). We then showed that these engineered thymic epithelial cells could make T cells in a dish (see Figure 7).

We have now just started testing whether these engineered thymic epithelial cells could grow into a new thymus in a mouse. We do not have results yet, but watch this space!

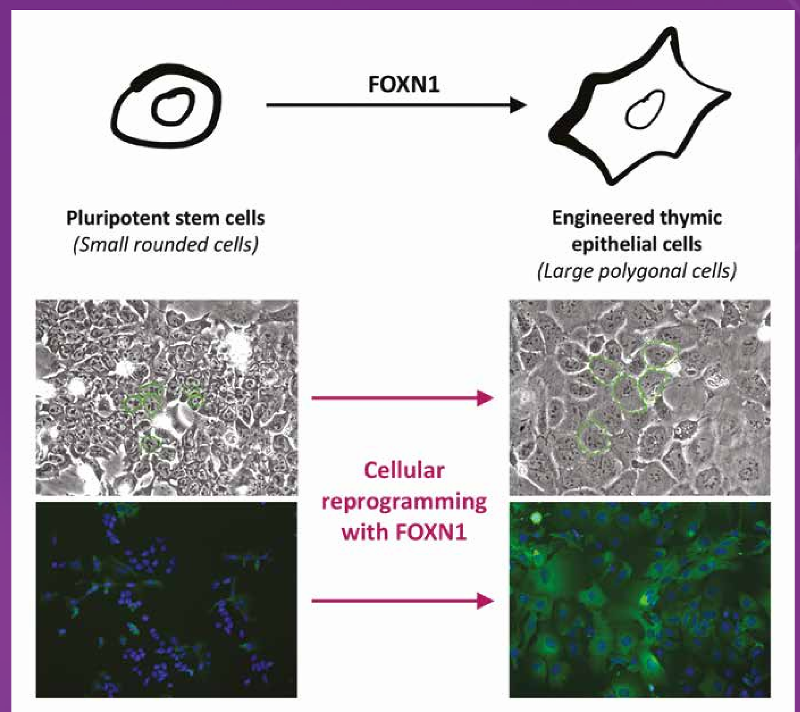

Figure 6 Using pluripotent stem cells to make thymic epithelial cells in a dish.

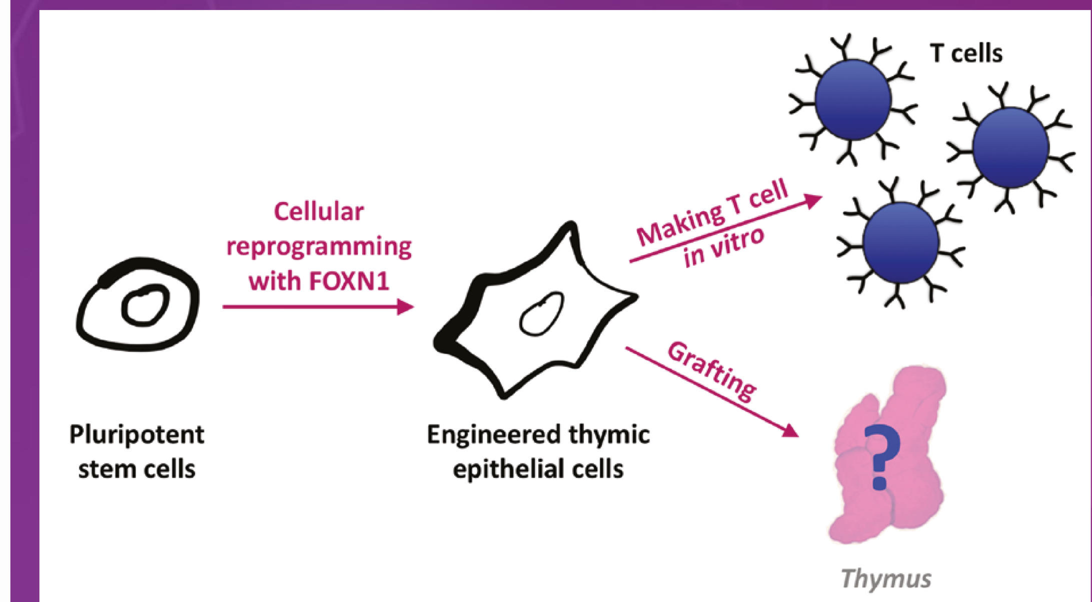

Figure 7 Making T cells in a dish (*in vitro*) using engineered (reprogrammed) thymic epithelial cells.

What does this mean?

Our findings show that mouse pluripotent stem cells are a good starting cell type for making functional thymic epithelial cells in a dish. This means that human pluripotent stem cells could possibly also be used to make thymic epithelial cells in a dish.

Altogether, our findings provide a proof of principle for the development of stem cell based strategies to repair or replace the aging thymus in patients.

Who am I?

I am a molecular biologist working at the MRC Centre for Regenerative Medicine in Edinburgh. I first trained as a biochemist, and then did a Master's and a PhD in molecular biology. After my PhD I worked as a postdoctoral scientist for a few years, and then took a career break to raise my children. I came back to academic research in 2015, thanks to a Daphne Jackson Fellowship sponsored by Medical Research Scotland. My current research involves using stem cells and cellular reprogramming approaches to figure out how to grow a functional thymus in a dish, with the ultimate goal of developing strategies to repair or replace the aging thymus in patients.

Dominique began her Medical Research Scotland sponsored Daphne Jackson Trust Fellowship, entitled *"Investigation of the mechanisms of transcriptional regulation of thymic epithelial cell fate"*, in 2015 at the University of Edinburgh, supervised by Professor Clare Blackburn and Professor Ian Chambers.

Daphne Jackson Trust