Janet Rossant, PhD, FRS, FRSC

- Research Institute, Developmental & Stem Cell Biology, Senior Scientist
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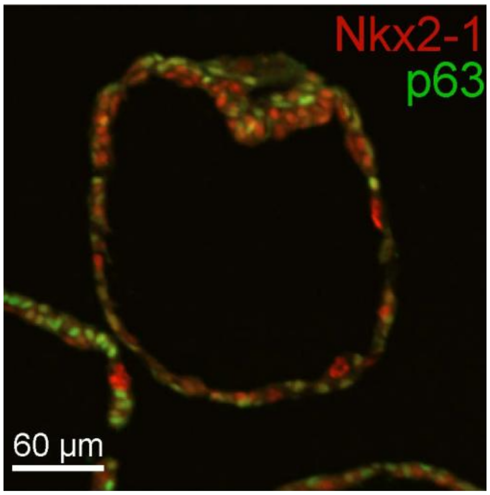
Our focus is trying to use human pluripotent stem cells to derive lung epithelial cells that we can use to study Cystic fibrosis (CF) and develop and test new drugs and potentially develop new screens for drugs for CF.

We can generate primary lung epithelial cells from patient material, but it is a limited resource. The ability to take skin cells and turn them into pluripotent cells means that we have the ability to generate stem cells from any CF patient. We can study a wide range of different mutations from any genetic background and begin to investigate why the different mutations have different effects on the lung and development of disease. We would like to be able to use these cells to measure Cystic fibrosis transmembrane conductance regulator (CFTR) function and measure the effects of drugs on CFTR function.

We have been able to generate human induced pluripotent (iPS) cells from CF patients and generate cells in culture that have many of the properties of proximal airway cells that can form tight junction coupled epithelia that express functional CFTR. In a proof of principle experiment, we were able to show a small molecule that is thought to aid in the relocation of mutant CFTR to the cell surface can result in cell surface expression of CFTR in lung epithelial cells derived from CF mutant iPS cells, Our goal is to improve this assay and generate pure populations of functional lung epithelial cells from CF mutant iPS lines.



Colony derived from an early trachea progenitor cell.

We hope to generate a bank of CF mutant iPS cells that reflect the different genetic variations of the disease so as to develop a personalized medicine approach whereby new drugs can be tested against this battery of cells, to understand which patients are more likely to respond to certain drugs more than others.

As an undergraduate student, I was very interested in developmental biology. I was taught at Oxford University by John Gurdon, who won the Nobel Prize in 2012 for his discovery that mature cells can be reprogrammed to become pluripotent, and I have been working with mouse developmental biology essentially ever since.

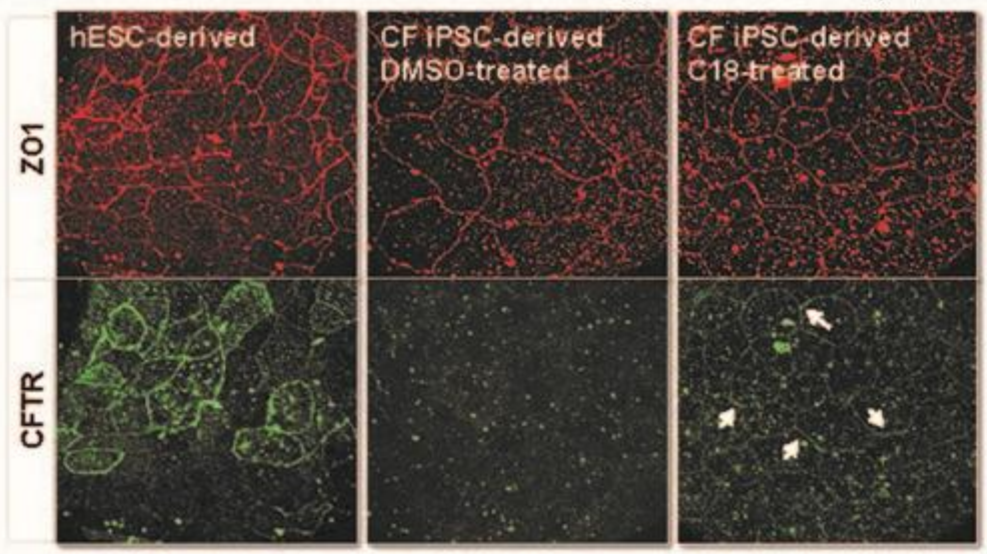
I joined Sick Kids in 2005 and a lot of my lab's work has been very basic. We work on lineage development in early mouse embryos in order to understand human embryo development and stem cell origins. Being at SickKids and being exposed to its clinical environment and its various centres that we are developing, I realized that we had the capacity to take our knowledge of development and apply it to the interesting clinical questions being investigated at SickKids. Cystic fibrosis is such a historical and current focus here at SickKids and the opportunity to make a contribution here is a lot of fun.

Click here for a complete list of Dr. Janet Rossant's publications at NCBI PubMed.

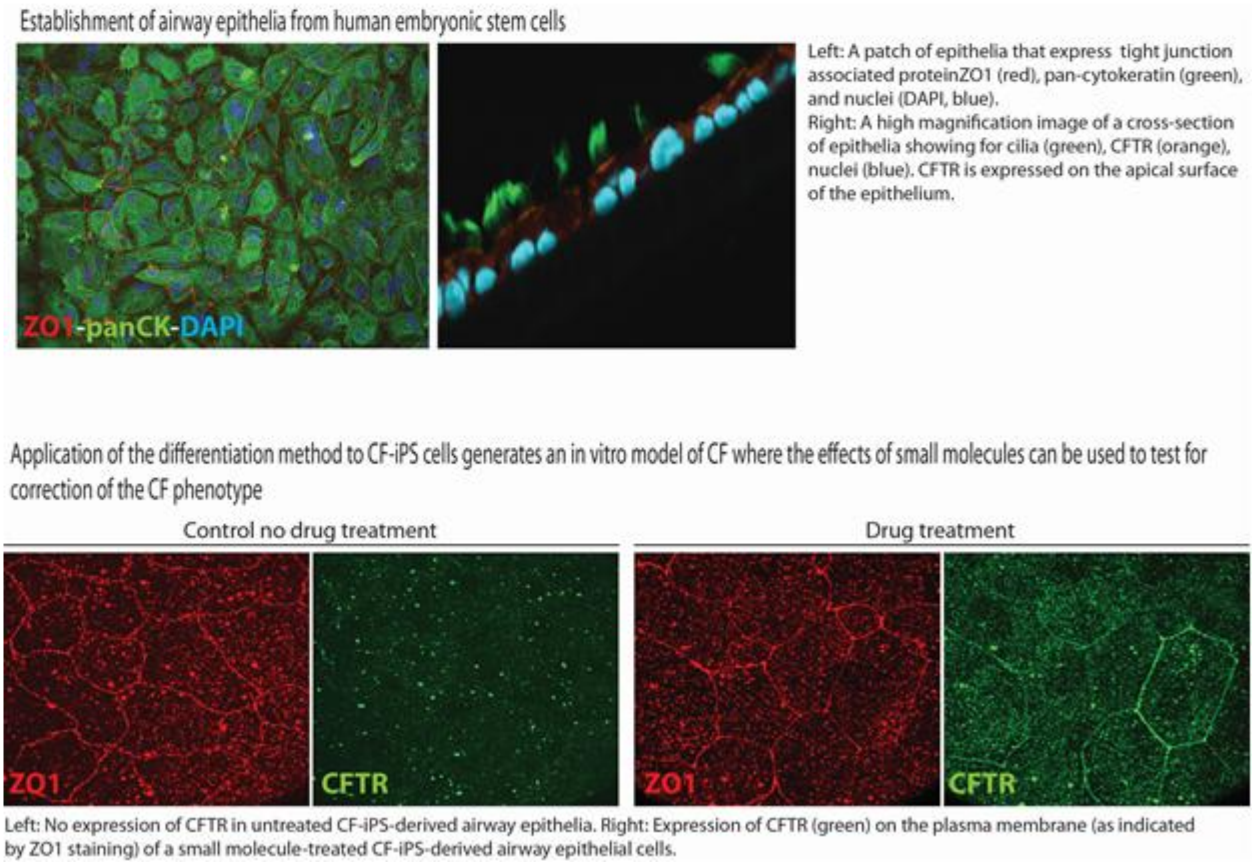
Trainees:

Amy Wong (post-doctoral fellow) – Wong, who was trained by Dr. Tom Waddell, has been the main driver of our research of turning pluripotent stem cells into lung epithelial cells, and is now working on trying to improve the differentiation of the pluripotent cells.

Wong et al. Nature Biotechnology, Sept 2013



Representative photomicrographs of hESC (CA1 line), CF-iPSC GM00997 Line 2 treated with either DMSO (control) or C18 (10 uM) and co-stained for tight junction– associated protein ZO1 and CFTR. As a proof of concept experiment to determine whether CF-iPSC-derived epithelial cells may be used to evaluate CF corrector compounds, we tested the effect of C18, an active analog of the small molecule VX-809 (currently in phase 2 clinical trials), in promoting plasma membrane localization of F508del-CFTR in CF-iPSC–derived epithelial cells. Notably, no surface-localized F508del-CFTR was detected in control DMSO-treated CF-iPSC cultures, but cultures treated for 24 h with C18 (10 uM) exhibited patches of cells expressing CFTR on their cell surface (white arrows) after 2 d of treatment with C18. Scale bar, 22 um.



Left: A patch of epithelia that express tight junction associated proteinZO1 (red), pan-cytokeratin (green), and nuclei (DAPI, blue).
Right: A high magnification image of a cross-section of epithelia showing for cilia (green), CFTR (orange), nuclei (blue). CFTR is expressed on the apical surface of the epithelium.

Left: No expression of CFTR in untreated CF-iPS-derived airway epithelia. Right: Expression of CFTR (green) on the plasma membrane (as indicated by ZO1 staining) of a small molecule-treated CF-iPS-derived airway epithelial cells.

Melanie Bilodau (post-doctoral fellow) – Bilodau, who was trained by Guy Sauvageau at the University of Montreal, is working on fundamental aspects of lung development. She has been using mice to try to identify early lung progenitors during embryonic development and to identify markers for these cells, and they may be useful to us as we work with pluripotent cells to identify the progenitors which we can expand in culture.

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