Daniela Rotin, PhD

- Research Institute, Cell Biology, Senior Scientist
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- Canada Research Chair, Biochemistry and Signal Transduction
- Cystic Fibrosis Centre, Centre Advisory Committee
- CIHR Team grant on treatment for Cystic fibrosis

We are currently focusing on two Cystic fibrosis (CF) research projects. First, we are trying to identify small molecules, proteins, and pathways that rescue the major mutation of the Cystic fibrosis transmembrane conductance regulator (CFTR), namely delta-F508 CFTR. We have developed a high-content screen, which enables the identification of proteins and pathways that are responsible for promoting rescue of delta-F508 CFTR on a global (proteomic) scale.

Using this approach, we recently performed a kinase inhibitor library screen to identify kinase inhibitors (drugs) that rescue delta-F508. The drug library we have used contains compounds that are already in clinics or in clinical trials for treatment of other diseases such as cancer and inflammation. Our utilization of drug repurposing is a faster method of developing treatments for CF, because the drugs used are already in clinical use or clinical trial. In parallel, we have performed a RNA interference (kinome) screen to complement the kinase inhibitor drug screen that we have developed, which helps delineate the biochemical pathways targeted by the kinase inhibitors we identified in the kinase inhibitor screen.

One of the proteins that we have found to be important in this study is the FGF receptor (e.g. FGFR1). We found that inhibiting or knocking down the FGFR1 results in substantial rescue of delta-F508. We are in the process of trying to understand the mechanism by which FGFR1 inhibition promotes delta-F508 rescue, as well as test delta-F508 rescue by FGFR1 inhibitors in delta-F508 mutant mice.

Our second project focuses on enzymes called ubiquitin ligases, especially the NEDD4 family of ubiquitin ligases. In particular, we are studying NEDD4-2 (NEDD4L), which is known to inhibit the epithelial sodium channel (ENaC).

Since mice do not develop CF lung disease, we have created lung epithelia-specific NEDD4-2 knockout mice. These mice develop CF-like lung disease due to elevated ENaC activity. This results in massive lung inflammation and mucus accumulation in the airways and the resulting immune response that is similar to that seen in lungs of CF patients. We are working now with Nades Palaniyar, using these NEDD4-2 knockout mice, to study the nature of this inflammation, as well as the ability of these mice to clear bacterial (Pseudomonas aeruginosa) from their lungs following infection, a process that is impaired in lungs of CF patients.
Trainees:

Dr. Agata Trzcinska-Daneluti has carried out all the screens to identify proteins and compounds that rescue delta-F508-CFTR, Leo Nguyen and Anthony Chen have carried out the validation of the screens, as well as investigating the role of FGFR1 suppression on rescue of delta-F508-CFTR. Dr. Chong Jiang has generated all the cell lines used for the screens.

Dr. Toshihiro Kimura and Dr. Chong Jiang have carried out the studies on knockout of NEDD4-2 in lung epithelial of mice.

Over the years, I also had several undergraduate students involved in our CF research (including Kevin Yoong, Lise Huyan, Dan Shilensky, Muhammed Sultan, and Michael Scott).

PUBLICATIONS, Rotin (Peer Reviewed)


**INVITED REVIEWS/BOOK CHAPTERS**


