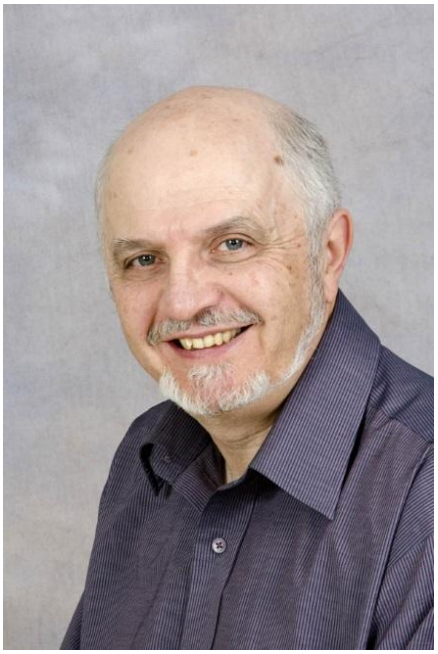
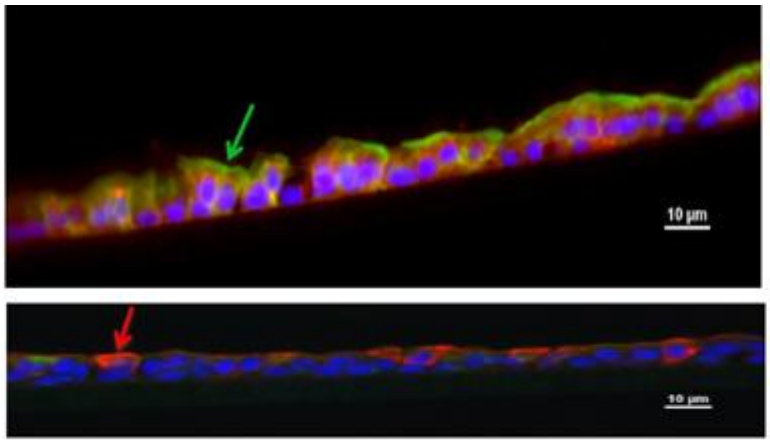


Herman Yeger, PhD

- Research Institute, Developmental & Stem Cell Biology, Senior Scientist
- University of Toronto, Laboratory Medicine and Pathobiology, Professor

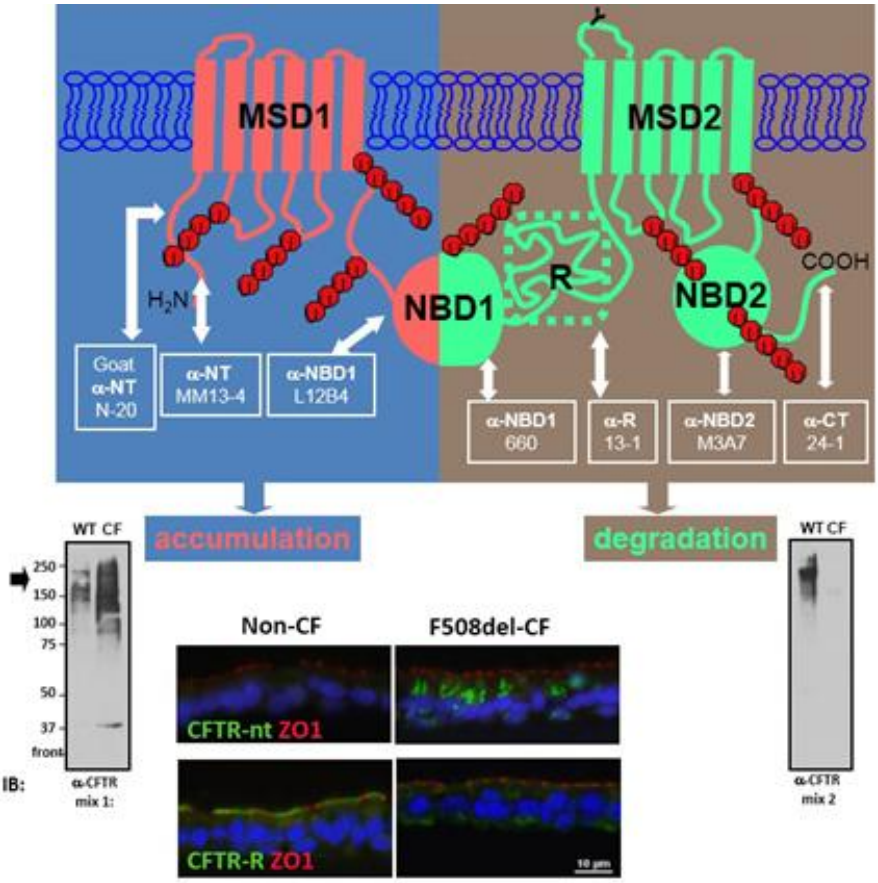
Our previous studies identify deficiencies and innervations of lung tissues in a mouse model of Cystic fibrosis (CF), and preliminarily in a CF pig model. We had also shown that the pulmonary endocrine cells, including neuroepithelial bodies were reduced in numbers and that the chemosensory function of pulmonary neuroendocrine cells appeared dependant on Cystic fibrosis transmembrane conductance regulator (CFTR). Alterations in innervation of CF lung have been documented.

We continue to explore these ideas but more recently made the discovery that human CF lung epithelial cannot properly process mutant F508del CFTR. This results in accumulation of the N-terminal half of CFTR in CF lung epithelial cells, including basal cell progenitors and prominently in the pulmonary endocrine cells. Implications are that this is a chronic pathogenic process, much like other storage diseases, where abnormal protein accumulations and the compromised recycling systems are toxic and could lead to the demise of these cells. If occurring in basal cells, the regenerative capacity could be compromised. If occurring in pulmonary endocrine cells, there could be alterations of their chemosensory and lung physiological regulations.



A new sensory system, the taste receptors, may play important roles in sensing of airway irritants including bacteria. We are studying these receptors as potential therapeutic targets in CF.

Fluorescent labeling for a taste receptor,T1R1(top,green, arrow) and T2R43 (bottom, red, arrow), showing strong apical staining on primary cultured bronchial epithelial cells; nuclei DAPI blue).



We are utilizing different antibodies to CFTR to discriminate the various domains in CFTR. These allow us to investigate normal and mutant CFTR processing.

Another exciting line of research in our lab, supported by the Catalyst grant of the CF Centre, is investigating a new class of lung receptors known as the bitter taste T2R receptors. It has been recently shown that one isoform, T2R38, comes in two variants that actually determine bitter substance sensitivity and production of nitric oxide and innate antibacterial compounds. Importantly, T2Rs are also sensitive to bacterial quorum-sensing molecules that can sense bacterial load. The result is production of NO. It is therefore conceivable in the nasal area and probably distally into the lung the T2Rs function to drive the innate immune capacity to rapidly sense and eliminate bacteria before they can lodge deeper into the lung and develop into a chronic infection.

Our studies are leading to new insights into the pathogenesis of CF lung disease and new therapeutic targets and modalities.

Noting the diversity in nature more than 50 years ago stimulated my interest in biology and specifically plants. This eventually led me to obtain a BSc from McGill University with a major in Botany. I then narrowed down my interest in drugs from plants with therapeutic potential and came to University of Toronto, Faculty of Pharmacy where I pursued an MSc in Pharmacognosy. Here I worked on plant alkaloids and specifically the ergot alkaloids (LSD precursors), especially prominent in these

later 1960s, however my prime focus. Although the MSc experience did not reinforce my research curiosity I started to drift towards the mammalian side and took off a couple of years to work as a research assistant with an immunologist. I became expert in purifying immunoglobulins for crystallization and analysis by NMR method, the harbinger of what is now known as structural biology. This experience was quite uplifting and I then decided to do a PhD with Dr. Kalnins in the Department of Anatomy working first on hematopoietic stem cells, which fell through due to lack of funding (believe it not again being early in what was to become a huge achievement in stem cell biology). With the appropriate collaboration I took on a project on leukemia virus assembly using morphological approaches that included TEM, SEM and immunogold labeling methodology, again a technique in its infancy. Many nice pictures later I then decided do go to SickKids, Pathology, to work with Dr. Sturgess on mucociliary differentiation in a rat model. Unfortunately Dr. Sturgess went shortly off to industry leaving me to pursue something else. This else turned out to be generating diagnostic polyclonals and with a strong sense of cell biology to initiate studies in pediatric cancers (xenograft models) and continue with lung work with Dr. Cutz. The collaboration with Dr. Cutz since the early 1980s focused on the pulmonary neuroendocrine cell system and has led to expanded ideas on lung development, physiology, and lung disease. In many ways things have come full circle as my cancer work focuses on plant derived anti-tumor compounds and my first attempts at stem cell work are now realized in my more recent studies on tumor stem cells and progenitors in lung. Being a cell biologist gives me a broad perspective on everything biological.

The work on lung development and lung disease made it natural to explore lung disease in the pediatric population and especially Cystic fibrosis as it might pertain to the cells we were studying. We explored the role of the pulmonary neuroendocrine system in the pathogenesis of CF and showed that CFTR was expressed in these neuroendocrine cells and that CFTR was needed for neuroendocrine specific cell functions. As our studies revealed pathological changes in CF mouse lungs we became further interested in pathological changes not readily obvious. Often the path is determined by the people hired to assist in such studies and in our case taking on a RA with CF biochemistry experience opened us up to the possibilities that CFTR processing needed to be better delineated, especially in human CF lung tissue which we now had access to. Serendipity is what happens when you keep your options open. These investigations into CFTR has now led us to discover a new pathogenic process in human CF lung involving the respiratory epithelium and especially the neuroendocrine cells. Our work has broad implications for how CF lung may be subject to significant functional problems and future therapeutic efforts. As we always tried to think outside the norms in the field it is the unexpected that has yielded new exciting directions for our research into CF. How it will all evolve cannot be predicted but keeping a very open mind keeps the mental wheels turning. We look forward to making contributions that will turn the tide on the solving and treatment of lung diseases.

Click here for a complete list of Dr. Hermen Yeger's publications at NCBI PubMed.

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