Gene knockout model to validate drug candidates for Cystic Fibrosis

Overview:
McGill University researchers have developed a CFTR knock out mouse model useful to study Cystic Fibrosis (CF) pathology and to validate novel therapeutic approaches for CF. Dr Danuta Radzioch studies the mechanisms controlling lung inflammation in Cystic Fibrosis and asthma. The research investigates inflammation parameters and lipid imbalance following infection with *Pseudomonas aeruginosa*. The model is a CFTR gene knockout C57BL/6-CFTR null mouse model backcrossed for 20 generations to the C57BL/6 strain. The mice display lung disease and other hallmark manifestations of CF; but do not express a calcium regulated alternative chloride channel substituting for the missing CFTR. The laboratory has also developed a novel method of infection which obviates need for surgical incision and results in less than 5% mortality in the CFTR KO mice. The research is reported in a number of publications (See AJRCMB 2007; 36:1-7, Laboratory Animals 2005; 39:336-352, AJRCMB 2008; 38:47-56).

The need:
The is an urgent need for safe and effective clinical candidates indicated for Cystic Fibrosis. CF is the most common fatal genetic disease affecting Caucasians. Patients exhibit abnormal mucus production, pulmonary inflammation, chronic lung infections and osteoporosis. CF patients consistently exhibit an imbalance of DHA and AA stemming from altered fatty acid metabolism. DHA and AA regulate cell function, membrane fluidity, trafficking, inflammation and mucin secretion. The characteristic lipid imbalance correlates well in organs most affected by CF, including lungs, pancreas and intestine. CF is an autosomal recessive disease with an incidence of 1 in 3,500 live births in North America and Europe. The prevalence is in the order of 30,000 in North America and 20,000 in Europe, which qualifies CF as an orphan disease.

Characteristics:
- CFTR KO mice display characteristics mimicking CF pathology in humans.
- CFTR KO mice do not express a calcium regulated alternative chloride channel rendering the strain ideal to test alternative approaches for correcting the trafficking defect.
**Originator:**

**Dr. Danuta Radzioch:**

Professor in the Department of Human Genetics and Medicine and a Medical Scientist in the Faculty of Medicine, of McGill University.

PhD in Biochemistry and Molecular Biology from Jagiellonian University.

Dr. Radzioch’s research focuses on the regulation of lung inflammation in CF and asthma, the genetics of asthma and the molecular mechanisms of macrophage activation.