

## **BioISI Research Seminar**

# **Phosphoinositide pathway and diacylglycerol kinase control of the epithelial sodium channel in cystic fibrosis.**



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**Host:** Margarida Gama-Carvalho (GER-BioISI)

**When: Thursday March 8 - 10h00**

**Where: Building C2, Room 2.2.15**

Cystic fibrosis is a condition caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride and bicarbonate channel. The epithelial sodium channel (ENaC) is also affected, being its action upregulated. This is thought as one of the causes of the thick dehydrated mucus that characterizes the disease and the cause of recurrent pulmonary infections and inflammation that will ultimately destroy the lungs of the affected subjects.

Phosphoinositides are rare signaling lipids that constitute a complex network regulating many cellular processes. One of phosphoinositides many functions is as cell membrane protein regulators, and several studies implicate phosphatidylinositol 4,5-biphosphate (PI(4,5)P2) in ENaC regulation.

Diacylglycerol kinase (DGK), an enzyme of the phosphoinositide pathway, is known to moderate ENaC function and this could be exploited as a therapeutic in cystic fibrosis. But the mechanism of DGK moderation of ENaC is not completely understood. The usually accepted hypothesis is that DGK influence PI(4,5)P2 production by halting the phosphoinositide recycling.

We have created two models: one of the phosphoinositide pathway and another of ENaC and ASL. Together, these models enabled us to study DGK and ENaC and strongly suggest that, contrary to the usually accepted hypothesis, this regulation is effected by the control of PI(4,5)P2 production by the type I phosphatidylinositol-4-phosphate 5-kinase (PIP5KI) that in turn is controlled by phosphatidic acid (PA), the product of DGK.