BioISI Research Seminar

PRECISION MEDICINE IN CYSTIC FIBROSIS

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Cystic fibrosis (CF) is caused by mutations in the CFTR gene that can reduce the amount and/or function of the CFTR chloride ion channel at the epithelial cell surface. A proven therapeutic strategy to treat CF is to enhance chloride transport by increasing the amount and/or function of CFTR at the cell surface using small molecules known as CFTR potentiators and correctors. Ivacaftor, a CFTR potentiator, enhances the function of CFTR by increasing the channel gating activity of CFTR channels at the cell surface. Lumacaftor and tezacaftor, CFTR correctors, increase the amount of CFTR at the cell surface by enhancing the processing and trafficking of CFTR.

A potential therapeutic strategy to enhance and expand the clinical benefit for the approximately 90% of people with CF who are heterozygous or homozygous for the F508del mutation is to combine ivacaftor with two CFTR correctors that act through different mechanisms to increase both the amount and function of CFTR at the cell surface. However, in the approximately 10% of people with CF who do not carry F508del, many different and rare CFTR mutations are present and cause a range of molecular defects in the CFTR protein that vary widely in type and severity and potential response to CFTR potentiators and correctors.

A number of nonclinical and/or clinical measures of CFTR function are being investigated in the field to identify which of these rare mutant CFTR forms may respond to a combination of CFTR potentiators and correctors. Model systems and assays include, but are not limited to, human bronchial epithelial cells derived from people with CF, human gut organoid preparations, intestinal current measurements, nasal potential difference recordings, and sweat chloride measurements. There are a number of important considerations when developing CFTR functional assays to predict which of the rare mutant CFTR forms may respond to CFTR potentiators and correctors. These include the onset of disease in different organs, severity of disease at the time of treatment, treatment duration, modifier genes, environment, drug exposure, and limitations in the sensitivity, reproducibility, and feasibility of the various CFTR functional assays under investigation.

When: April 3 🕑 14h30
Where: Building C1, FFCUL Auditorium
Faculdade de Ciências da Universidade de Lisboa
Campo Grande, Lisboa (Portugal)

Host: Margarida Amaral (FunGP-BioISI)

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