We have developed an intensive research program on rational therapies for cystic fibrosis (CF) based on the understanding of the complex pathophysiology of the disease. Mutations on the CFTR gene result in defective CFTR protein function leading to decreased chloride transport and increased sodium transport across epithelial cells. Dysregulated ion transport causes depletion of airway surface liquid volume and impairment in mucus clearance. Mucostasis in turn predisposes the CF lung to chronic bacterial infection. The nonresolving neutrophilic inflammatory response to this chronic infection causes progressive and permanent airway damage, such that bronchiectasis and respiratory failure are the common findings in end-stage CF lung disease. Hopes of preventing this cascade of events are provided by the development of new therapies that address the underlying defects of the disease.

### Therapeutic strategies

- **From gene to protein**
  - Gene therapy
  - Basic therapy
  - Protein therapy
  - Gene therapy

- **From mutant protein to disease**
  - Protein therapy
  - Osmotic therapy
  - Antibiotic therapy
  - Anti-inflammatory therapy
  - Symptomatic therapy

### 3 ILLUSTRATIVE PROJECTS UNDER DEVELOPMENT

- **SELECTIVE TYPE 5 PHOSPHODIESTERASE INHIBITORS TO ACTIVATE (POTENTIATORS/CORRECTORS) THE MUTANT CFTR PROTEIN**
  - Azithromycin
  - Mechanism of action: activation of CFTR function
  - In vitro experiments: evaluation of inflammatory responses in bronchoalveolar lavage
  - In vivo experiments: evaluation of inflammatory responses in isolated purified cells in culture

- **LUNG INFLAMMATION IN CF: BENEFICIAL EFFECTS AND MECHANISM OF ACTION OF AZITHROMYCIN**
  - Azithromycin
  - Mechanism of action: activation of CFTR function
  - In vitro experiments: evaluation of inflammatory responses in isolated purified cells in culture

- **ESSENTIAL FATTY ACID IMBALANCE IN CF: BENEFICIAL EFFECTS OF THE ORAL SUPPLEMENTATION WITH DOCOSAHEXAENOIC ACID (DHA)**
  - DHA enriched liposomes
  - DHA enriched eggs
  - DHA oral supplementation therapy

### Pathophysiology of the disease

- **From gene to protein**
- **From mutant protein to disease**

### Multidisciplinary therapy

- **Gene therapy**
- **Defective gene**
- **Protein therapy**
- **Osmotic therapy**
- **Mucolytics**
- **Respiratory physiotherapy**
- **Antibiotic therapy**
- **Chronic bacterial infection**
- **Anti-inflammatory therapy**
- **Lung transplantation**

- **Symptomatic therapy**
- **Defective mucociliary clearance**
- **Obstruction**
- **Bronchiectasis**
- **Irreversible lung injury**