Louvain centre for Toxicology and Applied Pharmacology

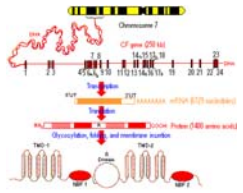
Treatment of Cystic Fibrosis: "From bench to bed"

Lubamba B, Panin N, Palmai-Pallag M,
Palem A, Leonard A, Leal T

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 results 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.

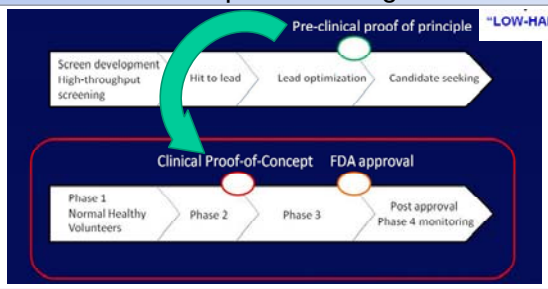
Pathophysiology of the disease

From gene to protein

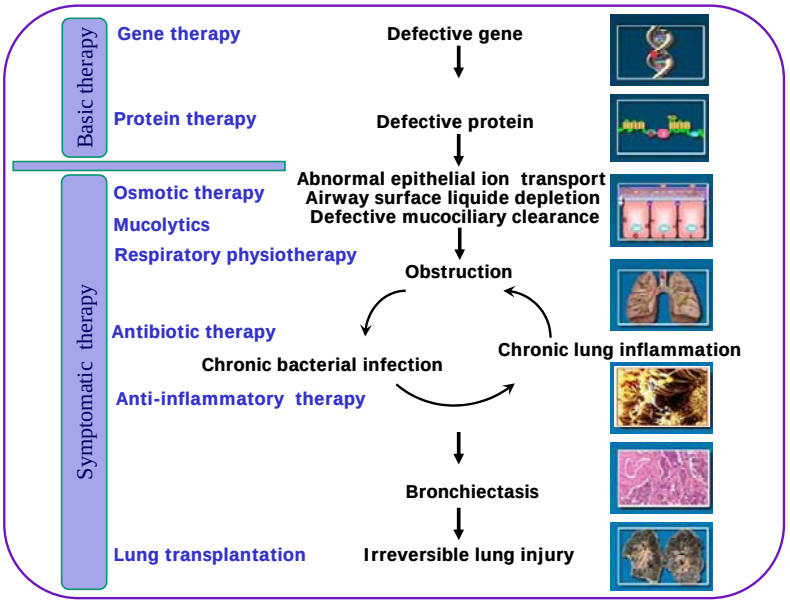


From mutant protein to disease

Therapeutic strategies



Multidisciplinary therapy

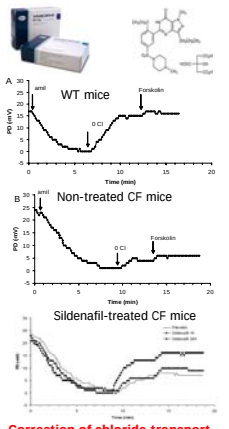


3 ILLUSTRATIVE PROJECTS UNDER DEVELOPMENT

SELECTIVE TYPE 5 PHOSPHODIESTERASE INHIBITORS TO ACTIVATE (POTENTIATORS/CORRECTORS) THE MUTANT CFTR PROTEIN

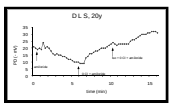
'Low-Hanging Fruit' - Phosphodiesterase type 5 inhibitors

Sidenafil: activation of CFTR function

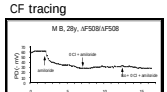


Correction of chloride transport

Normal tracing



CF tracing

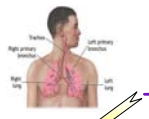


Vardenafil topical nasal instillation: activation of CFTR function

Clinical trial in CF F508del patients: ongoing

•Lubamba B, Lebacq J, Reychler G, Marbaix E, Wallemacq P, Lebecque P, Leal T. Inhaled PDE5 inhibitors restore chloride transport in cystic fibrosis mice. *Eur Respir J*, in revision
•Lubamba B, Lebacq J, Lebecque P, Vanbever R, Leonard A, Wallemacq P, Leal T. Airway delivery of low dose miglustat normalizes nasal potential difference in F508del cystic fibrosis mice. *Am J Respir Crit Care Med* 179:1022-8
•Lubamba B, Lecourt H, Wallemacq P, Bot A, Lebacq J, Lebecque P, De Jonge H, Leal T Preclinical evidence that sildenafil and vardenafil correct cystic fibrosis defects *Am J Respir Crit Care Med* 2008;177:506-15.

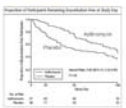
LUNG INFLAMMATION IN CF BENEFICIAL EFFECTS AND MECHANISM OF ACTION OF AZITHROMYCIN



Mechanism of action not understood

'Low-Hanging Fruit' - Azithromycin

- 4 clinical trials in CF
  - Wolter J et al. Thorax 1999
  - Equi A et al. Lancet 2002
  - Saiman L et al. JAMA 2003
  - Clement A et al. Thorax 2006
- Azithromycin
  - Improved lung function
  - Reduced exacerbations
  - Improved weight gain
- Azithromycin is recommended for chronic use for CF patients infected with *P. aeruginosa*

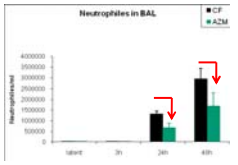


In vivo experiments

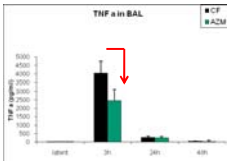
Evaluation of inflammatory responses in bronchoalveolar lavage

Azithromycin:

↓ cell infiltrate



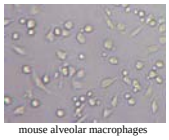
↓ cytokine response



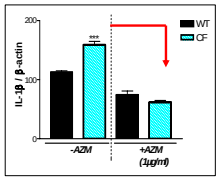
In vitro experiments

Azithromycin: ↓ cytokine expression

Evaluation of inflammatory responses in isolated purified cells in culture



mouse alveolar macrophages



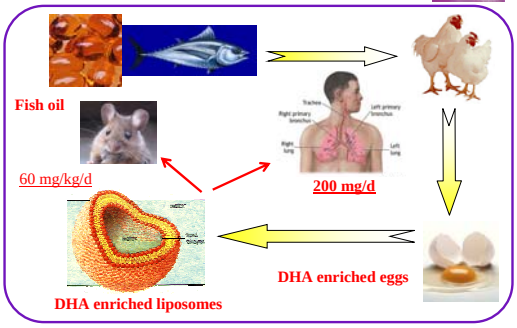
Azithromycin : anti-inflammatory effect

•Legssyer R, Huaux F, Lebacq J, Delos M, Marbaix E, Lebecque P, Lison D, Scholte BJ, Wallemacq P, Leal T. Azithromycin reduces spontaneous and induced inflammation in F508 cystic fibrosis mice. *Respir Res* 2006;7:134.
•Gavilanes X, Huaux F, Meyer M, Lebecque P, Marbaix E, Lison D, Scholte B, Wallemacq P, Leal T. Azithromycin fails to reduce increased expression of neutrophil-related cytokines in primary-cultured epithelial cells from cystic fibrosis mice. *J Cyst Fibros*, 2009;8:203-210.
•Meyer M, Huaux F, Gavilanes X, van den Brûle S, Lebecque P, Lison D, Scholte B, Wallemacq P, Leal T Azithromycin reduces exaggerated cytokine production by M1 alveolar macrophages in cystic fibrosis. *Am J Respir Cell Mol Biol*, 2009: 41:590-602

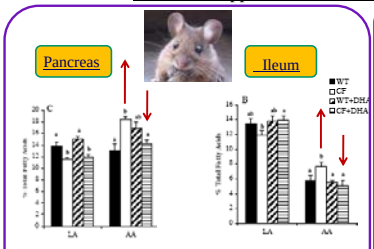
ESSENTIAL FATTY ACID IMBALANCE IN CF BENEFICIAL EFFECTS OF THE ORAL SUPPLEMENTATION WITH DOCOSAHEXAENOIC ACID (DHA)

Beyond lungs: Nutrition, the Cinderella of CF care

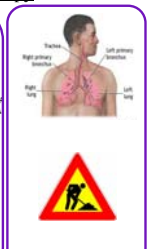
Our own source of DHA formulation



DHA oral supplementation therapy



Polyunsaturated fatty acid (omega3/omega6) imbalance Correction after DHA supplementation



Multicentric clinical trial: ongoing

•Mimoun M, Coste TC, Lebacq J, Lebecque P, Wallemacq P, Leal T, Armand M. Increased arachidonic acid and reduced linoleic acid in F508del cystic fibrosis mice are reversible by GPL-DHA supplementation. *J Nutr*, 2009;139:2358-64
•Coste TC, Deumer G, Reychler G, Lebecque P, Wallemacq P, Leal T. Influence of pancreatic status and sex on polyunsaturated fatty acid profiles in cystic fibrosis. *Clin Chem*, 2008;54:388-95
•Coste TC, Armand M, Lebacq J, Lebecque P, Wallemacq P, Leal T. An overview of monitoring and supplementation of omega 3 fatty acids in cystic fibrosis. *Clin Chem*, 2007;40:511-20

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