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Early Therapy for Cystic Fibrosis, Page 1/2

Field of Application

Cystic Fibrosis (CF) is an inherited, non-curable and life-limiting autosomal recessive metabolic disease of the lung. Other organs can also be affected, e.g. pancreas, intestine and gall bladder.
Over 5 % of the European population is carriers of the CF mutation; worldwide there are some 60,000 people suffering from CF. Between 300 and 400 babies with the disease are born each year in Germany alone.

State of the Art

At present, only the symptoms of CF are being treated, not the actual cause. Physical therapies in combination with mucus solvents help patients to remove mucus from the lung. Antibiotics are used against bacterial infections of the lung. Life expectancy under current therapeutic conditions is around 40 years.

Neonatal Screening for CF

The earlier the CF diagnosis occurs, the earlier treatment can commence and the better are the chances of the patient. Following this principle, the Cystic Fibrosis Center at the Heidelberg University Clinic under the leadership of Professor Marcus Mall has successfully applied a new, simple and safe biochemical CF-test (Sommerburg et al., JIMD, 2010) and is actively campaigning in support of a regular neonatal screening program for the early detection of metabolic diseases.

Advantages

- ✓ Early treatment with sodium channel blocker amiloride immediatley following birth:
  - o Reduces the thick mucus in the lung, improves respiration, reduces lung infections and prolongs survival,
  - o because the accelerated salt and water absorption in the airway is effectively suppressed.
- ✓ Simplified registration requirements due to the orphan disease status
- ✓ Tested active substance with novel application

Innovative Therapy for CF

In parallel with the development of the screening test, Professor Mall and his team developed a novel preventive therapeutic strategy (Zhou et al., AJRCCM, 2008) for the early treatment of CF before any disease-specific symptoms can be detected. The early therapy with amiloride commencing during the first days after birth prevents the development of CF in animal trials.

Results of the innovative CF Therapy

In animal trials, transgenic CF-mice (Mall et al., Nat. Med., 2004) were treated successfully with amiloride via nasal application, provided they were treated prior to CF-symptoms developing, i.e. immediately following birth (Zhou et al., AJRCCM, 2008).

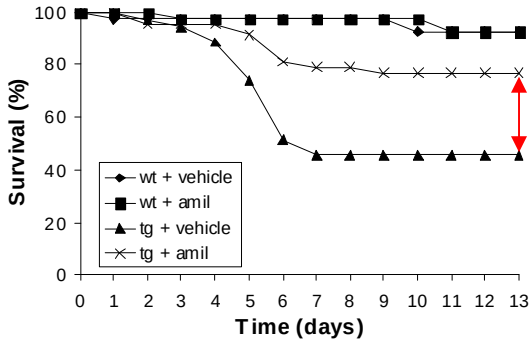

Figure 1: Early treatment with amiloride immediately after birth significantly reduces mortality in CF-transgenic mice (red arrow).

In addition, the early amiloride therapy positively affects the mucus membrane and the formation of mucus (Figure 2) as well as the goblet cell metaplasia, the chronic inflammation and the formation of lung emphysema. These results demonstrate that the preventive treatment with amiloride can be an effective therapy for CF.

wt + control CF + control CF + amiloride

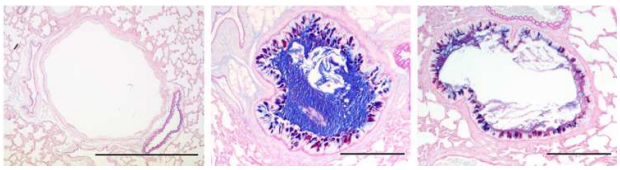

Figure 2: The congestion of the lung with mucus in CF-transgenic mice can be effectively treated by an early amiloride therapy commencing in the first few days after birth up to 14 days after birth.
Scale bar = 500 µm (wt), und 200 µm (CF);
AB-PAS staining.

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Preparation of Clinical Studies

Clinical trials of amiloride as a preventative early intervention therapy against CF are already in the planning phase. The start-up financing of the necessary toxicological investigations and the clinical pilot studies of amiloride, including the request for approval, is assured.

Amiloride

Amiloride is registered as a diuretic and was introduced to the market by Merck Sharp & Dohme in 1967. Amiloride acts as an epithelial sodium channel (ENaC) blocker but achieved no positive effect in inhalation studies with patients already exhibiting CF-typical symptoms.

Genetics

The CF mutation is located in the CFTR gene, which encodes a transmembrane protein acting as a chloride channel and regulator of epithelial sodium channels (ENaC). In the airways, CFTR is primarily responsible for the coordination of secretion and absorption of salt and water to maintain adequate hydration of airway surfaces and mucus, which is required for normal mucus clearance from the lungs.

Market Potential

The CF market is estimated to grow positively up to 2017 with a compound annual growth rate of 8.2 % and a market value greater than USD 2,140 million. The market is ready for new pharmaceuticals which satisfy the unmet medical need.

Technology Transfer

The Technologie-Lizenz-Büro GmbH is charged with commercialization and is currently looking for licensees, funding or cooperation partners for further development and clinical trials.

Patent Portfolio

A European Patent (EP211440B1) has been granted and validated in Germany, Great Britain and France.

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Reference number: 103/06TLB

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