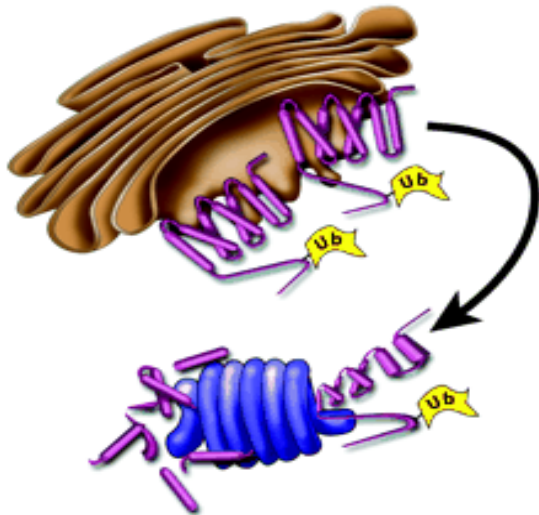


THERAPEUTIC / TARGET**Novel Target for Cystic Fibrosis – Drug Screening and Therapeutic Applications****Key Attributes**

- An approach to overcome the overprotective quality control system of epithelial cells
- A novel screen for new potential drugs and drug targets
- Relevant to protein misfolding diseases and related conditions

Axentis Pharma AG holds patent applications related to a cellular pathway directly linked to the pharmacological rescue of a receptor protein which is dysfunctional in cystic fibrosis. This patented method can be used to develop screens for new therapies and to identify new therapeutic targets.

Background: Cystic Fibrosis (CF) results from mutations in the CF transmembrane-conductance regulator protein (CFTR) which controls the epithelial transport. In about 70% of cases the defect is very simple, being the loss of the phenylalanine residue in position 508 in the protein ($\Delta F508$). Having lost this amino acid, the protein is subsequently tagged by ubiquitin and subject to degradation via the proteasome pathway.

Axentis Pharma AG of Switzerland holds intellectual property related to enzymes that specifically cleave ubiquitin from a receptor protein. It was shown that these USP enzymes (ubiquitin-specific proteases) act by relaxing the cell's quality control system and that these enzymes are a pharmaceutical target with therapeutic value.

Method: Small molecules can enhance the activity of USP enzymes and, thus, can facilitate the "rescue" of a receptor protein, such as CFTR. This working hypothesis has not been pursued by any pharmaceutical company as a strategy to enhance surface expression of mutated membrane proteins.

The original data with a model receptor were published in *Molecular Pharmacology* (Mol. Pharm. 2006, 69 (4), 1083-94). The editors consider these observations to be of major interest and commissioned an Editorial, where they call this approach an "exciting new direction that merits further investigation" (Mol. Pharm. 2006, 69 (4), 1075-8).

Potential applications: One potential application is the development of a cell-based assay for use as a method for the identification of small molecules which restore ("rescue") the function of mutated membrane proteins. If successful, this method could eventually lead to small molecule drugs that provide a causal cure for unmet medical needs such as CF.

The potential applications also include a stand-alone therapeutic approach with the already approved drug Bortezomib (Velcade®) which seems to be synergistic to the "rescue" approach. In vitro data are available that show enhancement of receptor protein levels on the cell surface by combining the effects of an USP enzyme and Bortezomib.

IP situation: Two families of patent applications have been filed in the US and in Europe. One family covers USP enzymes and combinations of USP enzymes and proteasome inhibitors. The other family specifically covers the proteasome inhibitor Bortezomib (second-medical-use patent).

Family A: Use of USP enzymes for the treatment of - inter alia - Cystic Fibrosis

- European Application EP 1 771 194 published as WO2006002453 (A2); publication date 2007-04-11. The application is pending. The first Office Action has been responded to in October 2008.
- US application US2007218043 (A1); Ser.No. 11/650,532; publication date 2007-09-20. A Final Office Action has been issued. A continuation application has been filed with a new set of claims as of 2010-03-18

Family B: Use of Bortezomib for the treatment of - inter alia - Cystic Fibrosis

- European Application EP 1 912 664 published as WO2007002972 (A3); publication date 2007-01-11. This application is pending. No Office Action has been issued so far.
- US Application US2009017006 (A1); Ser.No. 11/994,947; publication date 2009-01-15. This application is pending. No Office Action has been issued so far.

Future R&D steps (suggestion): Initiate a small molecule screening program to identify i) small molecule enhancers of USP enzyme activity and ii) inhibitors of CFTR degradation. Screen, re-test and counter screen lead-like compounds obtained from vendors or partner companies; advance lead-compound into chemical optimization program.

Initiate a preclinical development program with Bortezomib (or a Bortezomib analogue) as first drug candidate. Obtain all preclinical data required to initiate clinical trials. Negotiate with Takeda Pharmaceuticals regarding use of Bortezomib in the CF indication.

Commercial opportunity: commercial partner is sought for future R&D and a licensing arrangement. The primary objective is to produce a new class of drugs that will provide a causal cure for CF (the estimated worldwide market value for a new CF treatment is in the region of EUR 41 million). Additional information is available under a Confidentiality Agreement.

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