REQUEST for FUNDING

Losartan Drug Repurposing for REFLECT 2 Phase III Clinical Trial in Epidermolysis bullosa

The recessive dystrophic form of *epidermolysis bullosa* (RDEB) is characterized by life-long skin fragility and multi-organ involvement. The disease appears already in new-born children. Severe progressive fibrosis follows skin blistering and wound healing, which favours development of highly aggressive squamous cell carcinomas. Among the many symptoms, joint contractures and mitten deformities of hands and feet cause severe disability. To date, no cure exists for RDEB, and the unmet medical need remains very high.

In a preclinical research we have delineated the mechanisms of action of TGFβ in RDEB skin and used the collagen VII hypomorphic RDEB mouse model to demonstrate that losartan inhibits TGFβ activity and substantially prevents fibrosis *in vivo* (Nyström et al. EMBO Mol Med, 2015, see Fig. on the right).

Losartan, a small molecule is a well-established medication to treat hypertension.

Based on these data, a phase I/II clinical trial REFLECT 1 on the use of losartan in children with RDEB was initiated in June 2017. The trial, which is still running, has the objective to evaluate safety and tolerability of losartan in this patient population, but also to gain first data on the efficacy of the drug. Chief Investigator of this dual centre trial is Dr. Dimitra Kiritsi, Medical Center – University of Freiburg, Germany, who will also be the Chief Investigator of the planned REFLECT 2 trial.
Although losartan would not be a cure for RDEB, we expect an amelioration of the disease manifestations and a delay in the fibrosis progression. All treatment options that are currently being investigated focus on improving skin involvement (cell-, gene- and protein-based therapies). Losartan targets the systemic inflammation and fibrosis in RDEB.

For the expected phase III clinical trial, a suitable pediatric formulation needs to be developed, which should be an easy-to-swallow formulation of losartan for the treatment of children and adults with RDEB. A respective pharmaceutical development of such a formulation was initiated in 2019.
Orphan drug designation has been obtained from FDA and EMA (January 2019), providing fee reductions and support by the regulatory agencies.

Funding is needed to conduct the Phase III clinical trial REFLECT 2 and to develop the respective study medication of losartan.

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