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Project

Development of an otic stem cell based model of the inner ear: An *in vitro* model for drug development in the field of hearing loss

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Sensorineural hearing loss (SNHL) is the most frequent sensory deficit and the third most common chronic disease of mankind. In Germany alone, 12 million people are affected. Thus the socio-economic needs for the development of rational therapies to cure hearing loss are evident. Even so, no causal medical treatment of sensory hearing loss has been developed to this day. The current treatment options are limited to prosthetic devices. However, this technical help reaches only a fraction of affected patients. Moreover, the functional results and hence the acceptance of the technology are limited. Unfortunately, no rational pharmacological therapies targeting the underlying biological mechanisms are available. This medical need for drug development research is facing a serious lack of validated alternatives to animal testing. Therefore, in the hearing field even early stage drug development has little alternatives to animal experiments.

The main reasons for the lack of appropriate alternatives are based on the hidden anatomical location and delicate tissue structure of the inner ear. The organ is embedded in the temporal bone and it is very difficult to obtain tissue samples. The cytoarchitecture of the sensory organ is complex and difficult to handle experimentally. In addition, the number of sensory cells is limited making research in the organ a great challenge. However, recently stem cells have been discovered in the inner ear. These otic stem cells are self renewing and they have the potential to differentiate along different inner ear cell lineages. Based on these stem cells it is now possible to design experiments that allow promoting the principles of 3Rs.

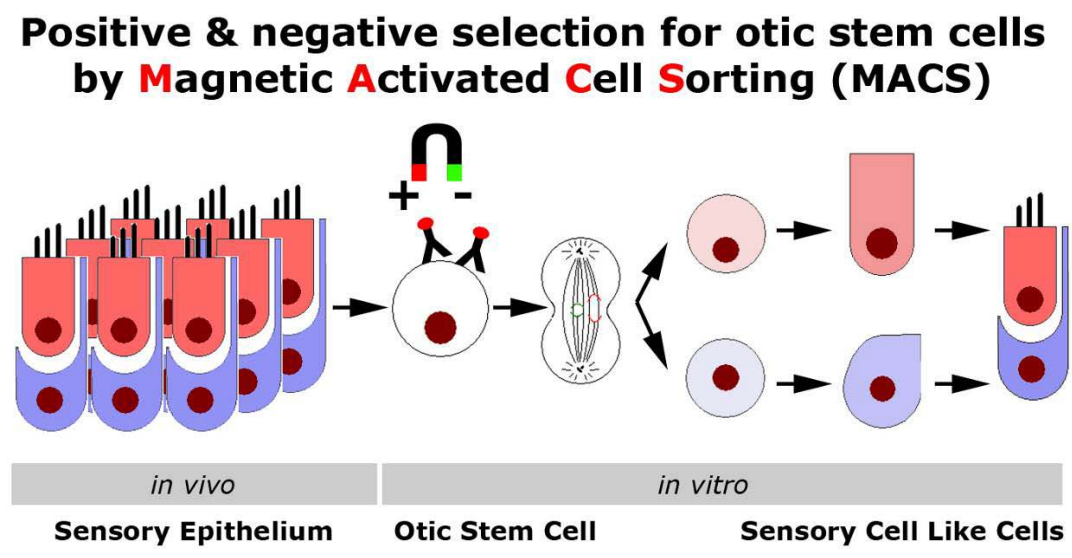

Fig. 1: Antibodies against various surface-expressed epitopes are used to identify and label stem cells in the sensory auditory epithelium - the organ of Corti - of mice. Consecutively, stem cells will be isolated using magnetically activated cell sorting, propagated, and finally differentiated again.

The aim of this research project is to develop and standardize an otic stem cell based *in vitro* model of the inner ear. This *in vitro* model is referred to as "mini-ear". The proposed project will start with a systematic search for cell surface markers in order to accumulate otic stem cells and consecutively differentiate them into inner ear cell types (fig. 1). For this purpose Magnetic Activated Cell Sorting (MACS) will be applied. Sorted cell populations will be compared regarding their sphere forming capacity (fig. 2A) and analyzed for their differentiation potential (fig. 2B-D).

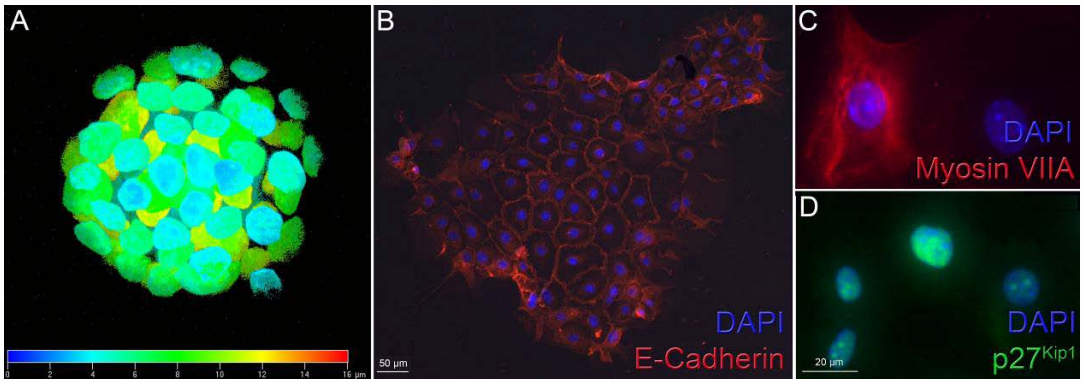

Fig. 2: The isolated stem cells from the organ of Corti form spheres (A) and differentiate into E-cadherin-positive epithelial islands (B), so-called "mini-ears". These include Myosin VIIa-positive (C) hair cell like and p27Kip1-positive (D) supporting cell like cells.

By developing a standardized experimental paradigm the project will provide improvements in terms of the 3Rs concept: (1) Replacement: animal experiments for compound screening for drug development will be avoided. (2) Reduction: reduction of animal numbers by efficient use of the isolated cells for stem cell culture. (3) Refinement: by obtaining pharmacological data *in vitro*, overdosing and adverse effects in animal experiments can be reduced. In addition, experimental conditions are more specifically controlled *in vitro* as compared to the *in vivo* situation. Successful development of a standardized procedure to generate “mini-ears” may allow for drug development in the field of hearing utilizing the 3Rs concept.

Project Manager

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Born in 1964. Study of Human Medicine in Frankfurt am Main (Germany). Since 1992 Postdoc at the Hearing Research Centre, Tübingen (Germany). Habilitation in Otorhinolaryngology at the University of Tübingen in 2006. Since 2009 Associate Medical Director. The main research focus is on regenerative Medicine.

Research Team

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