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Abstract

Development of a 3D-printed round window niche implant for cochlear pharmacotherapy

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Inner ear disorders are affecting people worldwide and there is an unmet need for effective cochlear pharmacotherapies. Intratympanic delivery of pharmaceutical agents represents a feasible option, as it offers a minimally invasive approach to application within the middle ear cavity while permitting local administration that can facilitate effective diffusion of the active compound into the inner ear, thereby reducing the risk of systemic side effects. We aim to develop an individualized drug-eluting round window niche implant (RNI) to achieve a controlled drug delivery into the cochlea. The RNI will be initially evaluated in guinea pigs (GP-RNI), an established animal model, to assess the safety and efficacy of the proposed concept. The temporal bones of Dunkin-Hartley guinea pigs were scanned by µCT (Xtreme CTII, Scanco Medical) and exported as DICOM (digital imaging and communications in medicine) files which can be used for segmenting and establishing models in 3D Slicer™ version 4.11(http://www.slicer.org). The individual RNI reconstructions were measured and a one-size-fits-all GP-RNI model was drawn based on the mean values of the 12 data sets using 3D Slicer. A handle that additionally illustrates the orientation of implantation and keeps the RNI in situ was added. The GP-RNI model was imported to Visual Machines software version 2.8.130r7 (EnvisionTEC GmbH, Gladbeck, Germany) and 3D printed using a 3D-Bioplotter® Manufacturers Series (EnvisionTEC GmbH, Gladbeck, Germany), equipped with a low-temperature printing head and a UV Curing Head (365 nm). Medical-grade silicone (60A MG, BIO-83-6001, EnvisionTEC, USP Class VI) with its catalyst (catalyst compound, EnvisionTEC) was prepared in a ratio of 50:1 and subsequently mixed with or without 1% dexamethasone (DEX) (w/w; Caesar & Lorentz GmbH, Hilden, Germany). The accuracy of printing was tested using CT scan (ZEISS Metrotom 6) and surface comparison software (GOM Inspect Pro, ZEISS). Twenty GP-RNIs were printed continually and weighted to assess printing precision. The DEX distribution in GP-RNI was checked by microscope (ZEISS). The biocompatibility, bio-efficacy and drug release test of GP-RNI containing 1% DEX were measured performing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, a tumor necrosis factor-alpha (TNFα)-reduction test and HPLC (high-performance liquid chromatography). The implantability of the GP-RNI was evaluated in 6 fresh guinea pig cadavers performing µCT imaging, CLSM (confocal laser scanning microscope) and grinding. The printing of the RNI was precise and accurate. DEX can be homogeneously stored in the silicone and the GP-RNI containing 1% DEX was biocompatible and reduced TNFα production in vitro. The drug release of the GP-RNI containing 1% DEX showed a burst within 24 h (up to 2 ng/hour), after which the release slowed down and decayed from 0.53 to 0.24 ng/h after 29 days. The designed model fitted in all tested guinea pig niches. The imaging and grinding showed that the RNI stayed in situ and was well attached to the round window membrane (RWM), which had no structural damage. The developed individualized RNI shows a good suitability as a precise RWM drug delivery system in guinea pigs. Further research is needed to fully assess the effectiveness of the GP-RNI model in vivo.

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AUTHOR'S STATEMENT

Conflict of interest: Authors state no conflict of interest. Animal models: Animal cadavers were from an in-house breeding colony of pigmented guinea pigs kindly provided by the working group of Prof. Mazzouli-Weber, Department of Physiology, University of Veterinary Medicine Hannover, Foundation, Hannover, Germany. Those guinea pigs were humanely killed by bolt shot in combination with throat transection, as permitted by the local authorities (§4) within the framework of the German "Law on Protecting Animals" and the cochleae were subsequently harvested. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: not applicable.

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