Transposon-Based, Targeted Ex Vivo Gene Therapy to Treat Age-related Macular Degeneration: The TargetAMD project

Gabriele Thumann¹, Martina Kropp¹ and Nina Harmening⁰ on behalf of the entire TargetAMD Consortium
¹University of Geneva, University Hospitals of Geneva, Department of Ophthalmology, Geneva 14, 1211, Switzerland

Purpose
Side-effects, the high costs of current treatments for neovascular age-related macular degeneration (nAMD), the need for life-long, repeated intravitreal injections of anti-VEGFs (Vascular Endothelial Growth Factor), has stimulated the search for innovative treatments. The European-funded TargetAMD project aims at the development of reagents, devices and protocols for a once-in-a-lifetime gene-therapeutic treatment for nAMD by transplanting subretinally autologous PEDF-transfected pigment epithelial cells.

Methods
Autologous iris pigment epithelial (IPE) cells will be isolated from a patient’s iris biopsy, and transfected with the PEDF gene using the non-viral Sleeping Beauty (SB100X) transposon system followed by subretinal transplantation in the same patient within one surgical session lasting approximately one hour.

Results
The PEDF gene and the SB100X transposase will be encoded by pFAR4 miniplasmids, and delivered to IPE cells ex vivo by electroporation. A clinically approved electroporation device and a newly developed buffer have made possible the efficient transfection of freshly isolated IPE cells from human donors under GMP conditions. Evaluation of safety and efficacy of nAMD treatment with PEDF-transfected pigment epithelial cells has been shown to be safe while producing a significant reduction of choroidal neovascularization (CNV) in a rat model.

Conclusions
Significant and essential progress has been made toward the performance of a phase Ib/IIa clinical trial to treat neovascular AMD by additive gene therapy. Here we have shown that the approach is not only feasible, but it is effective as shown by the reduced neovascularization in a laser-induced rat model of CNV.