Delivery of Stem Cells to the Retina: Findings from our studies

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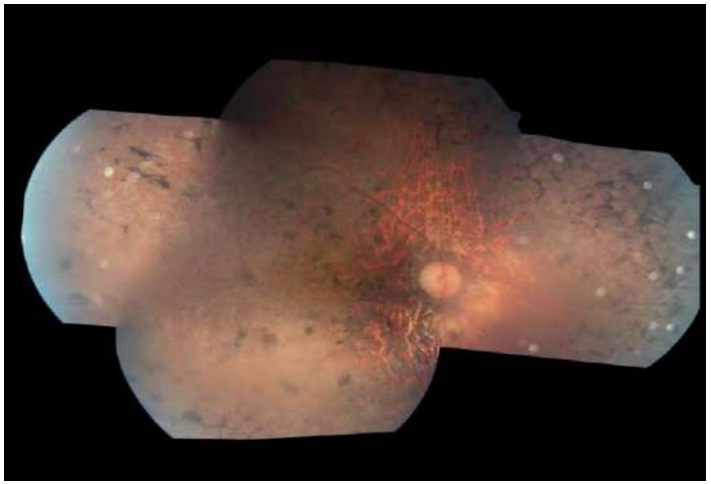
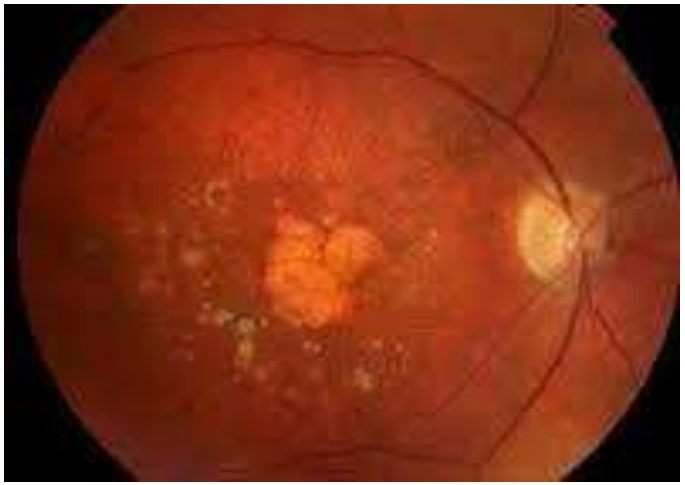
TURKEY

- Stem cell based treatment modalities are rising in trend for irreversible neuropathies and retinopathies.

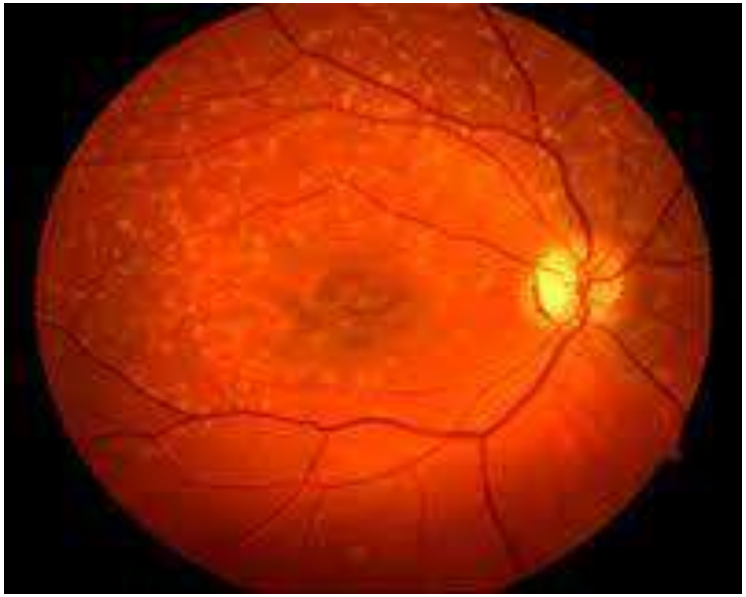
- These treatment options are giving hope for reversing the cell death or damage; or at least causing the functional enhancement of the remaining viable cells through nutritional support and anti-apoptotic effect.

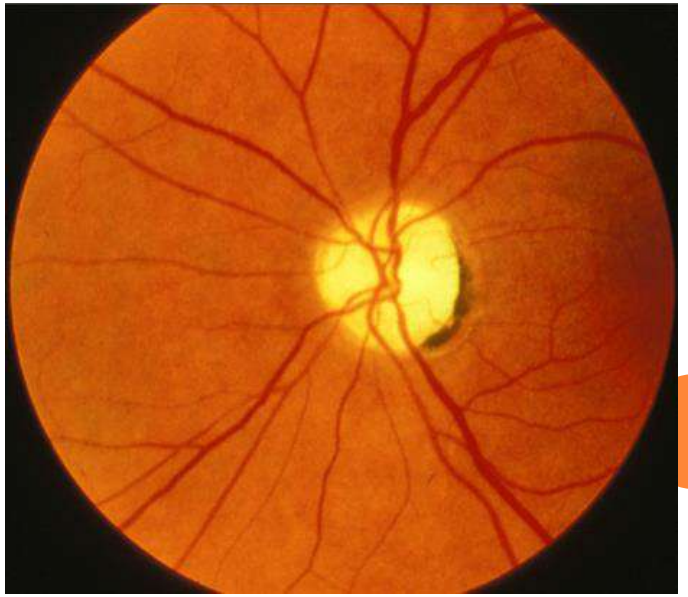
- Various ways of application routes and sources of the cells have been proposed up-to date





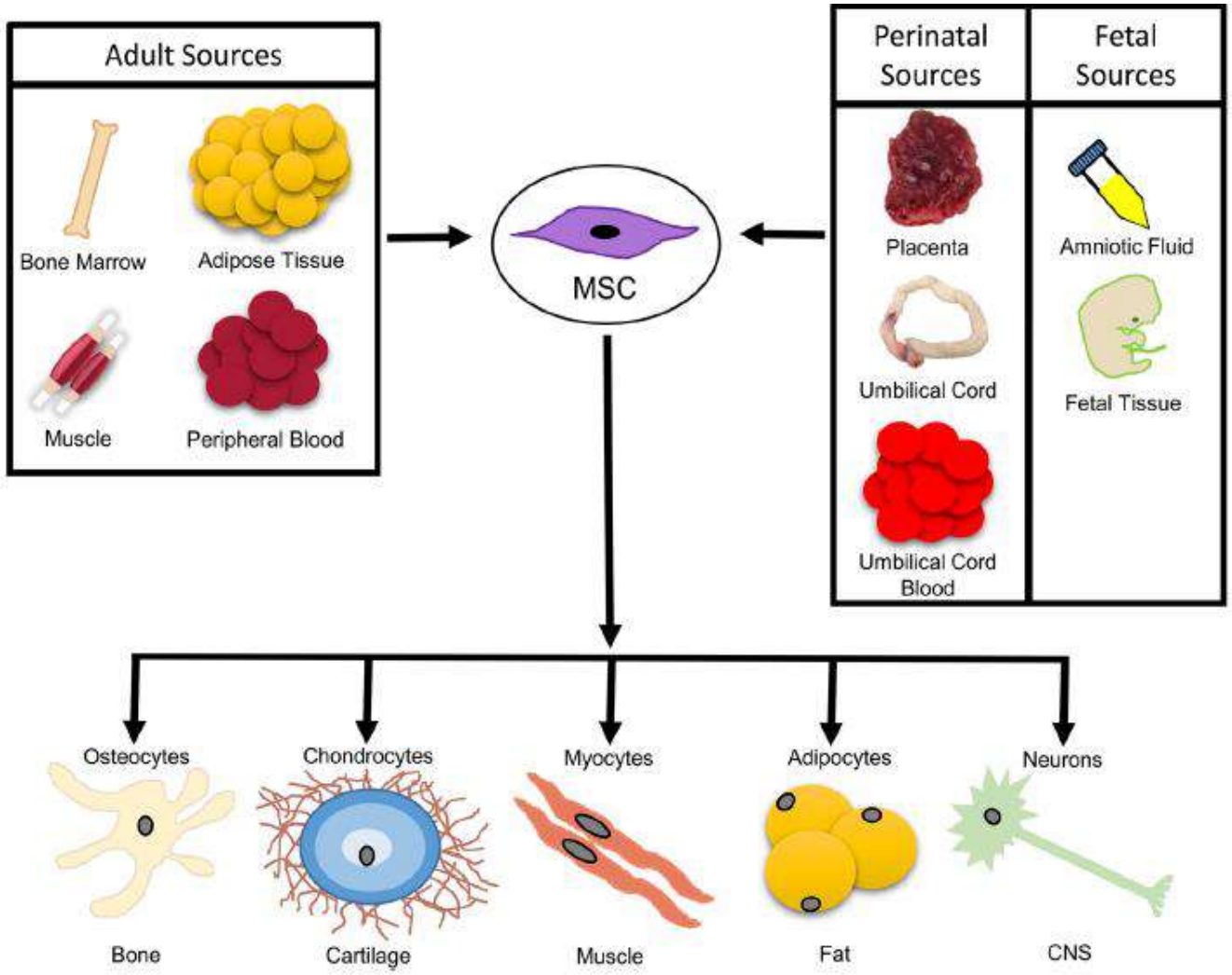
RP, AMD, STARGARDTS’ MACULAR DYSTROPHY, OPTIC NEUROPATHY





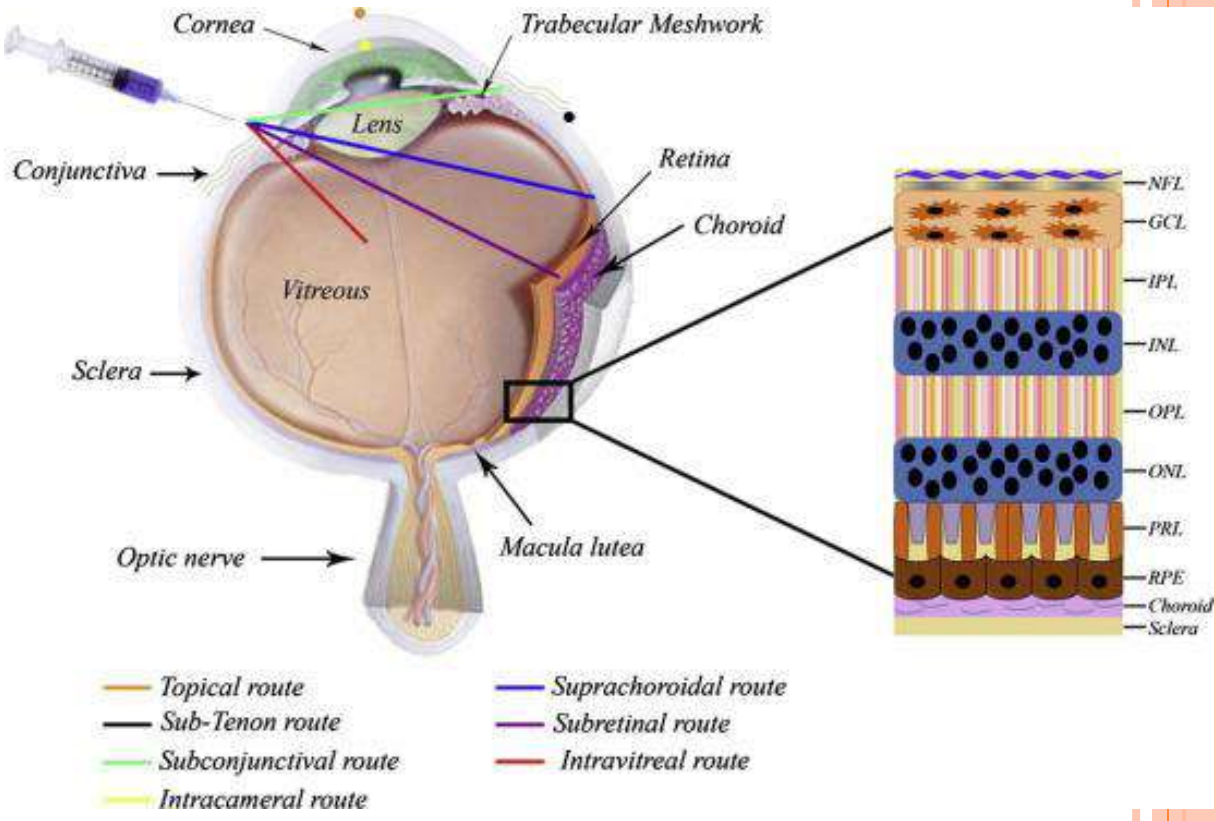
CLİNİCALTRİALS.GOV

- Embryonic stem cells
- Retinal progenitor cells
- Adult stem cells: Adipose tissue mesenchymal stem cells, Bone Marrow derived CD34+hematopoetic cells, Dental Pulp derived cells, Umbilical cord derived mesenchymal cells, Induced pluripotent stem cells


Adult Sources
Bone Marrow
Adipose Tissue
Muscle
Peripheral Blood
MSC
Perinatal Sources
Fetal Sources
Placenta
Amniotic Fluid
Umbilical Cord
Fetal Tissue
Umbilical Cord Blood
Osteocytes
Chondrocytes
Myocytes
Adipocytes
Neurons
Bone
Cartilage
Muscle
Fat
CNS

- The eye is a good target for cellular replacement therapies.
- The transplantation site and cells can be monitored via clinical examination and high resolution imaging devices.
- There are clinical measures ways like visual acuity, contrast sensitivity, microperimetry and electrophysiology.
- Small volumes and numbers of replacement cells can be enough compared to other bodily organs.
- Surgical accessibility to the eye and the retina permits the delivery of cells in suspension, or as sheets on a scaffolding material that could promote the survival of transplanted cells

- Intravitreal
- Subretinal
- Subtenon
- Retrobulber
- Peribulber
- Suprachoroidal

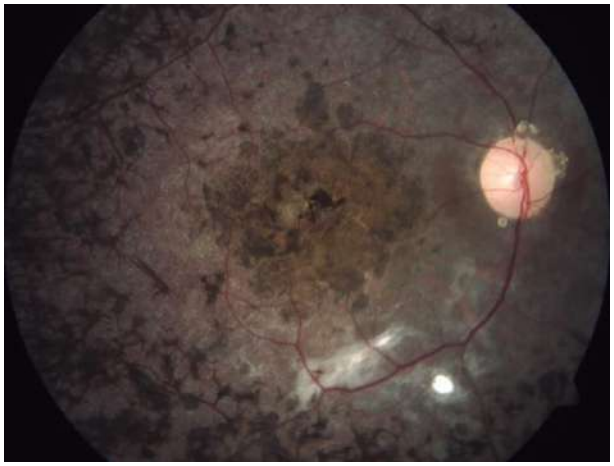


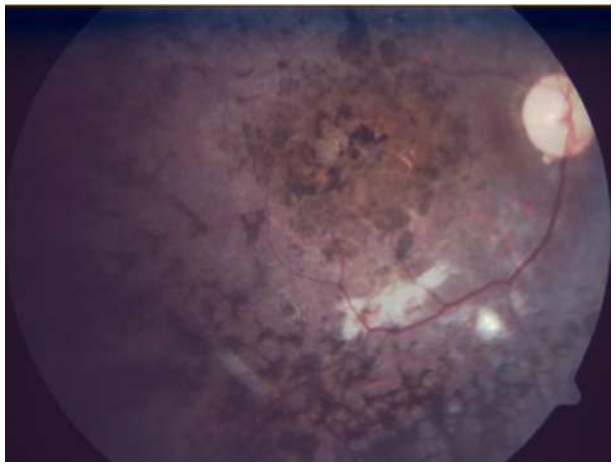
Subretinal Adipose Derived MSC

- First study of our group which included 11 patients with end-stage RP who received subretinal implantation of ADMSCs.
- All patients had a total visual field defect and five of them only had light perception.
- The worst eye of the patient was operated on and, after total vitrectomy with a 23 gauge, ADMSCs were injected subretinally.
- All 11 patients completed the 6-month follow-up. None of them had systemic complications.

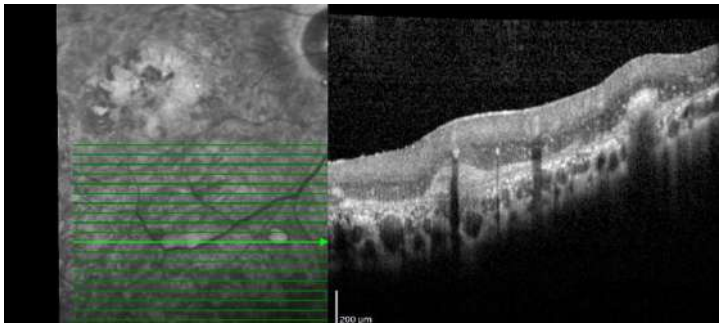
Öner A, Gönen ZB, Sinim N, Çetin M, Özkul Y. Subretinal adipose-tissue derived mesenchymal stem cell implantation in advanced stage retinitis pigmentosa: A Phase I clinical safety study. Stem Cell Research and Therapy, 2016;7:178.

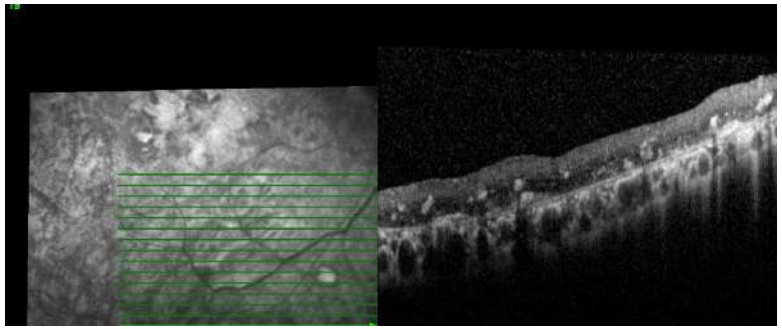
- Five patients had no ocular complications.
- One of the patients experienced CNVM at the implantation site and received an intravitreal anti-vascular endothelial growth factor drug once.
- Five patients had epiretinal membrane around the transplantation area and at the periphery, and received a second vitrectomy and silicon oil injection.
- Only one patient experienced an improvement in visual acuity (from 20/2000 to 20/200), visual field, and ERG.
- Three patients mentioned that the light and some colors were brighter than before and there was a slight improvement in BCVA.
- The remaining seven patients had no BCVA improvement (five of them only had light perception before surgery).

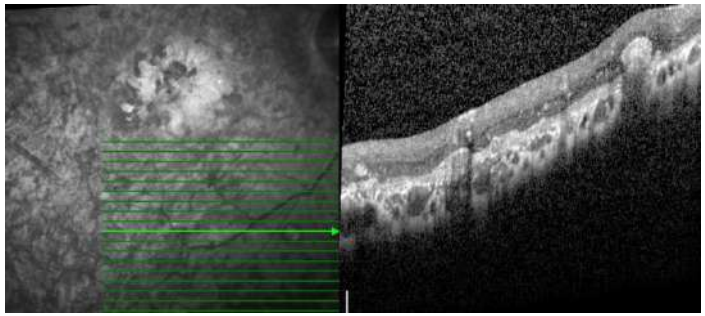




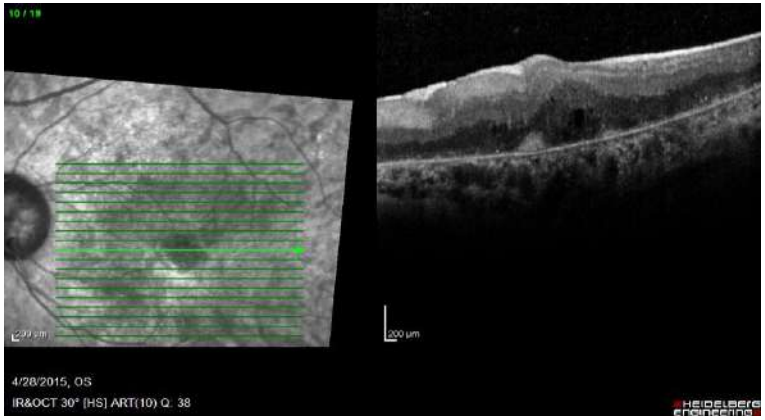
Fundus photos of postoperative 6 months and 4 years

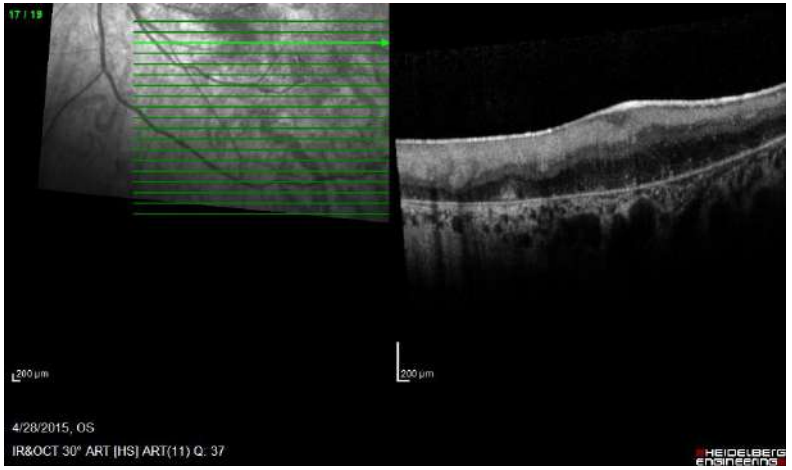


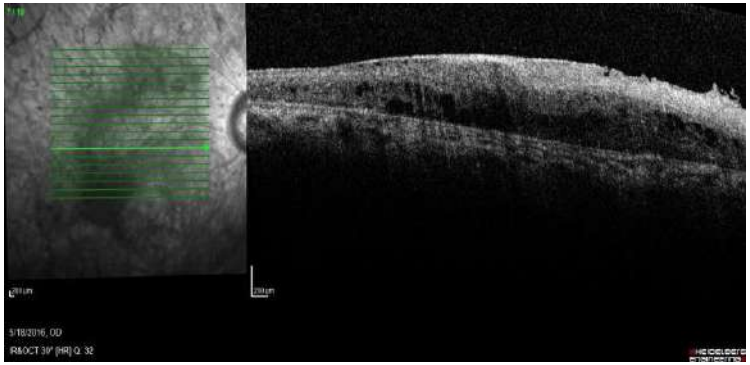




OCT of the injection side of a patient at first month, 1. year and 4. years







OCT scans of ERM formation

- Adipose-derived MSC preparations used for subretinal and intravitreal injection may contain cells differentiating into autologous fibroblasts.

- The presence of autologous fibroblasts can be explained as the cause of proliferative vitreoretinopathy and retinal detachment after injection.

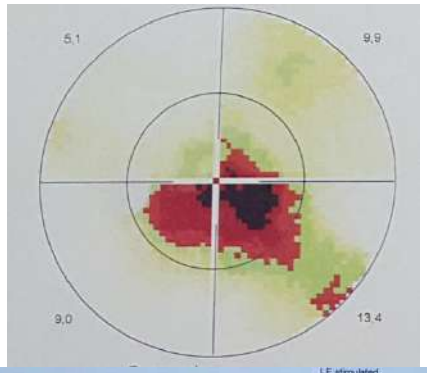
- Therefore, the transformation and proliferation abilities are very important after subretinal/ intravitreal stem cell therapy.

Gimble, J.M., Katz, A.J., Bunnell, B.A. Adipose-derived stem cells for regenerative medicine. Circ. Res. 2007; 100: 1249–1260.

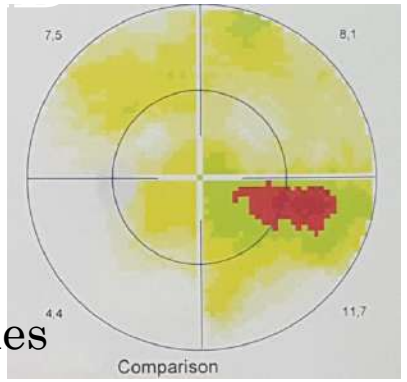
SUPRACHOROİDAL ADİPOSE DERİVED MSC

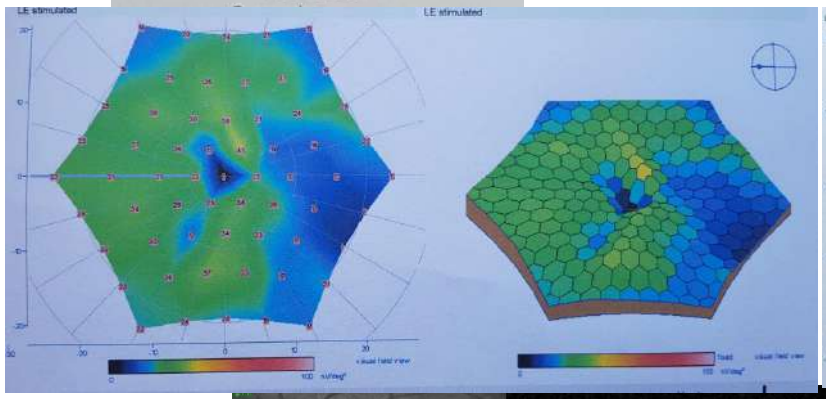
- In another study we aimed to investigate the safety and efficacy of suprachoroidal adipose tissue-derived mesenchymal stem cell (ADMSC) implantation in patients with dry-type age-related macular degeneration (AMD) and Stargardt's macular dystrophy (SMD).
- This study included four patients with advanced-stage dry-type AMD and four patients with SMD .
- None of them had any systemic or ocular complications. All of the eight patients experienced visual acuity improvement, visual field improvement, and improvement in mf-ERG recordings.
- Stem cell treatment with suprachoroidal implantation of ADMSCs seems to be safe and effective in the treatment of dry-type AMD and SMD.

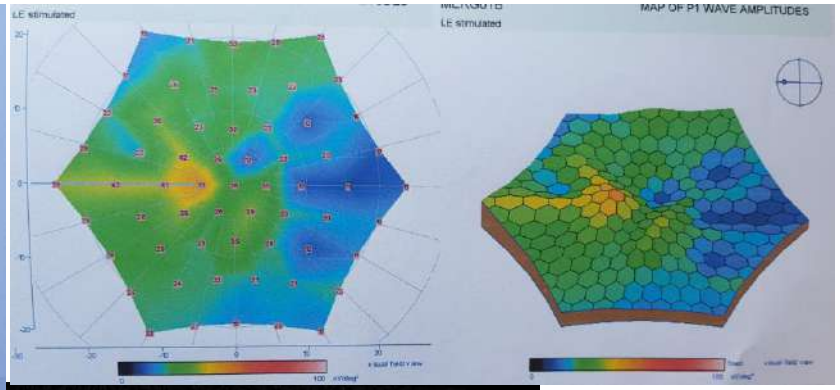
Oner A, Gonen ZB, Sevim DG, Sinim N, Unlu M. Suprachoroidal adipose tissue derived mesenchymal stem cell implantation in patients with dry type age-related maculardegeneration and Stargardt's macular dystrophy: 6 month follow-up results of a phase 2 study. Cellular Reprogramming. 2018;20(6):329-336.

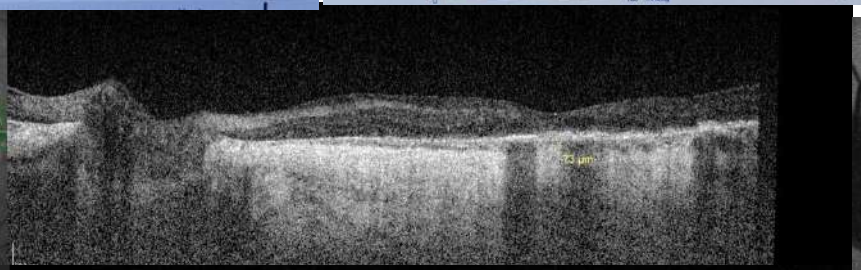


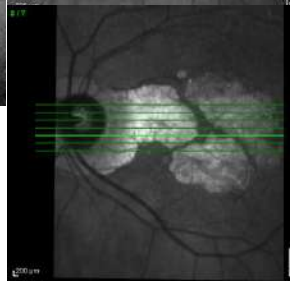
65 years old, Female ,
AMD patient
VA: Preop:1 meter counting finger
Post op: 0.05 Snellen lines

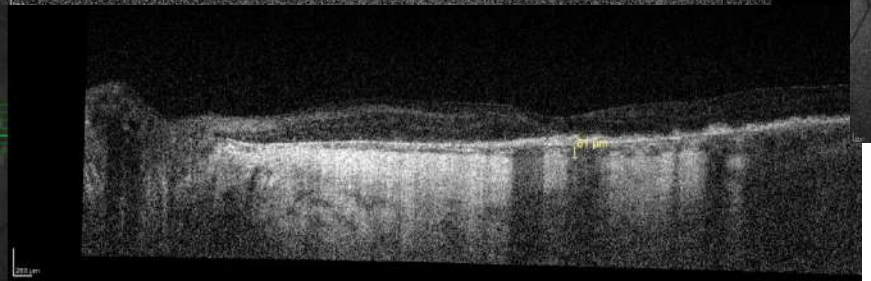


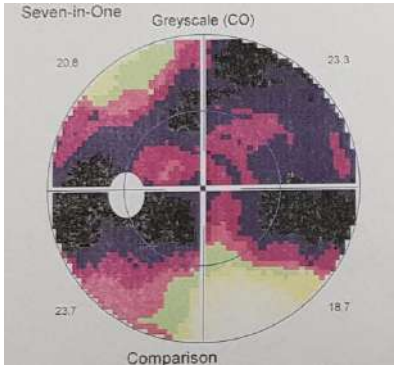




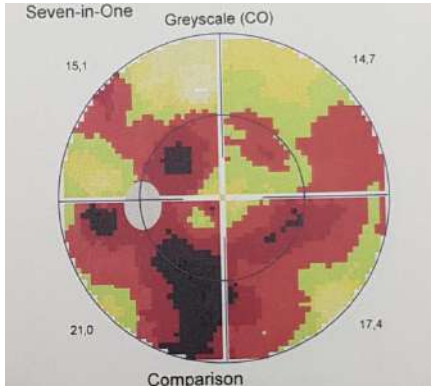


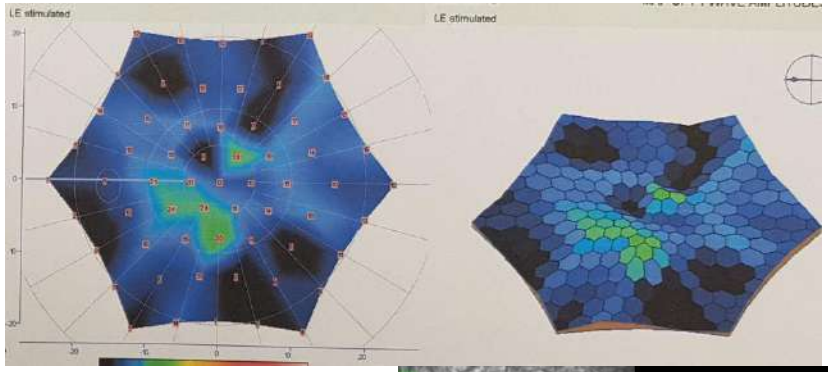


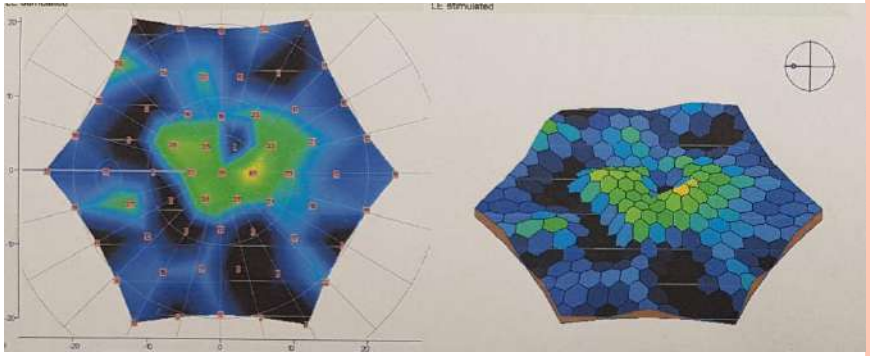


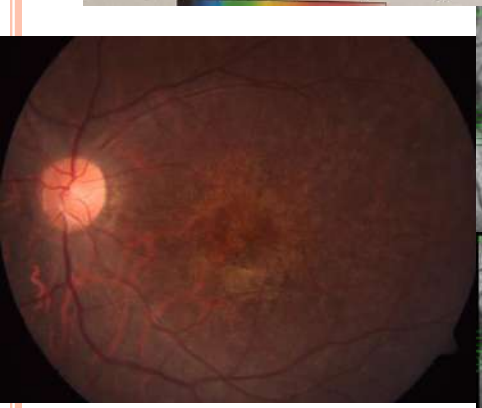


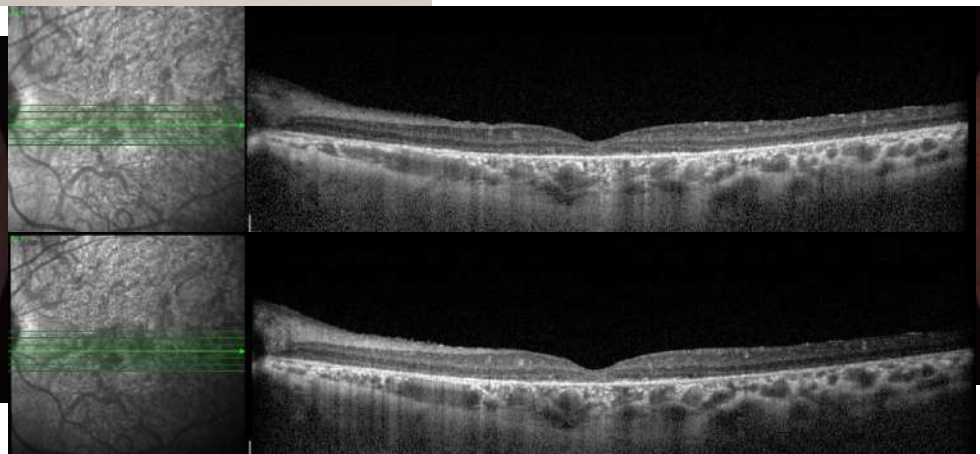
27 y Stargardts' MD
VA: From 1 mcf to 0.05

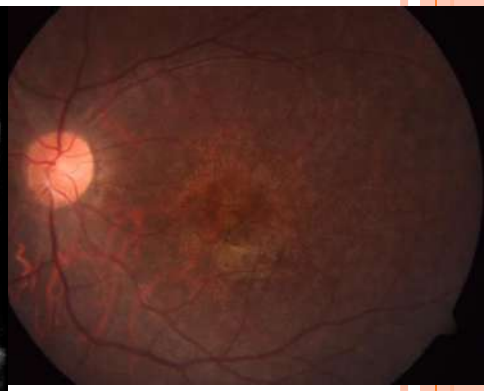






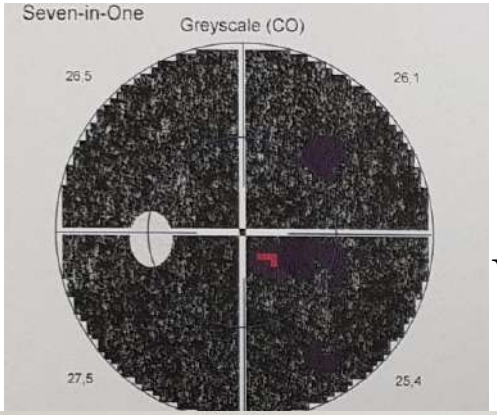




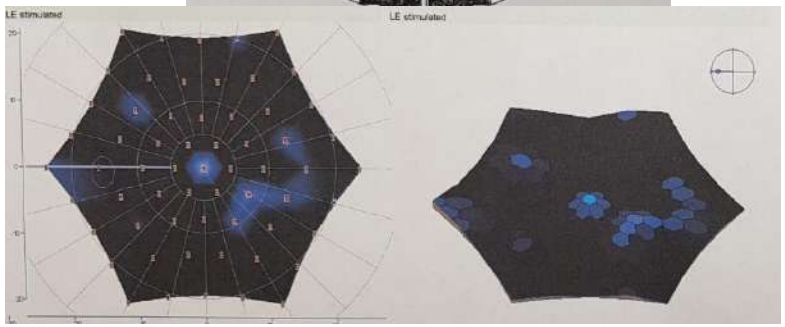


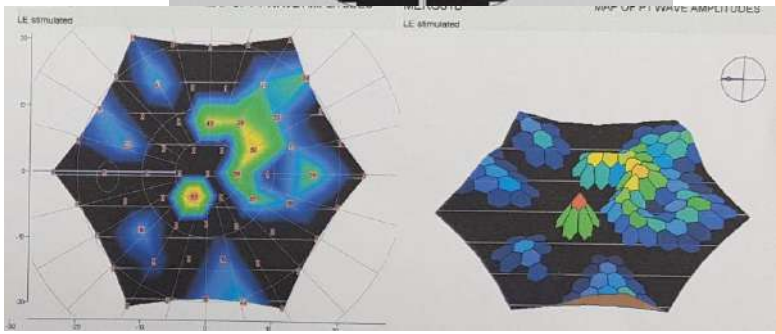
- In another patients group, same method and same stem cell source were used.
- Suprachoroidal adipose tissue-derived MSC implantation in patients with optic nerve diseases was performed.
- This prospective, single-center, phase ½ study enrolled 4 eyes of 4 patients with optic atrophy of various reasons.
- None of them had any systemic or ocular complications. All of the patients experienced visual acuity improvement, visual field improvement and improvement in the mfERG recordings.

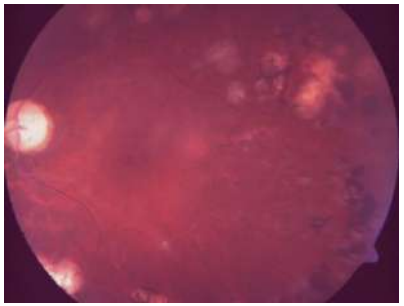
Oner A, Gonen ZB, Sevim DG, Sinim N, Unlu M. Six-month results of suprachoroidal adipose tissue derived mesenchymal stem cell implantation in patients with optic atrophy: A phase 1/2 study. Int Ophthalmology. 2019; 15.

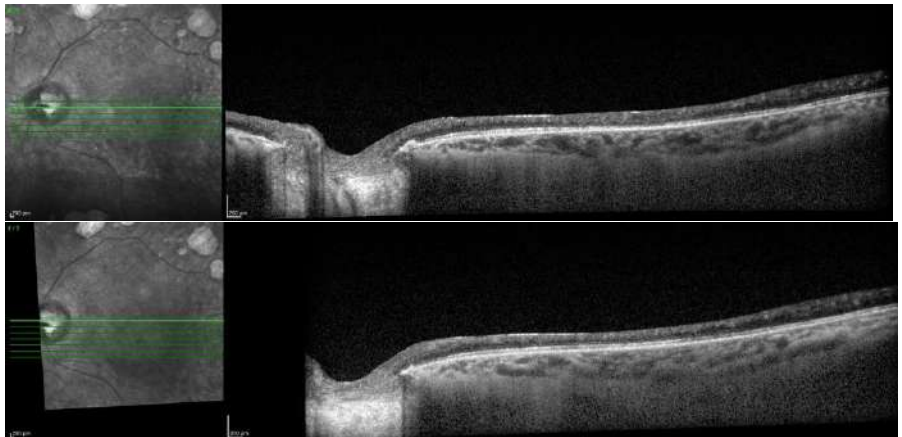


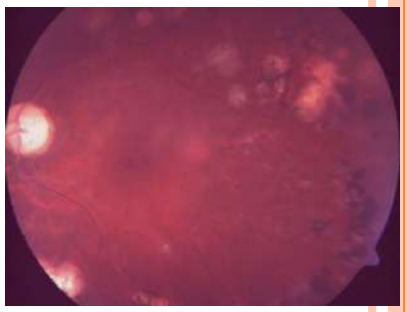
60 years, Male,
Diabetic OA
VA: Preop:30cm HM
Postop: 1 m. CF











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Suprachoroidal Umbilical cord derived MSC

- Prospective, single-center, phase 3 clinical study enrolled 124 eyes of 82 patients who had a confirmed diagnosis of RP.
- The patients received 5 million UC-MSCs to the suprachoroidal area with the same surgical procedure.
- There were statistically significant improvements in BCVA and VF during the study. The amplitudes of the P1 waves in the central areas showed significant improvements in mfERG recordings.

Vaka


There is always a way.