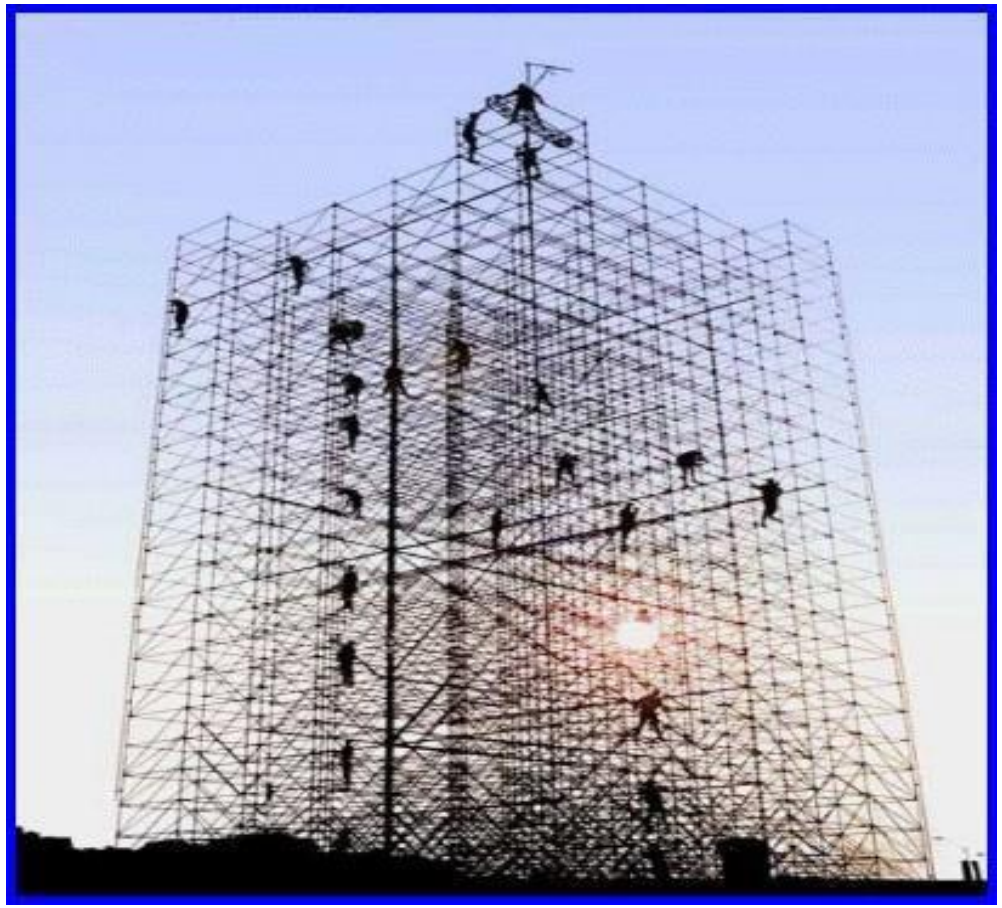
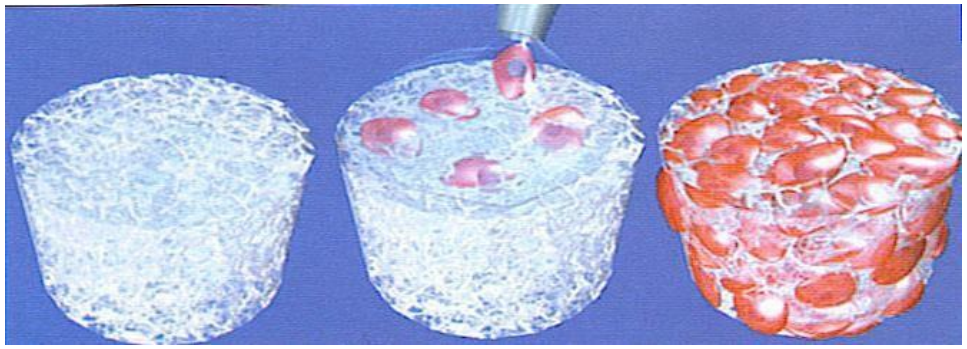
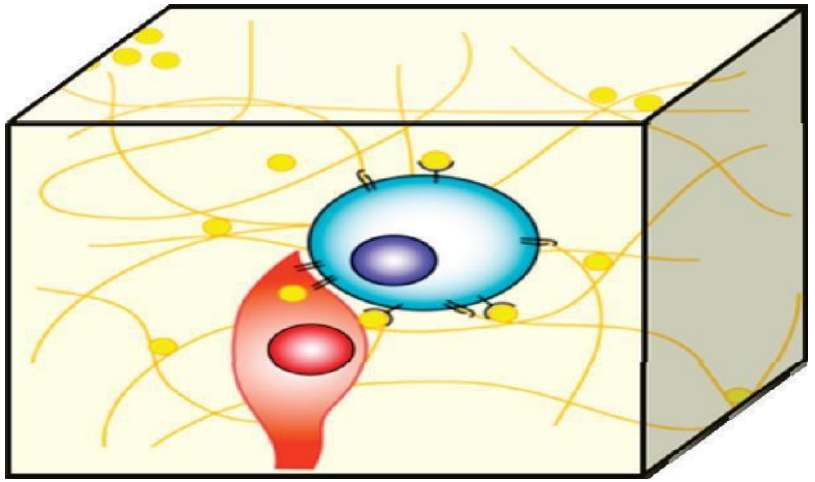
RETİNADA DOKU MÜHENDİSLİĞİ UYGULAMALARI
PROF DR AYŞE ÖNER Acıbadem Atakent Hastanesi





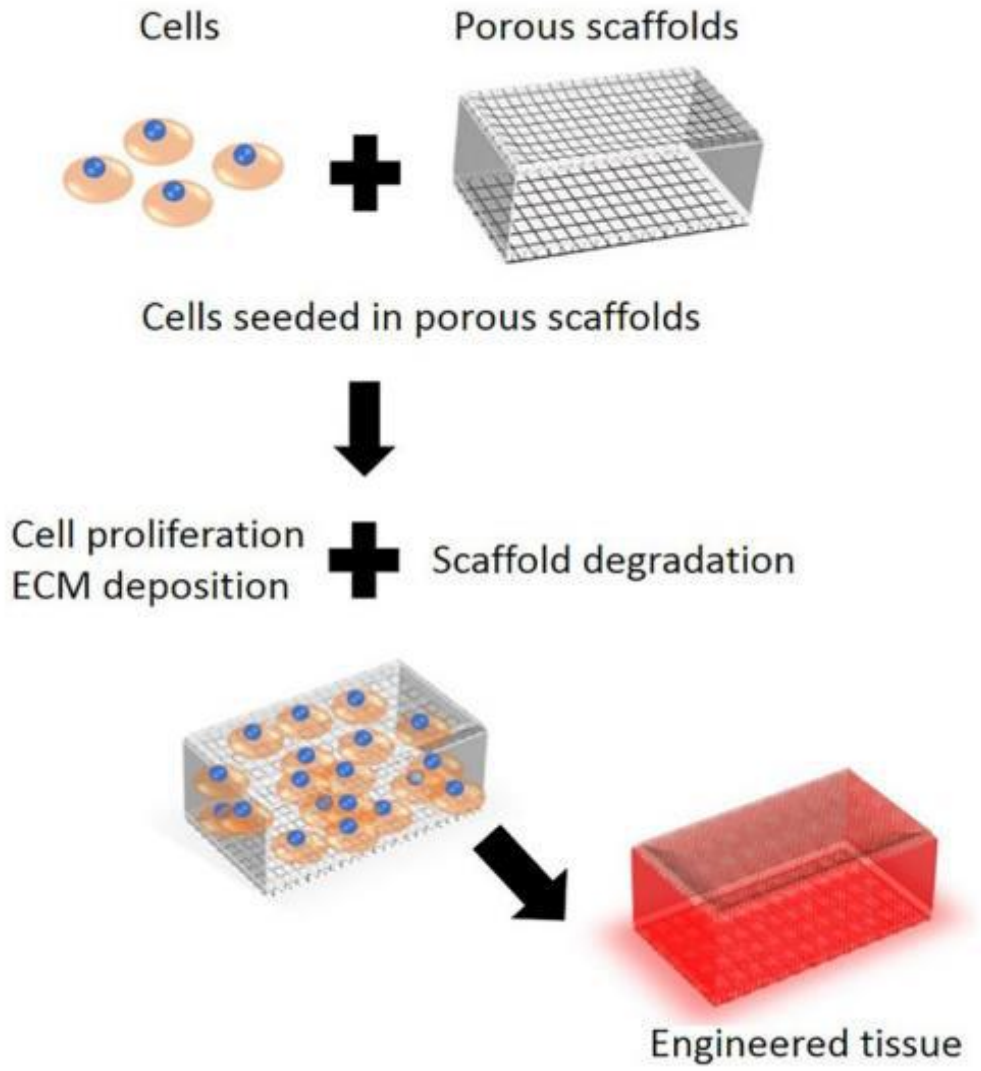


Doku mühendisliği triadı:

1-Skaffoldlar- İskeleler

2-Hücreler

3-Büyümeyi stimüle edici faktörler



OFTALMOLOJİDE DOKU MÜHENDİSLİĞİ ÜRÜNLERİ

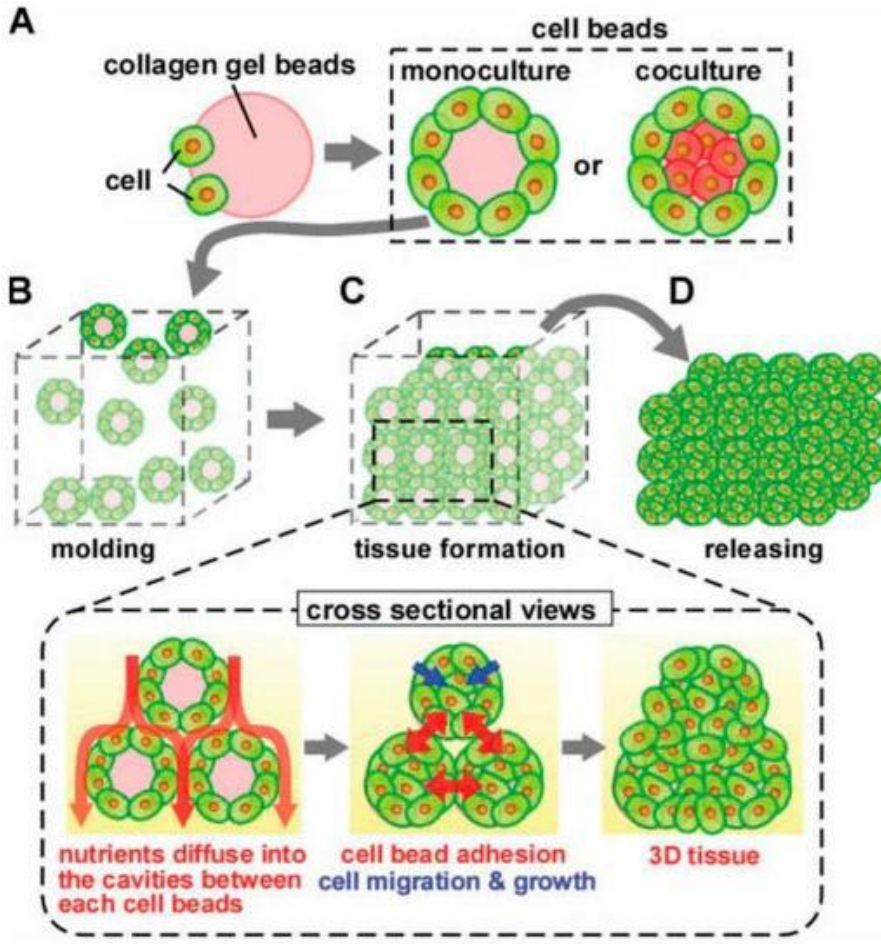
- Fibrin Glue: Doku yapıştırıcısı ve büyüme faktörü taşıyıcısı olarak kullanılır.
- Orbital implant: Biyoaktif camlar, cam seramikler, hidroksiapatit ürünleri

NEDEN DOKU MÜHENDİSLİĞİ GEREKLİ

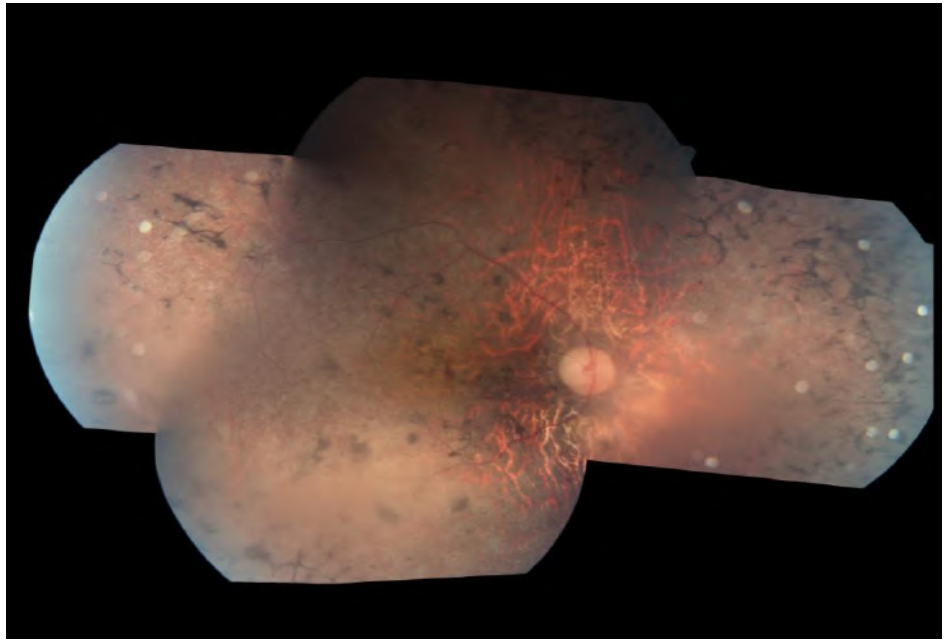
Hücrelerin doğru ve düzenli yerleşimi, adezyonu

İntegrasyonunu, proliferasyonu

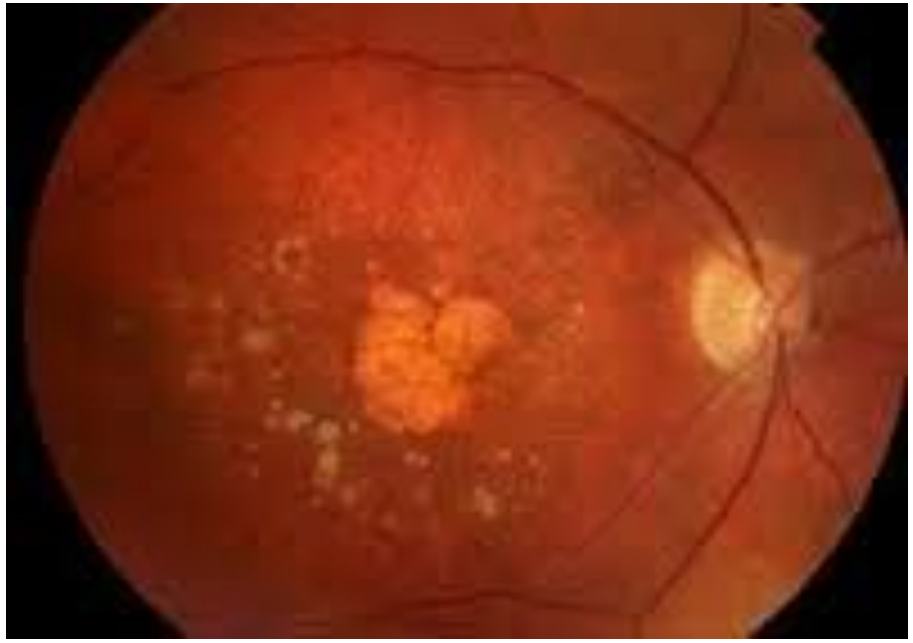
Düzenli differensiasyonunu sağlamak için



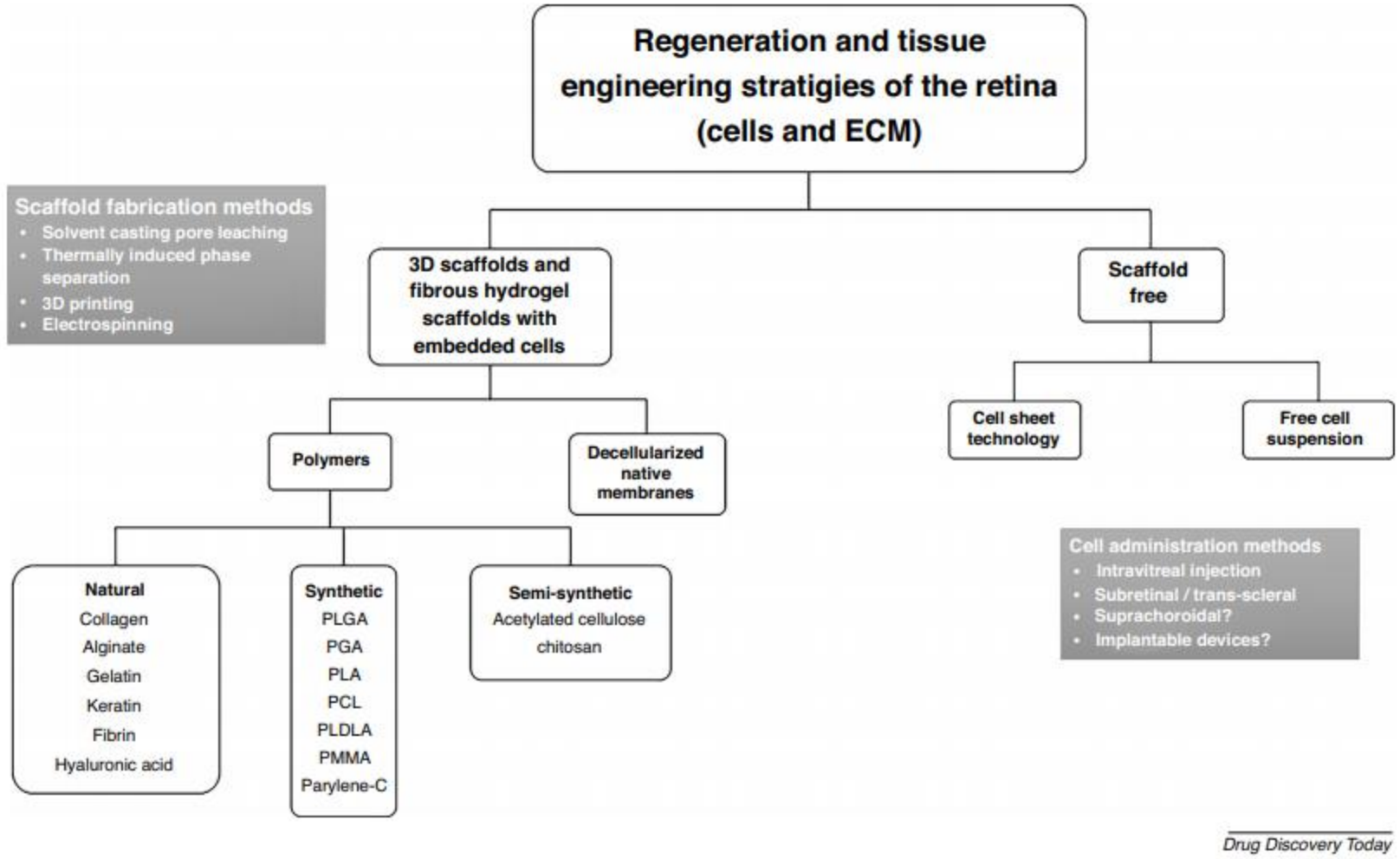
DOKU MÜHENDİSLİĞİ VE RETİNAL HASTALIKLAR



RP



YBMD

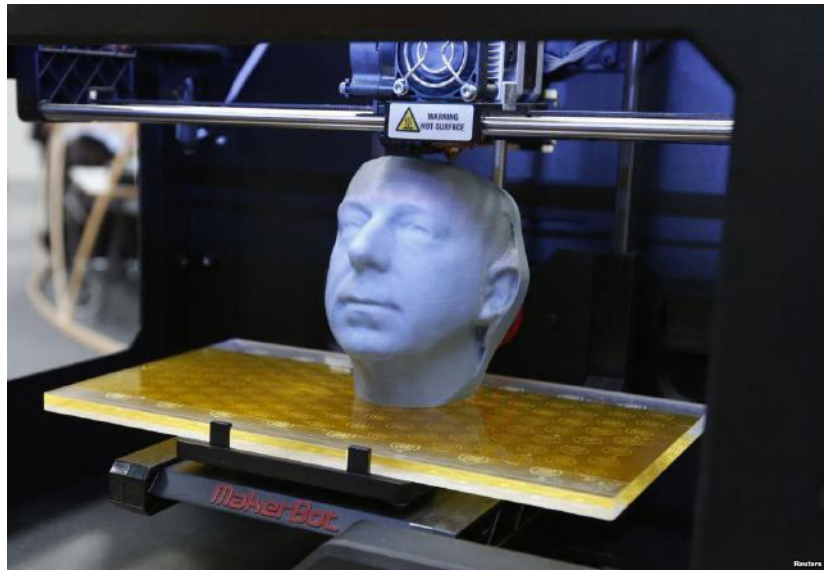

Regeneration and tissue engineering stratigies of the retina (cells and ECM)
Scaffold fabrication methods
Solvent casting pore leaching
Thermally induced phase separation
3D printing
Electrospinning
3D scaffolds and fibrous hydrogel scaffolds with embedded cells
Scaffold free
Polymers
Decellularized native membranes
Cell sheet technology
Free cell suspension
Natural
Collagen
Alginate
Gelatin
Keratin
Fibrin
Hyaluronic acid
Synthetic
PLGA
PGA
PLA
PCL
PLDLA
PMMA
Parylene-C
Semi-synthetic
Acetylated cellulose
chitosan
Cell administration methods
Intravitreal injection
Subretinal / trans-scleral
Suprachoroidal?
Implantable devices?
Drug Discovery Today

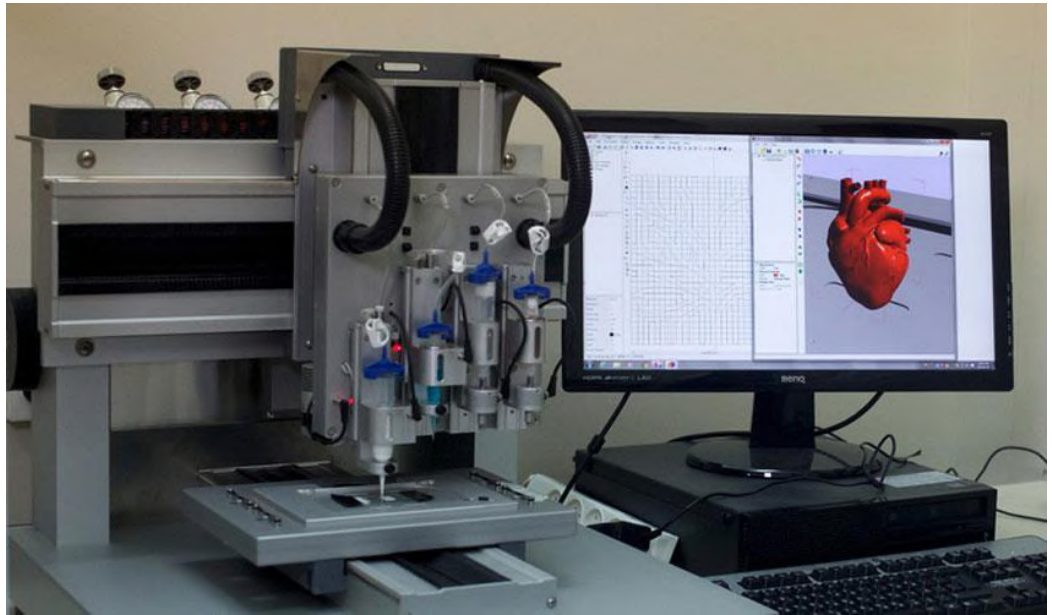
3D Bioprinting yöntemleri

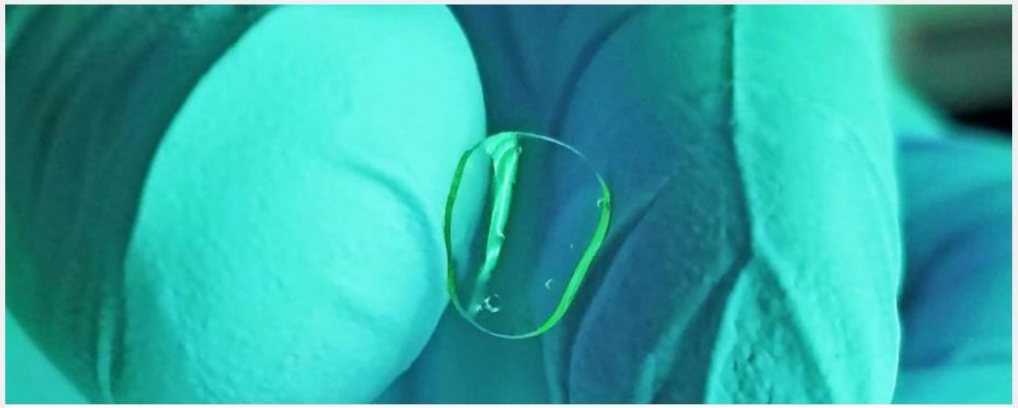
1-İnkjet bioprinting

2-Laser-assisted bioprinting

3- Extrusion bioprinting







BIOPRINTED CORNEAS ARE NEARLY READY FOR HUMAN TRIALS, SAYS STARTUP

3D bioprinting teknolojisi kornea, retina ve konjonktivada çalışılmaktadır.

3D RETİNA PRİNTLENMESİNDEKİ ZORLUKLAR

İnsan retinası oldukça kompleks, çok tabakalı, vaskülarize bir doku

Çok yüksek dansitede hücre içeriği: 60 farklı hücre tipi

Hücrelerin birbirleriyle sinaps yapması gerekliliği.

,

RETİNADA KULLANILAN BİYOMATERYAL İSKELELER

- BrM
- Amniotik membran
- Aljinat
- Sellüloz
- İpek
- Hyaluronik asit
- Desellularize retinal ESM

International Journal of
Molecular Sciences

MDPI

Article

Development of 3D Printed Bruch's Membrane-Mimetic Substance for the Maturation of Retinal Pigment Epithelial Cells

Jongmin Kim [1], Ju Young Park [1], Jeong Sik Kong [2], Hyungseok Lee [1,3], Jae Yon Won [4,5,*] and Dong Woo Cho [1,2,6,*]

Review

Tissue engineering of retina and Bruch's membrane: a review of cells, materials and processes

Yong Sheng Edgar Tan,[1] Pu Jiang Shi,[1] Chang-J Choo,[2] Augustinus Laude,[2] Wai Yee Yeong[1]

Biofabrication

International Society for Biofabrication

ACCEPTED MANUSCRIPT

Tissue engineering of retina through high resolution 3-dimentional inkjet bioprinting

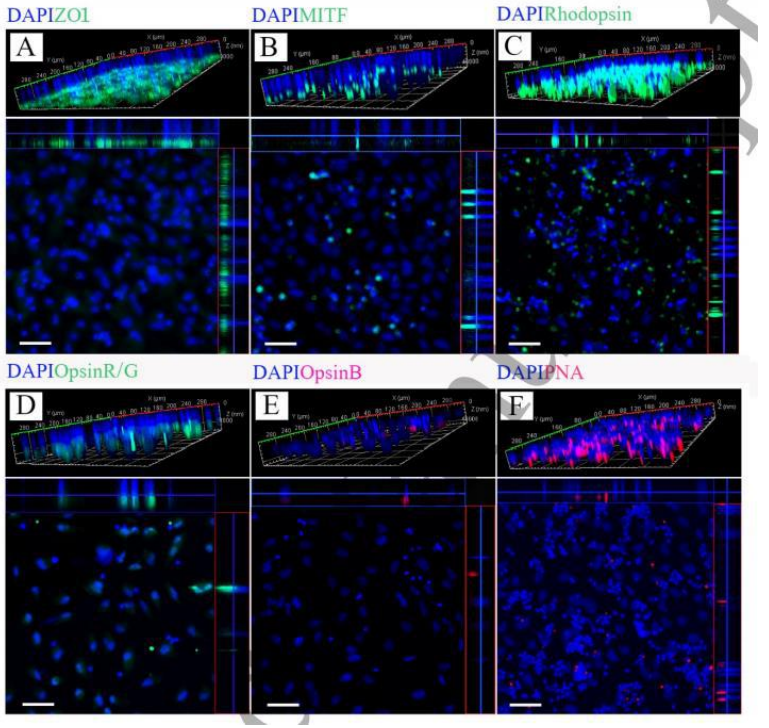
To cite this article before publication: Elahe Masaeli *et al* 2019 *Biofabrication* in press https://doi.org/10.1088/1758-5090/ab4a20

RPE ve fotoreseptörler biyoprinting yöntemiyle yapılandırılmış

RPE'lerin VEGF salgıladığı

RPE lerin apikal mikrovilluslu yapı gösterdiği

Fotoreseptörleri fagosite ettiği belirlenmiştir.



Control of Retinal Ganglion Cell Positioning and Neurite Growth: Combining 3D Printing with Radial Electrospun Scaffolds

Karl E. Kador, PhD,[1,*,†] Shawn P. Grogan, PhD,[2,†] Erik W. Dorthé, MS,[2] Praseeda Venugopalan, MS,[1] Monisha F. Malek, BS,[1] Jeffrey L. Goldberg, MD, PhD,[1,3] and Darryl D. D'lima, MD, PhD[2]

RGH'leri 3D biyoprinting ile yapılandırılmış

Ortama brain-derive nörotrofik faktör (BDNF) ve silier nörotrofik faktör (CNTF)

eklendiğinde hücrelerin yaşamlarına devam ettiği radiyal akson büyümesi gösterdiği saptanmıştır.

PUBLISHING PTE. LTD.

RESEARCH ARTICLE

Hybrid three-dimensional (3D) bioprinting of retina equivalent for ocular research

Pujiang Shi[1], Tan Yong Sheng Edgar[1], Wai Yee Yeong[1*] and Augustinus Laude[2]

[1] Singapore Centre for 3D Printing, School of Mechanical and Aerospace Engineering, Nanyang Technological University, 50 Nanyang Avenue Singapore 639798

[2] National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore 308433

Article

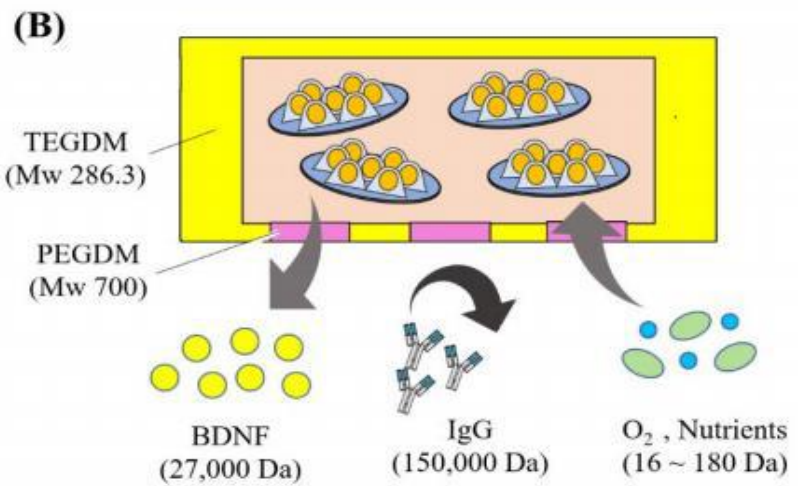
A 3D Printed Self-Sustainable Cell-Encapsulation Drug Delivery Device for Periocular Transplant-Based Treatment of Retinal Degenerative Diseases

Hideto Kojima [1], Bibek Raut [1], Li-Jiun Chen [1], Nobuhiro Nagai [2], Toshiaki Abe [2] and Hirokazu Kaji [1,3,*]

İnsan retinal pigment epitel hücreleri (ARPE-19)

Polistiren sheet üzerine yerleştirilip kollajen ile kaplanarak ilaç salınım sistemleri yapılmış

Hücrelerin yaşam süreleri daha uzamış



RETİNAL HASTALIKLARDA

KLİNİK DOKU MÜHENDİSLİĞİ UYGULAMALARI

CELL SHEET- Hücre Tabakası

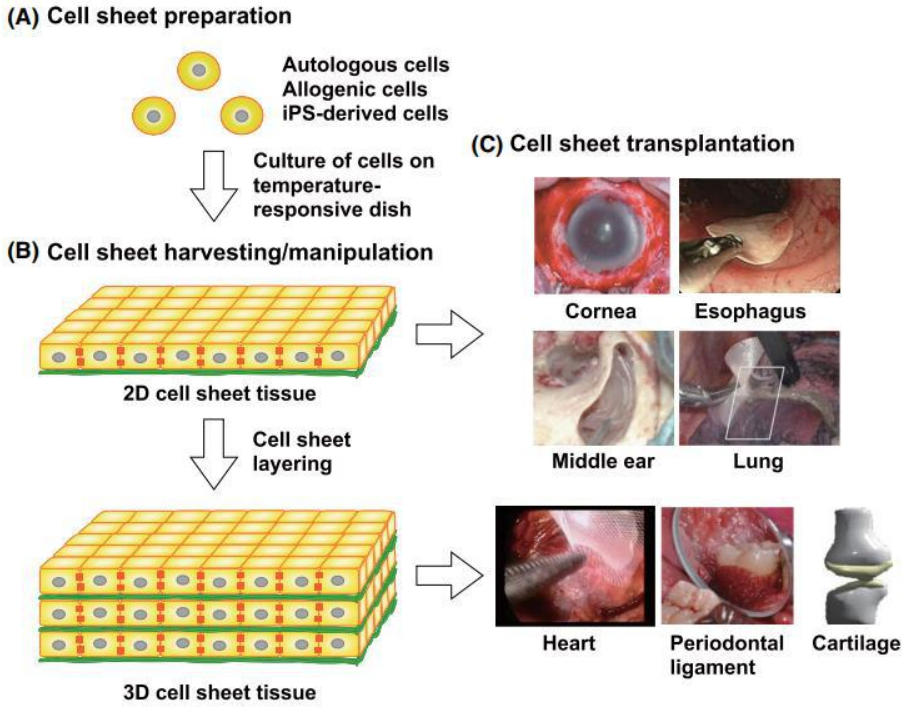
Hücreler polimer tabakalar (Örn: N-isopropilakrilamid) üzerine yerleştirilerek çoğaltılır.

Bu şekilde üretilen hücreler çoklu tabaka haline getirilir.

Special Issue

Cell sheet tissue engineering: Cell sheet preparation, harvesting/manipulation, and transplantation

Jun Kobayashi [1], Akihiko Kikuchi [2], Takao Aoyagi [3], Teruo Okano [1,4]



SUBRETINAL RPE SHEET ENJEKSİYONU

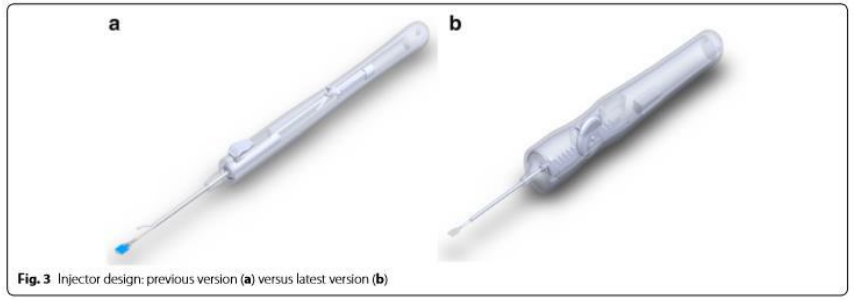


Fig. 3 Injector design: previous version (**a**) versus latest version (**b**)

ENJEKTÖR

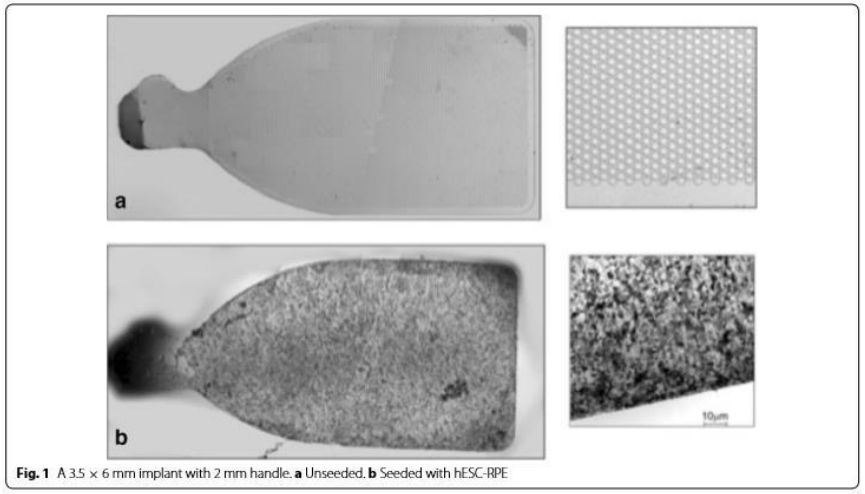


Fig. 1 A 3.5 × 6 mm implant with 2 mm handle. **a** Unseeded. **b** Seeded with hESC-RPE

RPE SHEET

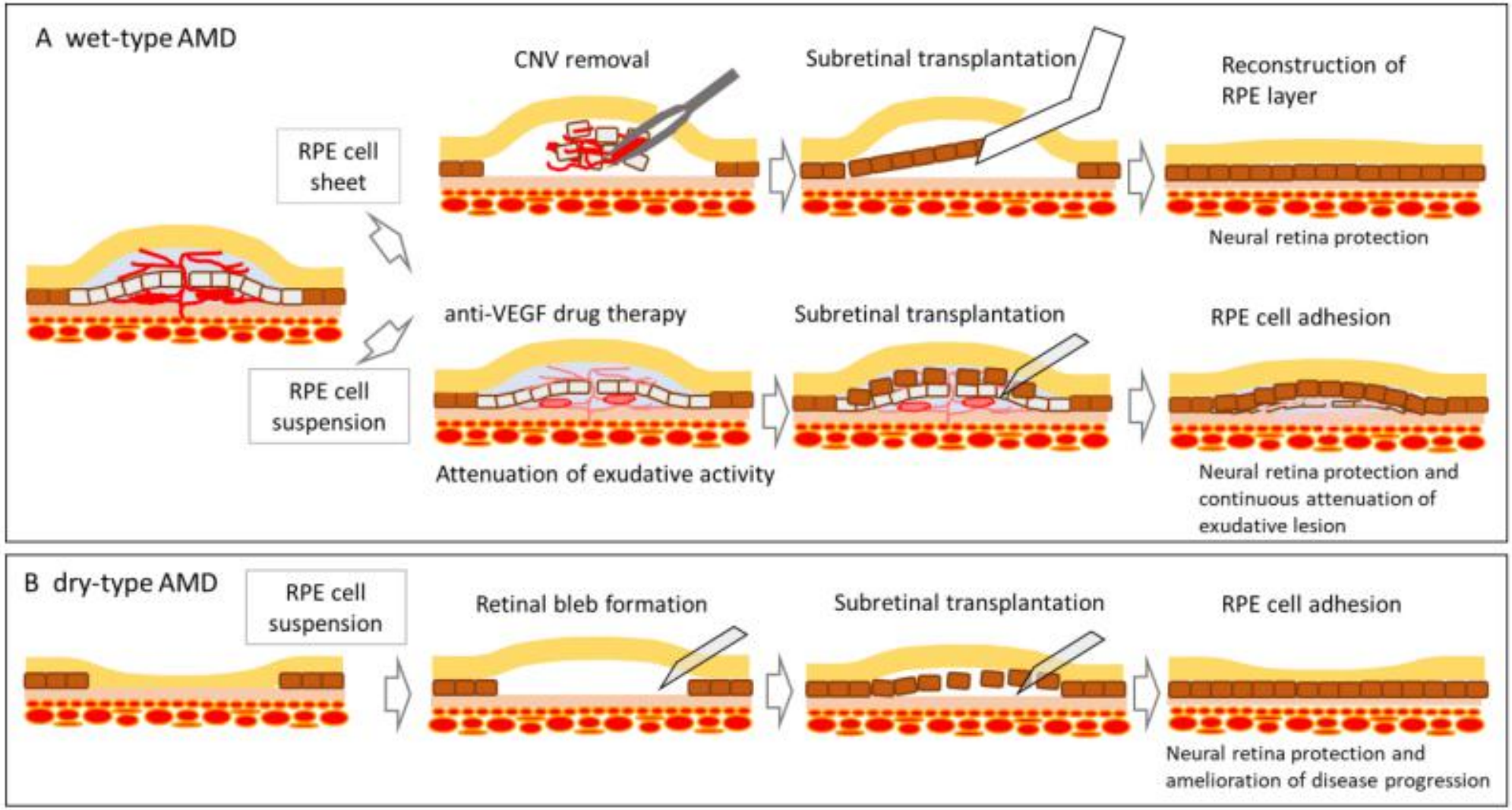
Fernandes *et al. Int J Retin Vitr (2017) 3:41*
DOI 10.1186/s40942-017-0095-6

International Journal of Retina and Vitreous

ORIGINAL ARTICLE Open Access

Development of a new tissue injector for subretinal transplantation of human embryonic stem cell derived retinal pigmented epithelium

Rodrigo A. Brant Fernandes[1,2†], Francisco R. Stefanini[1,2*†], Paulo Falabella[1,2], Michael J. Koss[1,3], Trent Wells[1], Bruno Diniz[1,2], Ramiro Ribeiro[1,2], Paulo Schor[2], Mauricio Maia[2], Fernando M. Penha[2,4], David R. Hinton[1,6], Yu-Chong Tai[5] and Mark Humayun[1,7]


A wet-type AMD
CNV removal
Subretinal transplantation
Reconstruction of RPE layer
RPE cell sheet
Neural retina protection
anti-VEGF drug therapy
Subretinal transplantation
RPE cell adhesion
RPE cell suspension
Attenuation of exudative activity
Neural retina protection and continuous attenuation of exudative lesion
B dry-type AMD
RPE cell suspension
Retinal bleb formation
Subretinal transplantation
RPE cell adhesion
Neural retina protection and amelioration of disease progression

DEVAM EDEN KLİNİK ÇALIŞMALAR

- EKH, İPKH

- YBMD, Stargardt ve RP

- Japonya, Amerika, İngiltere, Çin

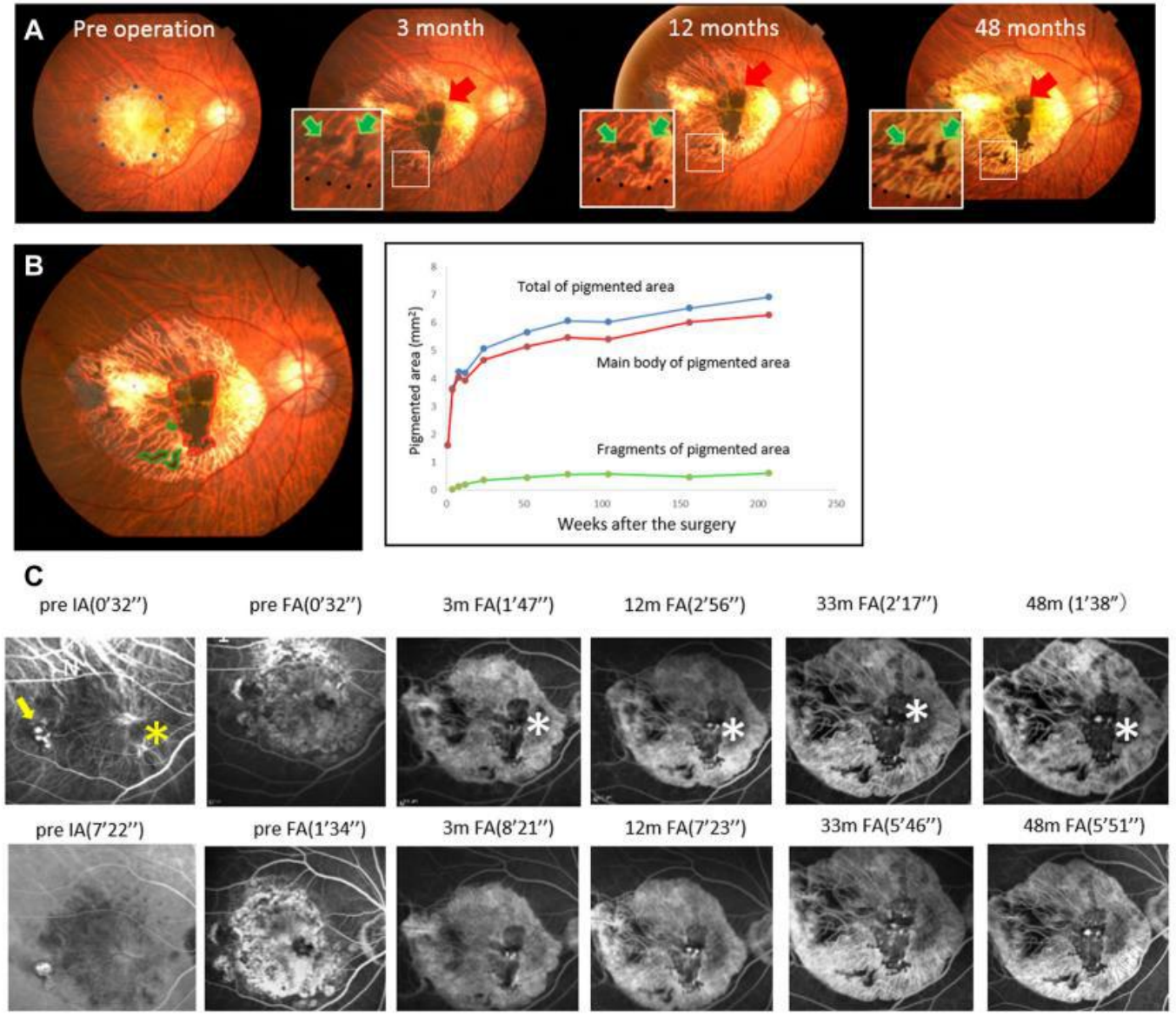
- Clinical Trials da kayıtlı 19 klinik çalışma mevcuttur.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Evaluation of Transplanted Autologous Induced Pluripotent Stem Cell-Derived Retinal Pigment Epithelium in Exudative Age-Related Macular Degeneration

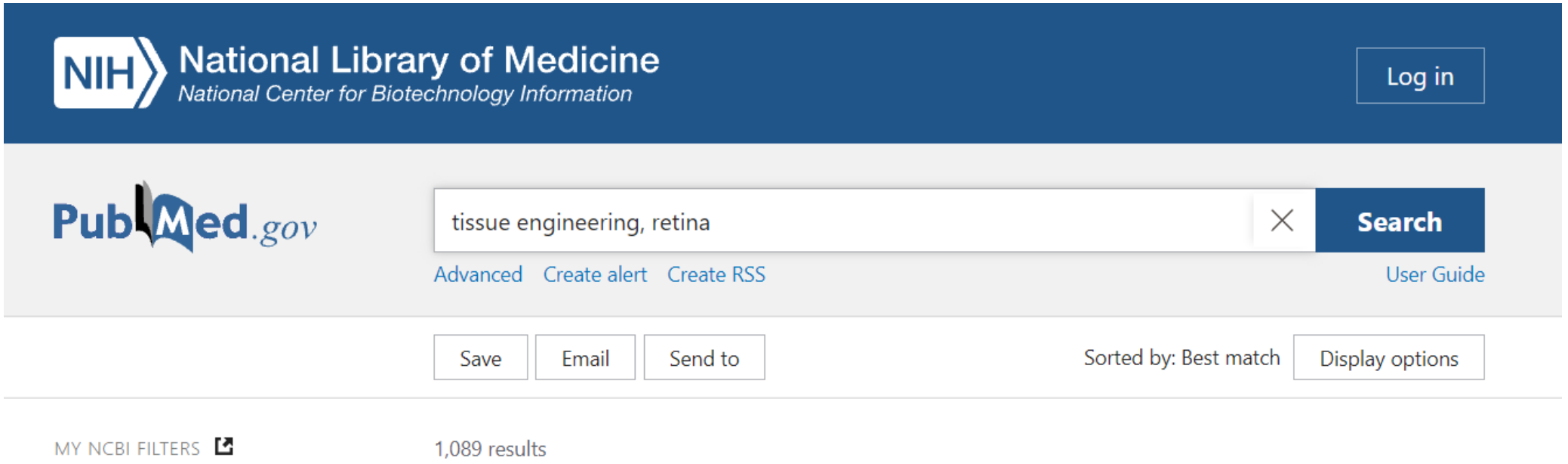
Seiji Takagi, MD, PhD,[1,2] *Michiko Mandai, MD, PhD,*[1,3] *Kiyoko Gocho, MD, PhD,*[4] *Yasuhiko Hirami, MD, PhD,*[1,3,5] *Midori Yamamoto, BA,*[1] *Masashi Fujihara, MD, PhD,*[1,5] *Sunao Sugita, MD, PhD,*[1,3] *Yasuo Kurimoto, MD, PhD,*[1,3,5] *Masayo Takahashi, MD, PhD*[1,3]

Tek olgu 4 yıllık takip otolog IPKH derive RPE sheet uygulaması



RPE grefti 4 yıl boyunca yaşamını sürdürmüş ve alanı genişlemiş

Doku mühendisliği ve retina



DOI: 10.4274/tjo.20270
Turk J Ophthalmol 2018;48:190-195

Original Article

The Effects of Anti-Vascular Endothelial Growth Factor Drugs on Retinal Pigment Epithelial Cell Culture

Mustafa Şahiner*, Dilek Bahar**, Ayşe Öner*, Zeynep Burçin Gönen***, Metin Ünlü*, Duygu Gülmez Sevim*, Çağatay Karaca*, Galip Ertuğrul Mirza*

*Erciyes University Faculty of Medicine, Department of Ophthalmology, Kayseri, Turkey
**Erciyes University Betül-Ziya Eren Genome and Stem Cell Center, Kayseri, Turkey
***Erciyes University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Kayseri, Turkey

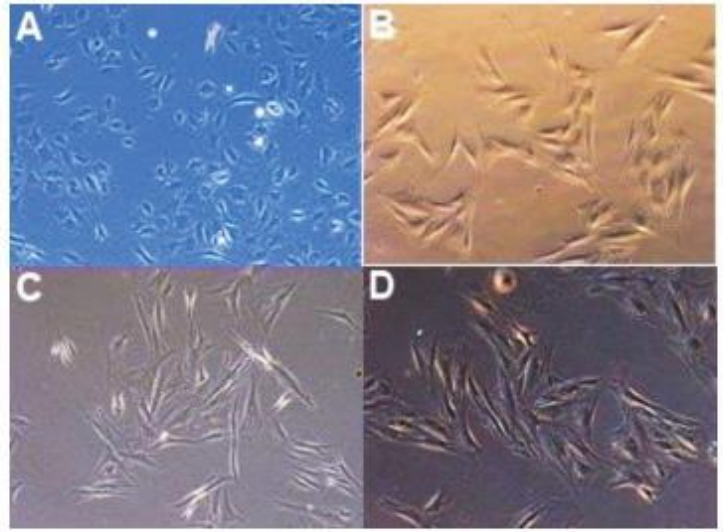


Figure 1. Comparison of phase-contrast microscopic appearance of 3 anti-vascular endothelial growth factor drugs and control culture showed no morphological changes of the retinal pigment epithelium (RPE) cell culture with any drug, and RPE cells maintain the hexagonal morphology at the end of 72 hours in the (A) control, (B) aflibercept (0.5 mg/mL), (C) bevacizumab (0.3125 mg/mL), and (D) ranibizumab (0.125 mg/mL) groups

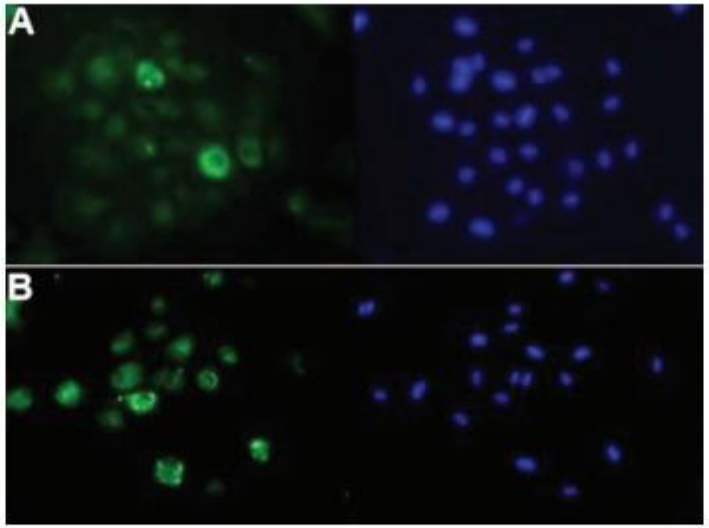


Figure 2. Immunocytochemistry staining of retinal pigment epithelium cell culture demonstrates expression of cytokeratin 18 (A) and tight junction protein zonula occludens protein 1 (B)

1. 100 mikron çapında 100 bin hücre topluluğu termoresponsif polimer ile kaplanmış,

   40-45 kürecik polietilen glikol matriks ile çevrelenmiştir.

2. Sferoid MKH, kendi mikroçevrelerini oluşturur, ortamda uzun süre kalabilir.

3. Sferoidlerin yapısı daha geç bozulur, dış ortamdan daha az etkilenir, etkinliği uzun sürer.

Today's science fiction, is often **tomorrow's science** fact

Bugünün bilim kurgusu, sıklıkla yarının bilim gerçeğidir