GEN KÖK
Genom ve Kök Hücre Merkezi
Genome and Stem Cell Center

KÖK HÜCRE TEDAVİSİNİN BUGÜNÜ VE GELECEĞİ

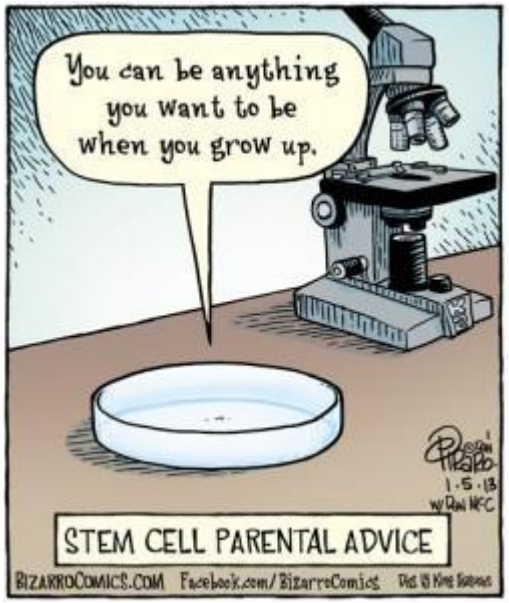
Prof.Dr. Ayşe Öner, FEBO
Erciyes Universitesi Tıp Fakültesi
Göz Hastalıkları AD KAYSERİ
ZONGULDAK OFTALMOLOJİ KURSU
HAZİRAN 2016

ERCİYES ÜNİVERSİTESİ
1978

KÖK HÜCRE NEDİR?

Kök Hücre:

* Hücrenin özelleşmemiş en temel ve saf halidir.
* Vücuttaki pek çok hücre tipine differensiye olabilir.
* Hasarlı hücre ve dokuları onarabilir.



KÖK HÜCRENİN TARİHÇESİ

* **1981:** Fare embriyosundan embriyonik kök hücrenin elde edilmesi
* **1998:** İnsan embriyosundan labaratuar şartlarında embriyonik kök hücre elde edilmesi
* **2006:** Erişkin hücrelerin yeniden programlanarak kök hücre elde edilmesi 'indüklenmiş pluripotent kök hücre'
* **2009:** FDA onayıyla spinal kord yaralanmasında ilk insan çalışmasının başlatılması

KÖK HÜCRELERİN ÖZELLİKLERİ

- Proliferasyon
- Self-renewal: Kendini yenileme
- Differensiasyon

DİFFERENSİASYON

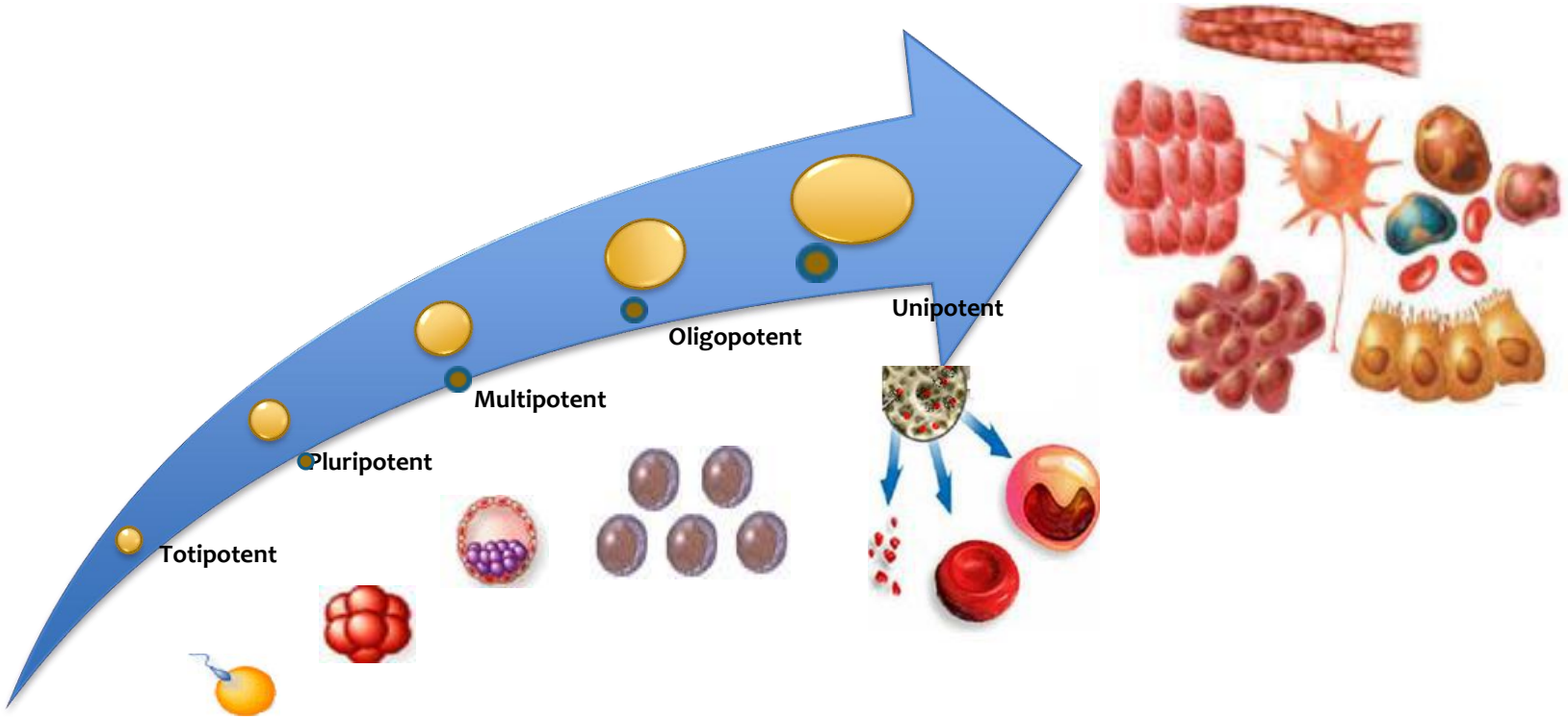
Differensiasyon: Farklı hücrelere dönüşebilir.

Bu süreçte internal ve eksternal faktörler rol alır.

İnternal faktörler: Hücrenin genleriyle ilişkilidir.

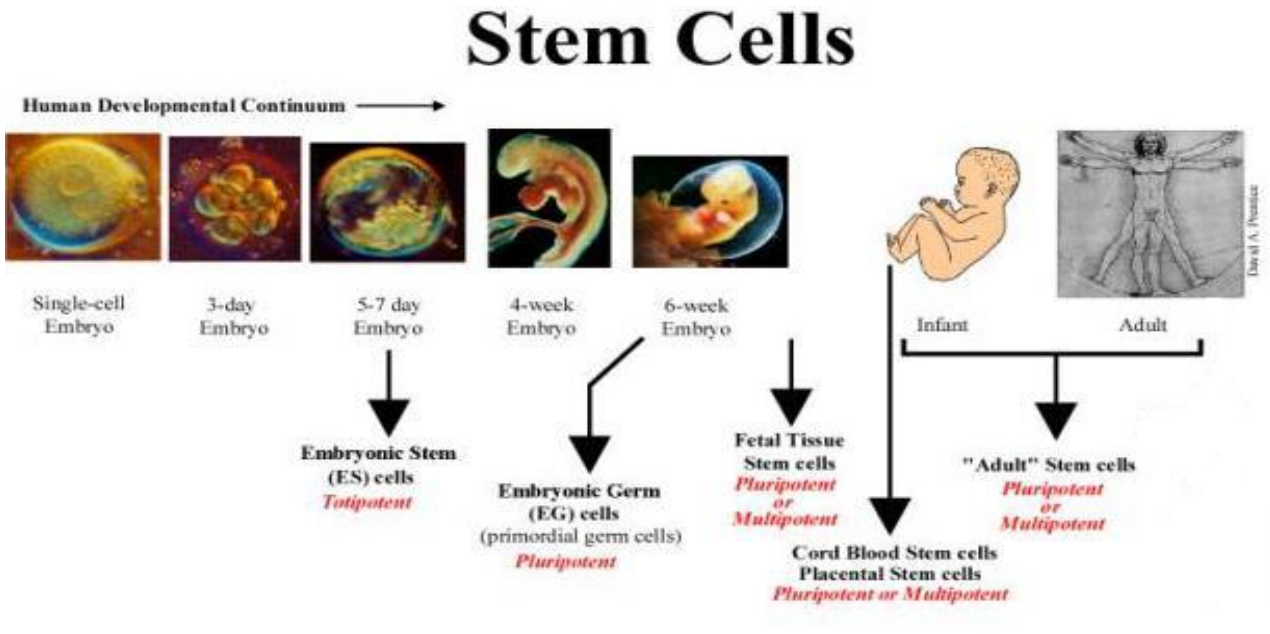
Eksternal faktörler hücrenin bulunduğu ortamdaki diğer hücreler ve moleküllerle (microenvironment) ilişkilidir..

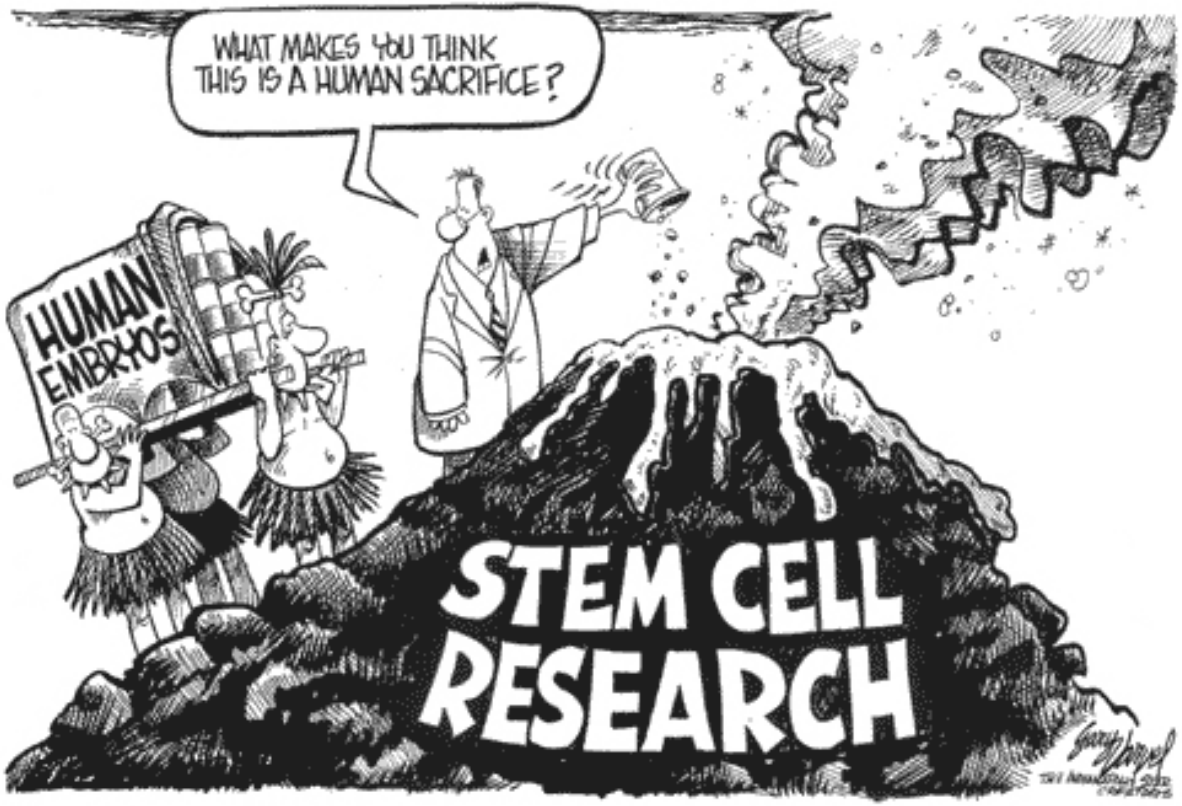
KÖK HÜCRELERİN POTANSİYELLERİ



KÖK HÜCRE TİPLERİ

1-EMBRYONİK KÖK HÜCRE
2- ERİŞKİN KÖK HÜCRE
- Mesenkimal KH
- İndüklenmiş pluripotent KH
3-KORDON KANI KÖK HÜCRESİ
4- AMNİOTİK SIVI KÖK HÜCRESİ





ETİK PROBLEMLER

ÜLKEMİZDE KÖK HÜCRE UYGULAMALARI

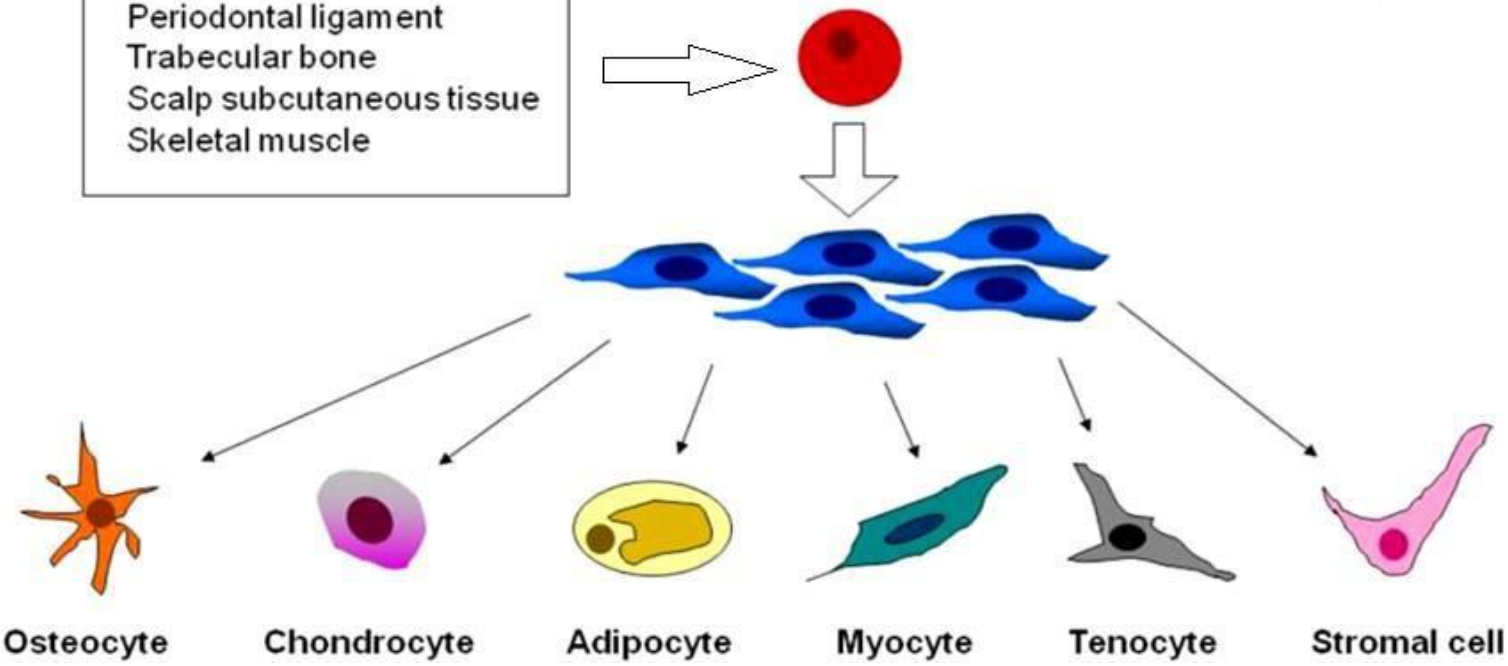
* İnsan embriyonik kök hücre kullanımı yasaktır (2005)

* Erişkin kök hücre ve İPKH kullanımı için ise Lokal Etik Kurumdan ve Sağlık Bakanlığı'ndan onay gereklidir.

(TCK: 90)

Adult tissues

- Bone marrow
- Deciduous teeth
- Fat
- Hair follicles
- Peripheral blood
- Periodontal ligament
- Trabecular bone
- Scalp subcutaneous tissue
- Skeletal muscle



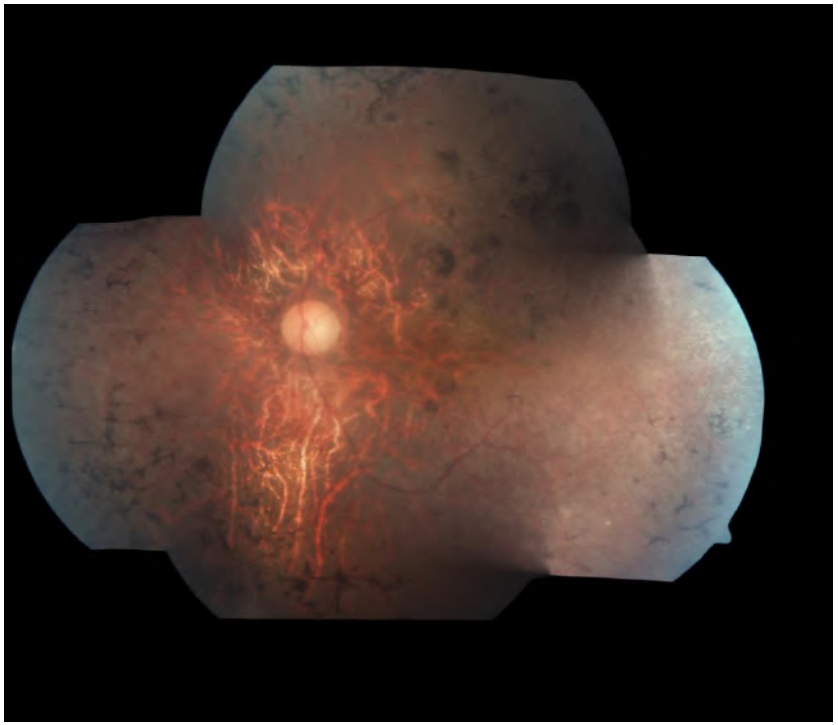
KÖK HÜCRE TEDAVİSİNİN MEKANİZMASI

* (1) Hücre Replasmanı: Sağlıklı kök hücreler dejenere hücrelerin yerini alabilir.
* (2) Nutrisyonel Destek: Sağlıklı kök hücreler salgıladıkları faktörlerle etraftaki hücrelerin yaşamlarını desteklerler.
* (3) Yeni bağlantılar oluştururlar.

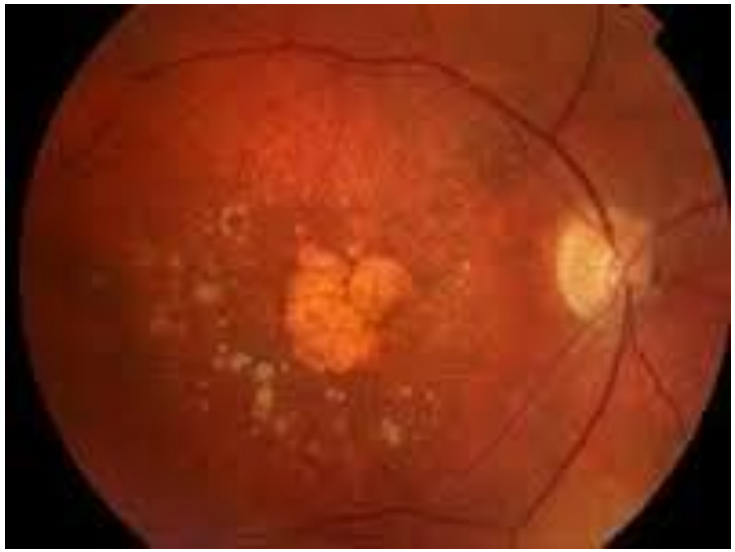
Gözde Kök Hücre Kullanımı

* Çok küçük dozlar yeterli olur.
* Cerrahi yaklaşım kolaydır.
* Nakledilen hücre kolayca izlenir.
* Gözün immün yapısı uygundur.
* Diğer göz kontrol olarak kullanılabilir.
* Ekstraoküler yayılım söz konusu değildir.

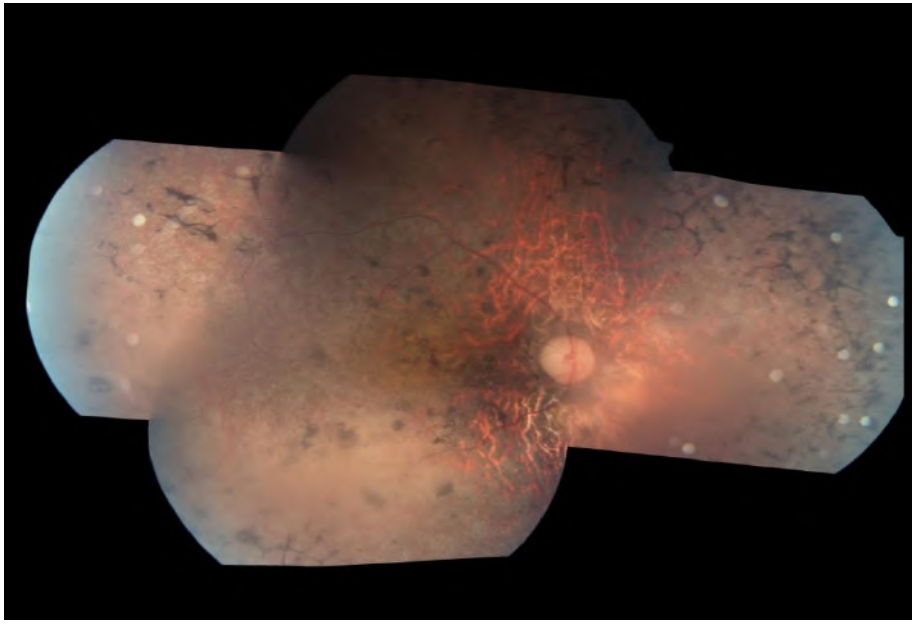
KÖK HÜCRE TEDAVİSİNİN UYGULANABİLECEĞİ RETİNAL HASTALIKLAR



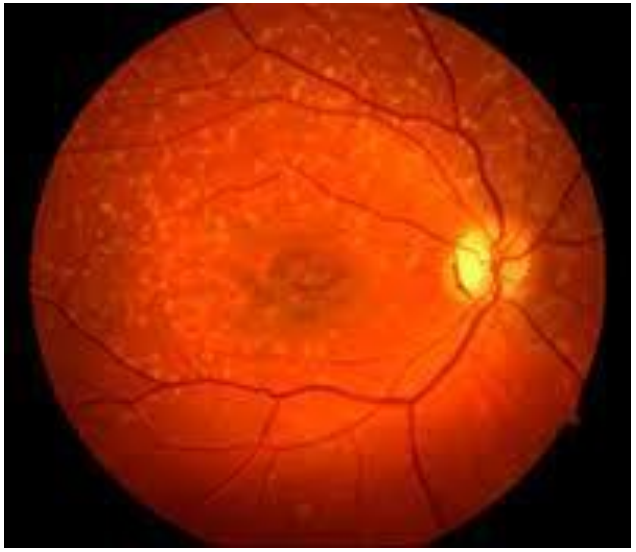
YBMD



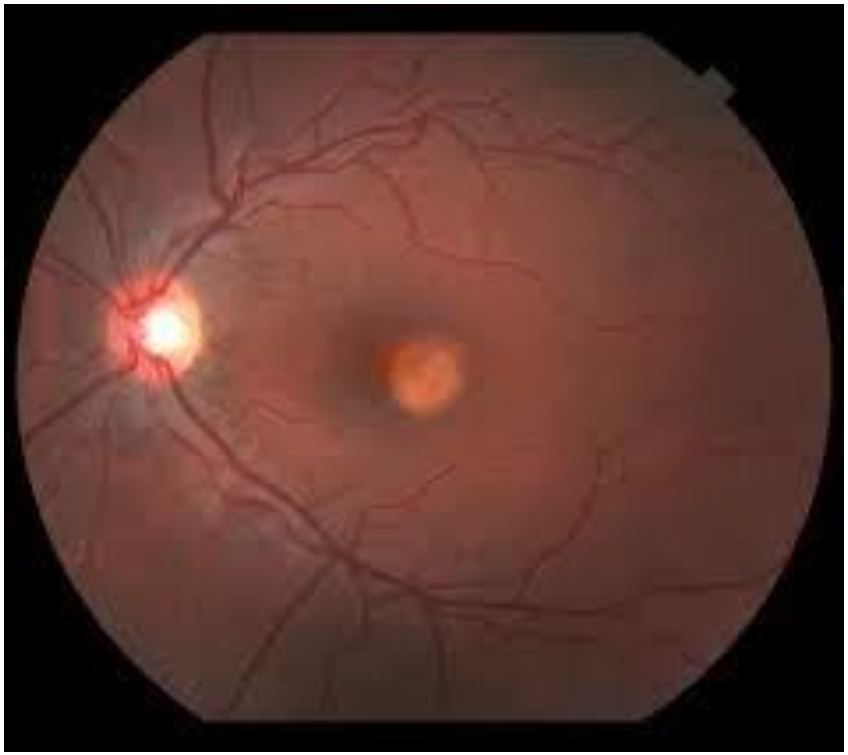
Retinitis Pigmentosa



Stargardt's MD



Best's Vitelliform MD



* KLİNİK ÇALIŞMALAR

EKH ÇALIŞMALARI

* Faz ½: Subretinal EKH
* 9 **Stargardt's MD** ve 9 kuru tip **YBMD** olgusu
* 22 ay takip
* Ciddi yan etki yok
* 13 (72%) olguda subretinal pigmentasyon artışı
* 10 olguda EİDGK artışı
* Görme ile ilgili hayat kalitesinde artış.

* Schwartz SD et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet. 2015 Feb 7;385(9967):509-16.

EKH ÇALIŞMALARI

Stem Cell Reports
Article

ISSCR

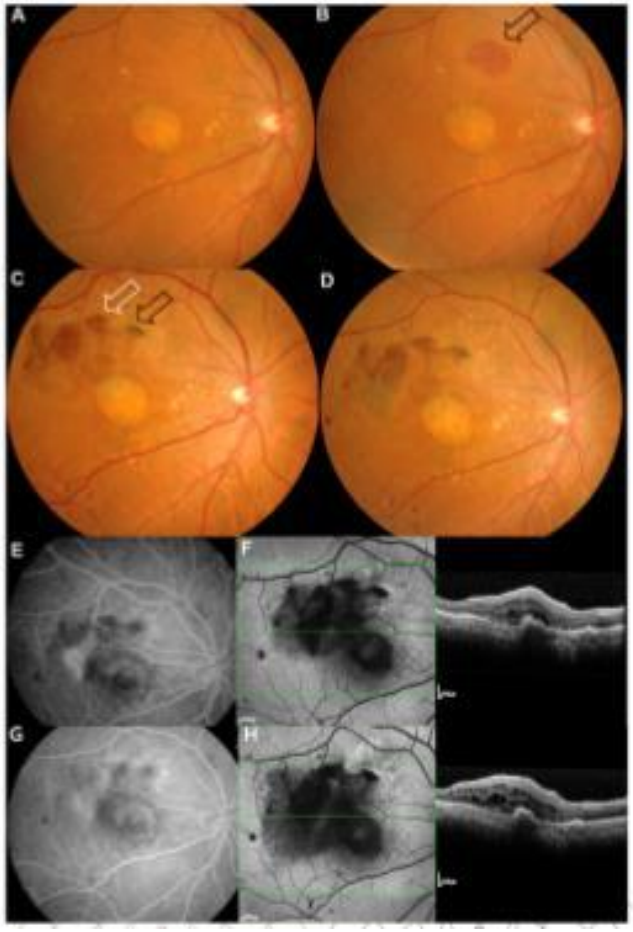
OPEN ACCESS

Treatment of Macular Degeneration Using Embryonic Stem Cell-Derived Retinal Pigment Epithelium: Preliminary Results in Asian Patients

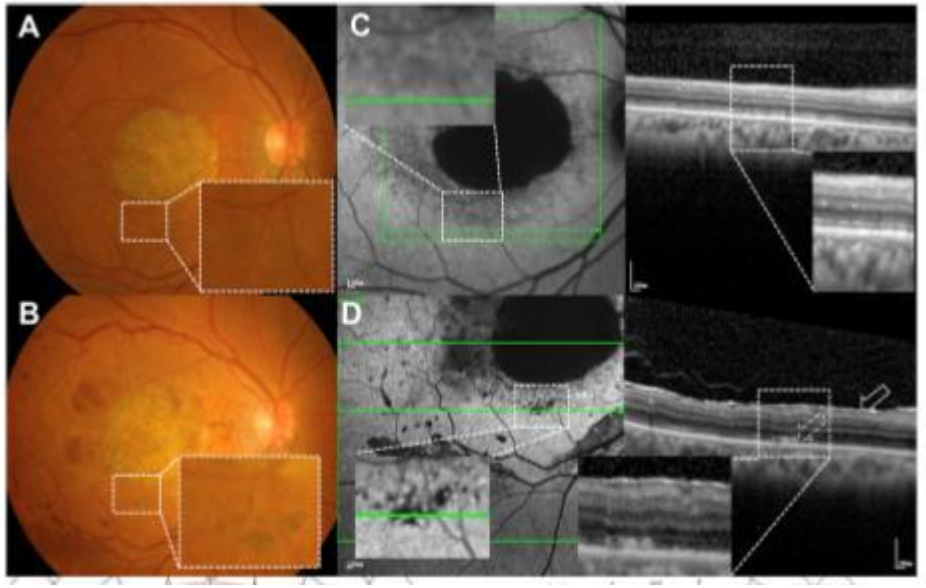
Won Kyung Song,[1,*] Kyung-Mi Park,[2] Hyun-Ju Kim,[2] Jae Ho Lee,[3] Jinjung Choi,[4] So Young Chong,[5] Sung Han Shim,[6] Lucian V. Del Priore,[7] and Robert Lanza[8,*]
[1]Department of Ophthalmology, CHA Bundang Medical Center, CHA University, Seongnam-si, Gyeonggi-do 463-712, Republic of Korea

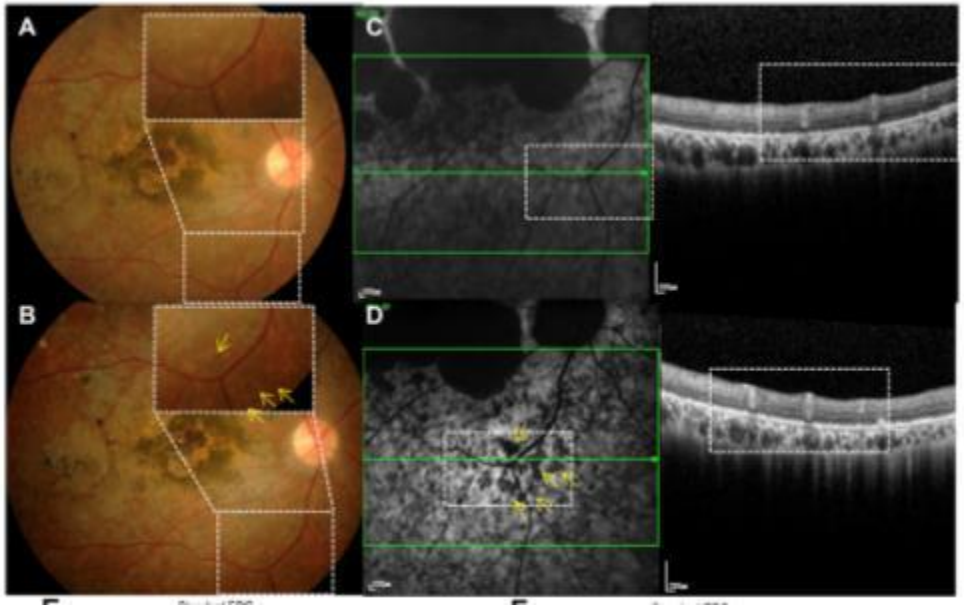
April 2015

* 4 YBMD, 4 Stargardt MD olgusu
* 1 yıllık takip
* Ciddi okuler ve sistemik yan etki yok
* 1 olguda KNVM ve 3 doz Lucentis
* Tüm olgularda pigmentasyon artışı
* Tüm olgularda GK artışı



KNVM





Subretinal pigmentasyon

KAYITLI EKH ÇALIŞMALARI clinicaltrials.gov

* (1) (NCT01469832) Safety and Tolerability of Sub-retinal Transplantation of hESC-RPE Cells in Patients with Stargardt's Macular Dystrophy (SMD)
* (2) (NCT01691261) A Study of Implantation of hESC-RPE Subjects with Acute Wet AMD and Recent Rapid Vision Decline
* (3) (NCT01674829) A Phase Ⅰ/Ⅱa, Open-Label, Single-Center, Prospective Study to Determine the Safety and Tolerability of Subretinal Transplantation of hESC-RPE (MA09hRPE) Cells in Patients With Advanced Dry AMD
* (4) (NCT02122159) Research With Retinal Cells Derived From Stem Cells for Myopic Macular Degeneration
* (5) (NCT01344993) Safety and Tolerability of Sub-retinal Transplantation of hESC Derived RPE (MA09-hRPE) Cells in Patients with Advanced Dry AMD
* (6) (NCT01345006) Sub-retinal Transplantation of hESC Derived RPE (MA09-hRPE) Cells in Patients with Stargardt's Macular Dystrophy;
* (7) (NCT01625559) Safety and Tolerability of MA09-hRPE Cells in Patients with SMD.

KAYITLI IPKH ÇALIŞMALARI clinicaltrials.gov

* (1) (NCT02162953) Development of Induced Pluripotent Stem Cells from Patients with Best Disease and Other Inherited Retinal Degenerative Diseases

* (2) (NCT01432847) Generation of induced pluripotent stem (iPS) Cell Lines from Somatic Cells of Participants with Eye Diseases and from Somatic Cells of Matched Controls.

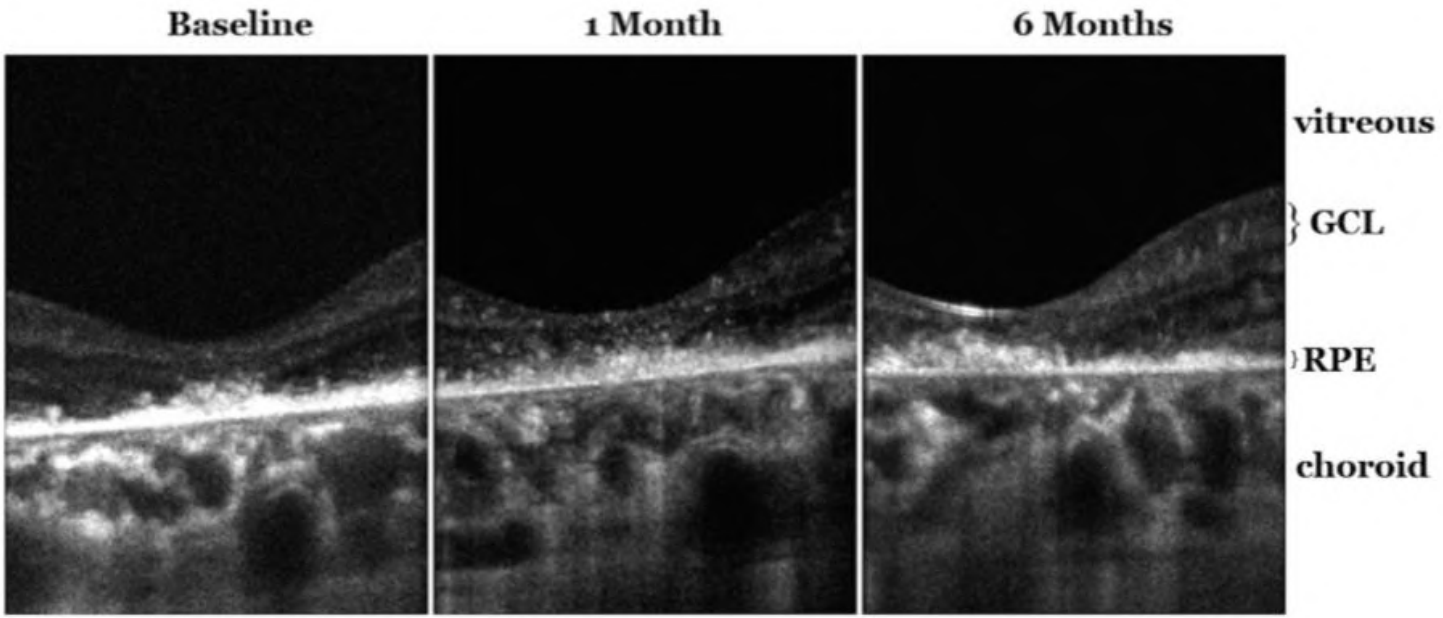
Clinical Trials

Intravitreal Autologous Bone Marrow CD34+ Cell Therapy for Ischemic and Degenerative Retinal Disorders: Preliminary Phase 1 Clinical Trial Findings

Susanna S. Park,[1] Gerhard Bauer,[2] Mehrdad Abedi,[3] Suzanne Pontow,[2] Athanasios Panorgias,[1] Ravi Jonnal,[1] Robert J. Zawadzki,[1] John S. Werner,[1] and Jan Nolta[2]

[1]Department of Ophthalmology and Vision Science, University of California-Davis Eye Center, Sacramento, California, United States
[2]Institute for Regenerative Cures, University of California-Davis School of Medicine, Sacramento, California, United States
[3]Division of Hematology and Oncology, University of California-Davis Cancer Center, Sacramento, California, United States

IOVS- January 2015



RPE HİPERREFLEKTİVİTE ARTIŞI

Reticell Study-NCT01560715

* RP ‘li 20 olguda intravitreal Kİ-MKH
* 3 ayda görme kalitesinde artış ancak 1 yılda eski haline geri dönüş
* Sistemik ve oküler komplikasyon yok.

* Siqueira et al. Stem Cell Research & Therapy (2015) 6:29 Quality of life in patients with retinitis pigmentosa submitted to intravitreal use of bone marrow-derived stem cells (Reticell -clinical trial)

Reticell Study

* RP ilişkili KMÖ'de iyileşme
* GK'de artış

* Siqueira, R.C.; et al. Resolution of macular oedema associated with retinitis pigmentosa after intravitreal use of autologous BM-derived hematopoietic stem cell transplantation. Bone Marrow Trans. 2013, 48, 612–613

Kİ-MKH ÇALIŞMALARI

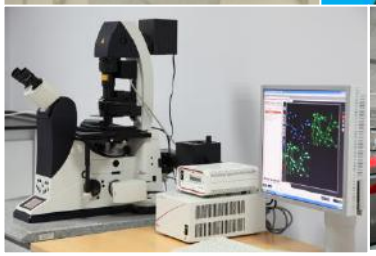
* 1) NCT01736059- Clinical Trial of Autologous Intravitreal Bone-marrow CD34+ Stem Cells for Retinopathy. Non-exudative AMD, Diabetic Retinopathy. RVO, RP, Hereditary Macular Degeneration.
* 2) NCT01560715- Autologous Bone Marrow-Derived Stem Cells Transplantation For RP **(RETICELL)**
* 3) NCT02280135- Clinical Trial of Intravitreal Injection of Autologous Bone Marrow Stem Cells in Patients With Retinitis Pigmentosa (TC/RP)
* 4)NCT01068561- Autologous Bone Marrow-Derived Stem Cells Transplantation For Retinitis Pigmentosa
* 5) NCT01914913- Clinical Study to Evaluate Safety and Efficacy of BMMNC in Retinitis Pigmentosa
* 6) NCT01531348-Feasibility and Safety of Adult Human Bone Marrow-derived Mesenchymal Stem Cells by Intravitreal Injection in Patients With Retinitis Pigmentosa
* 7) NCT01518127-Intravitreal Bone Marrow-Derived Stem Cells in Patients With Macular Degeneration (AMDCELL)

AD-MKH ÇALIŞMALARI

* (1) (NCT02024269) Study to Assess the Safety and Effects of Cells Injected Intravitreal in Dry Macular Degeneration

* (2) (NCT02144103) Effectiveness and Safety of Adipose-Derived Regenerative Cells for Treatment of Glaucomatous Neurodegeneration.

GENKÖK

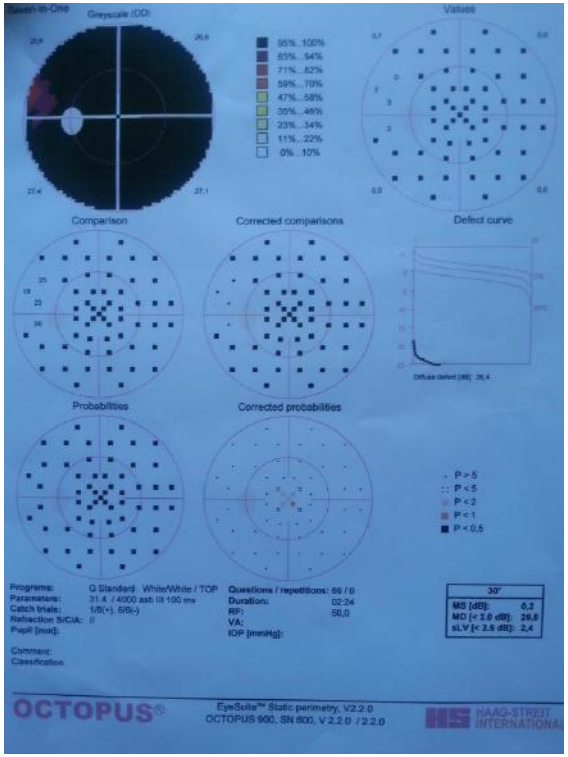


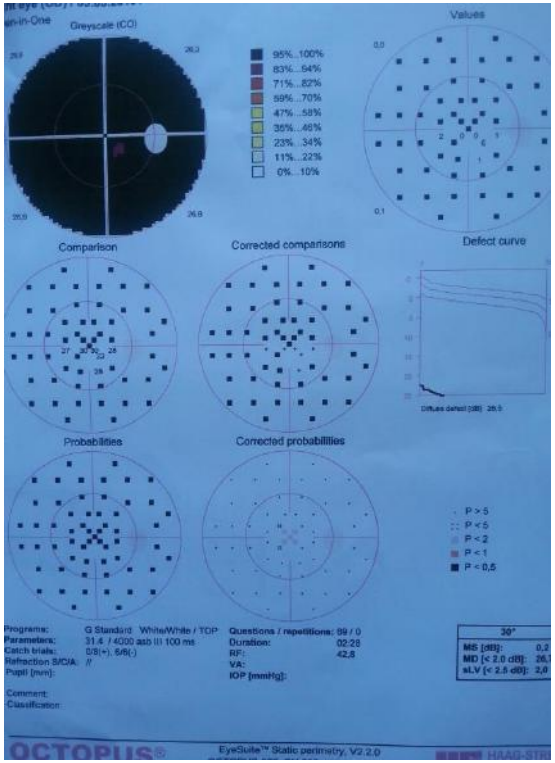
HASTALAR VE METOD

* 14 olgu opere edildi.
* Tüm olgularda total görme alanı defekti mevcuttur.
* Olguların yarısı p +
* En iyi gören olgumuz 1 mps.
* Tüm olgularda ERG silik.
* Görmesi düşük olan göz opere edildi.
* Adipoz dokudan derive edilmiş allojenik mezenkimal KH kullanıldı.
* 23 gauge ile total vitrektomi sonrası 1.000.000 subretinal mezenkimal KH enjekte edildi.

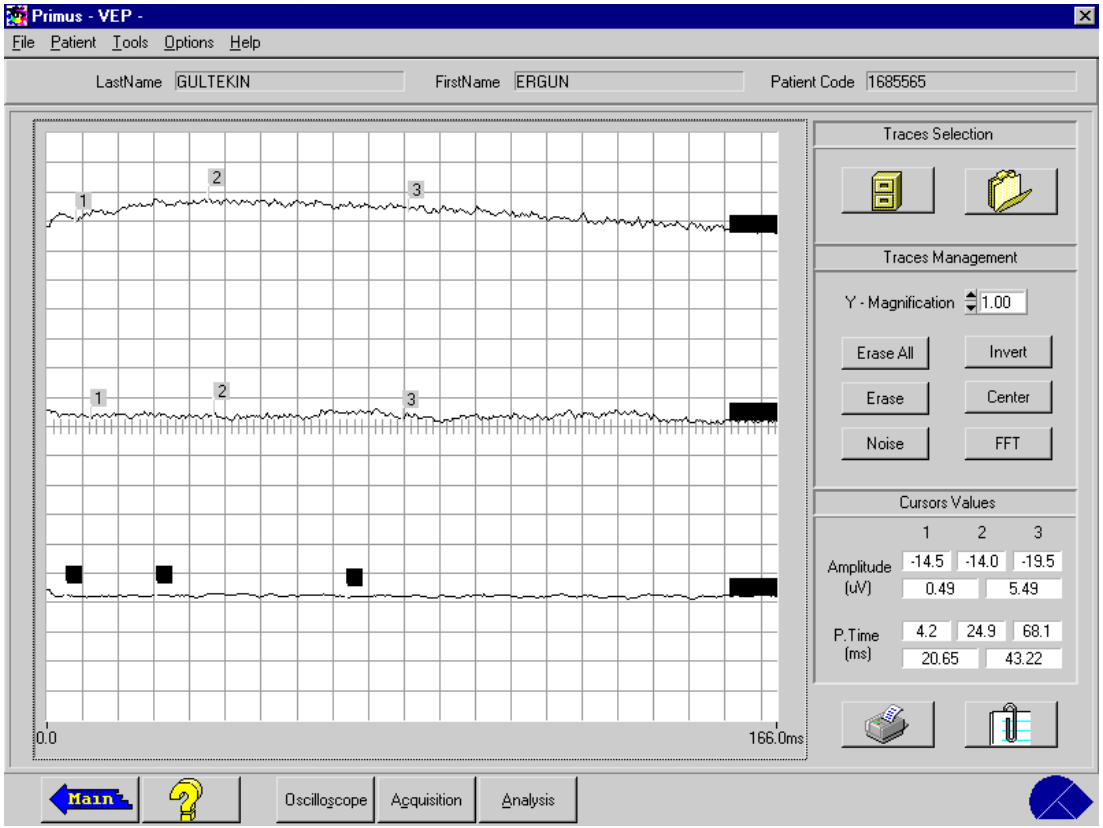
GMP (Good manufacturing practice) (İyi Klinik Uygulamalar)

ADMKH ler uluslar arası standartlarda üretildi





Görme alanı örnekleri



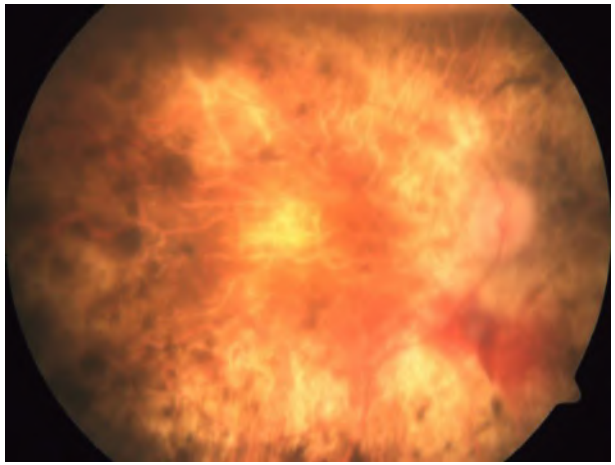
Tam alan ERG örneği

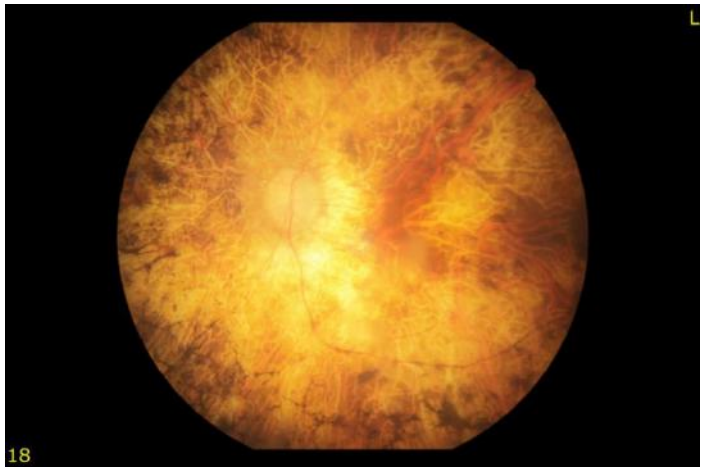
SONUÇLAR

* 14 olgunun takipleri devam ediyor.
* Hiçbir olguda sistemik komplikasyon olmadı.
* 5 olguda okuler komplikasyon gelişti.
* 1 olguda enjeksiyon sahasında KNVM (Cerrahi travma).
* 5 olguda ERM ve 2 olguda periferal membranlar (KH'lerin subretinal alandan retina yüzeyine dağılımı)

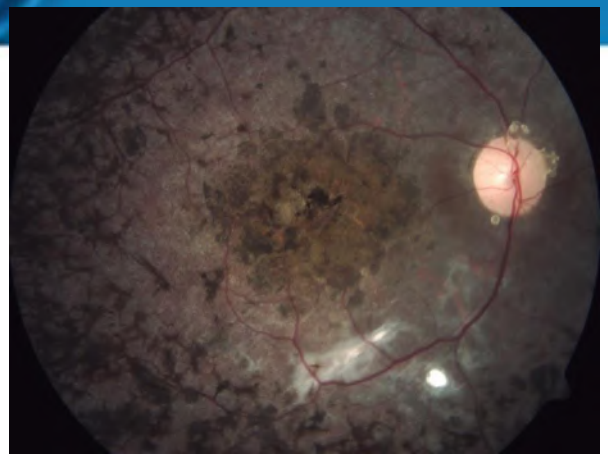
SONUÇLAR

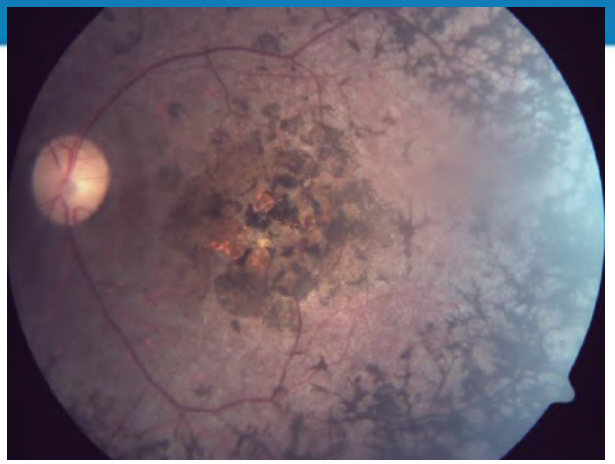
* 3 olguda belirgin görme artışı.
* Görme artışı olan olgular preop görmesi iyi olan olgulardır.
* Görme artışı olmayan diğer olguların 6 sı p (+)

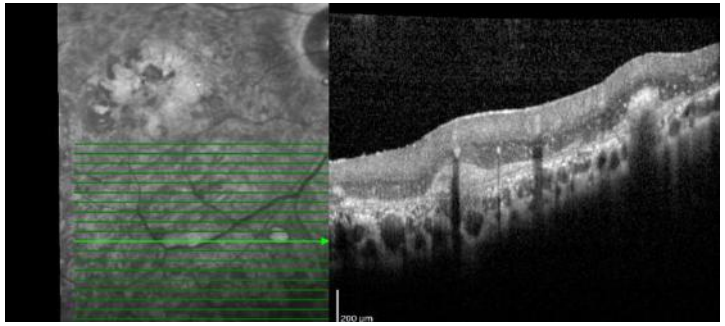


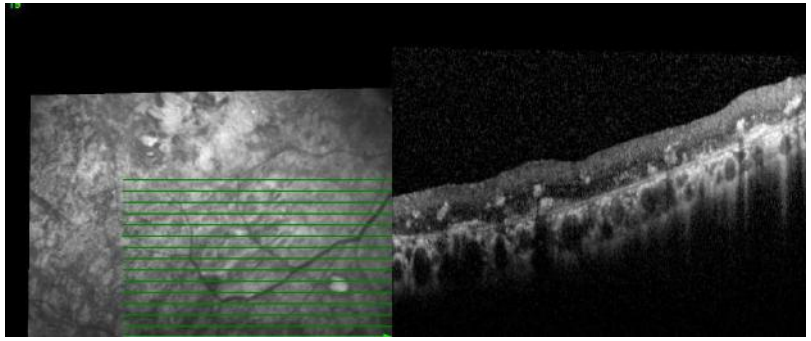


Aynı olgunun iki gözü: Sağda enjeksiyon alanında küçük subretinal hemoraji

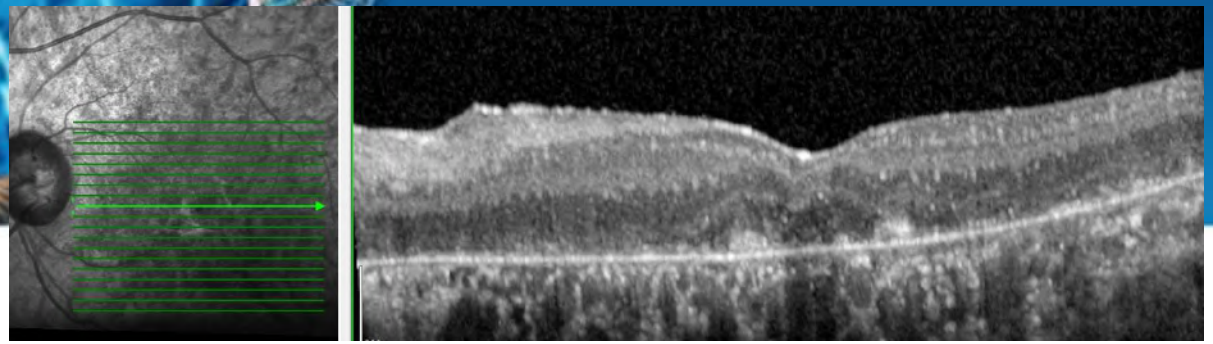




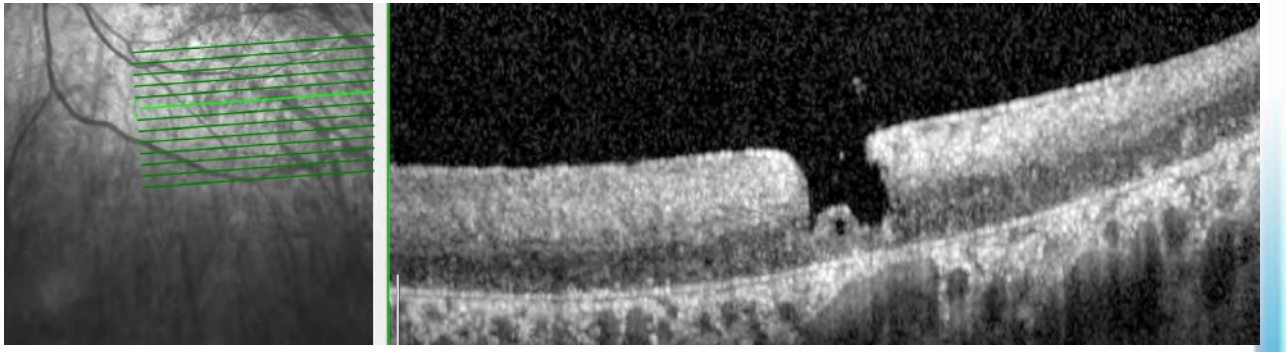




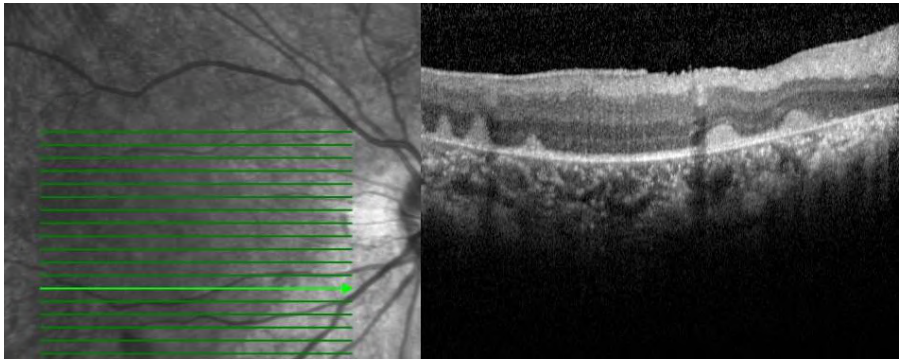
6. Ayda fundus görünümü
1 hafta ve 6. ayda enjeksiyon alanında OCT görünümü



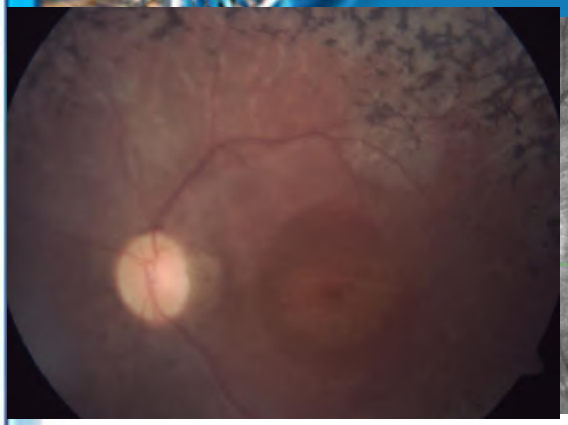
6. Ayda OCT görünümü

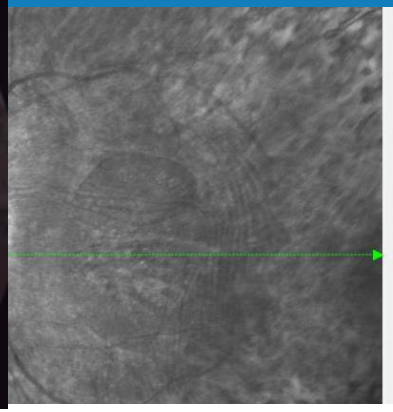


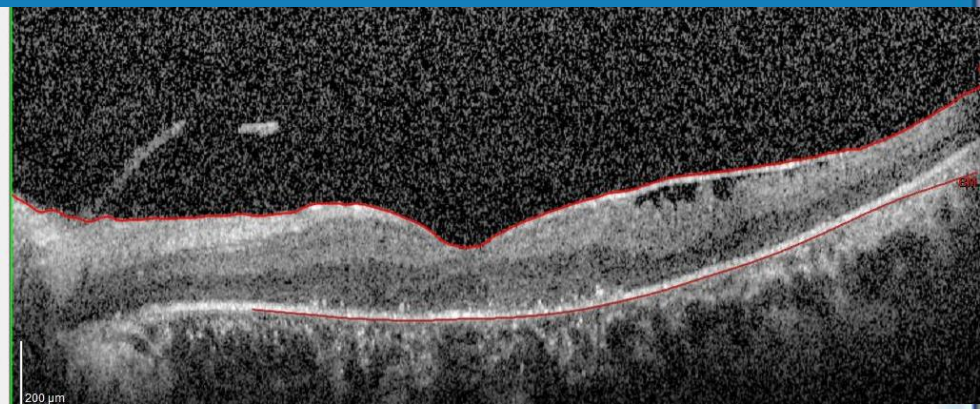
Enjeksiyon yerinden geçen OCT kesiti

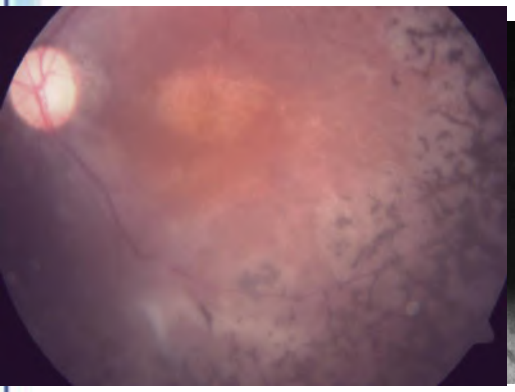


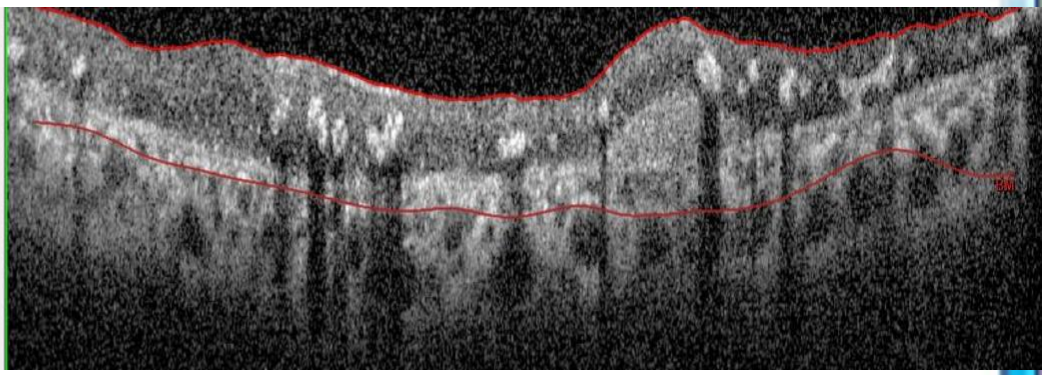
2. Haftada OCT






200 µm



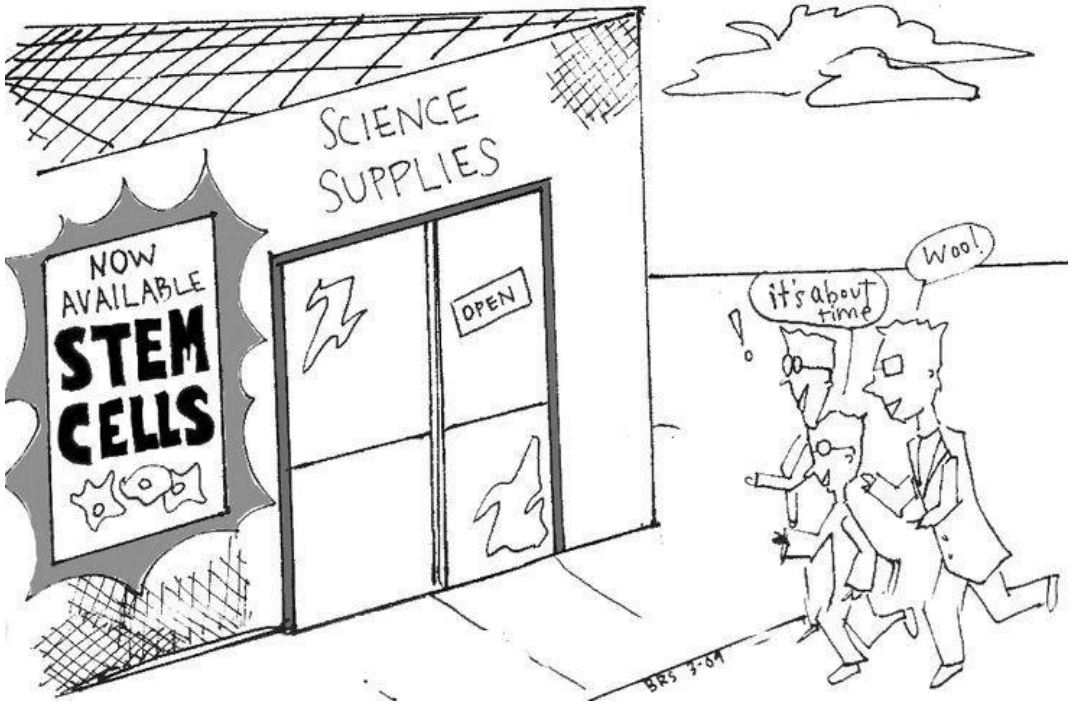


STANDART PROTOKOL?

* Hangi KH'yi kullanmalı?
* Hangi dozda kullanmalı?
* Hangi şekilde uygulamalı: Subretinal, intravitreal?
* Hastalığın hangi evresinde kullanmalı?


"Whatever you do, or dream you can, begin it!
Boldness has genius, power and magic in it".
...Goethe

Gelecekte…


SCIENCE SUPPLIES
NOW AVAILABLE
STEM CELLS
OPEN
it's about time
Woo!