HÜCRENİN GÜCÜNÜ KULLANIN

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TEKNOLOJİ

Tıbbi Sağaltımın Klasik Elemanları

- Kimyasal-farmakolojik ajanlar
- Fiziksel ajanlar
- Cerrahi İşlemler

Bugünün Yeni(?) Elemanı

Hücre Tedavileri

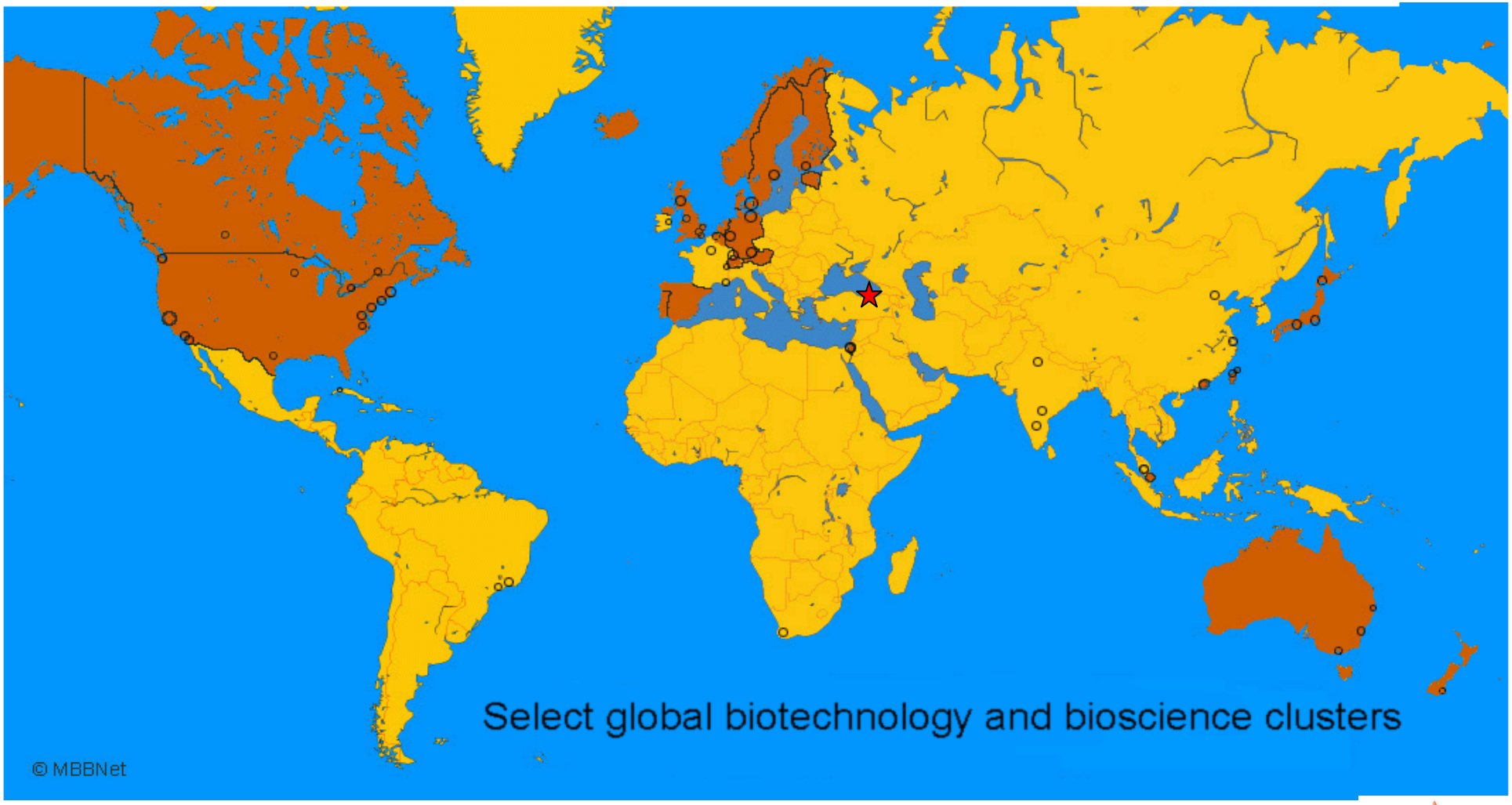
Hücre tedavilerinin bilimsel kayıtlardaki ilk örnekleri

Çiçek Aşısı- Dr Timonius 1713/İstanbul

İlk Başarılı Kan Nakli- Dr Blundell 1818

İlk Başarılı Kök Hücre Nakli Dr Donald Thomas 1955

Ülkemizde İlk Hücre Tedavisinin Uygulanması Dr.Süreyya Tahsin Aygün. 1973


Select global biotechnology and bioscience clusters
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Examples of cells involved in various diseases

Neurological disorders: stroke, Parkinson's disease, spinal cord injury .....Neurons

Cardiovascular disorders: myocardial infarction, congestive heart failure.....Cardiomyocytes, stem cells

Insulin dependent diabetes mellitus..... .....Islet cells

Osteoarthritis.....Cartilage cells

Immune and hematological disorders..... .....Blood cells,BMSC

Burns and wounds..... Skin cells

Disorders of the liver: cirrhosis, hepatitis..... .....Hepatocytes

Osteoporosis..... .....Bone cells

Muscular dystrophy.....Myocytes

Macular degeneration..... .....Retinal cells

Tedavi Amaçlı Hücre Grupları

Undifferansiye
Kök Hücreler

Kök hücre nakli

Organ rejenerasyon çalışmaları

Yeni organ taslakları

Diferensiye
Hücreler

Fibroblast/
Keratinosit

Kondrosit,
Kemik hücreleri

İmmünoterapi
Ürünleri

Dermal papilla hücreleri

Hepatositler
Myositler
Retinal hücreler
vb

TEKNOLOJİ

Organ rejenerasyonunda kullanılan kök hücreler

A- Embriyonik Kök hücreler

B- Non Embriyonik kök hücreler

1- Erişkin Kök Hücreler(Somatik Kök hücreler)
- Hematopoetik kök hücre
  - Kemik iliği kaynaklı kök hücreler
  - Periferik kan kaynaklı kök hücreler
- Stromal Kök hücre
  - MKH: Mezenkimal hkök hücre
  - MAPC: Multipotent erişkin kök hücresi
  - MİAMİ: Erişkin kemik iliği kaynaklı indüklenebilir multilineage hücre
  - hBMSC:İnsan kemik iliği kaynaklı kök hücresi
  - VSEL's:embriyonik hücre benzeri küçük kök hücreler
- Organ spesifik Kök Hücreler

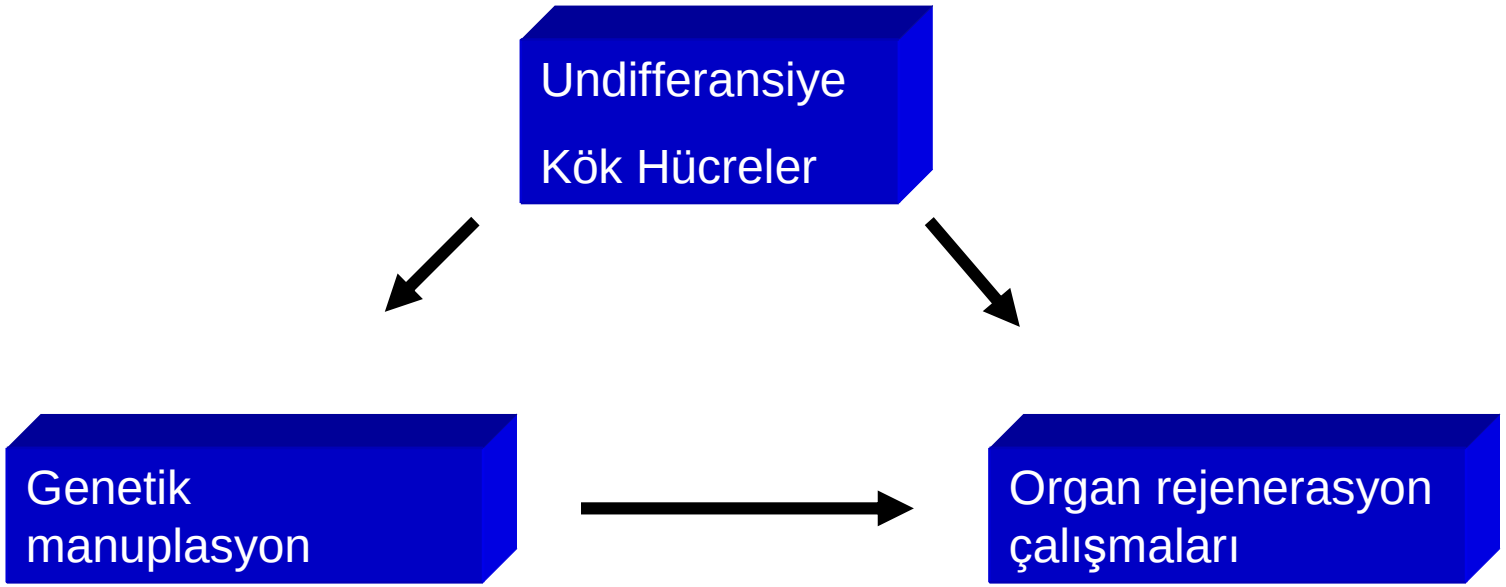
2- Fetüs Kök Hücreleri

3- Kadavradan elde edilen kök hücreler

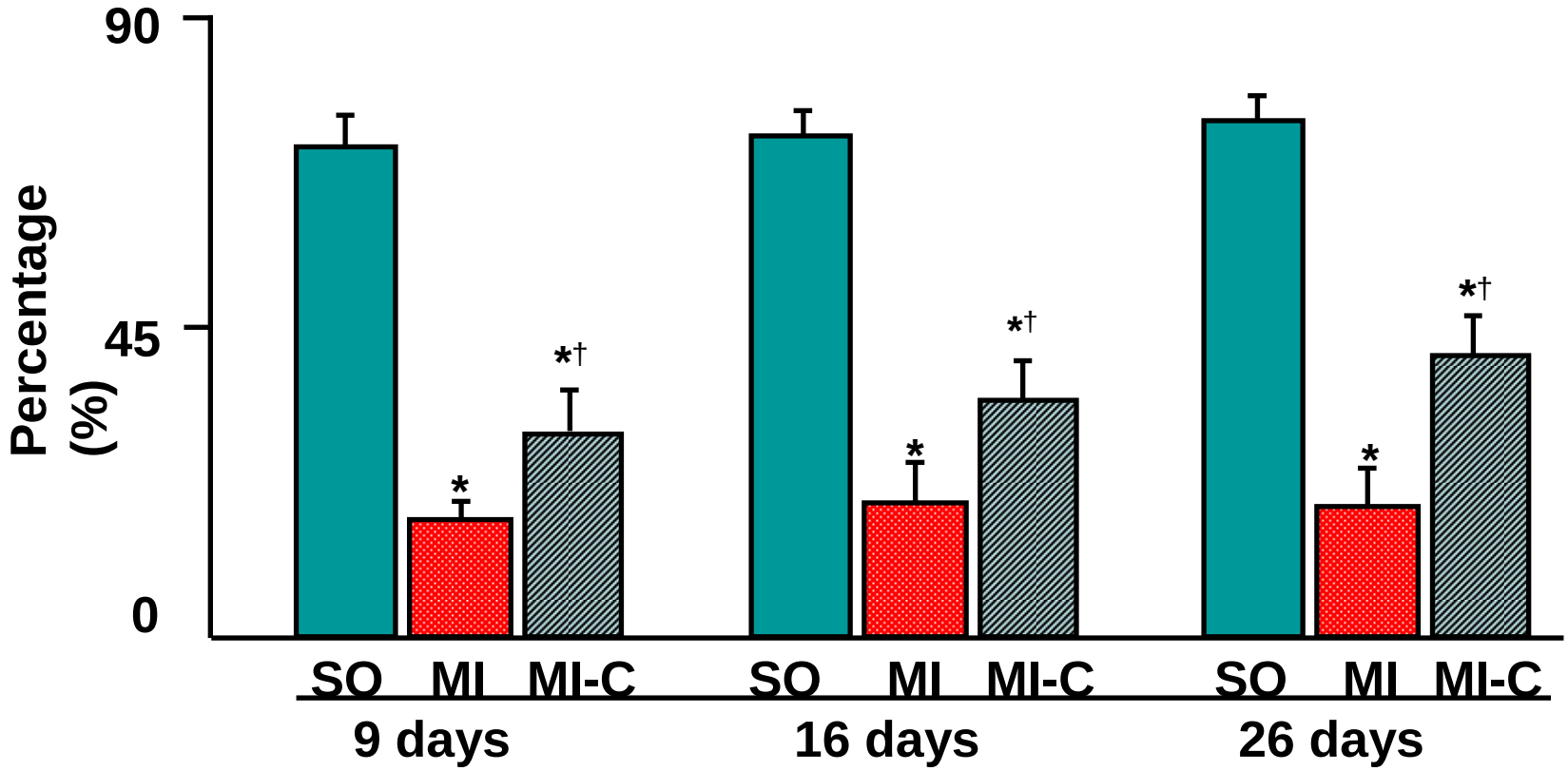
4- Göbek kordonu veya plasental kök hücreler

5- Partonod hücreler

5- Dedifferansiasyon ile herhangi bir hücre(Reversin etkisi)?


Undifferansiye
Kök Hücreler
Genetik
manuplasyon
Organ rejenerasyon
çalışmaları

Left ventricular ejection fraction



Hücresel kardiyomyoplastide Klinik Çalışmalar

Çalışma	n	Yöntem	K.Hücre	Takip	Komplikasyon
Hamano et al	5	direk inj.	Kİ	1y	-
Strauer et al	10	intrakoro infüz	Kİ	3ay	-
Assmus et al	20	“ “	progenitor h.	4ay	-
Menasche et al	10	direk injek	iskelet myobla.	11ay	1 ölüm
Stamm et al	6	“ “	Kİ	9ay	2 SVT
Pagani et al	5	“ “	İskelet myobla.	7ay	4 aritmi 1öl
Tse et al	8	kateter injek	Kİ	3ay	-
Perin et al	14	“ “	Kİ	4ay	1 ölüm
Wollert	30	İntrakoro infüz	Kİ	6ay	-
Brehm et al	20	“ “	Kİ	3ay	-
Smits et al	5	direk inj	İskelet Myoblas	6ay	1 VT
Ozbaran M	15	Direk İnj	Per. Kök. Hüc	25ay	3 ölüm

Cell Tissue Res (2004) 318: 261–273
DOI 10.1007/s00441-004-0946-y

REVIEW

Laurent Roybon · Nicolaj S. Christophersen · Patrik Brundin · Jia-Yi Li

Stem cell therapy for Parkinson's disease: where do we stand?

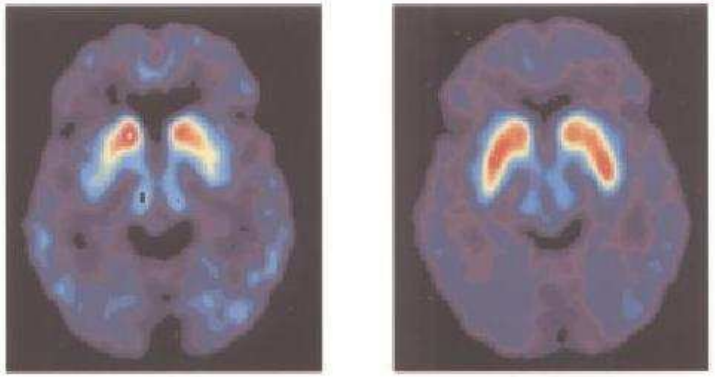
Received: 4 May 2004 / Accepted: 25 June 2004 / Published online: 11 August 2004

Abstract A major neuropathological feature of Parkinson's disease (PD) is the loss of nigrostriatal dopaminergic neuron. Patients exhibit motor symptoms, including bradykinesia, rigidity, and tremor. Neural grafting has been reported to restore striatial dopaminergic neurotransmission and induce symptomatic relief. The major limitation of cell replacement therapy for PD is the shortage of suitable donor tissue. The present review describes the possible sources of cells, including embryonic stem cells and somatic adult stem cells, both of which potentially could be used in cell therapy for PD, and discusses the advantages and disadvantages of each cell type.

Keywords Parkinson's disease · Neural grafting · Embryonic stem cells · Somatic adult stem cells

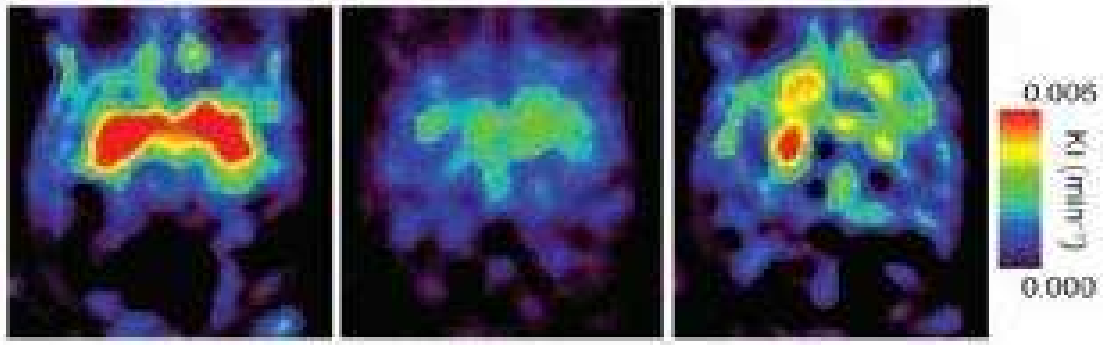
aggregates known as Lewy bodies (Giasson and Lee 2003). Despite major advances over the past decade, the etiology of PD remains unclear. Occurring most commonly as the sporadic idiopathic form, PD has been hypothesized to be attributable to genetic predispositions to either endogenous toxins or environmental factors such as pesticides, herbicides, and industrial chemicals. The neurodegenerative process in PD has been associated with increased protein misfolding, oxidative stress, mitochondrial dysfunction, and excitotoxicity (Olanow and Tatton 1999; Ciechanover and Brundin 2003). The recent identification of genetic mutations in rare familial cases of PD has provided important insights into the molecular pathogenesis of this disease. At present, four identified genes have been clearly linked to PD: alpha-synuclein, parkin, ubiquitin C-terminal hydrolase L1 (UCH-L1), and DJ-1

Dopamin Sentezleyen Sinir Hücresi Nakli



Önce Sonra

Şekil 8.3 : Bir parkinson hastasının beyninden nakil öncesinde ve hücre naklinden 12 ay sonra alınan PET (pozitron emisyon tomografisi) görüntü leri.



KÖK Hücre Çalışmalarında KTÜ-ATİ Deneyimi

Klinik Organ Rejenerasyon Çalışmalarında KTÜ Deneyimi

- 2004 yılından bu yana EGE üniversitesi bünyesinde 6 ALS'olgusunda ALS uygulamaları için hücre üretimi
  - Sonuç:Hastalık progresyonun a geçici gerileme ve progresyon yavaşlaması

TEKNOLOJİ

Eur Arch Otorhinolaryngol
DOI 10.1007/s00405-006-0093-z

CASE REPORT

Mesenchymal stem cells in iatrogenic facial nerve paralysis: a possible role in the future

Refik Caylan · Devrim Bektas · Tuner Dikmen · Oslen Bektas · Serdar B. Ozmy · Ercument Ovali

Received: 17 February 2006 / Accepted: 12 May 2006

Abstract Iatrogenic facial nerve paralysis is one of the major and drastic complications of ear surgery. We report a case of a 20-year-old female patient with simple chronic otitis media who underwent mastoidectomy and tympanoplasty. During the mastoidectomy process the facial nerve was unintentionally destroyed, leaving a gap of 8–10 mm in the third segment of the intratemporal facial nerve. The nerve was repaired with a nerve cable graft obtained from the vicinity. On the 42nd day, autologous mesenchymal stem cell transplantation was performed after facial nerve trauma. The patient's facial nerve paralysis has recovered from House-Brackmann grade VI to IV within a week and then to III in the fifth month. The rapid, postoperative progress, and the early follow-up results are discussed. This case represents the first bone marrow stem cell application in a peripheral nerve, namely the facial nerve.

Keywords Facial nerve · Mesenchymal stem cells · Transplantation · Traumatic facial neuropathy · Peripheral nerves

This case was presented at the XXXth World Congress of the International Society of Hematology, Istanbul, 28 September–2 October 2006.

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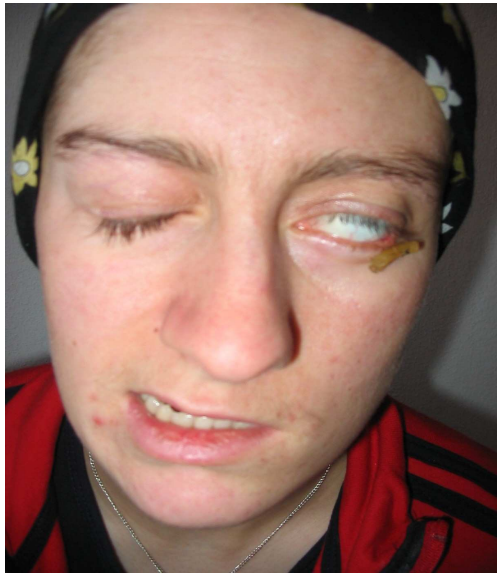
O. Bektas
Department of Internal Medicine, Karadeniz Technical University, Trabzon, Turkey

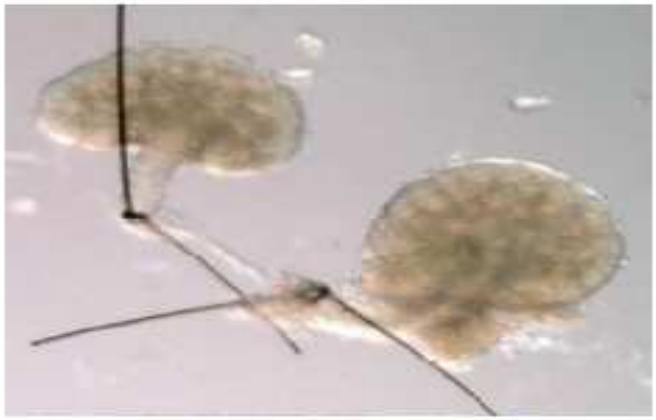
Introduction

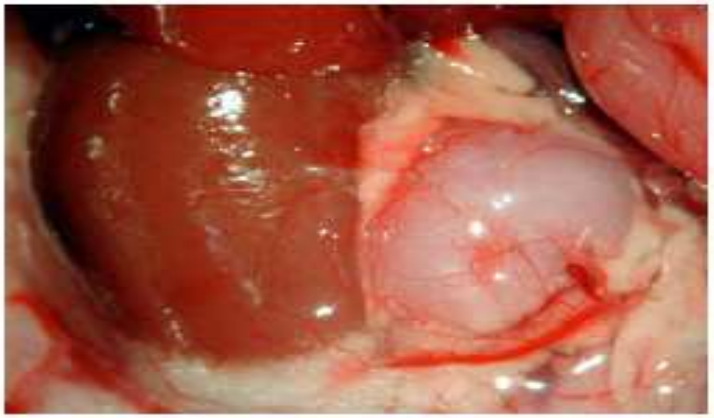
Iatrogenic facial nerve injury is a rare and feared complication of otologic surgery, confronting the patient with the functional, cosmetic, and psychological problems of paralysis. Despite advances in electrophysiology and imaging technology, which help to avoid injury, this devastating complication may occur especially in facial nerve course anomalies or in inexperienced hands. The continuity of the nerve is reestablished with or without a nerve graft. Nerve grafting allows only acceptable results varying from grade IV–III at best. Efforts to reach much better results are on going especially in eye closure and competent oral sphincter function, however problems such as mass moving of facial muscles, inability to raise forehead usually persists. House-Brackmann grading of facial nerve function is by far the most commonly used evaluation method of facial paralysis and recovery.

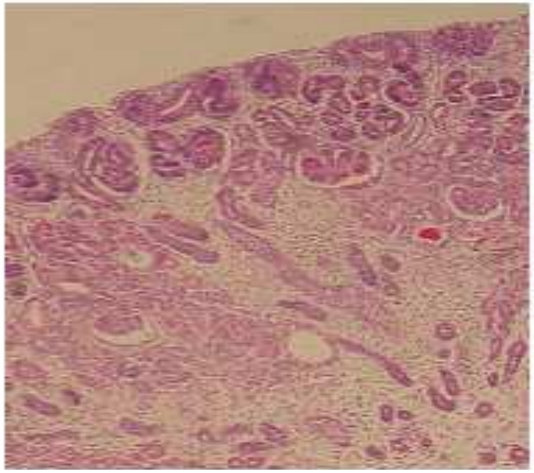
The development of new strategies to treat CNS and neuron injuries is a major ongoing clinical challenge. A variety of experimental strategies including stem cell transplantation are emerging to promote regeneration of the injured tissues [18]. The basic principle of cell therapy is restoration of lost function as a result of damage or disease in the CNS by the replacement of dead cells with new healthy ones [11]. Bone marrow derived mesenchymal stem cells (MSCs) constitute an alternative source of pluripotent stem cells and have

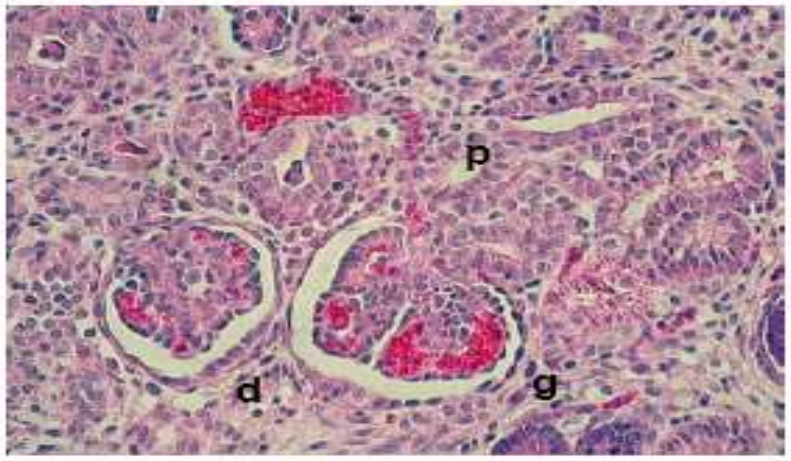


EKH’den Organ Taslaklarının Oluşturulması

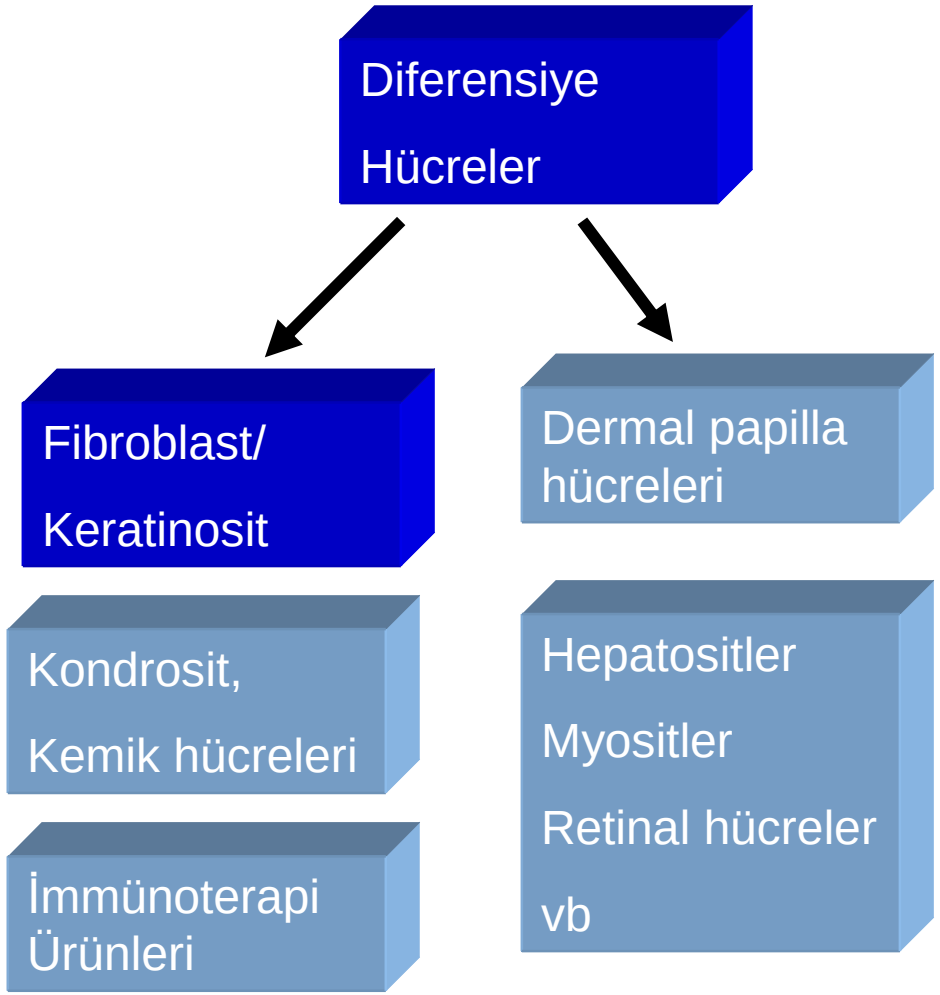


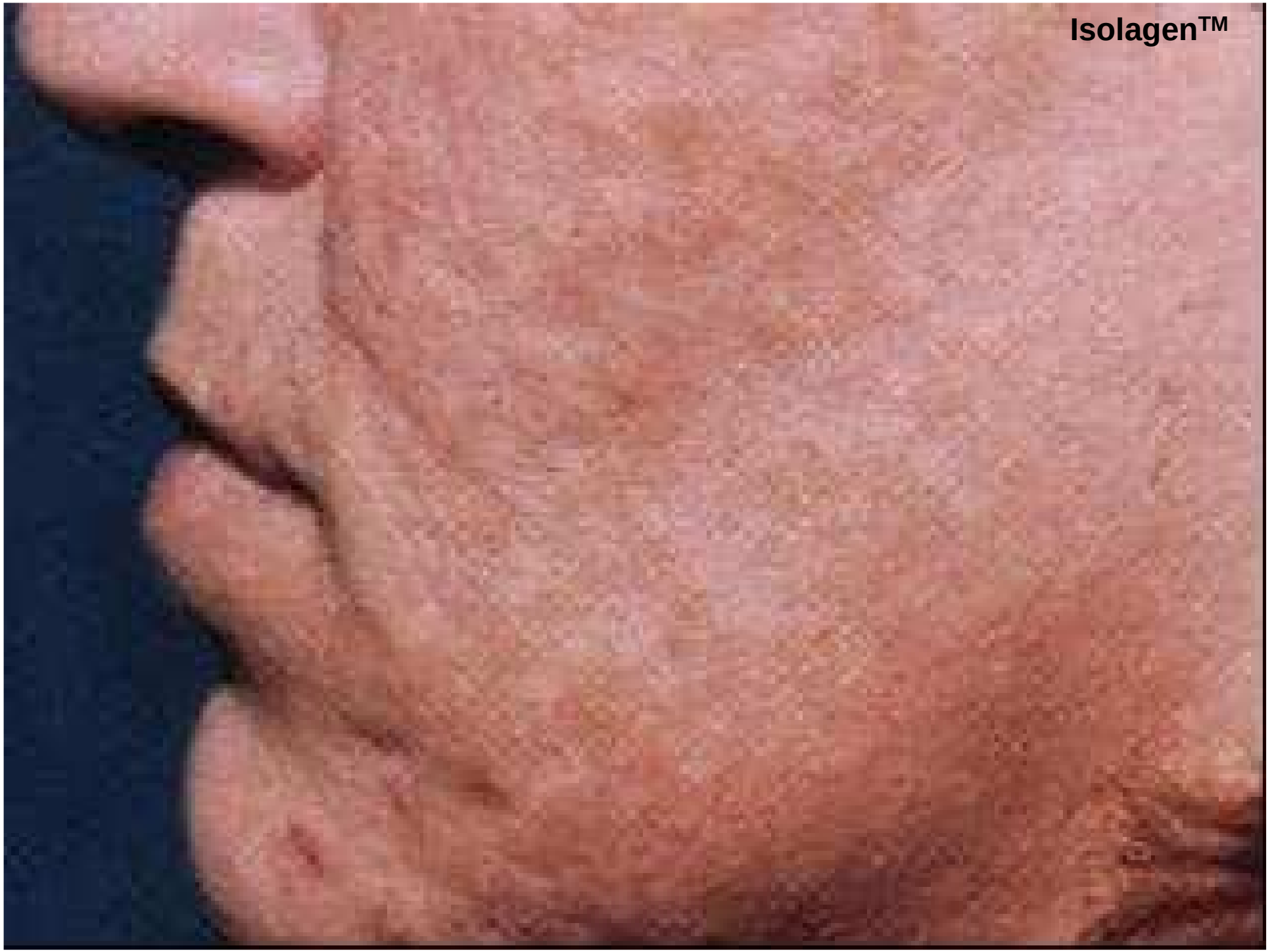


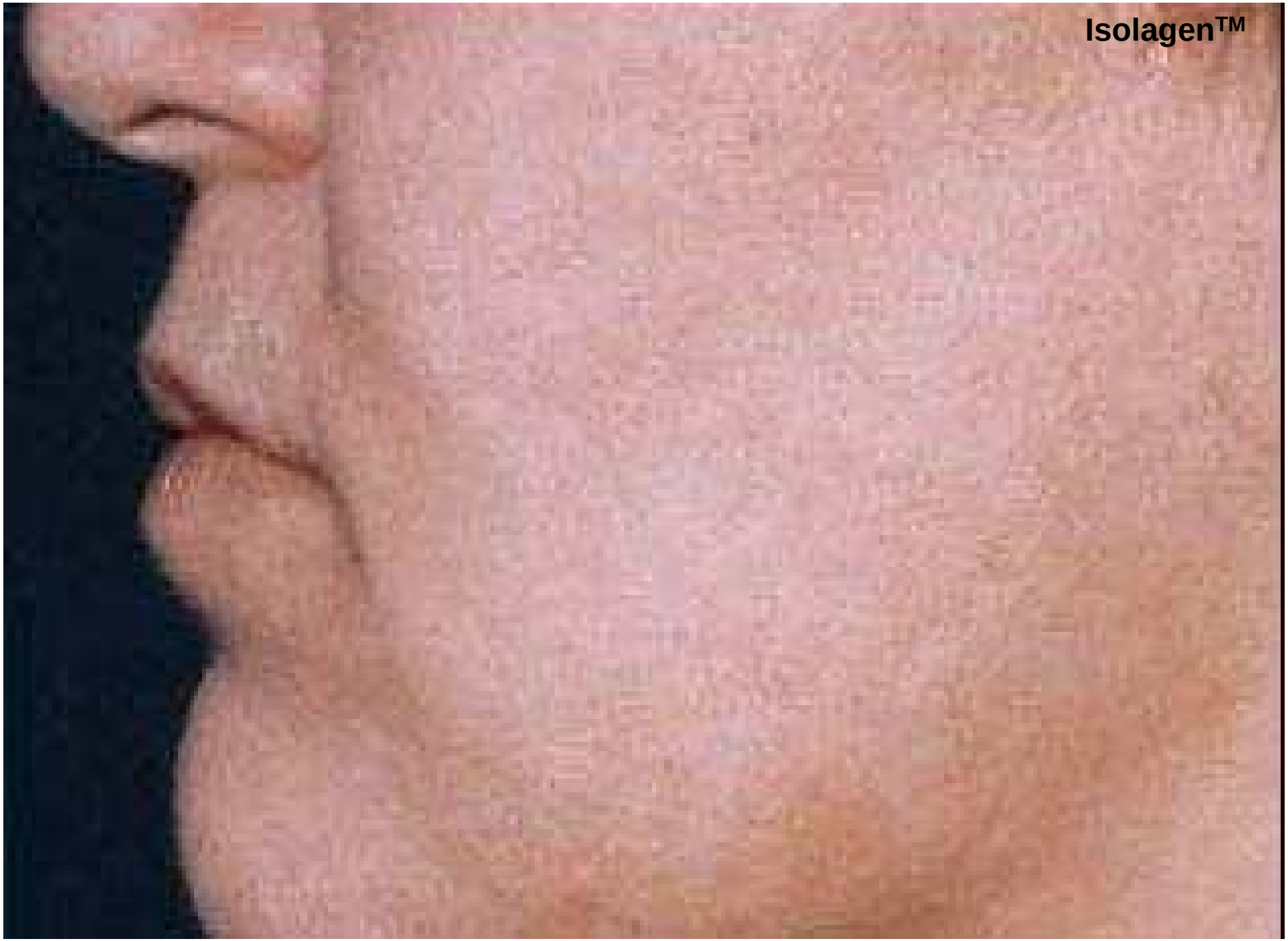




Diferansiye hücreler-1




Isolagen™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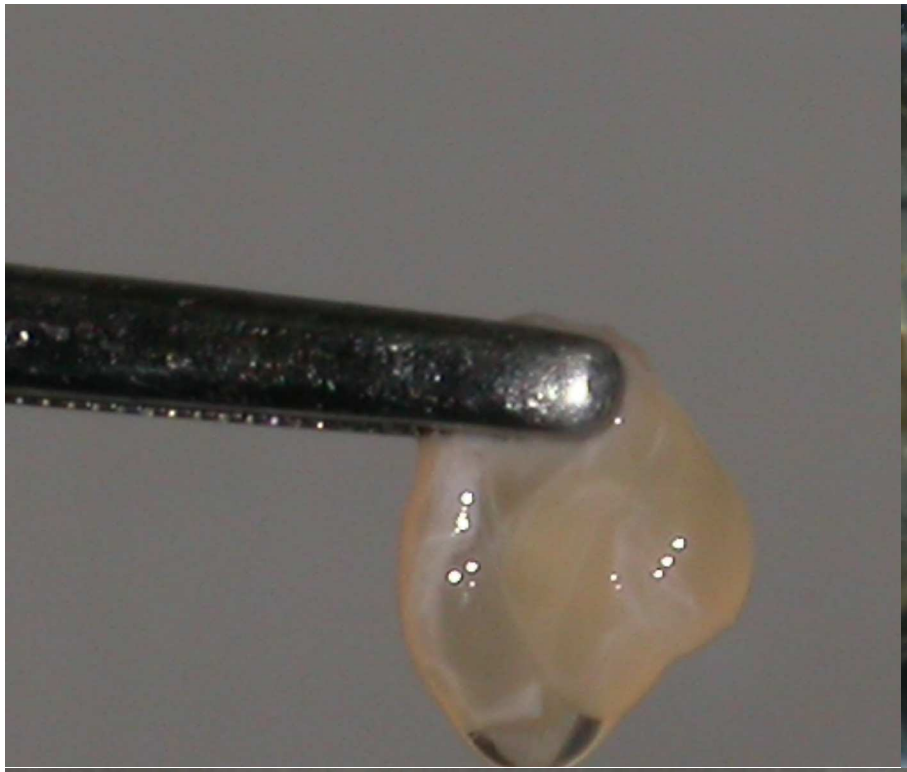

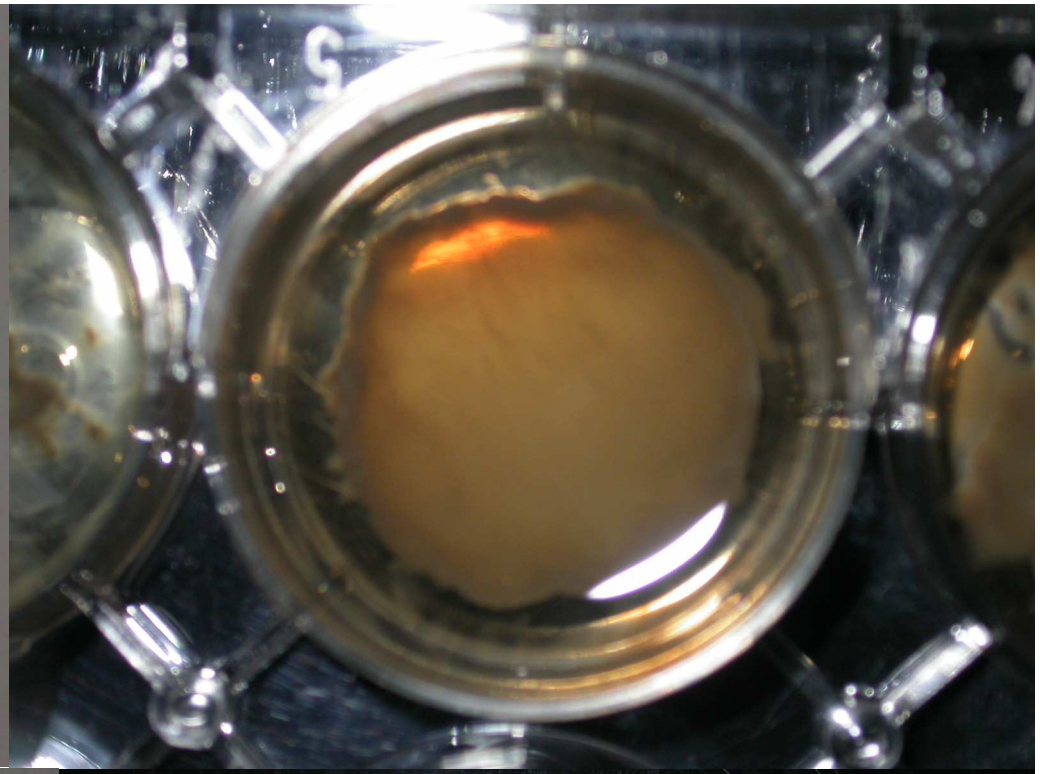

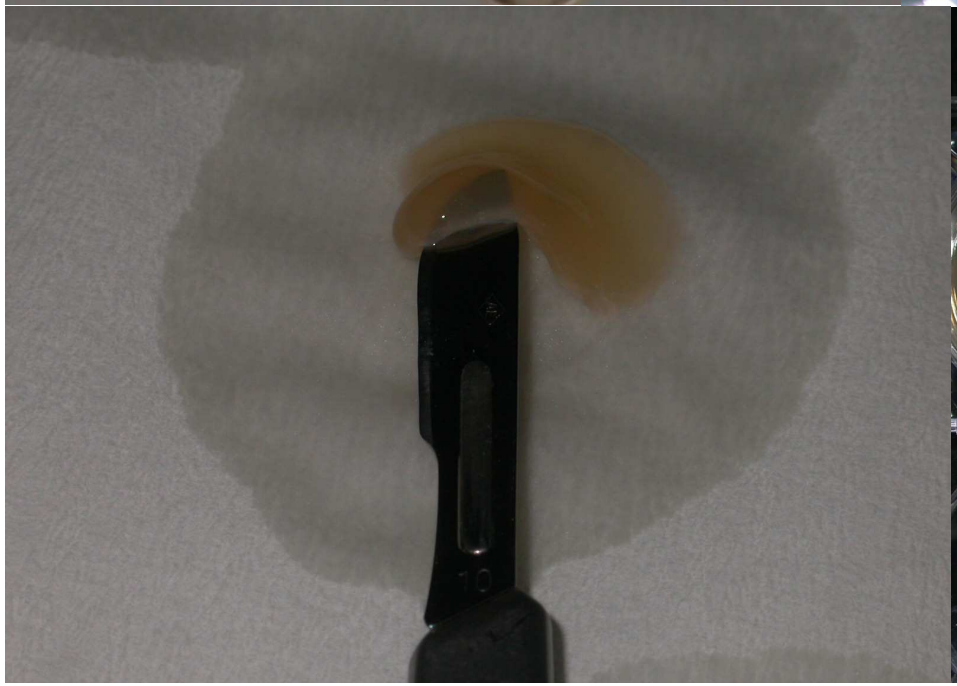


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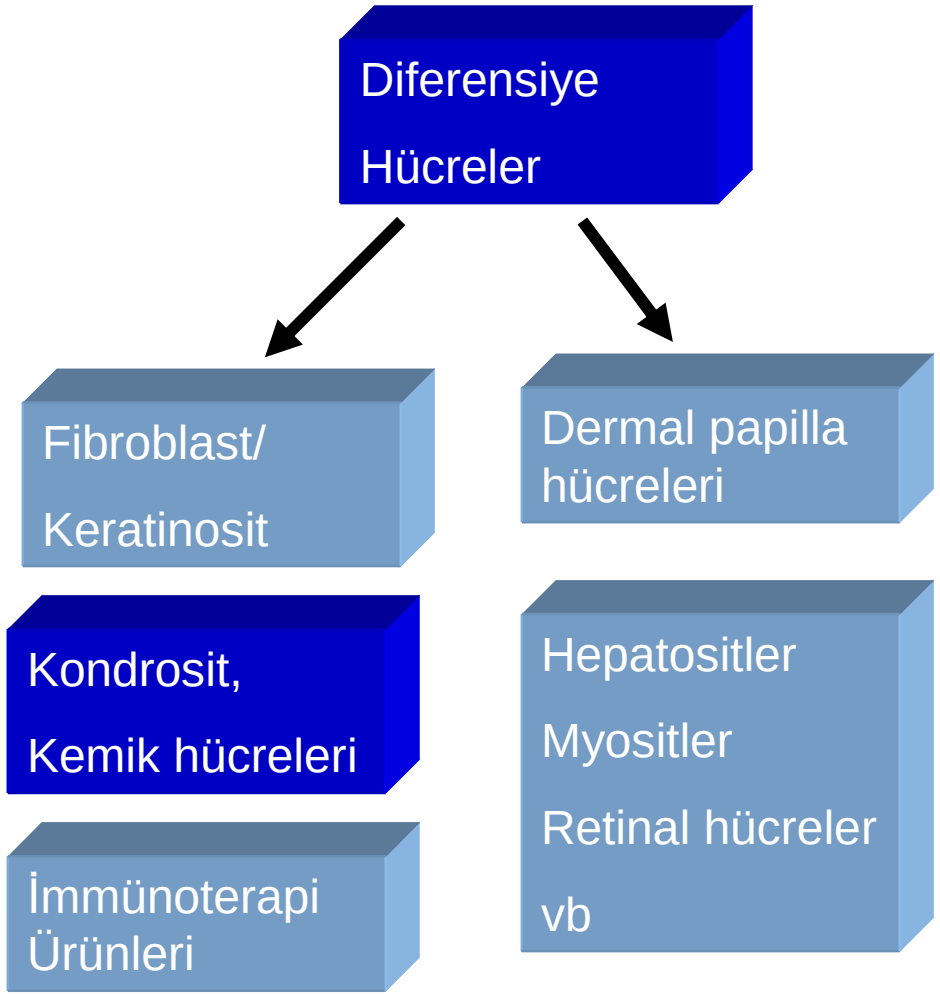
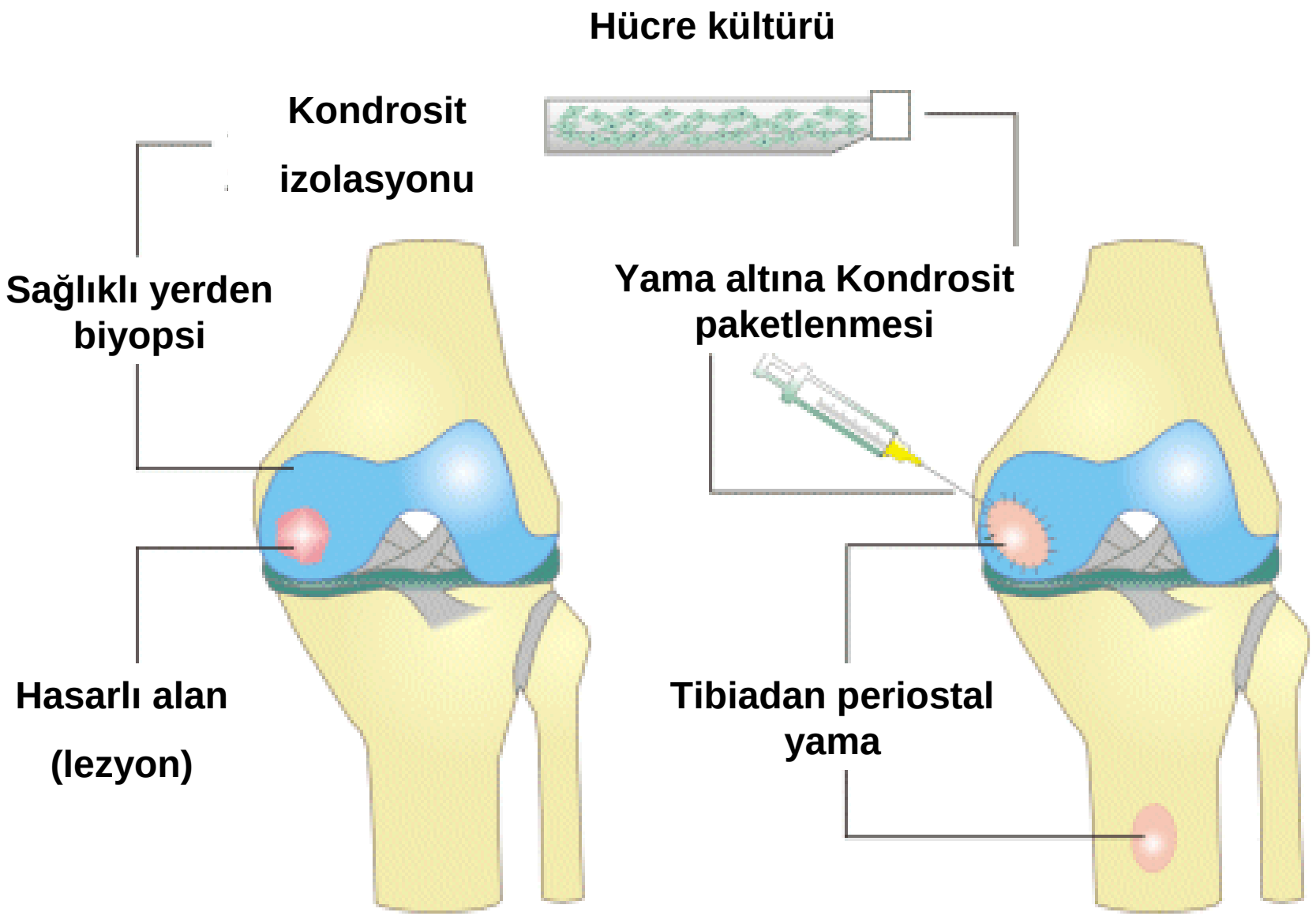
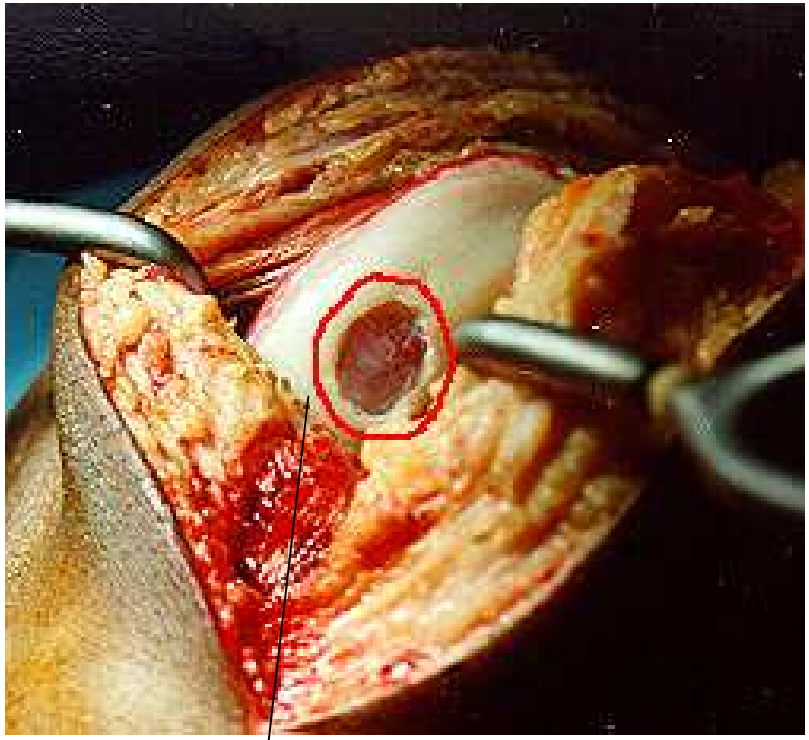
Diferansiye hücreler-1

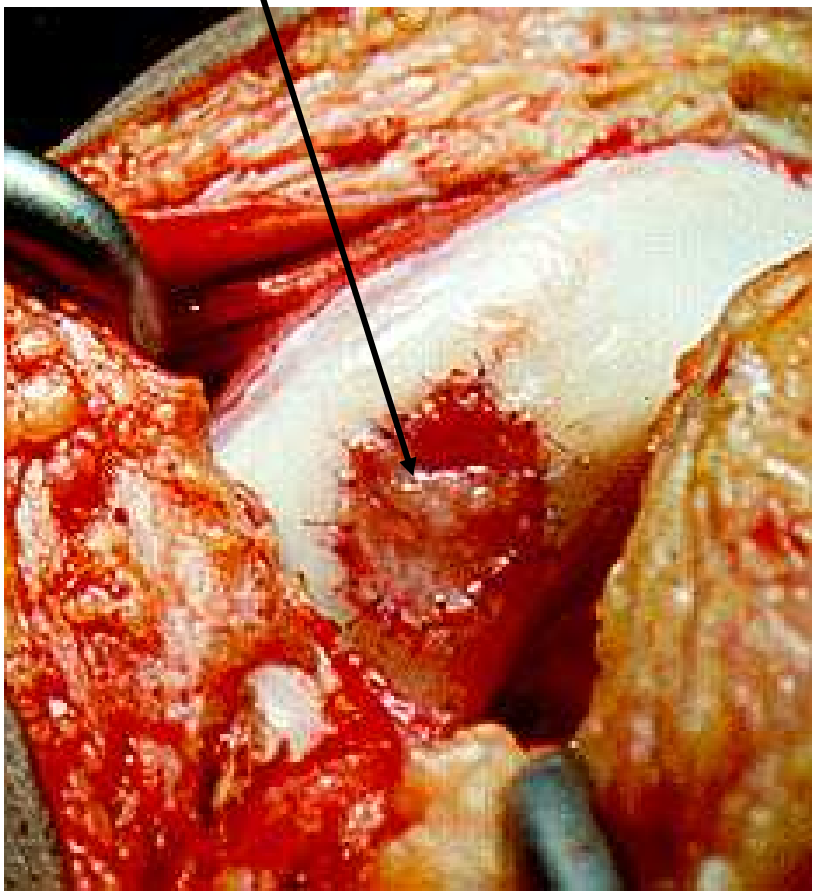



Hücre kültürü
Kondrosit izolasyonu
Sağlıklı yerden biyopsi
Hasarlı alan (lezyon)
Yama altına Kondrosit paketlenmesi
Tibiadan periostal yama

Tibial periosteum



İmplant yerinin hazırlanması



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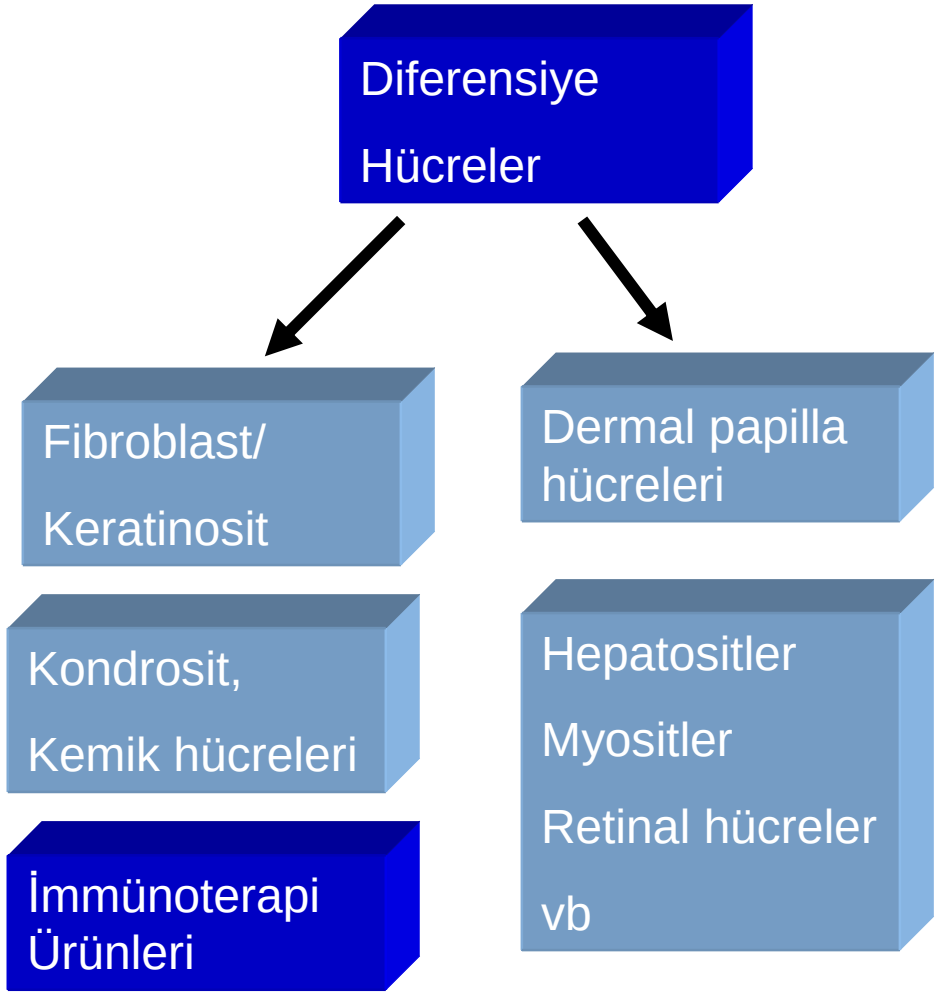


- İmmünoterapi ürünleri
  - Dendritik hücreler
  - NK hücreleri.
  - T lenfositler
    - DLI:
    - TIL/LAK:
    - ASH:
    - Treg (Regulatuar T lenfositler)
  - Granülositler: Ağır nötropenik ateşte yıllardır kullanılan hücrelerdir.

Renal cell karsinom

- 236 hasta 148 Otolog tümör lizat aşılaması 5 yıllık progresyon free survival ve overall survival T3N0M0 grubunda

- **kontrol grubunda % 25,**
- **aşı grubunda % 77,5.**

Repmann R ve ark. Anticancer Res. 2003 Mar-Apr;23(2A):969-74.

J. Exp. Clin. Cancer Res., 26, 2, 2007

Active Immunotherapy for Cancer Patients Using Tumor Lysate Pulsed Dendritic Cell Vaccine: a Safety Study

E. Ovali[1], T. Dikmen[1], M. Sonmez, M. Yilmaz, A. Unal[2], T. Dalbasti[3], K. Kuzeyli[4], M. Erturk[4], S.B. Omay[5]

[1]Karadeniz Technical University, Department of Haematology; [2]Erciyes University, Department of Oncology; [3]Ege University, Department of Neurosurgery; [4]Karadeniz Technical University, Department of Neurosurgery; [5]Karadeniz Technical University, Department of Microbiology; Trabzon - Turkey

Cancer vaccine therapy represents a promising therapeutical option. Consistently, with these new treatment strategies, the use of dendritic cell vaccines is becoming increasingly widespread and currently in the forefront for cancer treatment. The purpose of this study was to evaluate the feasibility and safety of tumor lysate-pulsed dendritic cell (DC) vaccine in patients with advanced cancers. For this purpose, eighteen patients with relapsed or refractory cancer were vaccinated with peripheral monocyte-derived DCs generated with GM-CSF and IL-4, and pulsed consequently with 100 μg/ml of tumor lysate before maturation in culture in the presence of IL-1β, PGE_2 and TNF α for two days. The first two vaccinations were given intradermally every two weeks while further injections were given monthly.

The DC injections were well-tolerated in all patients with no more than grade 1 injection-related toxicity. Local inflammatory response was mainly erythematous which subsided in 48 hrs time. No end organ toxicity or autoimmune toxicity was identified. Clinical responses observed in our study were satisfactory for a phase I clinical study. We observed 4 (22%) objective clinical responses. These responses are significantly correlated with delayed type hypersensitivity testing (DTH) ($p < 0.01$).

The results showed that this active immunotherapy is feasible, safe, and may be capable of eliciting immune responses against cancer.

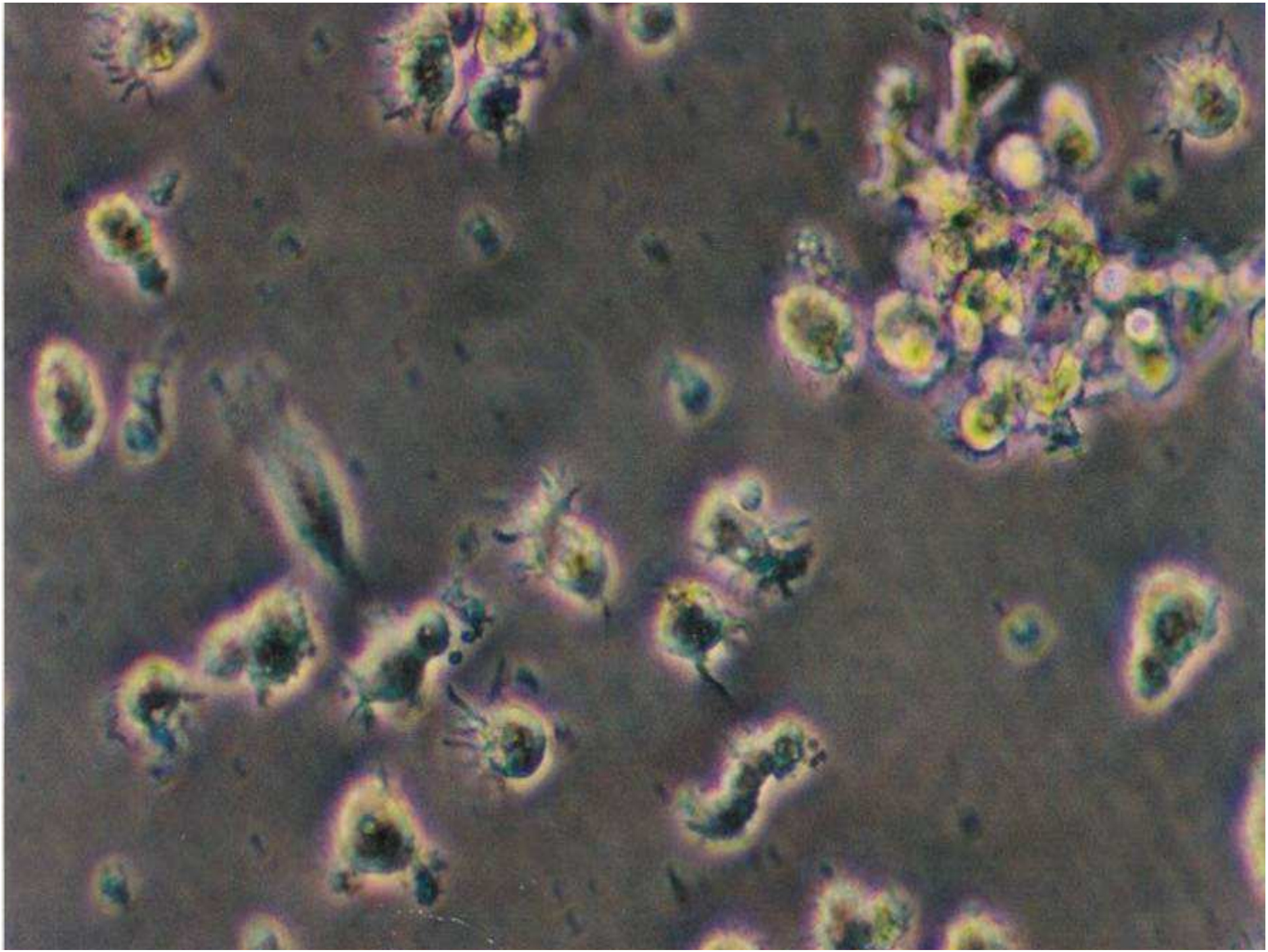
Key Words: Immunotherapy, Dendritic cell vaccine, Cancer

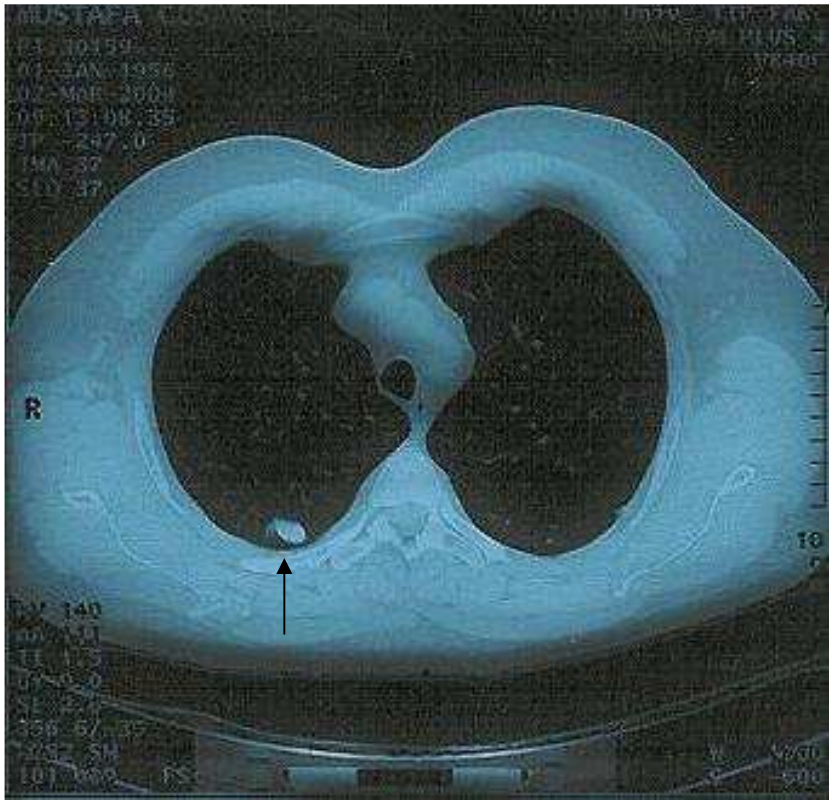
KTÜ-ATİ teknoloji deneyimi

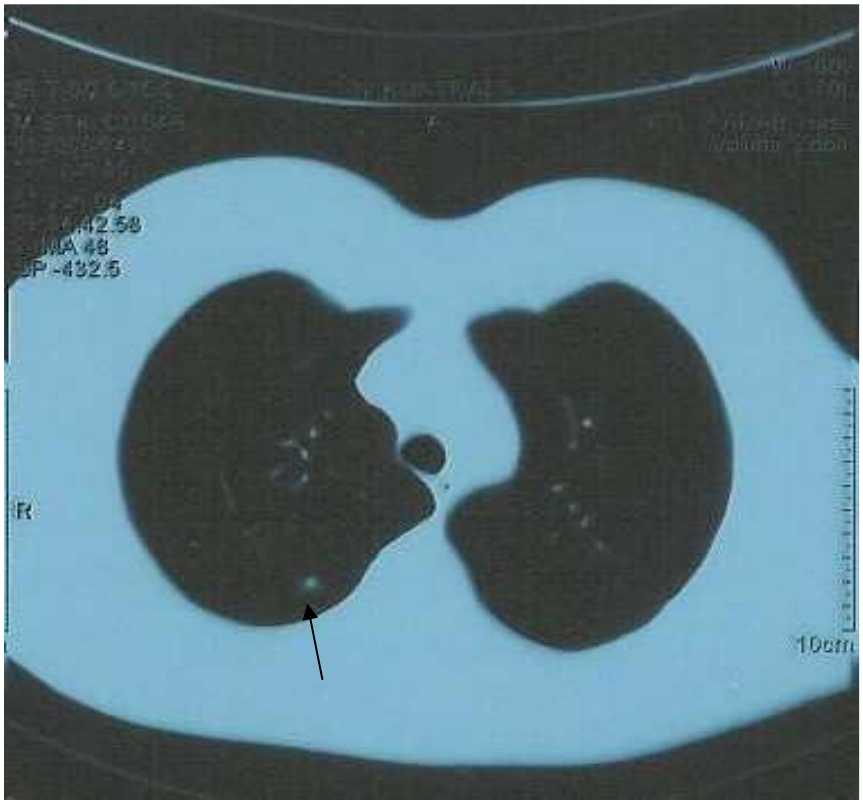
18 son dönem (no-hope) değişik türden kanser hastalarında dendritic hücre bazlı aşı uygulaması sonrası

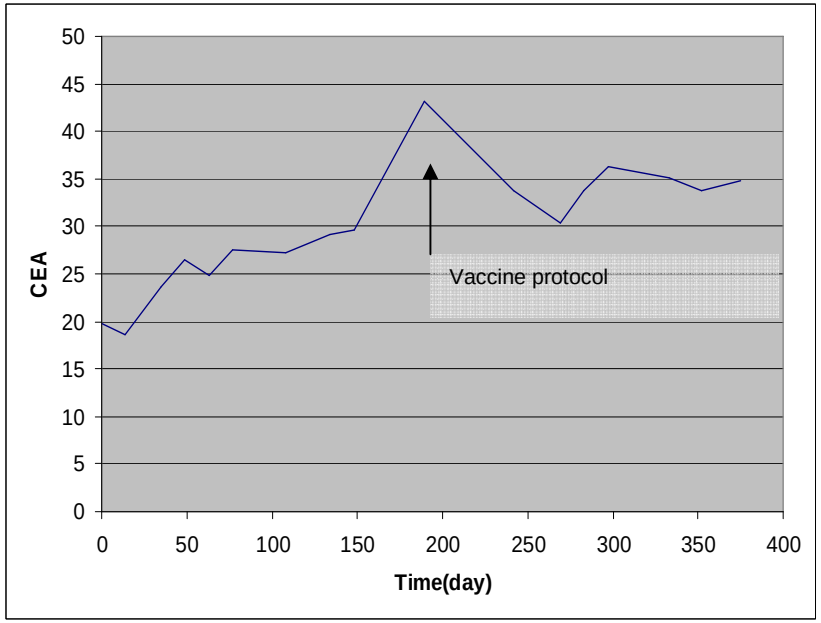
- 1 CR
- 1 NCR
- 2 PR
- 4 Primer tümör regresyonu

Toplam %22 objektif % 44 klinik yanıt








CEA
Time(day)
Vaccine protocol
0
5
10
15
20
25
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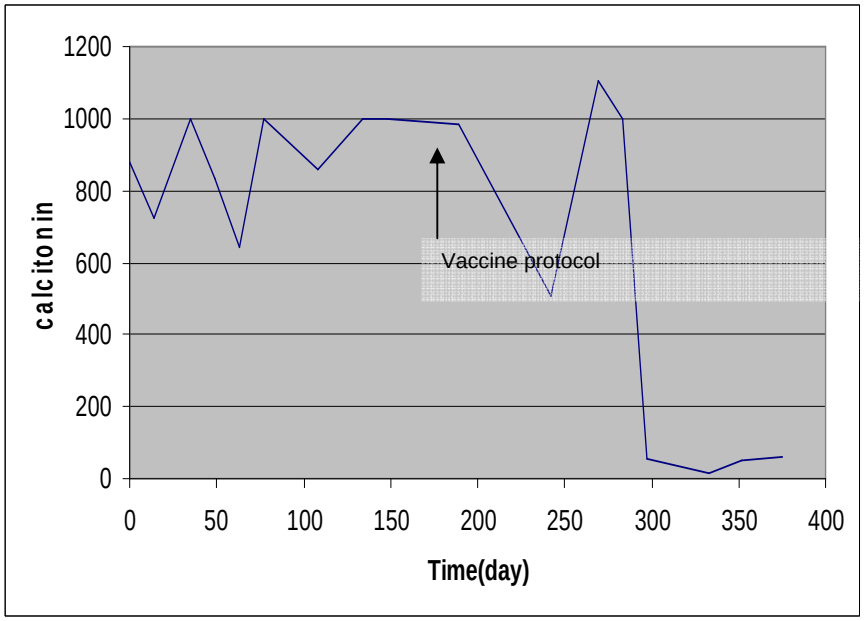
35
40
45
50
0
50
100
150
200
250
300
350
400


calcitonin
Time(day)
Vaccine protocol
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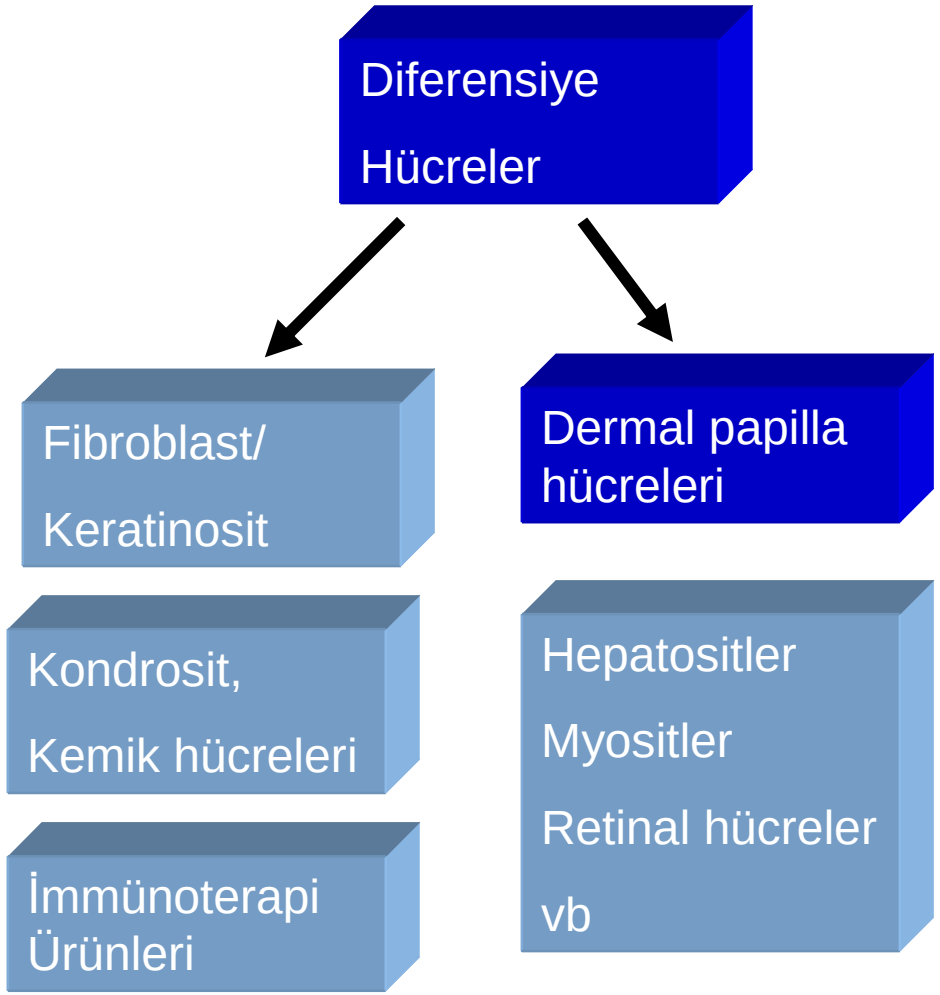
Diferansiye hücreler-1



Hücre Tedavilerinin Geleceği Ne Olacaktır?

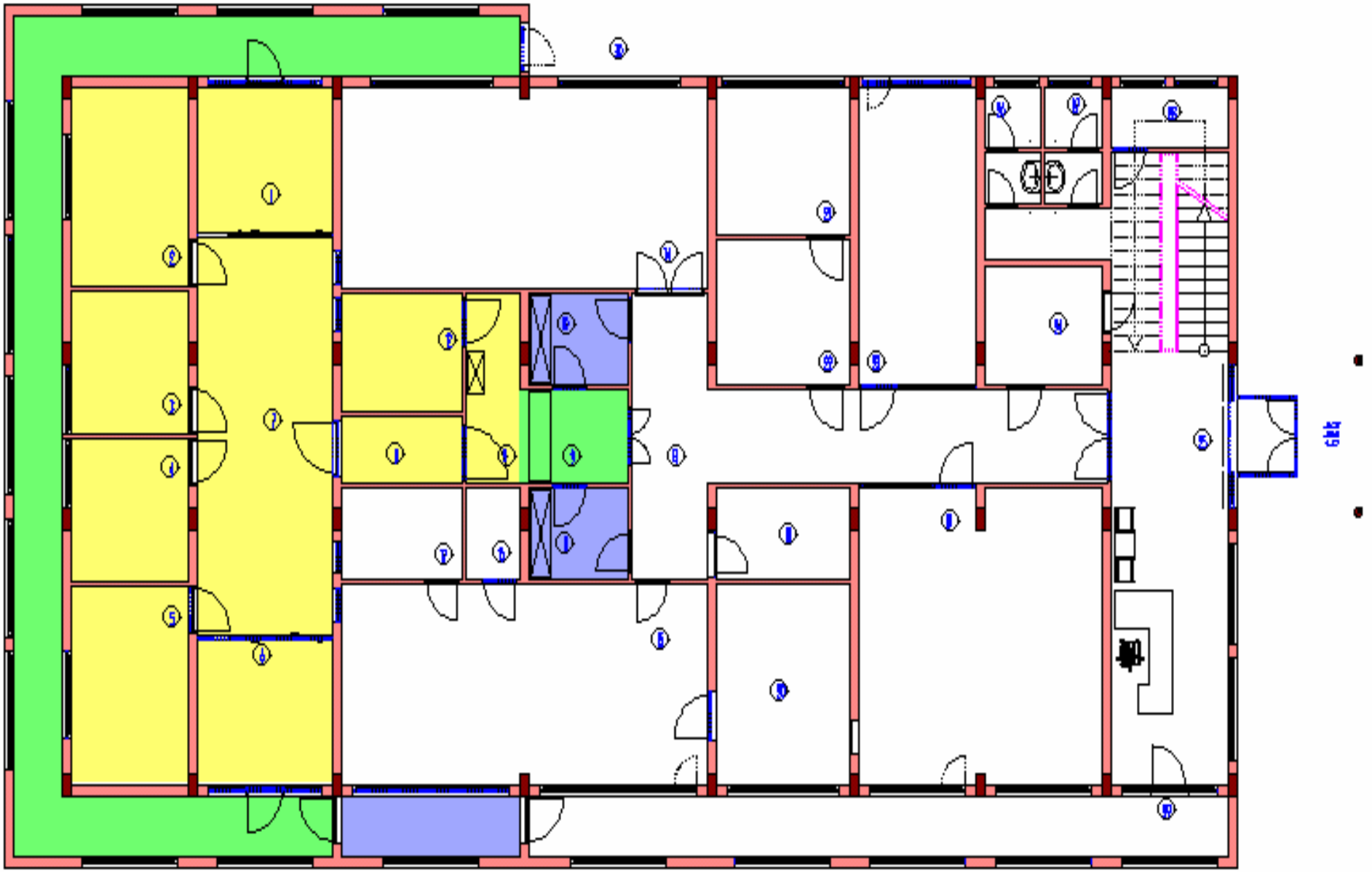
Ülkemizde Hücre Tedavileri Ne Durumdadır?

- Bu gün kök hücre nakli yapan 24 üniversite ve özel hastane mevcuttur.
- Kayıtlı 4 kordon kanı bankası ve
- Birçok Tüp bebek merkezi vardır
- Hemen tüm üniversitelerde hücresel tedaviler çalışılmaktadır.
- Ancak Tam anlamı ile hücre tedavi ürünlerini klinik kullanım için gerekli olan GMP standartlarında üreten merkez yoktur.

Bu anlamda İlk Girişim:

KARADENİZ TEKNİK ÜNİVERSİTESİ VE
ATİ Teknoloji. AŞ

Ülkemizin ilk GMP koşullarına uygun, Hücre tedavi Laboratuarını
CellGenix Lisansı
ICCE akreditasyonu ile
4 milyon Euro'luk Tesisini tamamlamış ve 28 mayısta ulusal denetimden Tam not alarak çıkmıştır.



GROUND FLOOR SCALE:1/50 (CLEAN ROOM CLASSIFICATION PLAN)
BLUE: D GREEN: C YELLOW: B

KTÜ-ATİ Teknoloji Üretim Hedefleri

- Kök hücre izolasyon, purging, ekspansiyon ve saklama işlemleri
- T-Hücre tedavileri ve immünoterapi programları
- DH üretimi ve Tümör aşıları (ATA-1,2,3)
- Organ spesifik kök hücre ve MPAC,MİAMİ,hBMSC izolasyonu ve üretimi
- ATİ-Mezenkimal
- ATİ-Fibro.
- ATİ-Fibroplazmajel
- ATİ-Keratinosit
- Ulusal doku veri bankası ve Kordon Kanı Bankacılığı
- Hücre tedavileri anlamında tüm ülkeye proje desteği

Yakın Gelecek

- ATİ-dp

– Otolog Kök Hücre işlemleri:
  - Kök hücrenin ek işlem yapılmaksızın dondurulması ve saklanması
  - Kök hücreden CD34 pozitif seleksiyon
  - Kök hücreden exvivo ekspansiyon*

Allogeneik kök hücre işlemleri:
  - Kök hücrenin ek işlem yapılmaksızın dondurulması ve saklanması
  - Kök hücreden CD34 pozitif seleksiyon
  - Kök hücreden CD3 deplesyonu*
  - Kök hücreden CD8 deplesyonu*
  - Kök hücreden exvivo expansiyon*
  - DLI için NK hücre seleksiyonu*
  - DLI için CD8 deplesyonu*
  - CMV spesifik DLI*

- Lizat aşılar*
- DNA aşıları*
- Protein-Peptit aşılar*:
  - Ig İdiotip aşıları
  - Tümör spesifik proteinler
  - Viral protein spesifik aşılar
- Dendritik hücre aşıları*:

Otolog dentritik hücrelerin üretimini takiben

  - Tümör lizatları ile yüklenmiş DH aşıları
  - Tümör spesifik peptitlerle yüklenmiş DH a
  - Tümör spesifik RNA,DNA ile yüklenmiş D aşıları.
  - Viral peptitlerle yüklenmiş DH aşıları

- Tümör spesifik T hücre üretimi*
- Virus protein spesifik T hücre üretimi*
- Ağır nötropenik ateşte kullanılmak üzere için T cell hücreleri azaltılmıs ışınlanmış allogeneik granülosit üretimi*.

- Tedavi Amaçlı Ürünler*:
  - Otolog cilt dokusu
  - Otolog kıkırdak dokusu(diz cerrahisi için)

- Araştırma amaçlı Ürünler*
  - Kardiyak rejenerasyon için otolog MKH üretimi
  - ALS olguları için otolog MKH üretimi
  - Hepatik rejenerasyon için MKH üretimi
  - Sinir sistemi tümör cerrahisi sonrası için MKH üretimi
  - Sipinal Kord ve periferik nöron tamiri için MKH üretimi
  - Çalışma kapsamında tanımlanan her tür organ rejenerasyo için MKH üretimi

Kordon Kanı ve kök Hücre Bankacılığı

- 10 yıllık hücre dondurma deneyimi
- 5 yıllık kök hücre dondurma deneyimi
- 2 yıllık kordon kanı saklama deneyimi
- Uluslar arası CellGenix deneyimi ile klasik kordon kanı bankacılığı
- Thermogenesis lisansı ile otomatize Bioarchive sistemi ile kordon kanı bankacılığı

- Bu gün için KTÜ-ATİ Teknoloji
  - Multiple myeloma, Lenfoma
  - Lösemi
  - Renal hücreli kanser
  - Kolon kanseri
  - Karaciğer kanseri
  - Mide kanseri
  - Akciğer kanseri
  - Cilt kanseri
  - ve diğer birçok kanser için aşı üretebilmektedi

HÜCRENİN GÜCÜNÜ KULLANIN

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