9. Ulusal

Transplantasyon İmmünolojisi ve Genetiği Kongresi

18-21 Nisan 2024

Papillon Zeugma Hotel Kongre Merkezi

Antalya

GEN NAKLİ, KİME, NE ZAMAN, NASIL UYGULANMALI?

EBMT
CIC: 913
JACIE : 815

Prof. Dr. Musa KARAKÜKCÜ

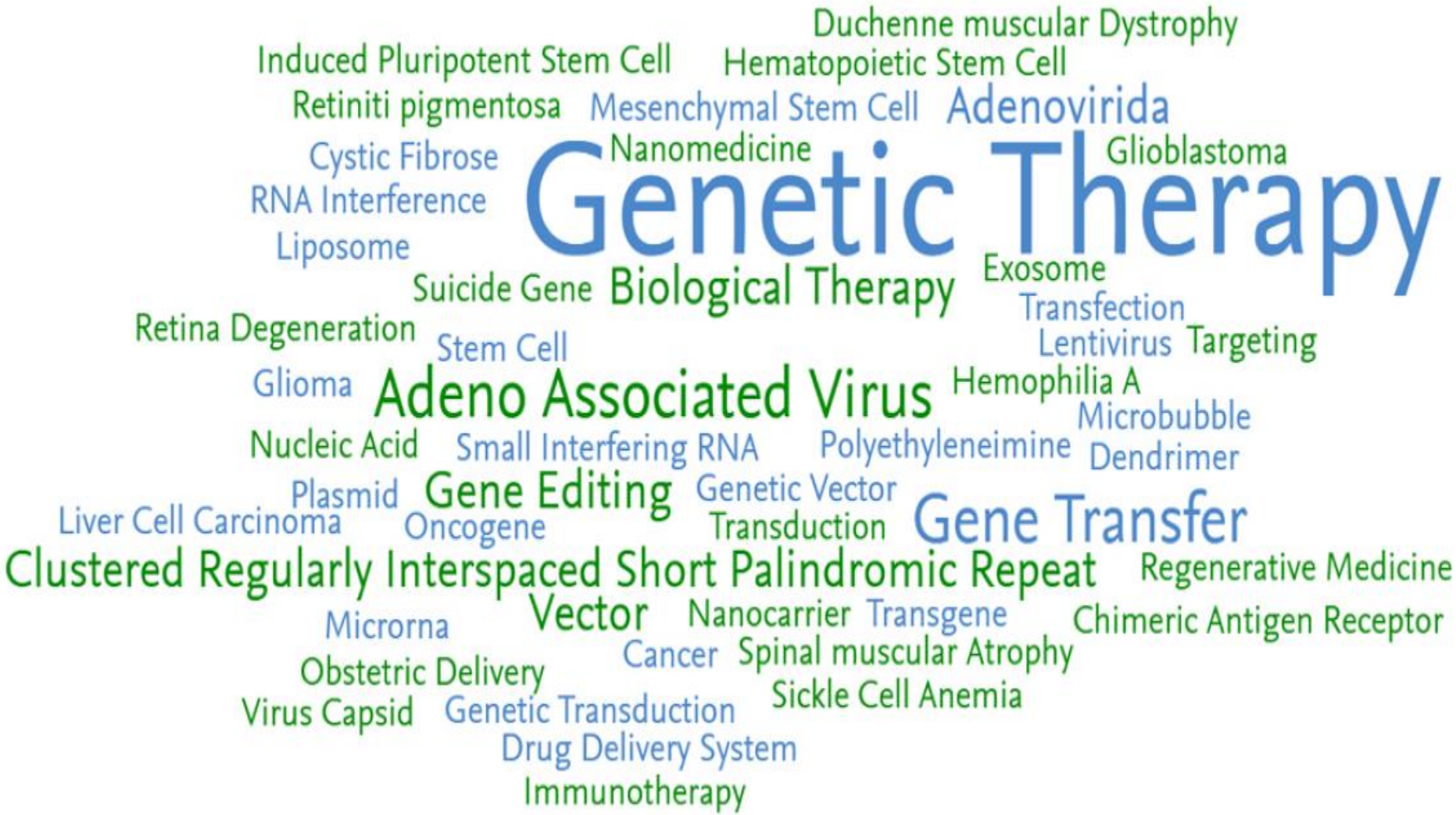
Erciyes Üniversitesi Tıp Fakültesi

Pediatrik Hematoloji Onkoloji

Erciyes KANKA Pediatrik KİT Merkezi

kan ka Kansere Karşı Birlikte Derneği

Gen Tedavisi



Gen Tedavisi

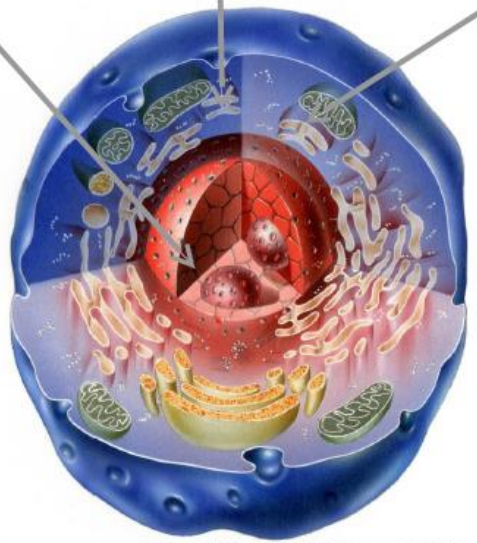
Gen Tedavisi ve Hücresel Tedaviler

Gen tedavisi, Genin Düzeltilmesi
- Gen eklenmesi
- Kusurlu Genin Kapatılması, değiştirilmesi, düzeltilmesi
- Başka bir genin aktive edilmesi
- Bir gene yeni bir gen işlev eklenmesi

Enzim Replasman Tedavisi

Farmakolojik Tedavi

gene → protein → function

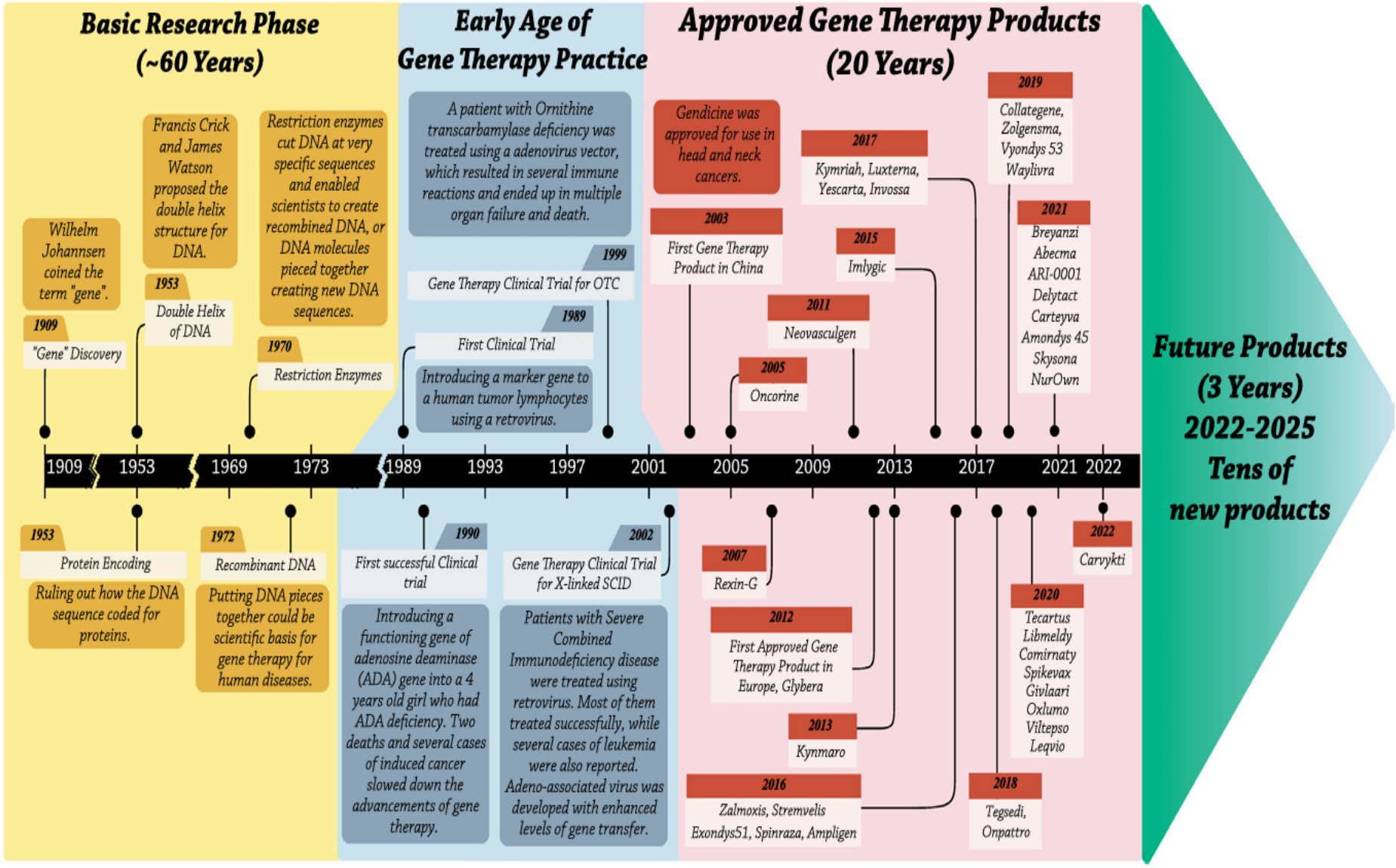


cell

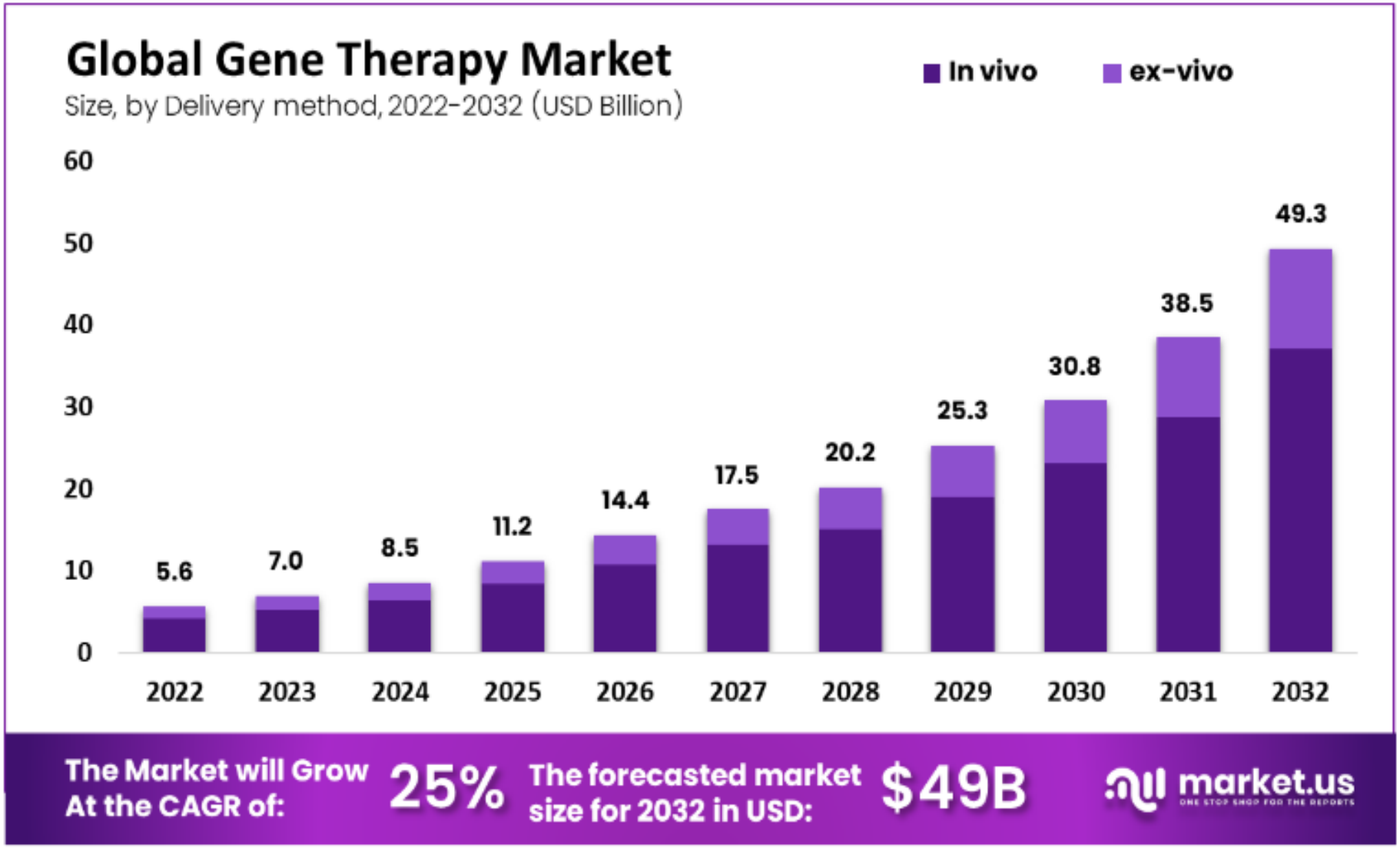
GENE and CELL THERAPY ADVANCED THERAPIES:

Hücre terapisi
Sağlıklı veya düzeltilmiş somatik Hücrelerin yönetimi

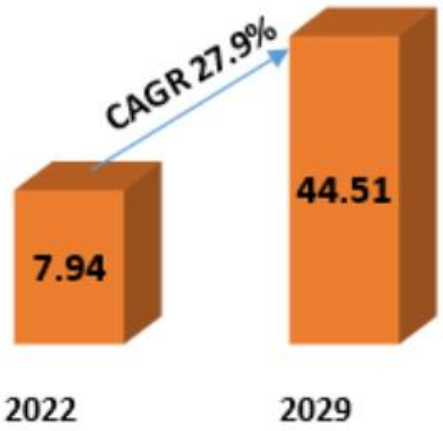
Gen Tedavisi Tarihçesi



Gen Tedavisi ve Gelecek



Gen Tedavisi Market

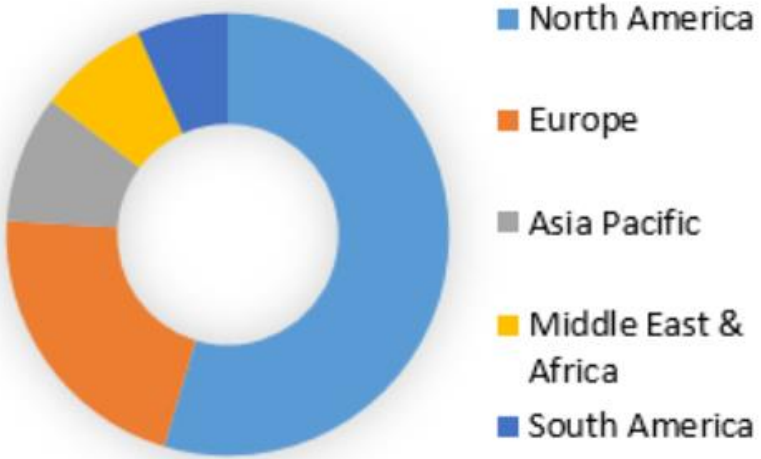


Market Size in US$ Billion

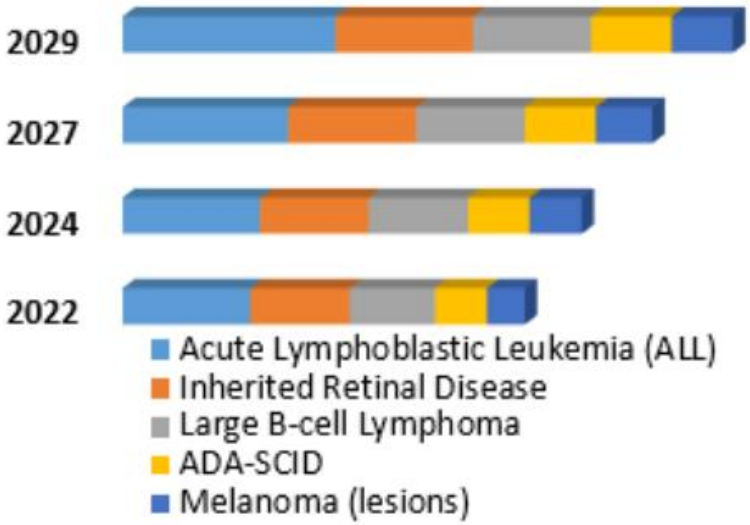
Key Players

REGENXBIO, Inc.
Bayer
Oxford BioMedica plc
Dimension Therapeutics,
Bristol-Myers Squibb Company
SANOFI
Applied Genetic Technologies Corp
F. Hoffmann-La Roche
Gilead Lifesciences, Inc.
Benitec Biopharma Ltd.
Sibiono GeneTech Co., Ltd.
Shanghai Sunway Biotech Co., Ltd
Gensight Biologics S.A.
Transgene
Calimmune, Inc
Epeius Biotechnologies

Regional Analysis in 2022 (%)



Indication Segment Overview

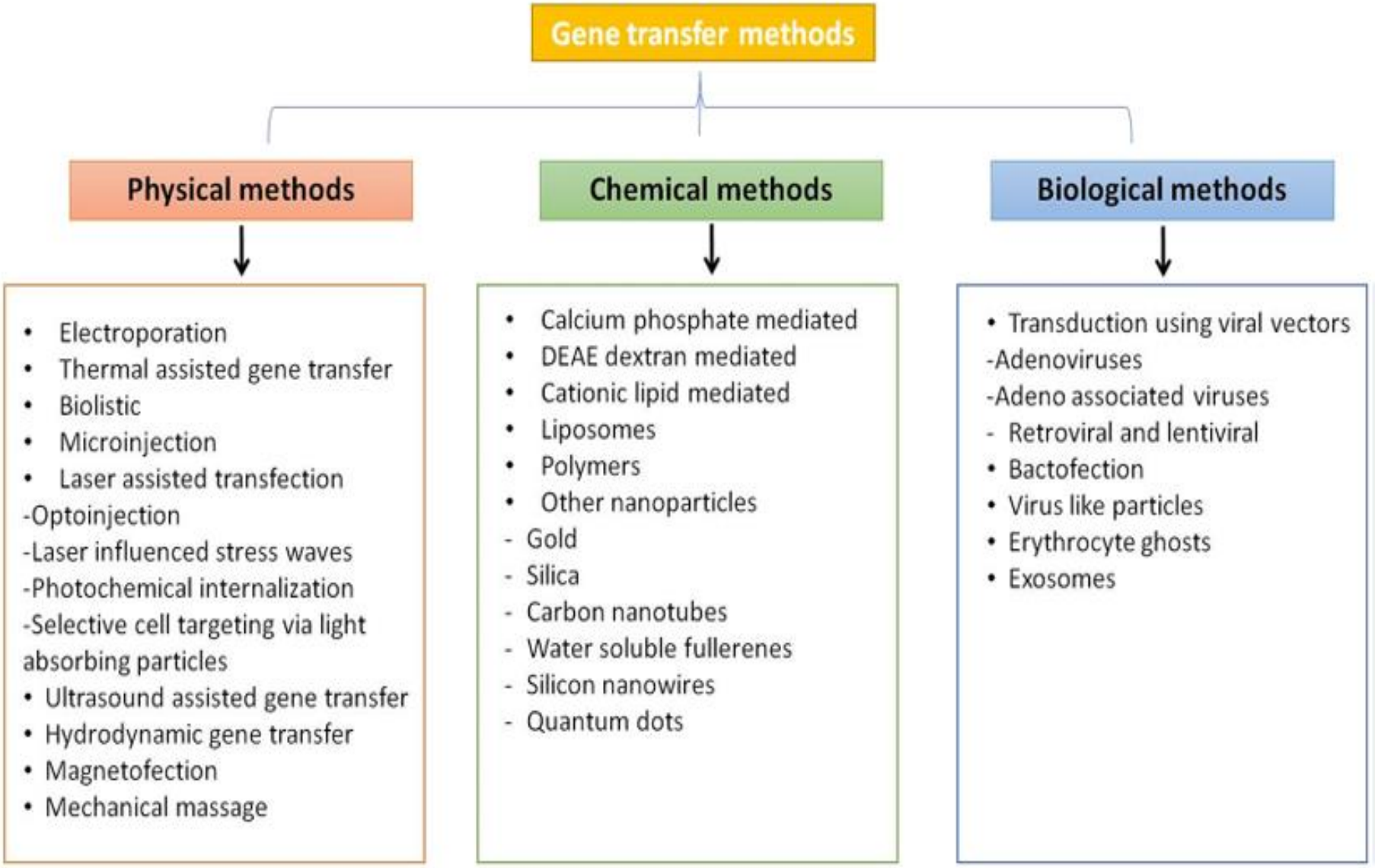


Gen Tedavi Platformu

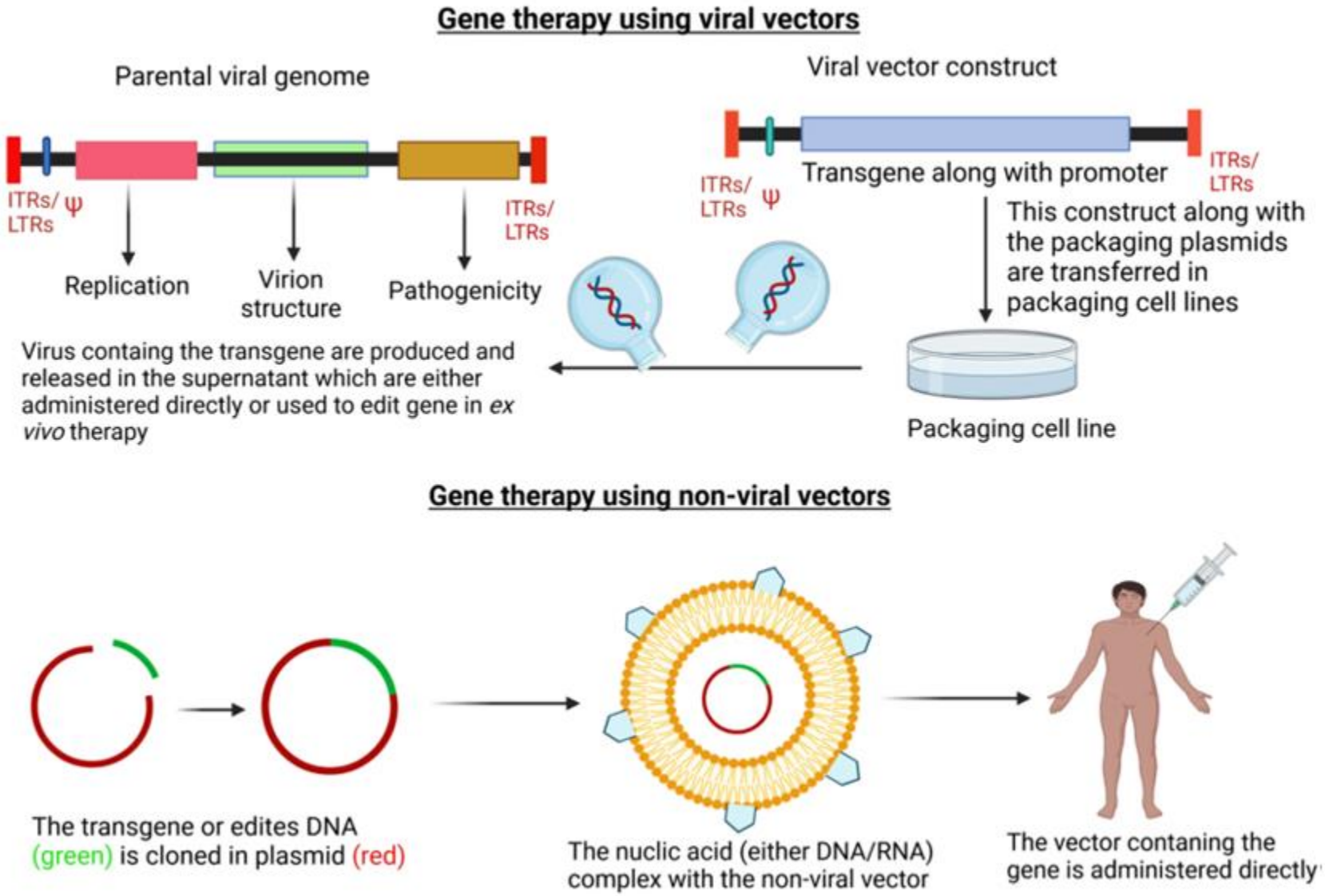
- **Entegre olan vektörlerle gen eklenmesi**
- Gen Editing (düzenleme)
    - Genin düzeltilmesi
    - Genin içinde (downstream of a promoter))
    - Güvenli limanlarda

  Teknoloji
        - Zinc fingers nükleaz
        - TALEN (transcription activator-like effector nucleases)
        - Crispr/Cas9 (RNA/protein)
- Gen bozulması
- İnhibitör aktiviteye sahip gen eklenmesi (shRNA)

Gen Transfer Metodları



Gen Tedavisi



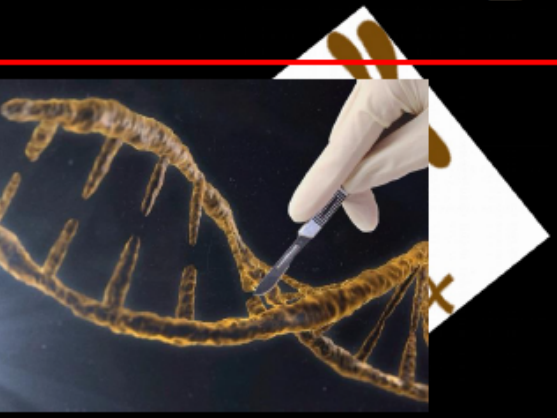
Gen Tedavisinde Viral Vektörler

		Adenovirus	Adeno-associated virus	Alphavirus	Herpesvirus	Retrovirus / Lentivirus	Vaccinia virus
Particle characteristics	Genome	dsDNA	ssDNA	ssRNA (+)	dsDNA	ssRNA (+)	dsDNA
	Capsid	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Complex
	Coat	Naked	Naked	Enveloped	Enveloped	Enveloped	Enveloped
	Virion polymerase	Negative	Negative	Negative	Negative	Positive	Positive
	Virion diameter	70 - 90 nm	18 - 26 nm	60 - 70 nm	150 - 200nm	80 - 130 nm	170 - 200 X 300 - 450nm
	Genome size	39 - 38 kb	5 kb	12 kb	120 - 200 kb	3 - 9 kb	130 - 280 kb
							
	Family	*Adenoviridae*	*Parvoviridae*	*Togaviridae*	*Herpesviridae*	*Retroviridae*	*Poxviridae*
Gene Therapy Properties	Infection / tropism	Dividing and non-diving cells	Dividing and non-diving cells	Dividing and non-diving cells	Dividing and non-diving cells	Dividing cells*	Dividing and non-diving cells
	Host genome interaction	Non-integrating	Non-integrating*	Non-integrating	Non-integrating	Integrating	Non-integrating
	Transgene expression	Transient	Potential long lasting	Transient	Potential long lasting	Long lasting	Transient
	Packaging capacity	7.5 kb	4.5 kb	7.5 kb	> 30 kb	8 kb	25 kb

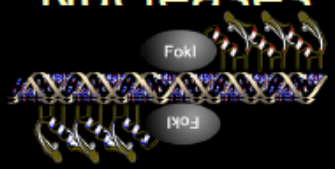
*Figure 2. A comparison of different viral vectors in use for gene therapy: overview of their advantages and disadvantages. * Adeno-associated viruses are able to integrate with low frequency into chromosome 19. Lentiviruses also infect non-dividing cells. You can also download the original image in high resolution as jpg or powerpoint file.*

http://www.genetherapynet.com/viral-vectors.html

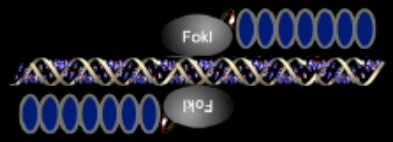
DNA “Nano-Surgery”



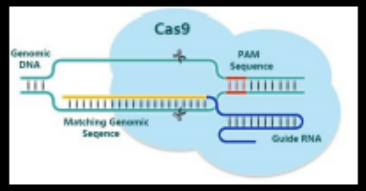
Zinc Finger Nucleases

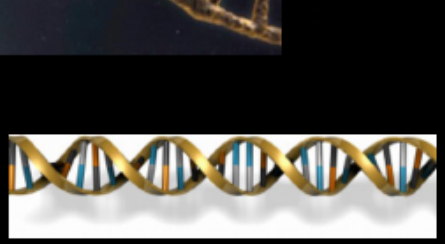


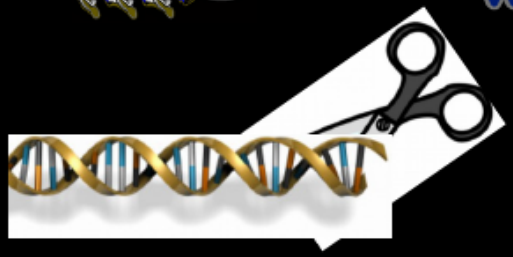
TALENs



CRISPR/Cas9



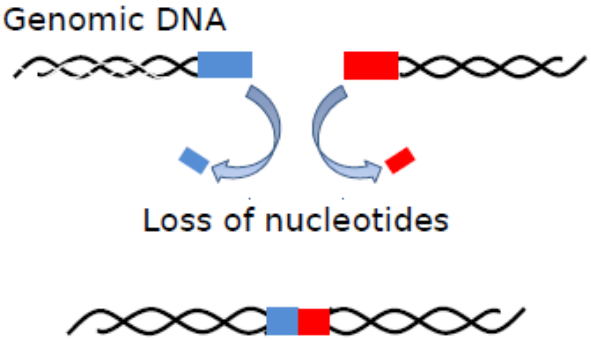




Repair by Non Homologous End Joining

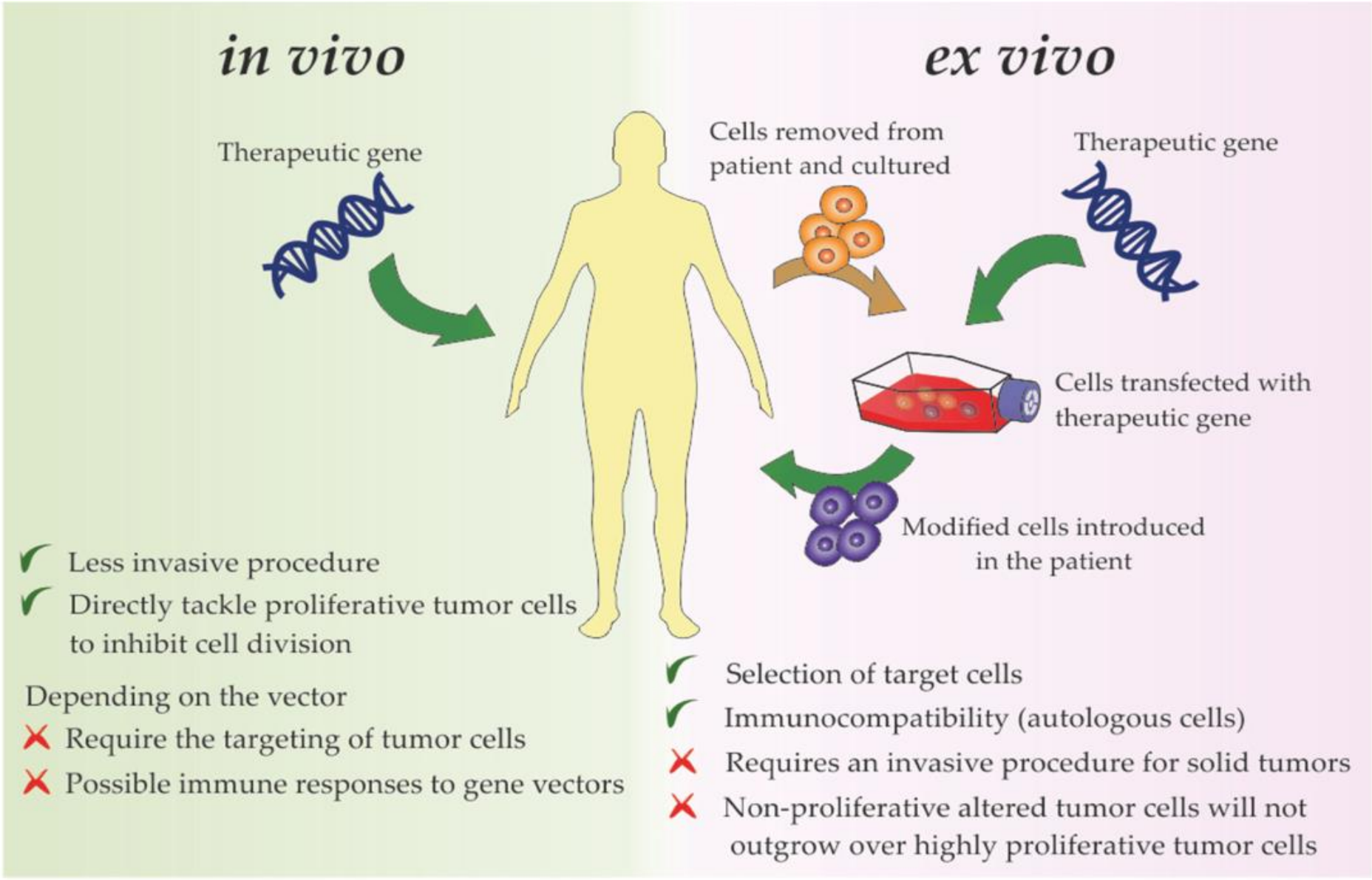
↓

Loss of Function

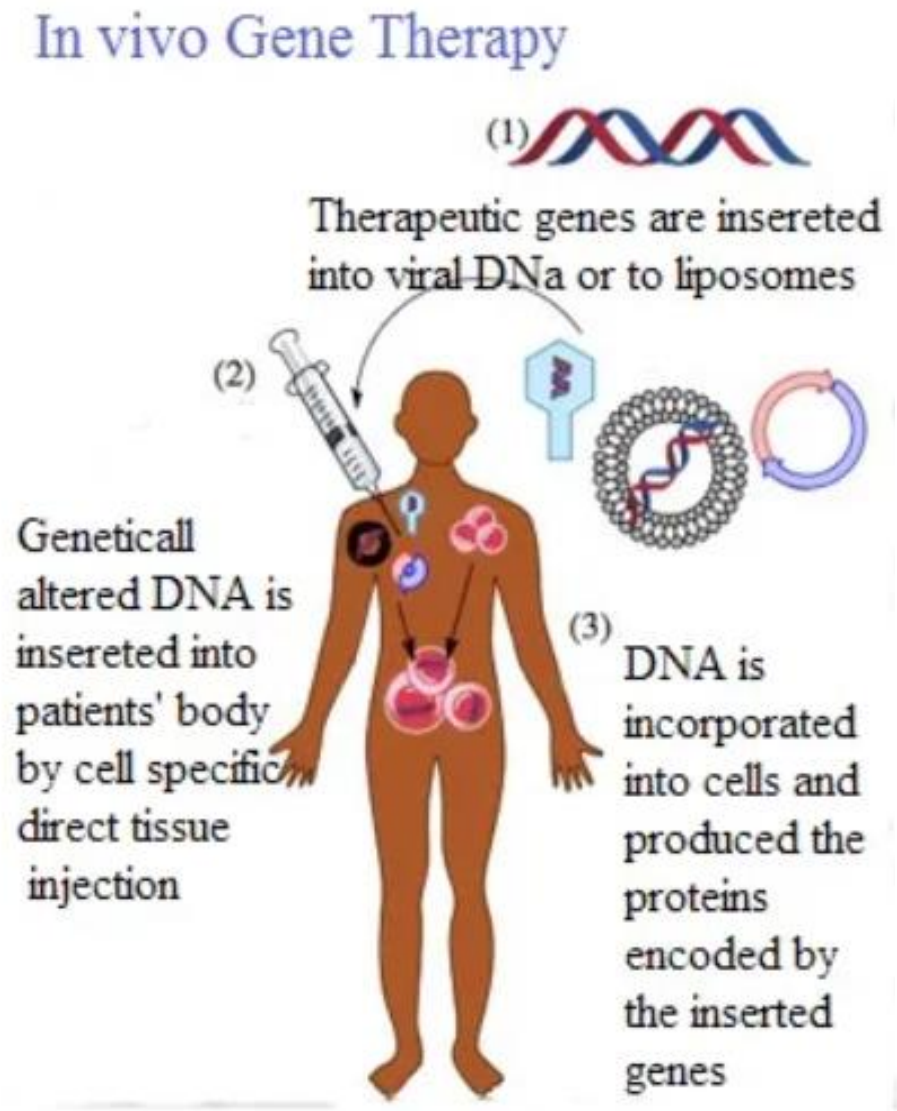


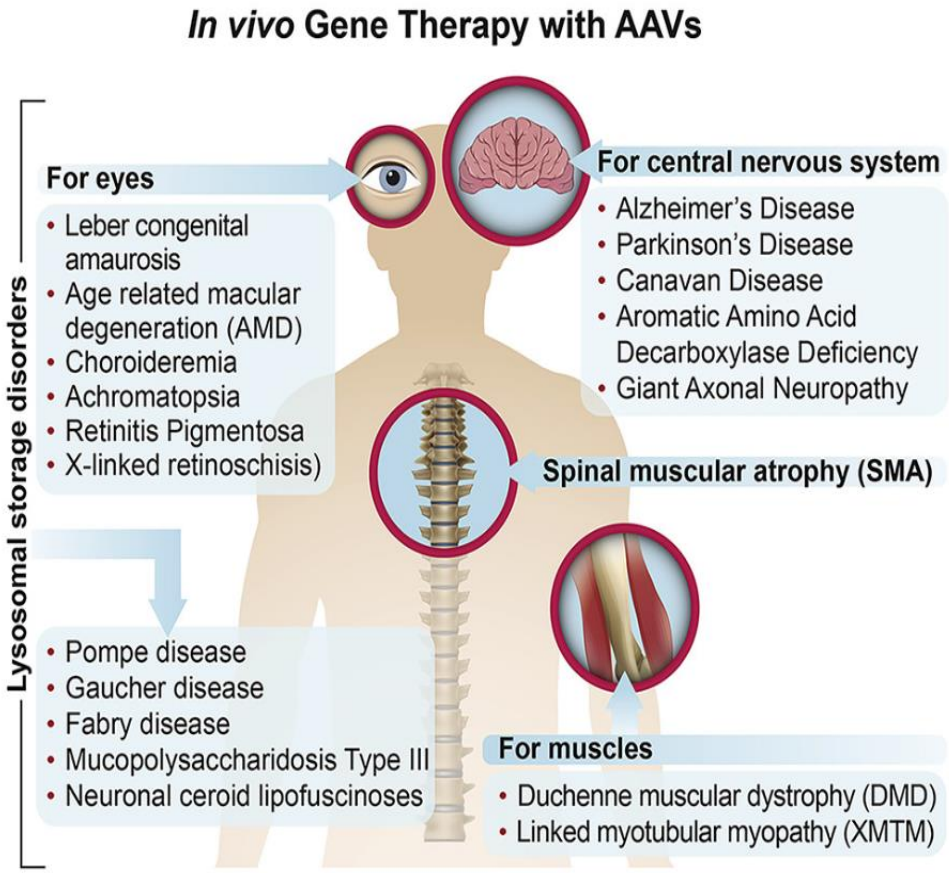
Gene Knock Out

Gen Tedavisi Nasıl Yapılır



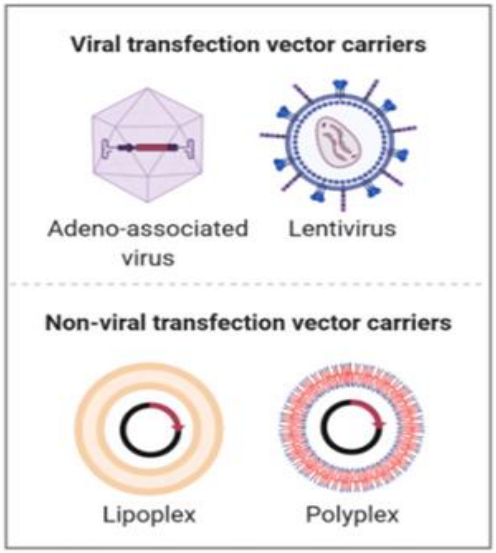
İn Vivo Gen Tedavisi

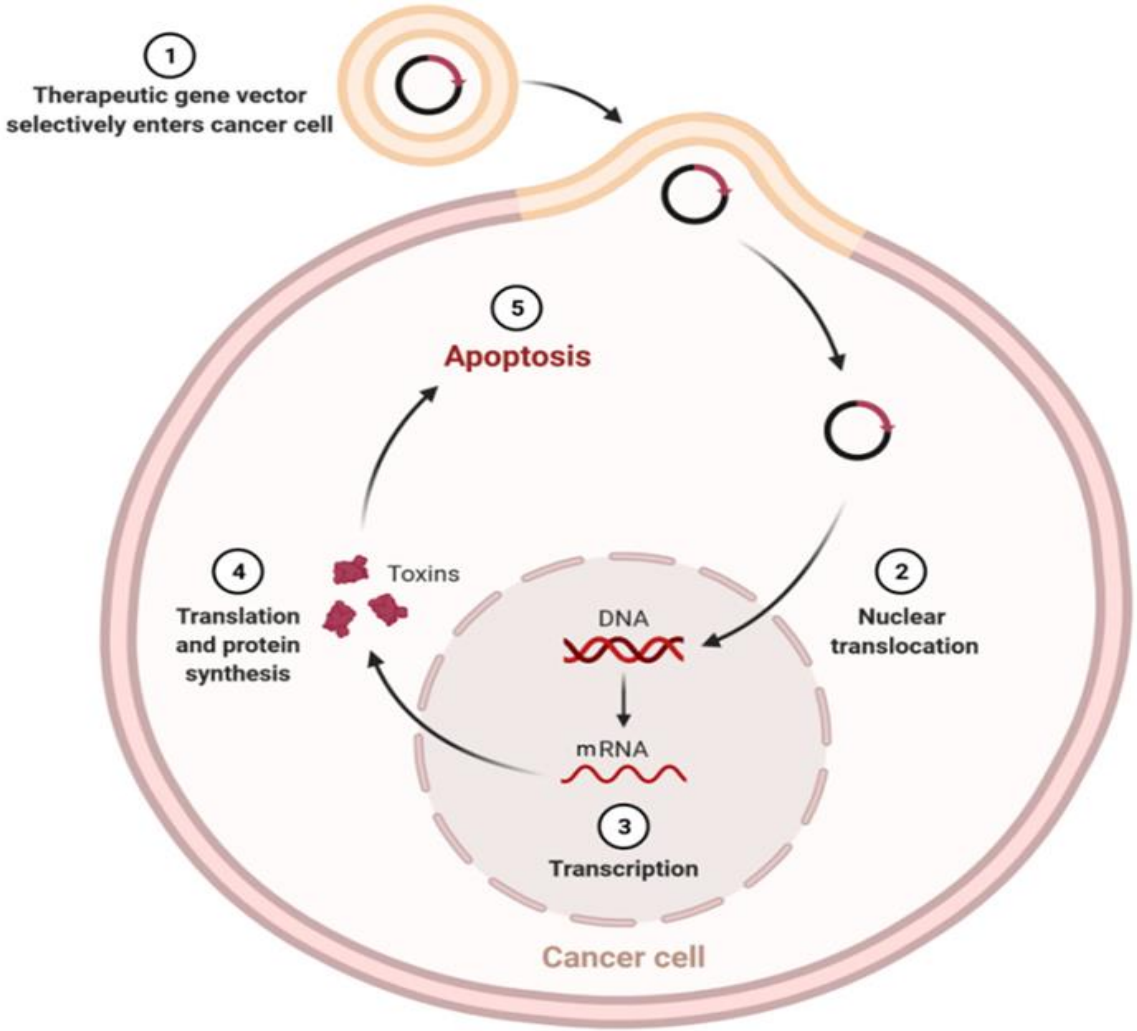




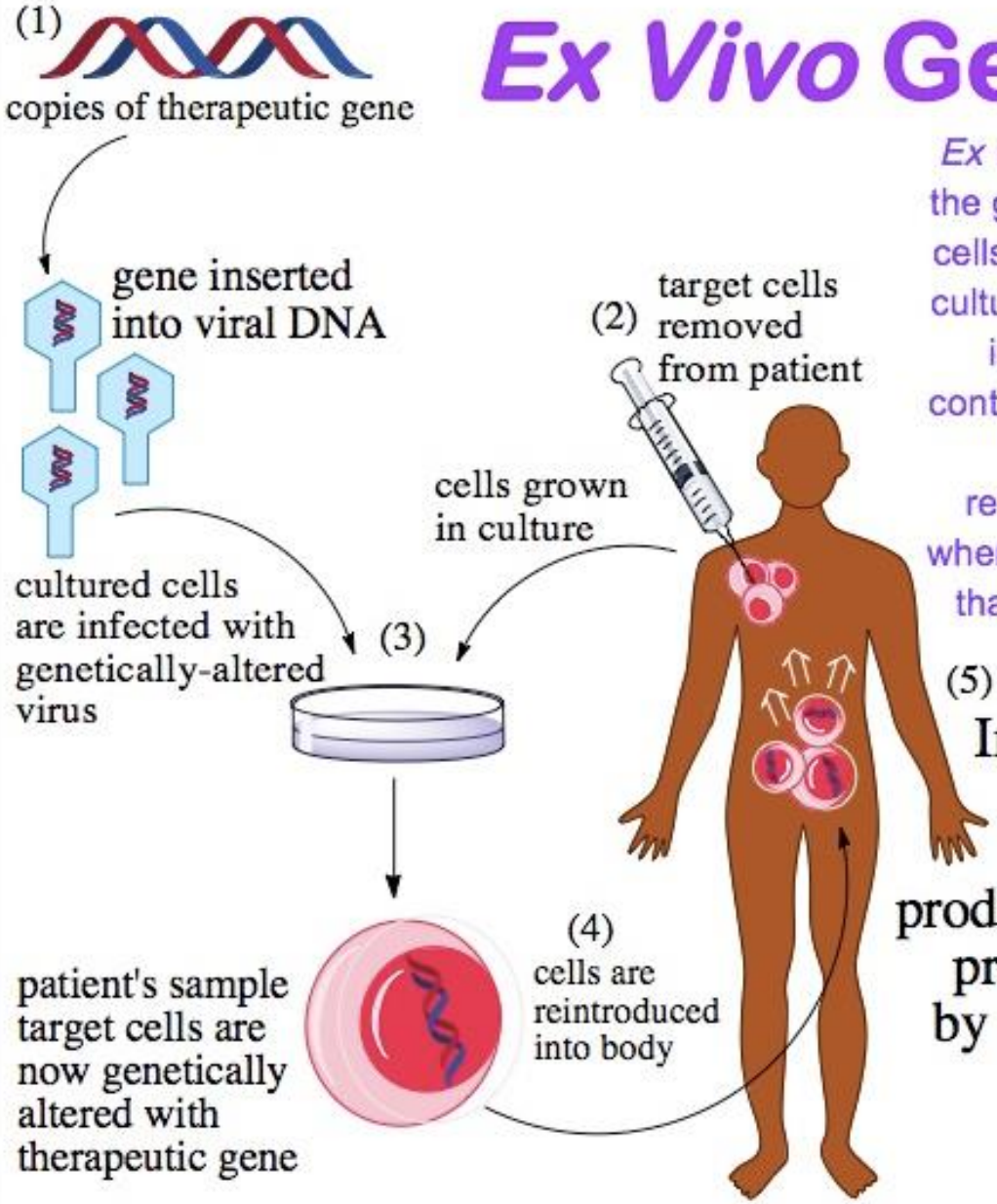
Gen Tedavisi

Cancer Cell-Targeted Gene Therapy



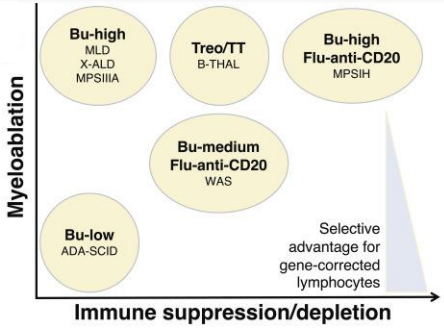


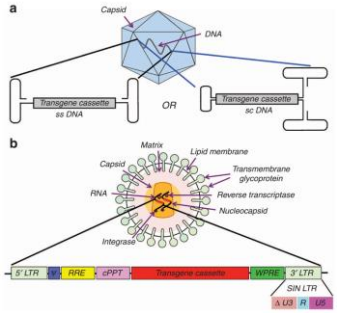
Ex Vivo Gene Therapy



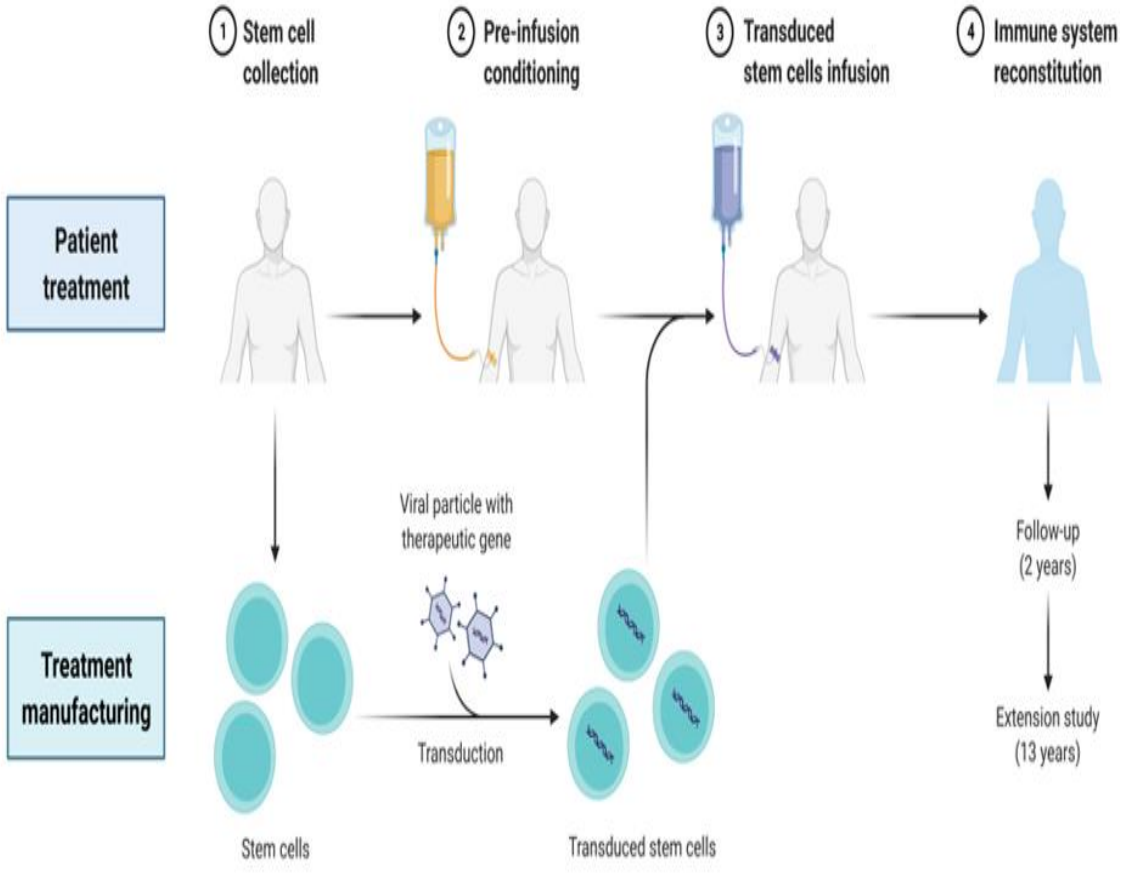
Ex vivo gene therapy is performed with the genetic alterations of patient's target cells happening outside of the body in a culture. Target cells from the patient are infected with a recombinant virus containing the desired therapeutic gene. These modified cells are then reintroduced into the patient's body, where they produce the needed proteins that correspond to the inserted gene.

Gen Tedavisi

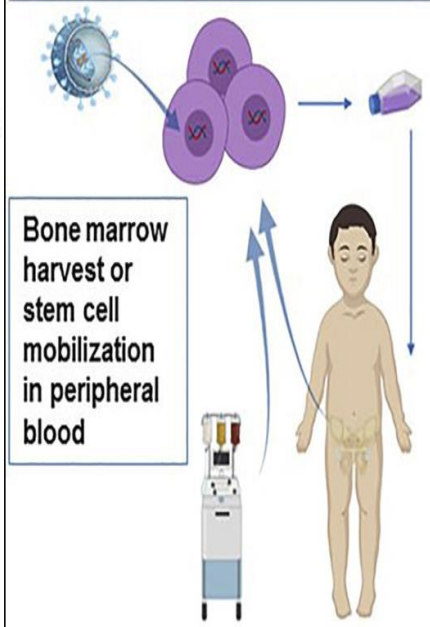




Ex vivo gene therapy cycle



Hematopoietic stem cells are transduced with vector containing a healthy copy of the gene causing the disease



Bone marrow harvest or stem cell mobilization in peripheral blood

+/– Patient Conditioning

Diseases

Immunodeficiencies
- Adenosine deaminase severe combined immunodeficiency
- X-Linked Severe Combined Immunodeficiency
- Wiskott Aldrich Syndrome
- X-linked chronic granulomatous disease

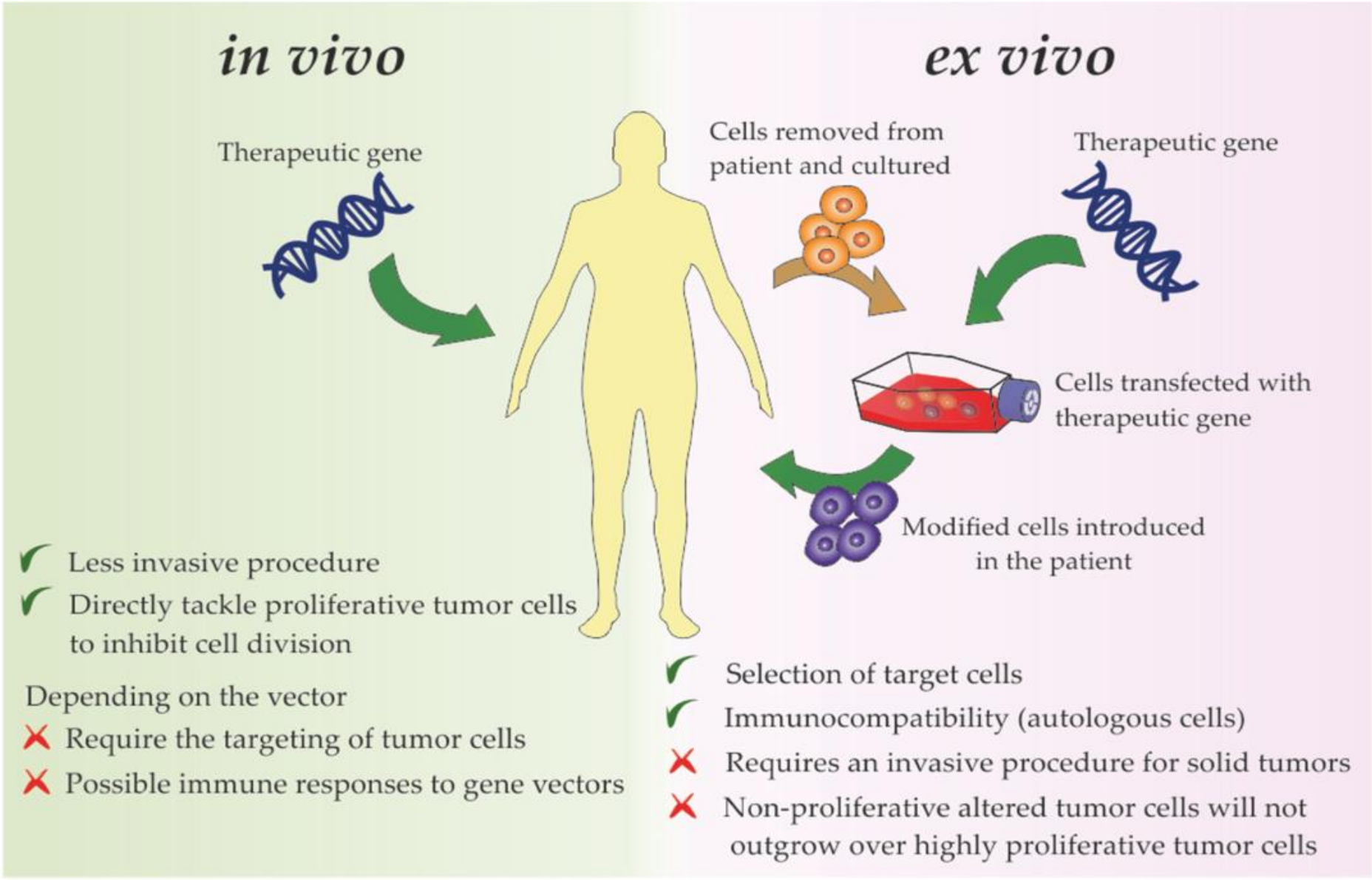
Hemoglobinopathies
- β thalassemia
- Sickle cell disease

Metabolic diseases
- Metachromatic leukodystrophy
- Mucopolysaccharidosis type 1
- Mucopolysaccharidosis type 3
- X-Linked Adrenoleukodystrophy

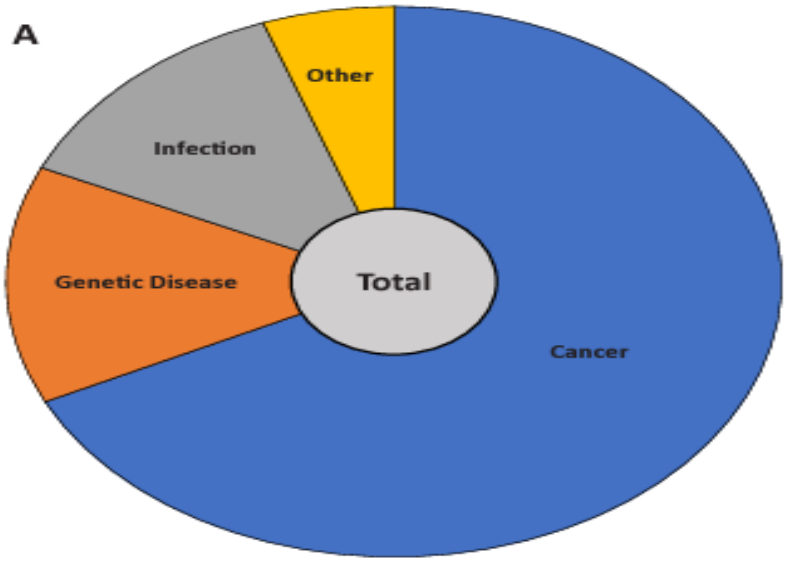
Gen Tedavisi Farkları

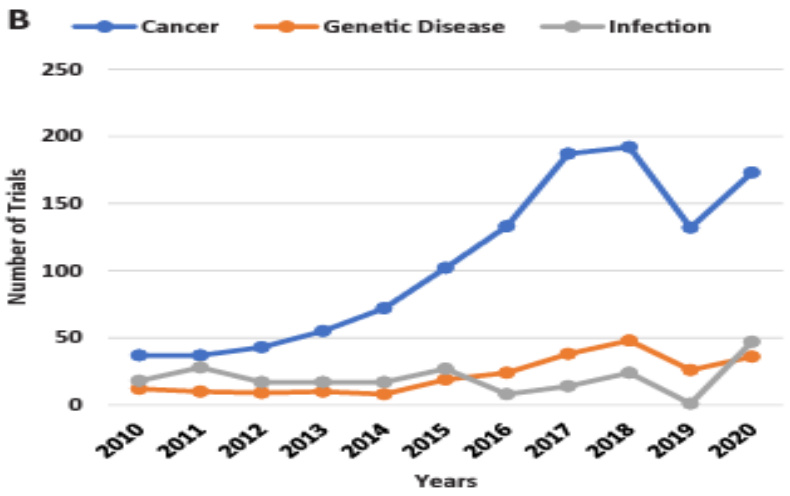
İn Vivo ve Ex Vivo Gen Tedavisi	
İn vivo gen terapisi, kusurlu hücreler hala vücuttayken doğrudan yapılan başka bir gen terapisi türüdür. Genler vücudun içindeyken değiştirilir.	**Ex vivo gen terapisi**, hastanın vücudunun dışında gerçekleştirilen bir tür gen terapisidir. Gen modifikasyonu vücut dışında yapılır.
İzolasyon ve Kültür	
Defektif hücreler izole edilemez ve laboratuarda kültüre gerek yoktur.	Defektif hücreler izole edilir ve laboratuarda kültüre edilir.
Seleksiyon ve Transformasyon	
Stabil transformatlar seçilemez.	Stabil transformantlar yeniden yerleştirilmeden önce seçilir.
İmmünolojik Yanıt	
Bu yöntem hastanın vücudunda olumsuz immünolojik reaksiyonlara sebep olabilir.	Bu yöntem hastanın vücudunda olumsuz immünolojik reaksiyonlara neden olmaz.

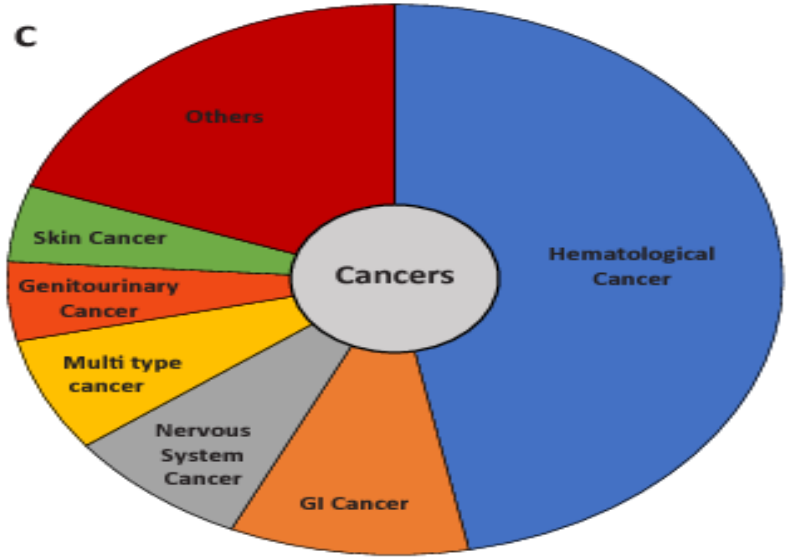
Gen Tedavisi Nasıl Yapılır

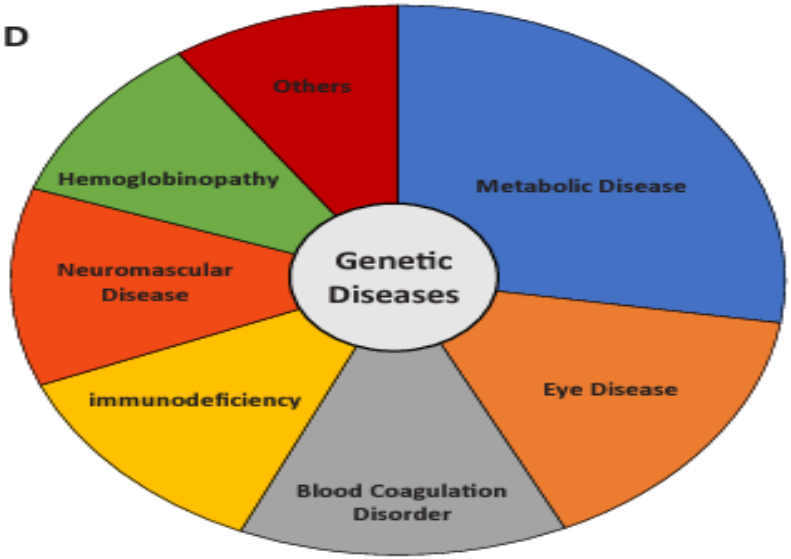


Gen Tedavisi Kimlere Yapılmalı

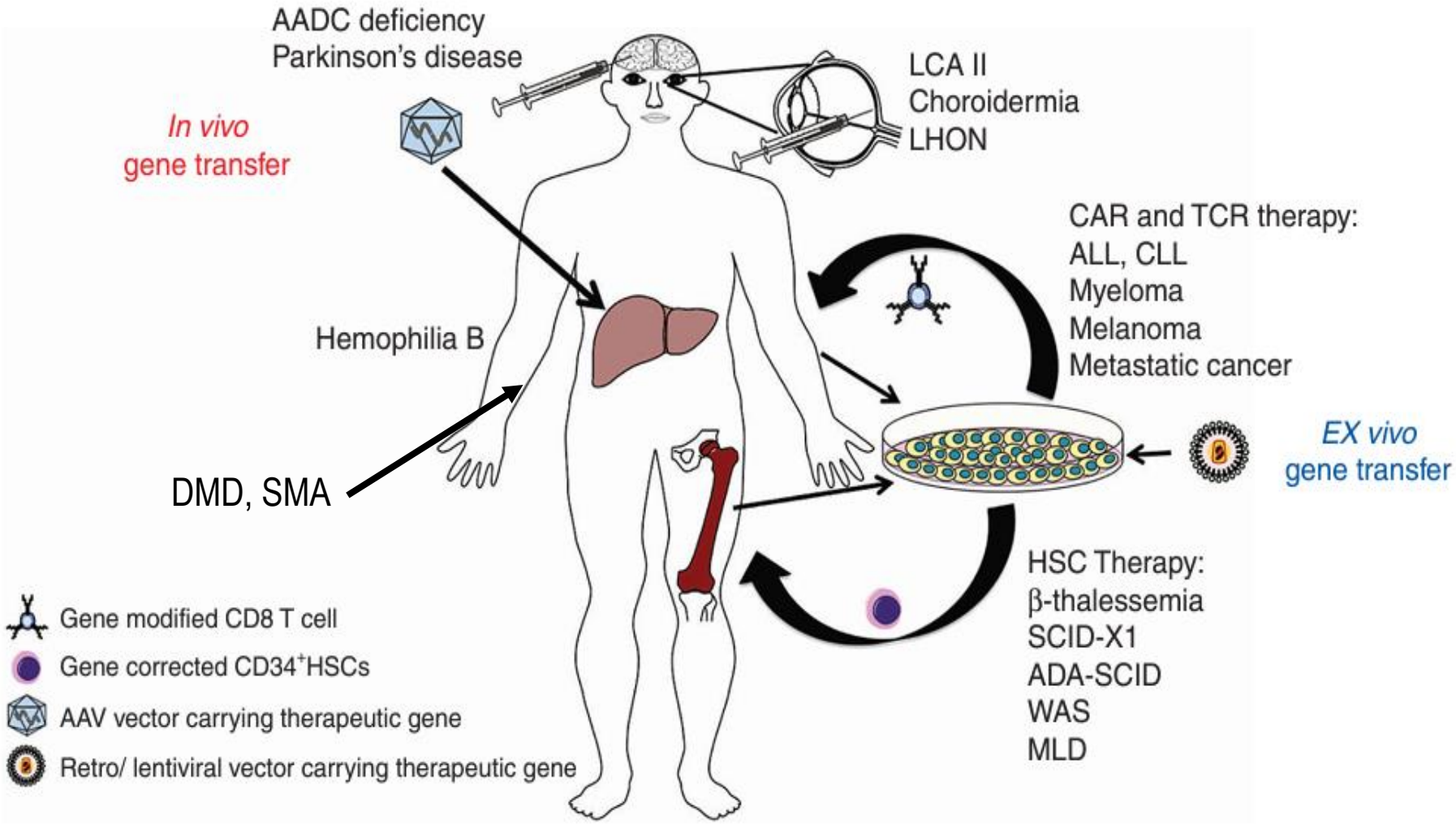






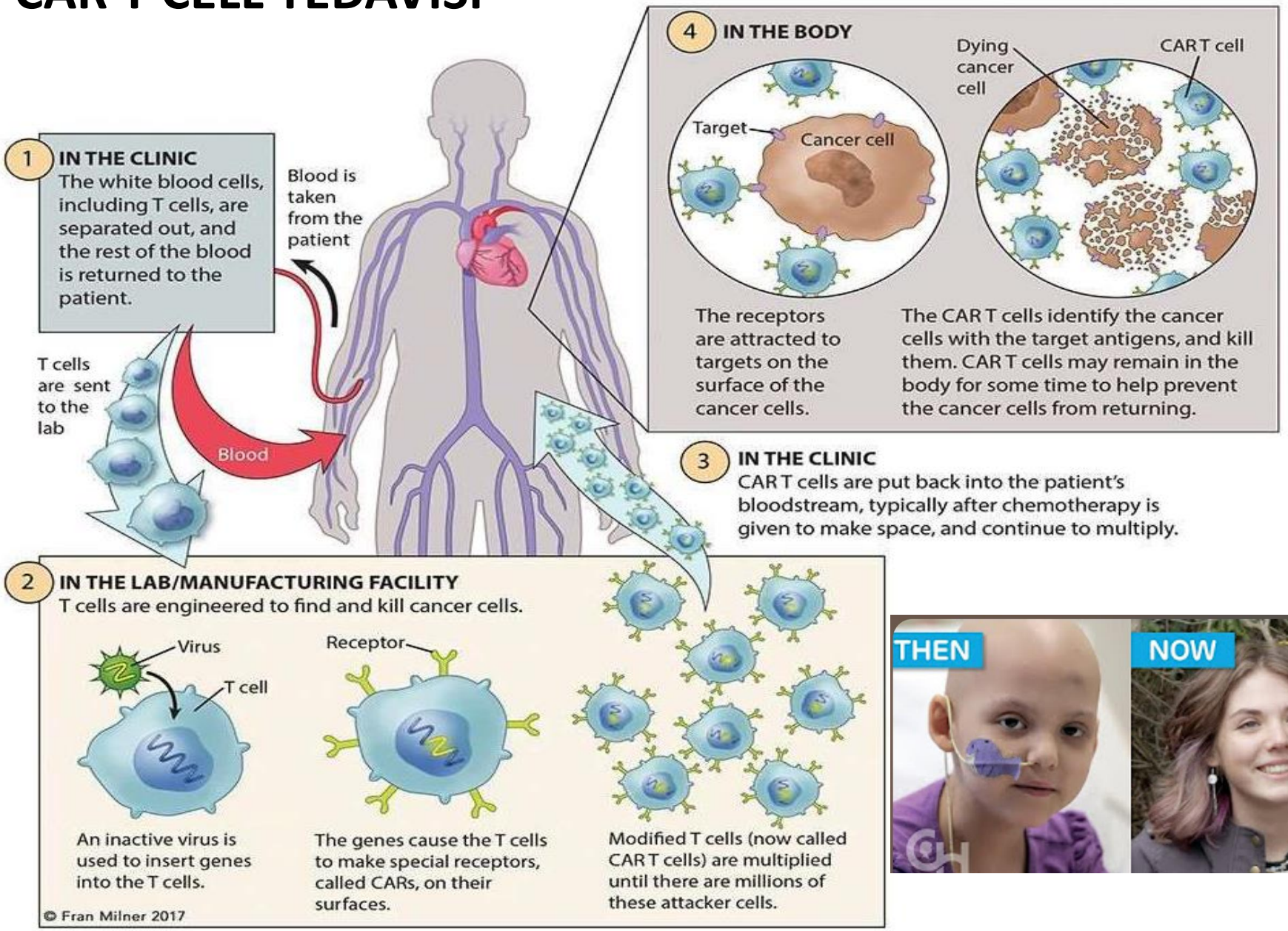


Gen Tedavisi Kimlere Yapılmalı

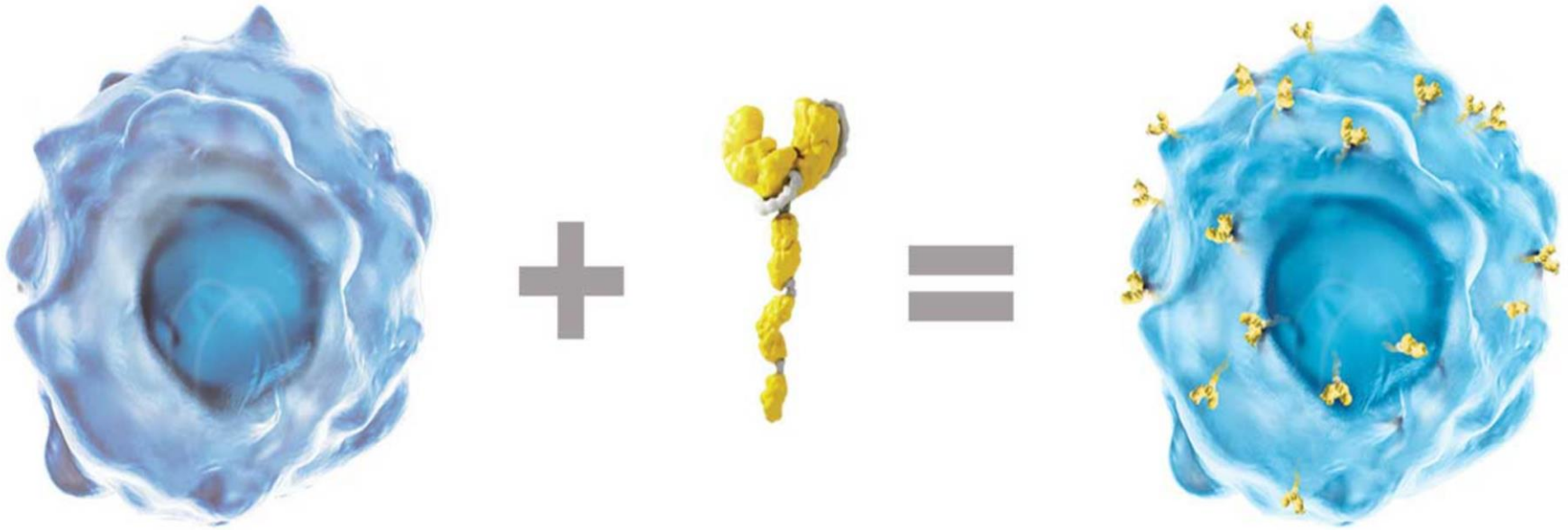


Gen Tedavisi Monogenetik her hastalığa yapılabilir.

CAR T CELL TEDAVİSİ



CAR T CELL Tedavisi



T CELL

A key fighter in your immune system

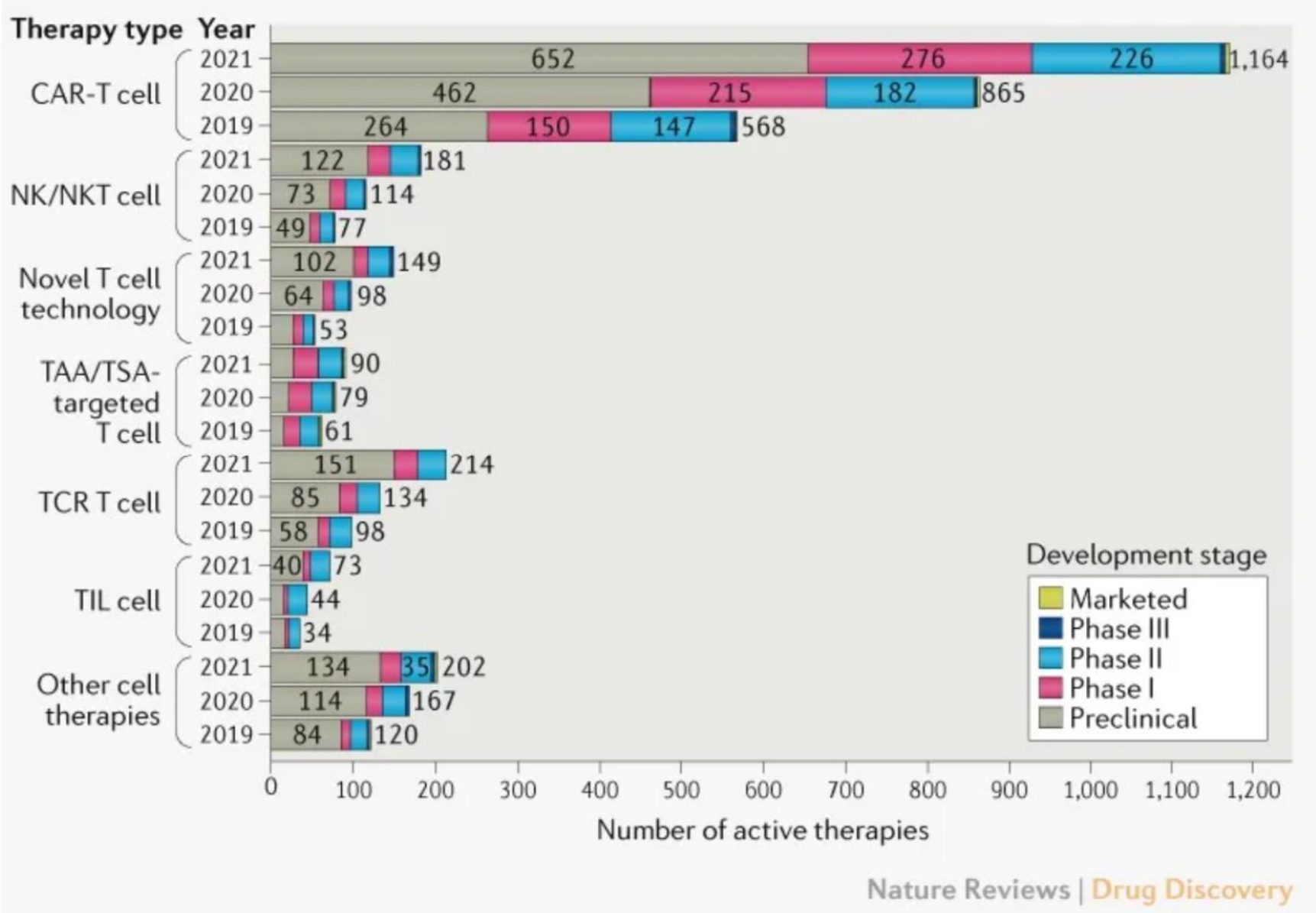
CAR

A specific receptor is added to the T cell

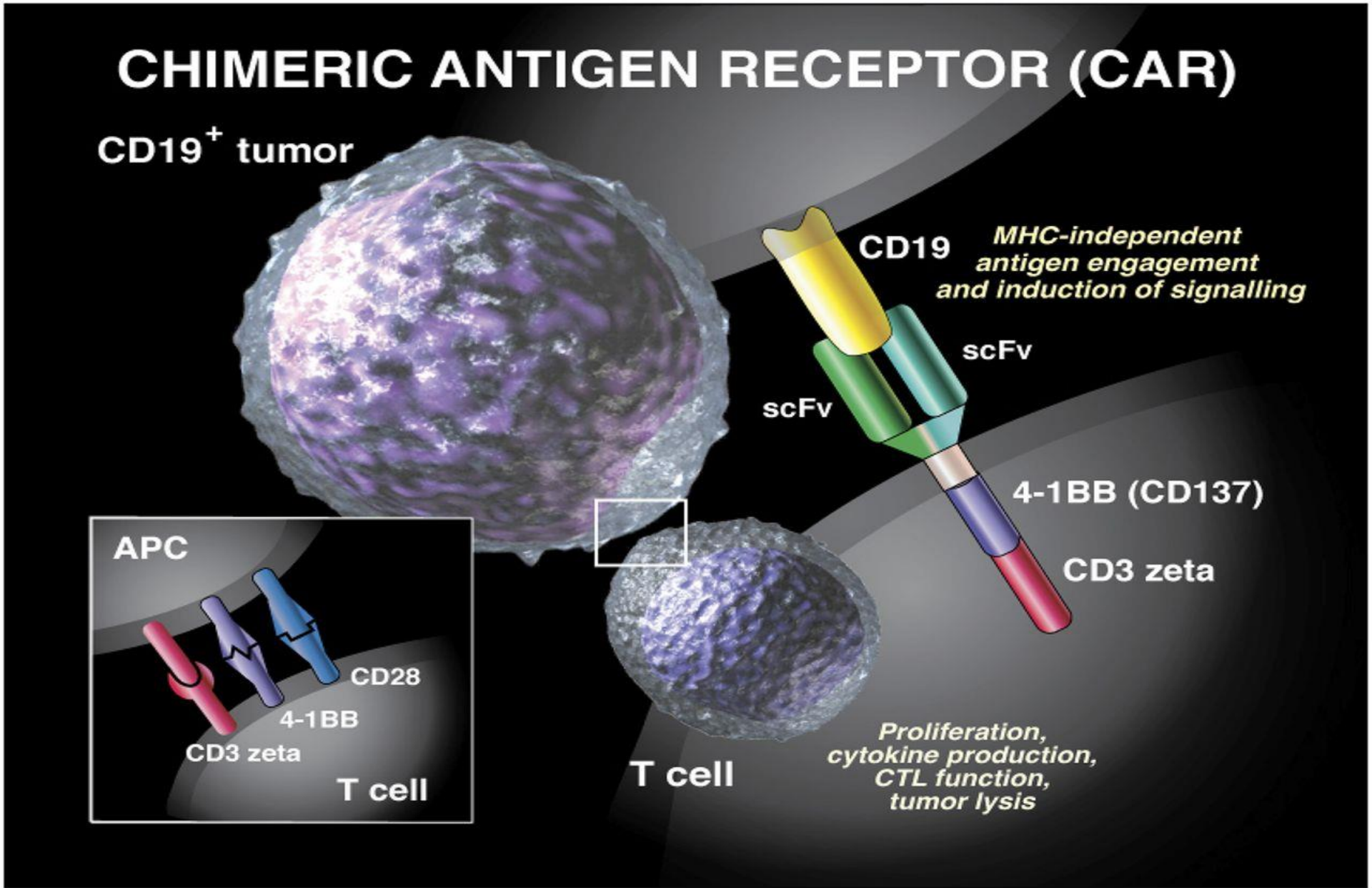
CAR T CELL

The T cell with the CAR added helps find and fight specific targeted cells

CAR T CELL Tedavisi



CAR T CELL Tedavisi



CAR T CELL Tedavisi Kimlere

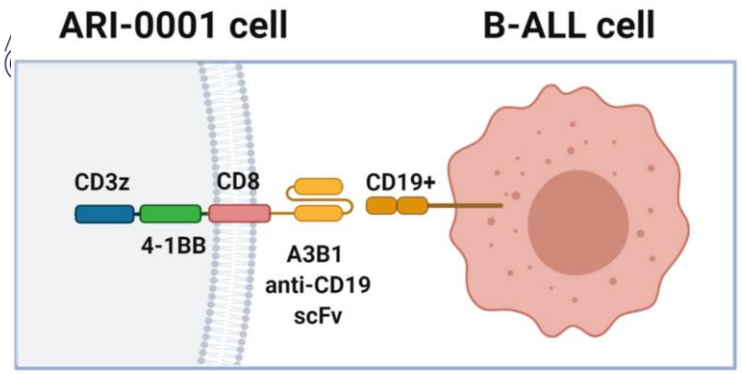
BRAND NAME	GENERIC NAME	TARGETED DISEASE
Kymriah™	tisagenlecleucel	Follicular Lymphoma, Diffuse Large B-cell Lymphoma, or Lymphoblastic Leukemia
Yescarta™	axicabtagene ciloleucel	Follicular Lymphoma or Diffuse Large B-cell Lymphoma
Tecartus™	brexucabtagene autoleucel	Mantle Cell Lymphoma or Acute Lymphoblastic Leukemia
Breyanzi®	lisocabtagene maraleucel	Large B-cell Lymphoma
Abecma®	idecabtagene vicleucel	Relapsed or Refractory Multiple Myeloma
Carvykti™	ciltacabtagene autoleucel	Relapsed or Refractory Multiple Myeloma

Akademik CAR T CELL Tedavisi

Molecular Therapy
Original Article

CART19-BE-01: A Multicenter Trial of ARI-0001 Cell Therapy in Patients with CD19+ Relapsed/Refractory Malignancies

Valentín Ortíz-Maldonado,[1] Susana Rives,[2,3] Maria Castellà,[1,4] Anna A
Miguel Caballero-Baños,[5] Tycho Baumann,[1,4] Joan Cid,[4,6] Enric Garcia
Montserrat Torrebadell,[3,9,10] Neus Villamor,[4,11,12] Eva Giné,[1,4,12] Mari
Mercedes Montoro,[1] Albert Català,[2,3] Anna Faura,[2] E. Azucena Gonzá
Nela Klein-González,[5] Laia Alsina,[13] Pedro Castro,[4,14,15] Iolanda Jorda
Guillermo Suñé,[1,4] Unai Perpiñá,[4,18] Josep M. Canals,[4,18] Miquel Lozar
Sara Varea,[20] Joaquín Sáez-Peñataro,[15,20] Ferran Torres,[4,20] Gonzalo C
Álvaro Urbano-Ispizua,[1,4,15,21] Manel Juan,[4,5,13,15,19] and Julio Delgado

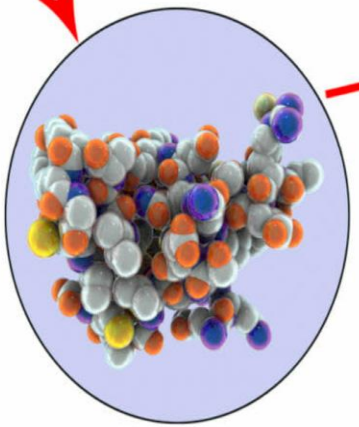


The CAR-T ARI-0001 developed by the Hospital Clínic obtains the PRIME designation from the European Medicines Agency

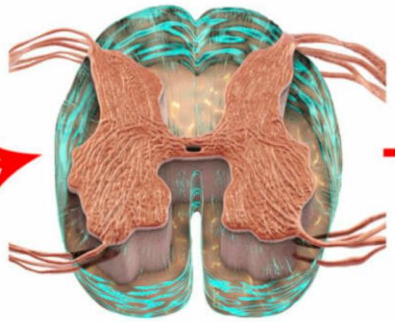
Gen Tedavisi Kimlere Yapılmalı

Spinal Muscular Atrophy (SMA)

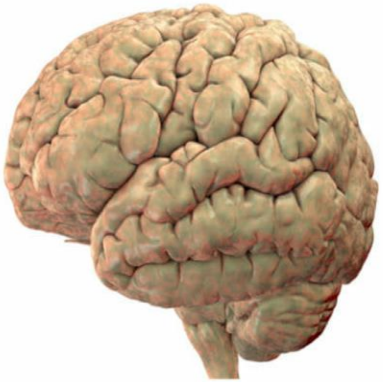
Mutation in the SMN1 gene

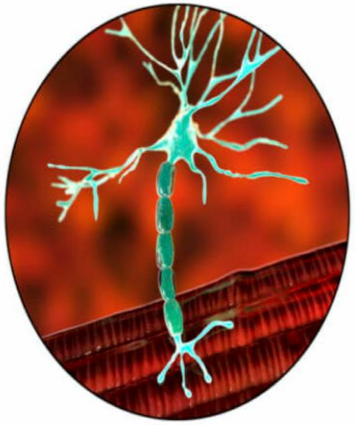


Deficiency in the SMN protein leads to splicing defects in motor neurons



Loss of motor neurons in the anterior horns of the spinal cord prevents signalling between the brain and skeletal muscles



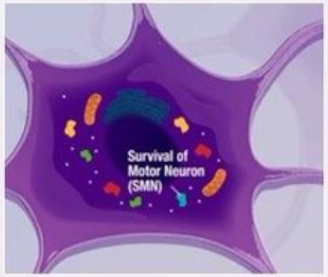


Progressive muscle weakness and atrophy

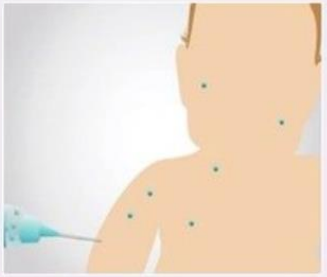
Gen Tedavisi Kimlere Yapılmalı

zolgensma®

How Zolgensma works?

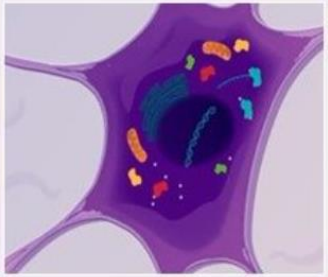


The genetic root cause of SMA the missing or improper working of SMN1 Gene.



Zolgensma, the gene therapy approved for children < 2 years is given as one time infusion into the veins over 60 minutes.

It is made up of new working copy of SMN gene and is given through a vector, targeting the motor neuron cells in the body.



The new gene delivered by the vector on reaching the destination tells the motor neuron cells to make SMN Protein

Zolgensma is not a cure and cannot reverse permanent damage already caused by SMA before treatment. So it is important to start the medication as early as possible

Gen Tedavisi Kimlere Yapılmalı

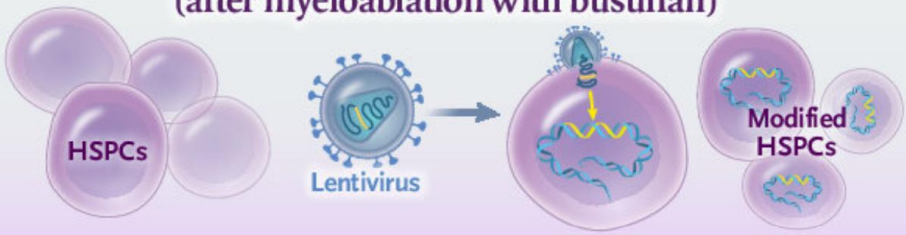
The NEW ENGLAND JOURNAL of MEDICINE

Betibeglogene Autotemcel Gene Therapy for Non–β^0/β^0 Genotype β-Thalassemia

OPEN-LABEL, PHASE 3 STUDY

23
Adult and pediatric patients with transfusion-dependent β-thalassemia and a non–β^0/β^0 genotype

Beti-cel gene therapy
(after myeloablation with busulfan)

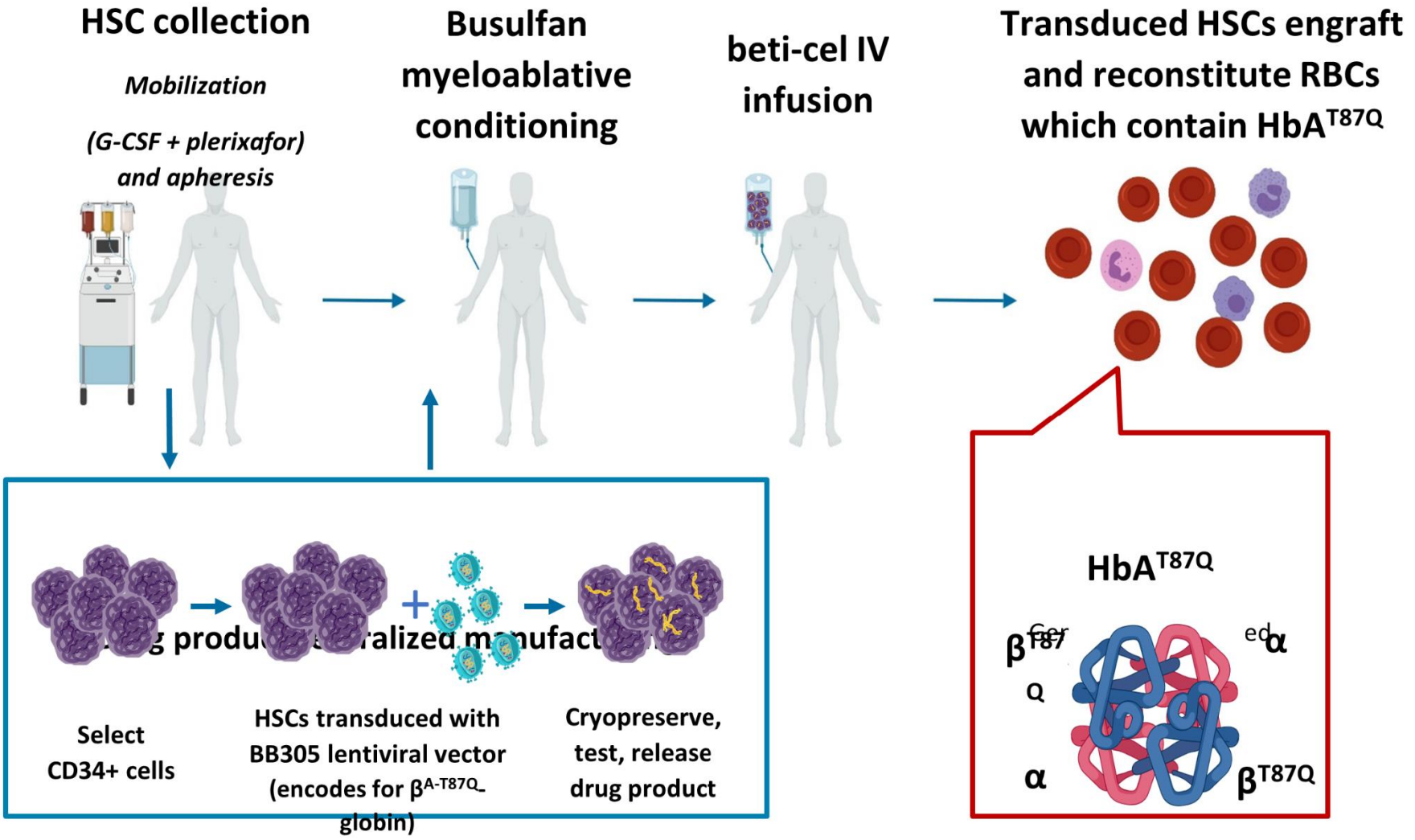


Transfusion independence (median follow-up, 29.5 mo)	20 of 22 patients
Average hemoglobin level during transfusion independence	11.7 g/dl (range, 9.5–12.8)
Median gene therapy–derived adult hemoglobin level at 12 mo	8.7 g/dl (range, 5.2–10.6)

Beti-cel treatment resulted in transfusion independence in most patients.

F. Locatelli et al. 10.1056/NEJMoa2113206

Gen Tedavisi Kimlere Yapılmalı



Gen Tedavisi Kimlere Yapılmalı

Lyfgenia
for sickle cell disease

Lyfgenia (lovotibeglogene autotemcel) is an approved gene therapy for sickle cell disease that's intended to reduce the frequency and severity of vaso-occlusive events.

Administration: Given as a stem cell transplant, via a single intravenous infusion, after a round of chemotherapy.

Indications: Approved for SCD patients, ages 12 and older, with a history of vaso-occlusive events.

Side effects: May include sores of the lips, mouth, and throat (stomatitis), fever, and low blood cell counts.

Contraindications: None, but the label includes a boxed warning for hematologic malignancy.

Casgevy
for sickle cell disease

Casgevy (exagamglogene autotemcel) is an approved gene-editing therapy for sickle cell disease that's intended to reduce the frequency and severity of pain crises.

Administration: Given as a stem cell transplant, via a single intravenous infusion after a round of chemotherapy.

Indications: Approved for SCD patients, ages 12 and older, who experience recurrent vaso-occlusive crises.

Side effects: May include inflammation in the mouth and gastrointestinal tract, fever, low blood cell counts, and decreased appetite.

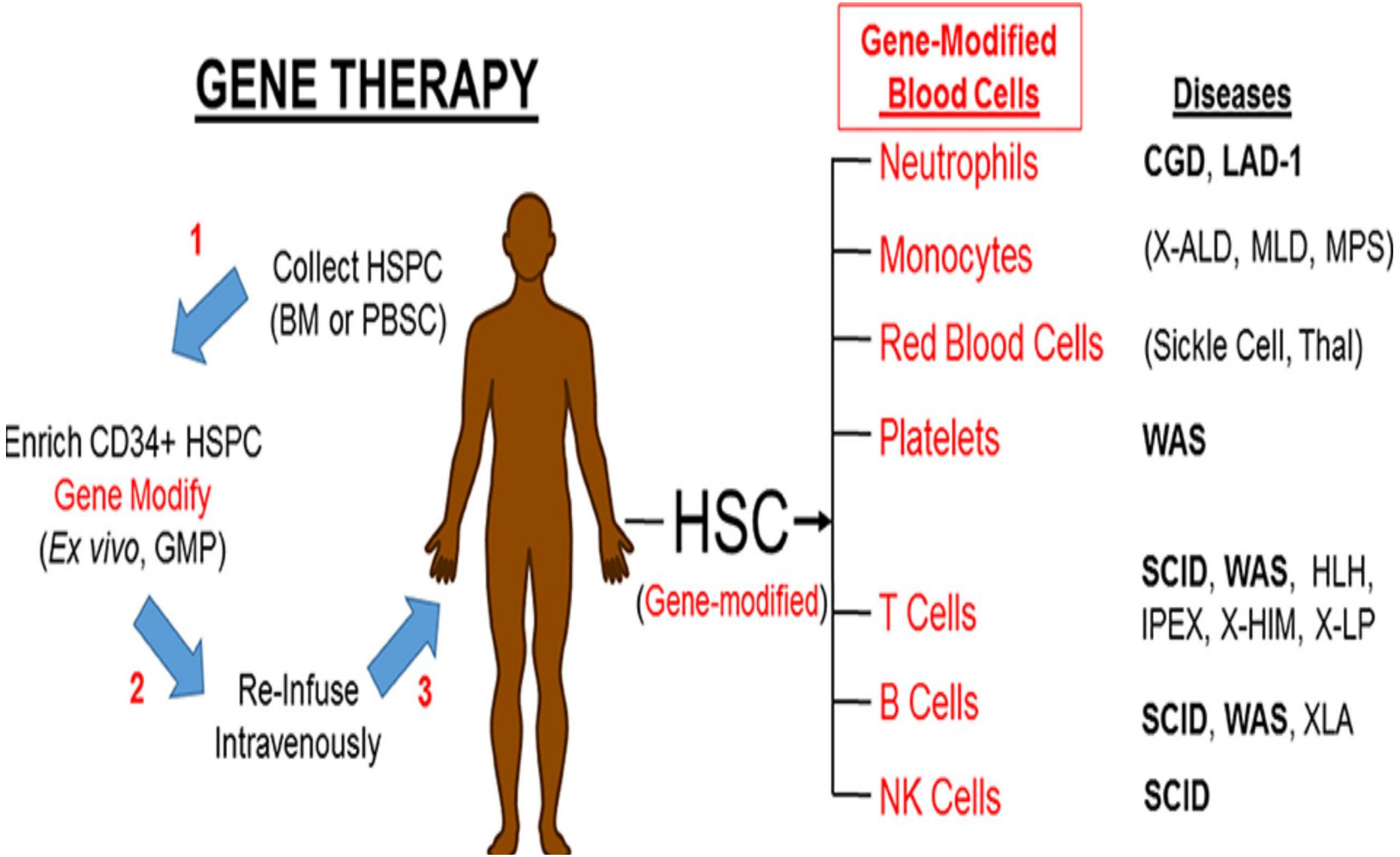
Contraindications: None, but should not be given to patients with active HIV, or hepatitis B or C virus infections.

PİY Hastalarında Gen Tedavileri

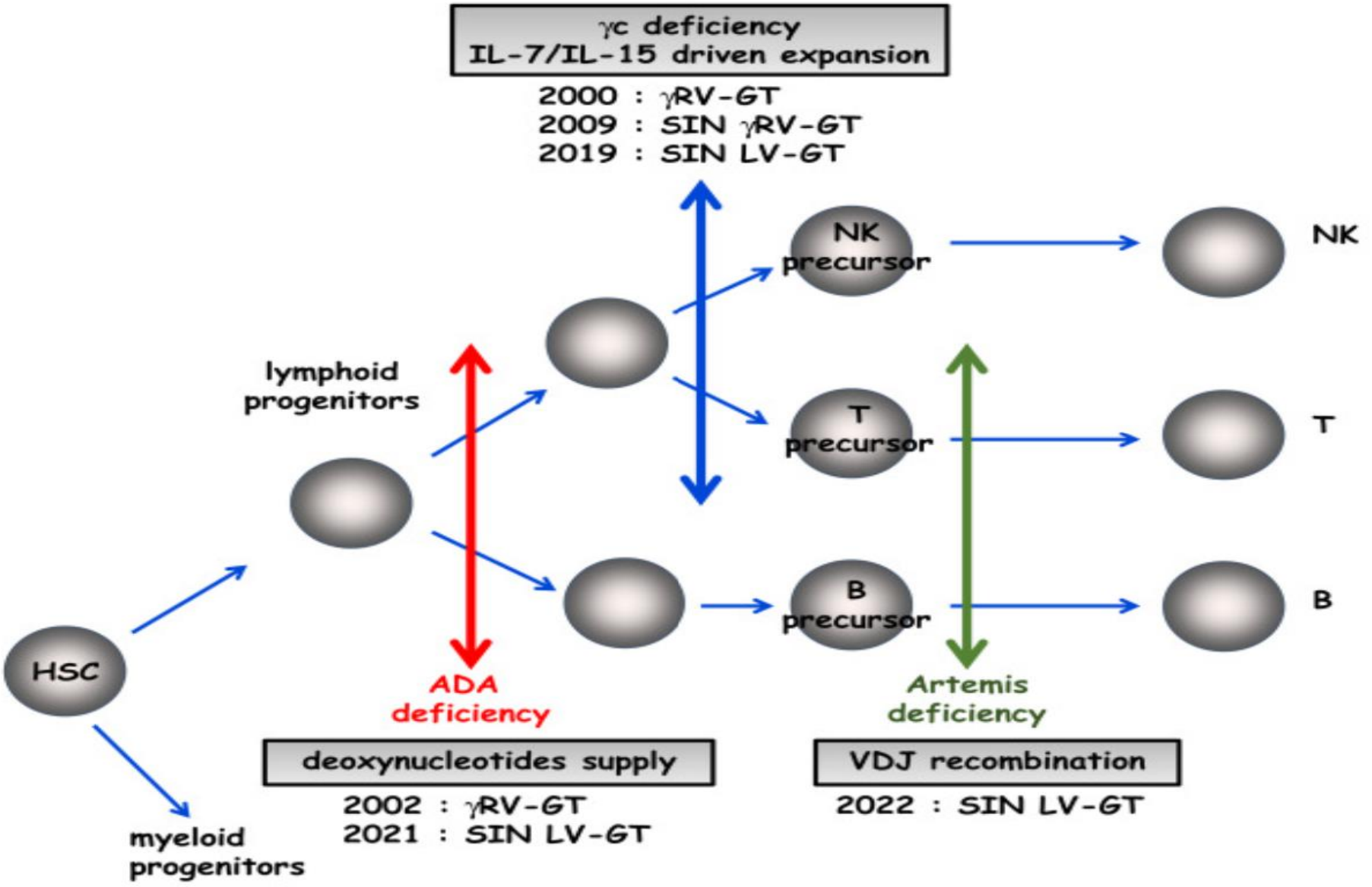
ADA-SCID	ADA	gRV	Commercial product in Europe (strimvelis)	[14]
	ADA	LV	Compassionate use (GOSH)/Human trial (UCLA/NIH)	[79▪▪]
X-SCID	IL2RG	SIN gRV	Human trial completed	[37]
	IL2RG	LV	Human trial GOSH/BCH/UCL open	[82,83] NCT03311503, NCT03601286
	IL2RG	LV	Human trial UCSF/St Jude/Seattle/NIH Suspended	NCT01306019 NCT01512888
Artemis SCID	DCLRE1C	LV	Human trial UCSF Open	[86▪▪] NCT03538899
	DCLRE1C	LV	Human trial Paris Necker hospital Open	NCT05071222
RAG1 SCID	RAG1	LV	Human trial Open LUMC	NCT04797260 [125]
RAG2 SCID	RAG2	LV	Mice	[126,127] (manuscript in preparation)
WAS	WAS	LV	Human trial completed	[90,91,92▪]
X-CGD	CYBB	LV	Human trial (UCLA and UCL/GOSH) Open	[96] NCT01855685 NCT02234934
Autosomal recessive CGD	NCF1	LV	Human trial at GOSH, starting soon at NIH	NCT05207657
LAD1	ITGB2	LV	Human trial (UCLA, HIUNJ, GOSH) Open	NCT03812263 [106]
IPEX	FOXP3	LV in T cells	Ongoing Human trial (Stanford)	NCT05241444 [110,111]
fHLH	PRF1	gRV in T cells	Mice	[128]
	PRF1	LV	Mice	[129]
	UNC13D	LV	Mice (Stanford)	[130--133]
XIAP	XIAP	LV	Mice	[134]
XLP1	SAP	LV	Mice	[135]
	SAP	gRV in T cells	Mice	[136]
XLA	BTK	LV	Mice	[137,138]
Reticular dysgenesis	AK2	LV	In vitro	[139]

ADA-SCID, adenosine deaminase-deficient severe combined immunodeficiency (SCID); CGD, chronic granulomatous disease; fHLH, familial hemophagocytic lymphohistiocytosis; gRV, gamma-retroviral; IPEX, immune dysregulation, polyendocrinopathy enteropathy X-linked; LAD, leukocyte adhesion deficiency; LV, lentiviral; RAG, recombination activating gene; WAS, Wiskott-Aldrich syndrome; XIAP, X-linked inhibitor of apoptosis protein deficiency; XLA, X-linked agammaglobulinemia; XLP, X-linked lymphoproliferative disease; X-SCID, X-linked SCID.

PİY Hastalarında Gen Tedavisi



SCID Hastalarında Gen Tedavisi



ADA SCID Gen Tedavisi

Strimvelis,

27 Mayıs 2016 yılında, a gRV vector ile
EMA onayı aldı.
Tam uyumlu vericisi olmayan ADA SCID hastalarında onaylı
594 000 Euro, 2 yıllık ERT fiyatı

Ancak şimdiye kadar bildirilen 1 hastada kanser (**Lösemi-2020**) gelişimi var
Diğer SCID gruplarında bu oran daha fazla

İlk hastalarda 1. kuşak gRV vektör kullanılıyor
Şimdi 3. kuşak LV kullanılıyor
Yaklaşık 50 hastaya SIN LV ADA SCID gen tedavisi yapılmış

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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

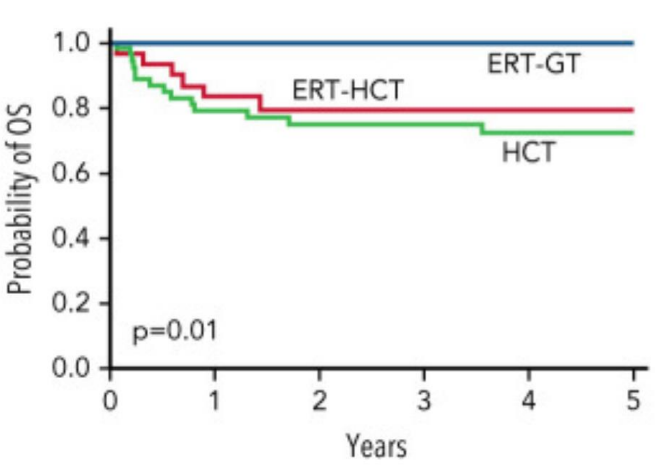
CME Article

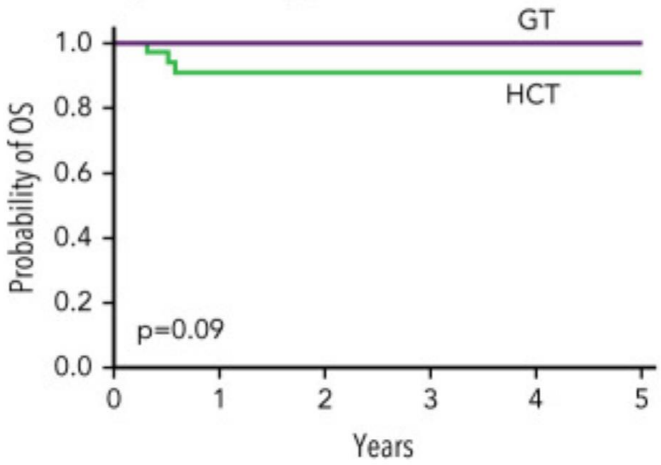
Outcomes following treatment for ADA-deficient severe combined immunodeficiency: a report from the PIDTC

Geoffrey D. E. Cuvelier,[1] Brent R. Logan,[2] Susan E. Prockop,[3] Rebecca H. Buckley,[4] Caroline Y. Kuo,[5] Linda M. Griffith,[6] Xuerong Liu,[2] Alison Yip,[7] Michael S. Hershfield,[4] Paul G. Ayoub,[8] Theodore B. Moore,[9] Morna J. Dorsey,[7] Richard J. O'Reilly,[10] Neena Kapoor,[11] Sung-Yun Pai,[12] Malika Kapadia,[13] Christen L. Ebens,[14] Lisa R. Forbes Satter,[15] Lauri M. Burroughs,[16] Aleksandra Petrovic,[16] Deepak Chellapandian,[17] Jennifer Heimall,[18] David C. Shyr,[19] Ahmad Rayes,[20] Jeffrey J. Bednarski,[21] Sharat Chandra,[22] Shanmuganathan Chandrak
Kenneth DeSantes,[29] Hesha
Monica S. Thakar,[16] Robert
Luigi D. Notarangelo,[38] Mc

131 ADA SCID Hastası
1982 ve 2017 arasında
56 HSCT
31 ERT+HSCT
33 ERT+GT

100% overall survival in adenosine deaminase deficient severe combined immune deficiency patients after gene therapy. Contemporary hematopoietic stem cell transplant approaches after the year 2000 and without an active infection resulted in similar overall survival to gene therapy





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Regular Article

GENE THERAPY

Long-term outcomes after gene therapy for adenosine deaminase severe combined immune deficiency

Bryanna Reinhardt,[1,*] Omar Habib,[1,*] Kit L. Shaw,[1] Elizabeth Garabedian,[2] Denise A. Carbonaro-Sarracino,[1] Dayna Terrazas,[1] Beatriz Campo Fernandez,[1] Satiro De Oliveira,[3] Theodore B. Moore,[3] Alan K. Ikeda,[3] Barbara C. Engel,[4] Gregory M. Podsakoff,[4] Roger P. Hollis,[1] Augustine Fernandes,[1] Connie Jackson,[1] Sally Shupien,[3] Suparna Mishra,[1] Alejandra Davila,[1] Jack Mottahedeh,[1] Andrej Vitomirov,[1] Wenzhao Meng,[5] Aaron M. Rosenfeld,[5] Aoife M. Roche,[6] Pascha Hokama,[6] Shantan Reddy,[6] John Everett,[6] Xiaoyan Wang,[7] Eline T. Luning Prak,[5] Kenneth Cornetta,[8] Michael S. Hershfield,[9] Robert Sokolic,[10] Suk See De Ravin,[11] Harry L. Malech,[11] Frederic D. Bushman,[6] Fabio Candotti,[12] and Donald B. Kohn[1,3]

10 ADA SCID Hastası
2009 ve 2012 arasında
Yaş 3 ay-15 yaş
Takip 8-11 yıl
9/10 TAM immün yapılanma

15-20 ml/kg Harvest
CD34 immünoseleksiyonu
gRv ADA SCID Gen Transfer
4 gün kültür
Hastaya RIC hazırlama rejimi
-3 gün 90 m2 Busulfan
Ürün infüzyonu

Vektör Copy Number
ADA Enzim aktivitesi
Deoxyadenosine nucleotides düzeyi
Normal immün yapılanma
Ciidi enf ve komp. yok

OLGU SUNUMU

AK

2 Aylık Kız Hasta, ADA SCID

Genetik; Homozigot ADA c.736 C>T, p.Q246 mutasyonu

ERT ve IVIG replasman tedavisi, proflaktikleri başlandı

I.R.C.C.S. Ospedale San Raffaele

Gruppo San Donato

27.10.2023 Kemik iliği Harvest

59.5 ml, 3.76x106 CD34 hücre

Transduce ADA gen hazırlanması

-3. Gün Busulfan 0.5mg/kg/gün 6 saat inf

-2. Gün Busulfan 0.5mg/kg/gün 6 saat inf

01.12.2023 Strimvelis ile ADA SCID Gen Tedavisi

6x106 CD34 hücre, VCN 3, Canlılık %98

27 gün sonra ayaktan takip

OLGU SUNUMU

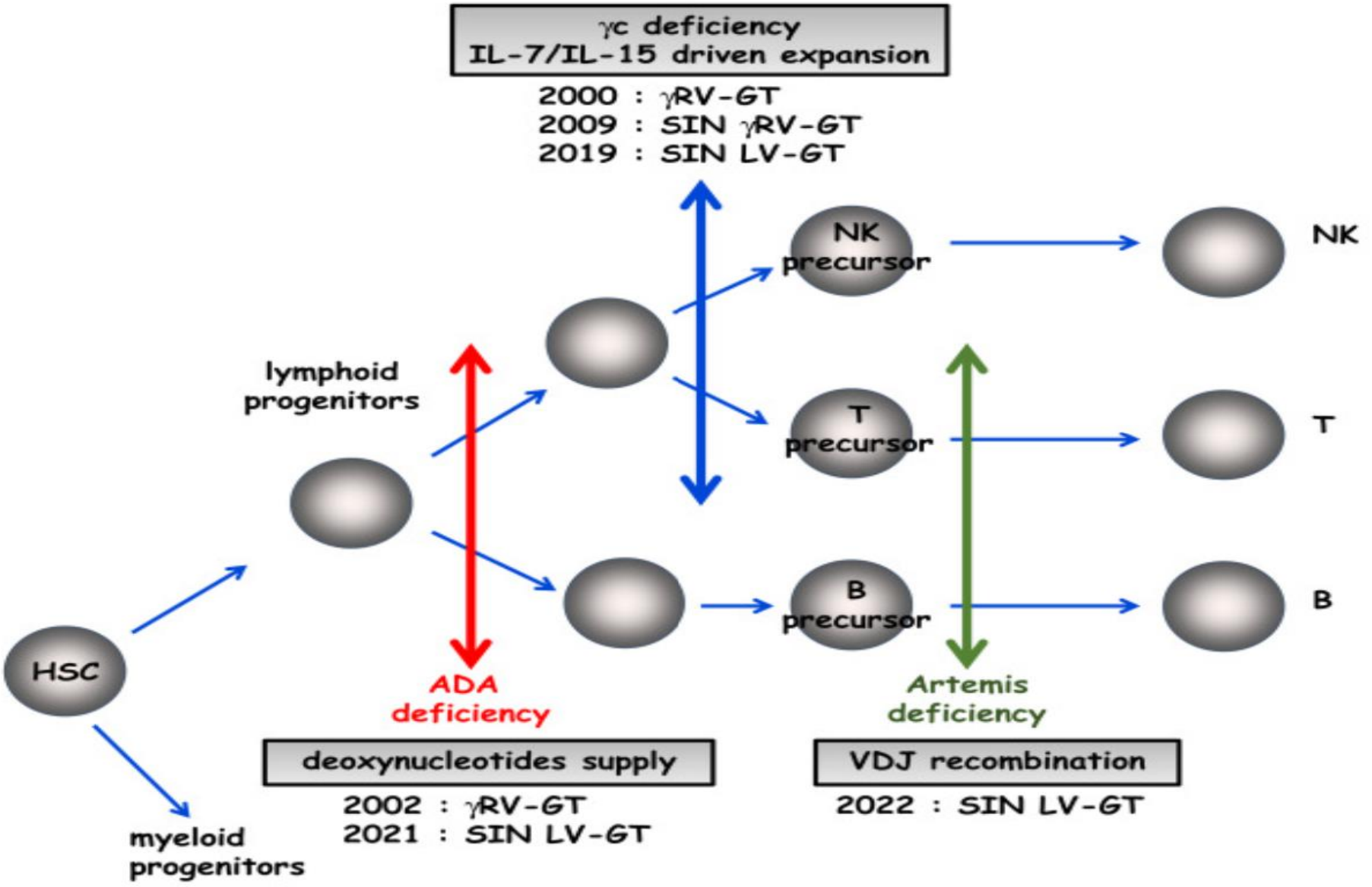
I.R.C.C.S. Ospedale San Raffaele
Gruppo San Donato

Molecular analyses (02-03.01.24)
- **Vector Copy Number (VCN) on BM**: CD15 0.014, CD34 0.027, CD19 0.065, CD3 0.009, CD56 0.008 GLYA 0.029
- **Vector Copy Number (VCN) on PB**: CD15 0.007, CD19 0.011, CD3 undetectable, CD56 undetectable
- **Purine metabolites on PB**: AMP 160 nmol/mL, ADP 366 nmol/mL, ATP 1125 nmol/mL, dATP 9 nmol/mL, AXP 1650 nmol/mL, %dAXP 0.55%, ATP/ADP 3.08
- **ADA activity on PB:**
  - **in lymphopcytes**: 439.83 µmol/h/ml packed cells
  - **in RBCs**: 7.04 µmol/h/ml packed cells

-Sweet Sendromu, Deltakortil

- Acyclovir 50 mg three times a day at 8.00, 15:00, 22:00
- Amoxicillin-clavulanic acid 165 mg (1.9 ml) three times a day at 8:00, 15:00, 22:00
- Fluconazol 50 mg (5 ml)/day
- Levofolene 4 mg 2 times a week (tuesday and wednesday)
- IgEV last on 21.12.23
- Pentacarinat aerosol 90 mg (last 02.01.24)

SCID Hastalarında Gen Tedavisi



X-SCID Gen Tedavisi

IL2RG gen T(-)
NK(-)
B disfonksiyone

İlk uygulamalarda gRV vektör, hazırlama rejimi olmadan kullanılmış, sonuç B yapılanma yetersiz.

İlk 20 hastanın 6 sında T ALL gelişimi mevcut!!!

Sonraki uygulamalarda LV vektör ve düşük doz Busulfan Hazırlama rejimi ile tam T ve B yapılanma sağlanmış

blood®

ISSUES FIRST EDITION ABSTRACTS COLLECTIONS

801.GENE THERAPIES | NOVEMBER 15, 2022

Lentiviral Gene Therapy with Low Dose Conditioning for X-Linked SCID Results in Complete Immune Reconstitution and No Evidence of Clonal Expansion

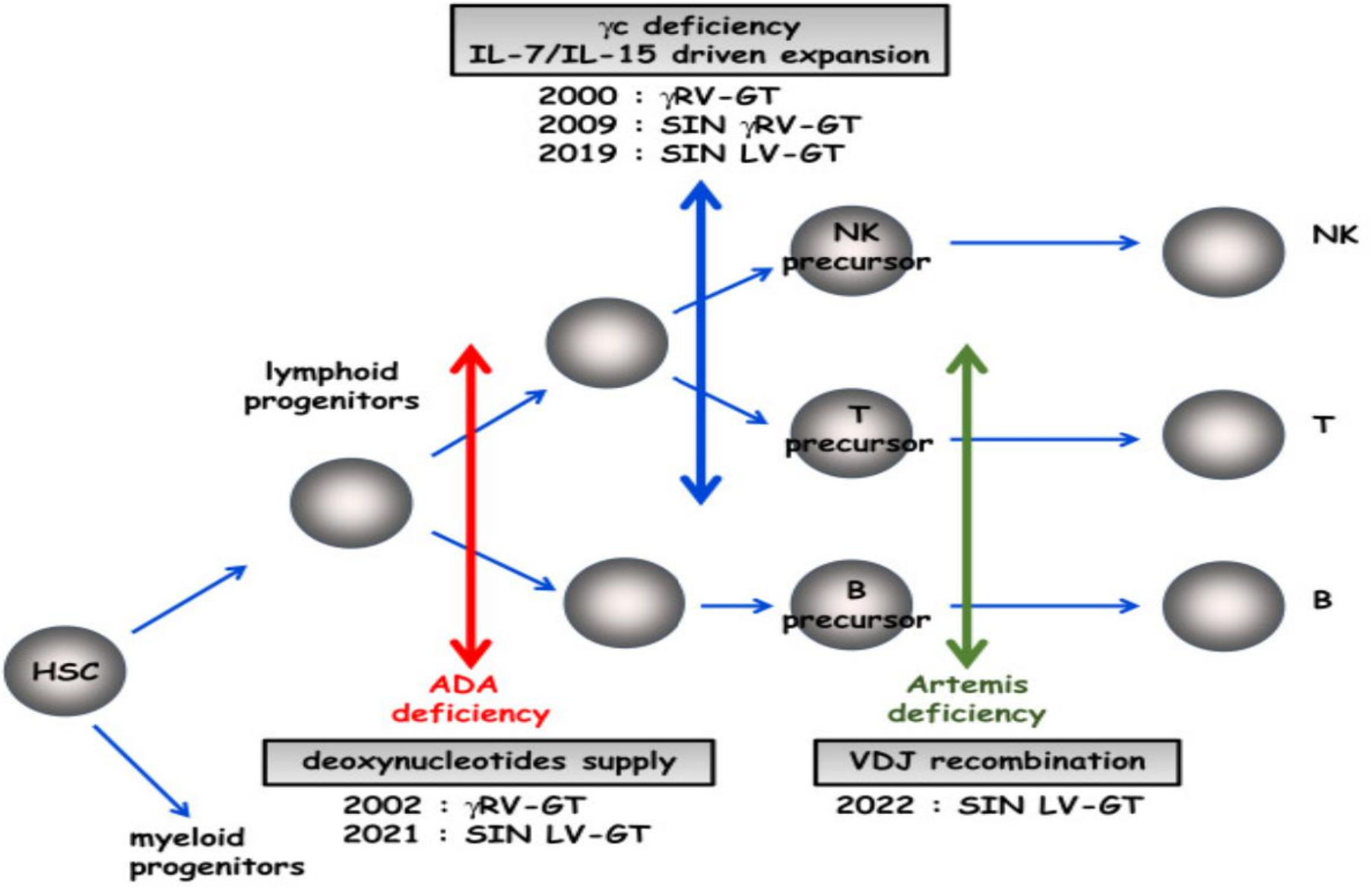
Claire Booth, Donald B. Kohn, Myriam Armant, Susan Prockop, Karen Buckland, Sharat Chandra, Shanmuganathan Chandrakasan, Kritika Chetty, Colleen Dansereau, Satiro de Oliveira, John Everett, Diego León Rico, Wendy B. London, Jin Hua Xu-Bayford, Theodore B. Moore, Nisha Nagarsheth, Suhag Parikh, Dayna Terrazas, Shanna L White, Axel Schambach, Frederic D. Bushman, Adrian J. Thrasher, David A. Williams, Sung-Yun Pai

Blood (2022) 140 (Supplement 1): 7770–7771.

https://doi.org/10.1182/blood-2022-159979

Temmuz 2022 kadar
LV vektör ve Düşük doz Busulfan Hazırlama rejimi ile Gen tedavisi
7 hasta medyan 2.2 yıl takip
%100 survival
Komplet T ve B yapılanma

SCID Hastalarında Gen Tedavisi



Published in final edited form as:
N Engl J Med. 2022 December 22; 387(25): 2344–2355. doi:10.1056/NEJMoa2206575.

Lentiviral Gene Therapy for Artemis-Deficient SCID

Morton J. Cowan, M.D.,
Jason Yu, Ph.D.,
Janelle Facchino, P.N.P.,

LV vektör ve Düşük doz Busulfan Hazırlama rejimi ile
DCLRE1C Gen tedavisi
10 hasta medyan 3.1 yıl takip
%100 survival
9/10 Komplet T yapılanma, 2. uygulama sonrası %100
Busulfan dozu %25 (HSCT hazırlama rejimine göre)
Artemis DNA kırıkları ile giden bir durum

The Journal of Allergy and Clinical Immunology

EDITORIAL | VOLUME 151, ISSUE 5, P1255-1256, MAY 2023

Download Full Issue

Gene therapy for SCID, now up to 3!

Alain Fischer, MD, PhD • Bénédicte Neven, MD, PhD

Published: February 22, 2023 • DOI: https://doi.org/10.1016/j.jaci.2023.02.015 •

RAG1-SCID Gen Tedavisi, UP TO 4

www.recomb.eu

RECRUITMENT PROCESS

GENE THERAPY FOR RAG1-SCID (RECOMB CONSORTIUM)

OPEN CLINICAL TRIAL

Recomb gene therapy

RECOMB consortium

RECOMB is a research consortium started in 2018, which brings together clinical and research professionals from 16 European and 1 Israeli institute with experience in the management of primary immunodeficiencies (PID) or inborn errors of immunity (IEI), such as severe combined immunodeficiency (SCID).
The project received funding from the European Union's Horizon 2020 programme.

PHASE I/II

RECOMB clinical trial

The infant with RAG1-SCID will be admitted to the gene therapy unit of the Vall d'Hebron Barcelona Hospital Campus to receive his treatment, thus avoiding travelling abroad.

The study consists of the infusion of autologous CD34+ cells transduced with the RAG1 lentivirus in patients with SCID due to RAG1 deficiency. The study has already enrolled two patients with satisfactory follow-up of up to two years.

Recomb

PROF FRANK STAAL

PROF ARJAN LANKESTER

PROF KARIN PIKE-OVERZET

WEBINAR

GENE THERAPY FOR RAG1-SCID

JAN 29, 2021, 15H CET

WWW.RECOMB.EU

(AVRUPA BİRLİĞİ, HORIZON 2020 - Tarih : 12-11-2021)

Protokol ID	**RAG1-2019-01**
Kısa Adı	**RAG1 GEN TEDAVİSİ**
EudraCT number	**2019-002343-14**
Version	**9.0**
Tarih	**17-02-2023**
Koordinatör Araştırıcı/ Proje Lideri	**Dr. D. Berghuis**
Sorumlu Araştırmacılar (Hollanda):	**Prof. Dr. F.J.T. Staal,** **Prof. Dr. A.C. Lankester**
Multicenter Araştırmacılar	**Türkiye (1),** **Prof Dr Musa Karakükcü,** Erciyes Üniversitesi TIP Fakültesi Pediatrik, Hemtoloji Onkoloji BD Erciyes Pediatrik Kemik iligi Nakli Merkezi, **Kayseri.**

RAG1-SCID Gen Tedavisi, UP TO 4

İngiltere

Prof. Dr. C. Booth (Great Ormond Street Hospital/University College London)
Prof. Dr. A. Gennery (Newcastle University Great North Children's Hospital)

Almanya

Prof. Dr. M. Albert (Dr. von Hauner Children's Hospital, LMU)
Prof. Dr. A. Schulz (Universitaet Ulm, Department of Pediatrics, Ulm)

İtalya

Prof. Dr. F. Locatelli (Bambino Gesù Children's Hospital, Roma)

İspanya

Dr. P. Soler Palacin (University Hospital Foundation Vall d'Hebron, Barcelona),

Polonya

Prof. Dr. K. Kalwak (Wroclaw Medical University)

İsrail

Prof. Dr. R. Somech (Sheba Medical Center, Tel Aviv)

Türkiye

Prof. Dr. M. Karakükcü (Erciyes University, KANKA Pediatric BMT Center, Kayseri)

Avusturalya

Prof. Dr. Theresa Cole (The Royal Children's Hospital, Melbourne)

AIM

To offer a new therapeutic option based on gene therapy to newborns and infants with one of the most common forms of SCID: RAG-1 deficiency

CRITERIA

INCLUSION	EXCLUSION
Genetically confirmed RAG1- SCID	HLA-matched donor available
Age below 2 years	Peripheral T cells >300/μL and/or naïve T cells > 1/μL
No HLA-matched donor available	Omenn Syndrome
Peripheral T cells <300/μL and/or naïve T cells < 1/μL	Previous stem cell transplantation
No Omenn Syndrome	Significant organ dysfunction

CONTACT

MÍRIAM GONZÁLEZ AMORES

miriam.gonzalezamores@vallhebron.cat

667 93 56 77

http://www.recomb.eu/

RAG1-SCID Gen Tedavisi, UP TO 4

Yeni Tedavi: Gen Tedavisi

G CSF + Mozobil

1. Kök Hücreler Hastadan Kendi Ülkesinde Toplanacak

2. Kök Hücreler Leiden a gönderilecek

3. Kök Hücreler Genetik olarak düzeltilecek

4. Sağlıklı Kök Hücreler geri gönderilecek

5. Kök Hücreler Hastaya infüzyonla verilecek

Busulfan AUC 60-70, 4 gün
Fludara 160 mg/kg total

6. Kök Hücreler başarılı bir şekilde büyüdükten sonra hastanın RAG1-SCID hastalığı düzelecek

SIN-LV RAG1 Vektör

Wiskott–Aldrich Sendromu Gen Tedavisi

WAS geni

İlk uygulamalarda **gRV vektör** kullanılmış,

Sonuç; immün yapılanma yeterli ancak 7/9 hastada mutagenezis, onkogenezis gelişmiş !!!

Sonraki uygulamalarda LV vektör ve düşük doz Busulfan Hazırlama rejimi ile tam T ve B yapılanma sağlanmış

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01641-x

Check for updates

OPEN

Long-term safety and efficacy of lentiviral hematopoietic stem/progenitor cell gene therapy for Wiskott–Aldrich syndrome

A. Magnani[1,2,31], M. Semeraro[3,31], F. Adam[4], C. Booth[5,6], L. Dupré[7,8,9], E. C. Morris[10,11], A. Gabrion[1,2], C. Roudaut[1,2], D. Borgel[4,12], A. Toubert[13,14], E. Clave[13], C. Abdo[15,16], G. Gorochov[17,18], R. Petermann[19], M. Guiot[1], M. Miyara[17,18], D. Moshous[20,21], E. Magrin[1,2], A. Denis[22], F. Suarez[21,23], C. Lagresle[22], A. M. Roche[24], J. Everett[24], A. Trinquand[15,16], M. Guisset[7], J. Xu Bayford[5], S. Hacein-Bey-Abina[25,26], A. Kauskot[4], R. Elfeky[5], C. Rivat[5], S. Abbas[27], H. B. Gaspar[5], E. Macintyre[15,16], C. Picard[21,28],

LV vektör WAS Gen Tedavisi + RIC (BU FLU) Hazırlama Rejimi
8 hasta median 7.6 yıllık takip
Güvenilirlik; Ciddi yan etki yok, lösemi gelişimi yok.
Etkinlik; Ciddi enfeksiyonlar ve egzama düzelmiş, Otoimmün hastalıklar azalmış, trombosit sayısında parsiyel düzelme olmasına rağmen, kanama atakları önemli ölçüde azalmış

Kronik Granülomatozis Hastalık (CGD)

X Linked CGD geni CYBB
Otozomal Resesif CGD geni NCF1

30 yıl önce İlk uygulamalarda **gRV vektör** kullanılmış,
Sonuç; Nötrofil fonksiyonları düzelmiş ama hastalarda MDS gelişmiş

Sonraki uygulamalarda LV vektör ile mutagenezis yok ancak 2 çalışmada nötrofil engraftmanından bir ay sonra nötrofil düzeltilmiş nötrofilsayısı düşmeye başlamış, bu konuda yeni çalışmalar gerekli

Otozomal resesif CGD için fare çalışmaları sonrası GOS ta yeni çalışma başlatıldı

Europe PMC Funders Group
Author Manuscript
Nat Med. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:
Nat Med. 2020 February 01; 26(2): 200–206. doi:10.1038/s41591-019-0735-5.

Lentiviral gene therapy for X-linked chronic granulomatous disease

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LV vektör X linked CGD Gen Tedavisi + **MAC Hazırlama Rejimi**
9 hasta median 1 yıllık takip,
Güvenilirlik; lösemi gelişimi yok. 2 hasta Ex, 1 hastada VCN kaybı
Etkinlik; & hastada Ciddi enfeksiyonlar düzelmiş, Antibiyotik kesilmiş, fayda görmüşler

Lökosit Adezyon Defekti (LAD-1) Gen Tedavisi

LAD-1 geni ITGB2

İlk uygulamalarda **gRV vektör** kullanılmış,

Sonuç; Başarısız, hücreler düzeltilememiş ve çalışmalar erkenden kapatılmış.

Lentiviral-Mediated Ex-Vivo Gene Therapy for Pediatric Patients with Severe Leukocyte Adhesion Deficiency-I (LAD-I): Interim Results from an ongoing Phase 1/2 Study

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64th Annual Meeting of the American Society of Hematology (ASH)
December 10 - 13, 2022

Abstract # 3460

Sonuç Olarak;

Gen tedavisi çalışmaları baş döndürücü,

Game Changer, Life Changer Uygulamalar

Viral Vektör ve Gen editing gelişmeleri

Hazırlama rejimleri, destek tedavileri ve immün yapılanmada gelişmeler ile çok daha iyi olacaklar

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