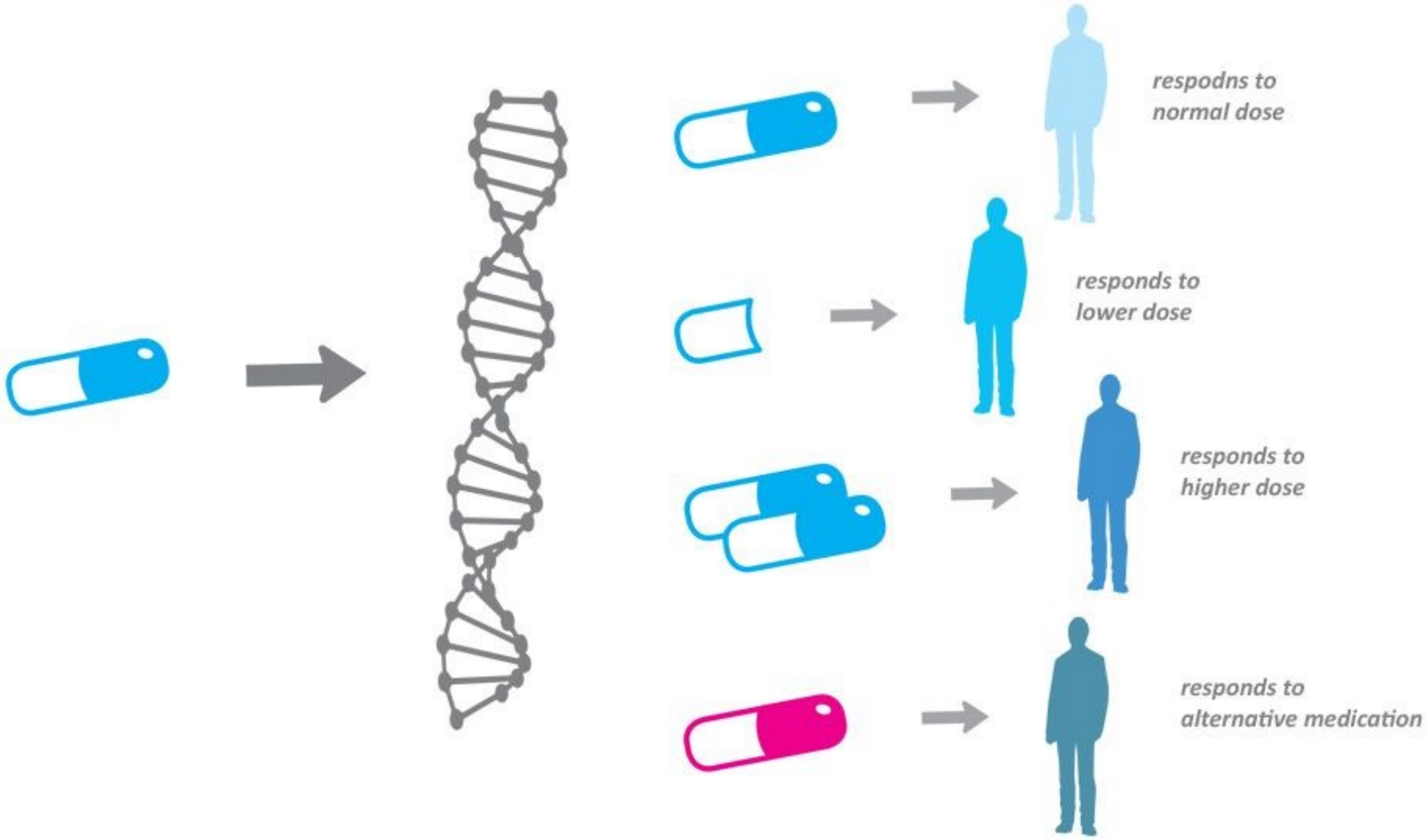
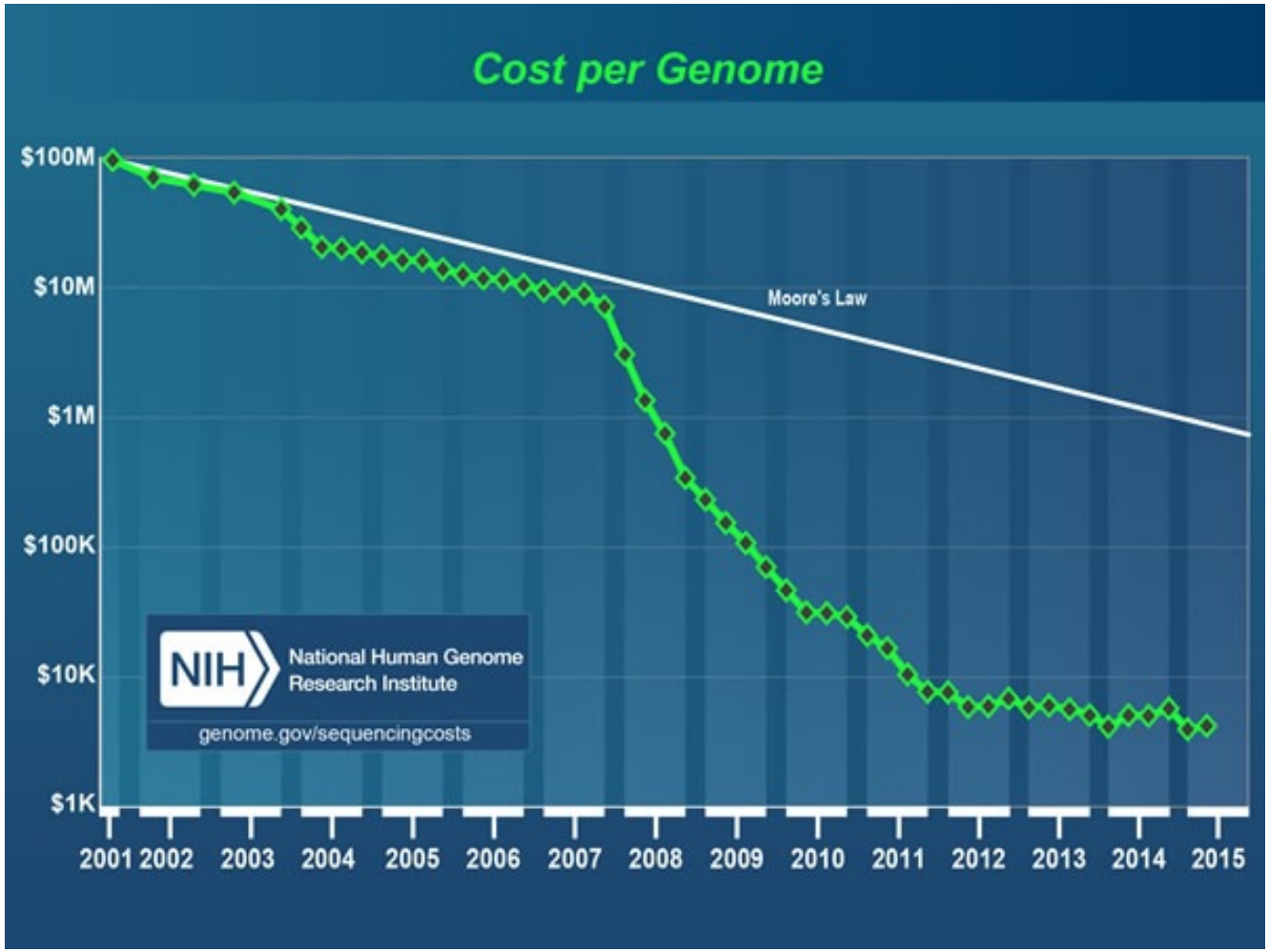
Chapter 4: Personalized/Precision medicine



- **Precision medicine** (PM) is a medical approach with medical decisions, practices, or products being tailored to the individual patient.
- PM integrates research disciplines (genetic or otherwise) and clinical practice to build a knowledge database to better guide individualized patient care.

Nature (2015) 526, 335

The cost per genome sequencing



Basically, the first human genome cost nearly $3 billion to sequence

SOPHIA Genetics: Data driven medicine

- SOPHIA GENETICS was founded in 2011
- Located in previously in St. Sulpice now in Rolle
- Goal: Develop bioinformatics approaches for rapid genomic data analysis
- Collaboration with 334 hospitals in 53 countries

SOPHiA GENETICS™

Jacques Fellay

- Professor of genomics and precision medicine at EPFL and CHUV

World Health Organization

Monogenic diseases (inherited)

- Monogenic diseases: result from mutations in a single gene in all cells of the body.
- Dominant
- Recessive

Monogenic diseases

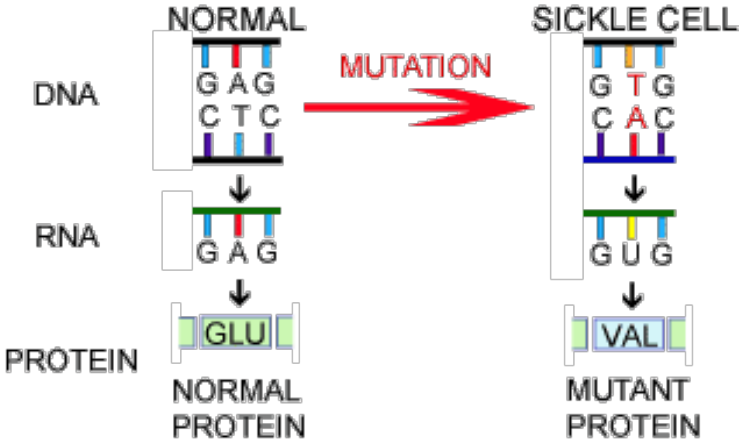
- Example: **Sickle cell disease**, **recessive disease**
  Occurs only when maternal and paternal copies of the HBB (hemoglobin subunit beta) gene are defective.
- atypical hemoglobin molecules called hemoglobin S, which can distort red blood **cells** into a **sickle**, or crescent, shape. Sickle shaped blood cells have a short lifetime. They can block blood flow and cause pain.
- Higher rate of infections, fatigue, pain
- Frequency 1-5 /10 000 people

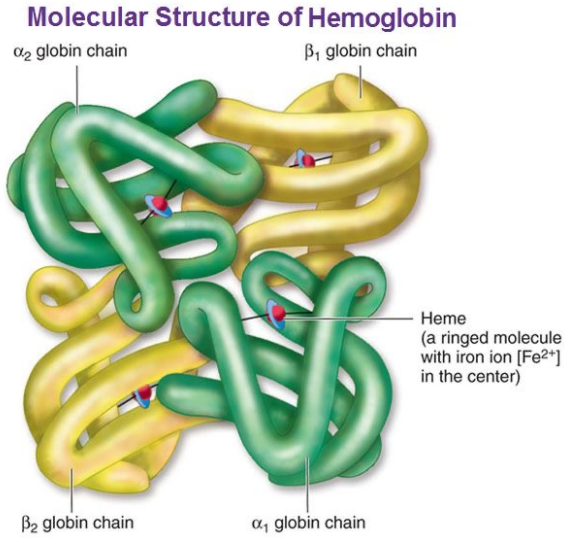
"Sickle"

Normal Red Blood cell

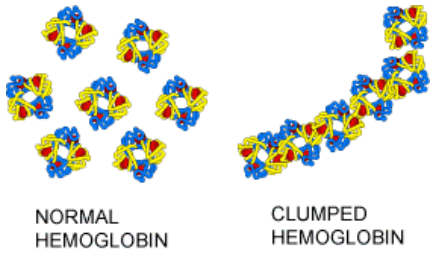
Sickle cell disease

- Effects at the DNA level





- Effects at the protein level



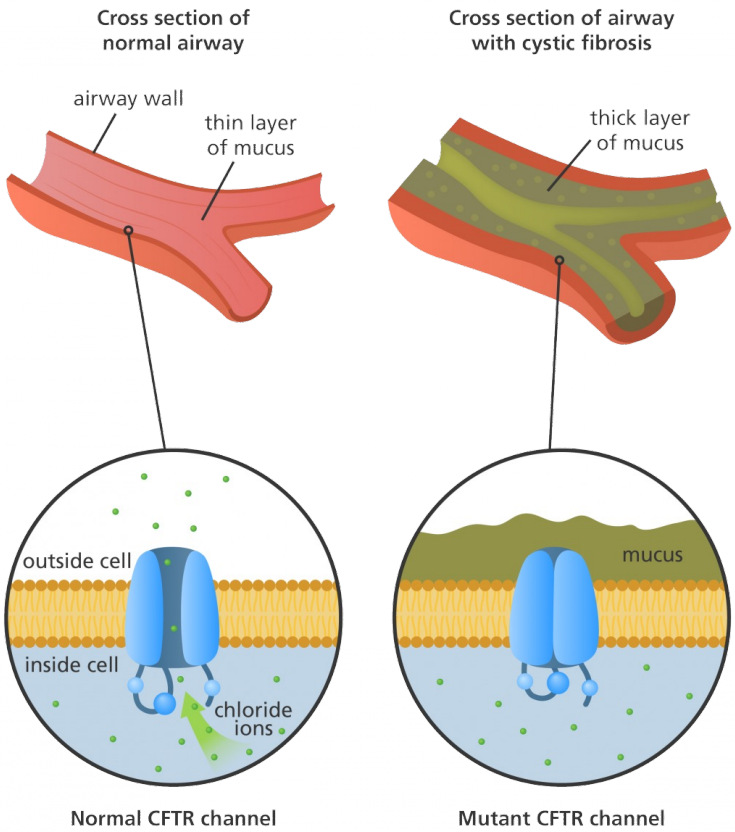
Monogenic diseases

- **Cystic fibrosis (CF), recessive**
- Cystic Fibrosis is a genetic disorder that affects the respiratory, digestive and reproductive systems involving the production of abnormally thick mucus linings in the lungs and can lead to fatal lung infections.
- CF frequency in EU: 1 in 2000/3000 newborns

Cystic fibrosis

Mutation in CFTR: Cystic fibrosis transmembrane conductance regulator.

- Mutation disrupts the function of the CFTR gene encoding a chloride channel, inhibiting the flow of chloride ions and water in and out of the cells.

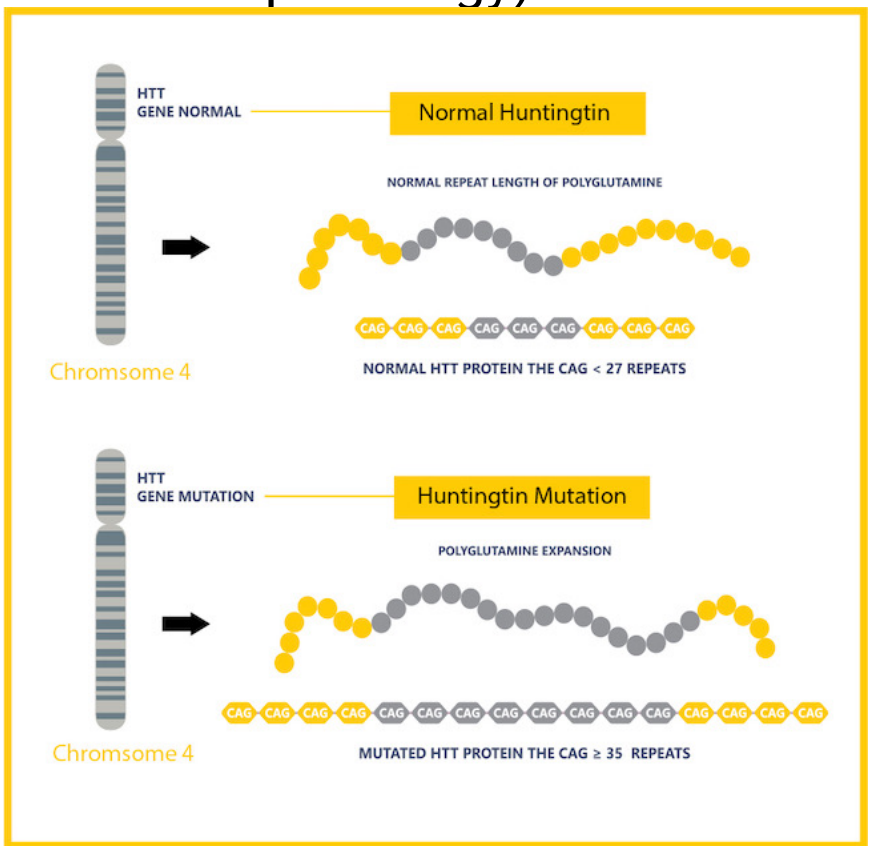


Monogenic diseases

- **Huntington disease**
- **Progressive breakdown (degeneration) of nerve cells in the brain** that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition).
- **Dominant** having a change (mutation) in only one of the 2 copies of the **HTT gene** is enough to cause the condition.
- Frequency: 3-7 in 100 000 people

Huntington disease

- The extra “CAG” nucleotides in the gene lead to an instability that causes the resulting huntington protein to be extra-long and difficult for the body to maintain and remove from brain cells.
- Over many years, the mutant protein forms clumps in brain cells, which causes them to become damaged and die (similar to those seen in Alzheimer disease pathology).



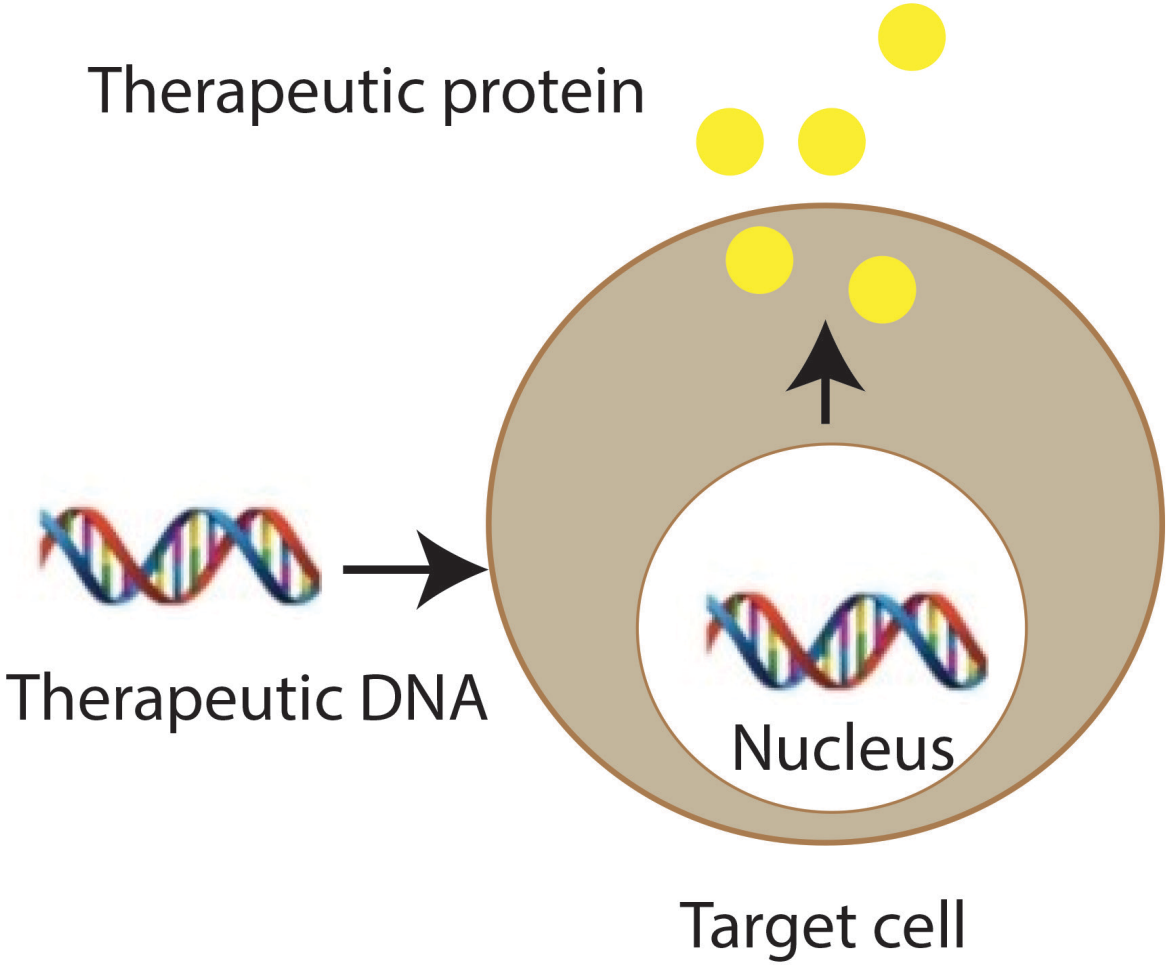
Polygenic diseases (inherited)

- A genetic disorder that is caused by the **combined action** of more than one gene
- Polygenic diseases are **more frequent** than monogenic diseases. Examples: Hypertension, Cancers, Obesity, Atherosclerosis, Diabetes, Autoimmune diseases, Osteoporosis, Asthma, Schizophrenia
- *Nature Medicine* **22**, 1065–1066 (2016)

Genetic predisposition

- Most diseases involve mutations in many genes in complex interactions, in addition to environmental influences.
- An individual may not be born with a disease but may be at high risk of acquiring it. This is called as genetic **predisposition** or **susceptibility**.

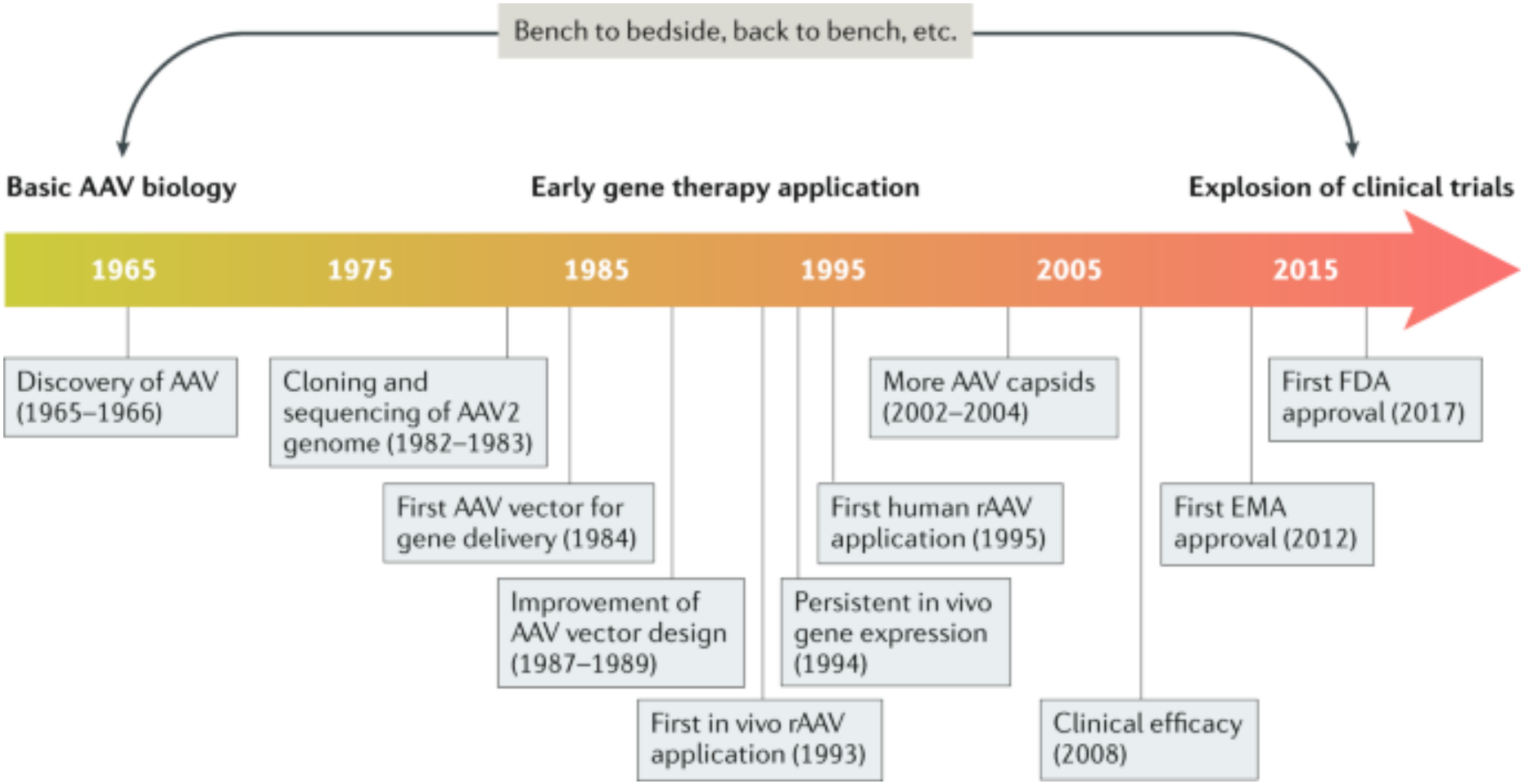
Principle of Gene Therapy



“Adeno-associated virus (AAV) vectors are the leading platform for gene delivery for the treatment of a variety of human diseases”

Wang et al., *Nature Reviews Drug Discovery* **volume 18**, pages358–378(2019)

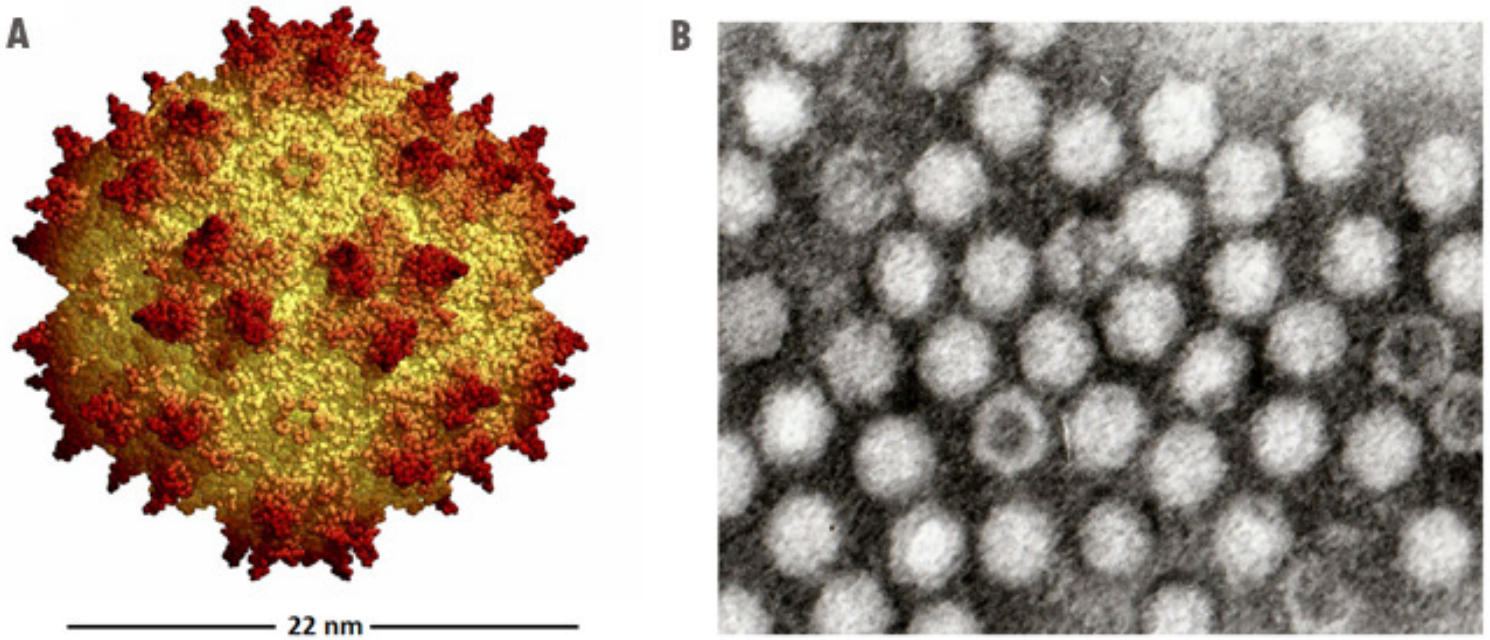
Timeline: key milestones in adeno-associated virus (AAV) gene therapy development



Wang et al., *Nature Reviews Drug Discovery* **volume 18**, pages358–378(2019)

Adeno-associated viruses

- Viral vectors for gene therapy



- **Figure 1. Adeno-Associated Virus (AAV) Structure and Genome map. A: A cartoon showing simulated AAV size and 3-D structure; B: A picture showing electron microscopy of purified AAV vector.**

SignaGen® Laboratories

Some characteristics of AAVs

- Small (20 nm capsid diameter), non-enveloped virus
- Single stranded DNA genome, ~4.8 kb
- Dependovirus: They replicate only in the presence of a helper virus that can be Adenovirus (AdV) or Herpes simplex (HSV)

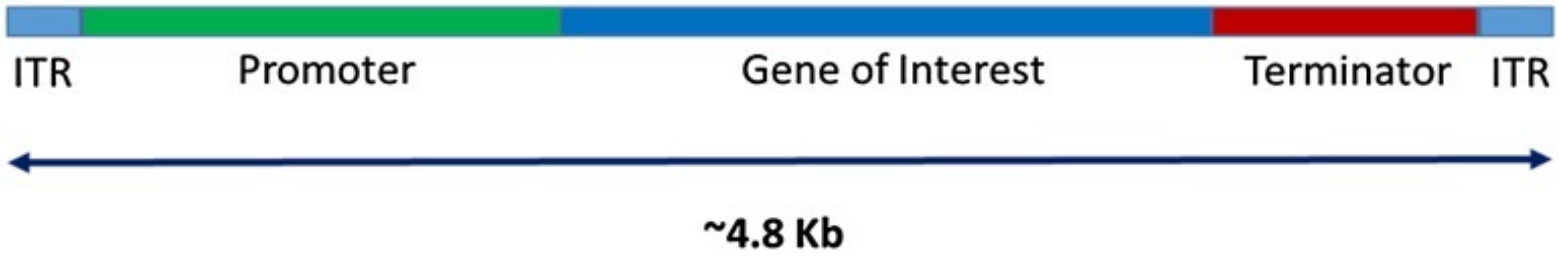
11 AAV serotypes: indicating the optimal serotype(s) for transduction of a given organ

Tissue	**Optimal serotypes**
CNS	AAV1, AAV4, AAV5
Heart	AAV8,
Kidney	AAV2
Liver	AAV8, AAV9
Lung	AAV9
Pancreas	AAV8
Photoreceptor Cells	AAV5
RPE (Retinal Pigment Epithelium)	AAV4, AAV5
Skeletal Muscle	AAV1, AAV2, AAV6, AAV7, AAV8, AAV9

Wu et al., (2006) Molecular therapy, 14: 316-327

Limitations of rAAVs

- Small packaging size (~4.8 kb, including ITRs) compared with other viral vectors. (No big transgenes can be packed into the virus)



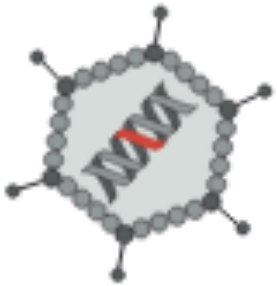
Schematic representation of the basic components of a gene insert packaged inside recombinant AAV gene transfer vector. *AAV* adeno-associated virus, *ITR* inverted terminal repeat

Naso et al., BioDrugs. 2017; 31(4): 317–334

Limitations of rAAVs

- They persist mostly as non-replicating episomes (can persist 5 years and more in transfected tissue), but are then gradually lost.
- (However it can also stably integrate at a specific position in human chromosome 19)
- A patient who had already an infection with “natural” AAVs, might have developed immunity against certain AAVs.

Gene Therapy



Zolgensma (Novartis gene therapies)

Gene defect SMN1 (Survival motor neuron protein 1)

Disease: Spinal muscular atrophy

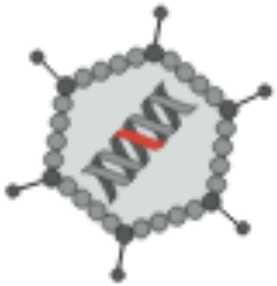
Cost of treatment: 2 125 000$ (2019)

FDA approved 2019

EMA approved: 2020

Symptoms: Weakness in muscles used for movement (skeletal muscles)

Gene Therapy



Luxturna (Spark Therapeutics, USA)

Defect in gene RPE65/blindness

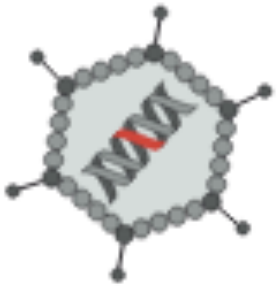
Enzyme in visual pigment regeneration

Cost of treatment: 850 000 Dollar

FDA approved: 2017

EMA approved: 2018

Gene Therapy



Glybera (uniCure,Netherlands)

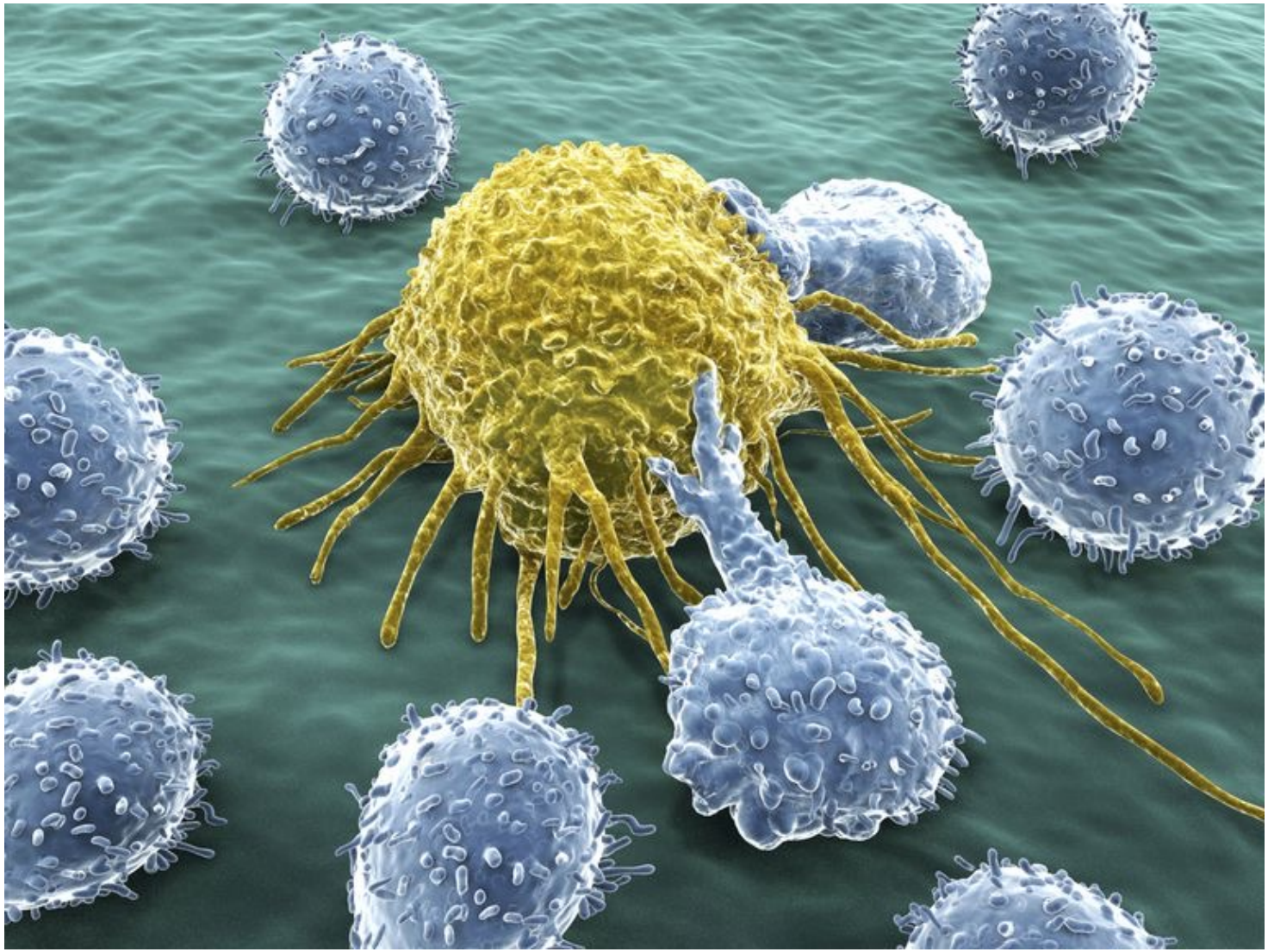
Defect in gene encoding Lipoprotein lipase

Cost of treatment: 1600 000 $ (2012)

1000 000 $ (2015)

EMA approved: 2012, withdrawn 2017

T cell engineering to fight cancer



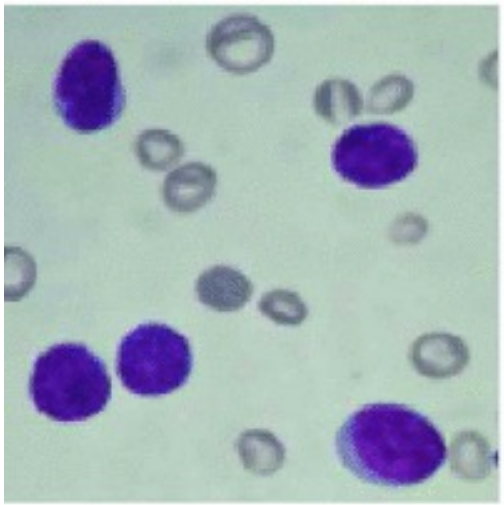
https://www.verywell.com/t-cells-2252171

CAR T-cell therapy

- **Chimeric antigen receptor** (CAR) T-cell therapy is a type of immunotherapy that uses a patient's own genetically modified T cells to find and kill cancer cells.

Acute Lymphoblastic Leukemia (ALL)

- ALL occurs at an annual rate of approximately 41 cases per 1 million people aged 0 to 14 years and approximately 17 cases per 1 million people aged 15 to 19 years



High number of lymphoblasts (precursor B cells)

Neural Computing and Applications (2014) Volume 24 Issue 7-8, Pages 1887-1904

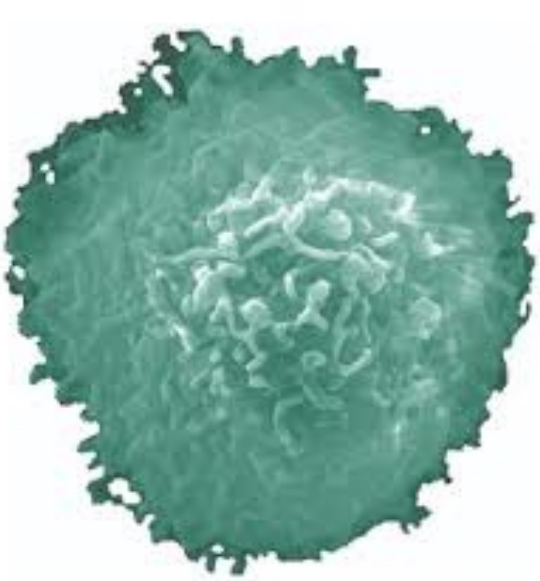
T cells

- T cells from our immune system can identify and kill cancer cells however cancer cells have developed strategies do evade the immune system, making T cells ineffective and a tumors can develop

NOVARTIS

FDA approval, July 13, 2017

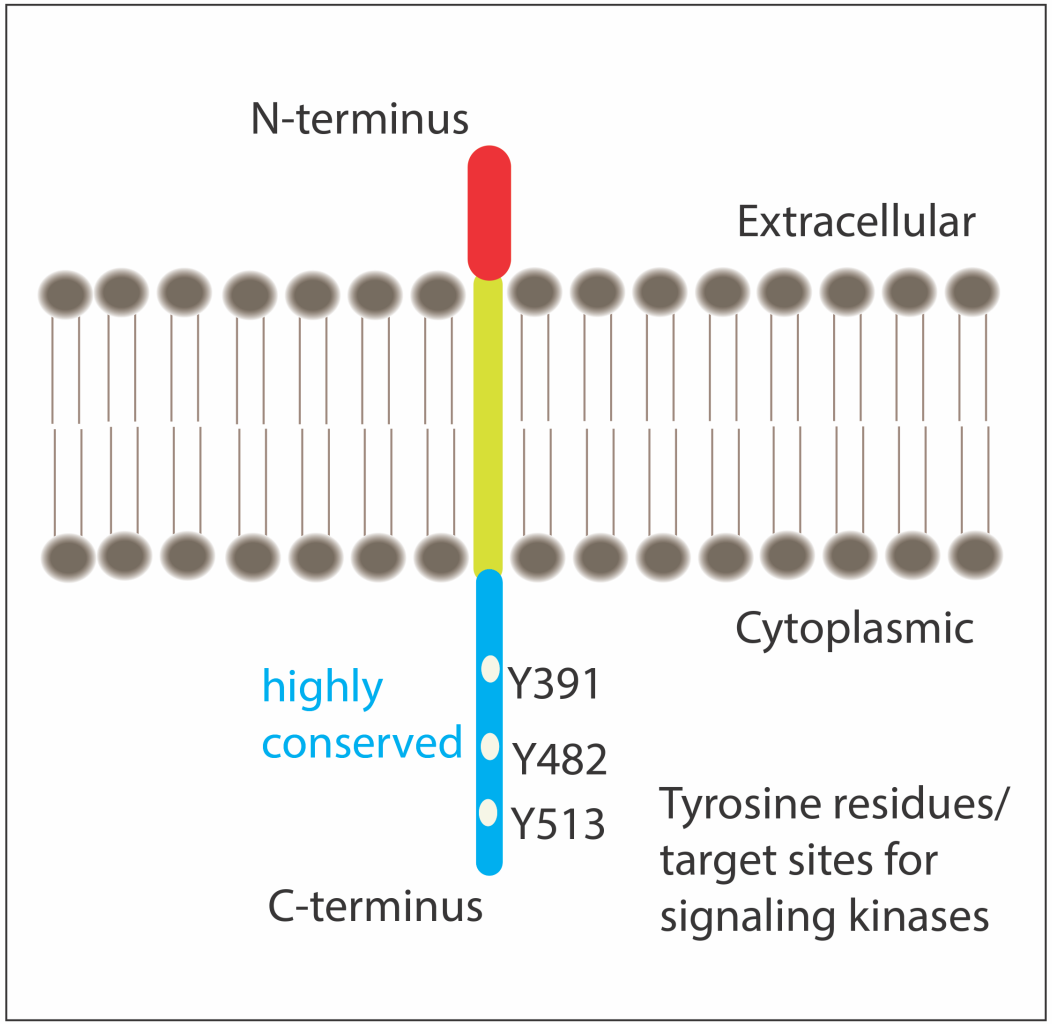
- CAR T-cell therapy CTL019 (Kymriah)



New York Times, July 12, 2017

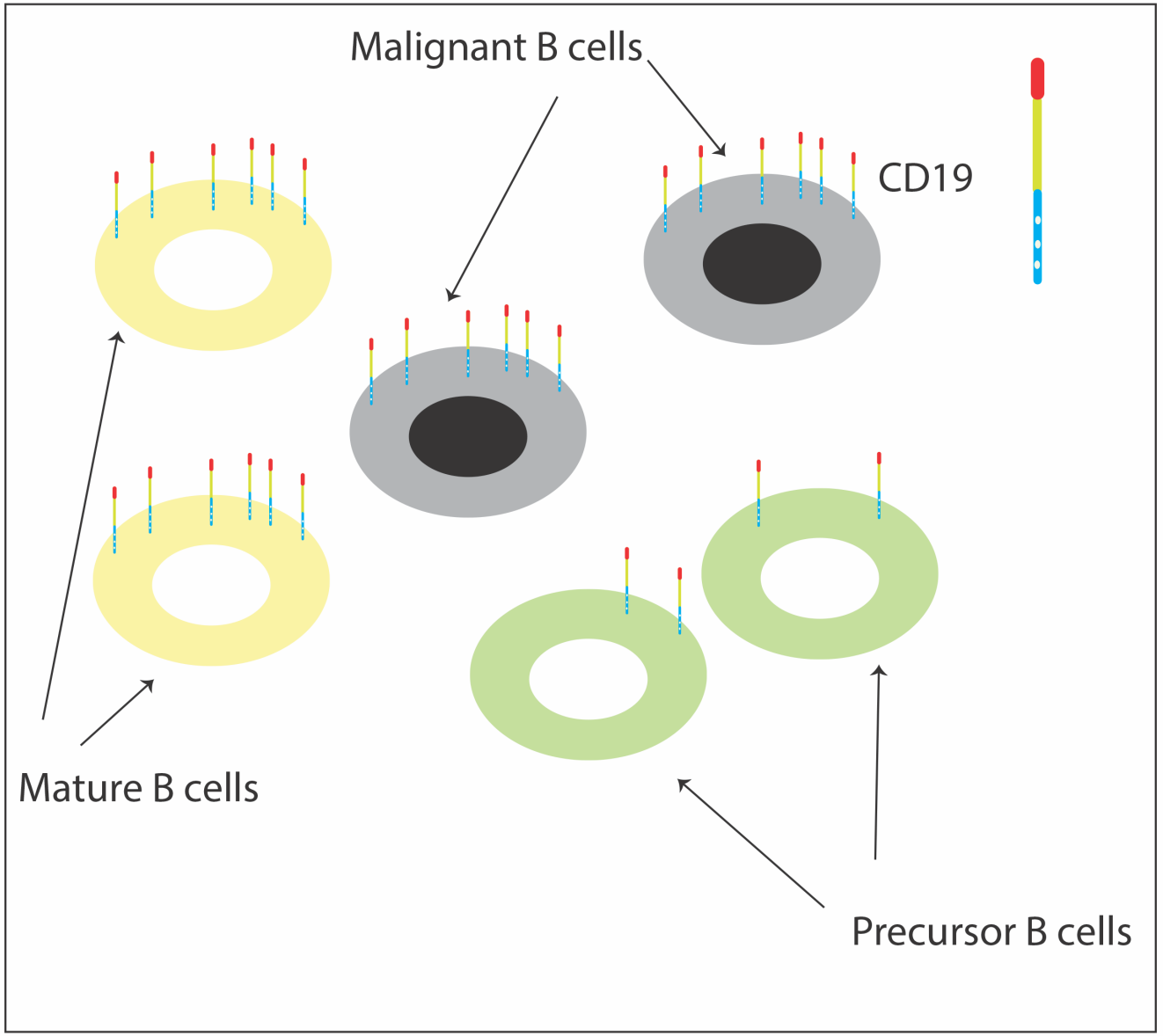
- Emily Whitehead, 12, and her parents, Tom and Kari Whitehead, appeared at an F.D.A. hearing on Tuesday about a treatment for leukemia that had saved Emily's life

CD19 structure

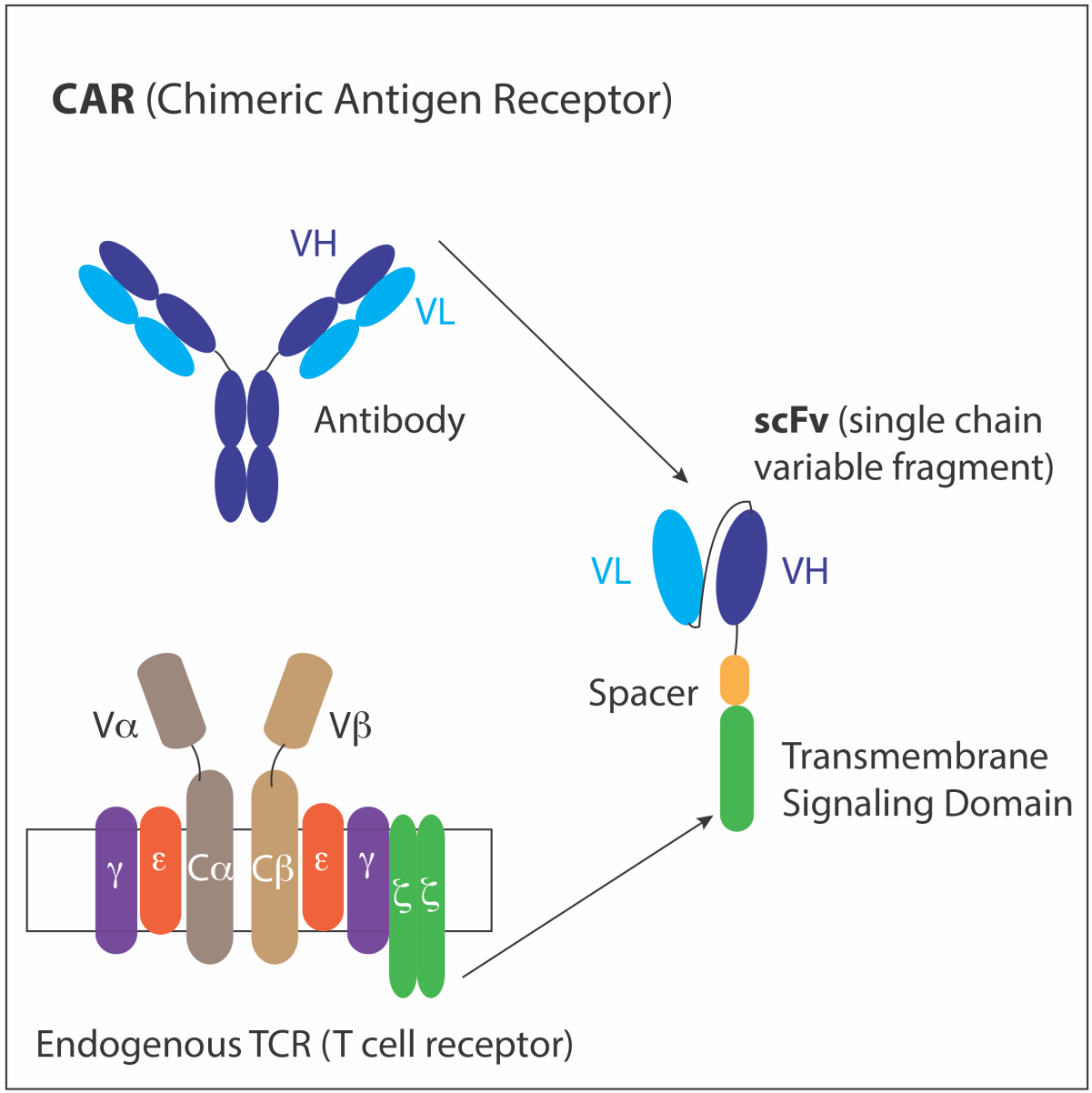


CD19 is a cell surface molecule that assembles with the antigen receptor of B lymphocytes in order to decrease the threshold for antigen receptor-dependent stimulation

Targeting malignant B cells via CD19



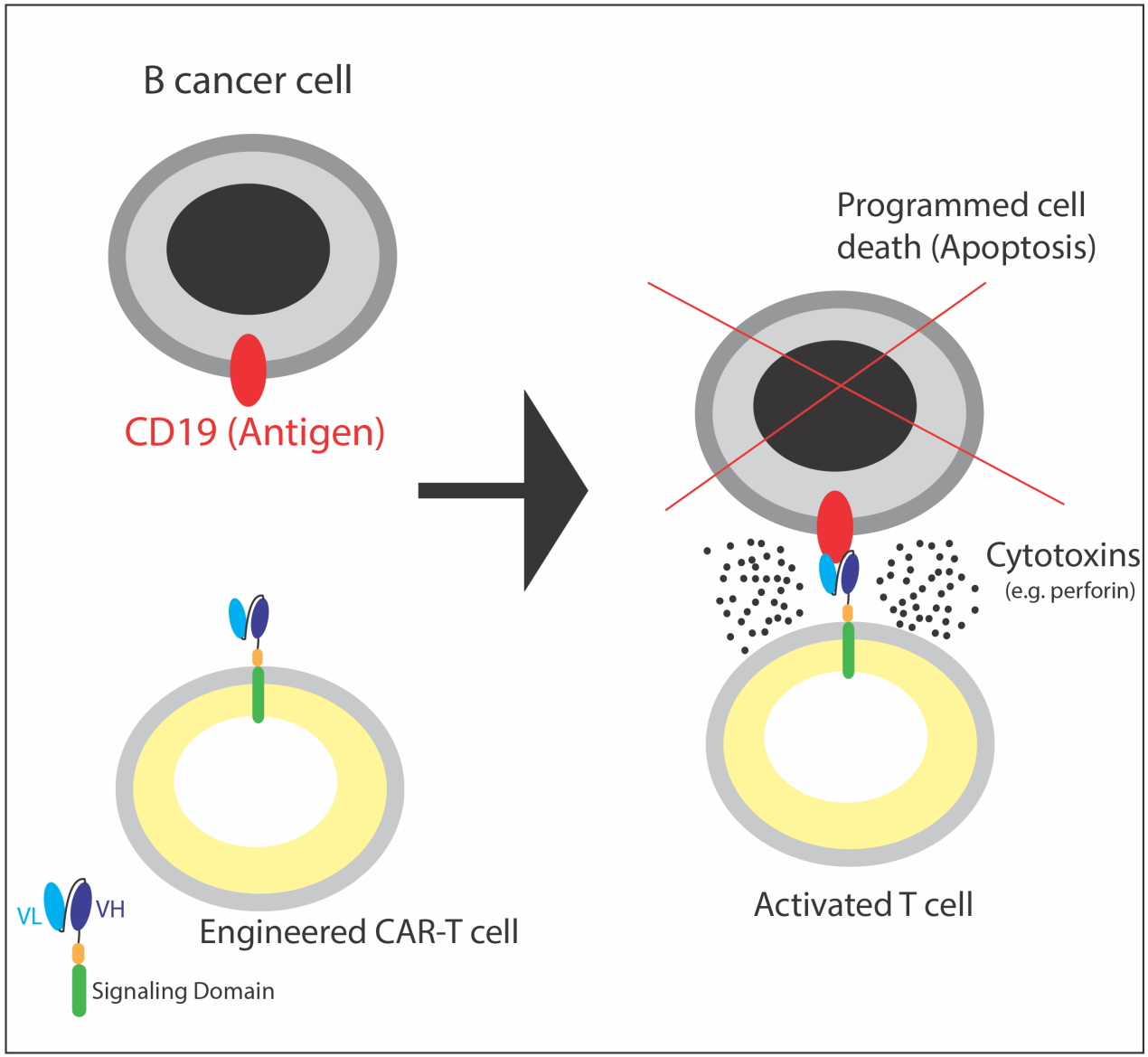
1st generation CAR



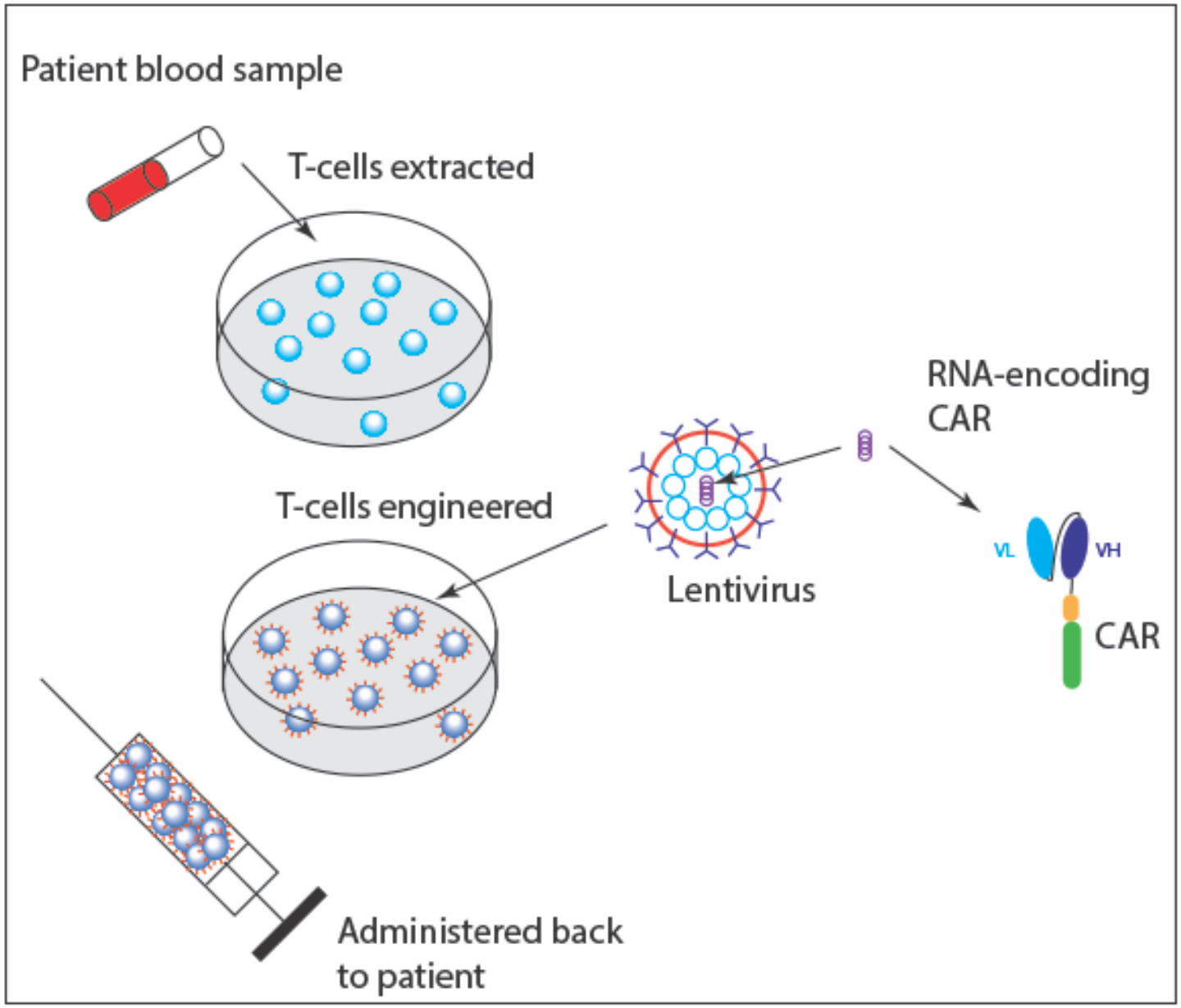
Recognizes and binds to CD19

Induces T-cell proliferation

Activated CAR T-cells killing B cancer cells



CAR T-cell therapy

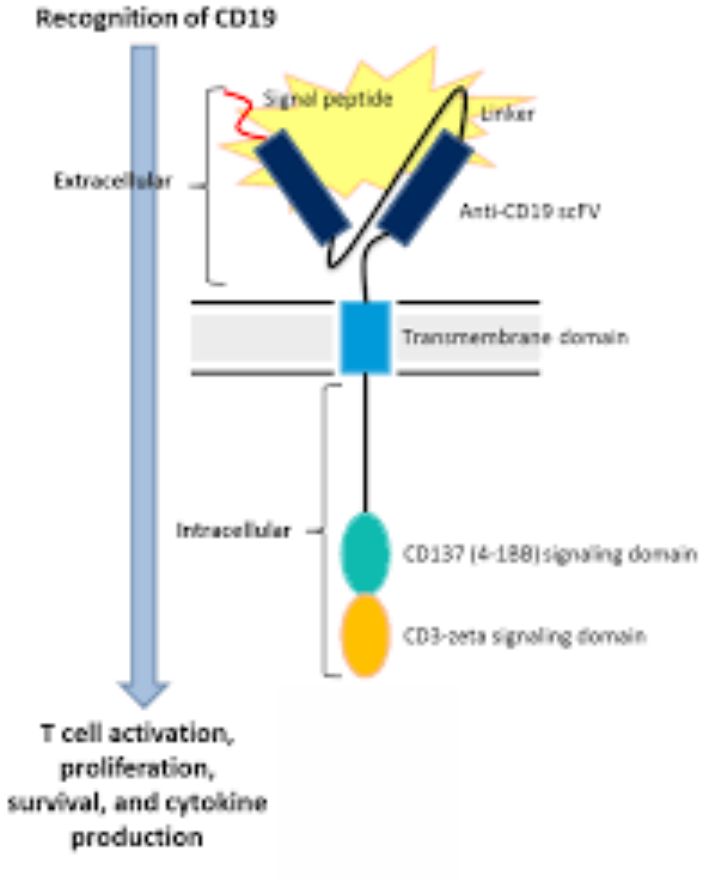


CAR T-cell multistep process

- **Evaluation**: Tests if CAR T-cell is an appropriate therapy
- **Collection**: T cells are collected from patients
- **Engineering**: T cells are genetically engineered to express chimeric antigen receptors (CARs) on their surface
- **Multiplication**: The genetically modified T-cells are "expanded" by growing cells in the laboratory until there are millions of them
- **Conditioning**: Chemotherapy: killing of other immune cells to “create space” for the infused CAR T-cells to expand.
- **Infusion**: Engineered CAR T-cells are infused. Patients need to stay in hospital for a few days up to few weeks depending on side effects.
- **Recovery**: 2-3 months

“CTL019” CAR T-cell therapy

- Novartis



Pharma Intelligence “modified”

“CTL019”

- CTL019 is a second-generation CAR-T that has an anti-CD19 extracellular scFv and CD3-zeta and CD137 (4-1BB) intracellular signaling domains. CD19 is a cell surface protein that is expressed in the majority of B cell leukemias and lymphomas, and therefore targeting it is an attractive therapeutic approach

Clinical trial results

- Novartis-sponsored ELIANA study (NCT02435849)
- the first global CAR-T cell trial involving 25 centers in the US, EU, Canada, Australia and Japan. In the Phase II study, 82% (41 of 50) of patients infused with CAR-T cells achieved complete remission.

CAR-T cell therapy costs (estimations)

- In 2017, Novartis' Kymriah became the first CAR-T therapy approved by the FDA
- Costs for one T cell treatment course: $475,000 per patient
- Existing treatment options: Chemotherapy + stem cell transplantation: $100,000 to $200,000

Downsides

Severe side effects

- High fewer (due to cytokine release)
- Dramatic decrease in blood pressure (hypotension)
- Respiratory and renal problems
- B cell aplasia (complete removal of B cells)

(Maude et al., N Engl J Med. 2014)

- It may be argued however that antibody deficiency is an acceptable price to pay for an effective new treatment for otherwise untreatable malignancy, particularly since it can be corrected with immunoglobulin replacement therapy.

Emily Whitehead was the **first** child to be enrolled in a clinical trial for CAR-T cell therapy

- 2012 (age 7)

2021

2022: Celebrating 10 years cancer free

2023: Celebrating 11 years cancer free

5 FDA-approved CAR T-cell Therapies (Hematological cancers)

- KYMRIAH™
- ABECMA®
- BREYANZI®
- TECARTUS™
- YESCARTA™

Indications

- Diffuse large B-cell lymphoma (DLBCL)
- Primary mediastinal B-cell lymphoma
- High grade B-cell lymphoma
- DLBCL that results from follicular lymphoma
- Follicular lymphoma