Sickle Cell Disease and CRISPR/Cas9 Based Therapy

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- Pharm.D. from University of Washington in 2000
- MHA from University of Cincinnati 2018
- BCBBS certified in 2022
- Certified pharmacogenomics specialist in 2024
- 24 years of specialized experience in the pharmaceutical industry, involving for-profit and non-profit organizations

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Agenda

- New gene therapy for Sickle Cell Disease
- Summary of CRISPR/Cas 9 platform
- Sickle Cell Disease and traditional treatment
- CLIMB trial and HGB trial outcomes

New Gene Therapies for Sickle Cell Disease

The first 2 curative gene therapy agents for sickle cell disease in patients 12 years and older

exagamglogene autotemcel (**exa-cel), CRISPR/Cas9**

lovotibeglogene autotemcel (**lovo-cel), autologous hematopoietic stem cell-based** gene therapy

The first gene therapy using: CRISPR/Cas 9)

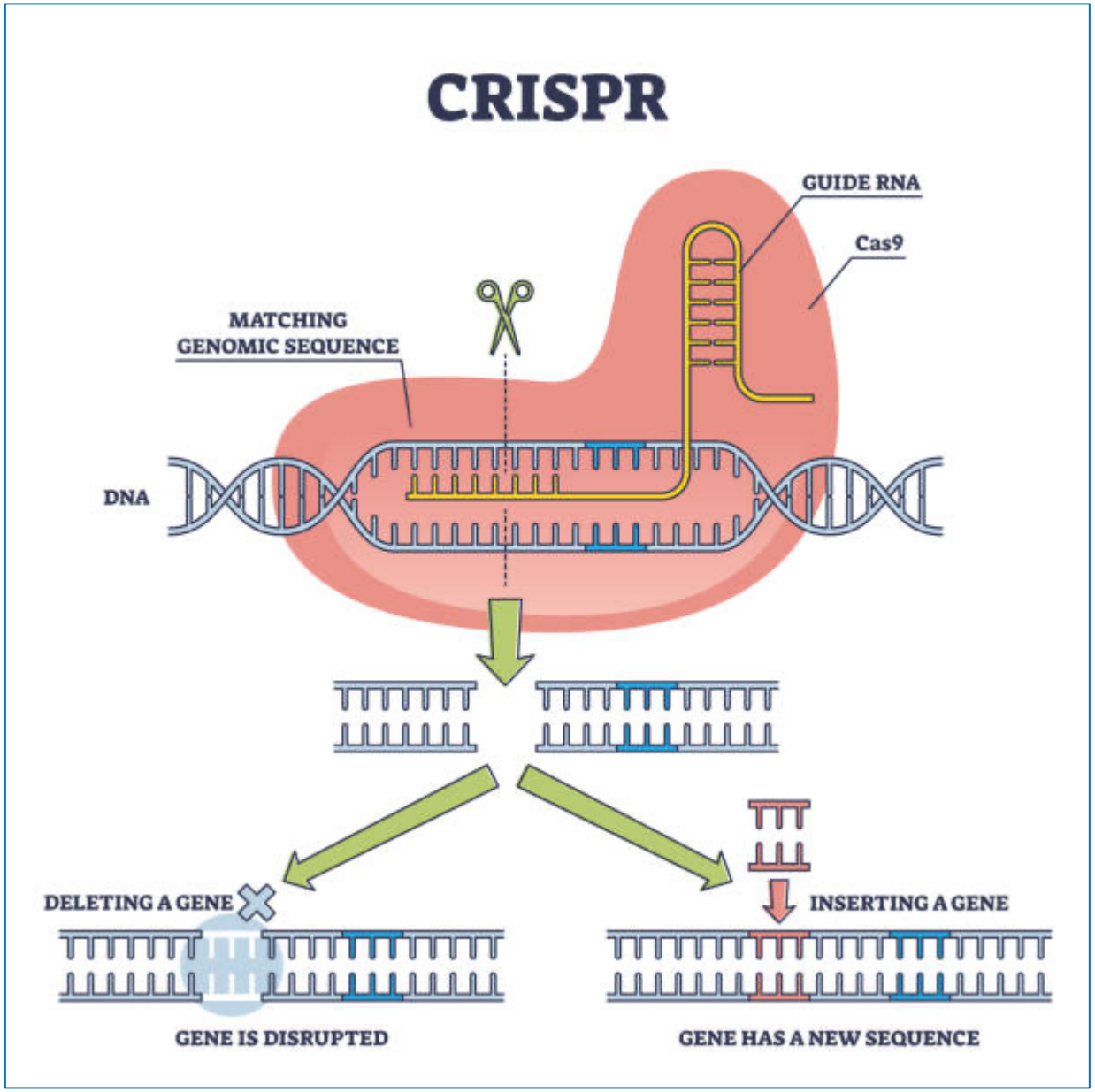
What is CRISPR/Cas9

Clustered regularly interspaced short palindromic repeats (CRISPR)

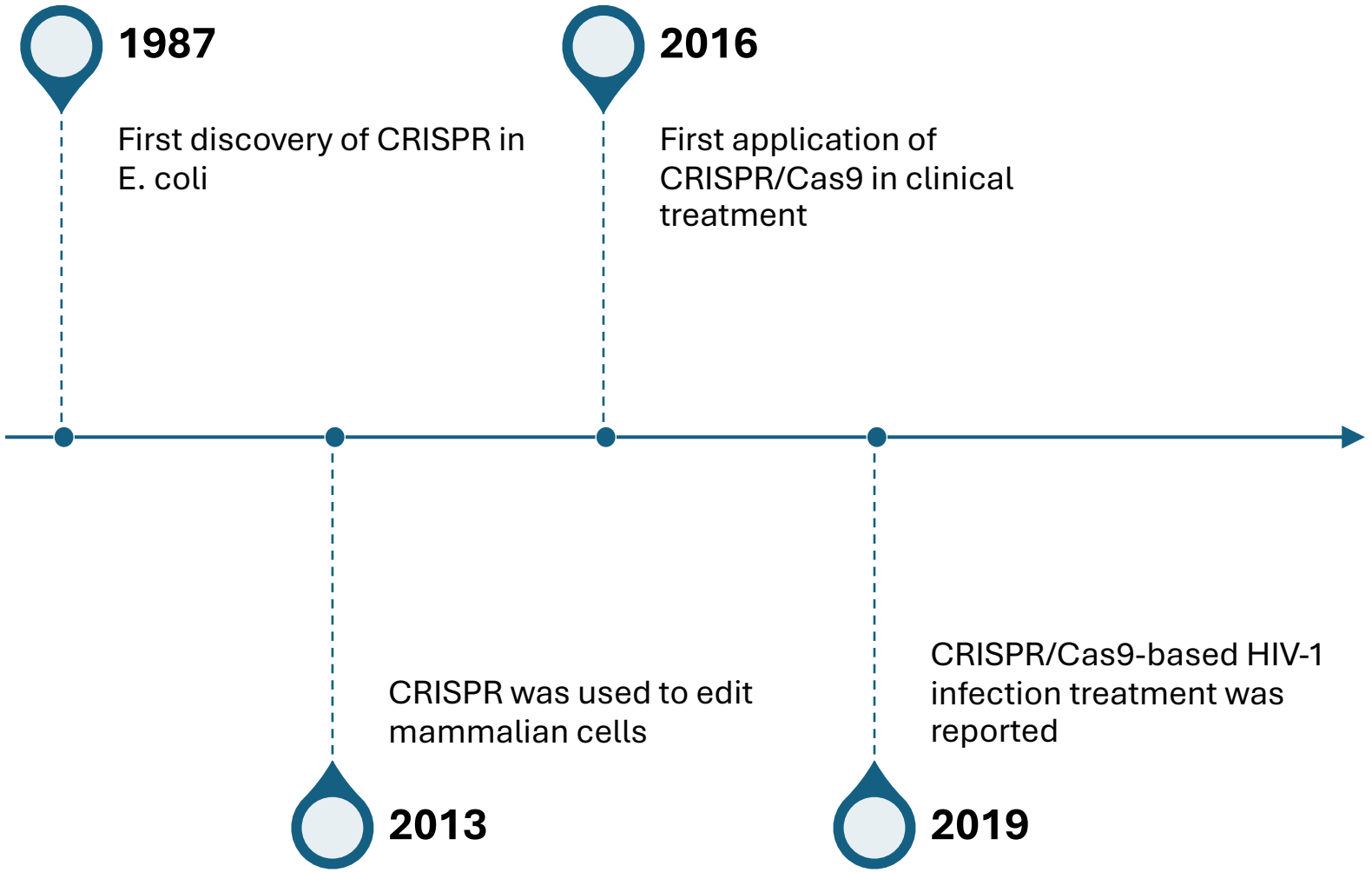
CRISPR-associated protein 9 (Cas9) technology (CRISPR/Cas 9)

Guide RNA

The Structure & Functions of CRISPIR/Cas9 System



History of CRISPIR/Cas9



The Nobel Prize and Commercial Implications

2020: Dr. Doudna and Dr. Charpentier were awarded the 2020 Nobel Prize in Chemistry

2021: First clinical treatment of SCD & β-thalassemia were reported

2023: First marketing approval of a CRISPR/Cas9 therapeutic

Future: treatment centers need to be established, local logistics and financial considerations addressed.

Sickle Cell Disease is Perfect for Gene Therapy

Sickle cell disease genetic cause: single base-pair gene mutation

Functional impact of this mutation: abnormal hemoglobin S (Hgb S), polymerization and red blood cell become sickle shaped.

Shorter red blood cell survival time	accumulation of red blood cells	reduced oxygen transport within the body

One hope is SCD patients: Fetal hemoglobin does not cause red blood cell sickling in newborn babies, thus young infants with sickle cell disease are asymptomatic.

Sickle Cell Disease Symptoms

Red Blood Cell Sickling:

- accumulation of red blood cells
- restricted blood flow
- vaso-occlusive crisis (VOC)

Symptoms:

- severe pain
- anemia
- stroke
- multiorgan damage.

Lifespan for patients with sickle cell disease: 52.6 years,

Sickle Cell Disease Traditional Treatments

sickle cell disease management:

- frequent blood transfusions
- hydroxyurea for disease management.

The only curative treatment prior to the approval of exa-cel and lovo-cel was bone marrow transplant (BMT).

Challenges for BMT:

- Less than 20% patients can find matching donors.
- graft-vs-host disease
- graft failure
- organ damage
- infections.
- Patients also need lifelong immunosuppressants

Disease Burden

Frequent blood transfusions

Emergency department visits

Hospital admissions to manage severe VOC

BMT lifetime management

Caregiver financial impact

The unmet need is great for both improved quality of life and extended life expectancy.

Two Gene Therapies for SCD

First curative agents for SCD

Wholesale acquisition cost (WAC) forexa-cel: $2.2 million

Lovo-cel WAC price: $3.1 million

Exa-cel: CLIMB SCD-121 trial (NCT03745287)

Lovo-cel: HGB-206 trial (NCT02140554)

Long-term follow-up posttreatment studies for the efficacy and safety of these therapies are ongoing

CLIMB SCD-121 Trail Efficacy

Trial Design:

- global multicenter, single-arm, open-label, phase 3 trial studying the safety and efficacy

Efficacy Outcome:

- 96.7% treatment response (24-month follow-up)
- 29 of the 30 patients achieved 12 months of freedom from severe VOC
- 100% (30 patients) were free of hospitalization due to severe VOC for 12 consecutive months

CLIMB SCD-121 Trial Safety

Safety outcome:

no incidence of hematologic malignancy
non-target gene editing
no treated graft failure
no graft rejection
no fatality
No Black Box warning

Common adverse effects (AEs):

low levels of platelets and white blood cells
mouth sores
Nausea
musculoskeletal pain
abdominal pain
Vomiting
febrile neutropenia
headache, and itching.

HGB-206 Trial Efficacy

Trial Design:

- Non-randomized
- Open label
- Multi-site
- Single dose
- Phase ½ study

Efficacy Outcome:

- 88% (32/36) were evaluated
- 88% (28/32) VOC free
- 94% (30/32) severe VOC-free

*6 months to 18 months post treatment

HGB-206 Trial Safety

Safety Outcomes:

- 2 cases of hematologic malignancy and patient death
- Black box warning for hematologic malignancy on the lovo-cel package insert
- No association between lovo-cel and the insertional oncogenesis was reported by the primary investigators.
- FDA requires:
  - long-term monitoring for hematologic malignancies
  - 15-year posttreatment prospective study to assess the risks of secondary malignancies

Common Adverse Event:

- Stomatitis
- low levels of platelets, white blood cells, and red blood cells
- febrile neutropenia

Exa-cel for Sickle Cell Disease

Mechanism of Action :

- CRISPR/Cas9 system
- diminish the *BCL11A* gene expression for β-globin
- reactivate the production of fetal hemoglobin (γ-globin)
- increasing the production of γ-globin;
- γ-globin does not cause the hemoglobin polymerization

Indication :

- sickle cell disease due to Hgb S w/recurrent VOC
- transfusion-dependent β-thalassemia (TDT)
- 12 years and older

Lower morbidity and mortality in patients with sickle cell disease and TDT

Pre-treatment Patient Care

8 weeks or more of red blood cell transfusion

Reduce the Hgb S level to less than 30%

achieve total hemoglobin level at 11 g/dL

Hematopoietic stem cell mobilization treatment **and** **a**pheresis

Genetic modification of the harvested cells via CRISPR/Cas9 **method**

Full myeloablation is necessary prior to the infusion of edited cells

Treatment Center Readiness

CENTERS CERTIFICATION

FACILITIES REQUIREMENTS

STAFF TRAINING

MULTIDISCIPLINARY TEAM: HEMATOLOGY, PHARMACY, NURSING, AND QUALITY LEADERSHIP TEAMS

MATURE CELLULAR THERAPY PROGRAM POLICIES AND PROCEDURES. PEDIATRIC PATIENT CARE

Financial Feasibility Considerations

Drug cost = $2.2 million

Payer coverage can be complicated.

Medicaid coverage varies state by state;

Medicare: may qualify for new technology add-on payments.

Hospital charges need to include:

- pretreatment care
- posttreatment hospitalization and AE management

No confirmation of 340B price availability

Individual contracts

Future of CRISPR Technology Based Therapy

CRISPR/Cas9-related treatments for other disease states are underway

61 clinical trials registered at ClinicalTrials.gov

Cancer, diabetes,

heart diseases

rare diseases

CRISPR/Cas9 technology is likely to revolutionize precision medicine

Thank you and stay in touch

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