The Clinical Manifestations of Sickle Cell Disorder and the Emerging Treatment Options

Cayenne Wellness Center Keynote Address
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Emmaus Medical, Inc.
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History of Sickle Cell Disorder

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Early Sickle Cell Disease (Disorder) Research

- 1910: First Description of Sickle Cell Disease (SCD)
  - James Herrick, MD makes 1st description in published literature
- 1911: Second Published Case of Sickle Cell Disease
  - 25-year-old female patient described with symptoms of SCD
- 1915: Suggestion of Genetic Link
  - 21-year-old female showed blood film indicative of SCD
  - Father of patient noted with abnormalities of red blood cells after a few days

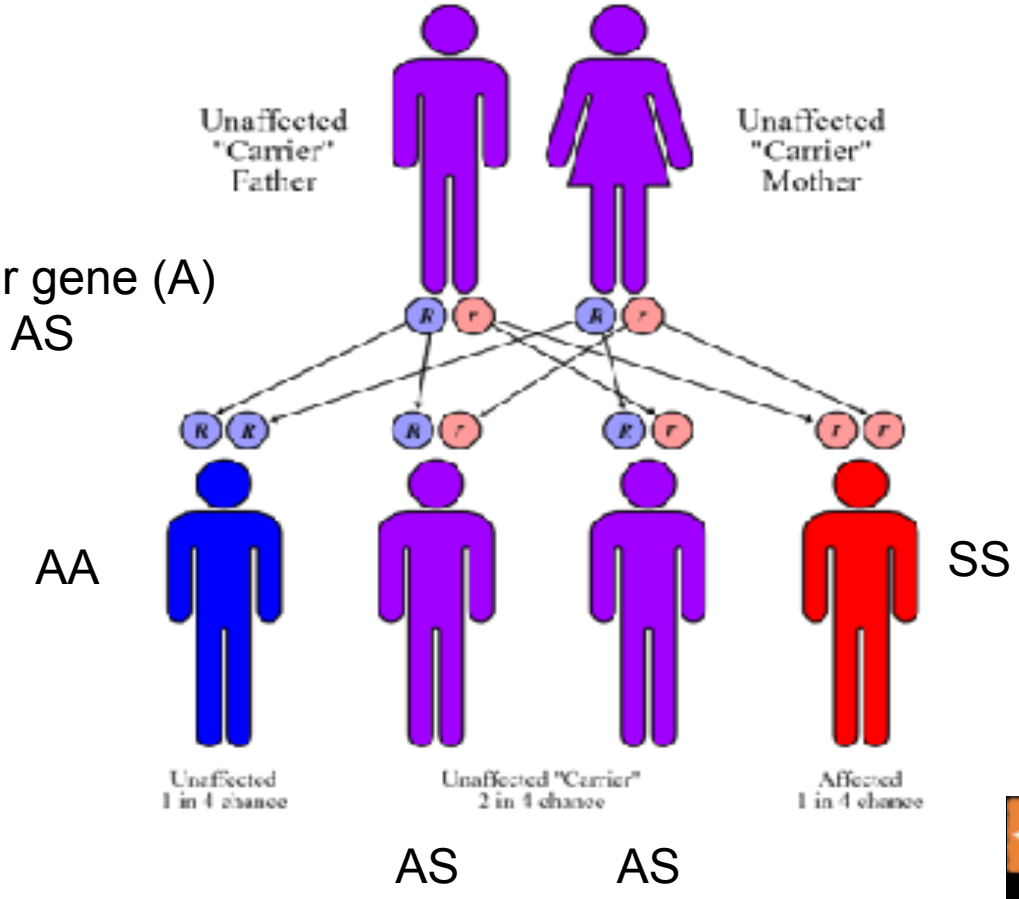
Early Sickle Cell Disease Research

- 1922: Sickle Cell Anemia (SCA) Terminology
  - 21-year-old male patient becomes the fourth known case of SCD
  - Published literature of this case used the term “sickle cell anemia”
- 1949: Sickle Cell Anemia Identified as the First Molecular Disease
  - Electrophoresis shows that in SCD, there is a modified form of hemoglobin
  - Linus Pauling published his findings in *Science*

Sickle Cell Disorder: A Single Genetic Mutation

- It is a group of **inherited blood disorders** (passed on) from parents

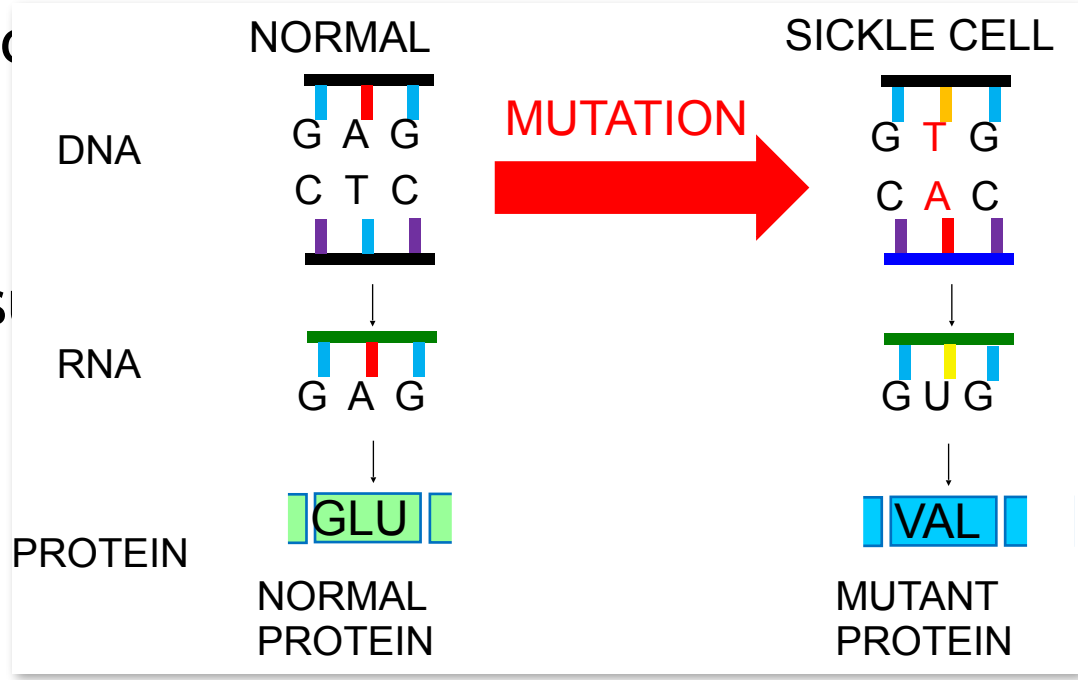
Sickle Cell Trait (SCT = **Purple**) → one regular gene (A) and one mutated (changed to S) is inherited = AS



Sickle Cell Disease: A Single Point Mutation (Change)

- Caused by a single mutation (change) in the ß-globin gene of hemoglobin (oxygen carrying protein)
  - Glutamate is replaced with Valine (6th plac
- Deoxy-HbS (SS) will polymerize
  - When hemoglobin S gives up oxygen to tiss
  - Causes hemoglobin to come together

    Polymerize = clustering together = sickle



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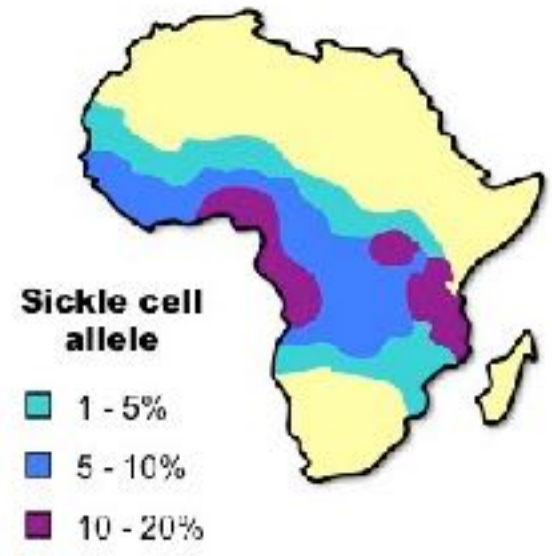
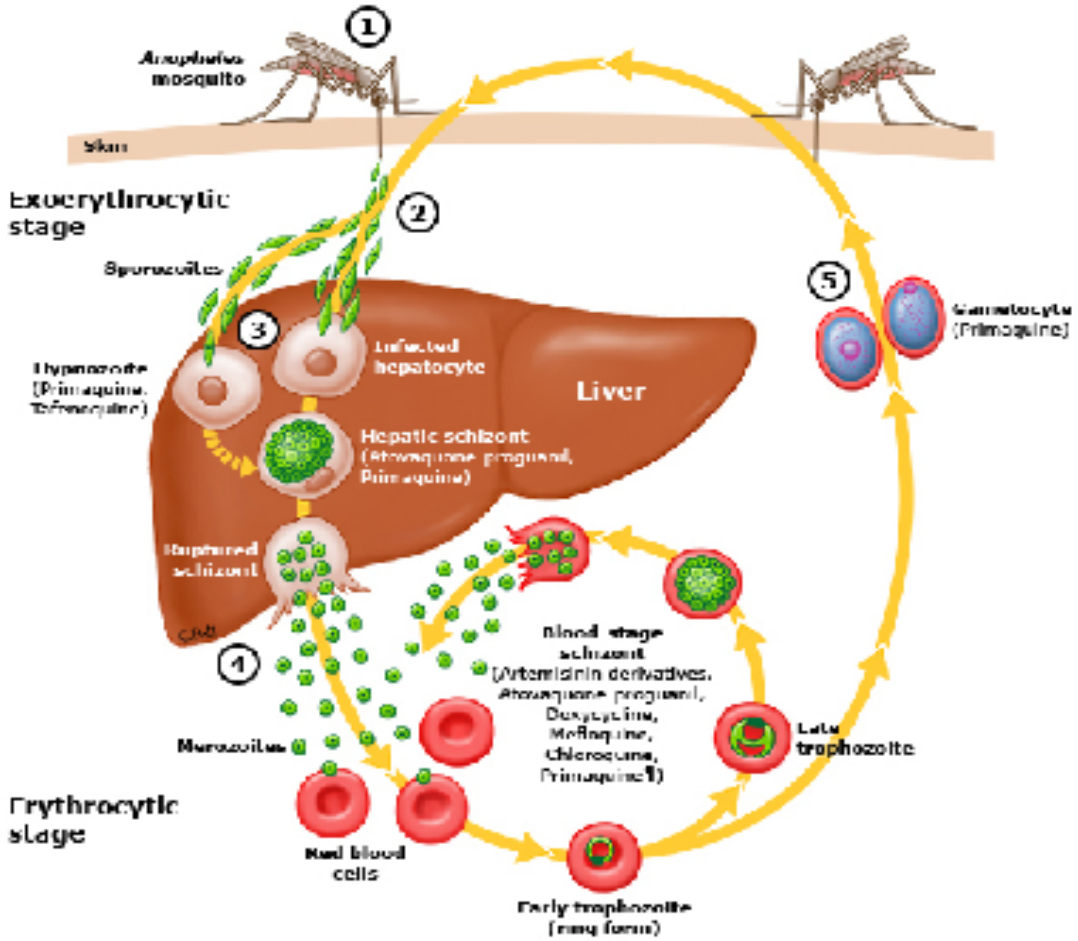
Sickle Cell and Malaria

- It has been suggested that the prevalence of sickle cell disease is due to sickle cell trait carriers being resistant to malaria
- This is supported by a high prevalence of sickle cell in areas with a high incidence of malaria



Malaria Life Cycle



Malaria: Epidemiology, prevention, and control. Breman JG.

Sickle Cell Disease Genetic Variations

- Hemoglobin SS
- Hemoglobin Sβ^0-thalassemia
- Hemoglobin Sβ$^+$-thalassemia
- Hemoglobin SC
- Hemoglobin SD
- Hemoglobin SE

- **other less common variations exist*

Pathophysiology of Sickle Cell Disease

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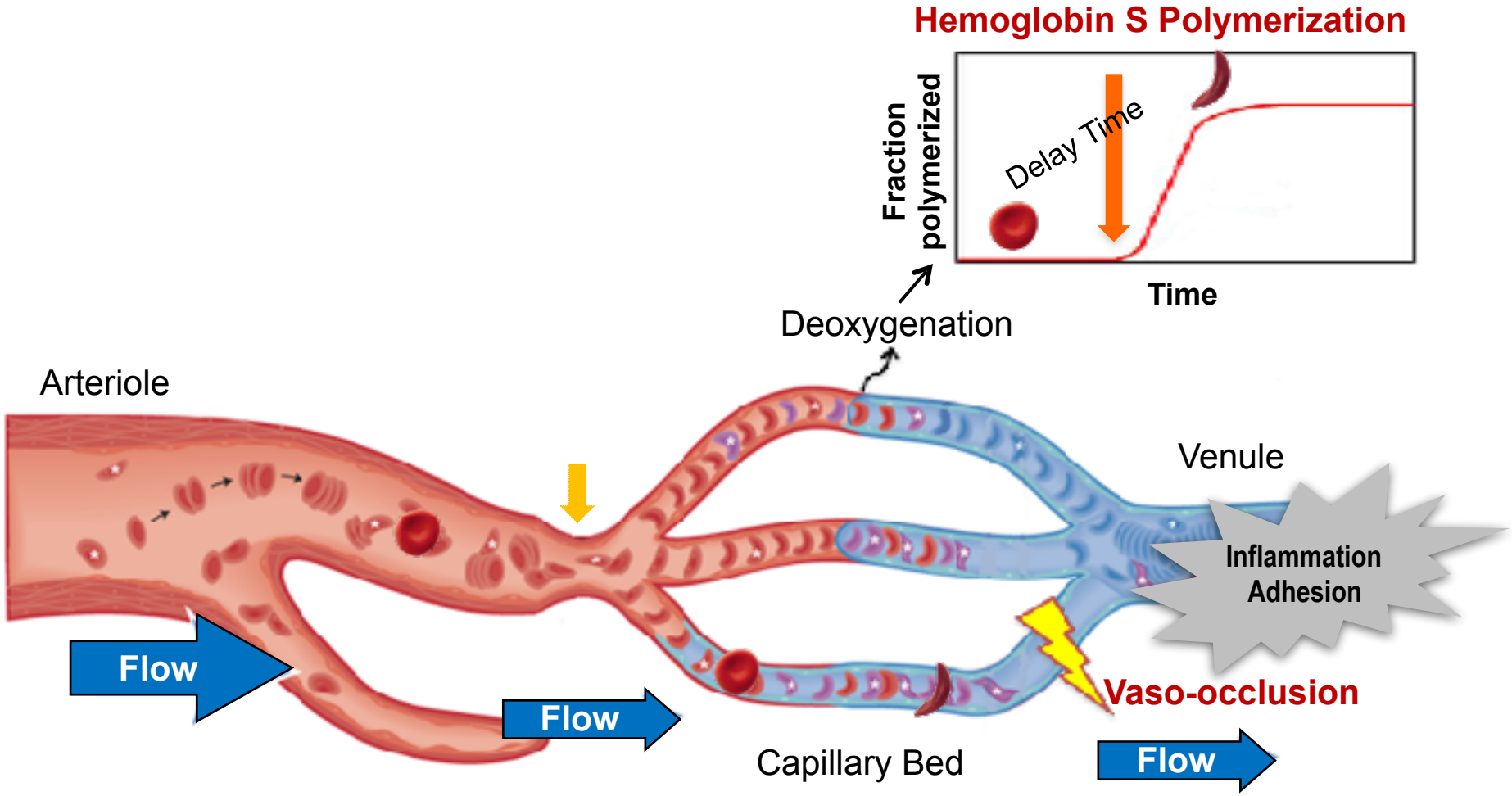
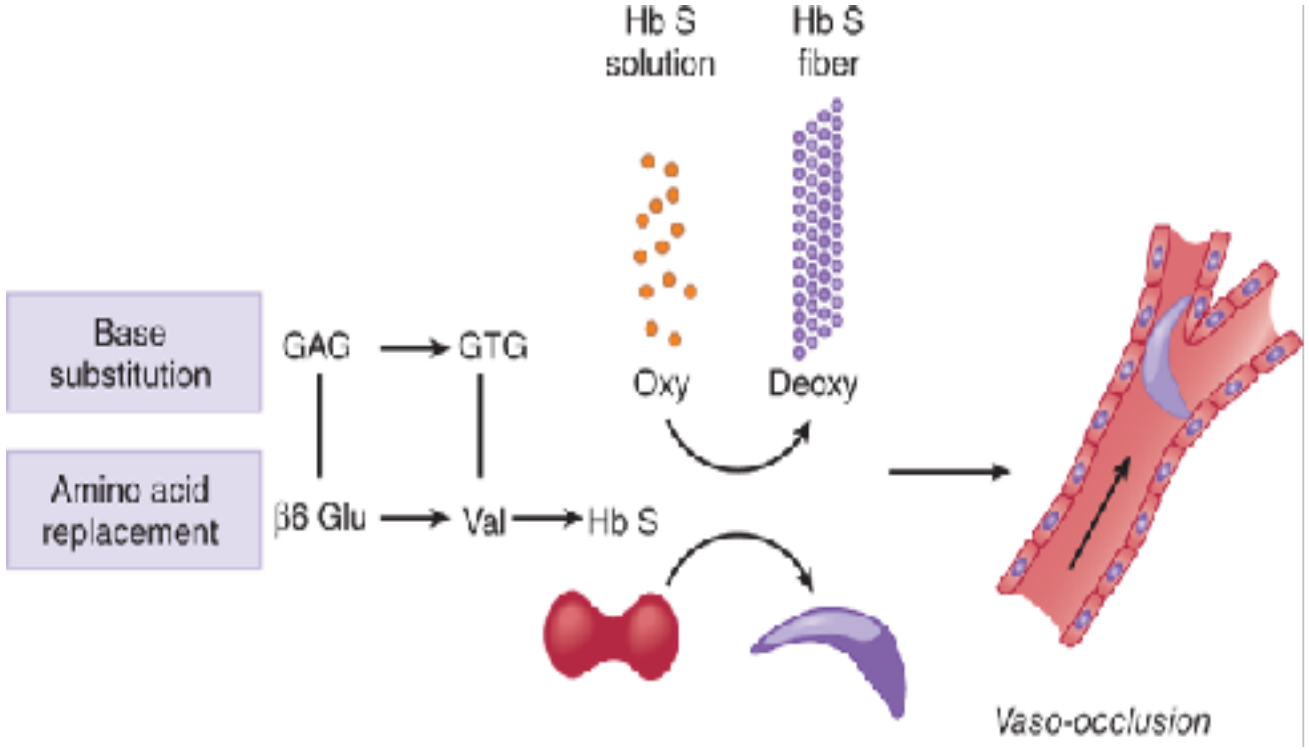
Sickle Cell Crisis

- Deoxygenation leads to hemoglobin polymerization



Adapted from Eaton WA, et al. *Blood.* 2017;129(20):27190-2726.

Polymerization of Hemoglobin



Source: Jon C. Aster, H. Franklin Bunn:
Pathophysiology of Blood Disorders, Second Edition
www.hemonc.mhmedical.com

Complications of Sickle Cell Disease

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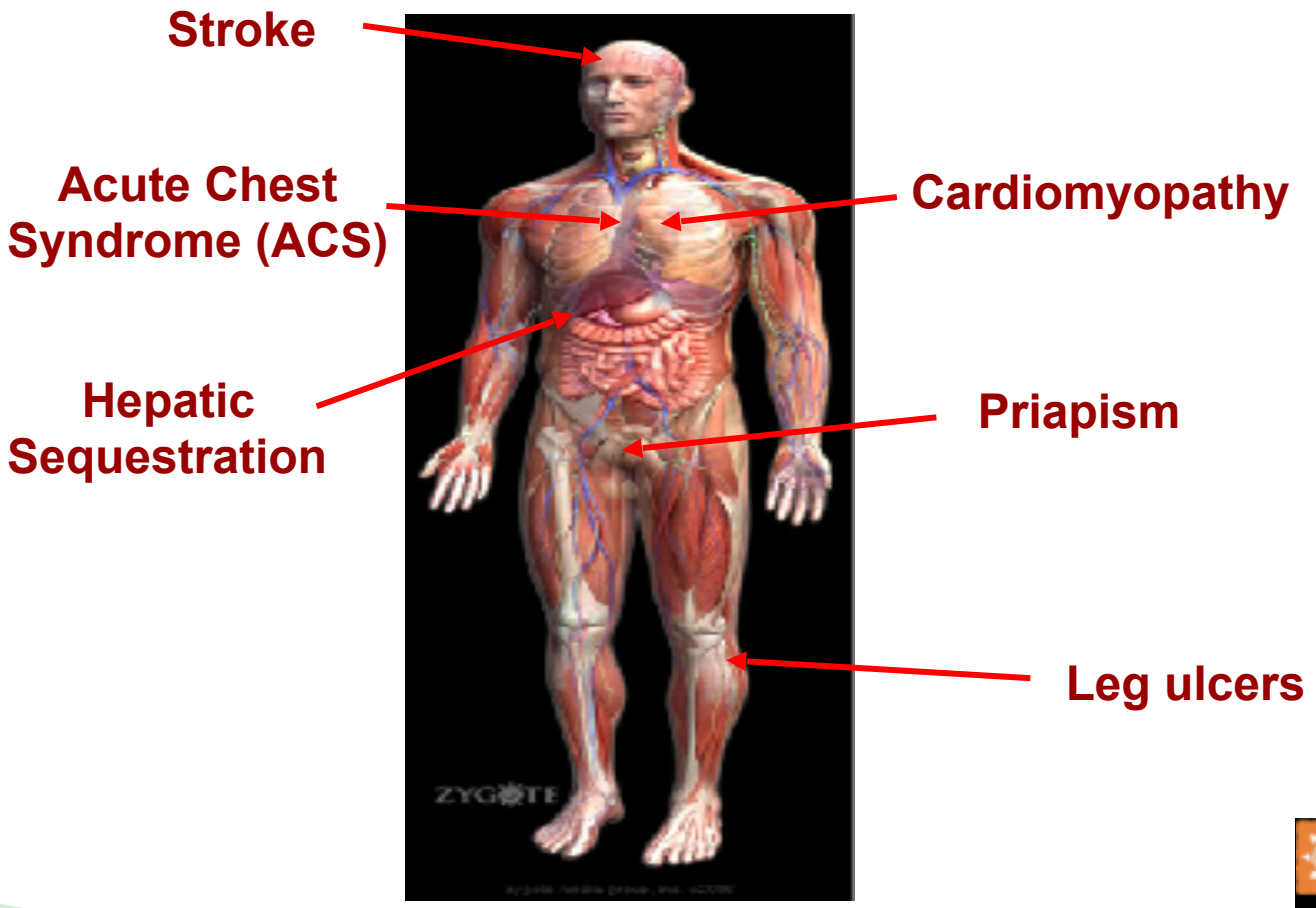
Sickle Cell: Multisystem Organ Damage



Acute Complications in Sickle Cell Disorder

- Sickle Cell Disease has a highly variable presentation

- Common:
  - Excruciating Pain
  - Severe Fatigue
  - Jaundice
    - Yellowing of the eyes and skin
  - Frequent Infections
  - Swelling and Pain in Hands and Feet

Management and Treatment Options

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Available Treatment Options

Therapeutic Agents

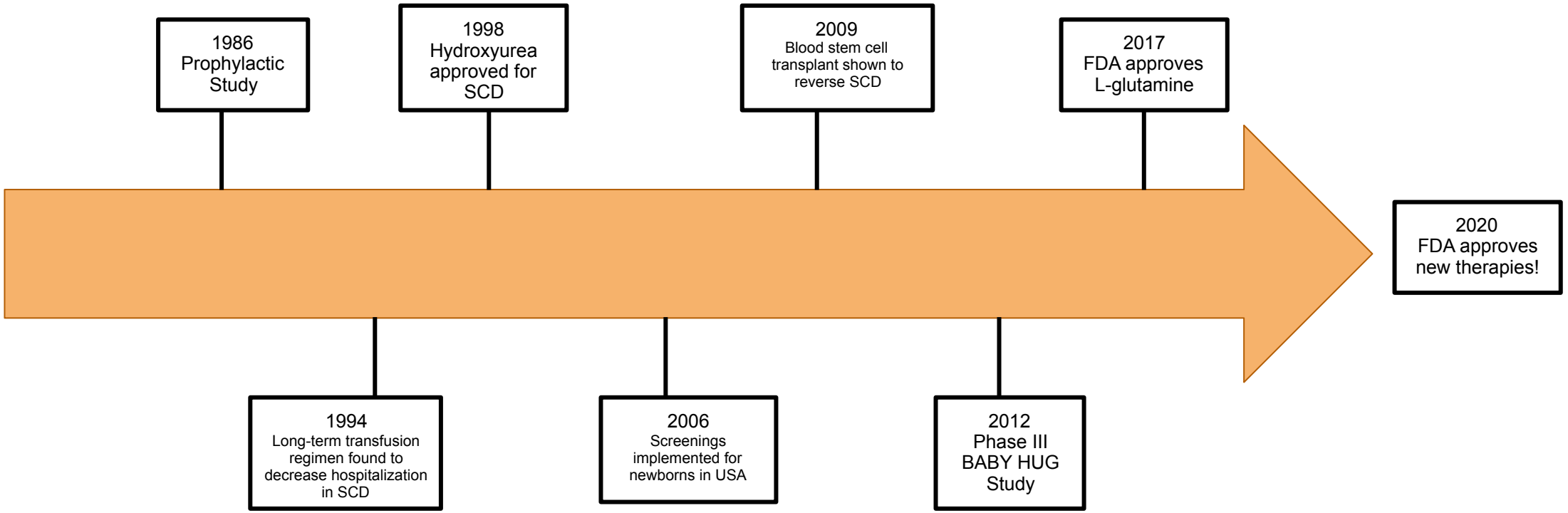
- Hydroxyurea
  - Anti-cancer agent for reduction of painful crises
  - Approved for sickle cell disease in 1998
- Endari (L-glutamine oral powder)
  - Approved for sickle cell disease in 2017

Available Management Options

Management

- Blood Transfusions
- Iron Chelating Agents
- Prevention by Hydration and Diet

Treatment Milestones in Sickle Cell Disease



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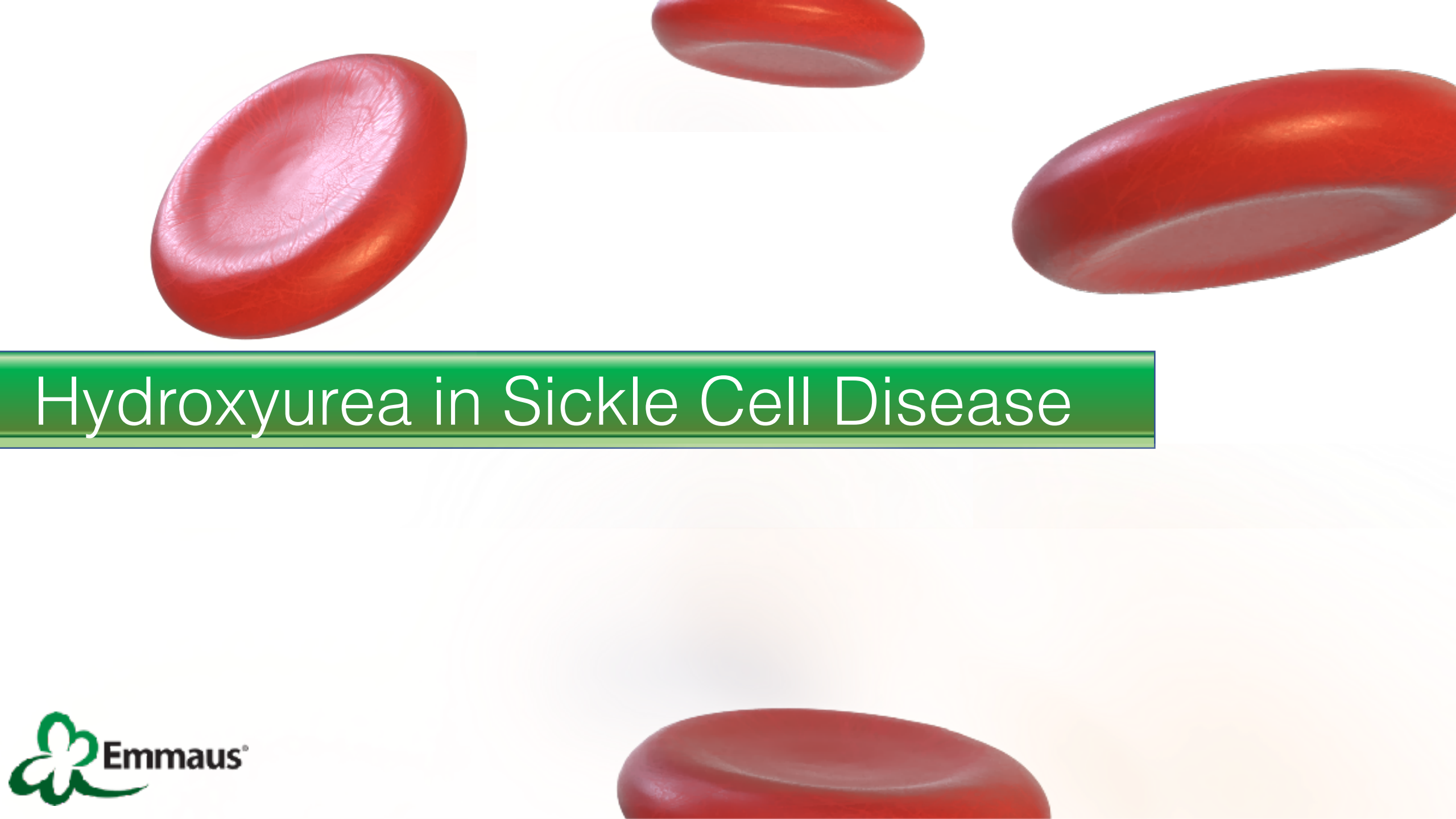

Hydroxyurea in Sickle Cell Disease

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Hydroxyurea Treatment

- Initially developed for use in chronic myeloid leukemia and other cancers
- **1987**: Early HU studies SCD were published
  - Researchers saw benefit to increasing HbF with 5-azacytidine in SCD
  - Hydroxyurea was believed to be a safer alternative to 5-azacytidine for long-term use
- **1995**: Phase 3 study of HU in SCD published
  - Investigators found an annualized median difference of 2 crises between HU and placebo
- **1998**: HU was approved by the FDA for use in SCD

Blood. 1987;69(1):

Hydroxyurea Mechanism of Action

- Increases HbF
  - Helps to prevent polymerization of HbS
  - Leads to increased Hgb levels
- Decreases WBCs
  - Elevated WBCs associated with increased morbidity and mortality in SCD
  - Decreasing neutrophils and reticulocytes may decrease vascular adhesion
- Releases Nitric Oxide
  - Leads to vasodilation

Ware et al. Blood. 2010; 115:5300-5311

Hydroxyurea Summary

- The gold-standard for disease modifying therapy in SCD
  - Approved for over 20 years with an abundance of evidence
- Numerous benefits in SCD with multiple mechanisms of action
- Side effects can be burdensome but can be managed in most cases if monitored regularly

Oral L-Glutamine in Sickle Cell Disease

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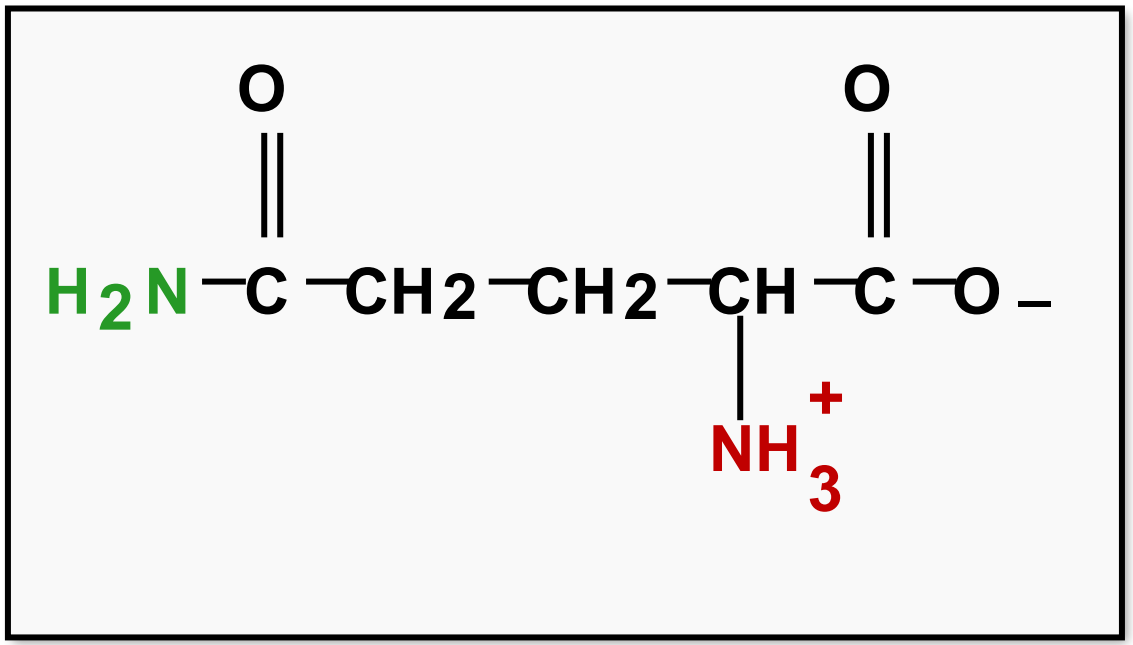
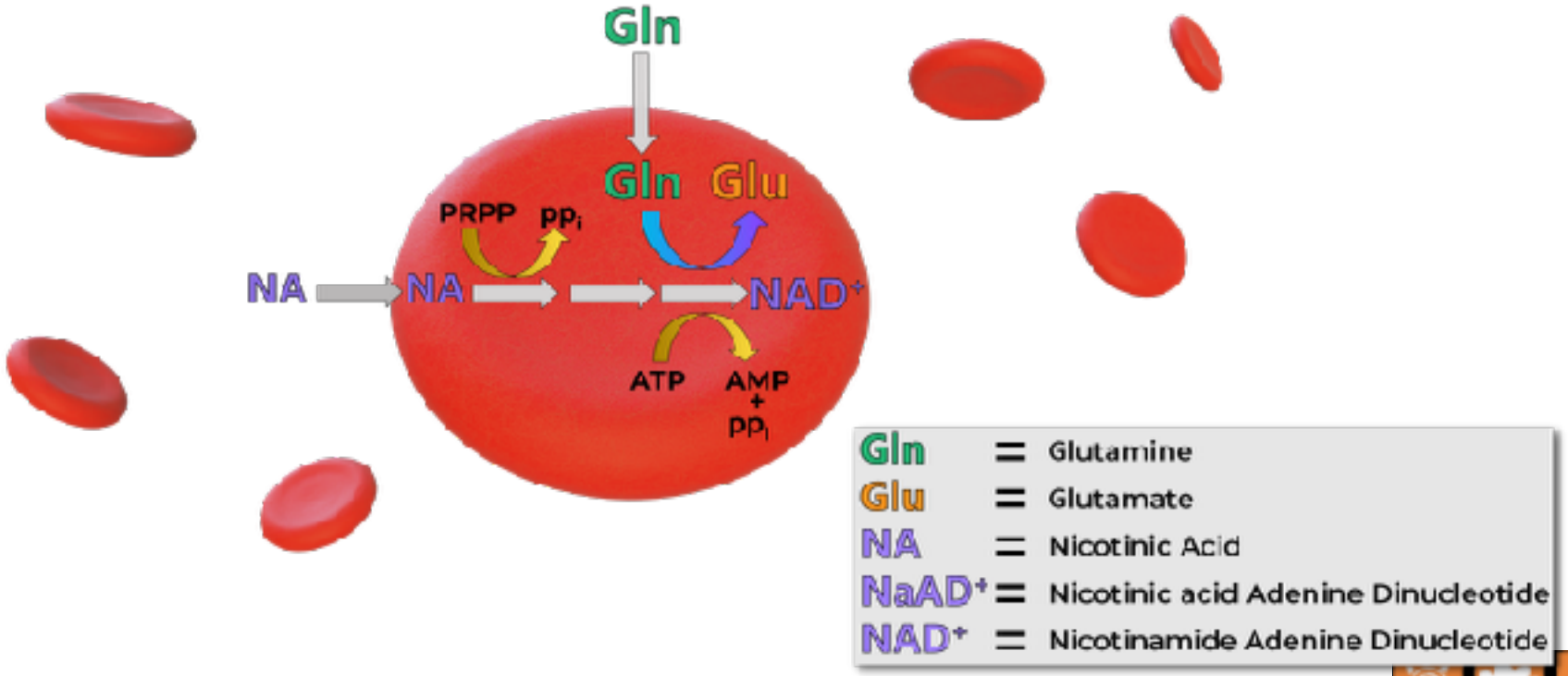
L-Glutamine Structure



L-Glutamine Mechanism of Action

- L-Glutamine donates an amino group in the final step of NAD^+ biosynthesis in red blood cells



J Lab Clin Med 1997;

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Nicotinamide Adenine Dinucleotide (NAD^+)

- NAD^+ is involved in oxidation-reduction reactions in red blood cells

Oxidation Reduction (Redox) potential

$$\frac{\text{NADH}}{\text{NAD}^+ + \text{NADH}} \qquad \frac{\text{Reduced}}{\text{Total}}$$

Oxidative Stress and Sickle Cell Disease

Is the NAD^+ redox system overwhelmed in sickle cell disease?

- The NAD^+ Redox Potential is decreased in sickle cell disease [1,2]
- Treatment with L-glutamine normalized NAD^+ Redox Potential [3]

(1) Zerez, et al, Blood, Vol 71, No 2 (February), 1988: pp 512-5 15
(2) Al-Ali, et al, Acta Haematologica 2002;108:19-22

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Phase 3 Study Design and Outcome

INCLUSION CRITERIA:

HbSS

Sickle β^0-thalassemia

HU use permitted

≥ 5 years old

≥ 2 SCC prior 12 mos

PRIMARY ENDPOINT:

Number of SCCs in the 48-week treatment period

PRIMARY ENDPOINT RESULT:

3 vs 4 median SCC

CLINICAL BENEFITS
(Compared to Placebo):

25% lower SCCs

63% fewer ACS occurrences

33% fewer hospitalizations

41% fewer cumulative days in hospital

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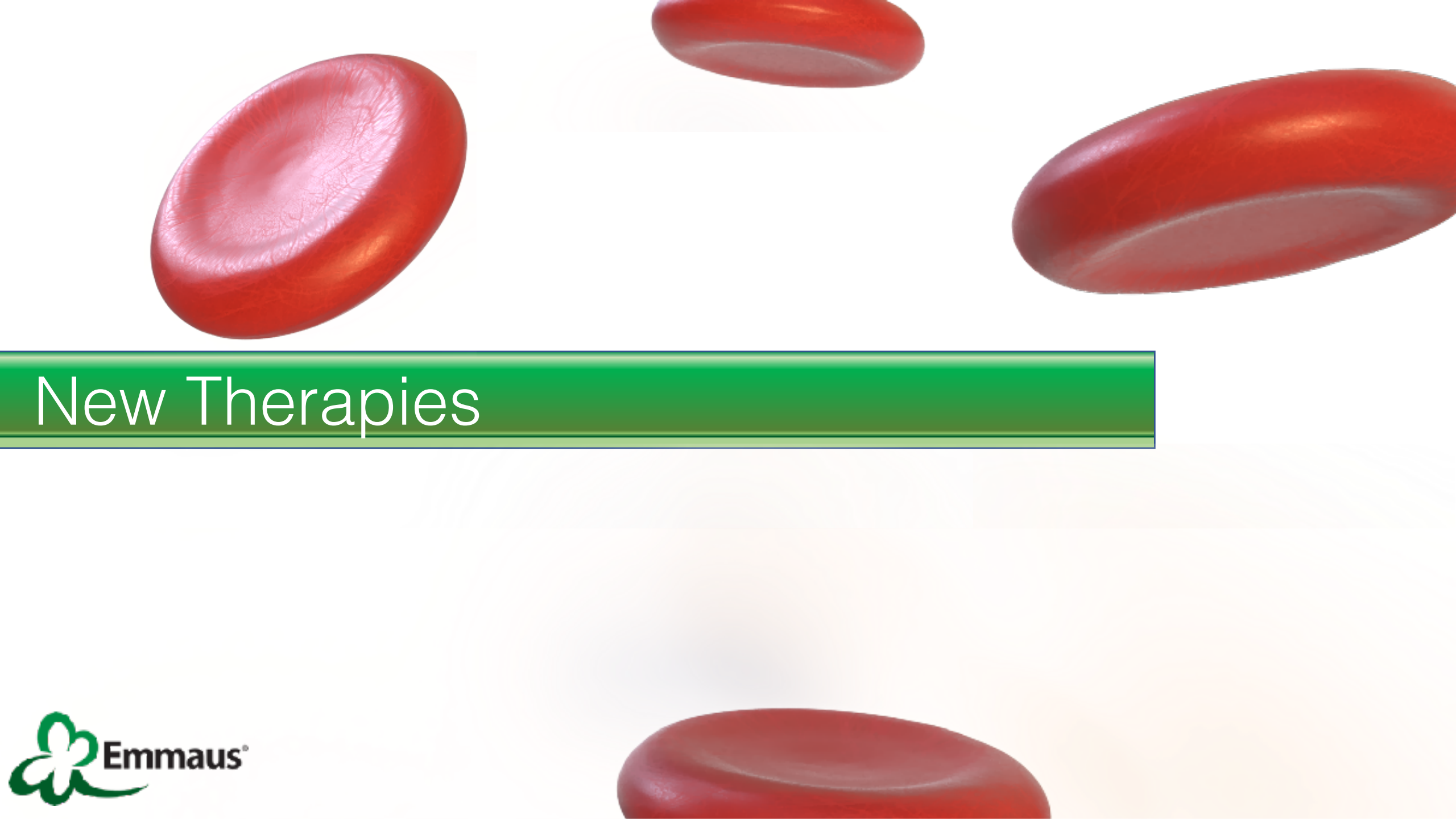

New Therapies

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Therapies in Clinical Development

: **Voxelotor** (GBT-440)

- MoA – Increases hemoglobin affinity for oxygen (Polymerization Inhibitor)
  - Once daily oral therapy
- Phase 3 **HOPE** study completed 2019
  - Mean change in Hgb from baseline of 1.1 mg/dL in 1500mg dose vs -0.1 mg/dL in placebo
- Priority review with a Prescription Drug Users Fee Act (PDUFA) date: **February 26, 2020**

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Therapies in Clinical Development

NOVARTIS : **Crizanlizumab** (SEG101)

- MoA – P-Selectin Inhibitor
- Monoclonal antibody given as IV infusions every 4 weeks
- Phase 2 **SUSTAIN** Study completed in 2017 – Priority Review
  - 5 mg/kg dose reduced median annual VOCs leading to hospitalization by 45%
- Phase 3 **STAND** Study (A2301) investigating the efficacy and safety of crizanlizumab in patients aged 12 and above

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Therapies in Clinical Development

cyclerion : **Olinciguat** (IW-1701)

- MoA – Guanylate Cyclase Agonist, increasing cGMP for vasodilation
  - Once Daily Oral Tablet
- Currently in Phase 2 Development

imara : **IMR-687**

- MoA – Inhibition of phosphodiesterase-9 (PDE9i) increasing cGMP for vasodilation
  - Once daily oral tablet
- Currently in Phase 2 Development

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Therapies in Clinical Development

bluebirdbio : **LentiGlobin gene therapy**

- MoA – Adds functional copies of a modified form of beta-hemoglobin gene into the patient's own stem cells

- Patients may then make their own functional RBCs
- Currently in Phase 1/2 Development

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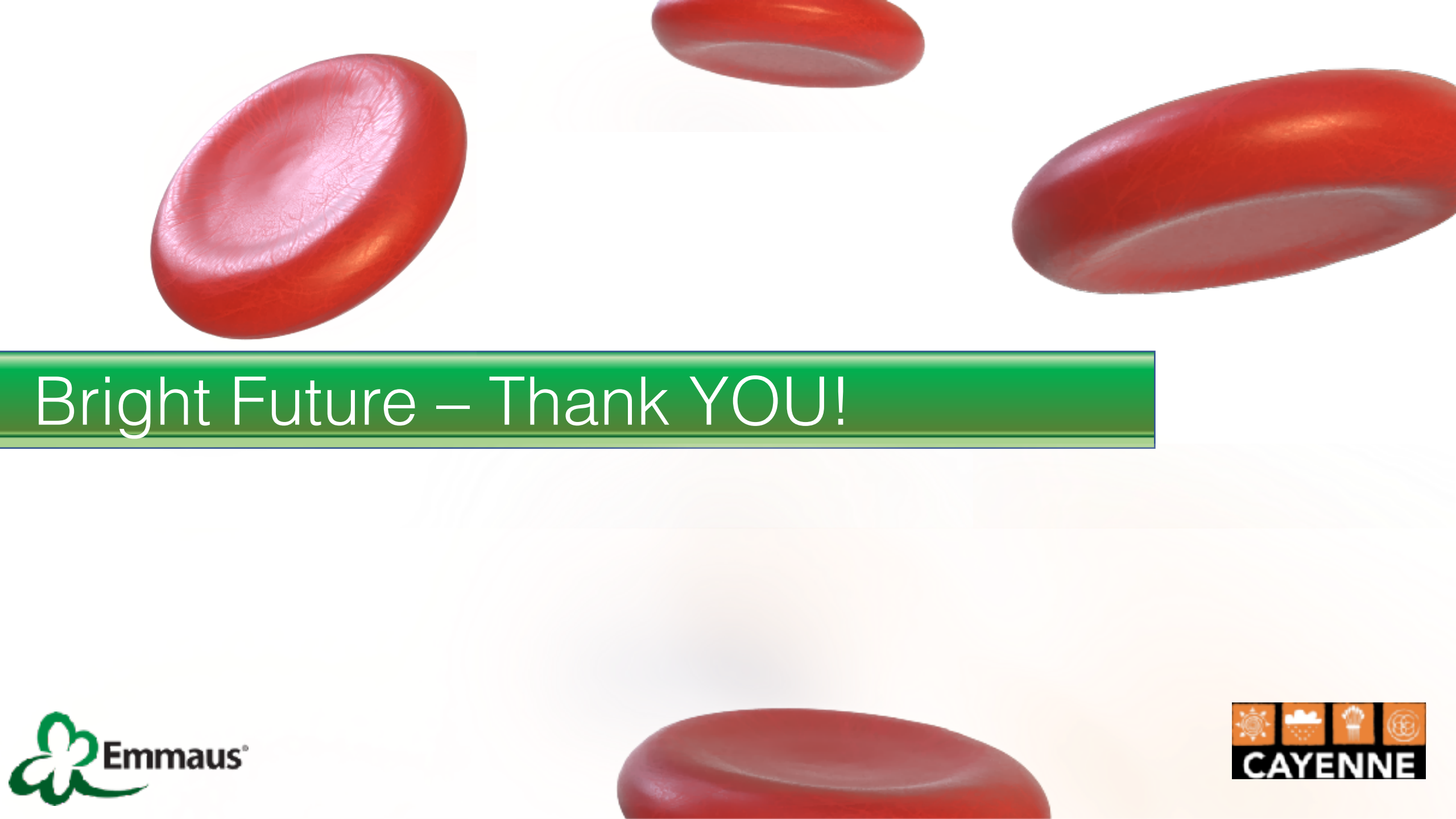

Bright Future – Thank YOU!

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