DETERMINING OPTIMAL ENDPOINTS FOR GENE THERAPY IN SICKLE CELL DISEASE

Julie Kanter, MD
Director, Adult Sickle Cell Program
Co-Director Lifespan Sickle Cell Research Center
Associate Professor

Hematology/Oncology

University of Alabama at Birmingham

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

DISCLOSURE/CONFLICT OF INTEREST

- **Consultancy:** Guide point Global, GLG, Imara, Novartis, Editas
- **Honorarium:** Terumo, Bluebird Bio, Novartis, Global Blood Therapeutics
- **Honorarium:** Medscape, Rockpointe, Peervoice, Axis
- **Research Funding: NHLBI, HRSA**
  - **1R01HL133896-01A1, U01HL133990-01**
- **Steering Committee:** Novartis, Astrazeneca
- **Membership on a Scientific Advisory Committee:** Astrazeneca, BPL, Editas, Novartis, Modus, Sangamo

Discussion of off-label drug use: N/A

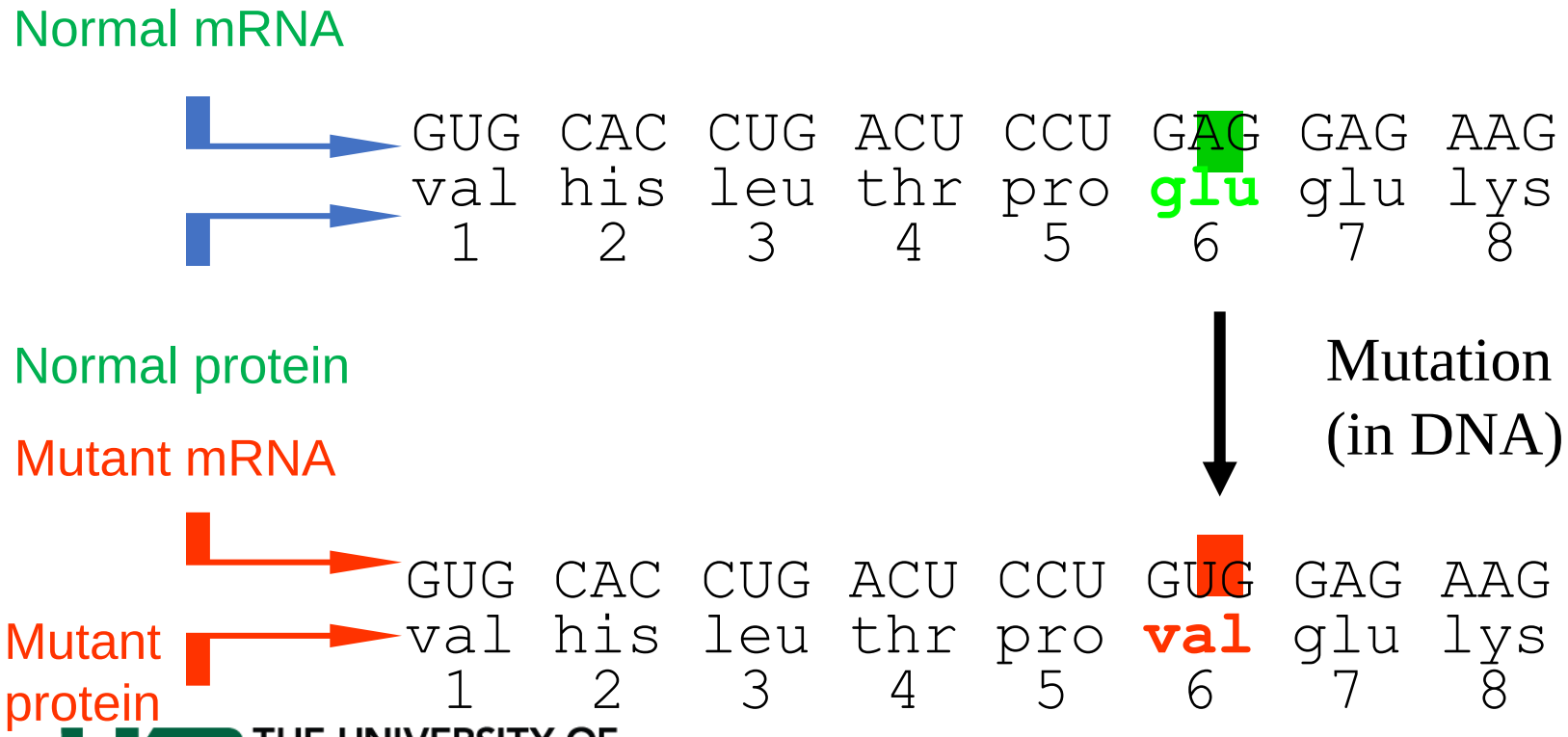
OUTLINE:

- Sickle Cell Disease: Definitions and Pathophysiology
- Current Therapies in Sickle Cell Disease
- Challenges and Barriers
- Defining the endpoints for gene therapy in treating sickle cell disease

SICKLE CELL DISEASE

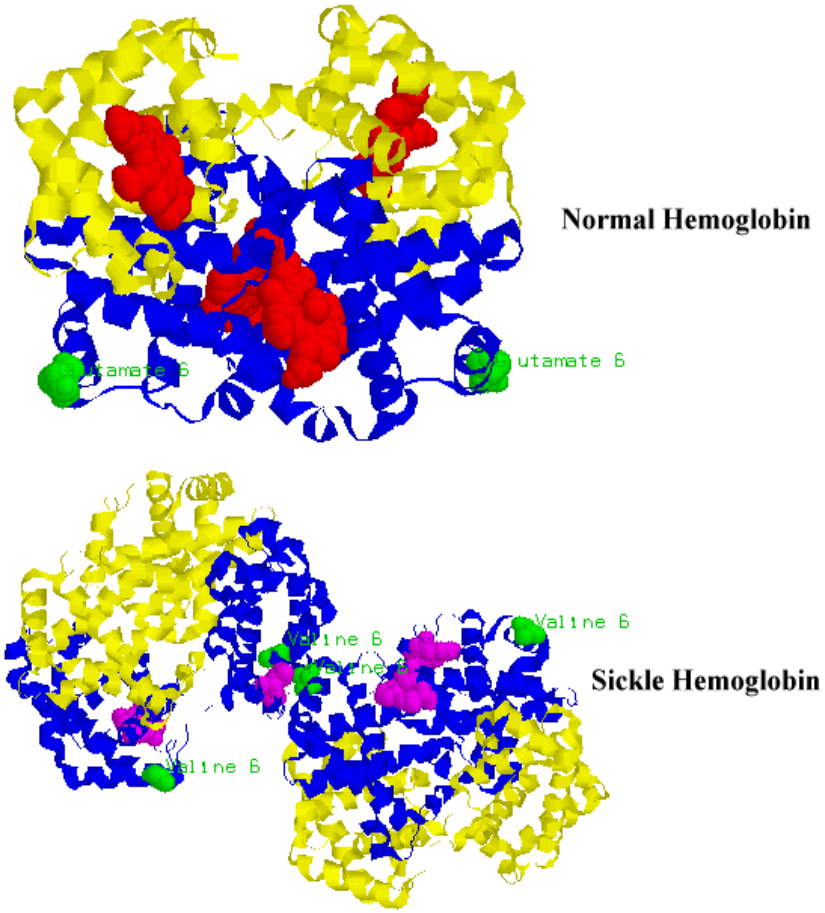
PATHOGENESIS: SCD

Glutamate (glu), a negatively charged amino acid, is replaced by valine (val), which has no charge.



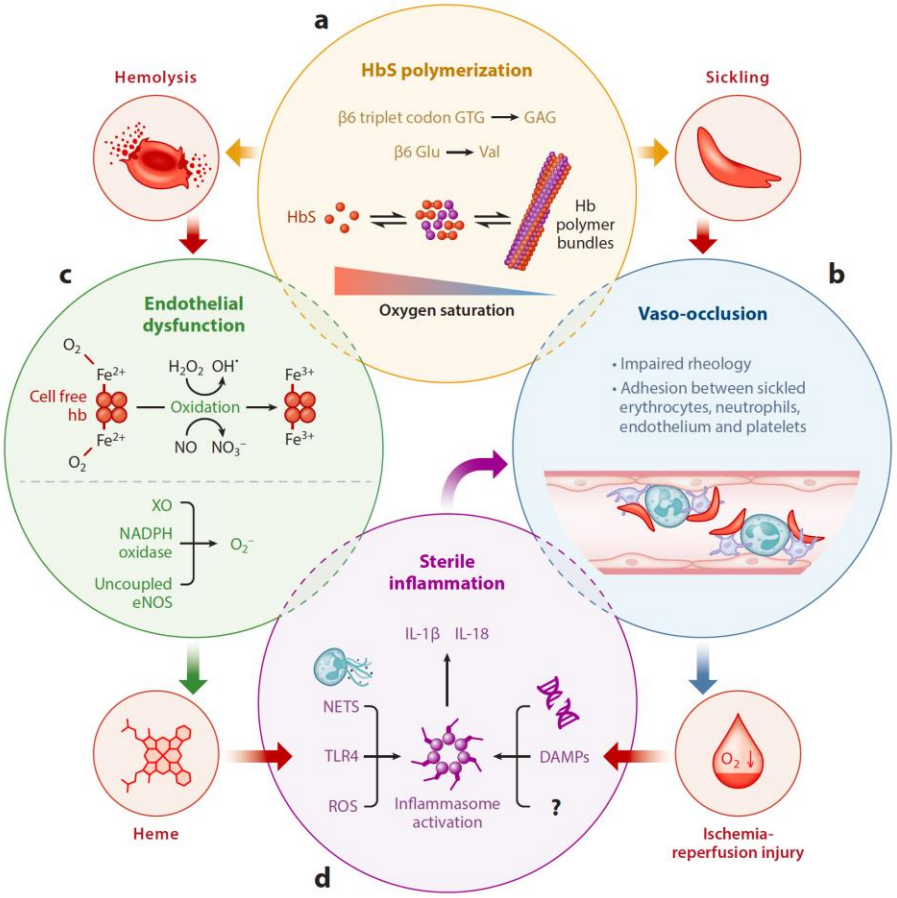
PATHOGENESIS: SCD

- The result of a single point mutation is a significant change in hemoglobin structure which leads to an entire disease



Note: The Sickle hemoglobin image is drawn at 50% of the size of the Normal hemoglobin

MOLECULAR PATHOPHYSIOLOGY OF SCD



Sundd et al. *Annu Rev Pathol Mech Dis*. 2019;14:261-290.

PATHOPHYSIOLOGY OVERVIEW

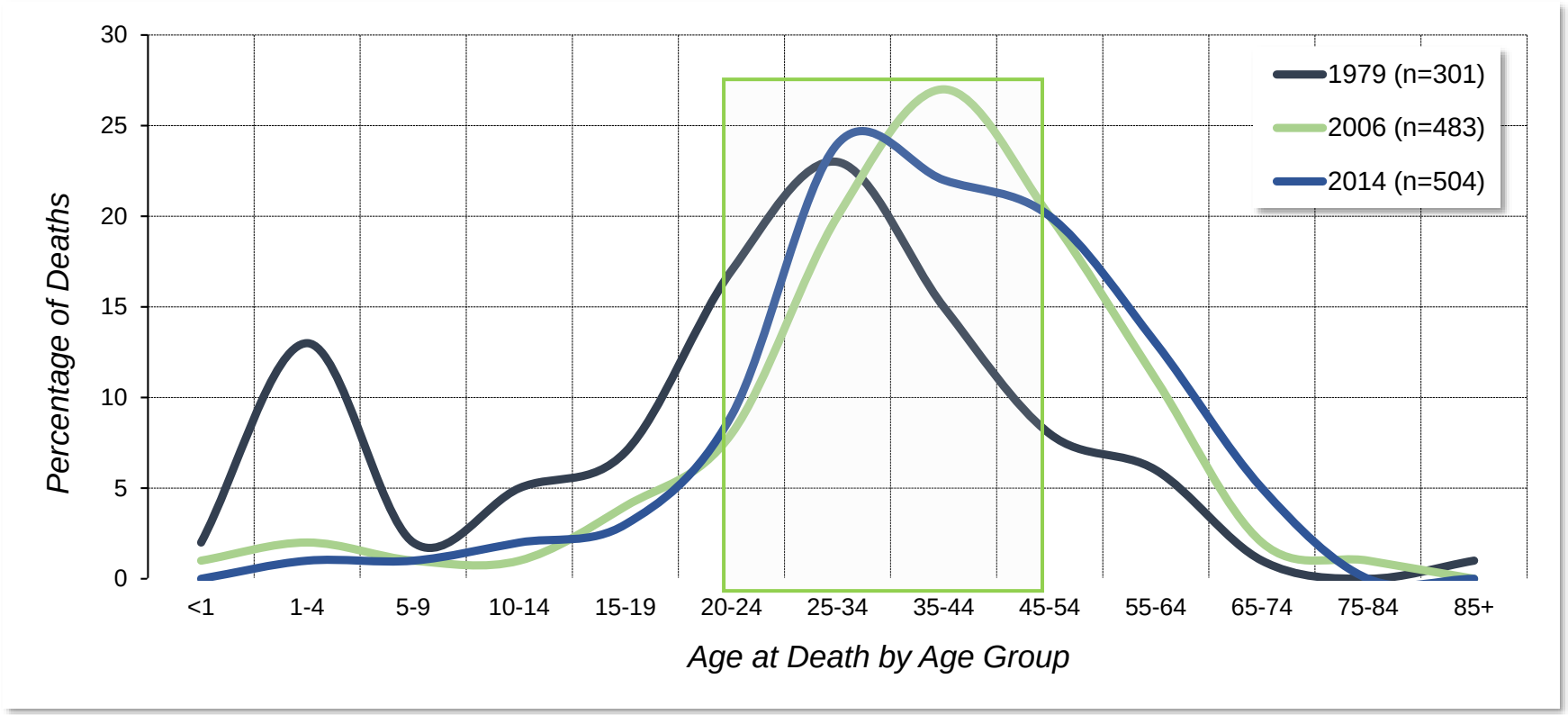
- A single gene mutation is responsible for hemoglobin S
- There is significant phenotypic diversity not accounted for by hemoglobin genotypes
- Other genetic polymorphisms and differences in gene product function contribute to the complexity of phenotypic expression
- *Although clinical patterns exist based on genotype, each individual with SCD has a unique clinical course*

PAIN: THE HALLMARK FEATURE OF SCD

- Hallmark of disease
- Primary reason people seek care
- Ischemic
- Secondary to vaso-occlusion
- Ubiquitous
- Present throughout life

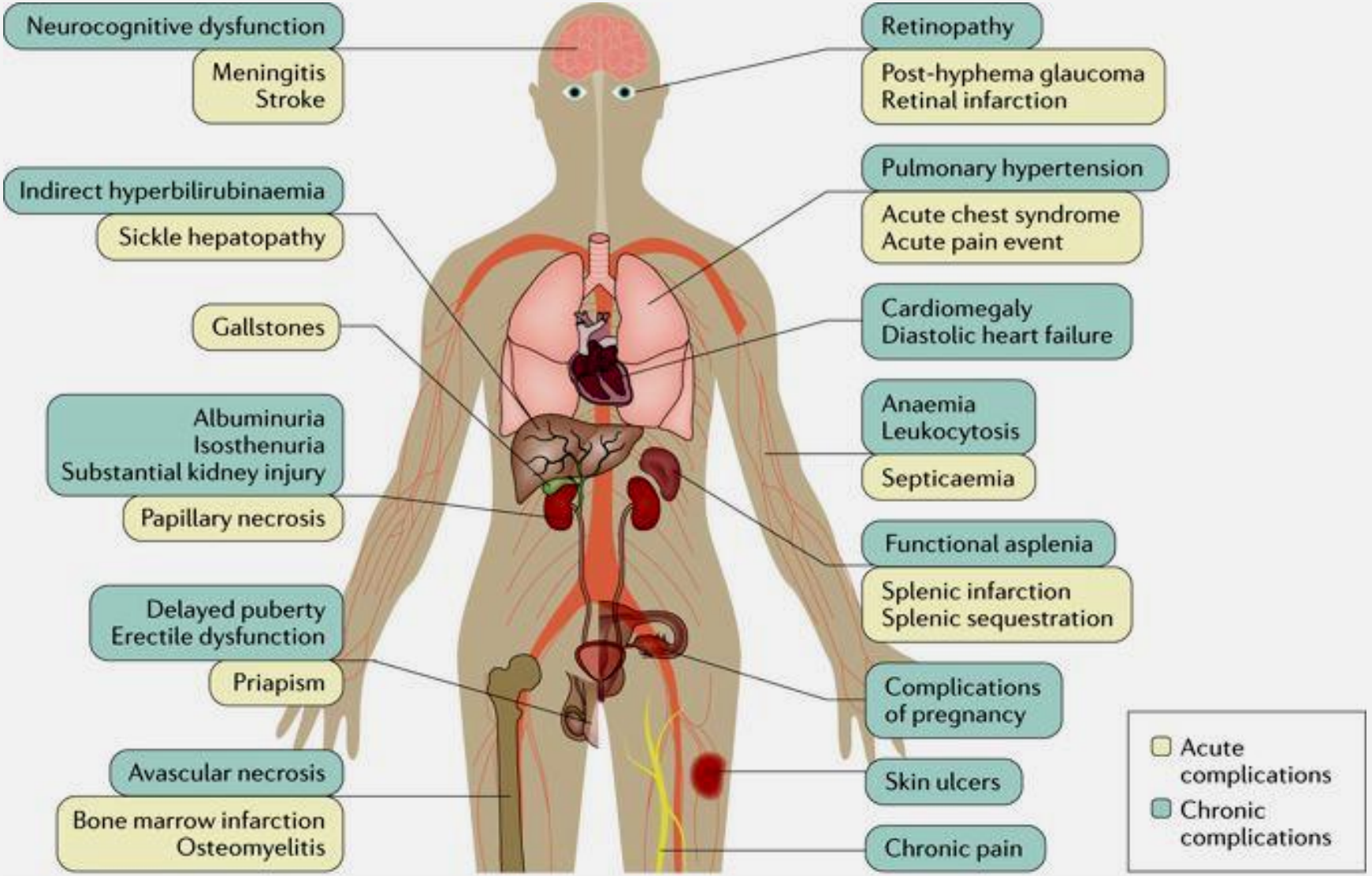
SCD AND MORTALITY IN THE US

- Childhood survival 96%-98% for all genotypes
- In 2014, most deaths (66%) occurred at ages 25-54 years
- More recent surveillance data from Georgia and California showed mean age at death was 43 years for women, 41 years for men



Quinn CT et al. *Blood.* 2010;115:3447.
Paulukonis ST et al. *Public Health Reports.* 2016;131:367-375.

COMPLICATIONS IN SCD



Kato GJ et al. *Nature Reviews Disease Primers.* V4: 18010 (2018).
https://media.nature.com/m685/nature-assets/nrdp/2018/nrdp201810/images_hires/nrdp201810-f5.jpg.

CURRENT THERAPIES FOR SCD

DISEASE MODIFYING OPTIONS

- Hydroxyurea
  - First approved therapy
  - Modifies the course of SCD
  - Decreases the frequency of pain crisis for sickle cell anemia
  - Not universally accepted
- L-Glutamine
  - Anti-inflammatory
- Blood Transfusions
  - Improve stroke risk
  - Decrease recurrent acute chest syndrome in several studies
  - Multiple unwanted complications
- Palliative management
  - Pain management, opioids

STEM CELL TRANSPLANT FOR SCD

STEM CELL TRANSPLANT

- Bone Marrow (STEM CELL) Transplant is the only cure for sickle cell disease at this time
- Results of many studies show that transplants from matched related donors offer approximately an 85% chance of cure
- Risk-vs-benefit considerations for BMT in adult patients with SCD are more complex than those in pediatric patients due to increased organ damage
- Early studies are optimistic for improved outcomes and improved quality of life

Aslam HM et al. *Bone Marrow Transplant.* 2018. [Epub ahead of print].

CHALLENGES IN BONE MARROW TRANSPLANT FOR EVERYONE WITH SCD

- Not everyone has a “great” match
- There is still a risk of graft-versus-host disease
- Immune suppressive medication can be long-term
- Risk of late-rejection

GENE THERAPY FOR SCD: CIRCUMVENTS THE NEED FOR FINDING MATCHED DONORS

TWO MAIN TYPES OF GENE THERAPY

- **Gene Addition Therapy**
  - ADD A NEW GENE
  - Don’t remove or change any of the existing genes
- **Gene Editing**
  - Edit a gene that is in the body
  - Sometimes-also add a new gene (HDR)

DEFINING ENDPOINTS IN SCD

ENDPOINTS IN PREVIOUS SCD THERAPEUTIC TRIAL

- Vaso-occlusive crisis/Pain severity

PROBLEM: Pain is subjective, has multiple causes, and can be difficult to differentiate nociceptive/ischemic from chronic pain

- Biologic endpoints
  - Transcranial doppler velocity
  - Proteinuria: marker of renal dysfunction
  - TR jet velocity
  - Pulmonary hypertension
  - DLCO
- Predictors of disease severity =/= disease modifiers
  - Fetal hemoglobin
  - Total hemoglobin
  - White blood cell count

ENDPOINTS FOR GENE THERAPY FOR SCD

GENE THERAPY ENDPOINTS

- Outcomes of stem cell transplant in SCD demonstrate that sufficient engraftment of donor stem cells leads to curative therapy
  - Resolution of vaso-occlusive pain crisis
  - Decreased/absent risk of stroke
  - Stabilization of end organ dysfunction
- Outcomes achieved through a sufficient myeloid engraftment to yield stable hemoglobin production
- Mixed chimerism is acceptable as long as the resulting normal hemoglobin A >>HbS

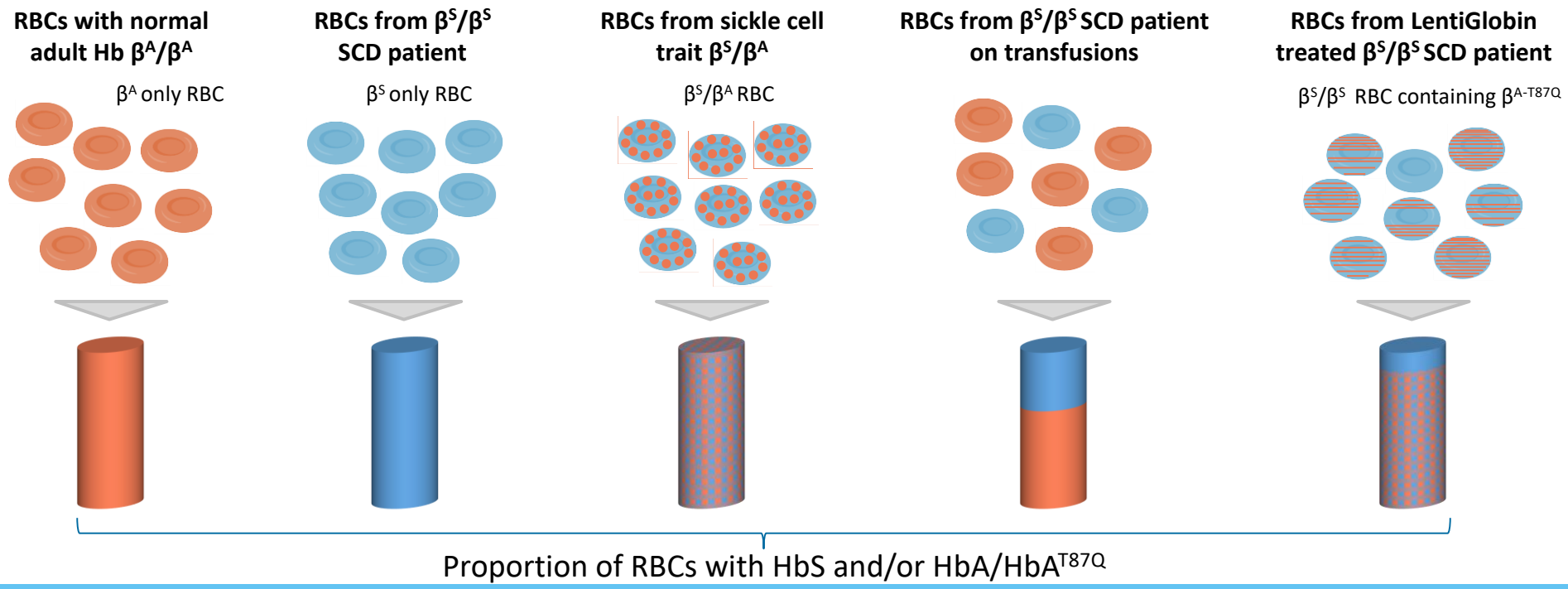
HOW DO WE MEASURE GENE THERAPY

- **Vector copy number (VCN) per cell:** Average number of gene therapy letters delivered to a sample of blood stem cells
- **Percentage of stem cells transduced with the vector:** Percentage of blood stems cells which have received a gene therapy letter
- **Cell dose** Amount of patient's own blood stem cells returned to the patient after gene therapy letter was delivered

HOW ELSE TO MEASURE EFFECT?

Exploratory assay allows for single-cell resolution of Hb expression to assess pancellularity of HbA^{T87Q}

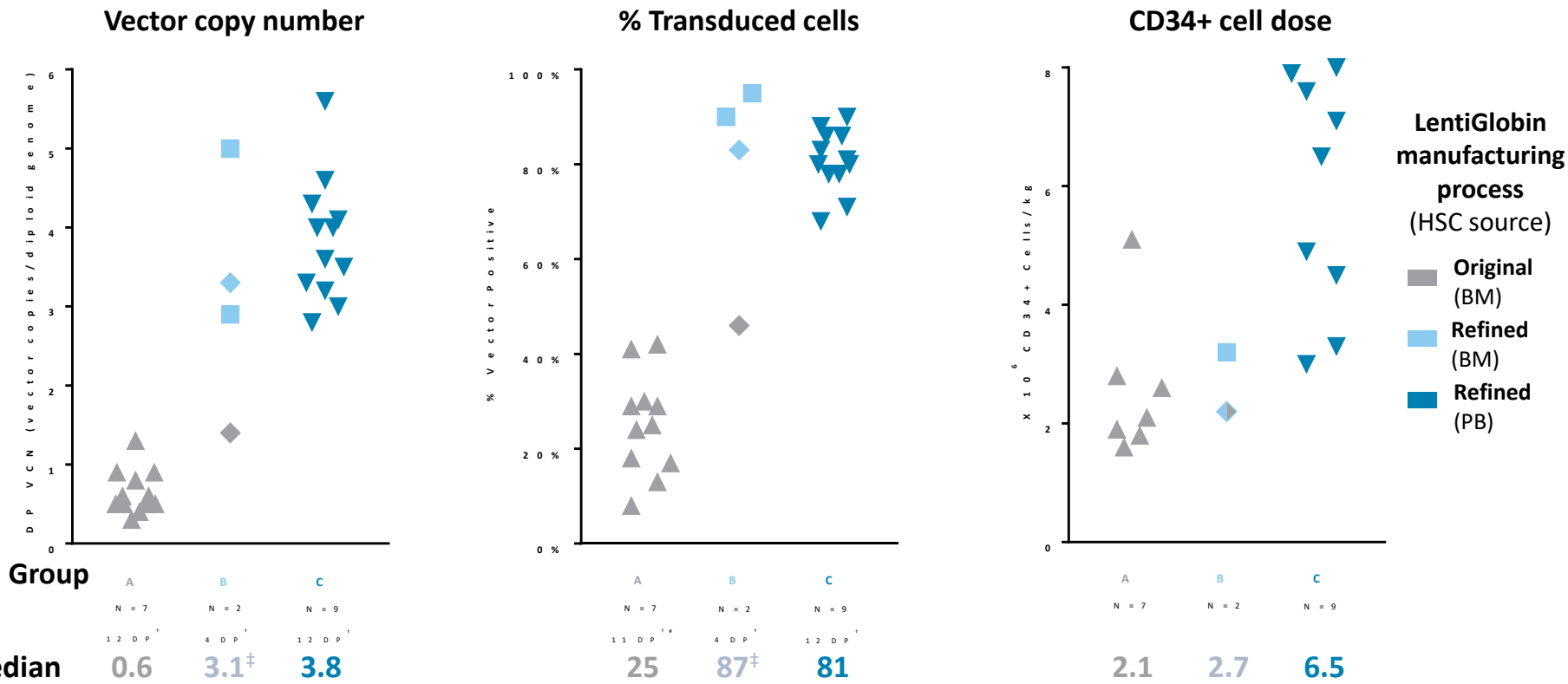
- Exploratory assay: Single red blood cell western blot with anti-β^S or anti-$\beta^A/\beta^{A\text{-}T87Q}$ antibodies



RBCs, red blood cells

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

REFINEMENTS TO MANUFACTURING AND CELL HARVEST IMPROVED DRUG PRODUCT CHARACTERISTICS

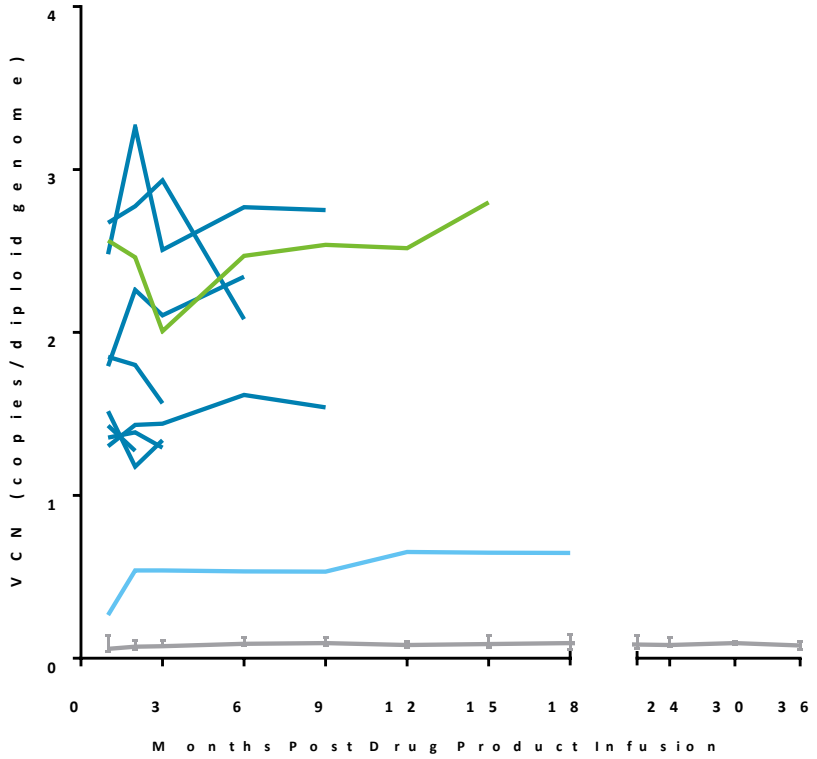


*Group A shown as median (min – max); †Number of DP exceeds number of patients since some patients were harvested or mobilized more than once; ‡1 Group B DP lot was made using original manufacturing process, while the other 3 DP lots were using refined manufacturing process

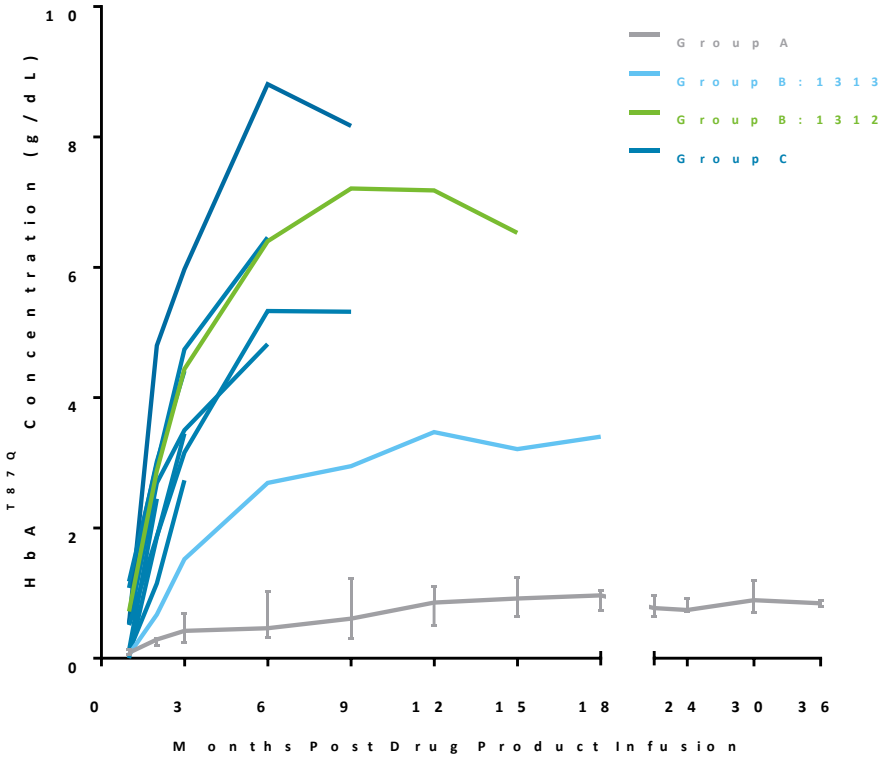
BM, bone marrow; DP, drug product; HSC, hematopoietic stem cell; PB, peripheral blood; VCN, vector copy number

PERIPHERAL BLOOD VCN AND HBA^{T87Q} OVER TIME

Peripheral blood VCN



HbA^{T87Q} levels

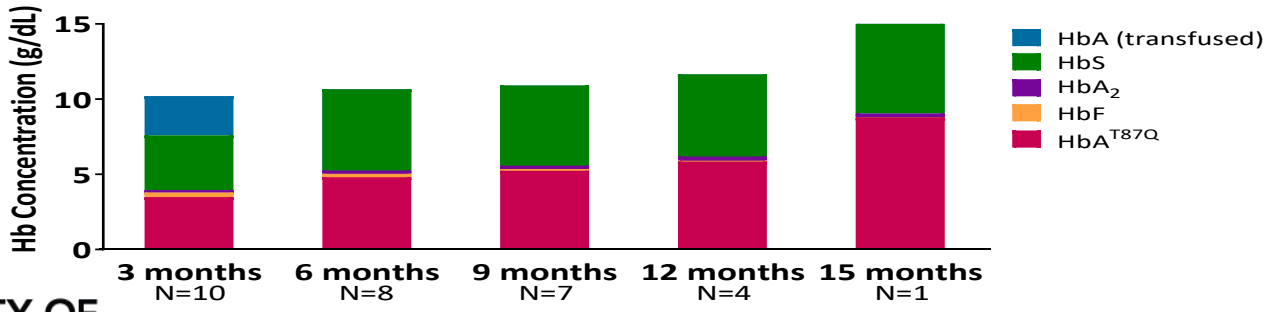


Hb, hemoglobin; VCN, vector copy number

Data as of September 14, 2018

HOW ELSE TO MEASURE EFFECT?

- The new or edited gene has to make the “healthy” hemoglobin (protein)
- We have to know HOW MUCH hemoglobin the new gene is making?
- How much hemoglobin is stable?
- How is the new hemoglobin packaged?



GENE THERAPY ENDPOINTS

- We can translate stem cell transplant endpoints to gene therapy
- Sufficient VCN and transduction efficiency (or editing efficiency) to result in normal hemoglobin A>>HbS
- Pancellular expression is necessary
- Resolution (or near resolution) of hemolysis
- Rheologic properties equal to those of individuals with HbAS (sickle cell trait)
- Outcomes in studies with production of HbF are less defined due to the lack of a similar biologic model
- Long term:
  - Eventual resolution of vaso-occlusive pain
  - Decrease in stroke risk
  - Stabilization of organ dysfunction

SAFETY CONCERNS IN GENE THERAPY

- Insertional oncogenesis
- Random insertion
- Lack of sustainable gene to protein production

- Off target effects
- Difficulties and expense of identifying those off target effects
- Novel mutations

- Chemotherapy and secondary complications
- Lack of engraftment

Stopping points in all therapies must be defined

When is poor protein expression grounds for stopping ongoing investigation

WHAT IS THE FUTURE OF GENE THERAPY

- We have to define success
- We have to ensure successful therapy is approved by the FDA
- We have to monitor LONG TERM to see if these therapies give LONG TERM DISEASE MANAGEMENT/CURE
- We have to work to figure out how to make this type of therapy available, affordable and universal?