University of Pittsburgh

UPMC LIFE CHANGING MEDICINE

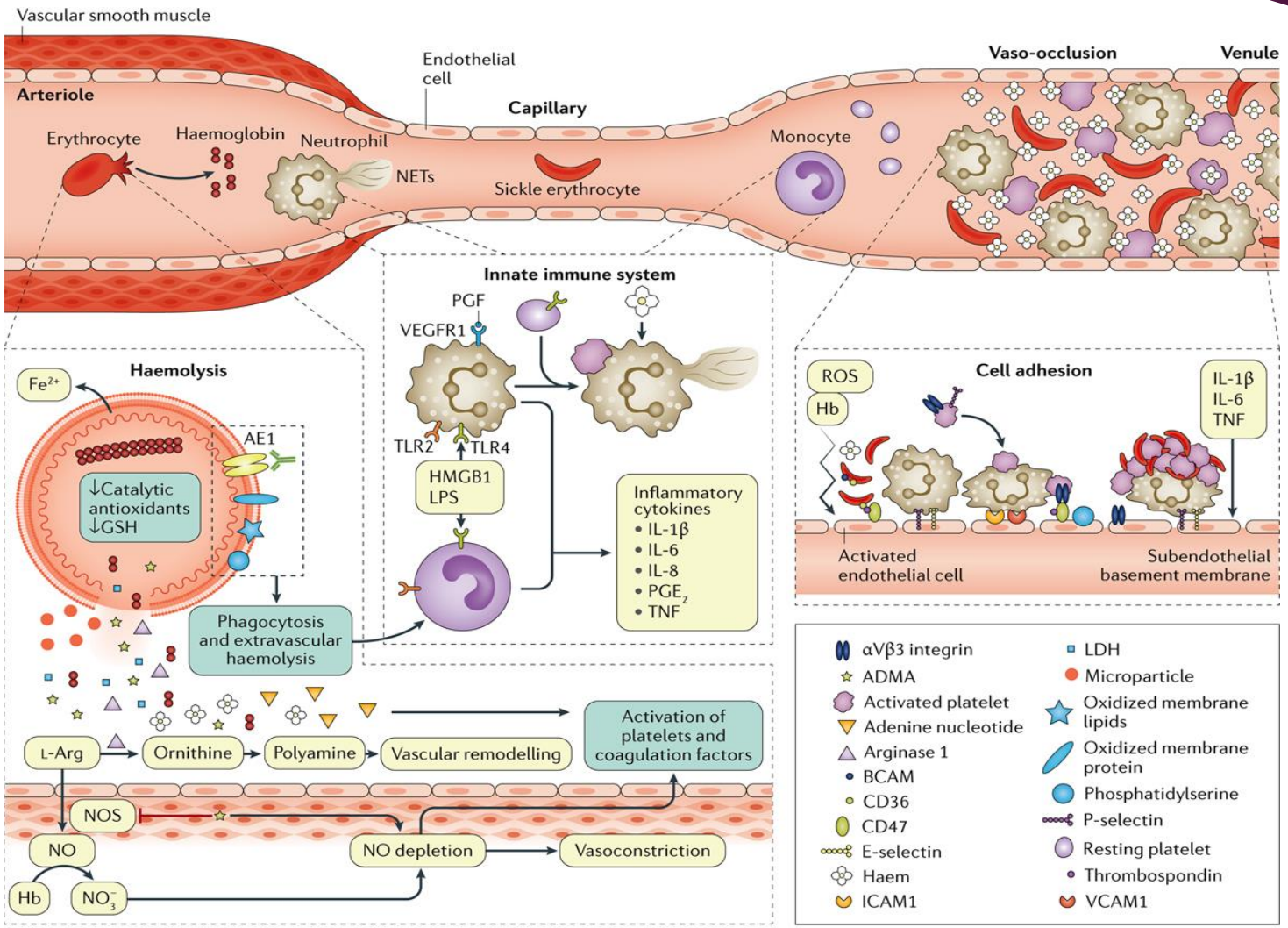
Taking Part in Clinical Trials Speeds Up the Cure for Sickle Cell Disease

Laura M. De Castro, MD MHSc
Associate Professor of Medicine
UPMC Adult Sickle Cell Program
June 19, 2018

How Many of you have Participated in a Clinical Research in **Sickle Cell Disease?**

UPMC LIFE CHANGING MEDICINE

Figure 4 Mechanisms in sickle cell disease



Kato, G. J. et al. (2018) Sickle cell disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2018.10

Research

- Basic Science
- Clinical Trials
- Translational
- From bench to bed

Clinical Research

- Involves research using human volunteers –participants-
- Intended to:
  - Add to medical knowledge.
  - Answer specific health questions.

Patient-oriented research includes:

- Mechanisms of human disease,
- Treatment / interventions,
- Clinical trials, or
- New technologies development.

Epidemiologic and behavioral studies.

Outcomes research and health services research

Clinical Trials: Experiments done in clinical research

- Final steps in a long process that begins with research in a lab
- Design to test new ways to:
  - Treat diseases
    - Drugs or vaccines
    - Ways to do surgery or give radiation therapy
    - Combinations of treatments
  - Find and diagnose diseases
  - Prevent diseases
  - Manage symptoms of diseases and side effects from their treatment
  - Phase: I II III
    - Very early -phase 0- and later -phase IV-.

http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials/team

Phase I Clinical Trials

Purpose:

- Find a **safe dose**
- Find **how the new treatment should be given**
- See how the **drug affects the human body**

Outcome: Safety and tol

Sites: Single

Participants: 15–80

Phase II Clinical Trials

Purpose:

- Determine if the **new treatment** has an **effect on a disease**
- See **how the drug affects** the **human bo**

Outcome: Efficacy

Sites: Single or Multiple

Participants: Less than 100 to few 100s

Phase III Clinical Trials

Purpose:

- **Compare the new drug** -or new use of a drug- **with** the **standard treatment**

Outcome: Effectiveness and long term safety

Sites: Many (> 10). Occasionally multiple countries

Participants: From a 100s to 1,000s

Potential Therapies for SCD

Table 2. Novel agents in clinical trials

Category*	Therapeutic agent	Mechanism of action	Reference
HbF augmentation	Vorinostat, panobinostat	HDAC inhibition	43
	Sodium dimethylbutyrate	HDAC inhibition	31
	Decitabine	DNA demethylation	33
	Pomalidomide	Histone acetylation of γ-globin promoter	30
Adhesion	GMI-1070	Pan-selectin inhibitor	21
	IVIG	Inhibits neutrophil activation and RBC capture	22, 23, 25
	SelG1	Humanized anti-P-selectin monoclonal antibody	Selexys
	Heparin (tinzaparin)	Inhibits P-selectin	37
	Propranolol	Inhibits RBC adhesion to the endothelium	7
Inflammation	Regadenoson	A2AR agonist, blocks iNKT activation	39
	Statins	Anti-inflammatory	44
	Zileuton	5-lipoxygenase inhibitor, used in asthma	45
	Fructose-1,6-diphosphate (FDP)	Reduces ischemia–induced tissue damage	46
	MP4CO	PEG carboxy-hemoglobin	47
Antiplatelet therapy	Prasugrel	ADP receptor blockade	42
	Eptifibatide	αIIb/β3 antagonist	48
Oxidative injury	Omega-3 fatty acids		40
	Glutamine	Increases NADPH	49
	NAC	Increased glutathione	41
	Alpha-lipoic acid	Inhibits NF-κB, increases glutathione	50
	Acetyl-L-carnitine	Decreases lipid peroxidation	
Antisickling agent	Aes-103	Binds sickle hemoglobin and shifts oxyhemoglobin dissociation curve to the left	51
Viscosity	Poloxamer-188	Non-ionic surfactant, improves microvascular flow	52
Vascular tone	IV magnesium	Vasodilatation	53
NO	L-arginine	Substrate for NO	54

Manwani D et al, Blood 2013; 122 (24) 3892-98

How Many of you is Planning to Participate **SOON**

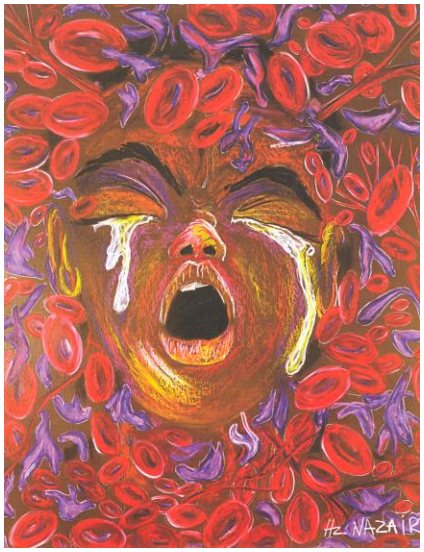
in a

Clinical Research in

Sickle Cell Disease?

UPMC LIFE CHANGING MEDICINE

QUESTIONS ?



“The Best Prescription Is Knowledge.”

C. Everett Koop, MD