The Molecular Origins of SCD and New Opportunities for Therapy

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Management of Sickle Cell Symposium
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UNIVERSITY OF MINNESOTA

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- B.S. Physics, North Carolina State University, 2001
- Ph.D. Physics, University of California – Santa Barbara, 2007
- Postdoctoral training, MIT, 2007-2012.

A major focus of my research is to understand the mechanisms of vaso-occlusion in sickle cell disease (SCD). I have spent much of the last decade studying sickle blood flow under physiologic conditions and trying to understand the biophysical processes that lead to vaso-occlusion in vivo. My laboratory has developed a range of tools and methods to facilitate these studies, including physiologically sized microfluidic channels, tools to regulate blood pressure, methods to finely control blood oxygen, and methods to monitor blood flow in real time. Using these tools, we were the first to show that a precise characterization of SCD patient rheologic phenotype might help explain clinical heterogeneity, a long-standing question in SCD. We have also performed studies to show that sickle blood flow may be impaired in oxygen tensions commonly found in the arterial circulation, which helps explain the conundrum that patients experience complications throughout the body and also establishes a new basis for quantifying the effects of therapy.

1. Wood DK, Soriano A, Mahadevan L, Higgins JM, Bhatia SN. A biophysical indicator of vaso-occlusive risk in sickle cell disease. Sci Transl Med. 2012 Feb 29;4(123):123ra26. PubMed PMID: 22378926; PubMed Central PMCID: PMC3633235.
2. Lu X, Higgins JM, Wood DK. Deoxygenation Reduces Sickle Cell Blood Flow at Arterial Oxygen Tension. Biophys J. 2016;110(12):2751-8.
3. Lu X, Galarneau MM, Higgins JM, Wood DK. A microfluidic platform to study the effects of vascular architecture and oxygen gradients on sickle blood flow. Microcirculation. 2017;24:e12357.
4. Lu X, Chaudhury A, Higgins JM, Wood DK. Oxygen-dependent flow of sickle trait blood as an in vitro therapeutic benchmark for sickle cell disease treatments. *Am J Hematol*. 2018 Jul 23.
5. Castle BT, Odde DJ, Wood DK. Rapid and inefficient kinetics of sickle hemoglobin fiber growth. Sci Adv. 2019 Mar 13;5(3):eaau1086.

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- John Higgins, MGH
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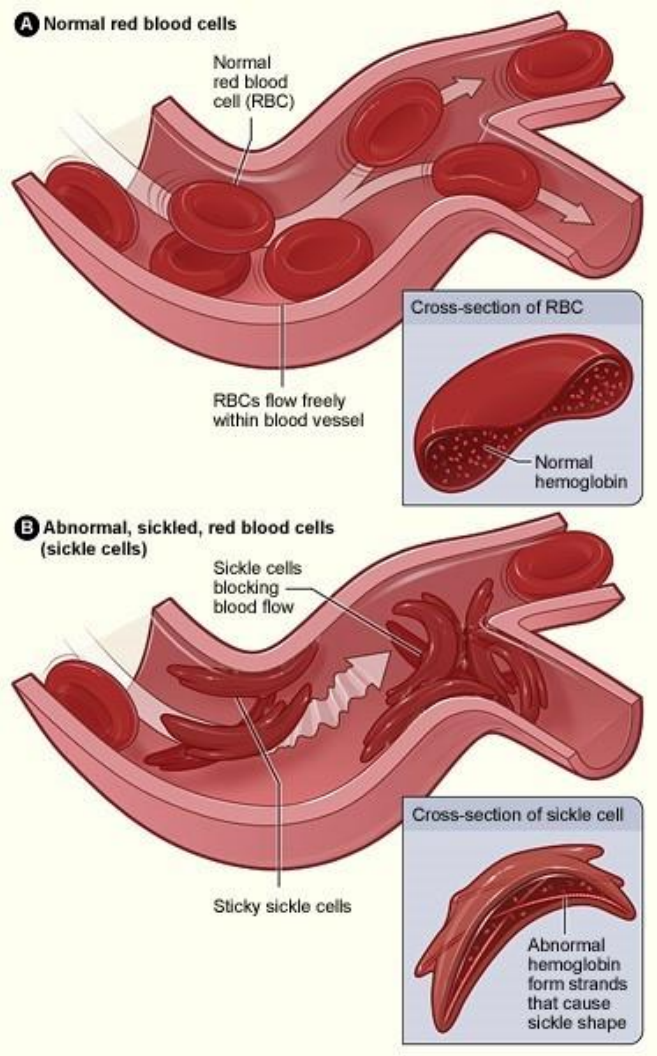
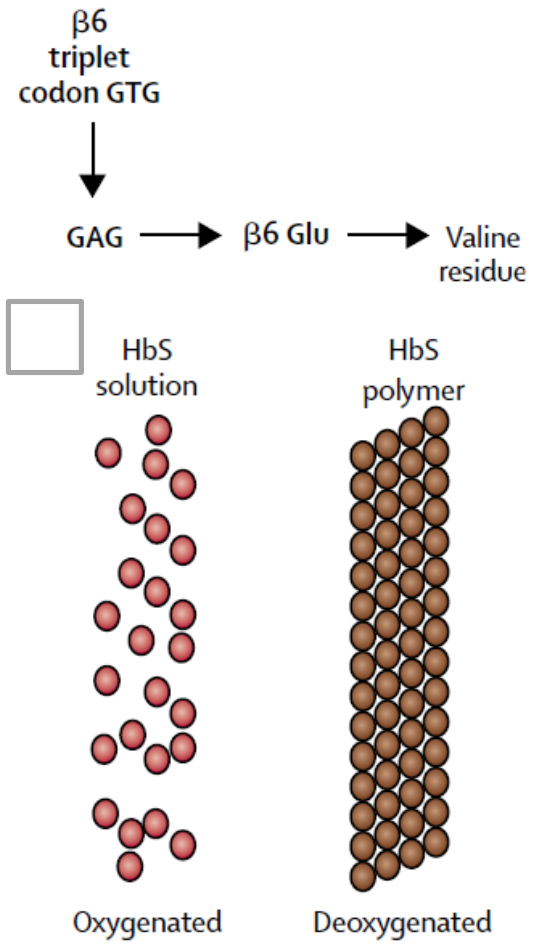
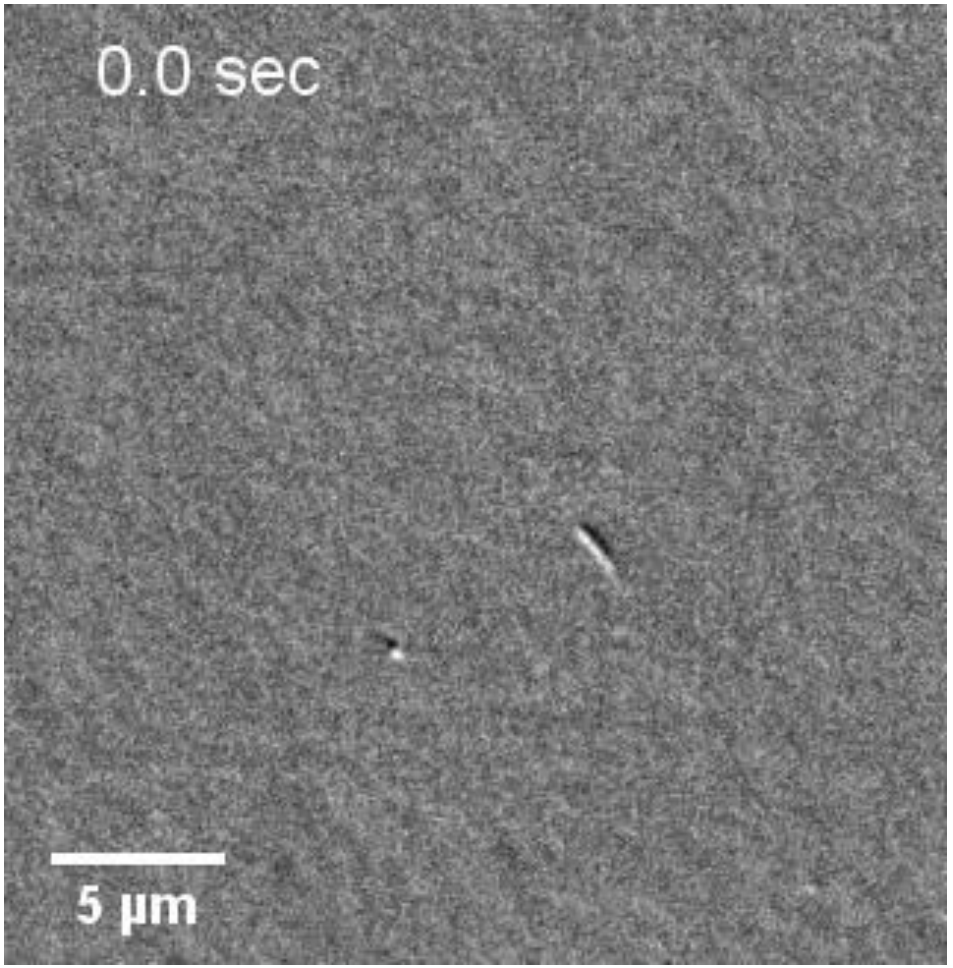
The Origins of SCD

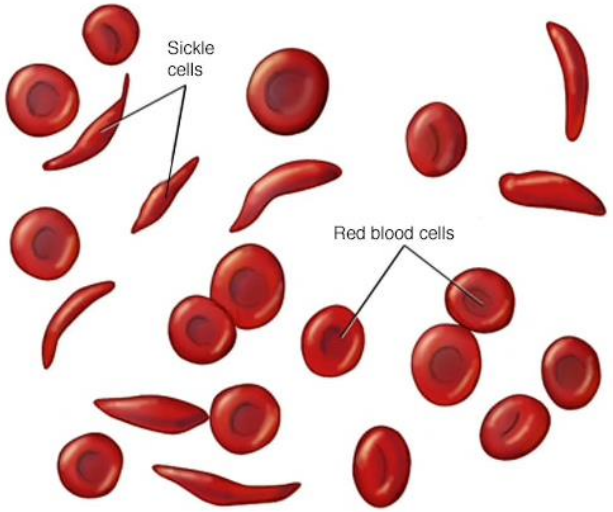


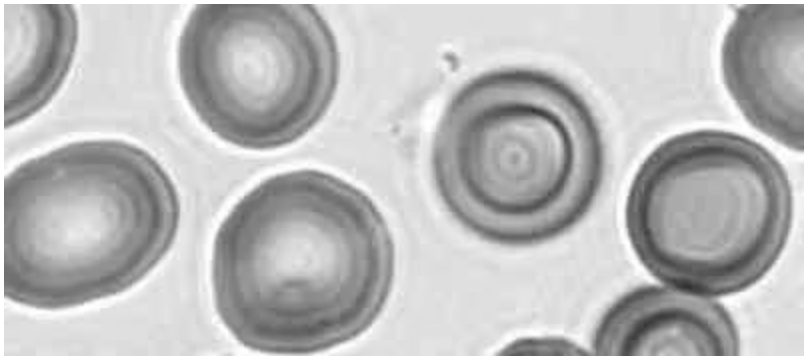
Seeing is Believing: HbS Polymerization



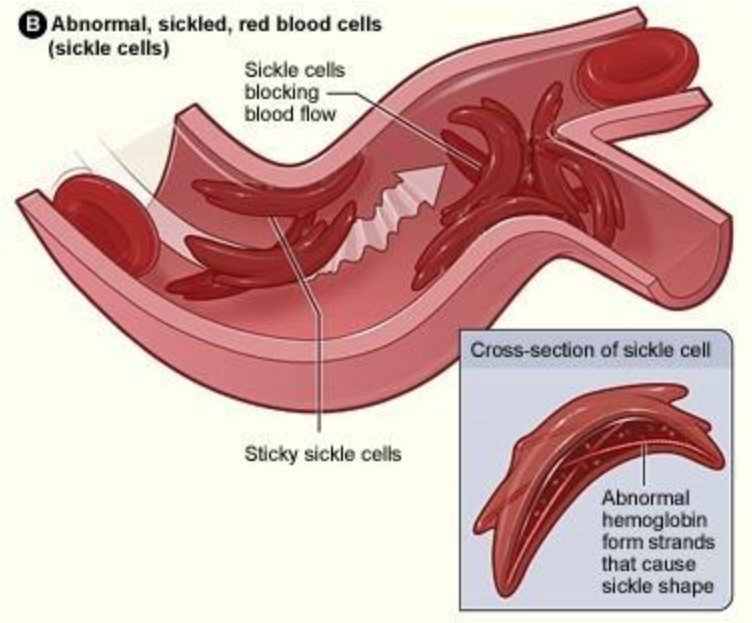


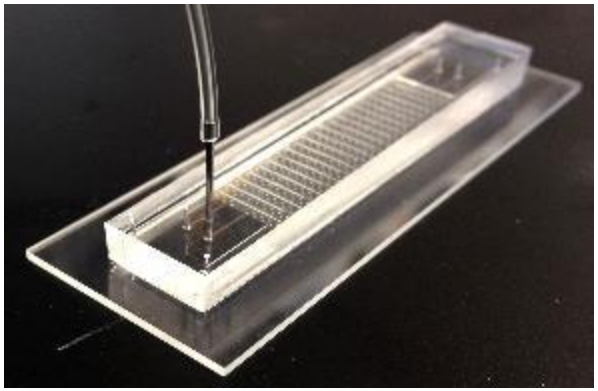
Seeing is Believing: Red Cell Sickling



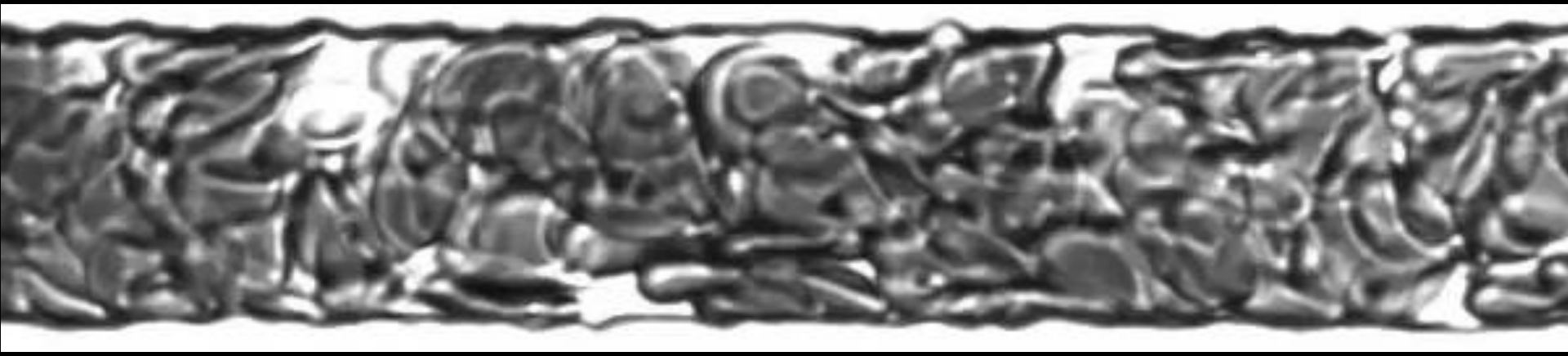


Seeing is Believing: Impaired Blood Flow





In Vitro Occlusion and Rescue of Whole Blood from an Individual with Sickle Cell Disease



Wood *et al*. Sci Trans Med, 2012.

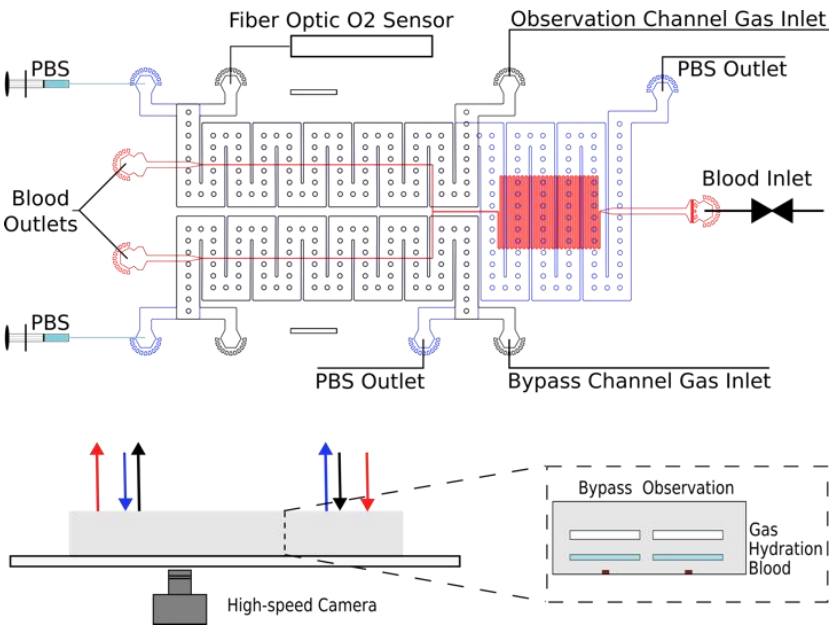
Can we therapeutically target HbS polymerization?

- Compounds that alter hemoglobin oxygen binding
  - Voxelotor – currently in Phase III trial
  - AES103 – Phase I/II trial stopped

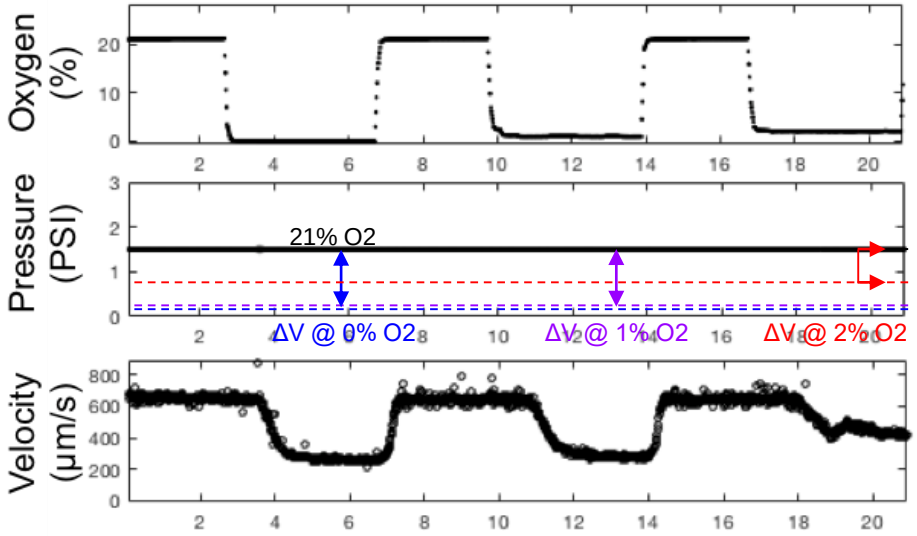
- Compounds that directly inhibit HbS polymerization
  - none currently in trials

Testing potential therapies in whole blood from sickle patients – a preclinical model of disease

Device and Experimental Setup

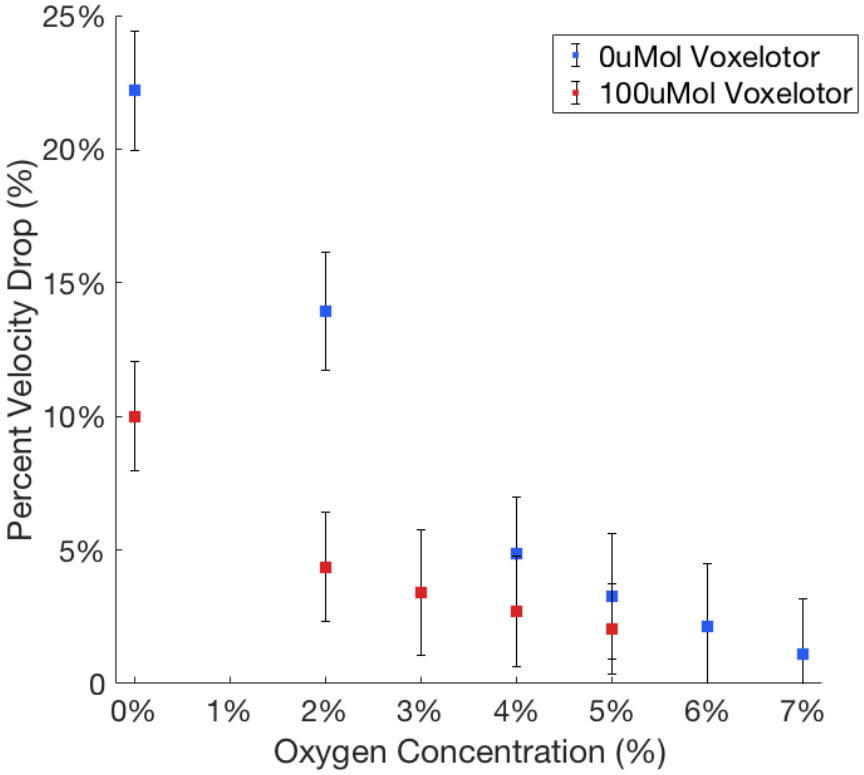


Raw Data

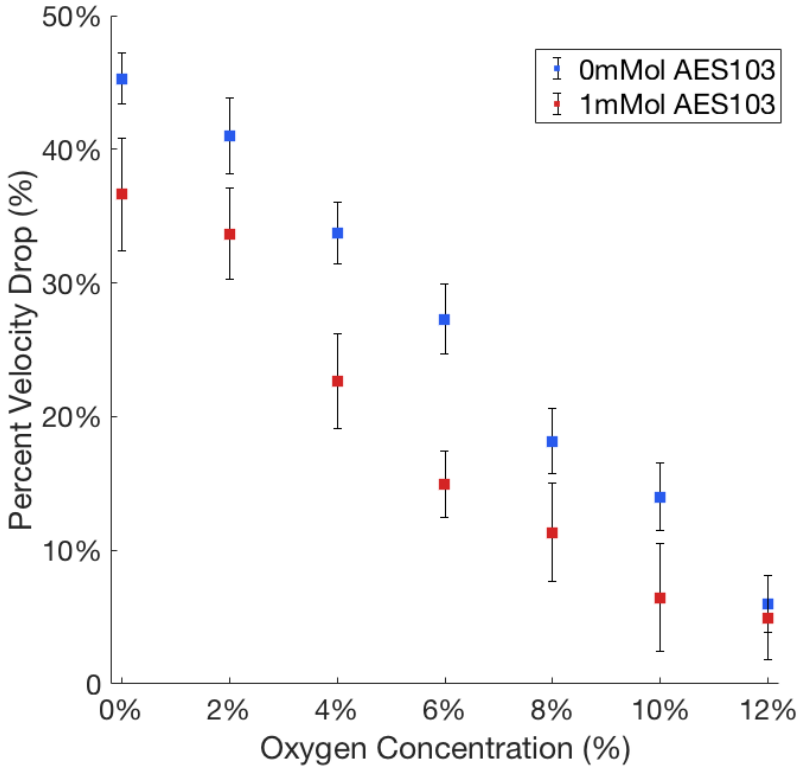


Blood treated with Voxelotor or AES103 showed reduced hypoxic response

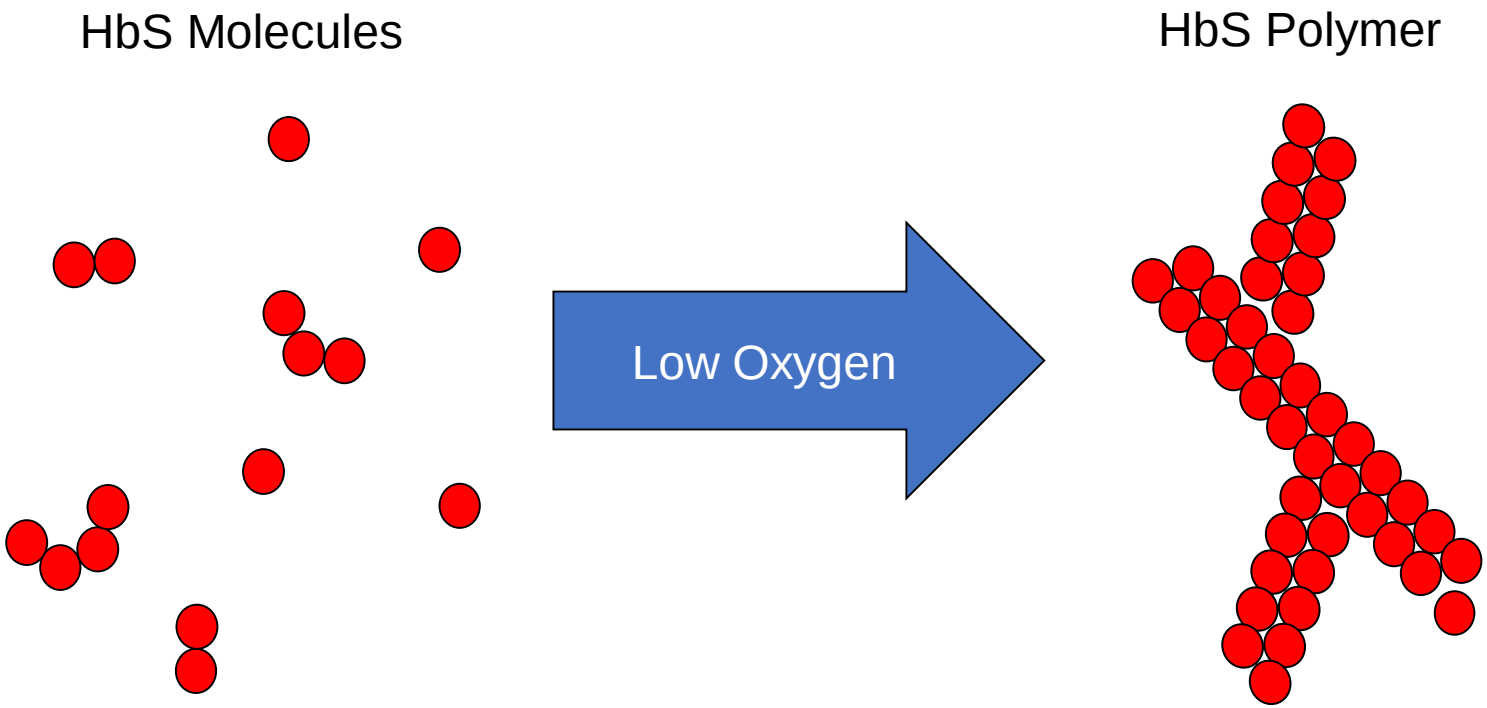
Voxelotor



AES103



Why Have So Few Compounds Been Tested?



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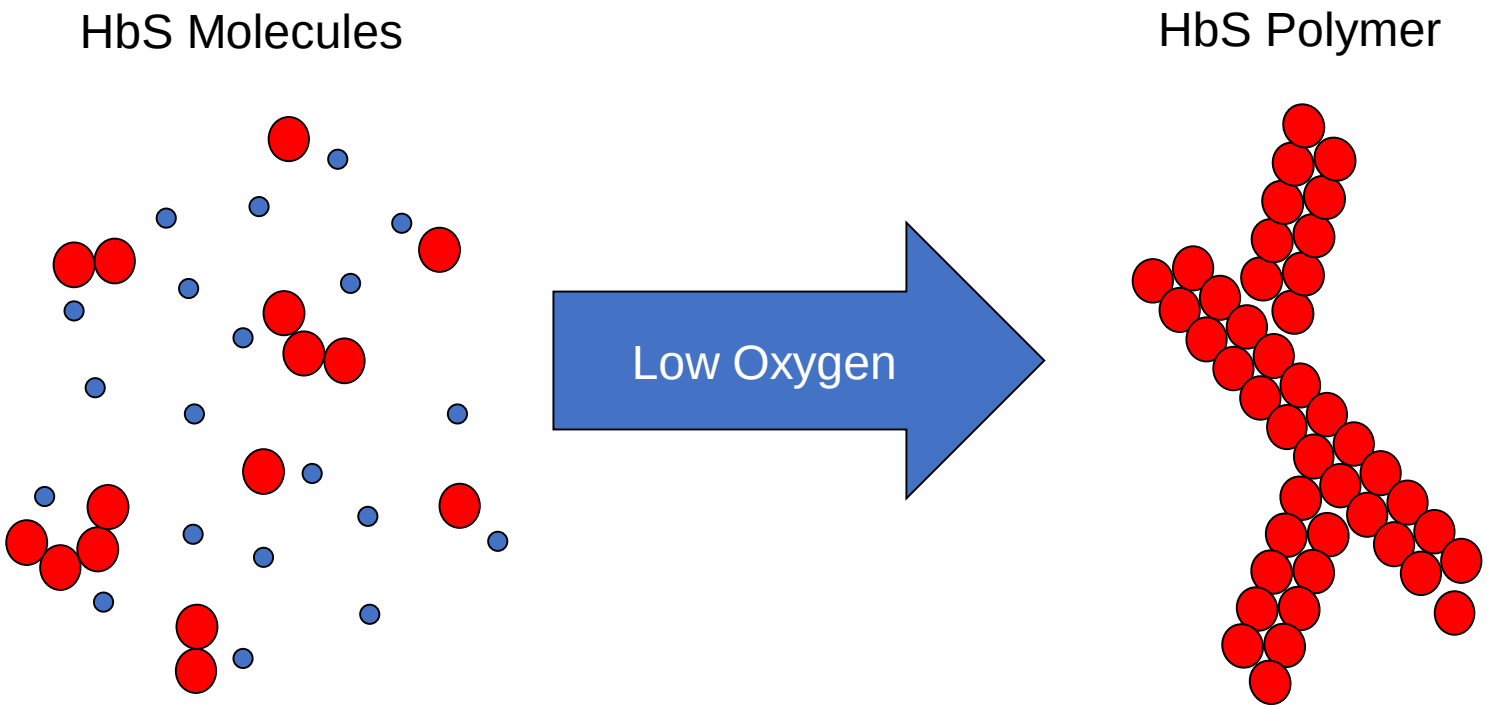
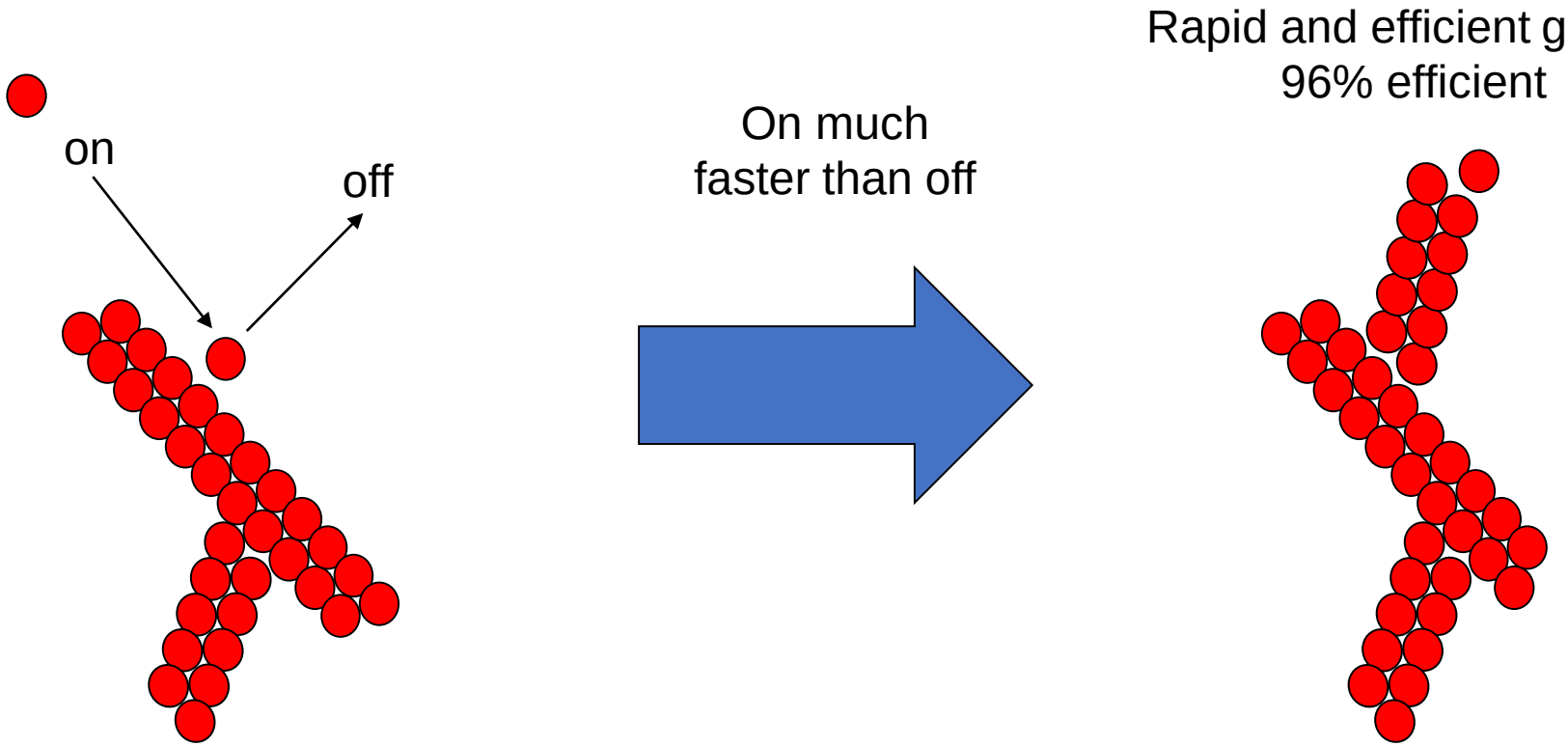


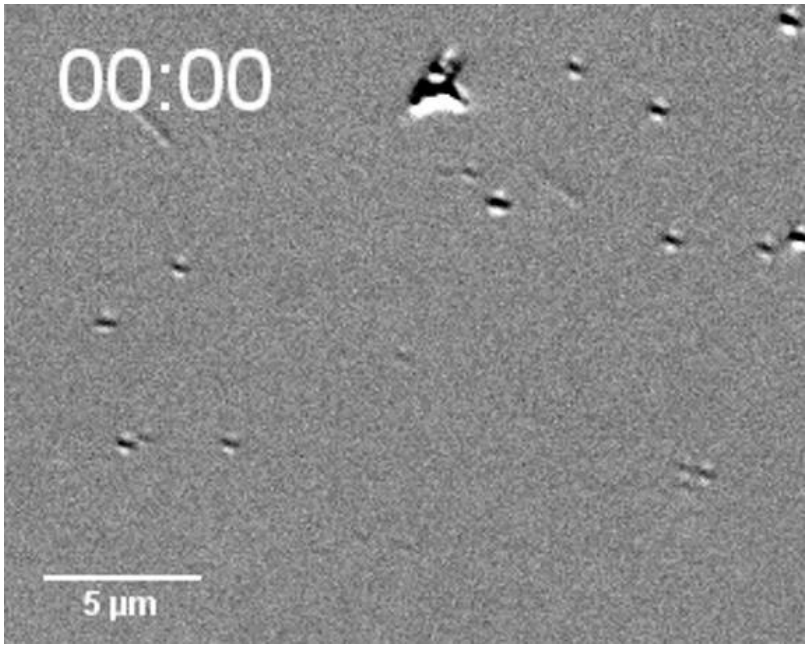
Such high drug concentrations will cause side effects.

The conventional wisdom says that HbS polymerization is very efficient

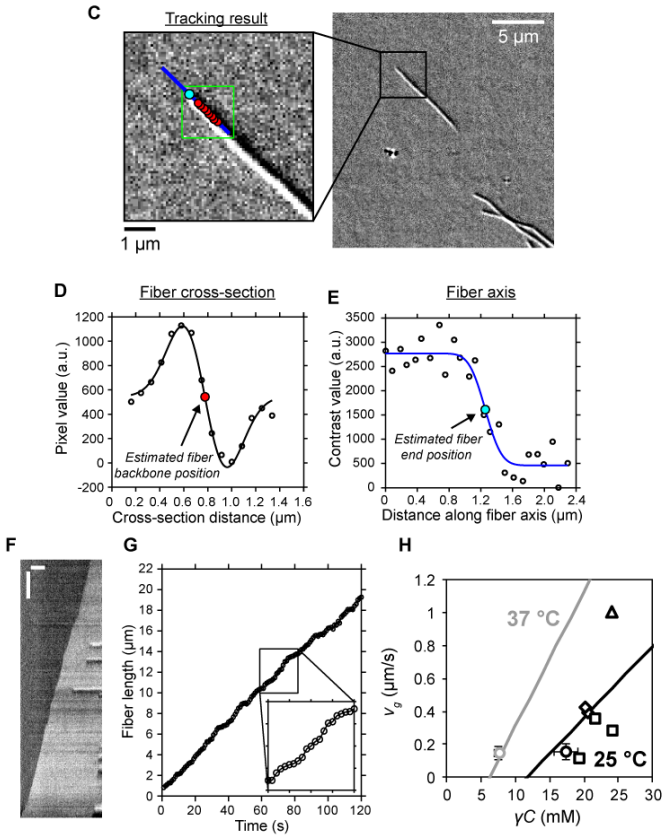


We tested this assumption by measuring the on and off rates directly

Highest resolution measurements of HbS polymerization ever made



These measurements allow us to quantify on and off rates



Castle, Odde, Wood. *Science Advances. 2019.*

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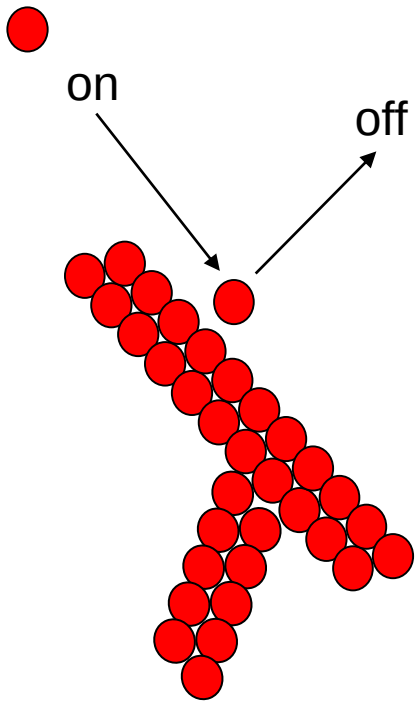
We may not need such high doses of treatments to have therapeutic effect



- On rate is fast but off rate is also fast
- Polymerization is only 4% efficient
  - only 4% off molecules added actually stay
- Much lower doses of drug are needed to inhibit polymerization
- Much less concern about side effects

The State of the Art

- We have new tools to study SCD at the level of molecules, cells, and tissues
  - A preclinical model for testing new therapies
- A new understanding of the molecular mechanisms of the disease suggest that HbS polymerization is therapeutically targetable
- We have new tools to discover and validate new compounds that inhibit HbS polymerization
  - **We have found and validated several new compounds that inhibit HbS polymerization**