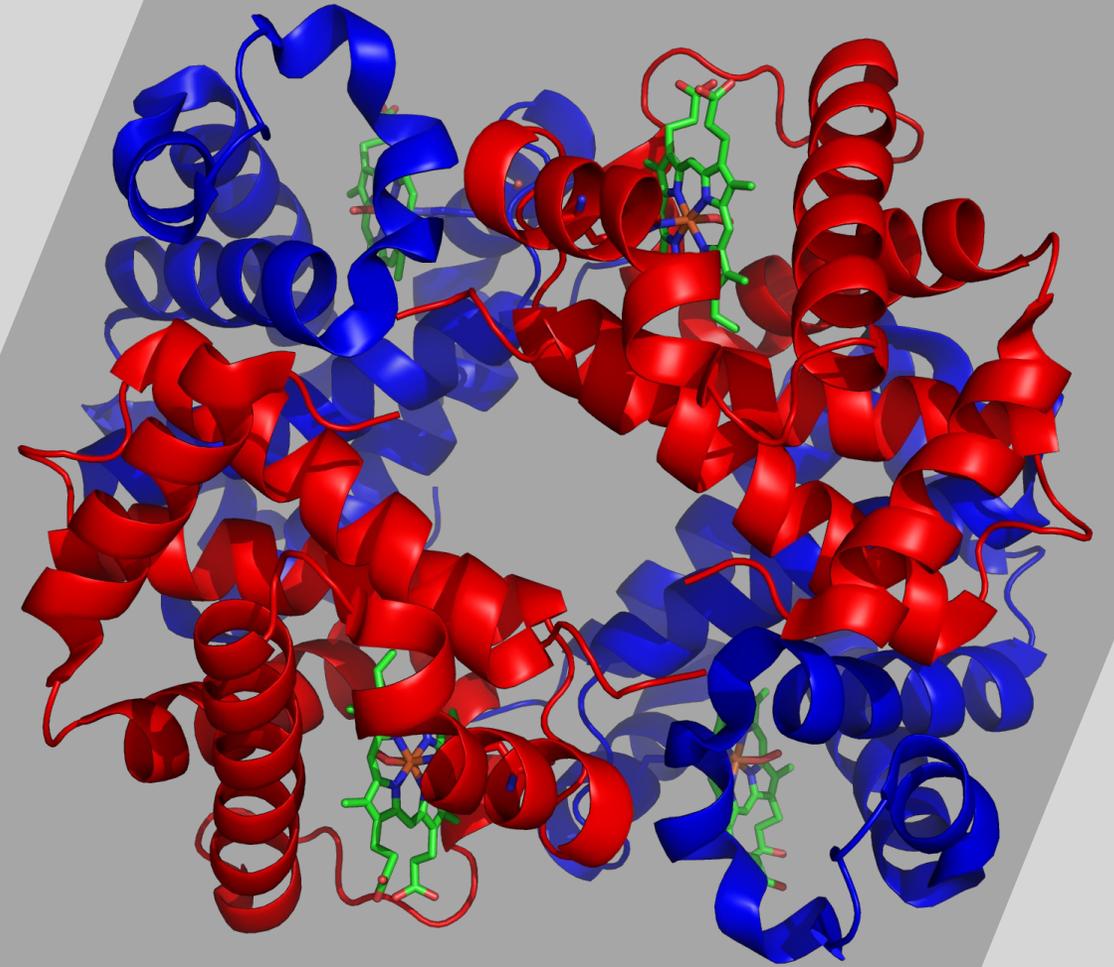


# Direct Polymerization Inhibitors for Sickle Cell Disease



**ILLEXCOR**  
THERAPEUTICS

# Executive Management Team



**Andrew N. Fleischman, MD** – Founder, Chief Executive Officer

- Biotech drug hunter and company builder
- Founded three successful biomedical companies (Illexcor Therapeutics, CLEU Diagnostics, and AmpedRNA Biosciences)
- Broad expertise in discovery, clinical translation, IP, regulatory and business strategy



**Martin K. Safo, PhD** – Founder, Chief Scientific Officer

- Professor of Medicinal Chemistry, Virginia Commonwealth University
- Over 30 years of experience in drug discovery with multiple drugs reaching clinical stage, such as RSR13 and Aes-103
- World renowned expert in sickle cell disease and hemoglobin modifying drugs



**David R. Light, PhD** – VP of Research & Development

- Senior PI with 4 decades of industry experience with Sanofi, Biogen, Bayer, Genentech, among others
- Led pre-clinical teams for a # of INDs and several NDAs (Eloctate, Aprolix, Cablivi)
- Subject matter expert in hematology and rare disease



**Yash Shenoy, MBBS, MBA** – Head of Business Development

- Seasoned BD professional - closed over \$500M in licensing and partnership deals
- Previously led growth capital investments (>\$100M) in life science sector for InvAscent
- Also serves as Associate Director of BD for Apollomics, a clinical stage oncology company, and was principal to in-licensing 5 key drug assets



# Key Personnel & Scientific Advisory

**Sarath Kanekal, DVM, PhD, DBT, RAC** – Toxicology

- Decades of expertise in pre-clinical drug development, > 40 IND/NDA/BLAs

**Loren Kim, CSSBB, CPM, CPE** – Quality and Regulatory

- Over 30 years of experience in pharmaceutical QSI and CMC

**Abdelsattar Omar, PhD** – Managing Director, Xeed Life Sciences

- Drug discovery expert and Professor of Medicinal Chemistry

**Tarek Ahmed, PhD** – Key Scientist, Xeed Life Sciences

- Award winning expert in pharmaceuticals and Professor of Pharmaceuticals

**Osheiza Y. Abdulmalik, PhD** – Division of Hematology, Children’s Hospital of Philadelphia

- World expert on sickle cell disease animal models and anti-sickling agents

**Kenneth I. Ataga, MD** – Professor of Medicine and Pediatrics, University of Tennessee

- Director, UTHSC Center for Sickle Cell Disease and experienced clinical trial PI

**Wally Smith, MD** – Professor of Medicine, Virginia Commonwealth University

- Director, VCU Adult Sickle Cell Program and VCU Center on Health Disparities

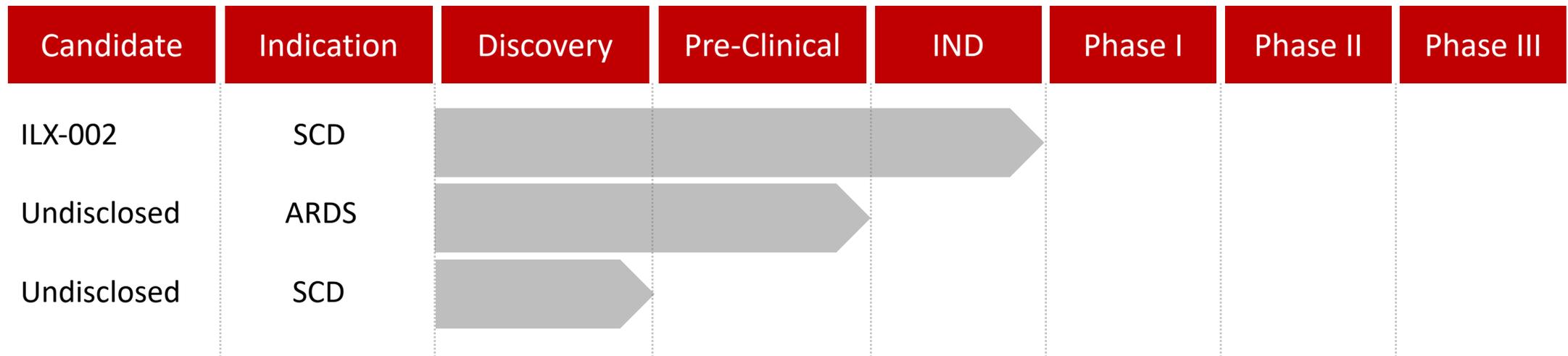
**Jurgen Venitz, MD** – Professor of Pharmaceuticals, Virginia Commonwealth University

- Recognized expert in early pre-clinical development and pharmacokinetics



# Pipeline Overview

- Illexcor is advancing its lead drug ILX-002, a first of its kind direct Hemoglobin S polymerization inhibitor for sickle cell disease
- We are also evaluating small molecule compounds for other hematologic, respiratory, and inflammatory disorders



The safety and efficacy of investigational agents have not been established or approved by the FDA or other regulatory authorities.

# Program Summary

- **Problem** - existing oral drugs have shown somewhat limited clinical benefit for sickle cell disease patients with clear signs of severe residual sequelae
- **Goal** - develop a once daily oral therapy with dramatic disease-modifying clinical benefits that can be the predominant therapy in the US and worldwide
- Our lead drug **ILX-002** is a Hemoglobin S polymerization inhibitor for sickle cell disease
- ILX-002 is the first and only drug that binds directly to HbS and directly blocks polymerization
- IND program to be completed in 2024 with first-in-human clinical trial to follow immediately



# Target Market

- One of the most common rare diseases globally with large addressable market
  - 160,000 individuals in the US and EU, and up to 10 million people worldwide
- Worldwide peak sales estimates of greater than \$3 billion per year
- Disproportionately affects underserved populations with significant unmet need
- Consequently, huge interest in this important scientific focus area from large pharma



## Pfizer to Acquire Global Blood Therapeutics for \$5.4 Billion to Enhance Presence in Rare Hematology

*Proposed acquisition drives growth by bringing leading sickle cell disease expertise, portfolio and pipeline to Pfizer with potential combined worldwide peak sales of more than \$3 billion*

# Competitive Landscape

- Bone marrow transplant and *ex vivo* gene therapies
  - Bone marrow transplants performed since 1980s offered as a potential cure for sickle cell disease
  - First *ex vivo* gene therapies for SCD (Casgevy and Lyfgenia) received FDA approval in December 2023
  - However, bone marrow transplant and *ex vivo* gene therapies for SCD are extremely expensive and carry substantial risk due to myeloablative conditioning
  - Only accessible for a minority of patients with the most severe disease
    - An estimated 200 to 800 patients expected to be treated annually by 2030 (about 4,000 patients total)
- Disease modifying oral therapy remains the **holy grail for most patients**
  - But a clear efficacy gap exists for oral SCD drugs - no drug can yet deliver dramatic disease-modifying benefits tantamount to functional cures reported for *ex vivo* gene therapies
  - Modest clinical benefits observed for commercial and clinical-stage oral drugs for SCD

# Competitive Analysis

- Severe disease sequelae persists despite treatment with existing oral SCD drugs
  - Hb responses from 1-3 g/dL; residual hemolysis and moderate to severe anemia persists
  - Modest reductions in VOCs for most agents (no significant reduction of VOCs with Voxelotor)
- Could direct polymerization inhibitors finally be the answer?
  - ILX-002 has the potential to completely eliminate residual hemolysis and inflammation resulting in dramatic disease-modifying clinical benefits

## Observed or anticipated clinical profile for different therapeutic approaches

| Approach                           | Examples               | Pancellular | Polymer Destabilizing | VOC Effects | Disease-Modifying | Safety |
|------------------------------------|------------------------|-------------|-----------------------|-------------|-------------------|--------|
| Direct Polymer Inhibitors          | ILX-002                | ✓           | ✓                     | ✓✓✓         | ✓✓✓               | ✓      |
| O <sub>2</sub> Affinity Modulators | Voxelotor, GBT-601     | ✓           | X                     | ✓           | ✓✓                | ✓      |
| HbF Induction Agents               | Hydroxyurea, Pociredir | X           | ✓                     | ✓✓          | ✓✓                | ?      |
| PKR Activators                     | Mitapivat, FT-4202     | ✓           | X                     | ✓✓          | ✓                 | ✓      |

# Mechanisms of Sickle Inhibition

Two major biophysical mechanisms to reduce tendency of HbS to polymerize

## 1) Decrease level of polymer-forming HbS in RBCs (dilutional)

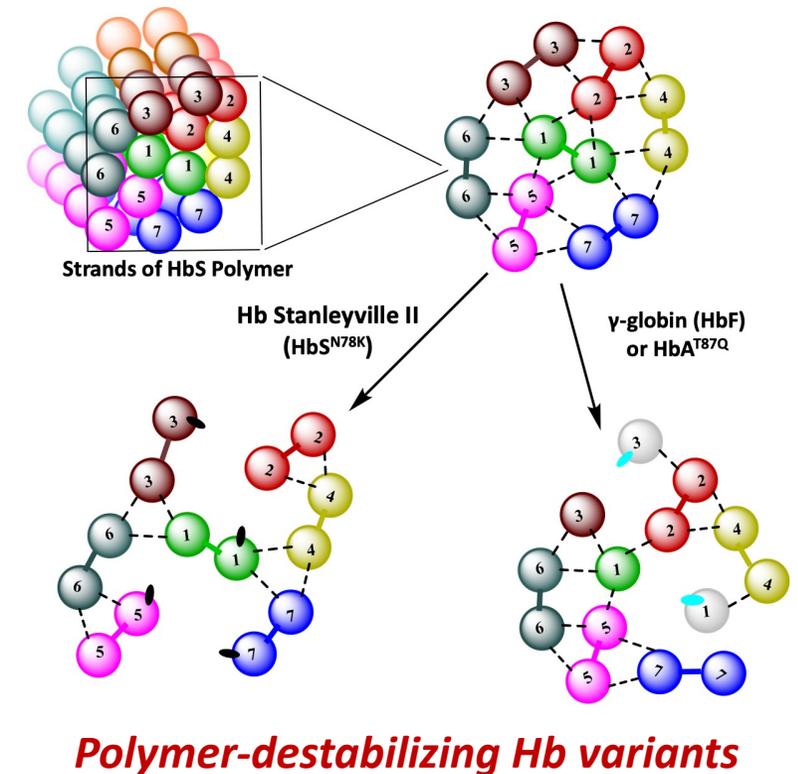
Increase RBC volume, increase O<sub>2</sub> affinity of HbS (less deoxy-HbS), introduce non-polymerizing Hb variants

Examples – Voxelotor, GBT-601, Mitapivat, FT-4202, Senicapoc

## 2) Directly destabilize polymer formation

Disrupt the key stabilizing intermolecular contacts of HbS insoluble fibers

Examples – Fetal Hb induction, Hb Stanleyville II (HbS<sup>N78K</sup>), Lentoviral HbA<sup>T87Q</sup>



# Direct Polymer Destabilization

How effective should we expect direct polymerization inhibitors to be?

What we know from natural direct polymer-destabilizing co-inherited mutations

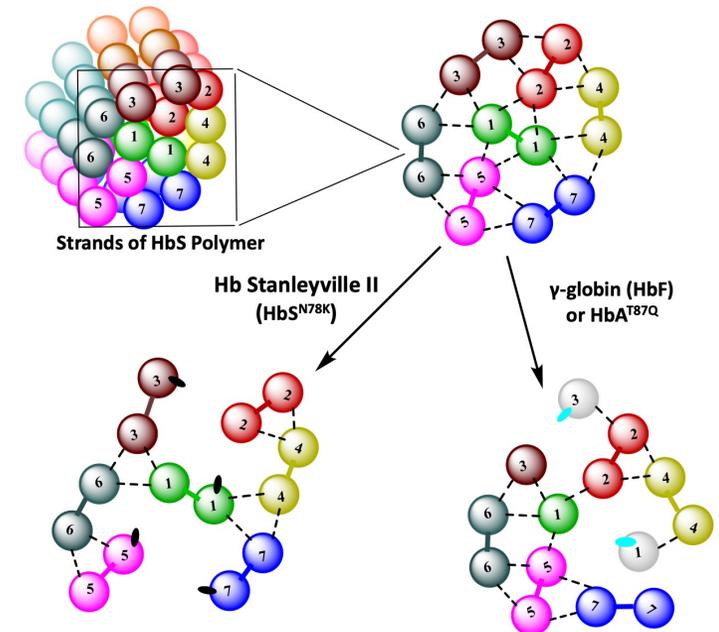
## Hb Stanleyville II (HbS<sup>N78K</sup>)

- Rare co-inheritance mutation on  $\alpha$ F-helix found in Congo and Sudan
- Lysine mutation on  $\alpha$ F-helix interrupts key polymer stabilizing contacts

## Hereditary Persistence of Fetal Hb

- Rare inherited condition – retain pancellular expression of HbF (~30% of Hb)
- Thr87 residue of Hb responsible for key lateral contacts between tetramers
- Thr87 replaced by Gln87 (Q87) on the  $\gamma$ -globin chain of HbF

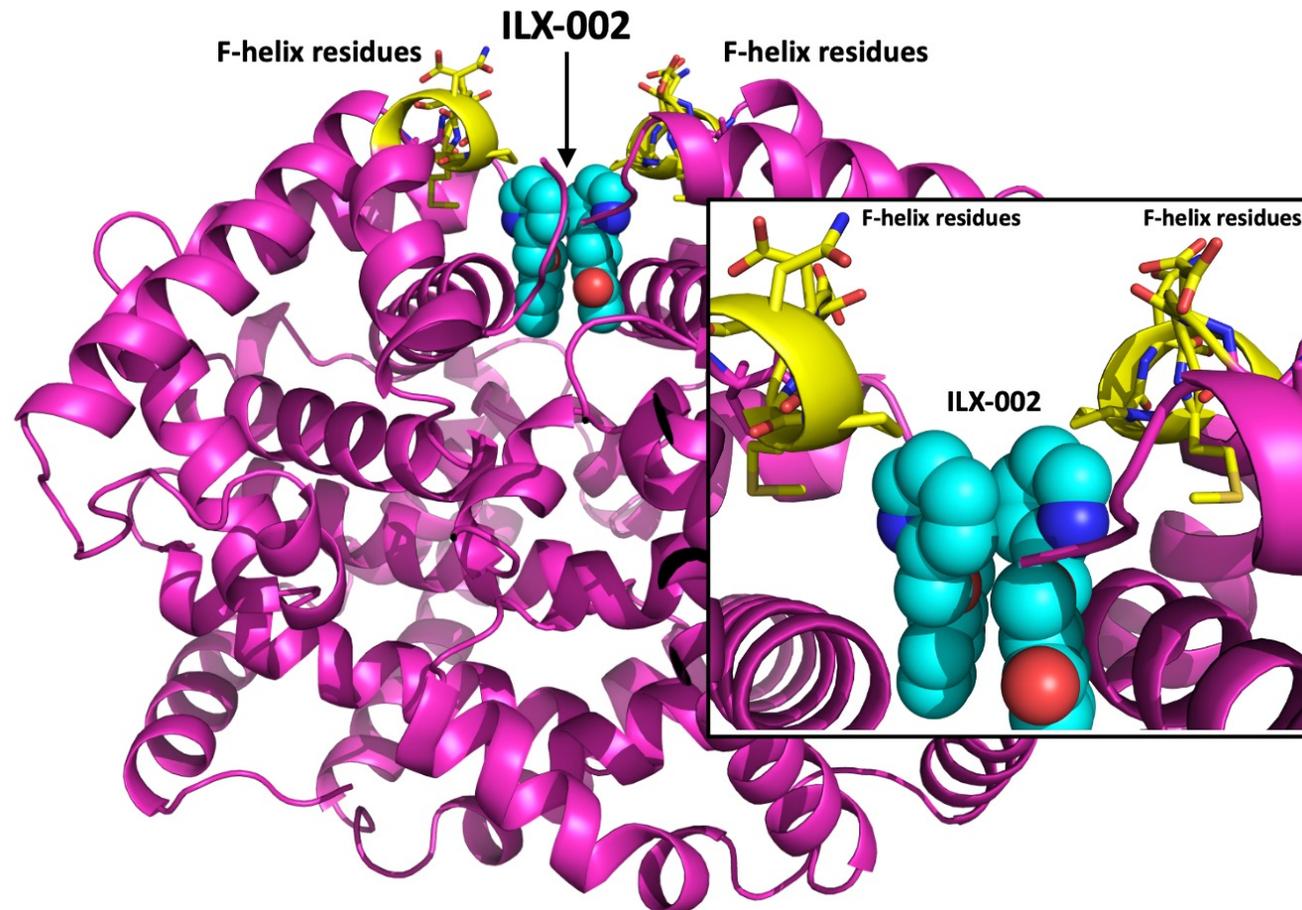
Rare co-inheritance mutations that directly inhibit polymerization result in a completely benign clinical phenotype



**Polymer-destabilizing Hb variants**

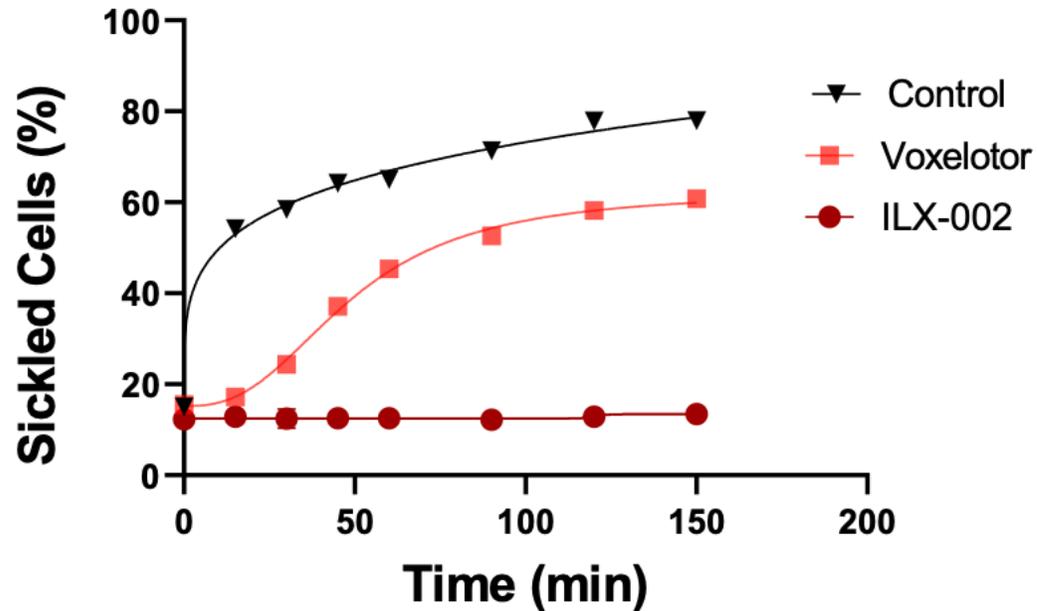
# How It Works

- ILX-002 inhibits polymerization by directly disrupting interactions within insoluble HbS fibers
- Engages with surface residues of the  $\alpha$ F-helix of HbS to fundamentally disrupt key polymer-stabilizing contacts (similar to co-inheritance of mutant Hb Stanleyville II)



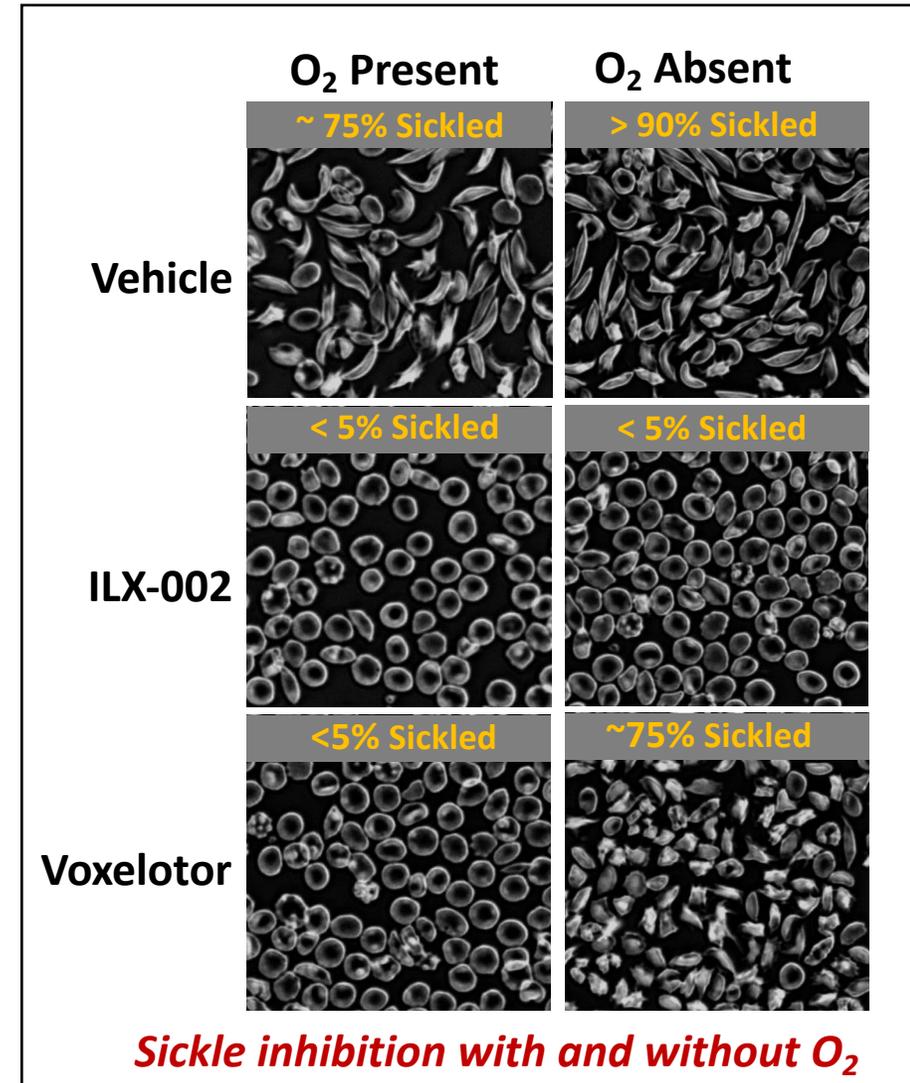
**Crystal structure of  
ILX-002 bound to HbS**

# Sustained Efficacy in Anoxia

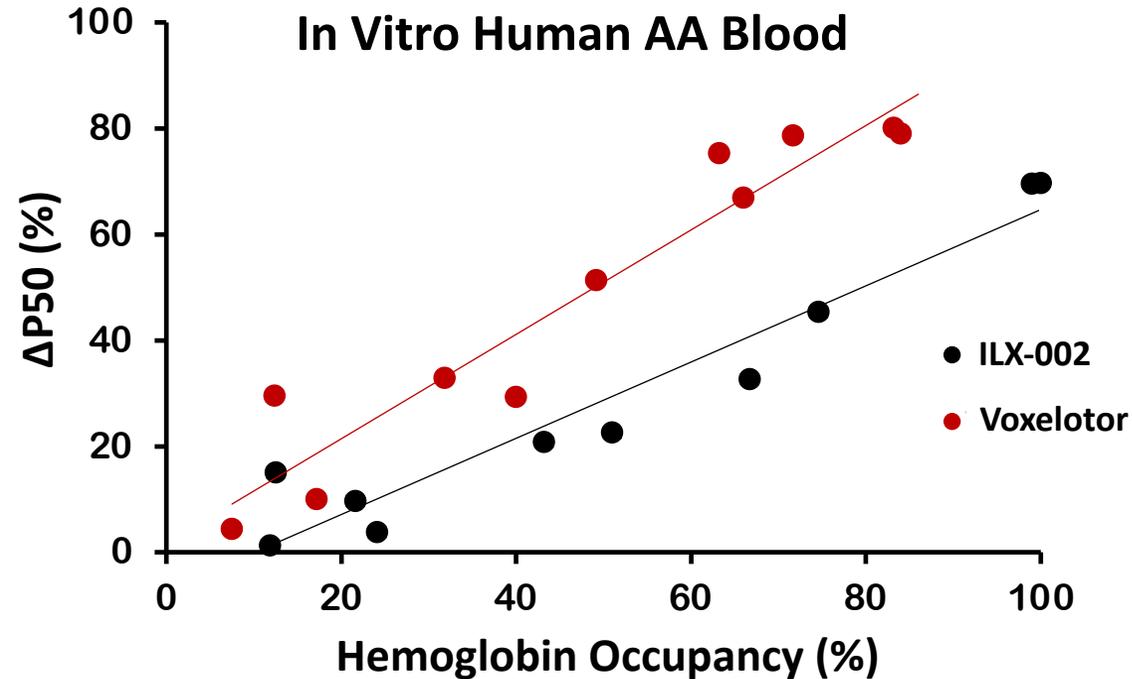


## Key Findings:

- ILX-002 exhibits sustained anti-sickling potency for greater than 2 hours even in conditions of total anoxia
- Pancellular distribution of ILX-002 prevents hemolysis and prolongs survival of essentially all circulating RBCs
- Voxelotor and GBT601 have no direct polymer-destabilizing effects



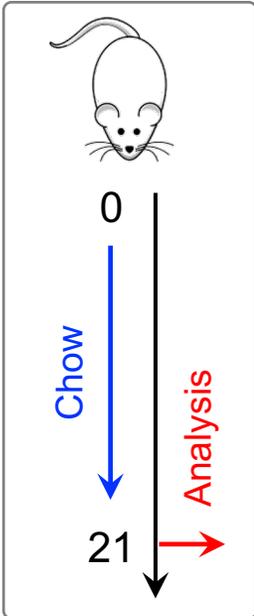
# Hemoglobin Allosteric Modulation



## Key Findings:

- ILX-002 also induces a shift in hemoglobin O<sub>2</sub> affinity, albeit significantly less so than Voxelotor and GBT601 despite having greater anti-sickling potency due to its direct polymer destabilizing effects
- Voxelotor induces a 50% shift in hemoglobin O<sub>2</sub> affinity at 50% occupancy which is dose-limiting and also limits the maximum therapeutic efficacy of the drug
- The shift in hemoglobin O<sub>2</sub> affinity with ILX-002 remains below 50% with a hemoglobin occupancy of up to 80%, which we anticipate will expand its therapeutic window and maximum therapeutic efficacy

# Townes Humanized $\beta^S/\beta^S$ SCD Mice



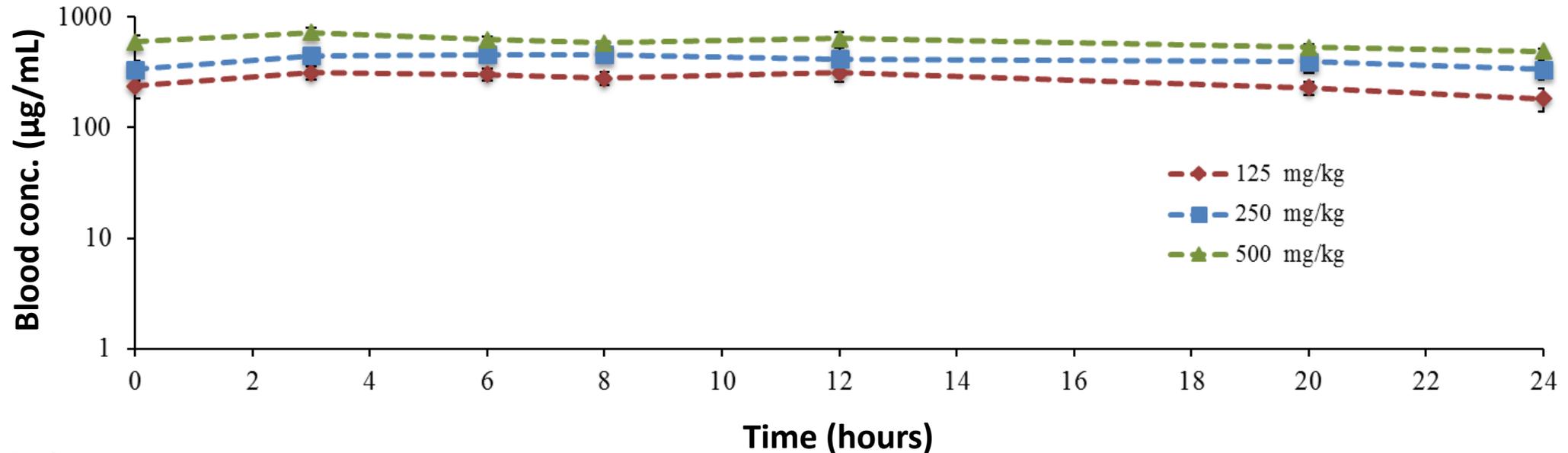
## Key Findings:

- ILX-002 was administered to humanized Townes ( $\beta^S/\beta^S$ ) mice in food chow for 21 days
- Drug exposure at about 50-60% hemoglobin occupancy for 21 days completely restored normal hemoglobin levels (110% increase)
- Dramatically reducing reticulocytosis, hemolysis, and inflammation
  - Reticulocytes reduced from about 50% at baseline to less than 20%
  - 60% reduction in bilirubinemia
  - 85% reduction in neutrophil count

These are preliminary results, and additional studies are currently underway to determine the dose response and assess other disease markers

# ADME and Safety

Day 14 oral TK in male SD rats



## Key Findings:

- ILX-002 has demonstrated impressive ADME properties ( $t_{1/2}$  20-60 hours with repeated doses in rodents) that project to once daily dosing in humans
- Nearly 3-fold higher molar equivalent blood concentration in rodents compared to same doses with Voxelotor
- No significant adverse effects observed at any dose level after 14-days in Sprague Dawley rats (about 3 to 4-fold above the anticipated therapeutic exposure level).