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# MPS II biology, standard of care, and rationale for the development of SB-913

Dr. Joseph Muenzer

August 1, 2018

# Forward Looking Statements

*This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, as amended. These forward-looking statements include, but are not limited to, the intended effect of SB-913, the design of the Phase 1/2 clinical trial and expected timing for release of data; the anticipated clinical development milestones; and the potential of SB-913 to successfully treat MPS II. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties. Factors that could cause actual results to differ include, but are not limited to, the potential for ZFNs to not work as intended, the dependence on the success of clinical trials of lead programs, the lengthy and uncertain regulatory approval process, uncertainties related to the timing of initiation and completion of clinical trials, whether clinical trial results will validate and support the safety and efficacy of SB-913, uncertainties related to the initiation and completion of clinical trials, the reliance on partners and other third-parties to meet their obligations. Actual results may differ from those projected in forward-looking statements due to risks and uncertainties that exist in Sangamo's operations and business environments. These risks and uncertainties are described more fully in Sangamo's Annual Report on Form 10-K and Quarterly Reports on Form 10-Q as filed with the Securities and Exchange Commission. Forward-looking statements contained in this presentation are made as of the date hereof, and Sangamo undertakes no obligation to update such information except as required under applicable law.*

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- Expert in diagnosis, management and clinical treatment of patients with inborn errors of metabolism and mucopolysaccharidoses (MPS)
- Principal Investigator of Phase 1/2 CHAMPIONS Study, evaluating Sangamo's SB-913 investigational *in vivo* genome editing treatment for MPS II

# Agenda

1. Mucopolysaccharidosis Type II (MPS II) and enzyme replacement therapy (ERT)

2. Rationale for the development of ZFN-based *in vivo* genome editing to treat MPS II

3. CHAMPIONS Study: a Phase 1/2 clinical trial evaluating SB-913

# Mucopolysaccharidosis Type II (MPS II)

Understanding the disease and current treatment options

# What is MPS II or Hunter syndrome?

## About MPS II (Hunter syndrome)

- Inherited, X-linked metabolic disease caused by mutations in the gene encoding the iduronate-2-sulfatase (IDS) enzyme
- Mutations in IDS gene result in loss of IDS metabolic enzyme activity
- Accumulation of toxic waste products called glycosaminoglycans (GAGs) in lysosomes leads to tissue and organ damage
- Enzyme replacement therapy (ERT) does not address all symptoms of the disease, e.g. neurocognitive decline

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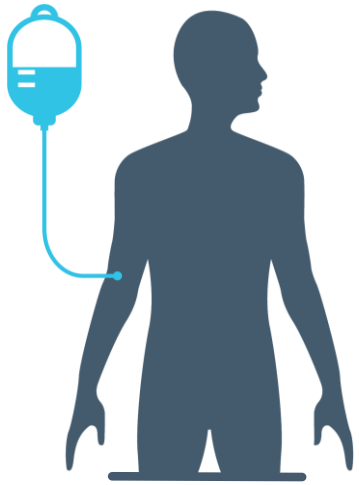
# The current treatment option for MPS II provides some, but limited therapeutic benefit

## Enzyme Replacement Therapy (ERT)



- Weekly, large bolus of enzyme requires hours of IV infusion
- Short enzyme half-life, unclear if sufficient enzyme taken up by tissues
- Uneven distribution to tissues

## Supportive Care

### Surgical Intervention

- Hernias, carpal tunnel, spinal stabilization, valve replacement

### Drugs

- Antibiotics
- Pain medication

### Airway Support

- CPAP / BiPAP
- Supplemental oxygen
- Tracheostomy

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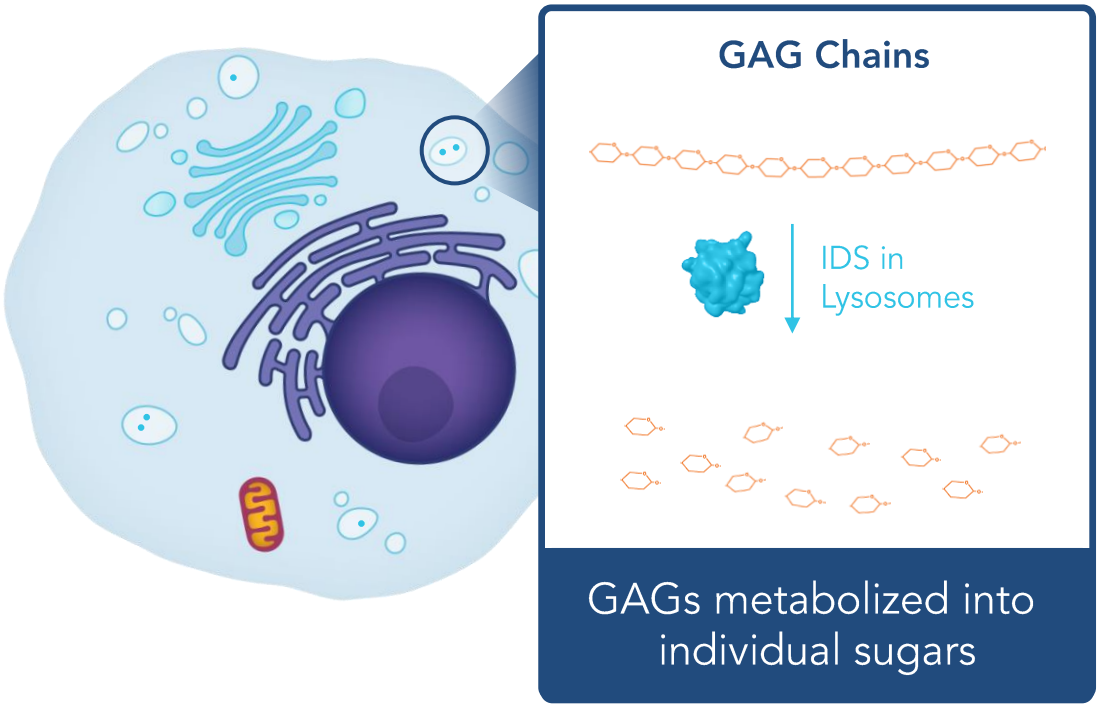
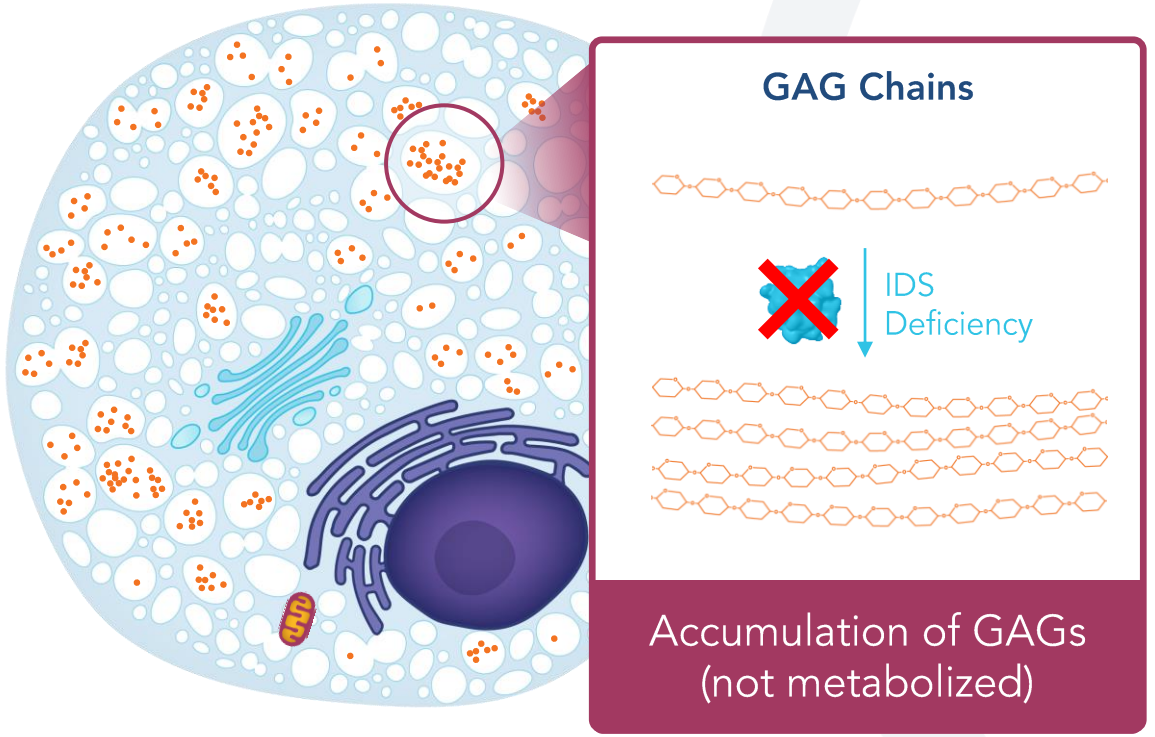
# A lack of active IDS enzyme results in accumulation of GAGs in the lysosomes, leading to loss of cellular function and organ damage

## Normal Cell




## MPS II Cell




Toxic build up enlarges lysosomes, crowds critical organelles and engorges the cell

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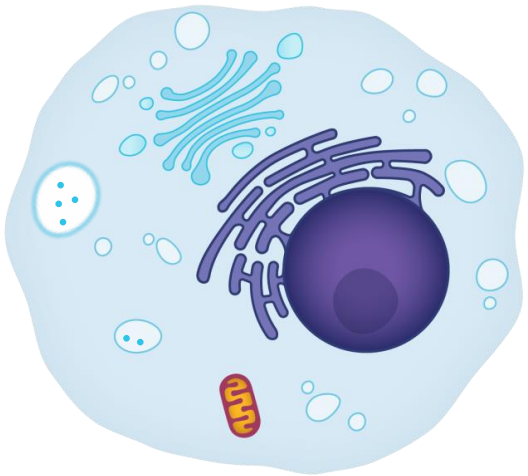
# A small fraction of IDS produced in normal cells leaks into circulation, which can be taken back up by the tissues

**1**

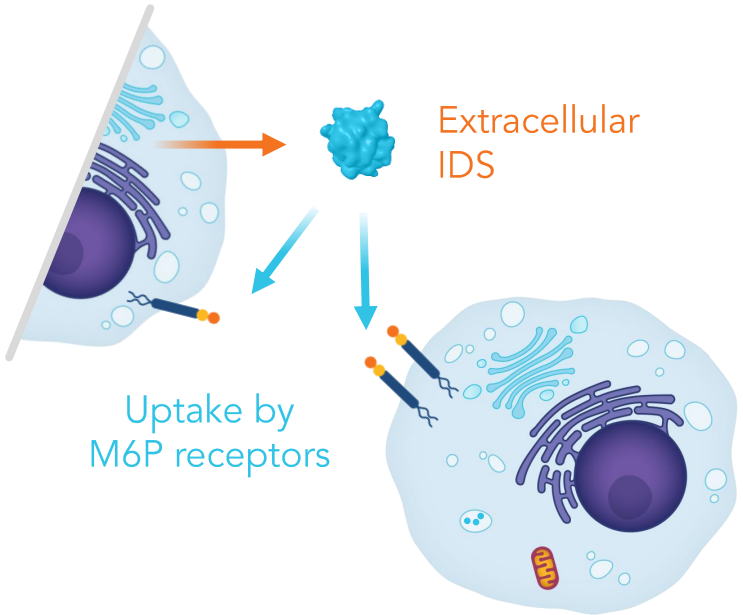
IDS is made in the endoplasmic reticulum and transported to lysosomes to break down GAGs

IDS metabolizes GAGs in lysosomes



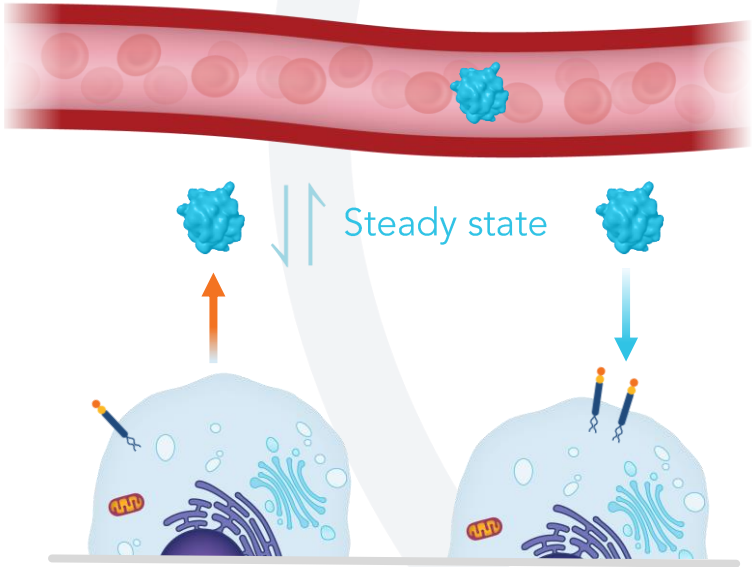
**2**

Imperfect intracellular transport leaks a small fraction of IDS into extracellular space. Cells may uptake extracellular IDS using receptors on the cell surface




**3**

Steady state is created as small amounts of IDS are secreted and reuptake occurs via receptor-mediated uptake




**Tissues [High]** ⇌ **Normal IDS Steady State** ⇌ **Circulation [Low]**

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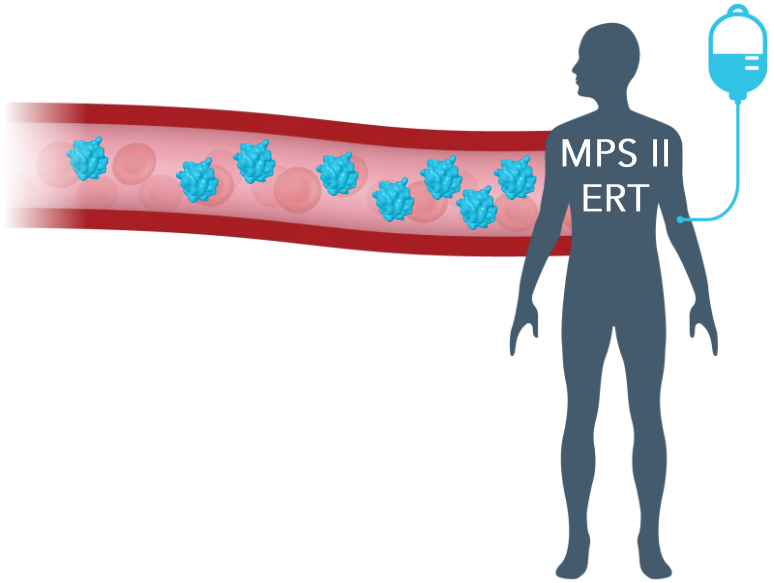
# ERT delivers high amounts of enzyme IV, to create a concentration gradient that may allow uptake into IDS-deficient cells

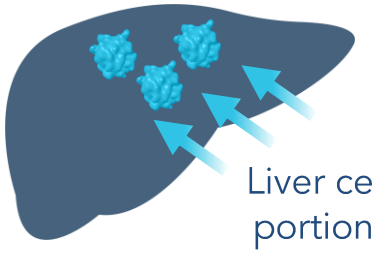
1

Large bolus of IDS enzyme infused into the blood




2

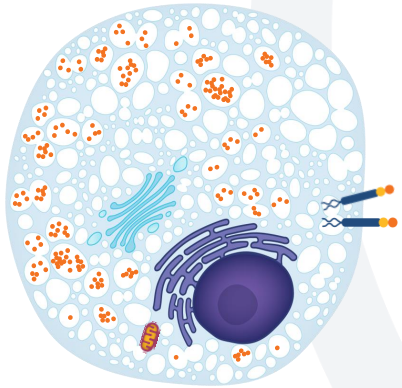
Large amounts of IDS taken up by liver cells, limiting enzyme uptake by other tissues



Liver cells take up large portion of enzyme due to high-capacity, low-specificity receptors

3

Remaining enzyme transiently bathes other tissues to promote receptor-mediated uptake. IDS exposure may be insufficient in tissues with limited contact with extracellular space or circulatory system (e.g. joints)



MP6 receptors can take up IDS enzyme

Tissues [Low] ← Transient ERT Exposure Gradient ← Circulation [High]

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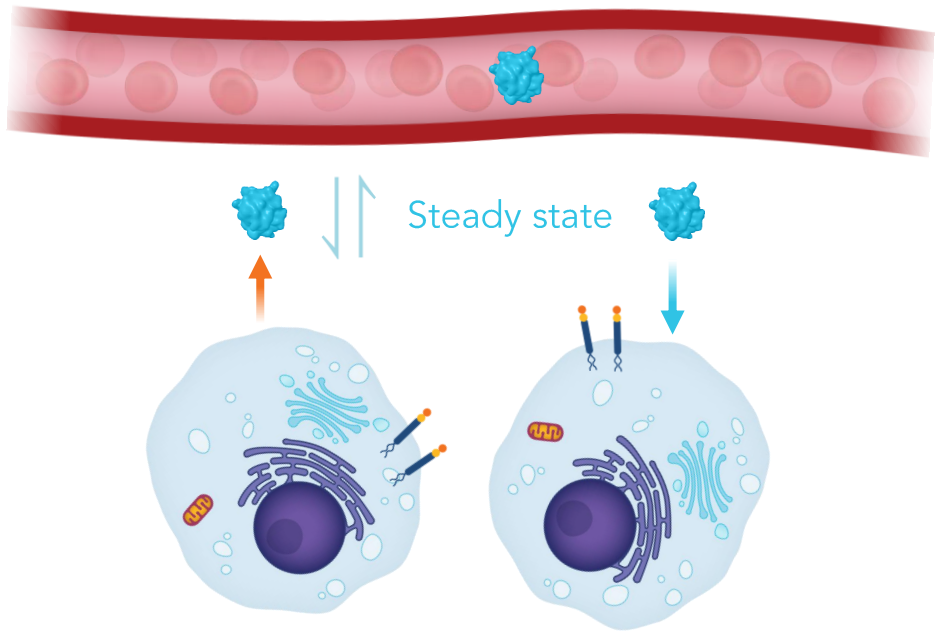
# An ideal therapy for MPS II prolongs exposure of tissues to enzyme by maintaining continuous, stable levels in the circulation

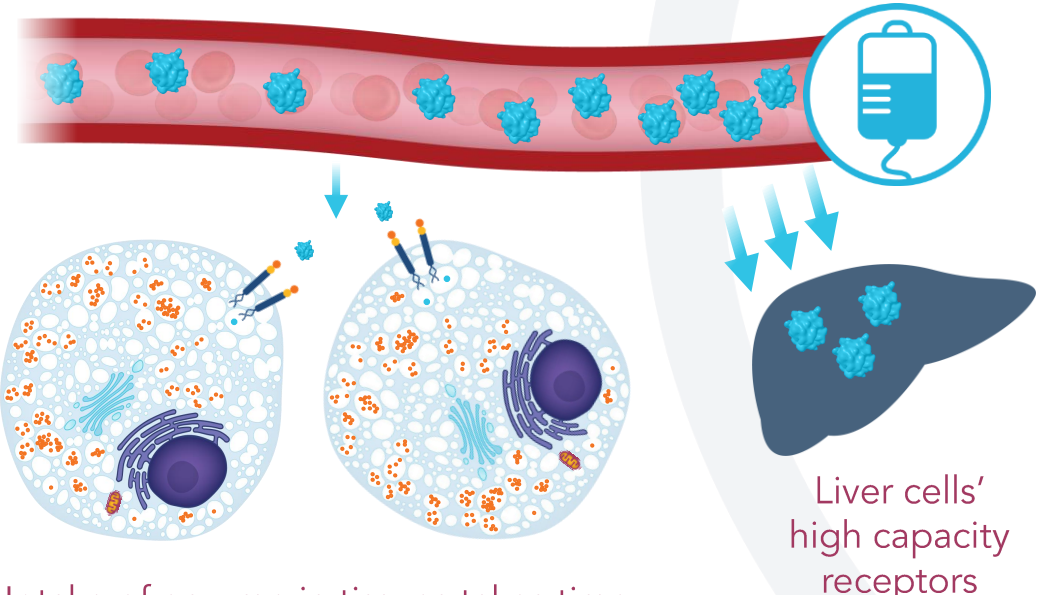
## Normal Serum IDS Enzyme

Steady state established as IDS enzyme is secreted and specific receptors mediate uptake




## Transient ERT Exposure Gradient

Bolus of enzyme infused IV weekly, rapidly increases IDS exposure around tissues for a short period of time



Uptake of enzyme in tissues takes time

Liver cells' high capacity receptors soak up IDS

Prolonged exposure to extracellular enzyme increases likelihood of receptor-mediated uptake into cells — a key advantage for a genome editing approach

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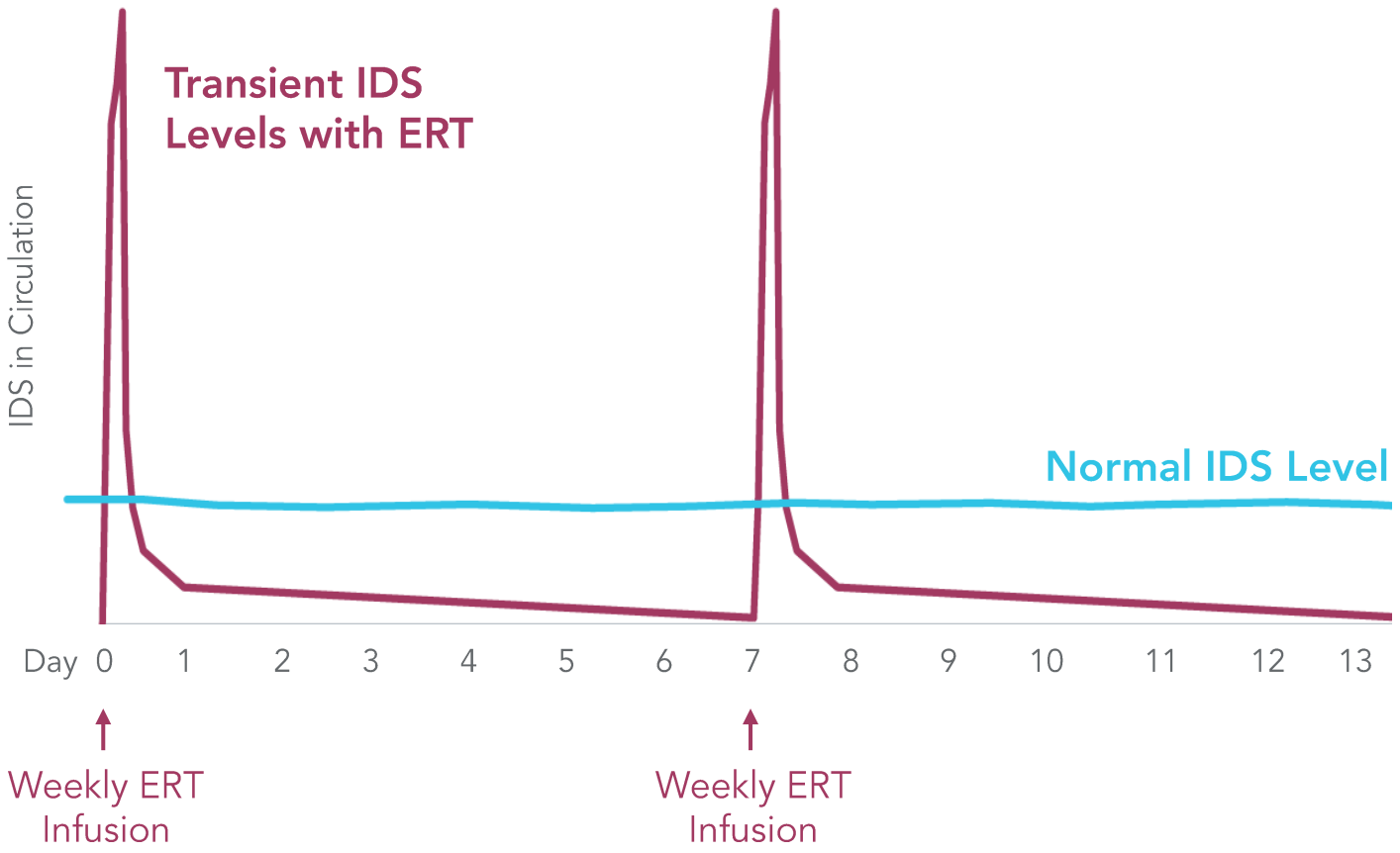
# Weekly ERT infusions do not provide sustained exposure of IDS to the tissues, enzyme is rapidly cleared from circulation within hours

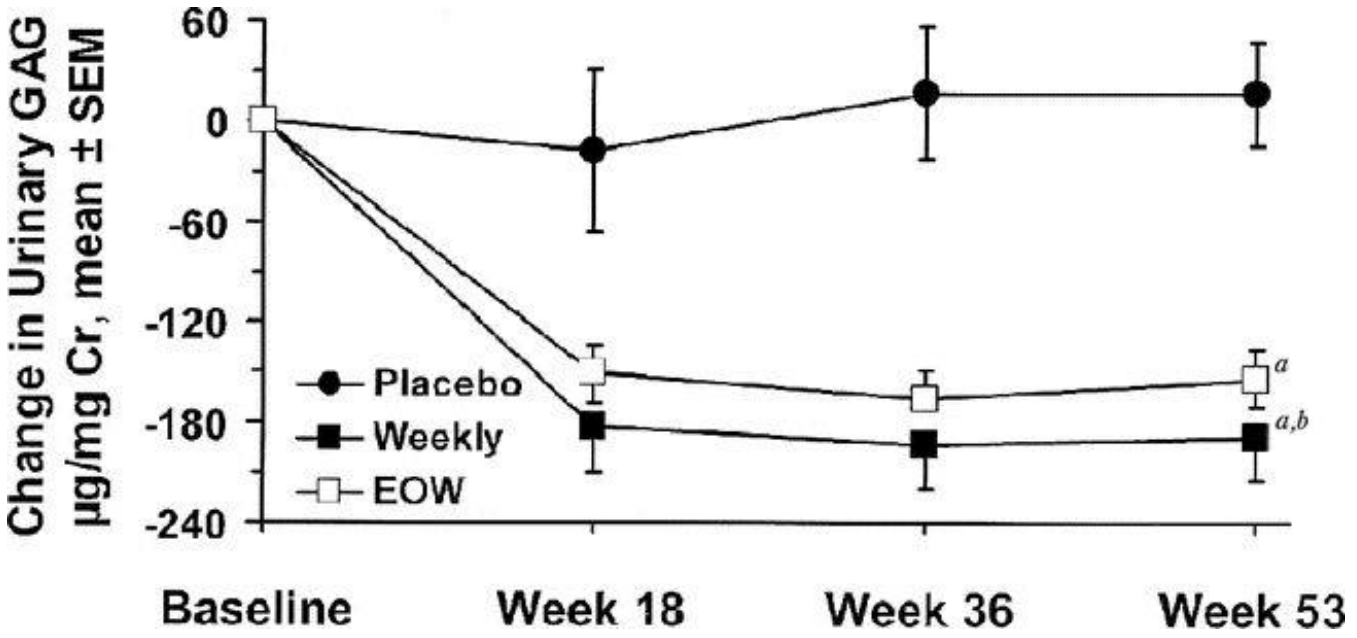
*Illustrative ERT infusion graph*




- Patients on ERT receive a large bolus of enzyme once a week
- ERT half-life is approximately 60 minutes[1], rapidly cleared from the system
- Large amount of enzyme is taken up by the liver, due to high-capacity, low-specificity receptors on liver cell surface
- For significant period of time (i.e. 5-6 days out of the week), patients' enzyme levels are very low or absent

1. Elaprase®

# ERT reduces urinary GAG levels over time, however urinary GAGs may not be representative of tissue GAG levels




[1]The effect of treatment with idursulfase or placebo on urine GAG levels in MPS II. All values are the observed means ± SEM. [a]$P < 0.0001$ for both weekly and EOW idursulfase compared with placebo at Week 53 (ANCOVA). [b]$P = 0.039$ compared to EOW dosing (ANCOVA). EOW, every-other-week; GAG, glycosaminoglycans



1. Muenzer et al., 2006

# There are still unmet needs not currently addressed with ERT

## ERT Limitations

- Disease symptoms may still progress, despite urine GAGs being reduced (but not normalized)
- May not deliver sufficient levels of enzyme to allow therapeutic uptake into cells
- Bolus dosing leads to extended periods of insufficient enzyme levels in the body

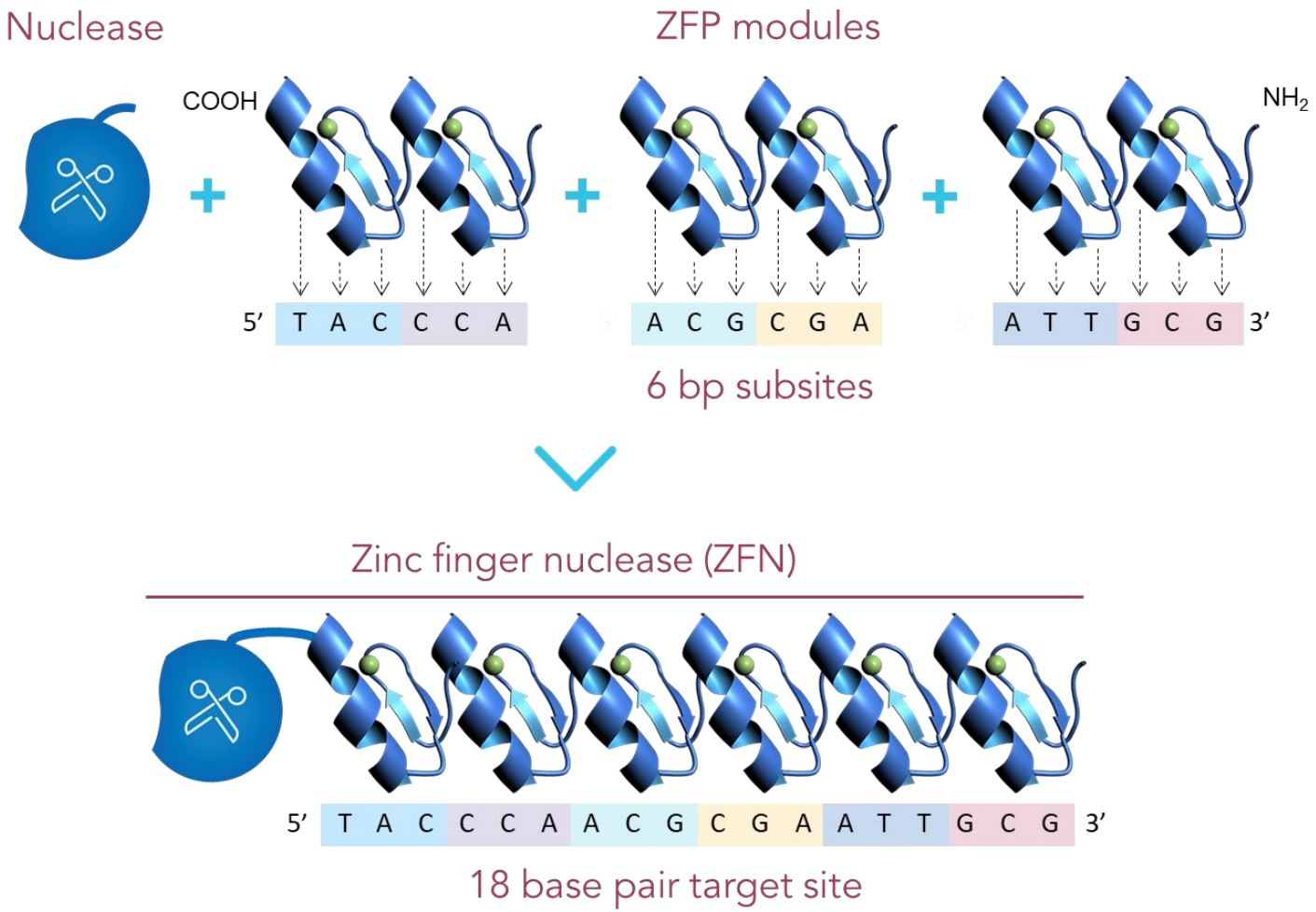
## Patient Burden

- Cardiac and pulmonary disease not fully prevented
- Progressive neurological disease not effectively impacted
- Familial and patient burden:
  - Weekly infusions may take several hours to an entire day
  - Infusing young children

# In Vivo Genome Editing

Rationale for the development of ZFNs to treat MPS II

# Zinc finger nucleases are engineered by attaching a nuclease to a zinc finger protein (ZFP)




- Naturally occurring class of proteins that upregulate or downregulate gene expression
- Engineered by Sangamo to edit DNA using a Fok1 nuclease
- Modularity of platform allows rapid assembly of hundreds of ZFN design constructs
- Protein-based platform can be optimized for precision, efficiency and specificity
- Two ZFNs are required to dimerize to facilitate a double strand break – additional safety feature to prevent unwanted cutting

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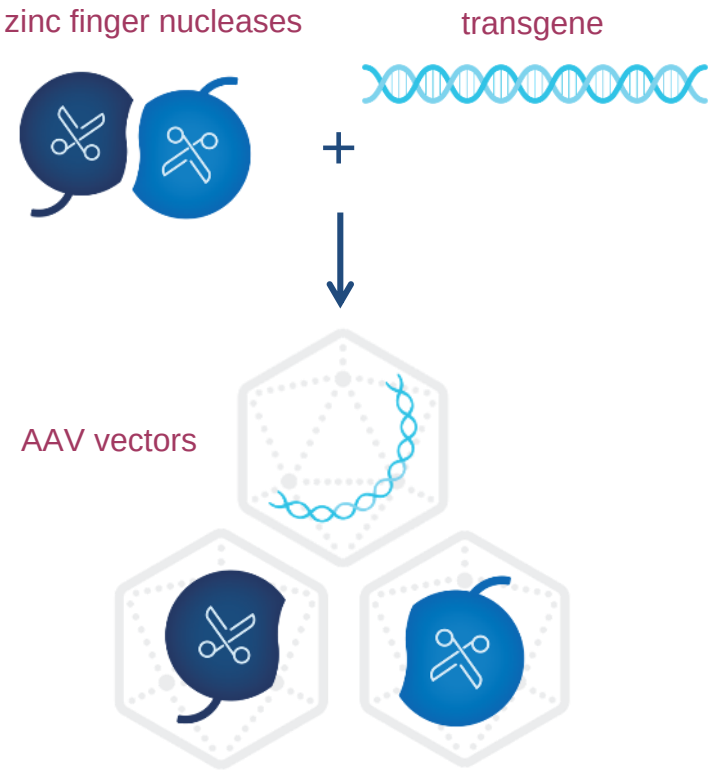
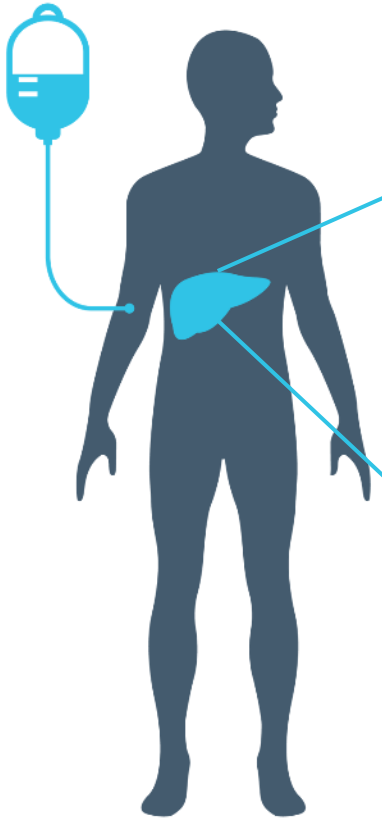
# In Vivo genome editing of albumin: harnessing the liver's most highly expressed locus

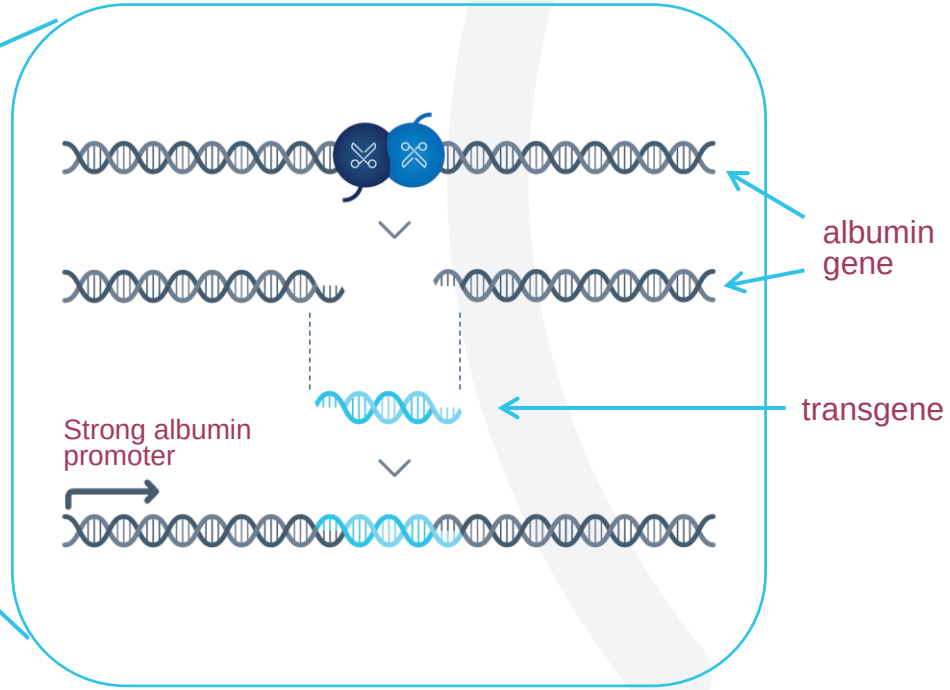
## Packaging into AAV vectors




## Delivery



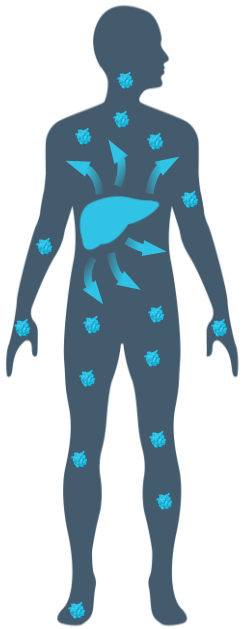
## In the liver



# Genome editing is designed to produce IDS continuously to increase enzyme exposure for receptor-mediated uptake

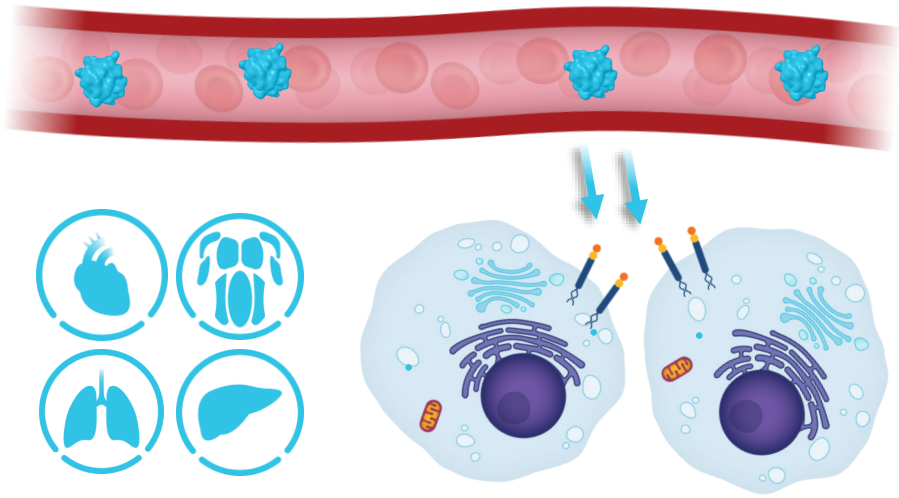
**1**

Edited liver cells steadily release IDS enzyme into the circulation



**2**

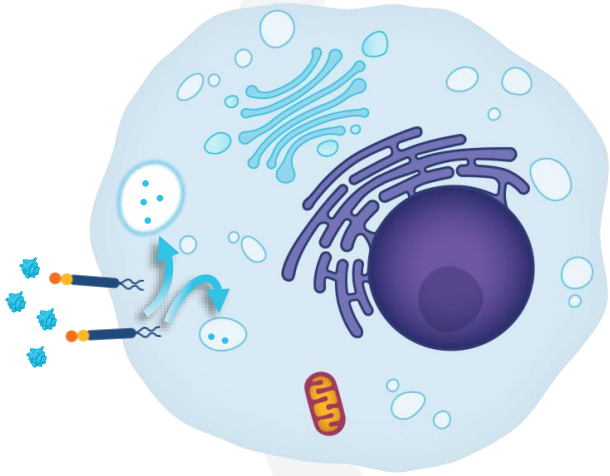
Stable enzyme levels in circulation increase IDS exposure in tissues throughout the body, facilitating receptor-mediated uptake of enzyme



Continuous IDS exposure may also facilitate uptake in tissues with limited vascularization

**3**

IDS enzyme is transported to lysosomes to metabolize GAGs



Goal is for continuous IDS production to stabilize or reduce GAG accumulation

Circulation [Stable] — **Stable IDS Levels from Genome Editing** — Tissues [Stable]

# The goal of ZFN-mediated genome editing for IDS enzyme production and urinary GAG levels

- A single dose of SB-913 is designed to **insert a corrective IDS gene** into the albumin locus in liver cells with the goal of **releasing therapeutic levels of IDS enzyme** into the bloodstream
- In contrast to ERT, which provides a large bolus of enzyme for a short period of time, SB-913 is designed to **allow continuous, stable levels of IDS enzyme** concentrations in circulation
- Enzyme uptake into the tissues is a slow process – stable levels of IDS in the circulation may **prolong the exposure of the tissues to enzyme**, allowing a greater chance that IDS enzyme will be taken up via receptor-mediated uptake
- The potential clinical efficacy of SB-913 will be assessed by demonstrating **stabilization of urinary GAGs** upon withdrawal of ERT

# CHAMPIONS Study

Phase 1/2 clinical trial evaluating SB-913

# SB-913: MPS II clinical program summary

## Phase I/II Open Label Study

### Patients

Up to 9 adult males (18+) with attenuated MPS II

### Cohorts

3 dose cohorts

### Data

Preliminary data expected at SSIEM Symposium

### U.S. Clinical Trial Status

- ✔ INDs open
- ✔ Study initiated
- ✔ 7 sites active
- ✔ 5 subjects treated (1 at highest dose)

### U.K. Clinical Trial Status

- ✔ CTA granted
- Plan to initiate U.K. study by YE 2018

### Regulatory Designations

**US** FDA
- Orphan Drug
- Fast Track
- Rare Pediatric Disease

**EMA**
- Orphan Medicinal Product

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# CHAMPIONS is the first clinical study to evaluate in vivo delivery of ZFNs and effect of genome editing on MPS II

- **Evaluate safety for AAV-based delivery of ZFNs – an entirely new class of therapeutics**
  - Identify any potential dose-dependent adverse effects and define safety profile
  - Acceptable safety profile will open the door to using this same platform for other monogenic diseases and expedite the clinical development of future products

- **Determine the effect of SB-913 on MPS II pathophysiology**
  - Evaluate plasma IDS enzyme activity, urine GAG levels, and clinical outcome measures
  - Evaluate efficiency of targeted genome modification by ZFNs
  - Evaluate effect of SB-913 after withdrawal of ERT

# Expected preliminary safety and efficacy data from the CHAMPIONS study to be presented at SSIEM 2018 Symposium

- Preliminary clinical safety and efficacy data will be provided from the first two cohorts (4 subjects total) at dose levels of 5e12vg/kg and 1e13vg/kg
- Summary of any adverse events and liver function testing
- Early IDS activity and GAG results (up to 3 months of data)
- Up to 6 months of data from all three cohorts expected in Q1 2019

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# Thank you.
# Q&A