Sangamo THERAPEUTICS

Sangamo Therapeutics R&D Day

Tuesday, December 17, 2019

Forward looking statements

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of United States securities law. These forward-looking statements include, but are not limited to, the therapeutic potential of Sangamo's product candidates; the design of clinical trials and expected timing for milestones, such as enrollment and presentation of data, the expected timing of release of additional data, plans to initiate additional studies for product candidates and timing and design of these studies; the expected benefits of Sangamo's collaborations; the anticipated capabilities of Sangamo's technologies; the research and development of novel gene-based therapies and the application of Sangamo's ZFP technology platform to specific human diseases; successful manufacturing of Sangamo's product candidates; the potential of Sangamo's genome editing technology to safely treat genetic diseases; the potential for ZFNs to be effectively designed to treat diseases through genome editing; the potential for cell therapies to effectively treat diseases; and other statements that are not historical fact. These statements are based upon Sangamo's current expectations and speak only as of the date hereof. Sangamo's actual results may differ materially and adversely from those expressed in any forward-looking statements. Factors that could cause actual results to differ include, but are not limited to, risks and uncertainties related to dependence on the success of clinical trials; the uncertain regulatory approval process; the costly and research and development process, including the uncertain timing of clinical trials; whether interim, preliminary or initial data from ongoing clinical trials will be representative of the final results from such clinical trials; whether the final results from ongoing clinical trials will validate and support the safety and efficacy of product candidates; the risk that clinical trial data are subject to differing interpretations by regulatory authorities; Sangamo's limited experience in conducting later stage clinical trials and the potential inability of Sangamo and its partners to advance product candidates into registrational studies; Sangamo's reliance on itself, partners and other third-parties to meet clinical and manufacturing obligations; Sangamo's ability to maintain strategic partnerships; competing drugs and product candidates that may be superior to Sangamo's product candidates; and the potential for technological developments by Sangamo's competitors that will obviate Sangamo's gene therapy technology. Actual results may differ from those projected in forward -looking statements due to risks and uncertainties that exist in Sangamo's operations. This presentation concerns investigational drugs that are under preclinical and/or clinical investigation and which have not yet been approved for marketing by any regulatory agency. They are currently limited to investigational use, and no representations are made as to their safety or effectiveness for the purposes for which they are being investigated. Any discussions of safety or efficacy are only in reference to the specific results presented here and may not be indicative of an ultimate finding of safety or efficacy by regulatory agencies. These risks and uncertainties are described more fully in Sangamo's Annual Report on Form 10-K for the year ended December 31, 2018 as filed with the Securities and Exchange Commission on March 1, 2019 and Sangamo's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 that it filed on or about November 6, 2019. Except as required by law, we assume no obligation, and we disclaim any intent, to update these statements to reflect actual results.

Sangamo THERAPEUTICS

Agenda

Sangamo's transformation from biosciences to therapeutics	Sandy Macrae, CEO
A vision for Sangamo's future	Adrian Woolfson, Head of R&D
Gene therapy for hemophilia A, Fabry disease and PKU	Bettina Cockroft, CMO
Engineering zinc finger proteins for therapeutics applications	Ed Rebar, Head of Technology
Gene editing of HSCs with ZFN: Beta thalassemia	Wes Miller, Medical Director
Cell therapy	Jason Fontenot, Head of Cell Therapy
TX200: CAR-T_{REG} cell therapy for renal transplantation	Essra Ridha, Medical Director
AAV engineering	David Ojala, Scientist
Regulating gene expression in the CNS with the ZFP-TF platform	Amy Pooler, Neuroscientist
Manufacturing strategy	Andy Ramelmeier, Head of Tech Ops
Closing remarks	Sandy Macrae, CEO

Sangamo's transformation from biosciences to therapeutics

Sandy Macrae, CEO

We are committed to translating ground-breaking science into genomic medicines that transform patients' lives

Sangamo has a history of leading from the front

1st

to edit endogenous human genes

1st

to treat patients with gene edited T cells

1st

to treat patients with in vivo genome editing

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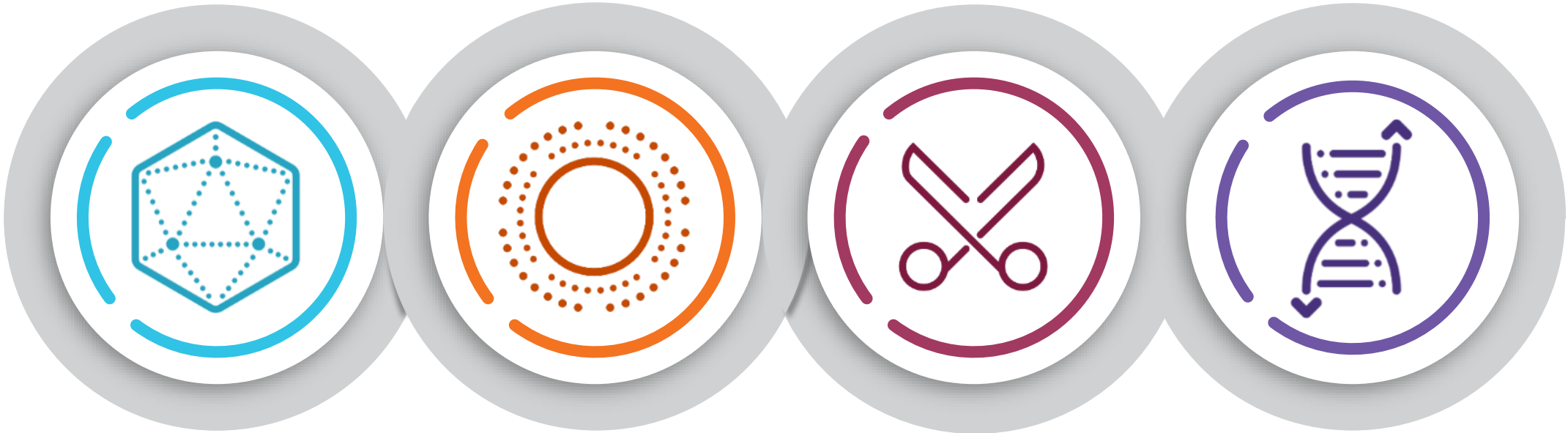
Our proprietary suite of genomic medicine technologies

Gene Therapy
AAV

Gene-Edited Cell Therapy
ZFN; AAV; LV

Genome Editing
AAV; ZFN

Genome Regulation
AAV; ZFP-TF



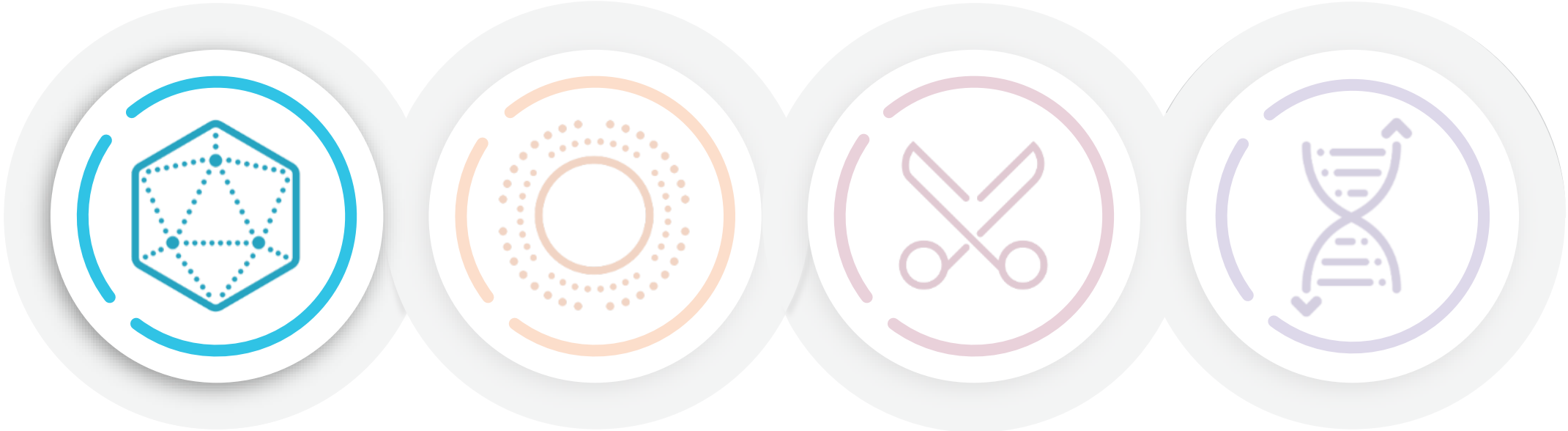
Gene therapy is a near term opportunity that delivers value for patients and shareholders

Gene Therapy
AAV

Gene-Edited Cell Therapy
ZFN; AAV; LV

Genome Editing
AAV; ZFN

Genome Regulation
AAV; ZFP-TF



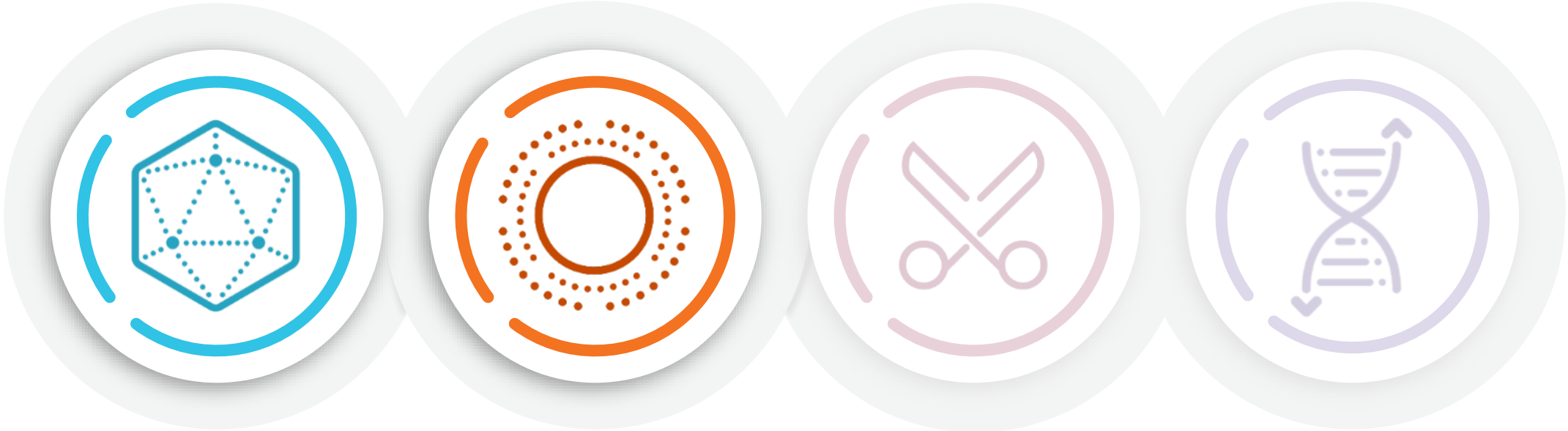
Ex vivo gene-edited cell therapy is the most straightforward application of gene editing

Gene Therapy
AAV

Gene-Edited Cell Therapy
ZFN; AAV; LV

Genome Editing
AAV; ZFN

Genome Regulation
AAV; ZFP-TF



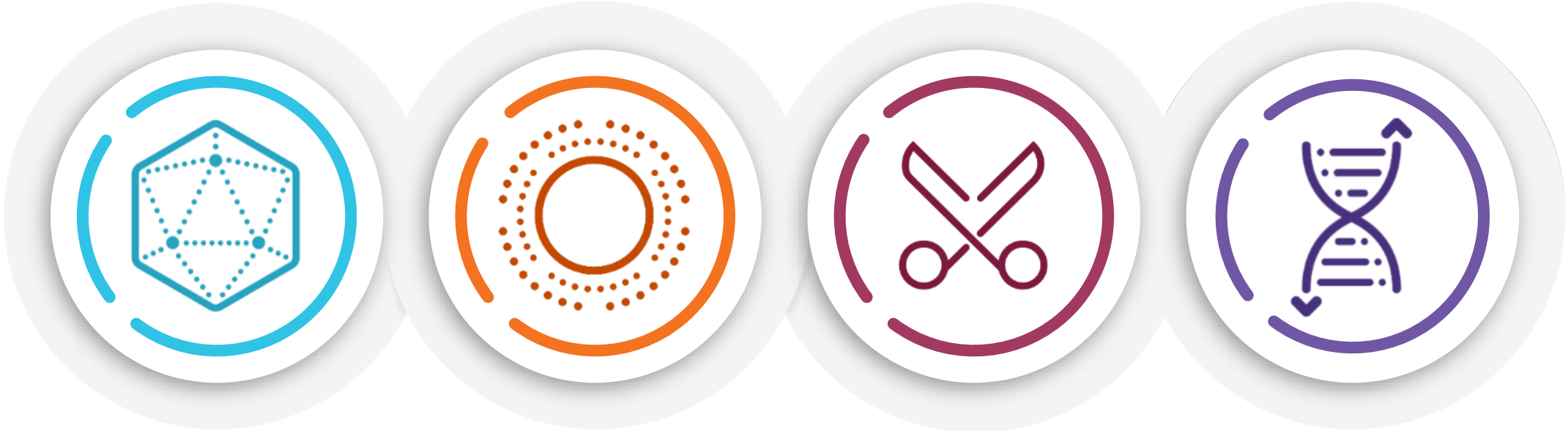
In vivo genome editing and regulation are the future of genomic medicine

Gene Therapy
AAV

Gene-Edited Cell Therapy
ZFN; AAV; LV

Genome Editing
AAV; ZFN

Genome Regulation
AAV; ZFP-TF



Key themes for R&D day

1. Core capabilities and talent enable transition to late-stage biotech
2. Clinical data yields useful new insights across platforms
3. Leading innovation in editing, cell therapy, and genome regulation
4. Advancing genomic medicines for larger patient populations

Key themes for R&D day

1. Core capabilities and talent enable transition to late-stage biotech
2. Clinical data yields useful new insights across platforms
3. Leading innovation in editing, cell therapy, and genome regulation
4. Advancing genomic medicines for larger patient populations

Sangamo today has the core capabilities and talent to drive our genomic medicine pipeline forward into late-stage development

Brisbane: headquarters and manufacturing

Valbonne: CAR-T_{REG} cell therapy

Richmond: research & development

London: clinical operations

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Functional leadership is prepared for Sangamo's evolution to a late-stage biotech

Adrian Woolfson
Head of R&D

Sung Lee
CFO

Gary Loeb
General Counsel

Andy Ramelmeier
Tech Ops

Bettina Cockroft
CMO

Jason Fontenot
Cell Therapy

Laurie Baylor-Curtis
Clinical Ops

Stephane Boissel
Strategy

Engaging with patients to ensure our clinical programs meet their needs

Key themes for R&D day

1. Core capabilities and talent enable transition to late-stage biotech
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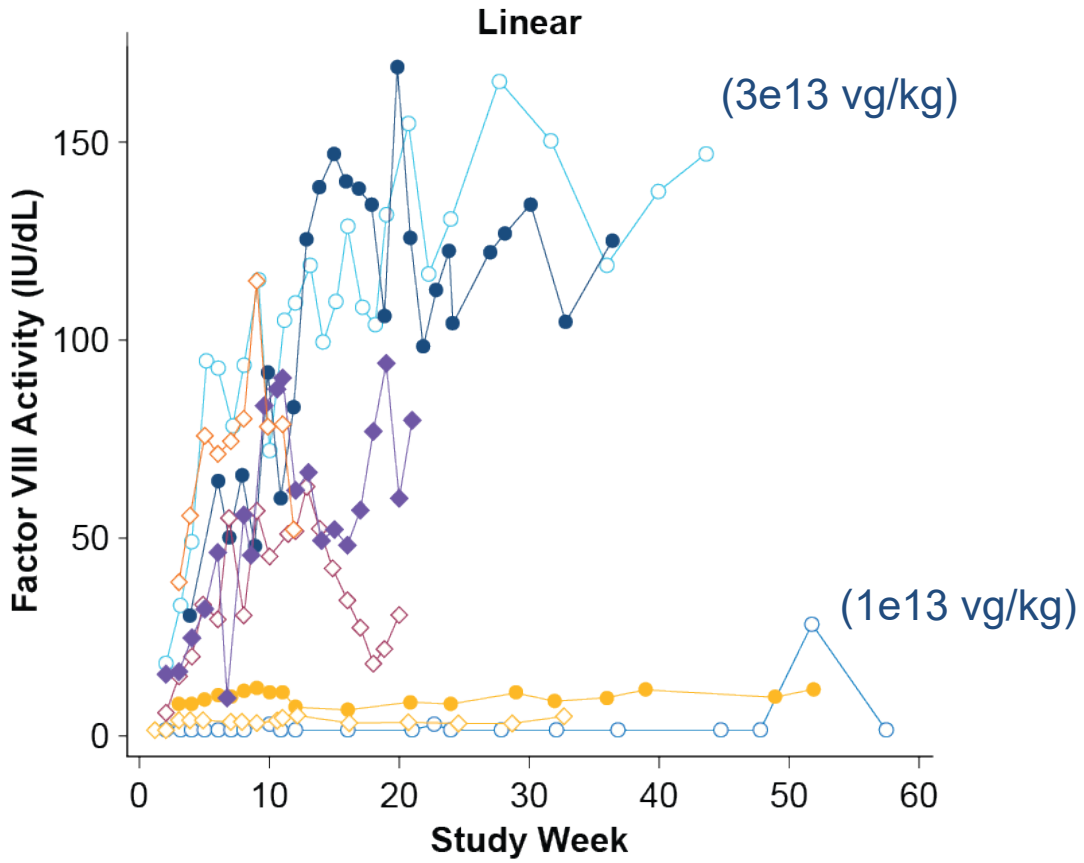
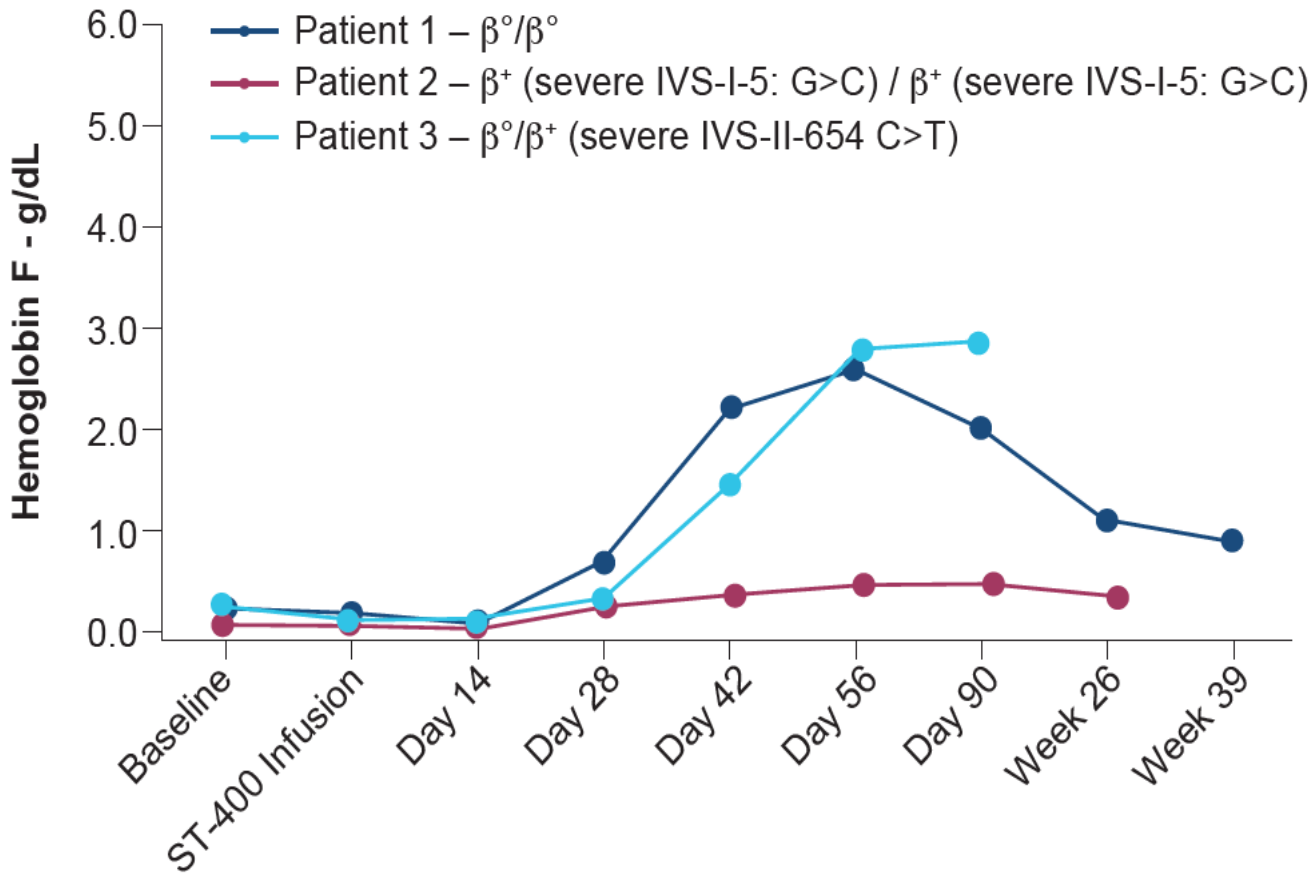
Key insight: AAV6 activity threshold



Insight translates from SB-525 hemophilia A to follow on gene therapy and genome editing programs

Insights from preliminary ST-400 data

ST-400: Fetal hemoglobin response



Data cuts: clinical, October 10, 2019; laboratory, November 8, 2019

Key themes for R&D day

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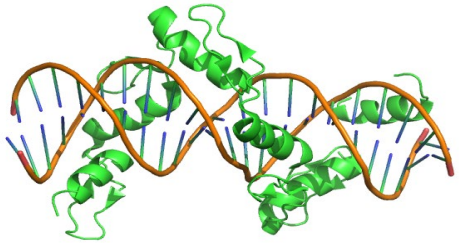
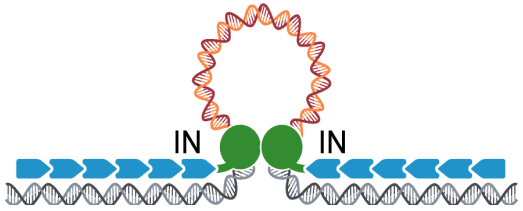
Leading innovation in genomic medicine technology



$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

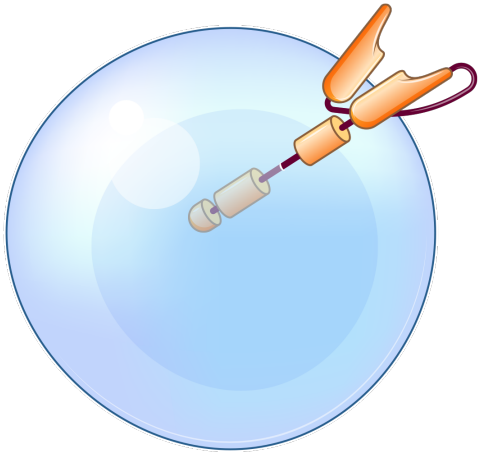
Zinc finger engineering



From genome editing to gene editing

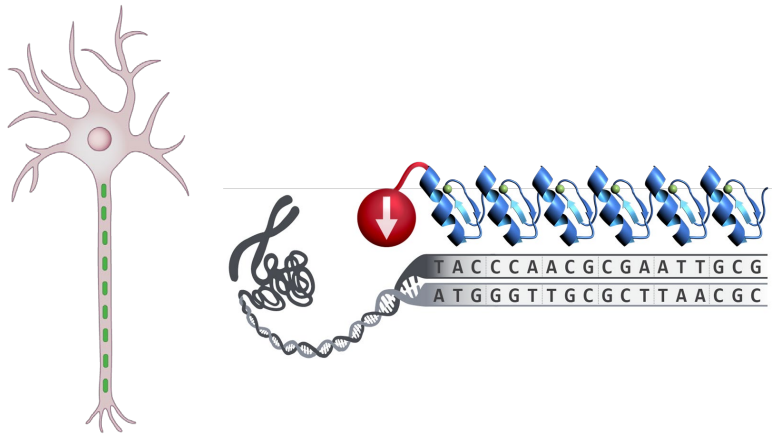
Leading innovation in genomic medicine technology

Sangamo France team

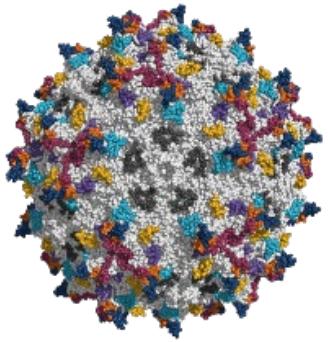


CAR-T_{REG} : the new frontier in cell therapy

Leading innovation in genomic medicine technology



Gene repression for CNS diseases



Engineering new viruses to access the brain

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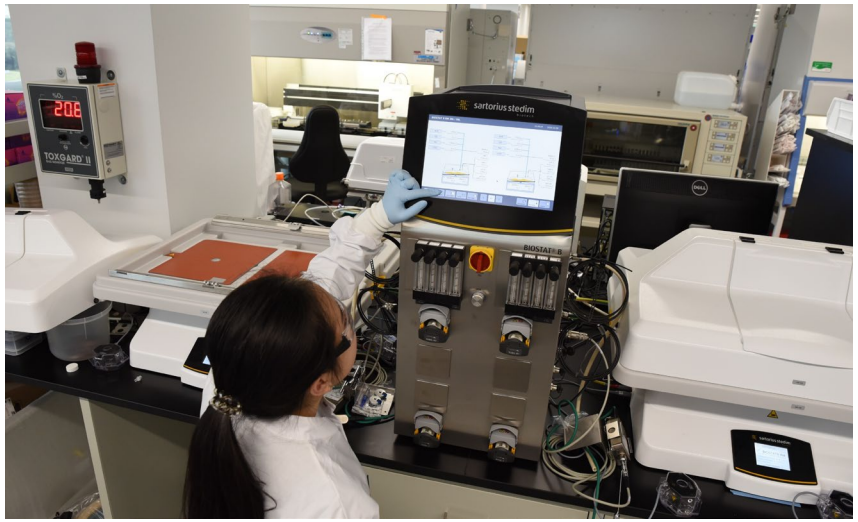
A world class manufacturing organization within Sangamo



Newly announced programs advancing toward clinical development

ST-101: Gene therapy for PKU
(IND projected 2021)

ST-501: Genome regulation for tauopathies
(IND projected 2021)

ST-502: Genome regulation for α-Synuclein
(IND projected 2022)

Key themes for R&D day

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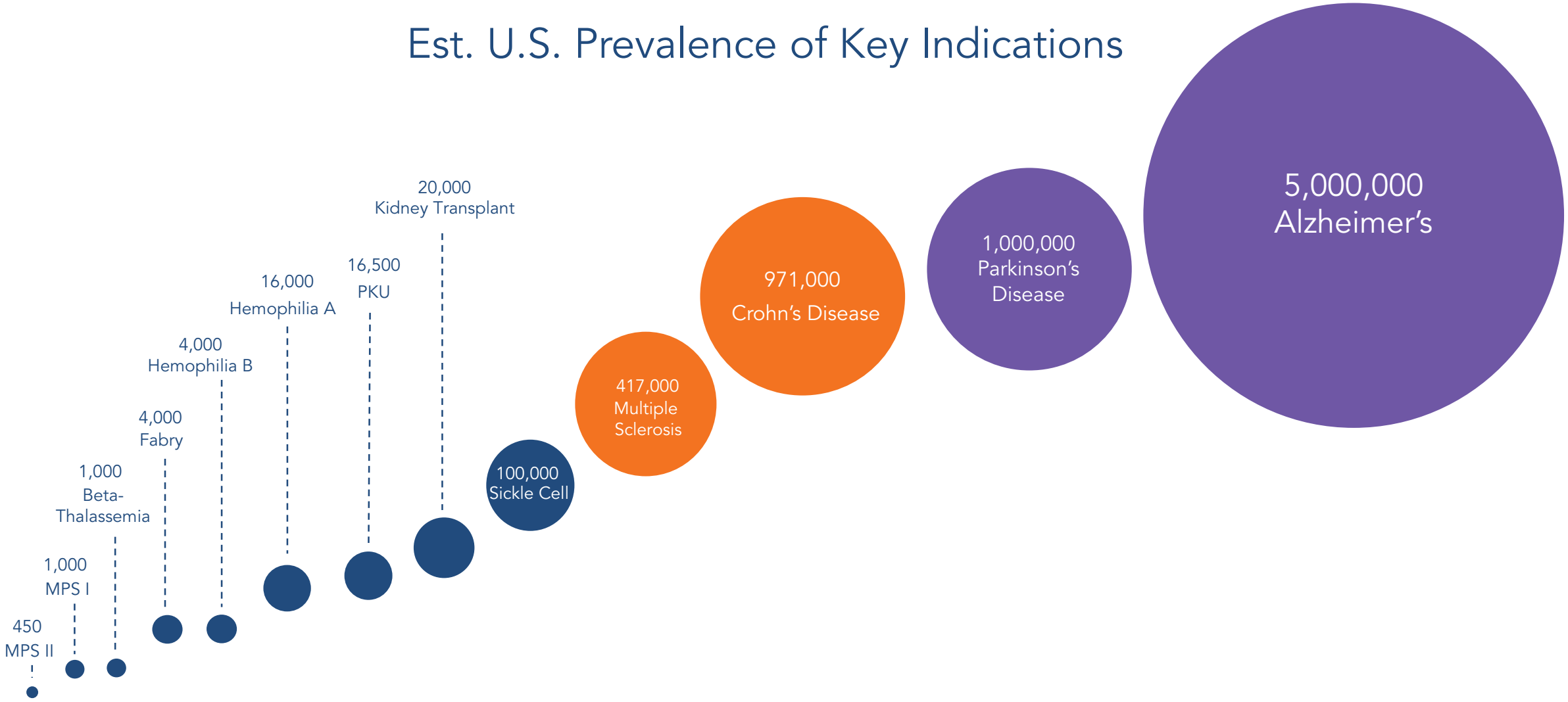
Sangamo's technology will address large markets with serious unmet need



Note: The size of the spheres presented are adjusted for visual representation and may not be proportional

Pipeline expected to broaden into late-stage development 1Q 2020

Preclinical

- PKU (ST-101) — SANGAMO WHOLLY OWNED
- IBD — SANGAMO WHOLLY OWNED
- MS — SANGAMO WHOLLY OWNED
- Oncology (KITE-037) — PARTNER Kite
- Oncology — PARTNER Kite
- α-Synuclein (ST-502) — SANGAMO WHOLLY OWNED
- ALS/FTD — PARTNER Pfizer
- Huntington's Disease — PARTNER Takeda
- Prion — SANGAMO WHOLLY OWNED
- Tauopathies (ST-501) — SANGAMO WHOLLY OWNED

Phase 1/2

- Fabry Disease (ST-920) — SANGAMO WHOLLY OWNED
- Beta Thalassemia (ST-400) — PARTNER SANOFI
- Sickle Cell Disease (BIVV003) — PARTNER SANOFI
- Solid Organ Transplant (TX200) — SANGAMO WHOLLY OWNED
- MPS II (SB-913) — SANGAMO WHOLLY OWNED

Phase 3

- Hemophilia A (SB-525) — PARTNER Pfizer

(Pfizer initiated Ph3 lead-in study Oct. '19)

Gene Therapy | *Ex Vivo* Gene-Edited Cell Therapy | *In Vivo* Genome Editing | *In Vivo* Genome Regulation

Sangamo THERAPEUTICS

A vision for Sangamo's future: Building & sustaining an innovative genomic medicine company

Adrian Woolfson, Head of R&D

R&D vision

‘To build a robust, sustainable, differentiated, innovative, and high value genomic medicine pipeline that addresses patients with high unmet medical needs’

Sangamo's platform technologies

Gene Therapy
AAV

SB-525: Hemophilia A
ST-920: Fabry disease
ST-101: PKU

Gene-Edited Cell Therapy
ZFN; AAV; LV

ST-400: Beta thalassemia
BIVV003: Sickle cell disease
TX200: Solid organ transplant
KITE-037: Allo-CD19 CAR-T
Undisclosed targets

Genome Editing
AAV; ZFN

SB-913: MPS II

Genome Regulation
AAV; ZFP-TF

ST-501: Tauopathies
ST-502: α-synuclein
C9ORF72-linked ALS/FTLD
Huntington's disease
Undisclosed targets

Pipeline expected to broaden into late-stage development 1Q 2020

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Vision: The three waves of Sangamo

Wave 1

Gene therapy

Cell therapy

In vivo editing

Wave 2

Gene therapy

Cell therapy

In vivo editing

Genome regulation

Wave 3

Cell therapy

In vivo editing

Genome regulation

Vision: The three waves of Sangamo

Wave 1

Gene therapy
- SB-525 (Hem A)
- ST-920 (Fabry)

Cell therapy
- ST-400 (BThal)
- BIVV-003 (SCD)
- TX200 (Transplant)
- KITE-037 (CD19)

In vivo editing
- SB-913 (MPSII)

Wave 2

Gene therapy
- ST-101 (PKU)

Cell therapy
- Allo CAR-T
- CAR-T_{REGS} (IBD/MS)

In vivo editing

Genome regulation
- ST-501 (Tauopathies)
- ST-502 (α-synuclein)
- Huntington's Disease
- ALS
- Prion

Wave 3

Cell therapy
- iPSC
- Allo CAR-TREG
- CAR-T
- Knock in/out
- New cell types

In vivo editing
- New functionalities

Genome regulation

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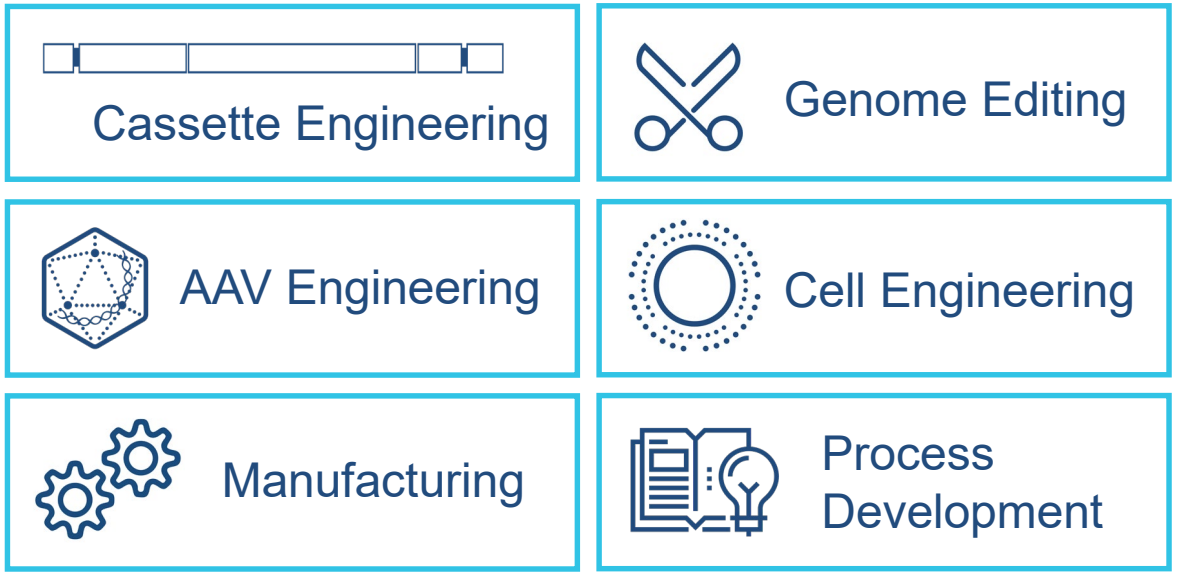
Sangamo's core capabilities allow for cross-platform synergy



Interconnectivity of core capabilities help guide other programs in development

Gene therapy: Building on recent success in hemophilia A

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(Ph3 lead in study initiated Oct. '19)

Gene Therapy | *Ex Vivo* Gene-Edited Cell Therapy | *In Vivo* Genome Editing | *In Vivo* Genome Regulation

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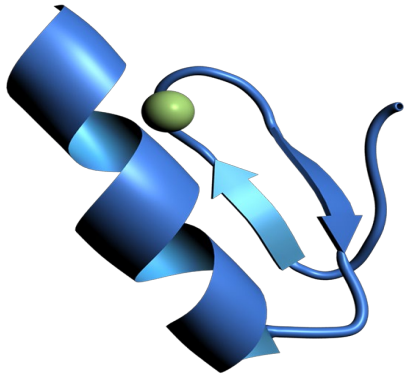
Three therapeutic platforms are based on ZFPs

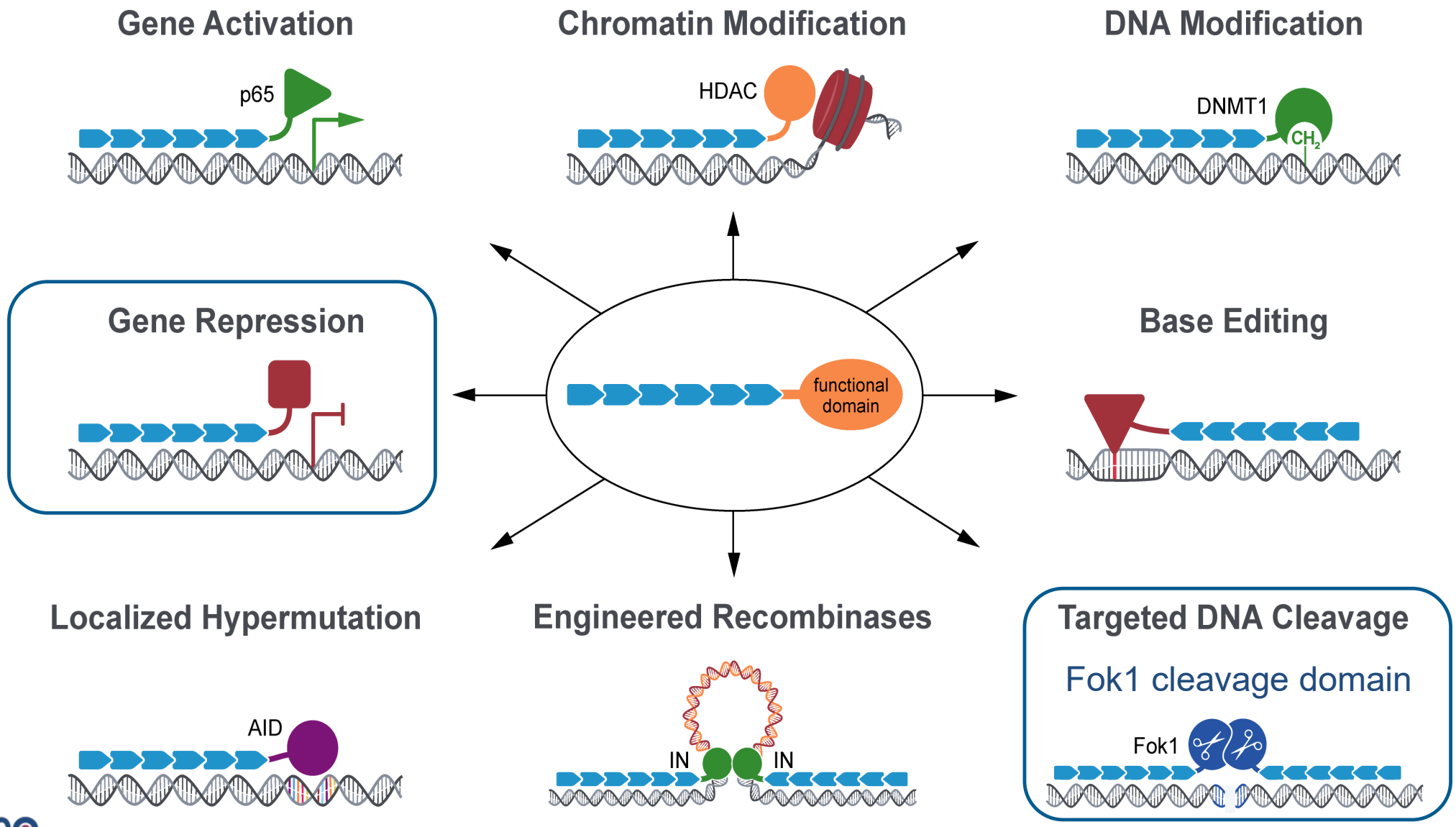


Gene-Edited Cell Therapy

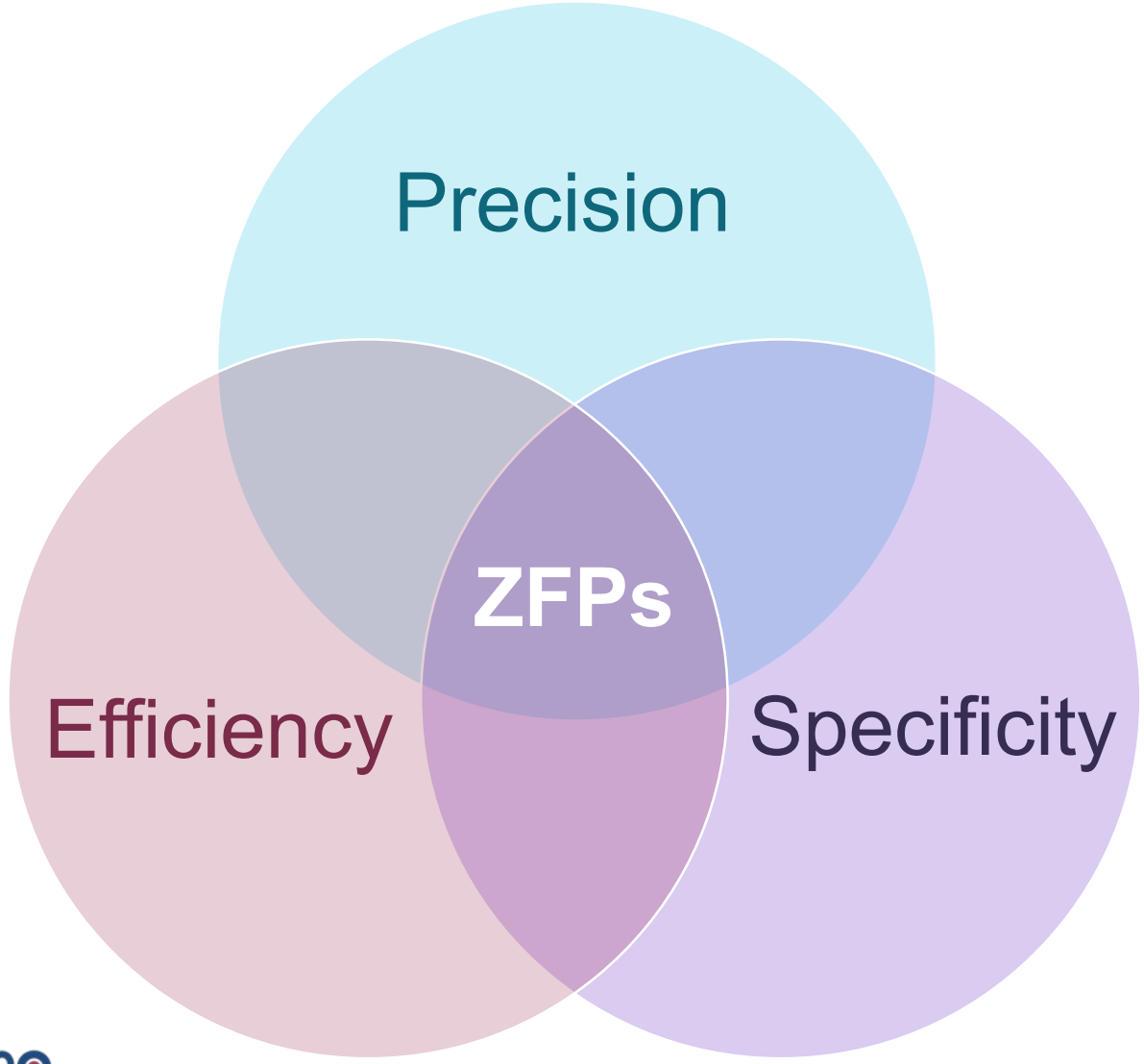
Genome Editing

Genome Regulation

Functional diversification of ZFPs



Features of synthetic ZFPs that make them preferred editors



Designable Proteins

Small size

Combinatorial complexity

Densely packed

PAM motif independence

Human-derived proteins

Higher order behaviors

Sangamo is at the forefront of gene-editing innovation

Technology validated by pharma partnerships

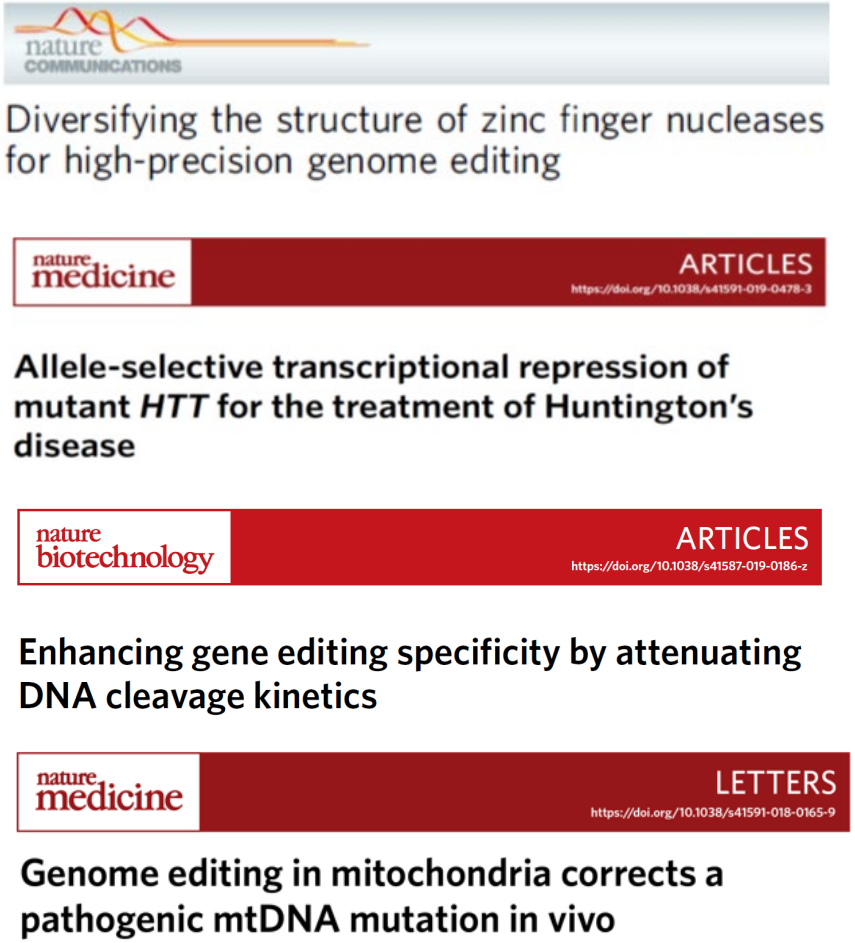
Pfizer

Kite
A GILEAD Company

SANOFI

Takeda

Continuous innovation demonstrated with recent publications



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Consolidate and expand in *ex vivo* gene-edited cell therapy

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Phase 3

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(Pfizer initiated Ph3 lead-in study Oct. '19)

Gene Therapy | *Ex Vivo* Gene-Edited Cell Therapy | *In Vivo* Genome Editing | *In Vivo* Genome Regulation

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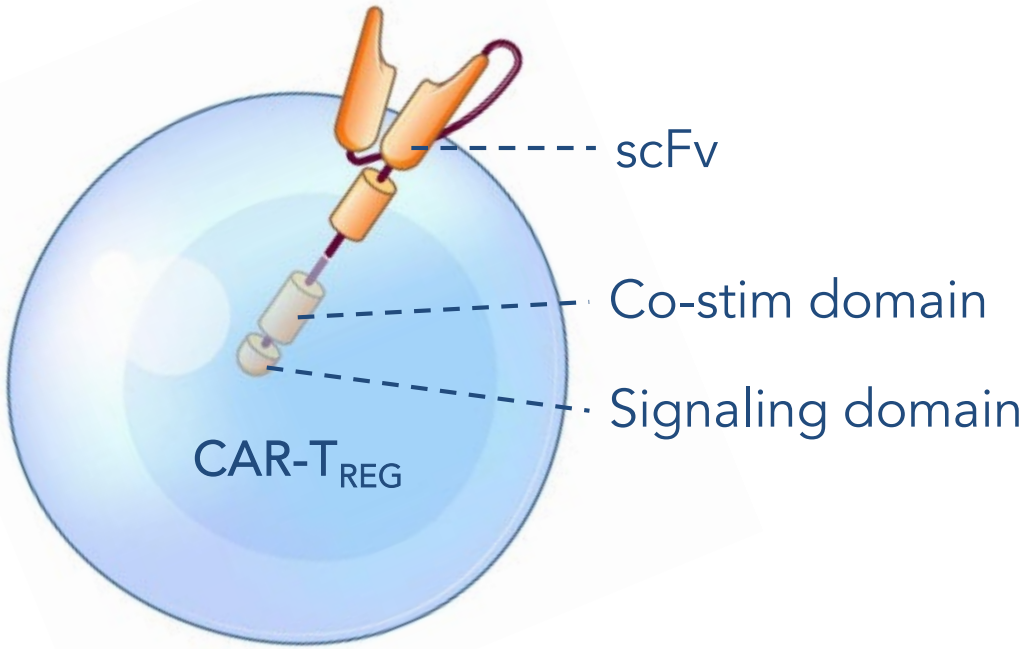
Pioneering new frontier: CAR-T_{REG} therapy

Personalized cell therapy based on modified antigen specific CAR-T_{REGS}



Initial target indication: Renal transplant

- TX200 CTA accepted
- Study to commence 2020

STEADFAST
Sangamo THERAPEUTICS

Optimize and diversify *in vivo* genome editing

Preclinical

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Phase 3

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(Pfizer initiated Ph3 lead-in study Oct. '19)

Gene Therapy | *Ex Vivo* Gene-Edited Cell Therapy | *In Vivo* Genome Editing | *In Vivo* Genome Regulation

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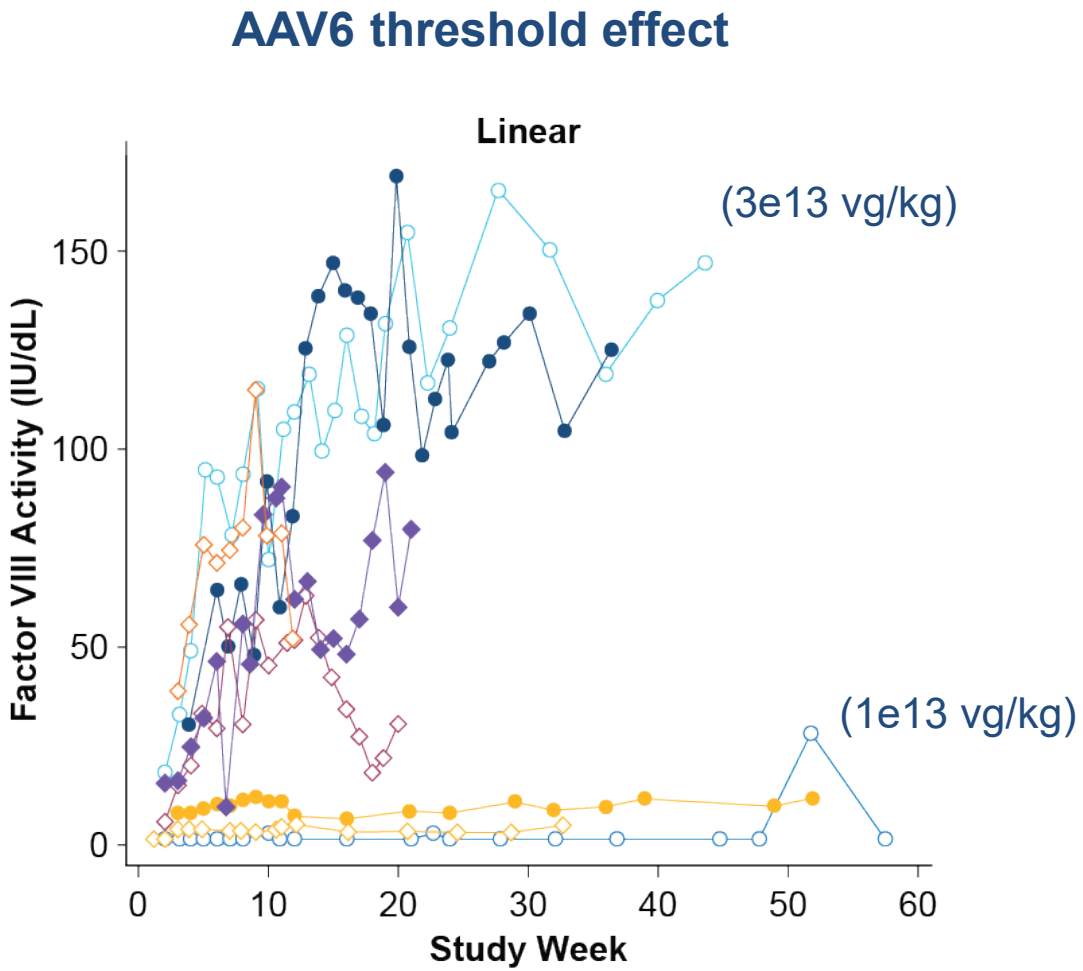
Evidence of successful *in vivo* editing in CHAMPIONS study

- Detection of chimeric albumin-IDS PCR product in 2 patients
- Substantial IDS synthesis in patient 6 (5e13 vg/kg)
- Patient 6 (125 kg), received ~2x vector dose

Non-linear AAV6 threshold effect in HemA gene therapy study



ZFNs were sub-threshold in CHAMPIONS study

1:1:8 Ratio

Total Vector dose	Effective dose of individual component		
5e13 vg/kg:	**5e12**	**5e12**	**4e13**

May only need to be better by a factor of 3x for therapeutic efficacy

Five potential levers for optimizing *in vivo* editing

Enhanced efficiency of ZFN delivery to hepatocytes is critical

HemA data suggests targeting ≥ 3e13 is necessary

Lever 1: Dose

Lever 2: AAV2.0

Lever 3: Second-generation ZFNs (phosphate contact residue modifications, etc.)

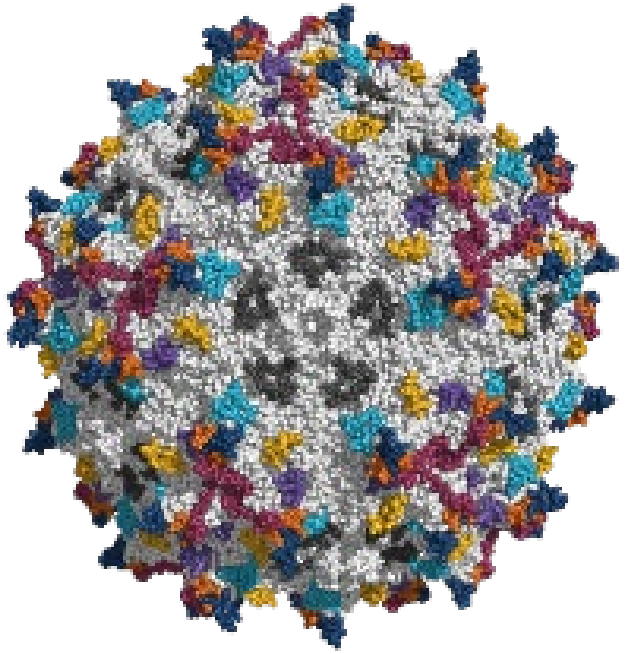
Lever 4: Donor 2.0

Lever 5: 2 in 1 ZFNs (co-package left and right ZFNs)

New delivery capabilities offer new possibilities

Exploring new delivery modalities

- Engineered AAV6
- Other AAV serotypes
- Lipid Nanoparticles (LNPs)
- Other modalities



AAV

In vivo genome regulation for CNS diseases

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- Sickle Cell Disease (BIVV003) — PARTNER SANOFI
- Solid Organ Transplant (TX200) — SANGAMO WHOLLY OWNED
- MPS II (SB-913) — SANGAMO WHOLLY OWNED

Phase 3

- Hemophilia A (SB-525) — PARTNER Pfizer

(Pfizer initiated Ph3 lead-in study Oct. '19)

Sangamo THERAPEUTICS

Gene Therapy | *Ex Vivo* Gene-Edited Cell Therapy | *In Vivo* Genome Editing | *In Vivo* Genome Regulation

Potential CNS applications for Sangamo's zinc finger protein transcription factors (ZFP-TFs) and ZFNs

ZFP-TF genome regulation

Pan-Allele	ZFP-TFs for single gene repression	• Tauopathies (IND 2021) • α-synuclein (IND 2022) • Prion
Allele-Selective	ZFPs target disease allele repeats selectively	• Huntington's Disease • C9ORF72-linked ALS
Epigenetic editing	ZFP-Epi to demethylate select sites	• Rett Syndrome • Fragile X

ZFN genome editing

Inflammation	T_{REGS} for inhibition of neuroinflammation and remyelination	• Multiple Sclerosis • ALS
Mitochondrial	ZFNs for selective clearance of mutant mitochondrial genomes	• Cerebellar Ataxia • Leigh Syndrome

Sangamo THERAPEUTICS

Vision: The three waves of Sangamo

Wave 1

Gene therapy

Cell therapy

In vivo editing

Wave 2

Gene therapy

Cell therapy

In vivo editing

Genome regulation

Wave 3

Cell therapy

In vivo editing

Genome regulation

Gene therapy for hemophilia A, Fabry disease and PKU

Bettina M. Cockroft, Chief Medical Officer

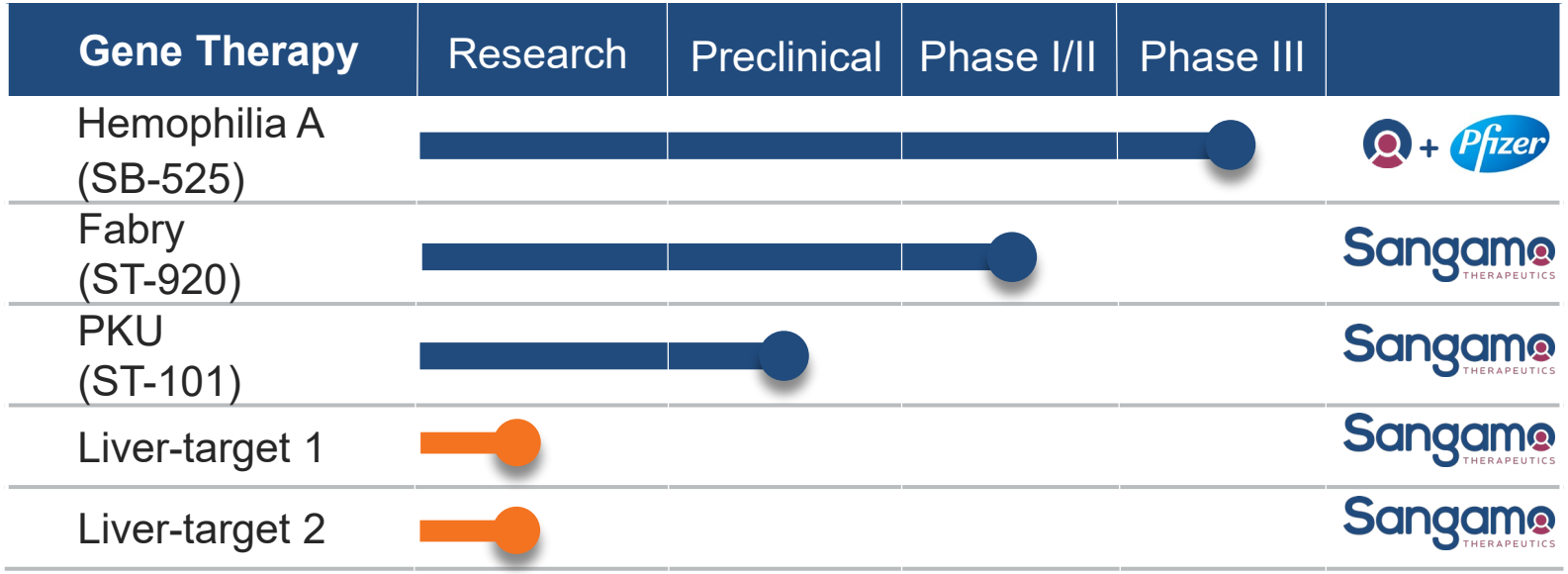
Clinical development at Sangamo

Therapeutic Targets → **Trial Design** → **Clinical Relevance** → **Data Disclosure**

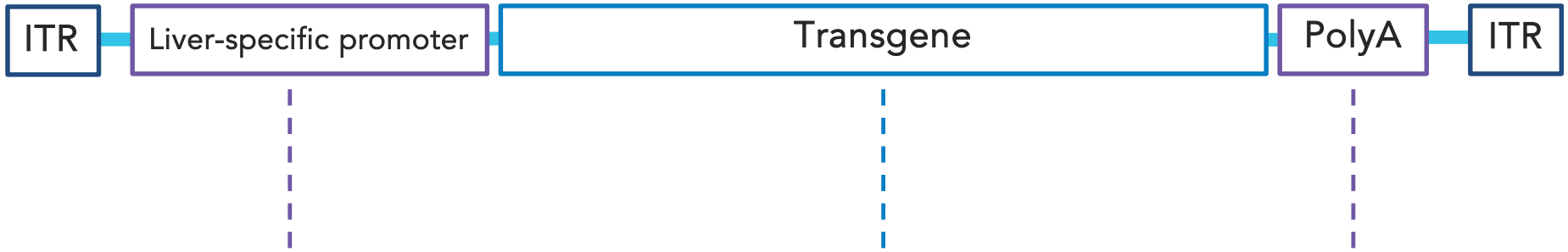
Gene Therapy

Gene Therapy programs help validate platform, show execution capabilities, and provide funding for future programs.

Projected 1Q 2020 gene therapy pipeline



Experience with AAV manufacturing and gene construct design can be translated across our gene therapy platform



Promoter module modifications

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Transgene modifications

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Other modifications

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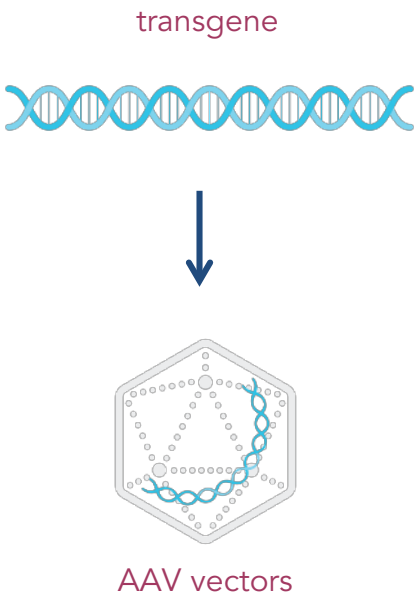
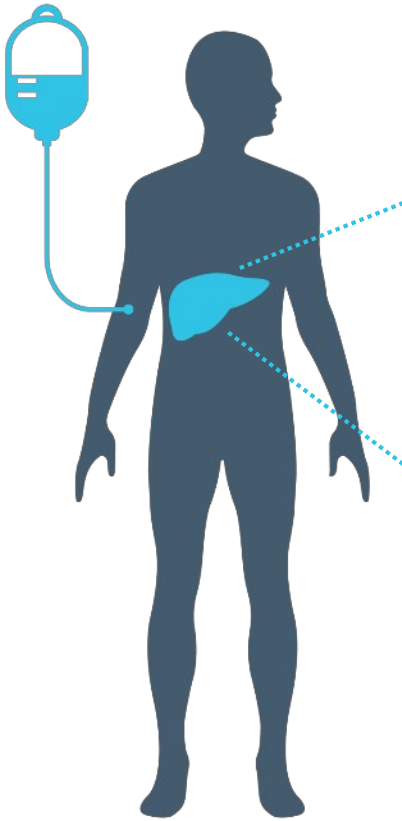
- Removed unnecessary nucleic acids to reduce size
- Optimized sequences outside transgene

Sangamo's gene therapy platform: potential for potent therapeutic solutions for monogenic diseases

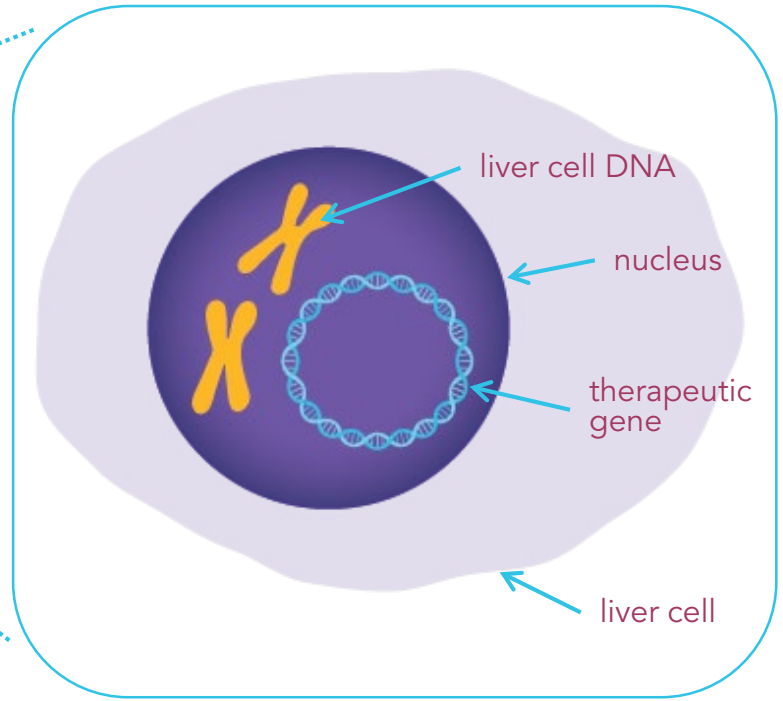
Packaging into AAV vectors



Delivery



To the liver



SB-525 gene therapy for hemophilia A

SB-525, gene therapy for hemophilia A

Phase I/II Open Label Study (ALTA)

Dose Escalation Complete

Cohort 1	Cohort 2	Cohort 3	Cohort 4
9e11 vg/kg	2e12 vg/kg	1e13 vg/kg	3e13 vg/kg

(Patients did not receive prophylactic steroids)

Ongoing Phase I/II Study

- Enrollment complete
- Updated results presented at ASH

Lead-in Phase III Study

- Trial open and first patients are enrolled

Manufacturing Transfer to Pfizer Completed

Next steps

- Regulatory discussions underway for Phase III
- IND transfer to Pfizer in process

- Orphan Drug
- Fast Track
- RMAT

- Orphan Medicinal Product

Goals

Patient safety	FVIII activity	Reduction of bleeding events	Reduction of factor replacement use

Sangamo + Pfizer

Sangamo THERAPEUTICS

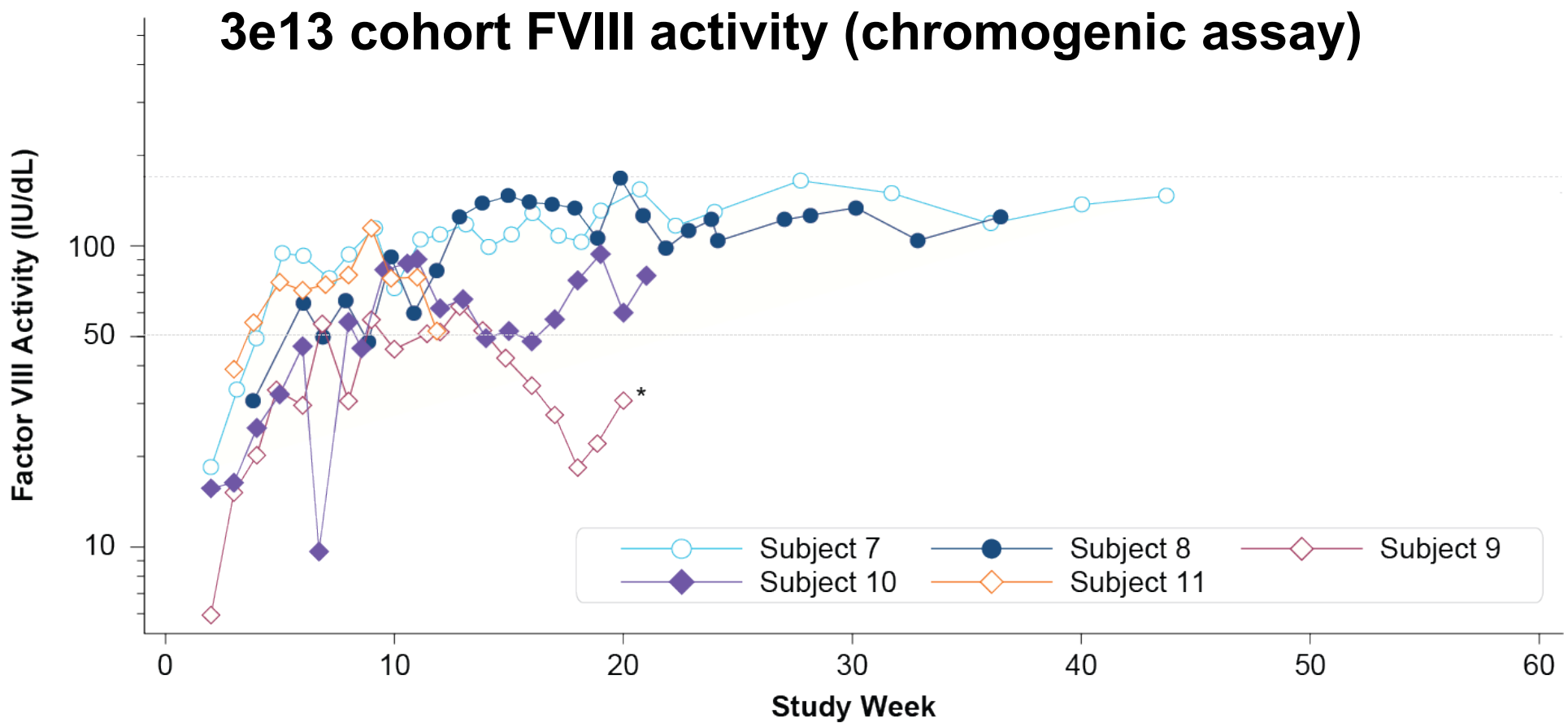
Presented at the 2019 American Society of Hematology Annual Meeting; Orlando, Florida; December 7, 2019

Updated Follow-up of the Alta Study, a Phase 1/2, Open Label, Adaptive, Dose-Ranging Study to Assess the Safety and Tolerability of SB-525 Gene Therapy in Adult Subjects With Hemophilia A

Barbara A. Konkle,[1] Kimo Stine,[2] Nathan Visweshwar,[3] Thomas Harrington,[4] Andrew D. Leavitt,[5] Adam Giermasz,[6] Steven Arkin,[7] Gregory Di Russo,[7] Ashley Snyder,[8] Adrian Woolfson,[8] and Didier Rouy[8]

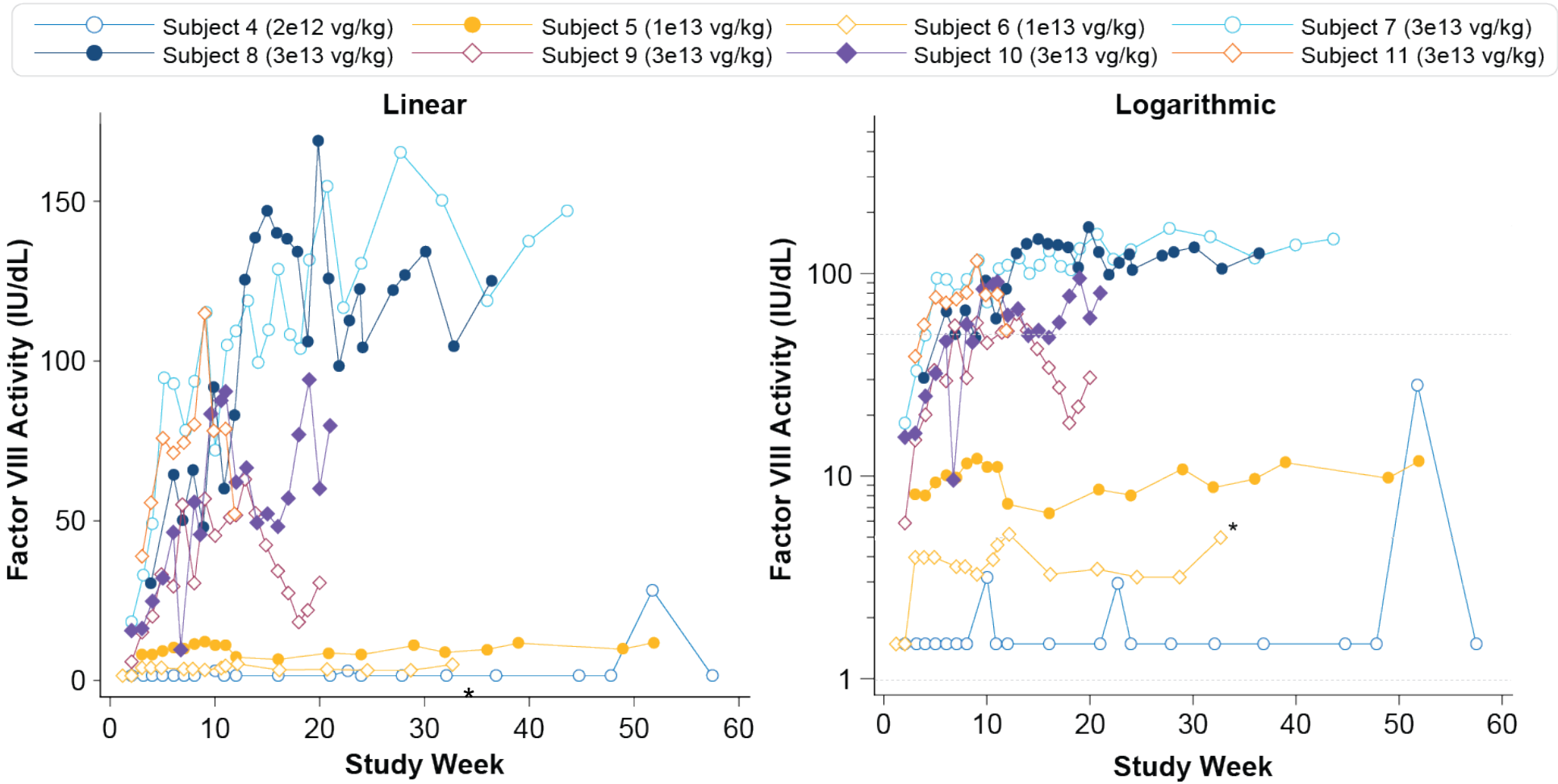
[1]Bloodworks Northwest and the University of Washington, Seattle, WA; [2]Arkansas Children's Hospital, Little Rock, AR; [3]Department of Internal Medicine, Division of Hematology and Medical Oncology, University of South Florida, Tampa, FL; [4]University of Miami Miller School of Medicine, Miami, FL; [5]Department of Laboratory Medicine and Department of Medicine, University of California, San Francisco, CA; [6]University of California, Davis, CA; [7]Pfizer Inc., Cambridge, MA.; [8]Sangamo Therapeutics, Brisbane, CA

High dose cohort FVIII durability up to 11 months



*von Willebrand factor levels for that subject dropped from 118% at week 1 to 48% at week 16
FVIII values with sample dates prior to treatment and up to 1 week after the treatment date or with sample dates within 3 days after an FVIII infusion are excluded.
Data cutoff date: October 17, 2019.

FVIII activity shows dose response between cohorts



Chromogenic Assay. FVIII values with sample dates prior to treatment and up to 1 week after the treatment date or with sample dates within 3 days after a Factor VIII infusion are excluded.
Data cutoff date: October 17, 2019.
*Subject missed follow-up visits and is no longer in contact with the site.

Zero bleeding events in high dose cohort

Dose Cohort (dose vg/kg)	Subject	Follow-up (weeks)	Bleeding Episodes ≥3 Weeks Post Treatment
9e11	1	112	7
9e11	2	103	5
2e12	3	93	8
2e12	4	86	5
1e13	5	70	10
1e13	6	61	0
3e13	7	44	0
3e13	8	37	0
3e13	9	24	0
3e13	10	22	0
3e13	11	12	0

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Bleeding episodes are being counted 21 days post dosing.
Days post dosing = October 17, 2019 - dosing day.

Eliminated FVIII replacement use in high dose cohort

Factor VIII Replacement Usage

Dose Cohort (dose vg/kg)	Subject	Follow-up (weeks)	Factor VIII Prophylactic Regimen Prior to Dosing	Factor VIII Infusions ≥3 Weeks Following SB-525 Treatment
9e11	1	112	2/week	115
9e11	2	103	2/week	26
2e12	3	93	2/week	13
2e12	4	86	3/week	9
1e13	5	70	Every other day	17
1e13	6	61	Every other day	0
3e13	7	44	Every 4 days	0
3e13	8	37	Every other day	1*
3e13	9	24	Every 3 days	0
3e13	10	22	Every 3 days	0
3e13	11	12	2/week	0

*Prophylactic coverage stopped 3 weeks and 2 days after SB-525 administration.
Factor VIII infusions are being counted 21 days post dosing.
Days post dosing = October 17, 2019 - dosing day.

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Safety Summary

Treatment-Related Adverse Event Summary

MedDRA Preferred Term	Cohort 1 9e11 vg/kg (N=2) n (%) [T]	Cohort 2 2e12 vg/kg (N=2) n (%) [T]	Cohort 3 1e13 vg/kg (N=2) n (%) [T]	Cohort 4 3e13 vg/kg (N=5) n (%) [T]	All Subjects (N=11) n (%) [T]
Any treatment-related event	0	2 (100) [4]	0	4 (80.0) [12]	6 (54.5) [16]
Alanine aminotransferase increased	0	2 (100) [3]	0	2 (40.0) [3]	4 (36.4) [6]
Pyrexia	0	0	0	3 (60.0) [3]	3 (27.3) [3]
Aspartate aminotransferase increased	0	1 (50) [1]	0	1 (20.0) [1]	2 (18.2) [2]
Tachycardia	0	0	0	2 (40.0) [2]	2 (18.2) [2]
Fatigue	0	0	0	1 (20.0) [1]	1 (9.1) [1]
Hypotension	0	0	0	1 (20.0) [1]	1 (9.1) [1]
Myalgia	0	0	0	1 (20.0) [1]	1 (9.1) [1]

N=Total number of subjects in each treatment group, n=number of subjects in each system organ class (SOC), [T]=total number of treatment-related adverse events. Each subject is counted only once for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted only once for that system organ class.
Table is sorted in descending order. Data cutoff date: October 17, 2019.

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ALT elevation did not result in loss of FVIII expression

4 out of 5 subjects in the high dose cohort had an ALT elevation

ALT Elevation Did Not Result in Loss of FVIII Expression

Subject number	Time of first ALT elevation (week)	Maximum ALT value (U/L / grade)	Steroids high dose (weeks)	Steroids taper (weeks)	FVIII levels (Chromo, IU/dl) at start of steroids	FVIII levels (Chromo, IU/dl) at end of taper	Time of second ALT elevation (week)	Weeks of steroids after second elevation
7	4.5	98 (Gr 1)	5	7.5	94.8	108.2	28.5	1.5*
8	12	66 (Gr 1)	2	9	83.1	112.6	N/A	N/A
10	5.5	63 (Gr 1)	5	6	46.4	57.1	20	4#
11	8	192 (Gr 2)	2.5	4.5	80.2	Pending	N/A	N/A

*After the end of the second course of steroids, the FVIII level was 150.4 IU/dL.
#Ongoing.

SB-525 (PF-07055480) program transitioning to Pfizer

- Manufacturing transfer to Pfizer completed in October 2019
- IND transfer to Pfizer in process
- Regulatory discussions underway for Phase 3
- Lead-in Phase 3 study sponsored by Pfizer
  - Trial open: first hemophilia A patient enrolled in October
  - Objective: To establish ≥ 6 months of prospective efficacy data of current FVIII prophylaxis replacement therapy in the usual care setting of hemophilia A subjects, who are negative for nAb to SB-525 capsid (AAV6), prior to the Phase 3 gene therapy study

Sangamo THERAPEUTICS

+

Pfizer

SB-525 data continues to show good promise in patients with severe hemophilia A

- SB-525 was generally well tolerated in all 11 subjects
- All treatment-related ALT elevations were low grade, and none were associated with a loss of FVIII expression thus far
- **Dose-dependent increases in FVIII activity** over baseline were observed. Subjects treated at the 3e13 vg/kg dose achieved normal-range FVIII activity after 5 to 7 weeks
- **No bleeding events** observed in subjects treated at high dose cohort
- **No follow-up factor replacement** for subjects treated at high dose cohort
- **Durable FVIII activity up to 52 weeks** of follow-up in lower-dose cohorts

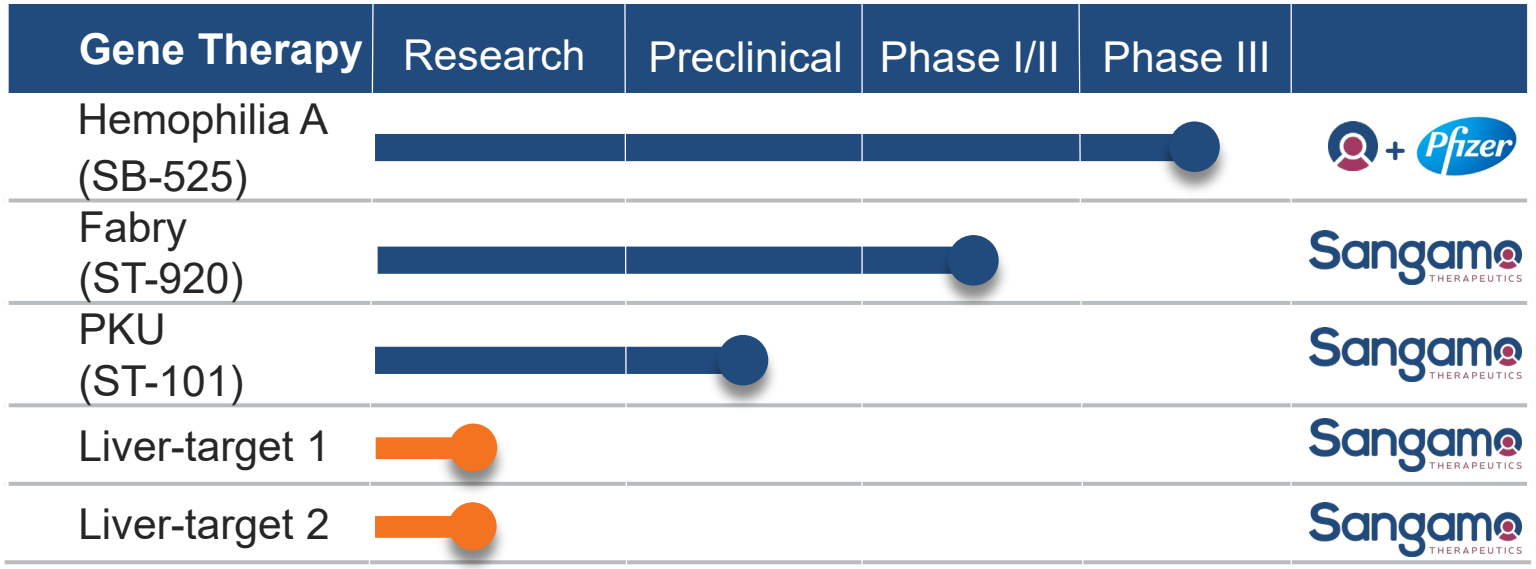
Hemophilia A helps guide our gene therapy platform

In SB-525, we learned a great deal

- AAV manufacturing
- AAV6 *in vivo* behavior
- Dosing threshold effects
- Cassette engineering

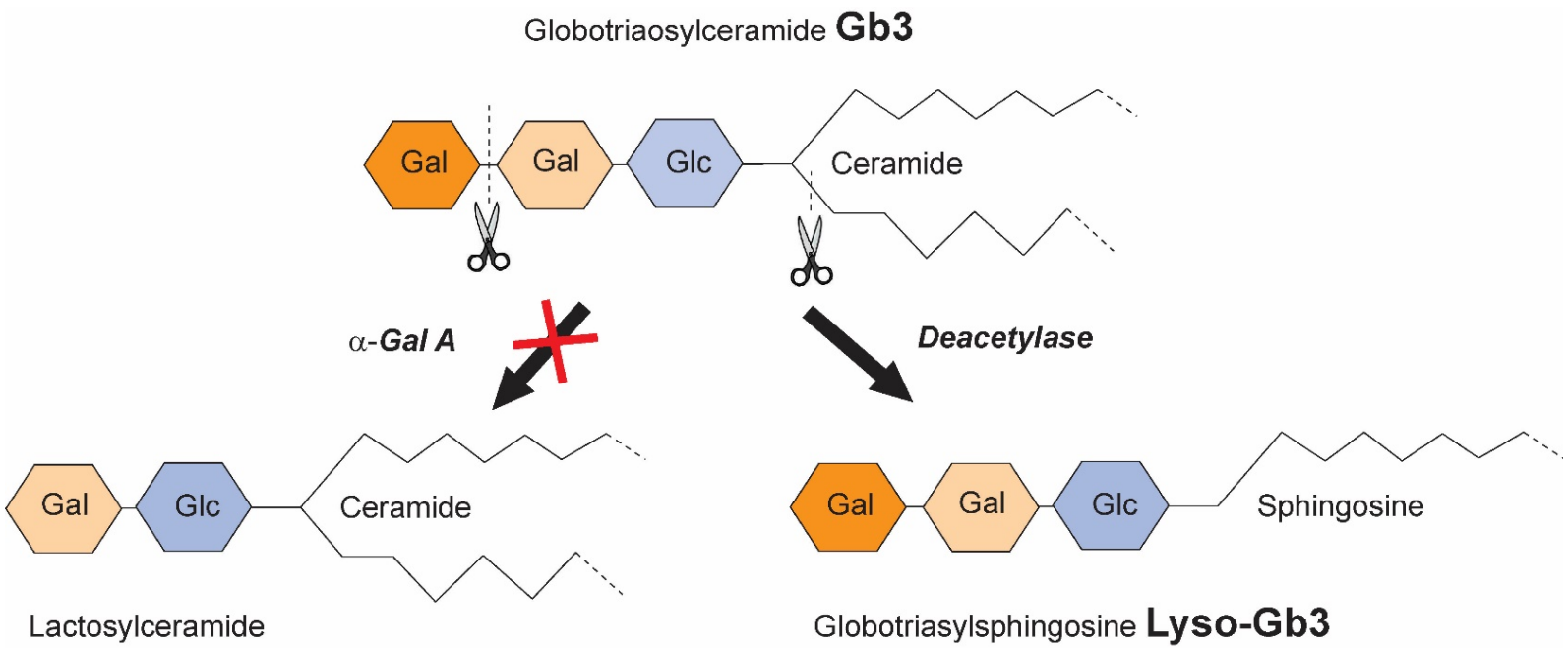
Sangamo wholly-owned programs: Fabry & PKU

Projected 1Q 2020 gene therapy pipeline



Leveraging gene therapy expertise for Fabry disease

Fabry disease: A lysosomal storage disorder

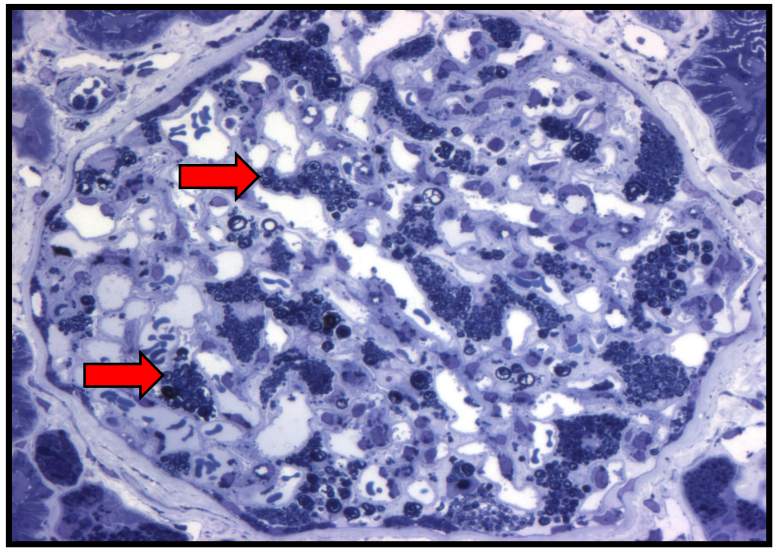


- Fabry disease is an **X-linked** monogenic disease caused by mutations in GLA gene encoding the enzyme alpha-galactosidase A **(α-Gal A**)
- **α-Gal A** plays a role in degradation of glycolipids in the lysosome
- The lack of functioning enzyme results in the accumulation of **Gb3** and its soluble form **lyso-Gb3**.

Fabry disease effects and classification

- Long-term, Gb-3 and Lyso-GB3 accumulates in the kidney, heart, skin and vessels and lead to **renal, cardiac and/or cerebrovascular disease**, with reduced life expectancy.
- Depending on residual enzyme activity there are two major phenotypes:
  - *Type I*: **Classic Fabry** ~1: 40,000
  - *Type II*: Later-onset Fabry ~1: 5,000
- Fabry patients: ~5,000 – 6,000 US/EU5
  - **Classic males ~ 30%**
  - Non-classic males ~ 10%
  - Females 60%

Lysosomal Gb3 inclusion (kidney)



Desnick et al 2001

Fabry disease

Prognosis

Premature death
- Males 58.2 years
- Females 75.4 years

Most common cause of death
- Cardiovascular disease
- Renal disease

Substantial list of symptoms include
- Neuronopathic pain
- Angiokeratomas
- Gastrointestinal
- Corneal opacities
- Etc.

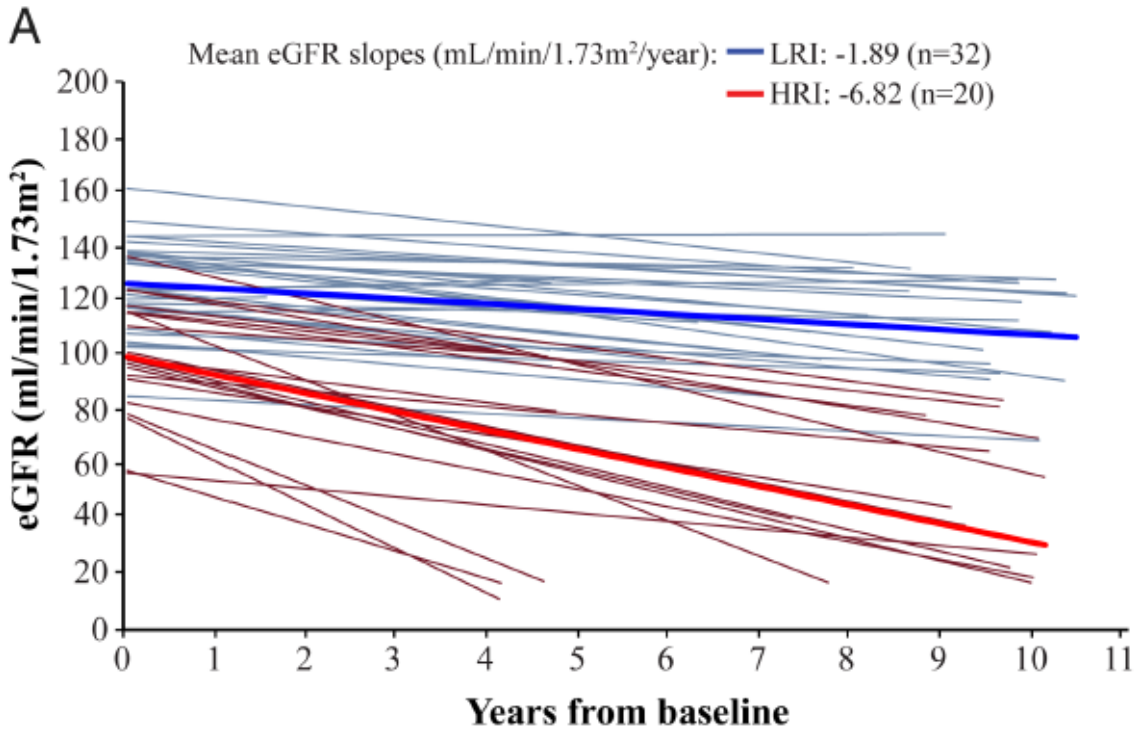
Standard of care

Enzyme replacement therapy (ERT)
- Biweekly infusions (2-4 hr) of α-Gal A
- “Peak and trough” enzyme levels
- Risk of infusion reactions and anti-ERT antibodies
- Annual cost: ~ $ 250,000 per patient

ERT still results in significant unmet need
- Cardiac Gb3 clearance
- Podocyte (kidney) Gb3 clearance
- Neuropathic pain
- Long-term stroke risk

ERT does not stop disease progression in Fabry

Replagal® 10 year follow up



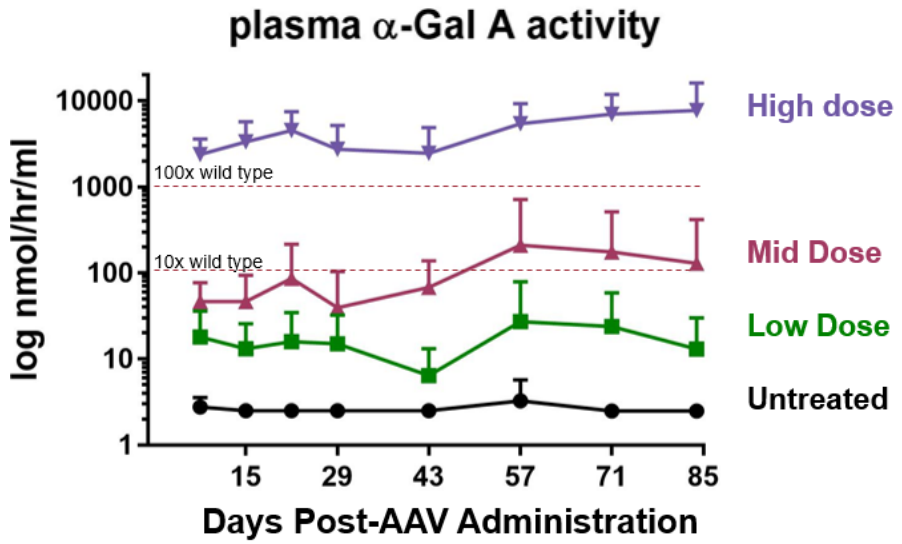
Source: Beck et al 2018 (FOS), Beck et al 2016 (FOS), Germain et al 2017, Lenders et al 2016, Schiffman et al 2009,

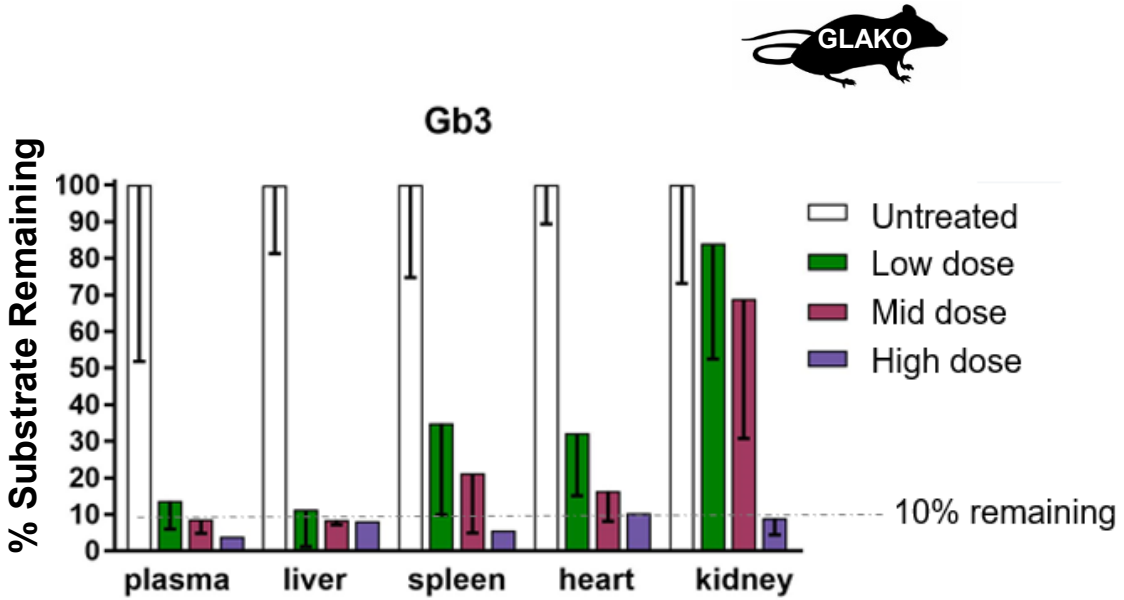
High treatment burden: bi-weekly infusions lasting 3-5 hours

ERT infusions do not clear all substrate from secondary organs

ST-920 preclinical models indicate promising potential

- ✓ US FDA orphan drug designation granted; UK approval granted for CTA
- ✓ AAV produced using clinical scale manufacturing methods





Sangamo's gene therapy demonstrated strong expression of α-Gal A and Gb3 substrate reduction across tissue types in GLAKO murine model

Fabry study design

Primary Objective

- Assess safety & tolerability of ST-920

Secondary Objectives

- Assess the pharmacodynamics of α-Gal A and the presence of its substrates in plasma over time
- Assess impact of ST-920 on ERT administration required for subjects on ERT
- Assess the impact of ST-920 on renal function
- Evaluate AAV2/6 vector DNA shedding over time

Patient Population

- Male subjects ≥ 18 years of age with classic Fabry disease
- On ERT regimen; or ERT-naïve; or ERT-pseudo-naïve and has not received ERT treatment in the prior 6 months

The goal is to abrogate the need for ERT with a recombinant AAV2/6 vector encoding cDNA for human α-Gal A, resulting in long-term expression of α-Gal A

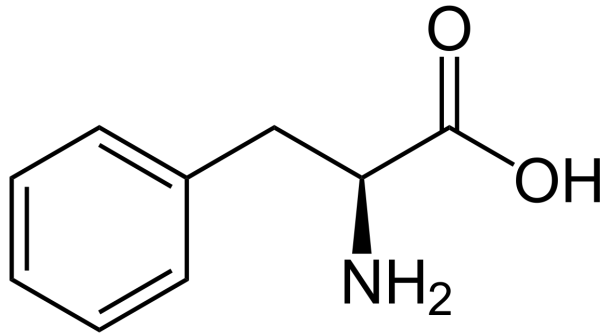
ST-920 offers a potentially differentiated treatment for Fabry

- In a single IV infusion, ST-920 may provide continuous, potentially life-long expression of endogenously expressed α-Gal A
- No preconditioning regimen
- Potential to deliver efficacy with preserved renal function and reduced cardiac morbidity
- FDA draft guidance may considerably shorten time to approval and allow ST-920 to be among the first gene therapy treatments on the market

ST-101 for PKU

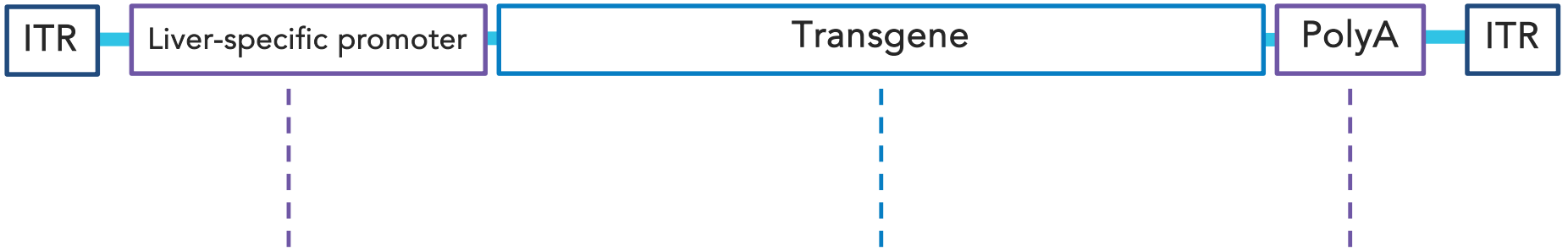
Rationale for PKU program ST-101

- PKU is a rare inherited disorder that originates from a defect in the PAH gene that results in phenylalanine building up to harmful levels in the body
- Unmet medical need
  - 16,500 patients USA and 50,000 globally
  - Standard of care: strict diet restrictions
  - Approved treatments offer minimal flexibility on diet
- Therapeutic target is straightforward
  - Early patient identification: newborn screening
  - Monogenic disorder with a clear loss of function leading to a clear phenotype and assessment



Phenylalanine

IND enabling studies initiated for ST-101 gene therapy for PKU



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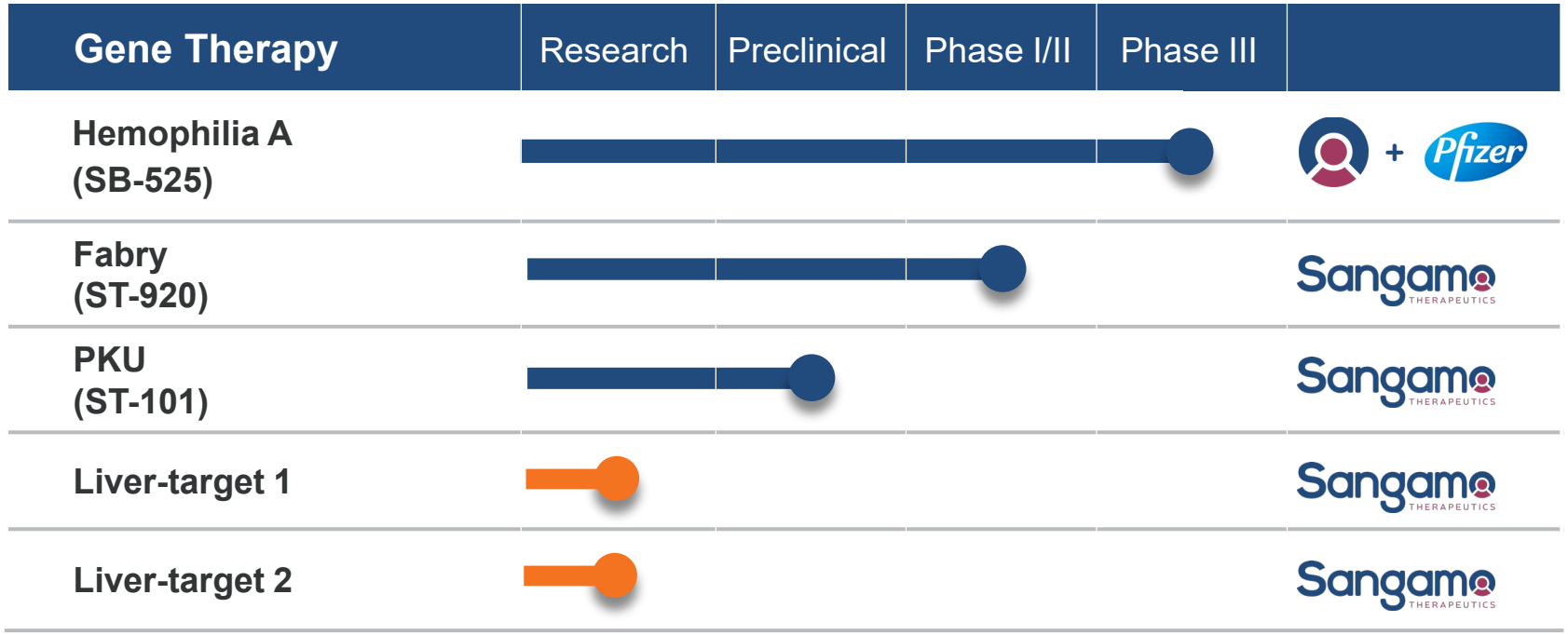
IND filing anticipated in 2021

Gene therapy pipeline has more to come

Projected 1Q 2020 gene therapy pipeline



Research goal of one new gene therapy IND per year

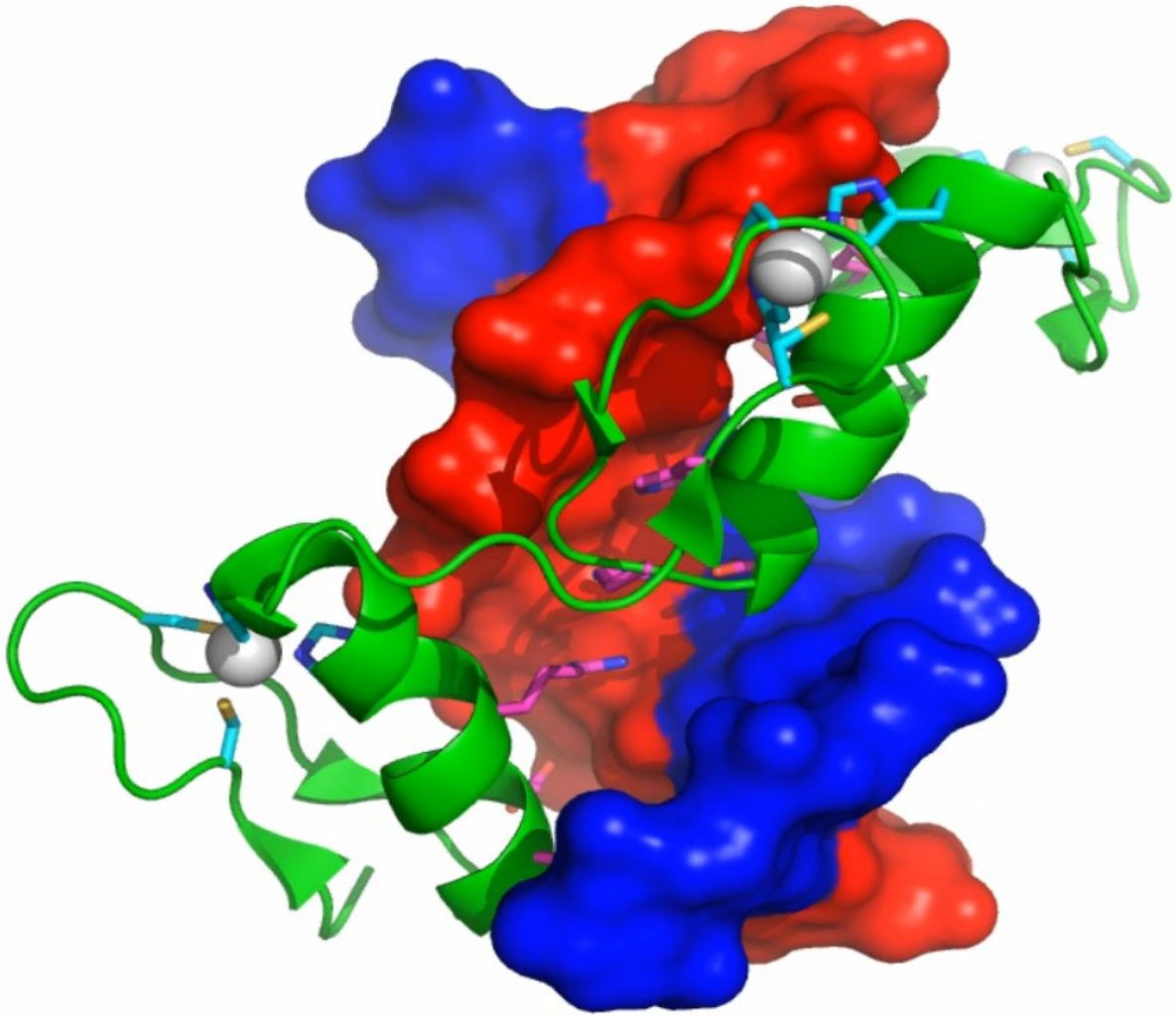
Engineering zinc finger proteins for therapeutic applications

Ed Rebar, Head of Technology

Genomic medicines offer powerful, new therapeutic possibilities

- Mechanistically sophisticated outcomes (not just binding/blocking)
- Potential to leverage fine-scale discrimination for therapeutic benefit
  - e.g. single base alternatives / methylation status / repeat element count
- Option for gene repair
- Permanence

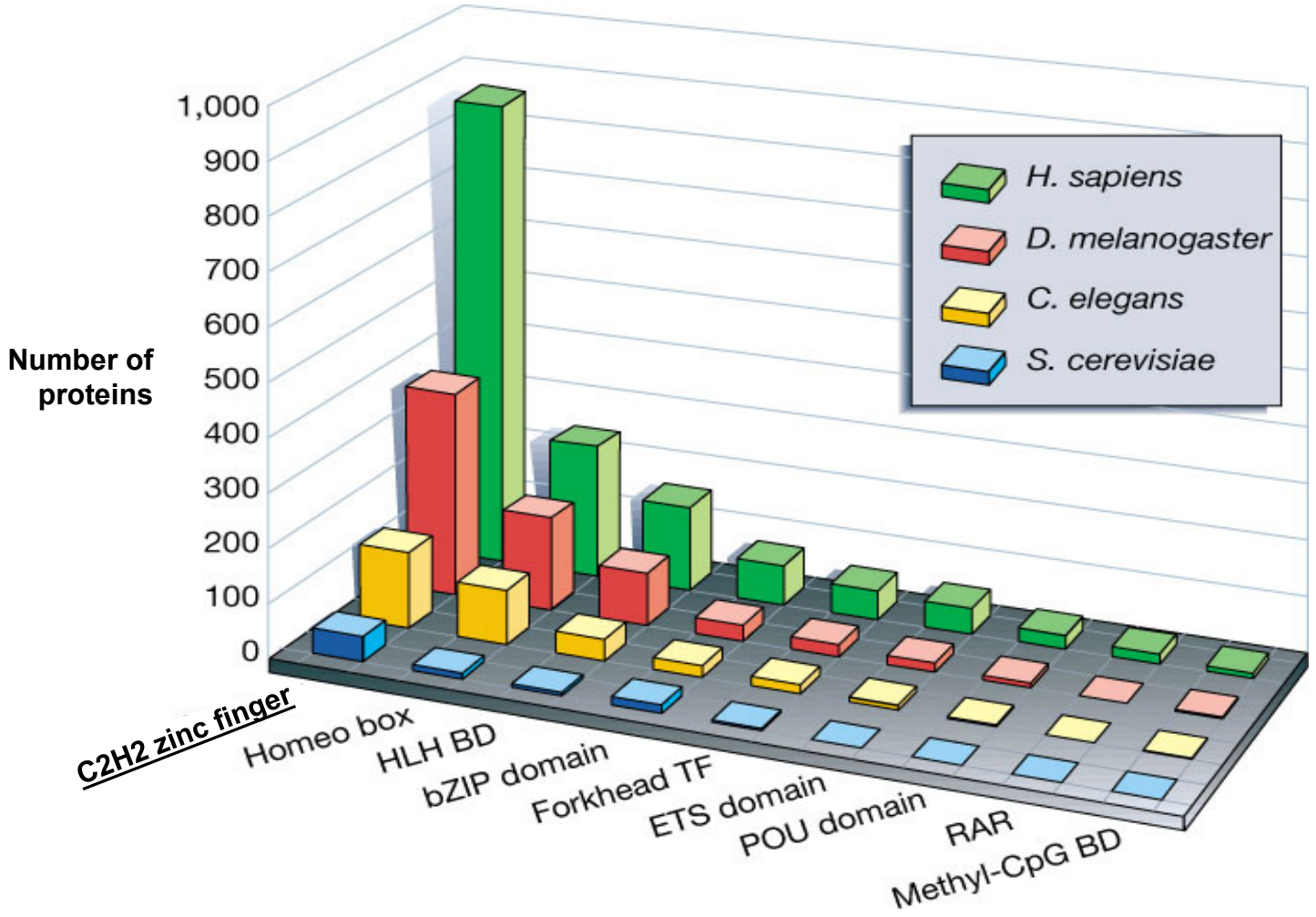
The C2H2 zinc finger:
Platform of choice for high performance DNA recognition



Sangamo THERAPEUTICS

The C2H2 zinc finger: Mediator of metazoan evolution

Genome-wide comparison of transcriptional activator families in eukaryotes



Tupler R, Perini G, Green MR, *Nature* **409**: 832.

The C2H2 zinc finger:
Core platform for Sangamo's genome-targeted therapies

Gene Therapy
AAV

Gene-Edited Cell Therapy
ZFN; AAV; LV

Genome Editing
AAV; ZFN

Genome Regulation
AAV; ZFP-TF

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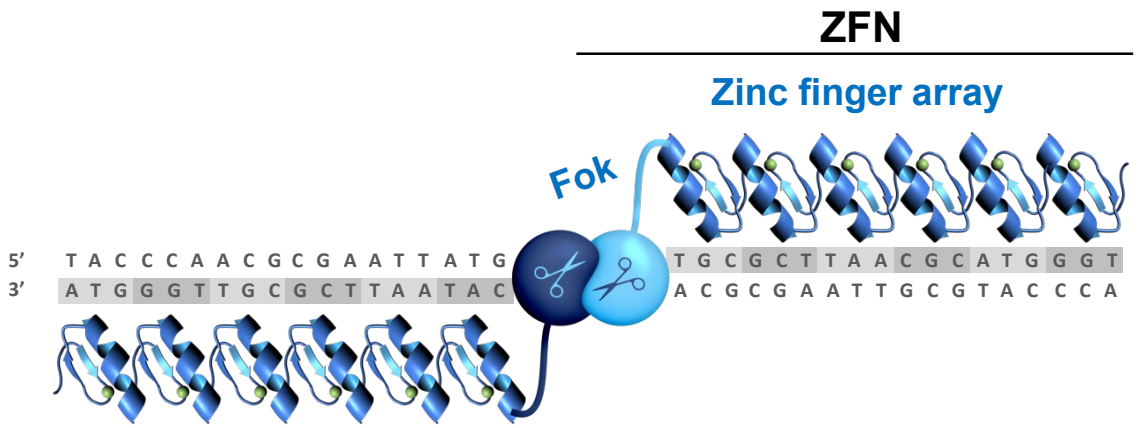
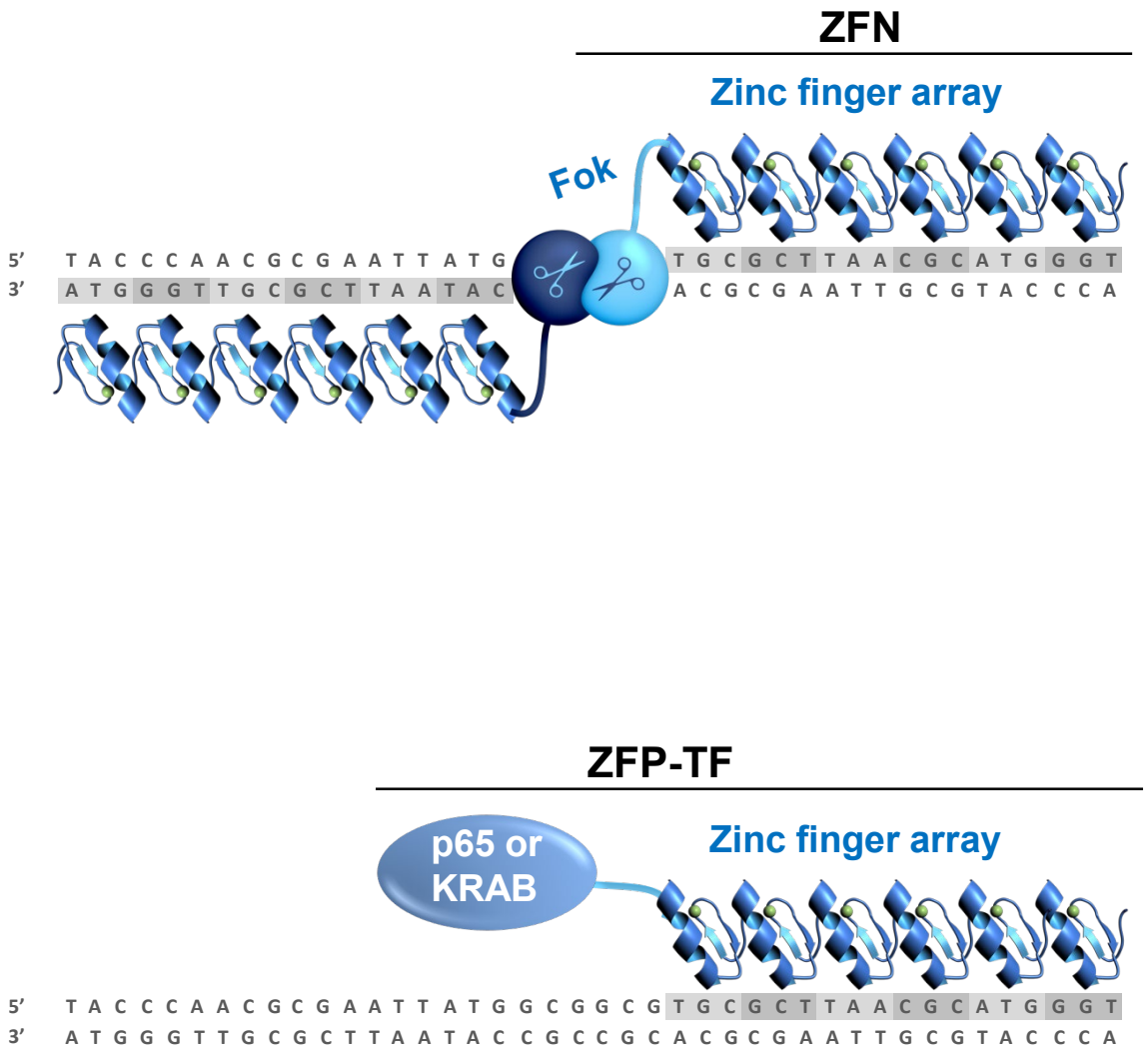
Zinc Finger Nuclease (ZFN)



- Synthetic, chimeric nuclease
  - zinc finger array (binds DNA)
  - FokI domain (catalyzes cleavage)
- Cleaves only when dimerized
- Specifies an extended target (36bp)

Zinc Finger Nuclease (ZFN) and Transcription Factor (ZFP-TF)

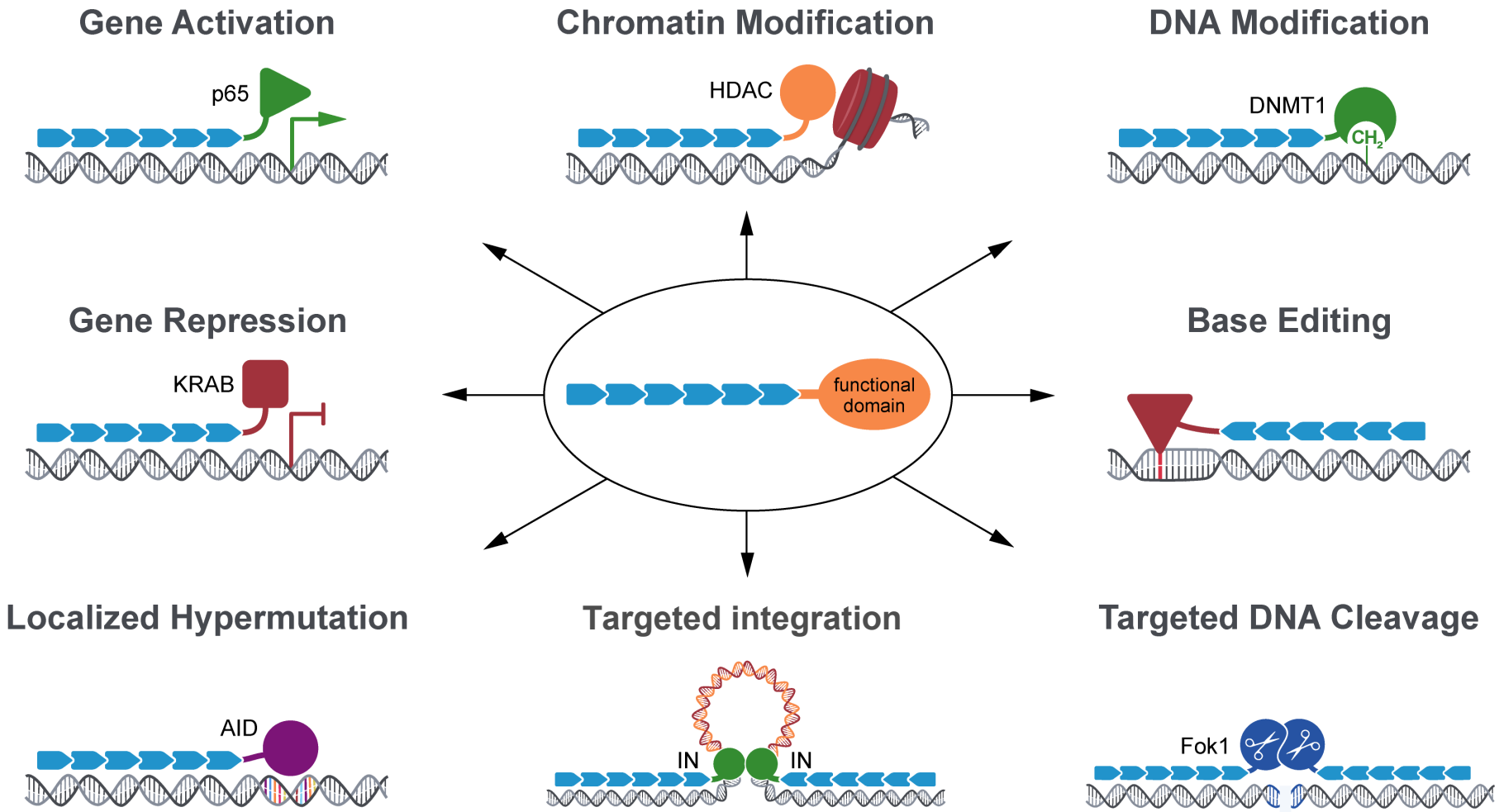


- Synthetic, chimeric nuclease
  - zinc finger array (binds DNA)
  - FokI domain (catalyzes cleavage)
- Cleaves only when dimerized
- Specifies an extended target (36bp)

- Synthetic, chimeric transcription factor
  - zinc finger array (binds DNA)
  - transcription activation or repression domain
- Binds 18 bp

Sangamo THERAPEUTICS

Alternative functional domains enable diverse possibilities



Adapted from Nat Rev Drug Disc 2 361

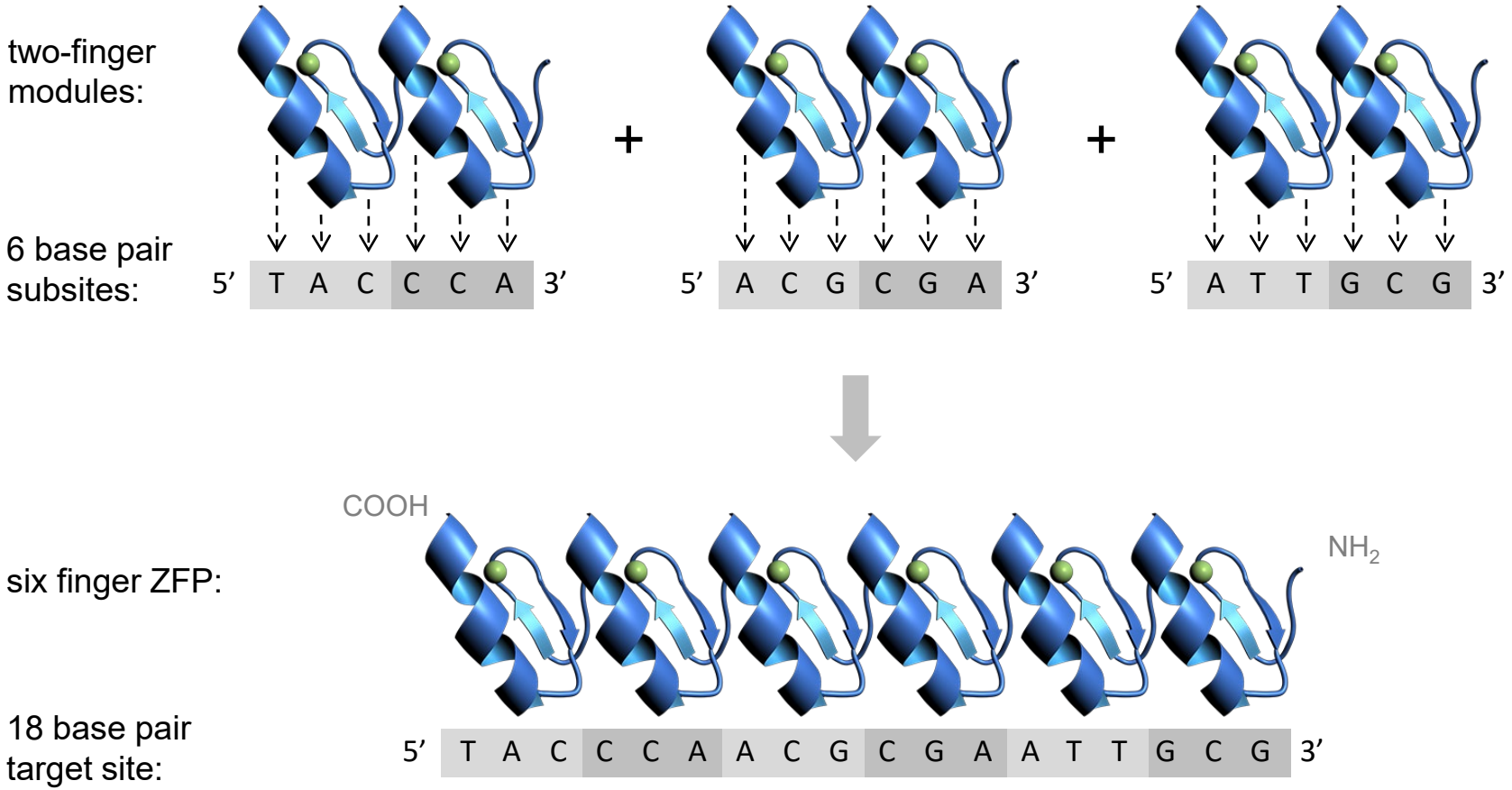
Diverse platforms available for site-specific genome targeting

- CRISPR-Cas
- TALENs
- Meganucleases
- MegaTALs
- Zinc Finger Proteins (ZFPs)

ZFPs: Key differentiating features

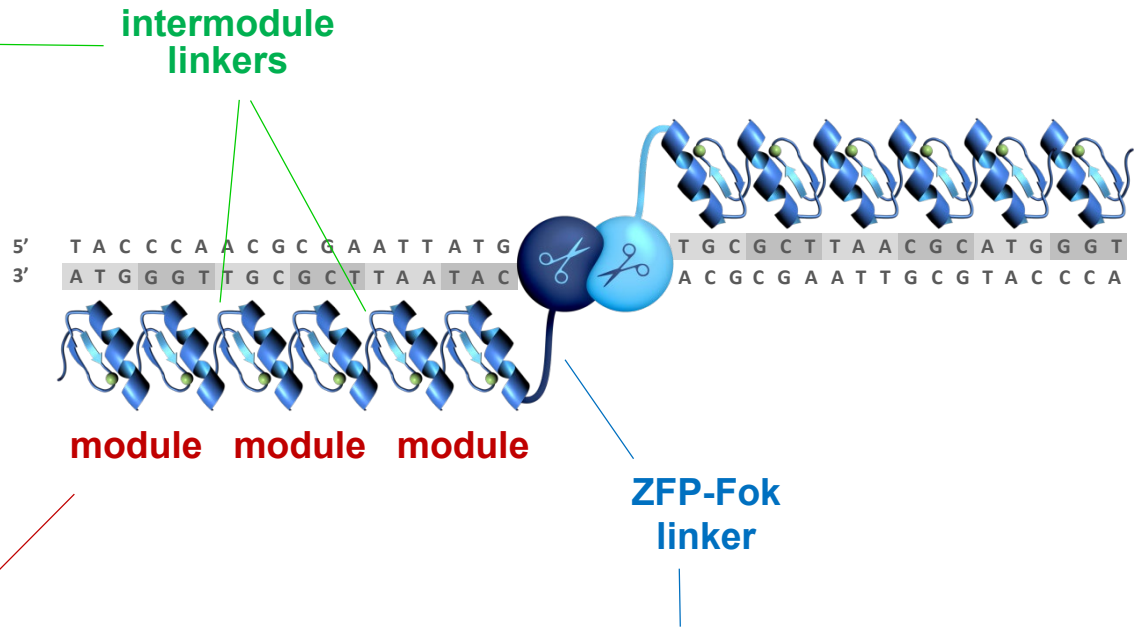
- High targeting precision
- Compactness (deliverability / accessibility)
- Nice balance of modularity vs customizability
  - enables rapid development of reagents with therapeutically beneficial properties
- Capacity for very high activity & specificity

Zinc finger protein design and assembly



Architectural diversification enables high targeting precision

6 alternatives for skipping 0, 1, or 2 bp

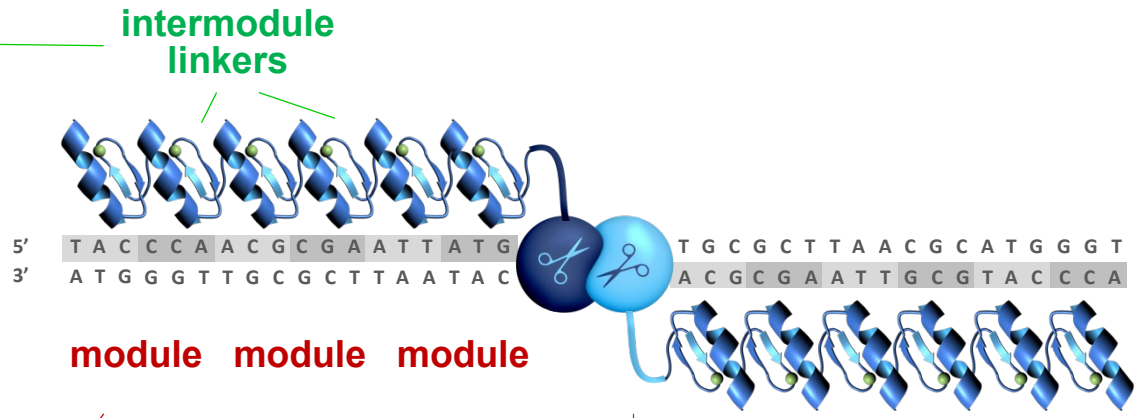


Repertoire of 8000 hexamer : module combinations available for design

5 alternatives for skipping 5-9 bp

Architectural diversification enables high targeting precision

6 alternatives for skipping 0, 1, or 2 bp



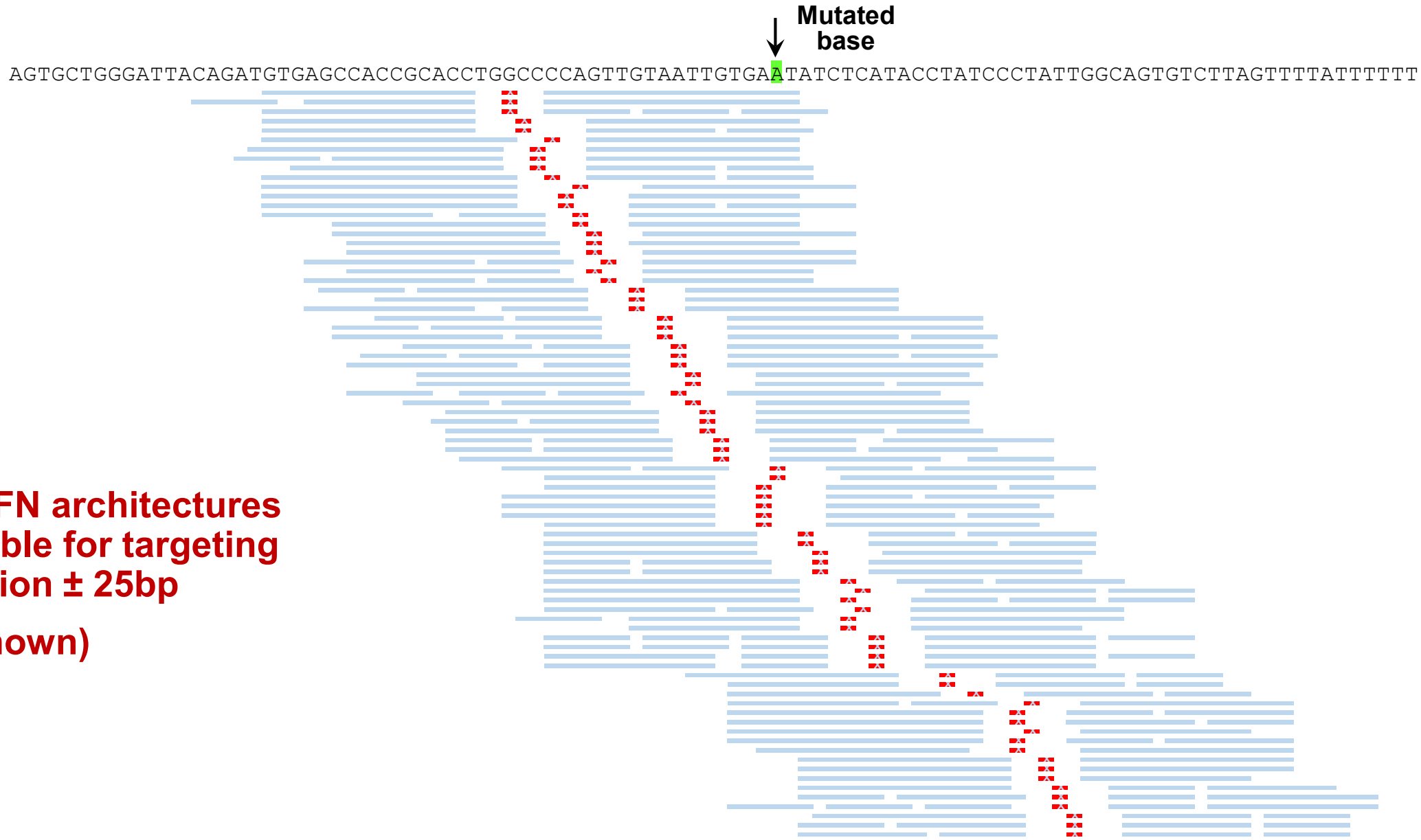
Repertoire of 8000 hexamer : module combinations available for design

5 alternatives for skipping 5-9 bp
4 alternatives for reversing Fok-ZFP polarity

Targeting example: LCA10 mutation in CEP290 gene

- Disease mutation is an A → G substitution within intron 26 of the CEP290 gene
- Mutation creates an aberrant splice site
- Inappropriate splicing disrupts the function of protein product
- Disruption leads to progressive vision loss

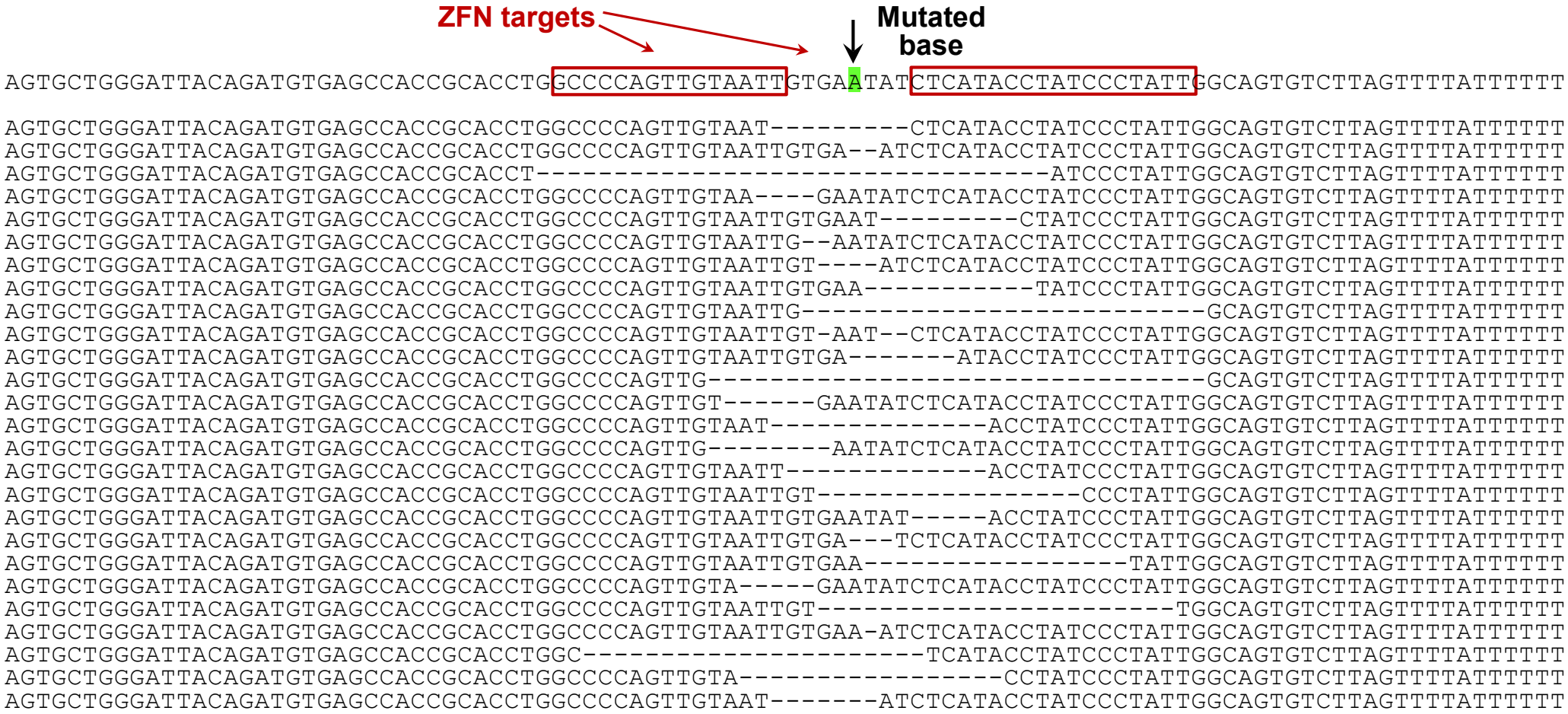
Platform enables dense tiling of targeted region



604 ZFN architectures available for targeting mutation ± 25bp

(80 shown)

ZFN treatment efficiently disrupts targeted base



K562 cells, RNA delivery (nucleofection)

Two weeks / 85% indels / first pass designs

K562 cells, RNA delivery (nucleofection)

Targeting capabilities featured in recent Sangamo manuscript

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-08867-x OPEN

Diversifying the structure of zinc finger nucleases for high-precision genome editing

David E. Paschon[1], Stephanie Lussier[1], Tenzin Wangzor[1], Danny F. Xia[1], Patrick W. Li[1], Sarah J. Hinkley[1], Nicholas A. Scarlott[1], Stephen C. Lam[1], Adam J. Waite[1], Lynn N. Truong[1], Nimisha Gandhi[1], Bhakti N. Kadam[1], Deepak P. Patil[1], David A. Shivak[1], Gary K. Lee[1], Michael C. Holmes[1], Lei Zhang[1], Jeffrey C. Miller[1] & Edward J. Rebar[1]

Genome editing for therapeutic applications often requires cleavage within a narrow sequence window. Here, to enable such high-precision targeting with zinc-finger nucleases (ZFNs), we have developed an expanded set of architectures that collectively increase the configurational options available for design by a factor of 64. These new architectures feature the functional attachment of the FokI cleavage domain to the amino terminus of one or both zinc-finger proteins (ZFPs) in the ZFN dimer, as well as the option to skip bases between the target triplets of otherwise adjacent fingers in each zinc-finger array. Using our new architectures, we demonstrate targeting of an arbitrarily chosen 28 bp genomic locus at a density that approaches 1.0 (i.e., efficient ZFNs available for targeting almost every base step). We show that these new architectures may be used for targeting three loci of therapeutic significance with a high degree of precision, efficiency, and specificity.

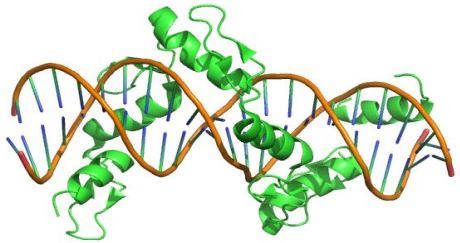
Nat Commun. 2019 Mar 8;10(1):1133

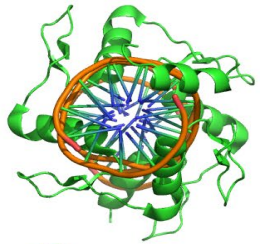
ZFPs: Key differentiating features

- High targeting precision
- Compactness (deliverability / accessibility)
- Nice balance of modularity vs customizability
  - enables rapid development of reagents with therapeutically beneficial properties
- Capacity for very high activity & specificity

ZFPs offer a sleeker recognition unit

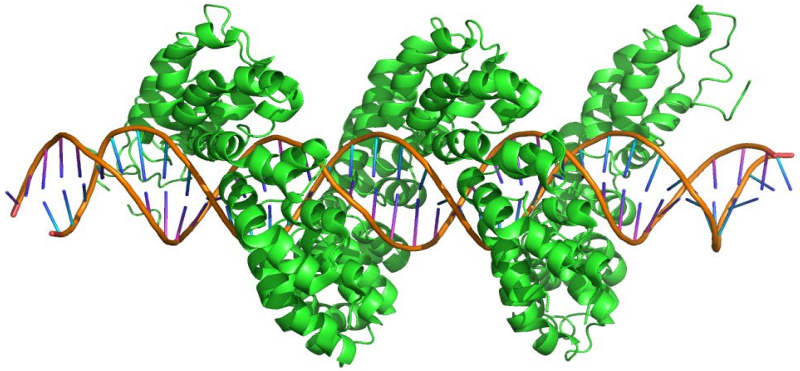
ZFP

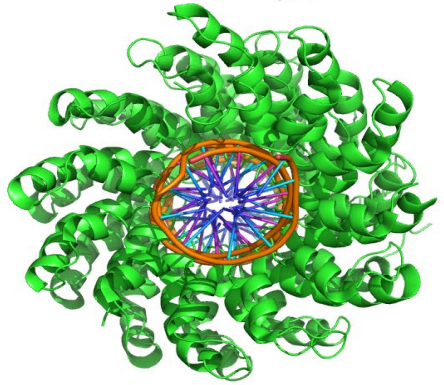




174 amino acids

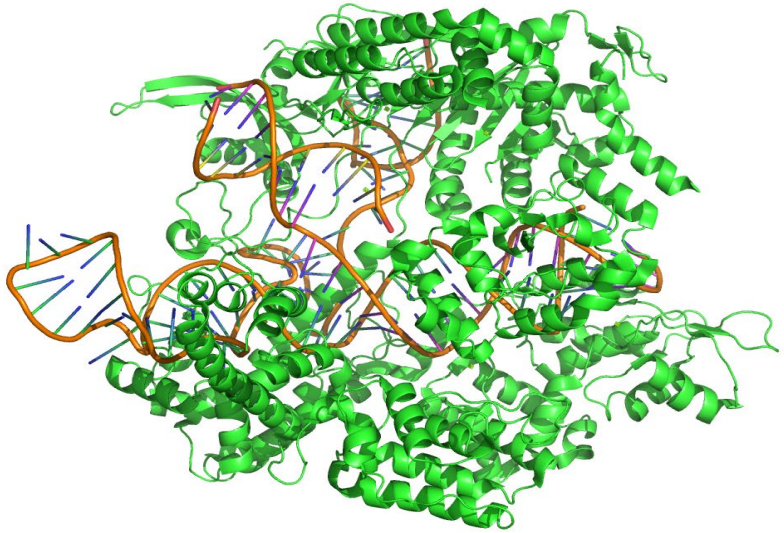
TALE

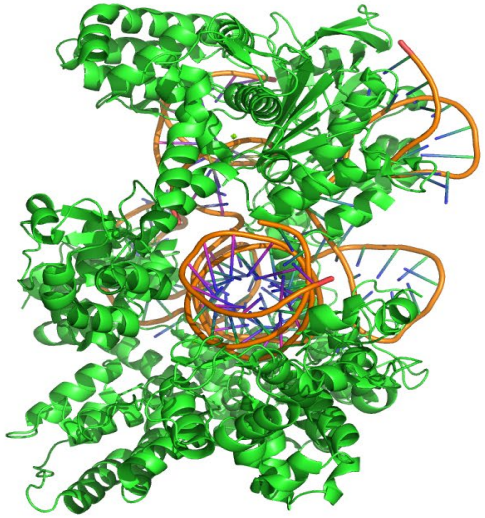




781 amino acids

CRISPR-Cas9





1,368 amino acids

Sangamo THERAPEUTICS

ZFPs: modular and optimizable

Finger: triplet concordance

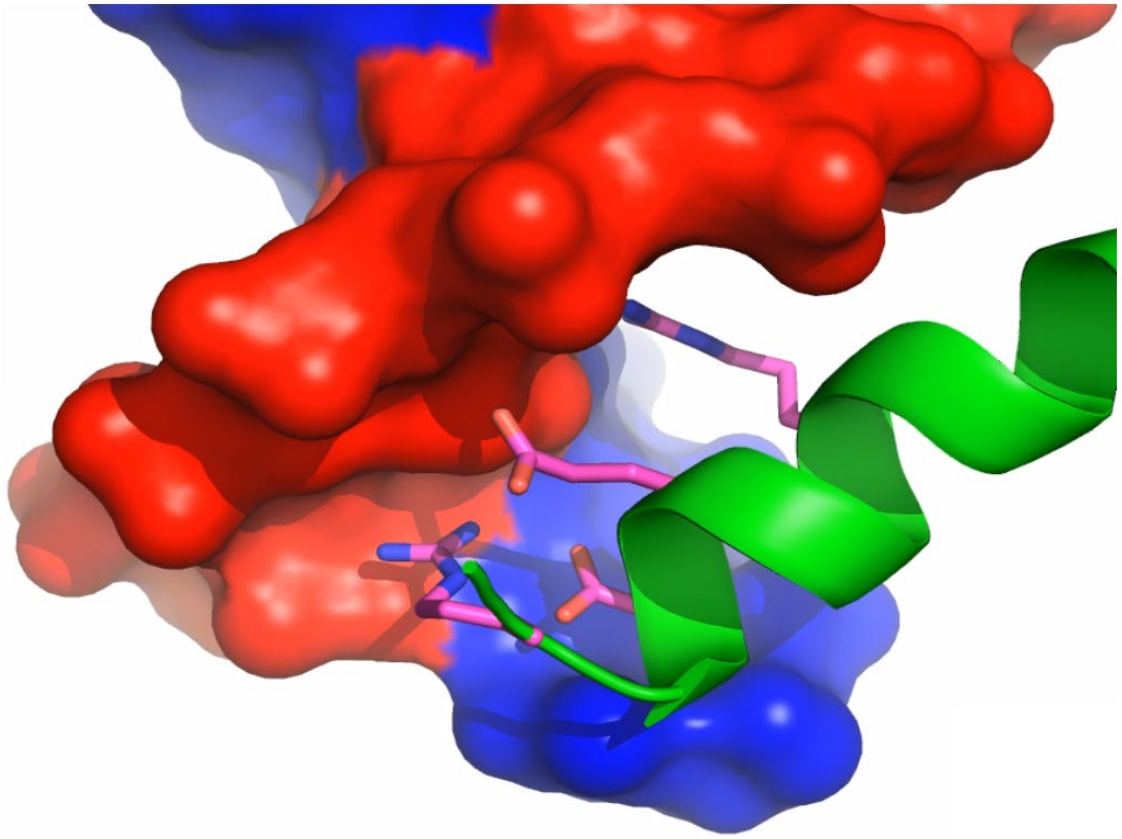
enables rapid design & assembly

Interface complexity (>10^7 options)

enables fine tuning of properties,

e.g.

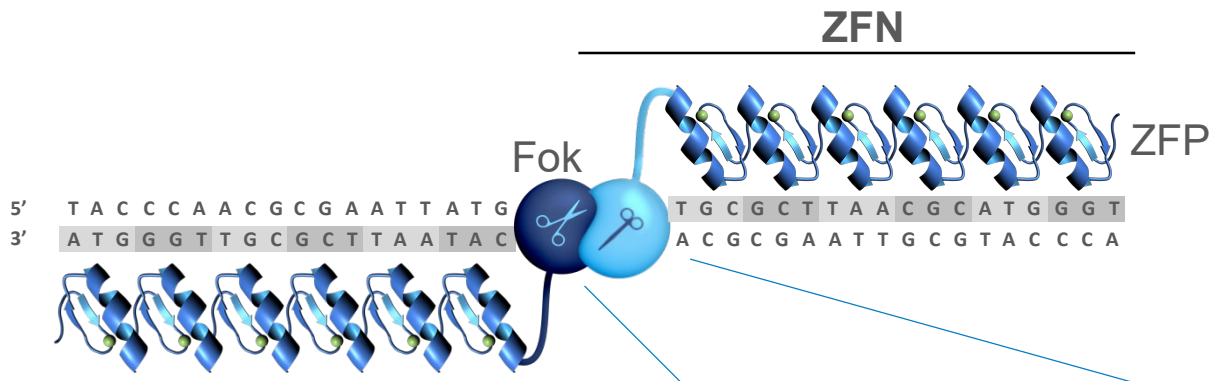
- allelic discrimination
- base modifications
- specificity vs affinity



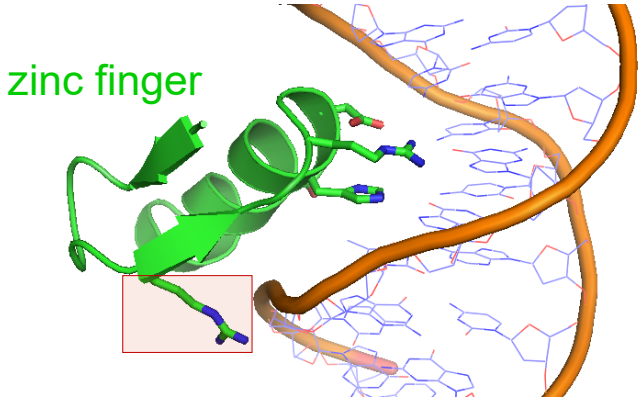
ZFPs: Key differentiating features

- High targeting precision
- Compactness (deliverability / accessibility)
- Nice balance of modularity vs customizability
  - enables rapid development of reagents with therapeutically beneficial properties
- Capacity for very high activity & specificity

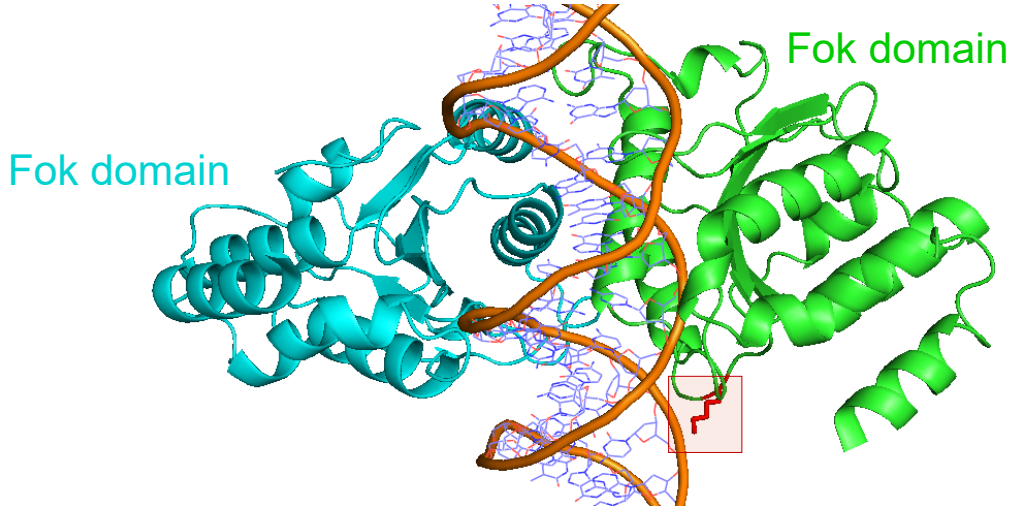
Chimeric structure enables two strategies for tuning specificity



1) Removing Arg-phosphate contacts



2) Substituting key FokI residues

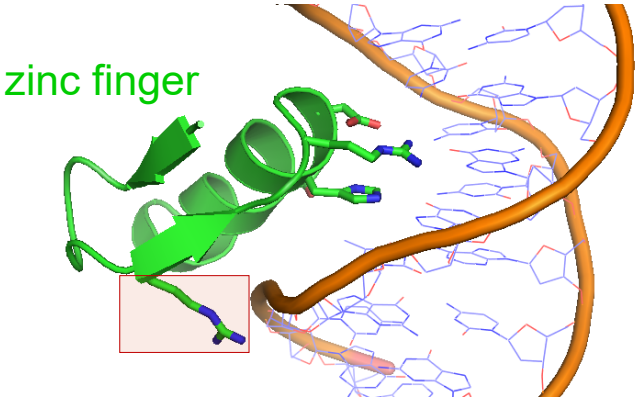


Sangamo THERAPEUTICS

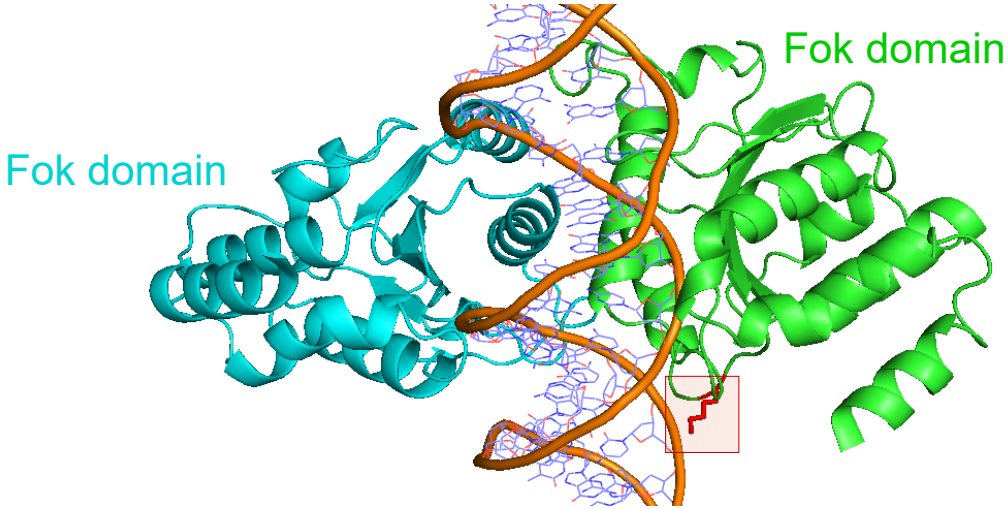
Independent tuning of dissociation and catalysis

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

1) Removing Arg-phosphate contacts
→ to tune dissociation rate (k_{-1})



2) Substituting key FokI residues
→ to modulate rate of catalysis (k_2)



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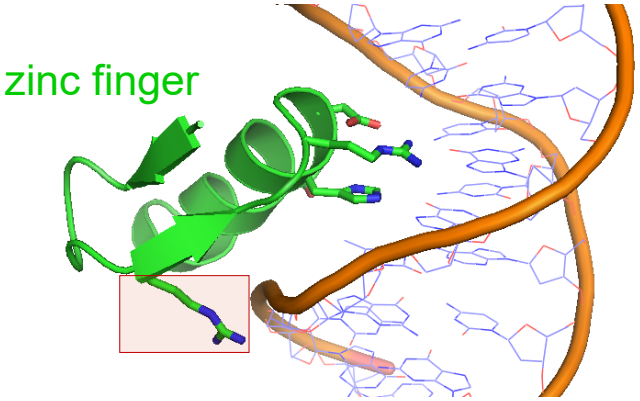
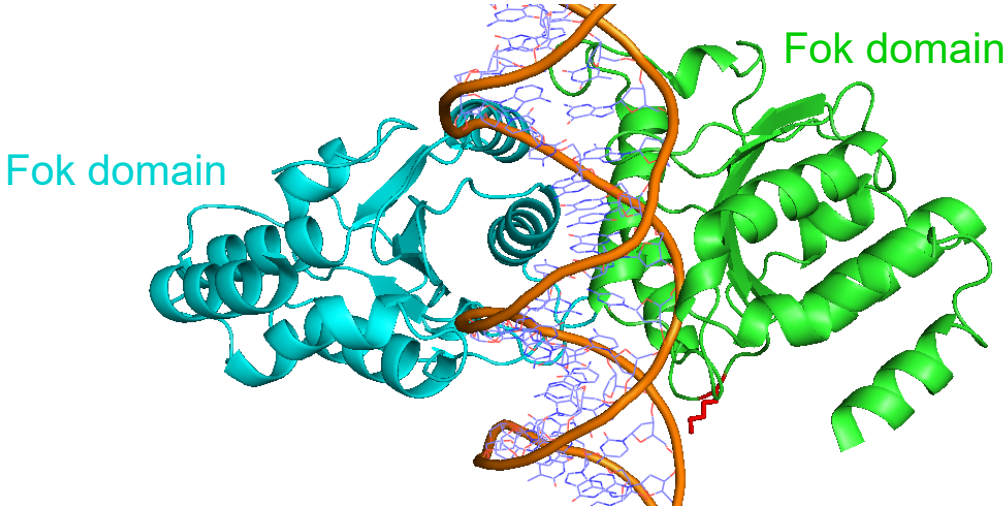
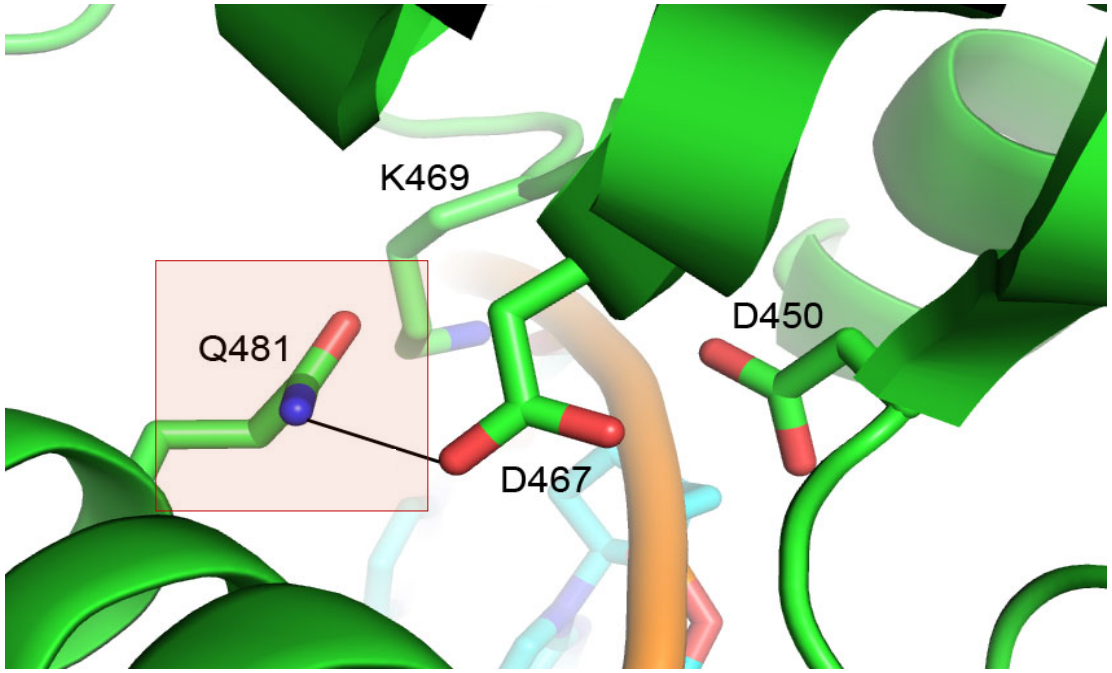


2) Substituting key FokI residues
→ to modulate rate of catalysis (k_2)

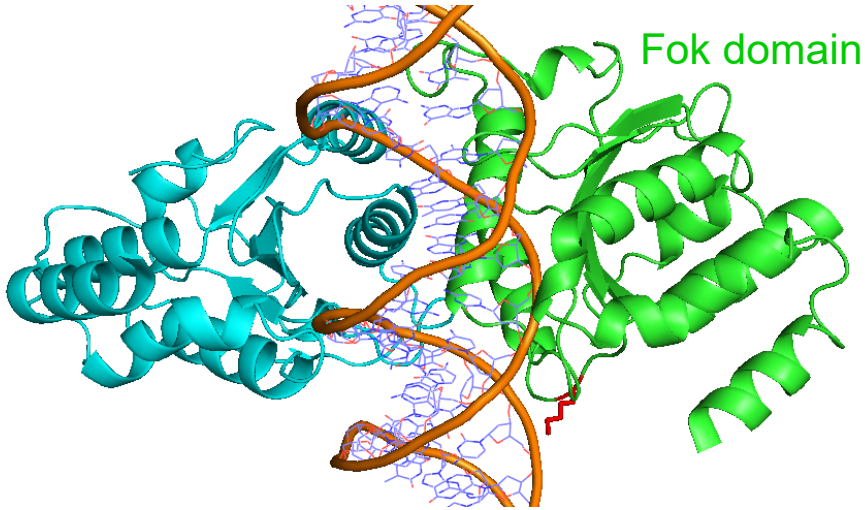


Residues identified (e.g. Q481) that enable catalytic tuning

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$



2) Substituting key FokI residues
→ to modulate rate of catalysis (k_2)



Independent tuning of dissociation and catalysis

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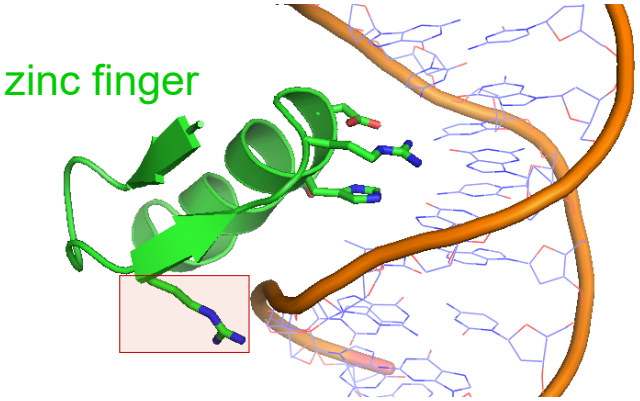
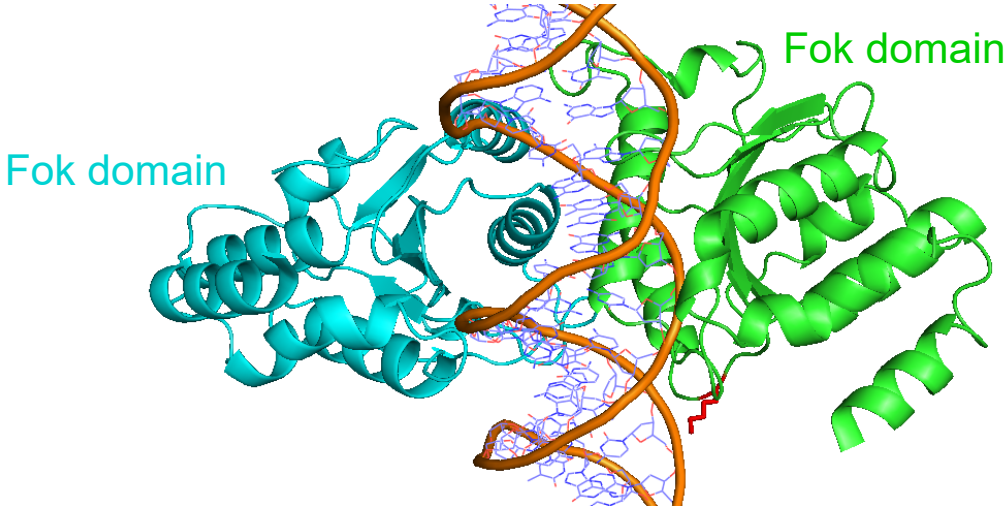
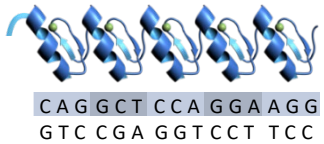
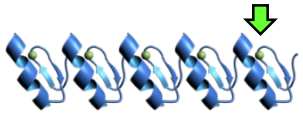
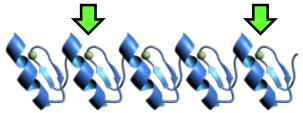
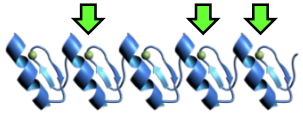
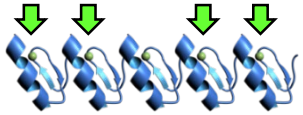
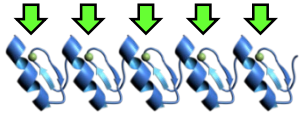
1) Removing Arg-phosphate contacts
→ to tune dissociation rate (k_{-1})



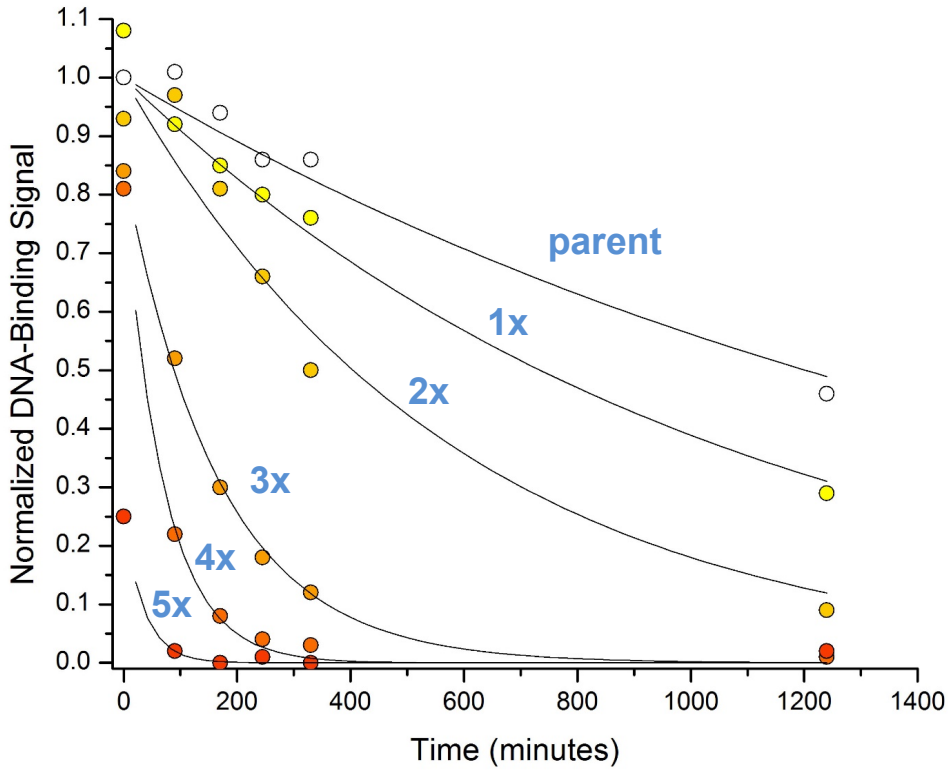
2) Substituting key FokI residues
→ to modulate rate of catalysis (k_2)



Arginine substitutions enable affinity tuning over 50x range

ZFN structure	# of fingers substituted	Binding half life (minutes)
	none (parent)	1200
	1x	740
	2x	410
	3x	120
	4x	50
	5x	25

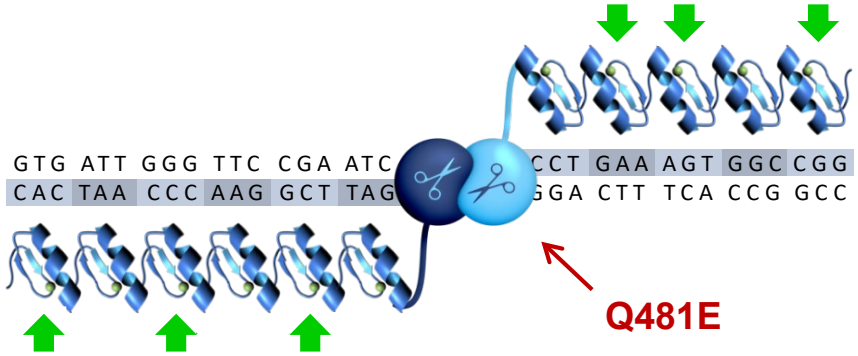
Half life analysis



Sangamo THERAPEUTICS

Complete gene modification achieved with no off-targets

ZFNs targeted to TCRα

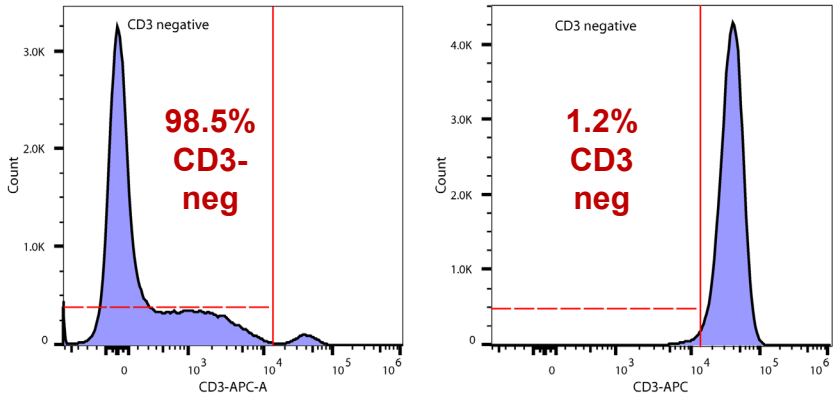


← Affinity-reducing mutations in 6 fingers

← Fok variant that slows catalysis

On-target activity assessment:

	ZFN-treated	Control
% DNA modification (via sequencing)	98.2% indels	0% indels
% functional knockout (via FACS)	98.5% CD3- neg	1.2% CD3 neg



Specificity assessment:

- Guide-Seq, followed by sequencing of candidate off-target loci
- High nuclease dose used for Guide-Seq & follow-up studies (90% & 98% on-target indels)
- No evidence off-target cleavage seen with median background levels of 0.01%

Study published July 2019

nature biotechnology

ARTICLES

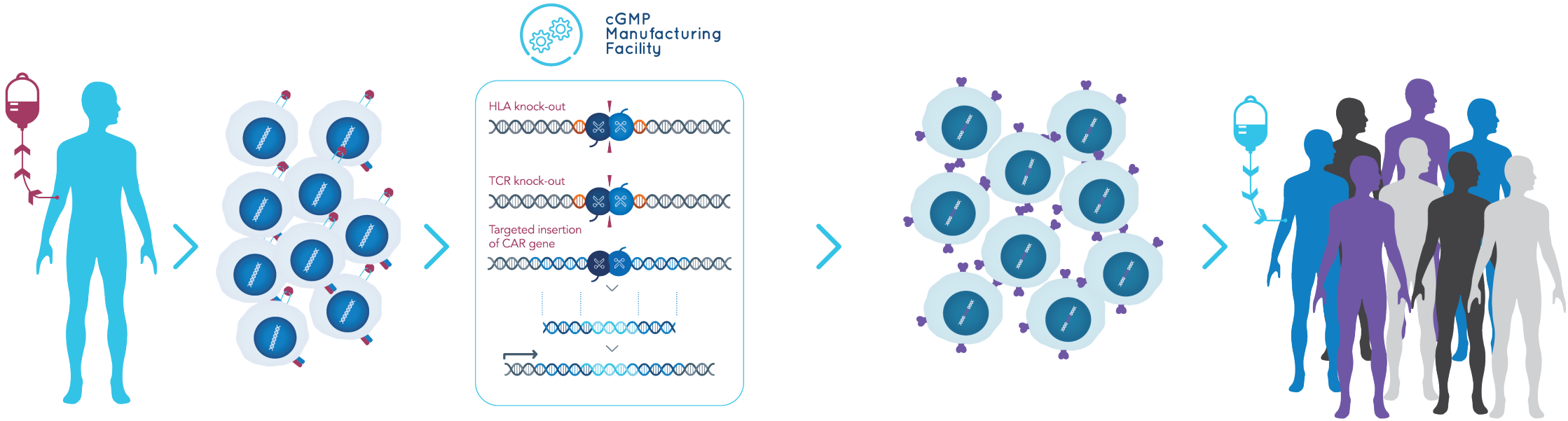
https://doi.org/10.1038/s41587-019-0186-z

Enhancing gene editing specificity by attenuating DNA cleavage kinetics

Jeffrey C. Miller, Deepak P. Patil, Danny F. Xia, Charles B. Paine, Friedrich Fauser, Hunter W. Richards, David A. Shivak, Yuri R. Bendaña, Sarah J. Hinkley, Nicholas A. Scarlott, Stephen C. Lam, Andreas Reik, Yuanyue Zhou, David E. Paschon, Patrick Li, Tenzin Wangzor, Gary Lee, Lei Zhang and Edward J. Rebar*

Engineered nucleases have gained broad appeal for their ability to mediate highly efficient genome editing. However the specificity of these reagents remains a concern, especially for therapeutic applications, given the potential mutagenic consequences of off-target cleavage. Here we have developed an approach for improving the specificity of zinc finger nucleases (ZFNs) that engineers the FokI catalytic domain with the aim of slowing cleavage, which should selectively reduce activity at low-affinity off-target sites. For three ZFN pairs, we engineered single-residue substitutions in the FokI domain that preserved full on-target activity but showed a reduction in off-target indels of up to 3,000-fold. By combining this approach with substitutions that reduced the affinity of zinc fingers, we developed ZFNs specific for the *TRAC* locus that mediated 98% knockout in T cells with no detectable off-target activity at an assay background of ~0.01%. We anticipate that this approach, and the FokI variants we report, will enable routine generation of nucleases for gene editing with no detectable off-target activity.

First point of application is T-cell programs



1

Apheresis (Healthy Donor)

Isolate T-cells from a healthy donor's blood

2

T-cell Manufacturing

Transient, non-viral delivery of ZFN mRNA to manufacture universal CAR-T cells via sinlge-step multiplexed gene editing

3

Harvest + Storage

Universal CAR-T cells are harvested, cryo-perserved and stored in a secure cell bank

4

Infusion

Universal, off-the-shelf CAR-T cells are infused into new patients, on-demand

Sangamo THERAPEUTICS

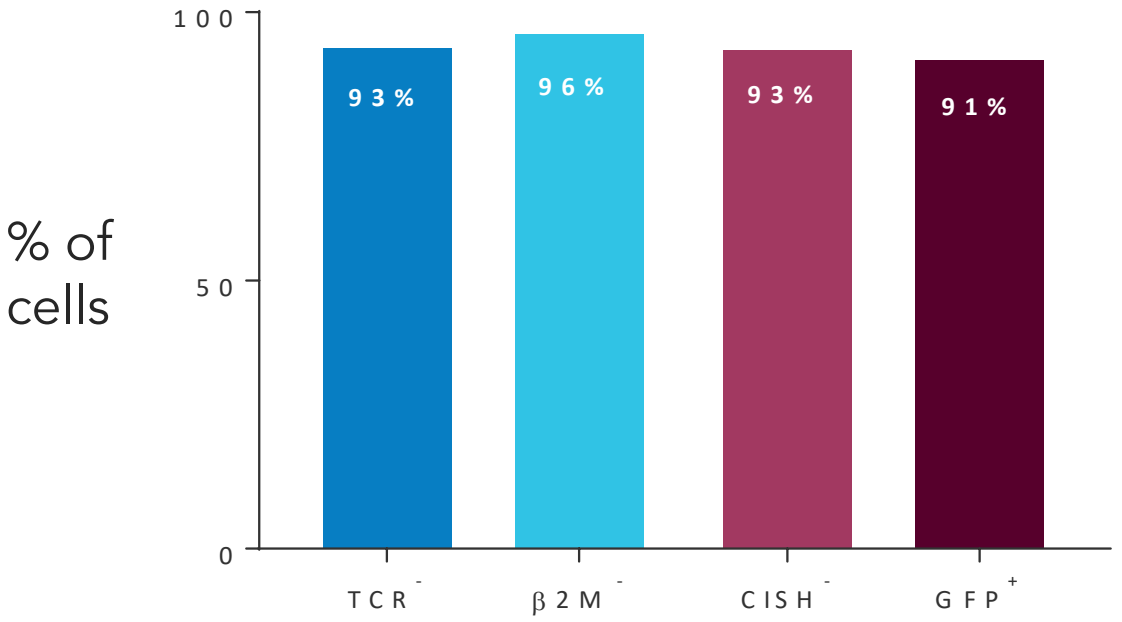
Highly efficient multiplexed edits

ZFN Knock-out

1. TRAC (TCR)
2. β2M (HLA-class I)
3. CISH (checkpoint gene)

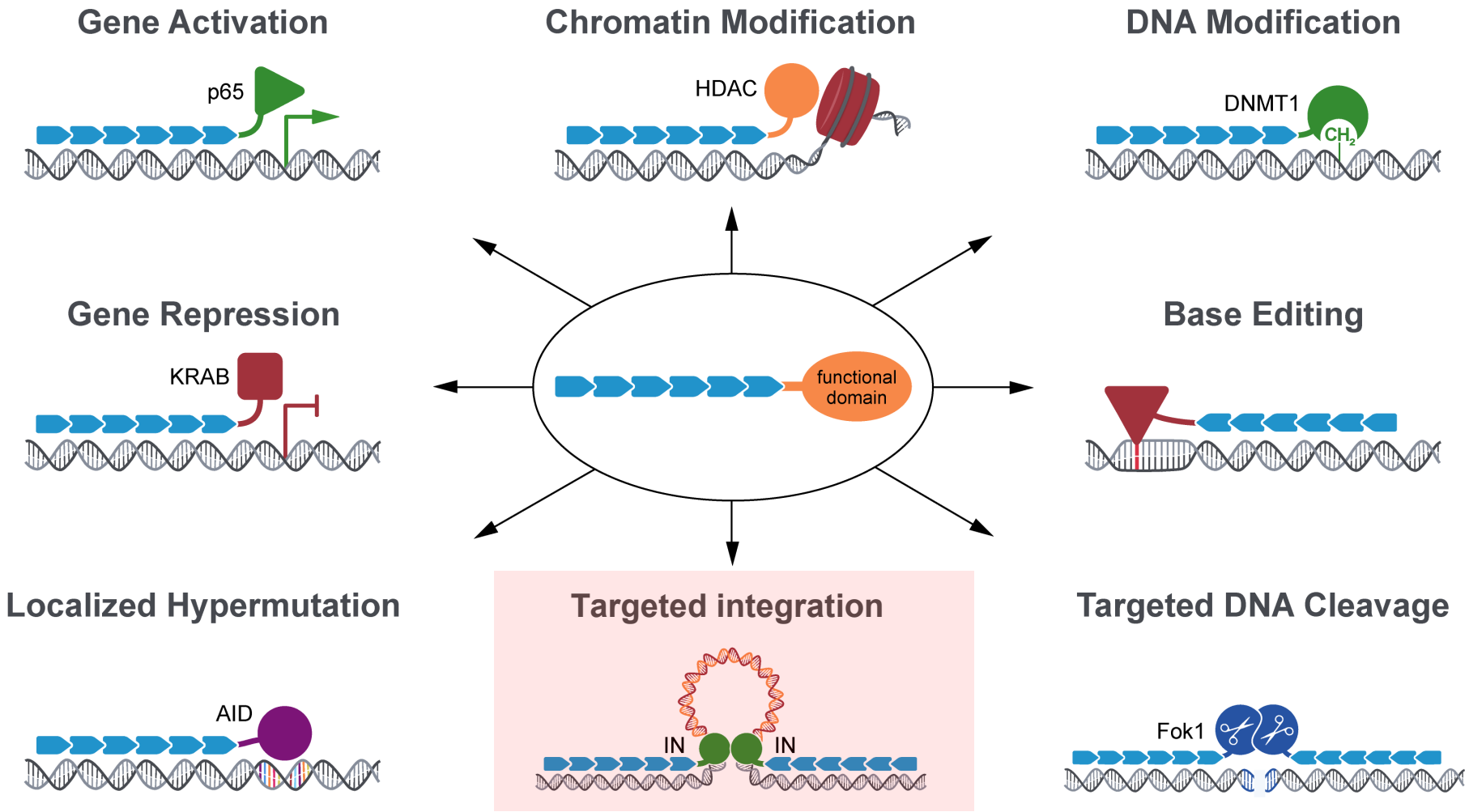
Targeted Insertion

4. GFP (into TRAC)

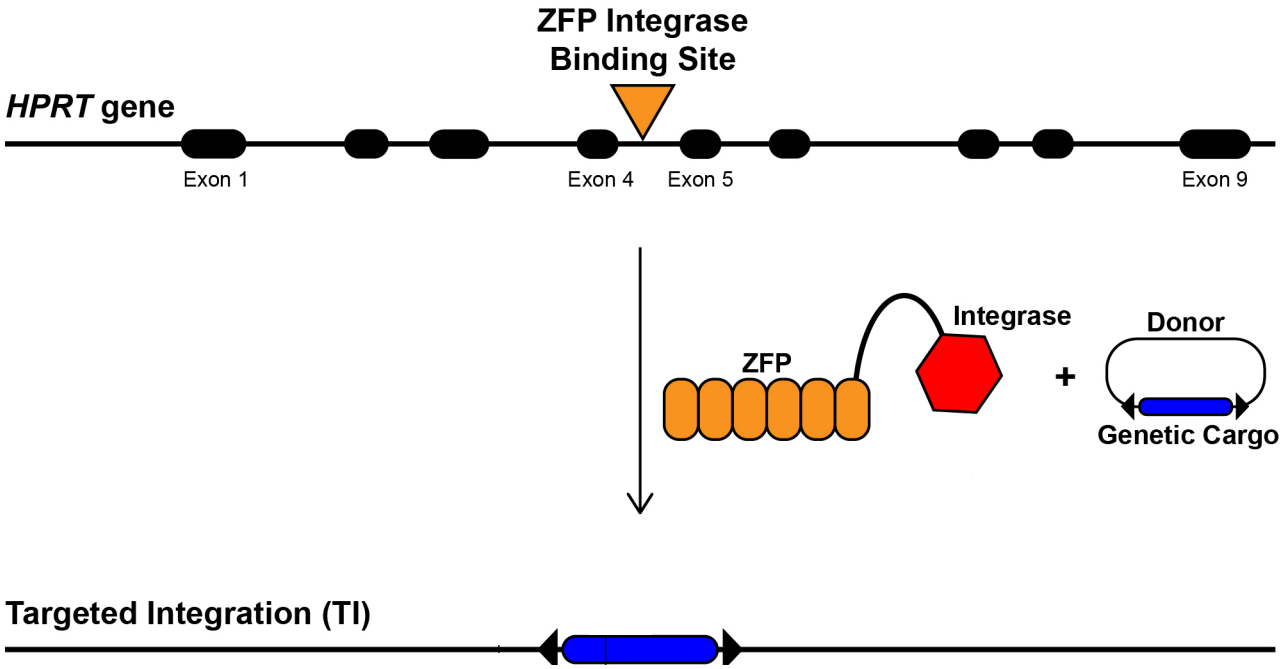


76% of cells have all four modifications

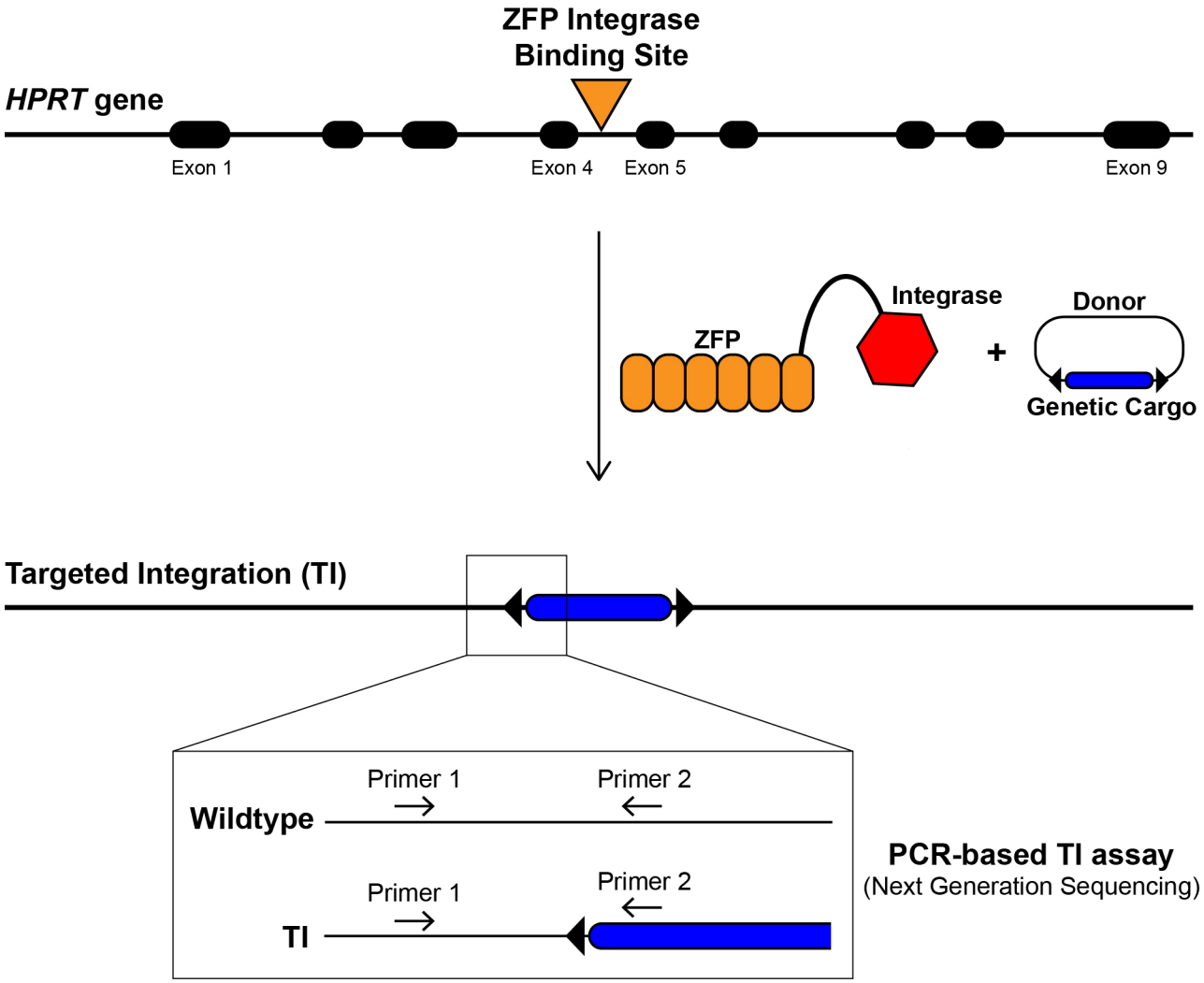
Recent focus: targeted integrases

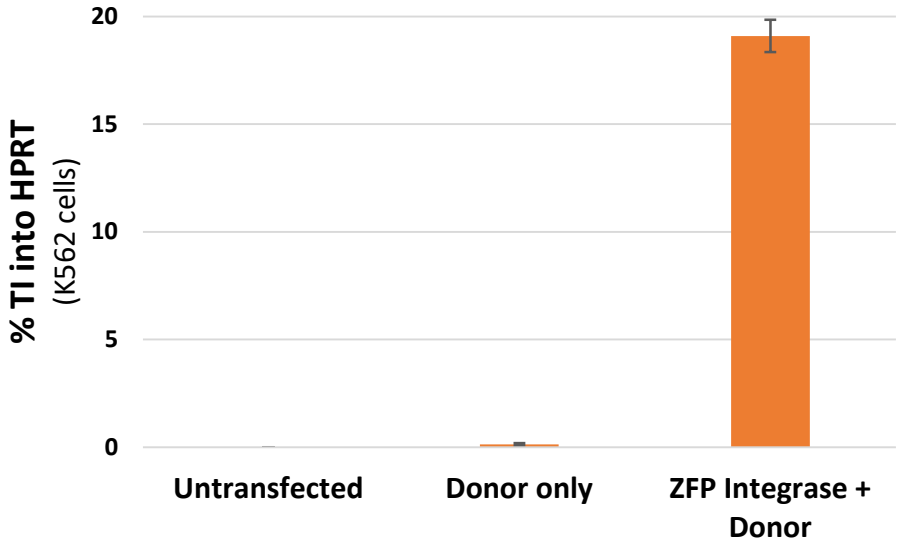


Goal: targeted integration into human HPRT gene

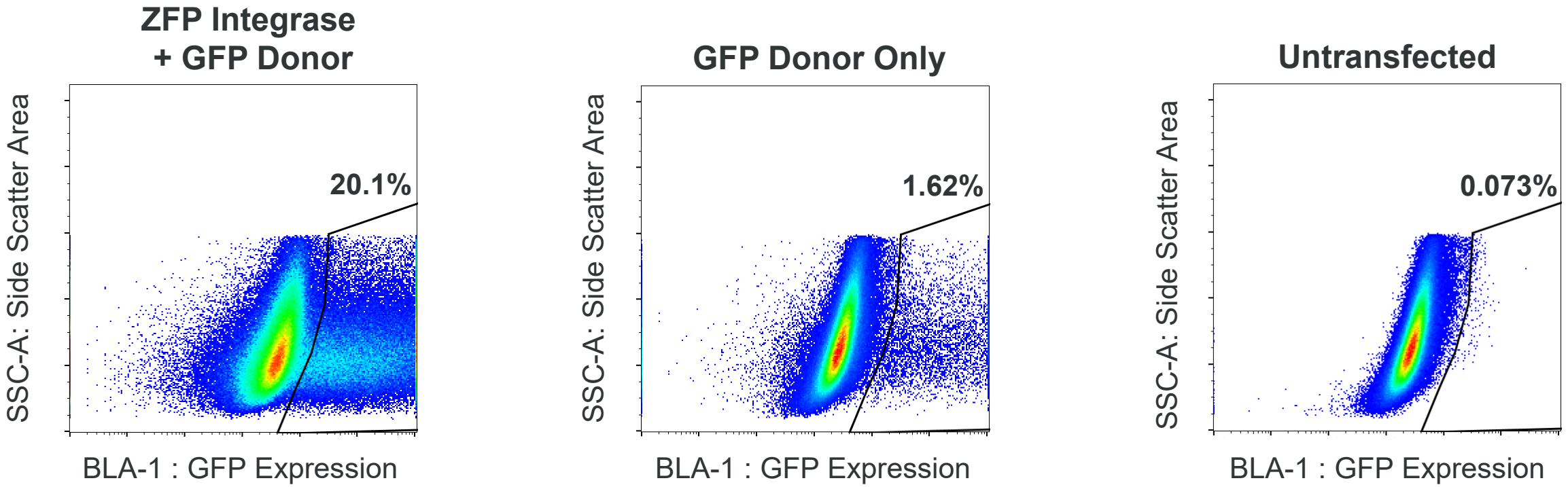


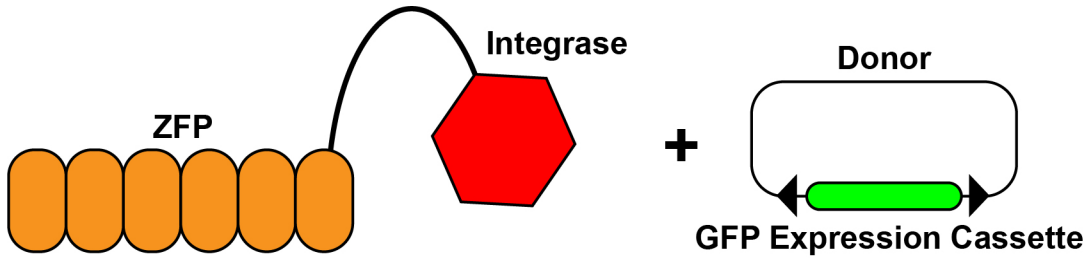
Preliminary results indicate high efficiency (PCR-based assay)





High efficiency integration confirmed via flow analysis





Washout study – 34 days

Key takeaways

- Designed zinc finger proteins provide the platform of choice for fully realizing the prospect of precision genomic medicines
- Design versatility enables genome targeting with base pair resolution
- Use of precharacterized, modular components enables rapid lead development

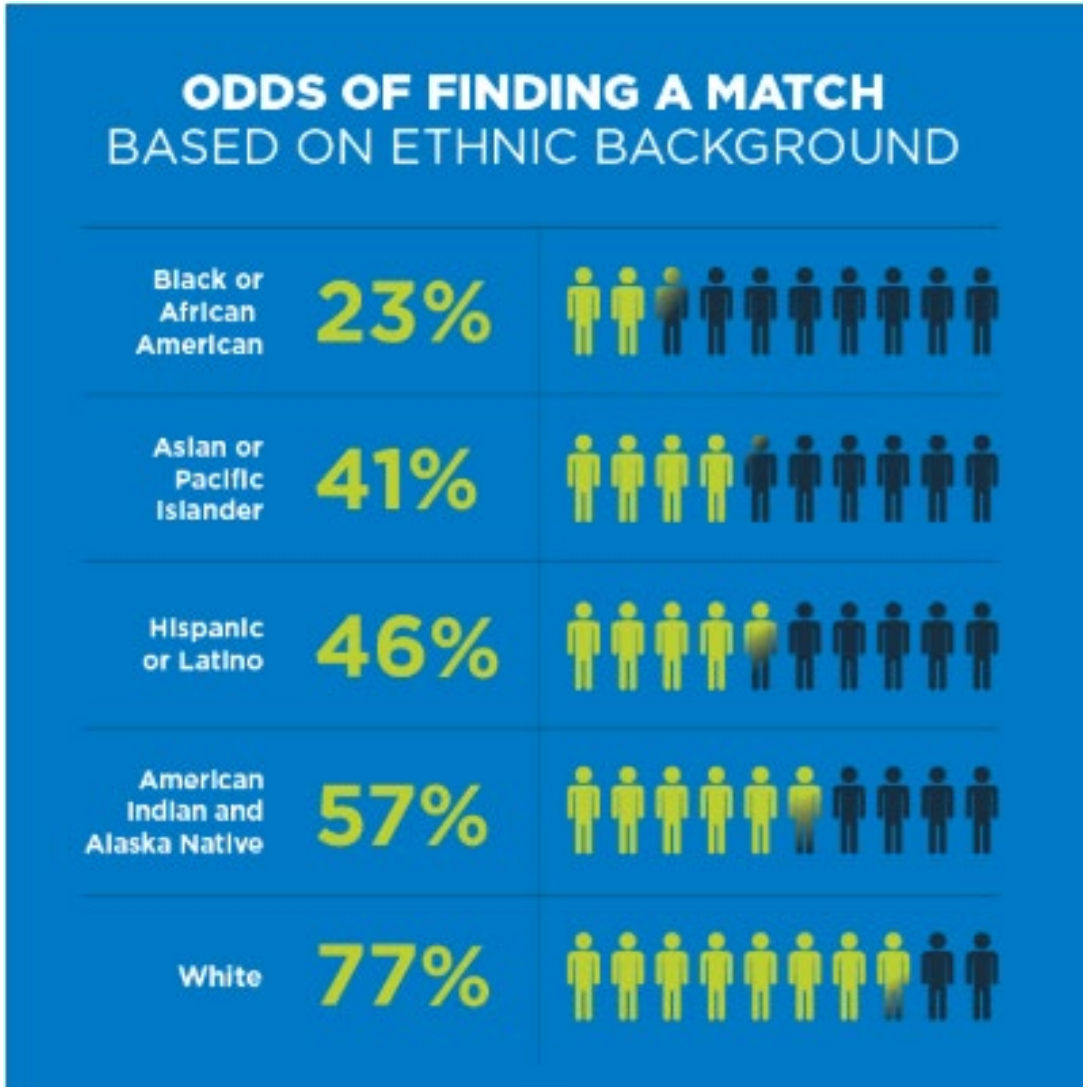
  → with option for fine scale tuning of properties
- New strategies for specificity optimization enable complete (>98%) gene editing with no detectable off-targets
- Modular nature of ZFPs enables continued extensions to capabilities

Gene editing of HSCs with ZFN: Early clinical observations in patients with Beta thalassemia (ST-400)

Wes Miller, Medical Director

Ex vivo HSC editing: Immense clinical potential and promise

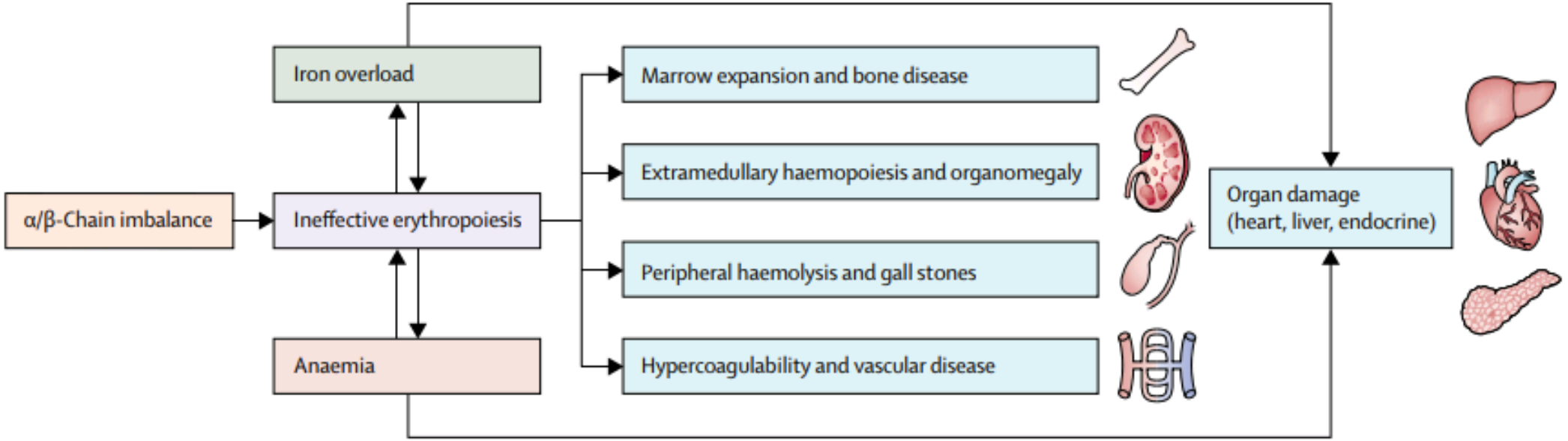
- Over 7,000 estimated annual HSCT in US
- Used in >47 severe, non-cancer disorders[1], most heritable
- But this curative therapy is limited by lack of donors and risk of GvHD
- Thus, *ex vivo* gene modified HSCT holds great promise
- Precise and efficient HSC editing is highly desirable



[1]bmtinfonet.org; Figure from bethematch.org

Beta thalassemia (BThal): overview

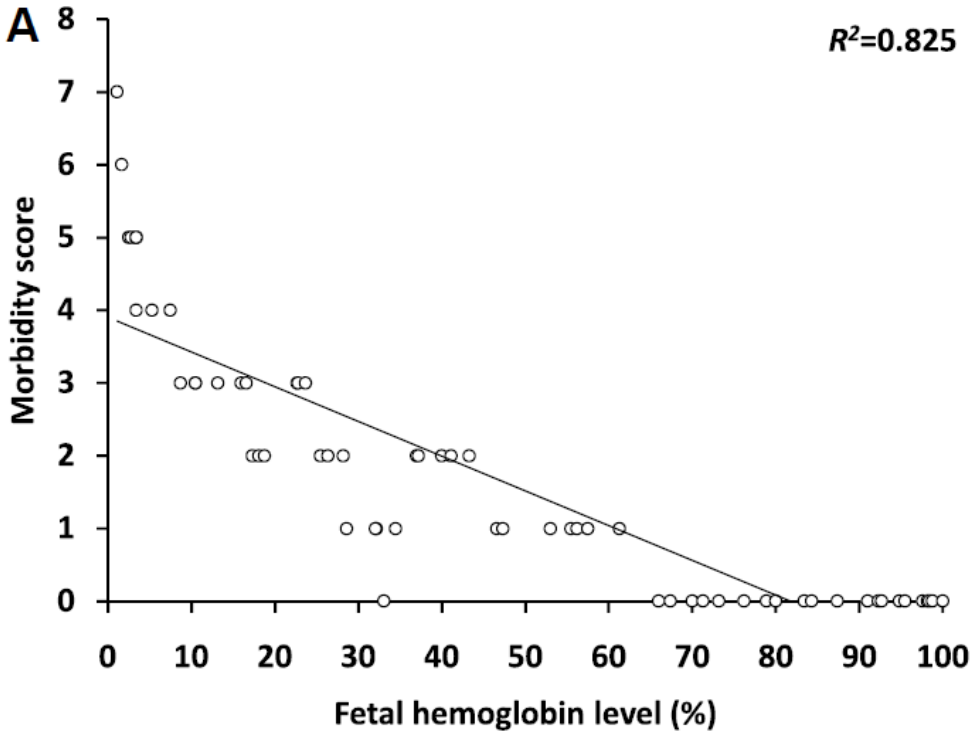
- > 25,000 born with severe TDT per year[1]
- Central problem: alpha globin and beta-like globin chain imbalance
- Consequences: severe anemia and ineffective erythropoiesis
- Standard therapies:
  - Non-curative: chronic transfusions + chelation
  - Curative: HSCT



[1]World Health Organization website; Figure from Taher et al. Thalassemia. *Lancet*, 2017.

Inducing fetal hemoglobin in BThal: Why?

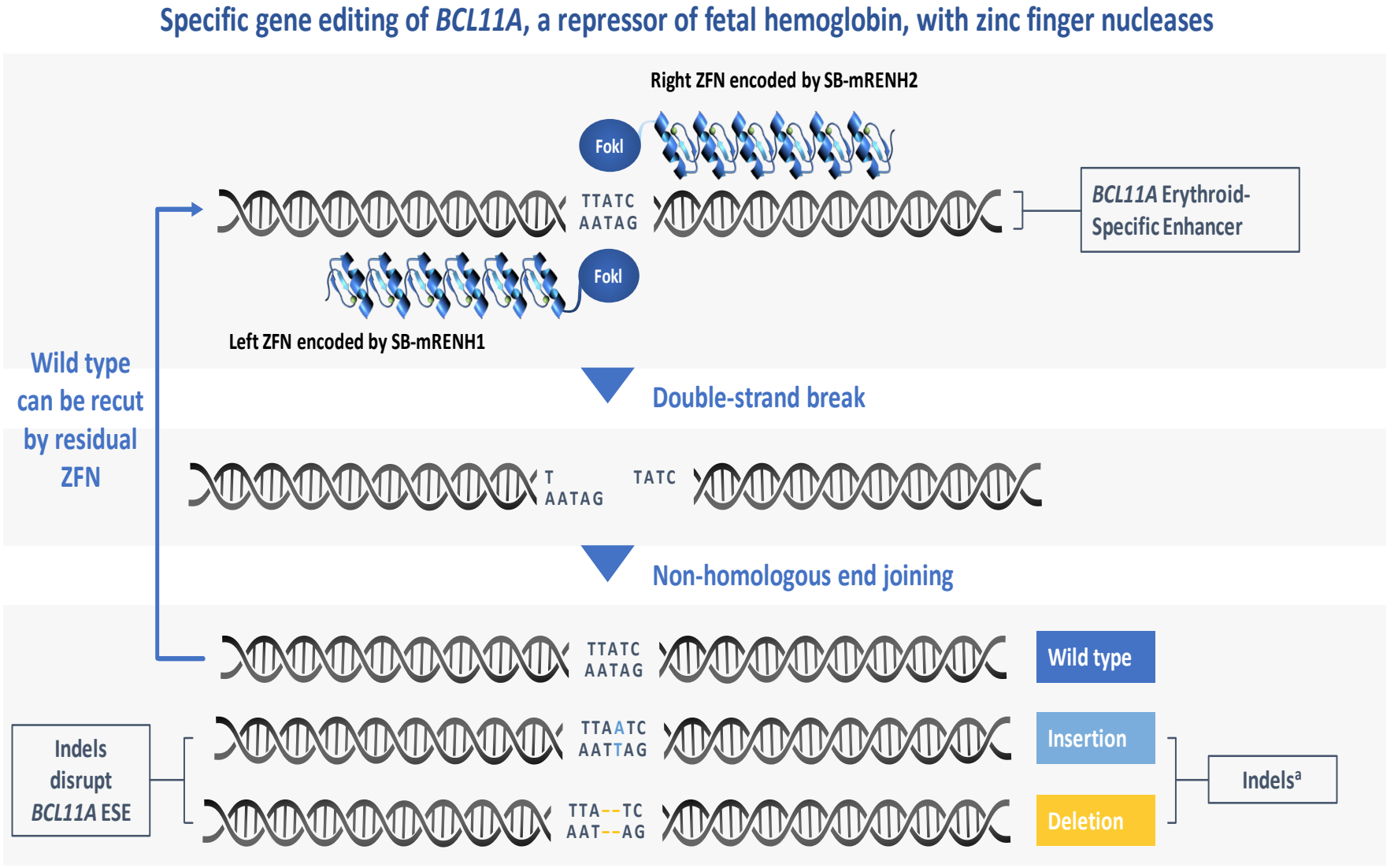
HbF Ameliorates BThal Syndrome[1]



[1]Musallam et al. Fetal hemoglobin levels and morbidity in untransfused patients with B-thalassemia intermedia. *Blood*, 2011

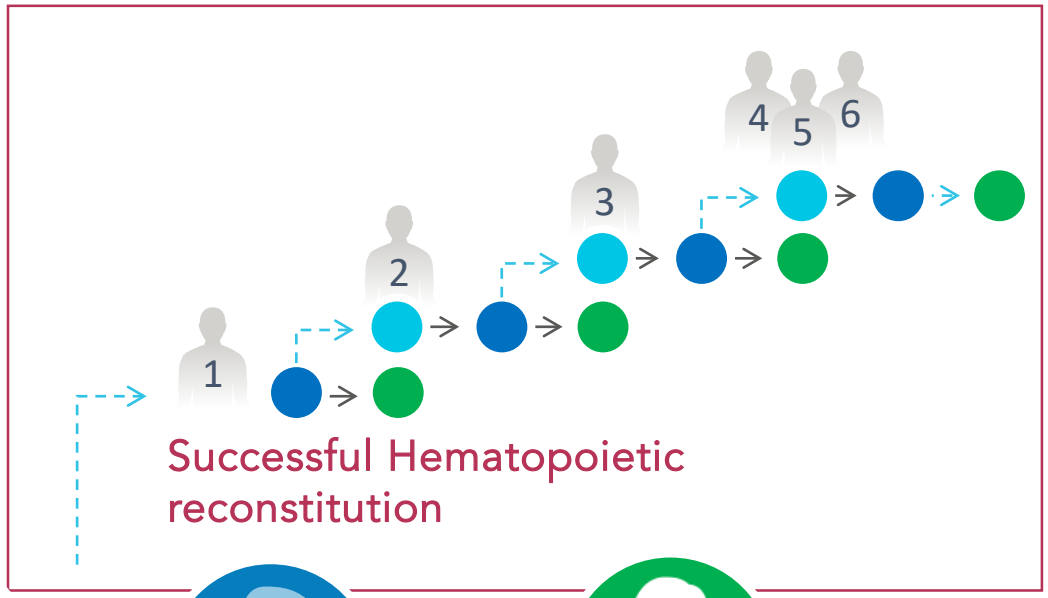
Inducing fetal hemoglobin in BThal: How?

BCL11A: Critical Regulator of Physiologic HbF → HbA Switch



Beta thalassemia: Study design (ST-400)

- First-in-human
- Autologous HCT with ST-400
- Adults, n=6
- 8+ annual PRBC transfusion events



Screening

Mobilization & Apheresis

Gene Editing: ST-400

Busulfan Conditioning

Engraftment

Follow-up 3 years

~ 4 months

RBC effect: ~ 6-12+ months

Sangamo THERAPEUTICS

ST-400 is an investigational therapy that has not been evaluated by any regulatory agency

Sangamo THERAPEUTICS

Presented at the 2019 American Society of Hematology Annual Meeting; Orlando, Florida; December 9, 2019

Preliminary Results of a Phase 1/2 Clinical Study of Zinc Finger Nuclease-Mediated Editing of *BCL11A* in Autologous Hematopoietic Stem Cells for Transfusion-Dependent β-Thalassemia

Angela R. Smith, MD, MS[1]; Gary J. Schiller, MD[2]; Gregory M Vercellotti, MD[3]; Janet L. Kwiatkowski, MD, MSCE[4]; Lakshmanan Krishnamurti, MD[5]; Erica B. Esrick, MD[6]; David A. Williams, MD[7]; Weston P. Miller, MD[8]; Adrian Woolfson, MD, PhD[8] and Mark C. Walters, MD[9]

[1]Pediatric Blood and Marrow Transplantation, University of Minnesota, Minneapolis, MN; [2]Division of Hematology and Oncology, Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA; [3]Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN; [4]The Children's Hospital of Philadelphia, Philadelphia, PA; [5]Aflac Cancer and Blood Disorders Center, Department of Pediatrics, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; [6]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA; [7]Boston Children's Hospital, Harvard Medical School, Boston, MA; [8]Sangamo Therapeutics, Brisbane, CA; [9]USCF Benioff Children's Hospital Oakland, Oakland, CA

Patient demographics and disease characteristics

Patient	Age at Consent (Years)	Genotype	Annualized PRBC Events Pre-Enrollment	Most Recent Study Visit
1	36	β^0 β^0	27	39 weeks
2	30	β^+ (severe IVS-I-5: G>C) β^+ (severe IVS-I-5: G>C)	18	26 weeks
3	23	β^0 β^+ (severe IVS-II-654 C>T)	15	12 weeks
4	18	β^{WT} ($\alpha\alpha$) β^0 ($\alpha\alpha\alpha\alpha$)	13	Recently Dosed
5	35	β^0 β^+ (severe IVS-I-110 G>A)	15	Recently Dosed

- β^0, absence of β–globin production; β^+, decreased β–globin production; β^{WT}, wild type (normal β–globin production); PRBC events, packed red blood cell transfusion
- **Patient 4: as expected from genotype, this patient has the least severe phenotype among all patients enrolled**

Sangamo THERAPEUTICS

Data cuts: clinical, October 10, 2019; laboratory, November 8, 2019

Enrolled patients, ST-400 product and engraftment

Patient	Cell Dose (10^6/kg)	CD34+ (%)	CFU Dose (10^5/kg)	On-target Indels[a] (%)	Neutrophil Engraftment[b] Day(s)	Platelet Recovery[c] Day(s)
1[d]	5.9	91	6.2	23[e]	14	25
2[d]	4.5	87	4.0	73	15	22
3[f]	11.4	90	14.8	54	22	35
4	5.4	86	7.3	80	Recently Dosed	Recently Dosed
5	9.5	98	10.5	76	Recently Dosed	Recently Dosed

[a]Percentage of all *BCL11A* ESE alleles with an indel; this is not equivalent to the percentage of all cells with at least 1 edited *BCL11A* ESE allele.

[b]Neutrophil engraftment was defined as occurring on the first of 3 consecutive days on which the patient's neutrophil count was ≥500 cells/μL.

[c]Platelet engraftment was defined as occurring on the first of 3 consecutive measurements spanning a minimum of 3 days (in the absence of platelet transfusion in the preceding 7 days) on which the patient's platelet count was ≥20,000 cells/μL.

[d]Patients 1 and 2 received G-CSF from Day +5 through neutrophil engraftment per site's standard operating procedure.

[e]Patient 1 underwent 2 cycles of apheresis and manufacturing of ST-400; on-target indel percentage for the lot not shown was 26%. All other patients underwent only 1 cycle of apheresis and manufacturing.

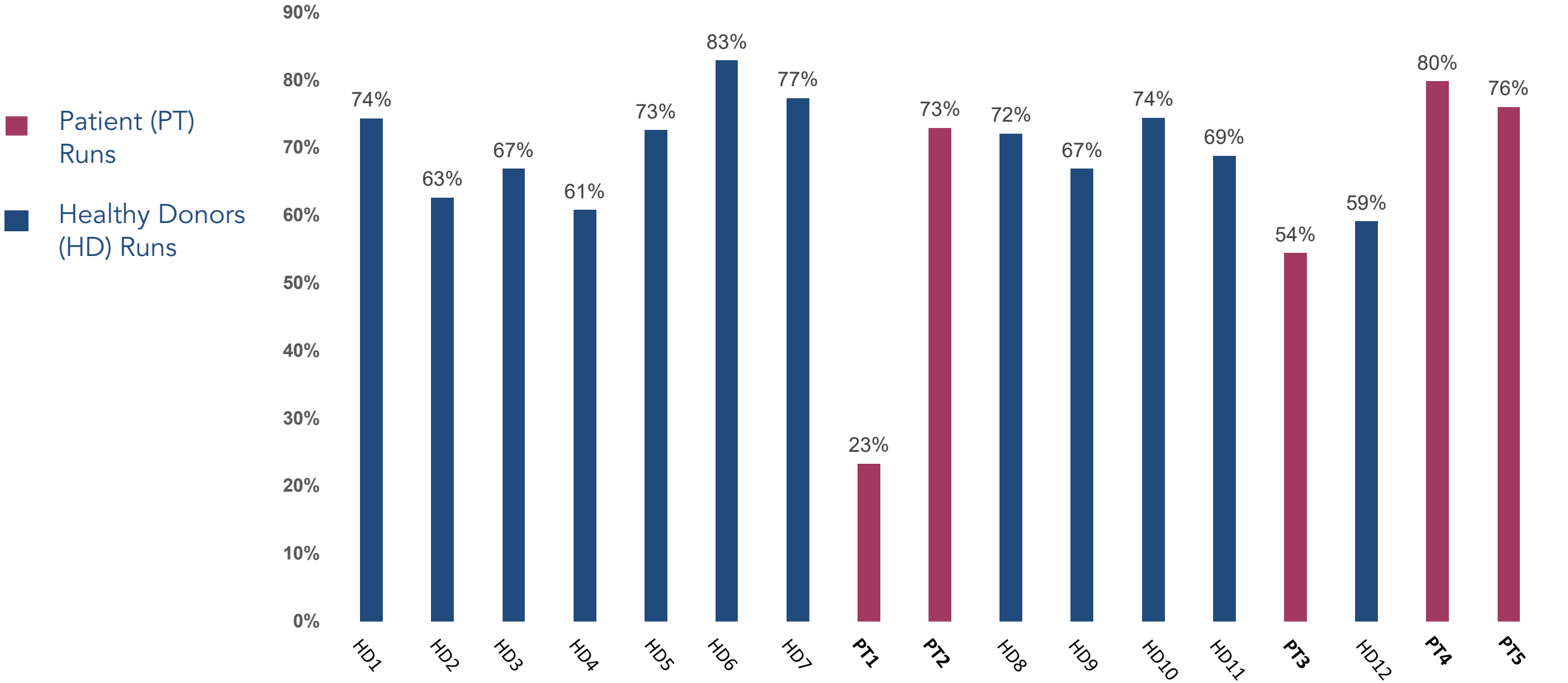
[f]Patient 3 received G-CSF from Day +21 through neutrophil engraftment per site's standard operating procedure.

CFU, total colony-forming unit; ESE, erythroid-specific enhancer; G-CSF, granulocyte colony-stimulating factor.

Sangamo THERAPEUTICS

Data cuts: clinical, October 10, 2019; laboratory, November 8, 2019

ST-400 editing efficiency: patients and healthy donors



- Healthy donor runs at clinical scale; all performed at GMP facility, using same reagents and processes for clinical/patient ST-400 manufacturing
- **Patient 1 underwent 2 cycles of apheresis and manufacturing of ST-400; on-target indel percentage for the lot not shown was 26%.**

Sangamo THERAPEUTICS

ST-400: Safety profile

- Reported adverse events (AEs) have been consistent with those expected with myeloablative autologous HCT
- Two serious AEs have been reported
  - #1: assessed as likely related to DMSO, the cryoprotectant excipient
  - #2: not related to ST-400
- No emerging clonal hematopoiesis observed by indel pattern monitoring

Sangamo THERAPEUTICS

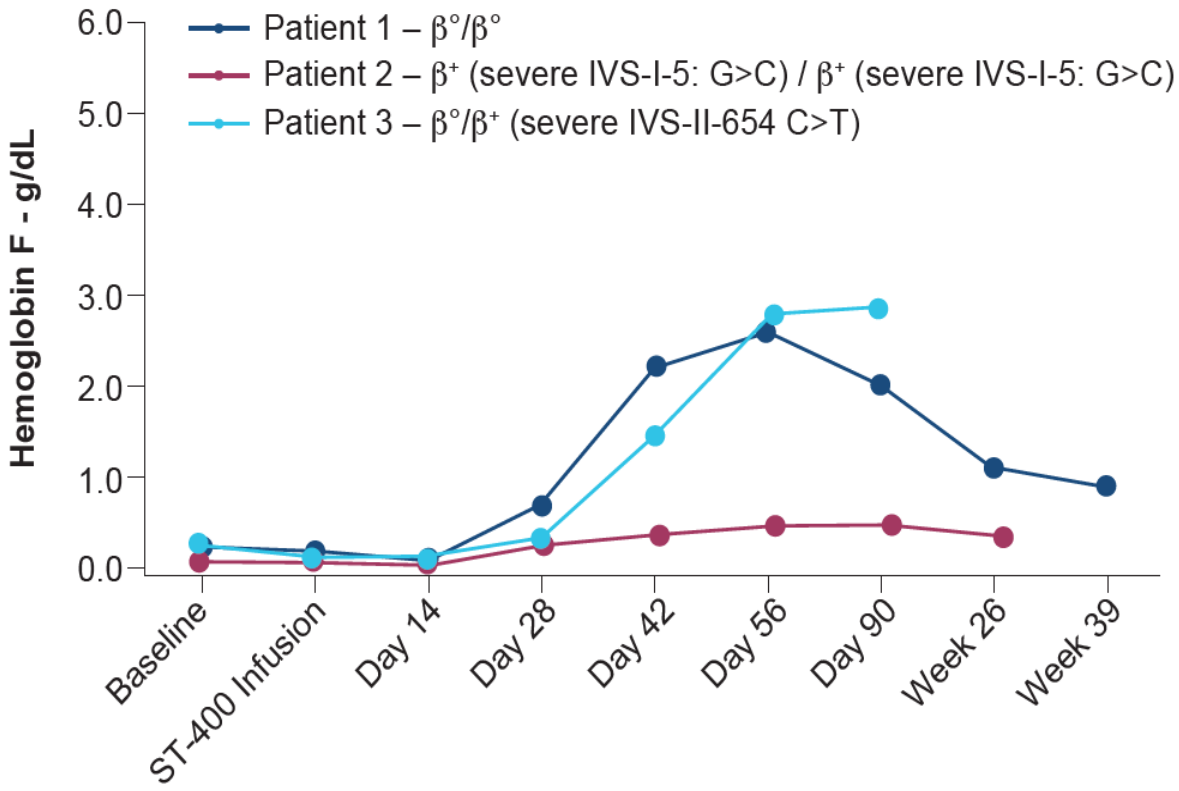
Data cuts: clinical, October 10, 2019; laboratory, November 8, 2019

ST-400: Fetal hemoglobin response

HSC Transplant Variable	Patients				
	1	2	3	4	5
Cell Dose	◑	○	●	◔	◕
Lot Potency	◔	○	●	◑	◕
Editing	○	◑	◔	●	◕
BThal Genotype	○	◔	◑	●	◑
Age (Youth)	○	◑	◕	●	◔

○ ◔ ◑ ◕ ●

Potentially more favorable



Sangamo THERAPEUTICS

Data cuts: clinical, October 10, 2019; laboratory, November 8, 2019

Summary: ST-400 and clinical ZFN-editing of HSCs

- ST-400:
  - Rapid hematopoietic reconstitution after full conditioning
  - Early HbF induction in 2 patients is promising; evolving understanding of impact of patient- and product-related characteristics
  - Early safety and efficacy findings merit further exploration of ST-400
- ZFN-edited, auto-HCT platform:
  - Clinically feasible
  - Efficient and specific
  - Reproducible at clinical scale in GCP

Cell therapy

Jason Fontenot, Head of Cell Therapy

Sangamo cell therapy

- Sangamo cell therapy: now and the future
- Regulatory T cells (T_{REGS})
- Sangamo CAR-T_{REG} program
- Next gen T_{REG} cell therapies

The era of engineered cell therapy has arrived

Company: Novartis

Therapy: CD19-targeted CAR-T cell

Approved: August 2017

Indication: Acute lymphoblastic leukemia and relapsed or refractory diffuse large B-cell lymphoma.

Company: Kite Pharma

Therapy: CD19-targeted CAR-T cell

Approved: October 2017

Indication: Large B-cell lymphoma, primary mediastinal B-cell lymphoma or transformed follicular lymphoma

Sangamo THERAPEUTICS

Cell therapy leverages Sangamo core strengths

Gene-Edited Cell Therapy

Cell Engineering

Genome Editing

Manufacturing

ST-400
Beta thalassemia

BIVV003
Sickle cell disease

TX200
CAR-T_{REG} transplant

KITE-037
Allo-CD19 CAR-T

Sangamo cell therapy is advancing

CCR5-edited Autologous T cells

CCR5-edited HSCs

ST-400
Beta thalassemia

BIVV003
Sickle cell disease

TX200
CAR-T_{REG} transplant

KITE-037
Allogeneic CD19 CAR-T

CAR-T_{REG}
Autoimmune Indications

Kite Collaboration
T cells/NK cells in Oncology

Engineered HSCs
Targeted Gene Correction

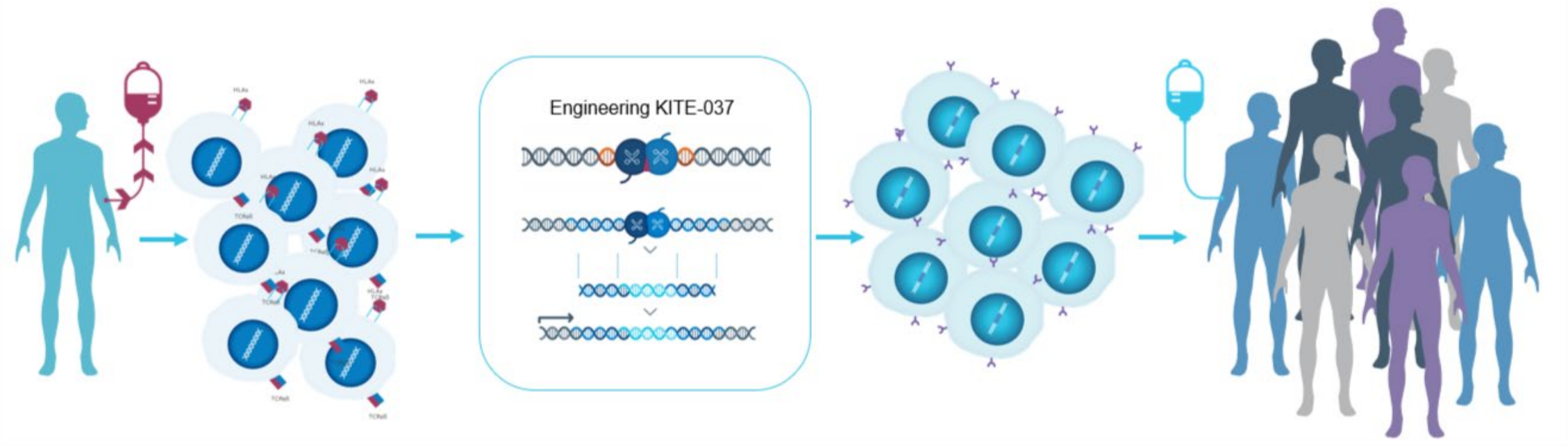
HIV CAR T Cells

Hypoimmunogenic Allogeneic iPSCs

Sangamo THERAPEUTICS

KITE-037, the first product candidate of the Kite collaboration

- KITE-037 is an allogeneic anti-CD19 CAR-T product candidate



- Kite is planning to initiate a clinical study evaluating KITE-037 in 2020

Sangamo is pioneering the next frontier in cell therapy

INSIGHTS | PERSPECTIVES

Science AAAS

IMMUNOTHERAPY

T_{reg} cells–the next frontier of cell therapy

Will regulatory T cells be a frontline therapy for autoimmunity and other diseases?

Science. 2018 Oct 12;362(6411):154-155

REVIEWS

Next-generation regulatory T cell therapy

Leonardo M. R. Ferreira[1,2,3,4], Yannick D. Muller[1,4], Jeffrey A. Bluestone[2,3]* and Qizhi Tang[1,2]*

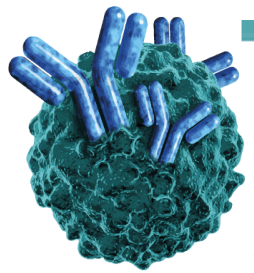
Nat Rev Drug Discov. 2019 Oct;18(10):749-769

THE Crafoord PRIZE

THE ROYAL SWEDISH ACADEMY OF SCIENCES

The Crafoord Prize in Polyarthritis 2017

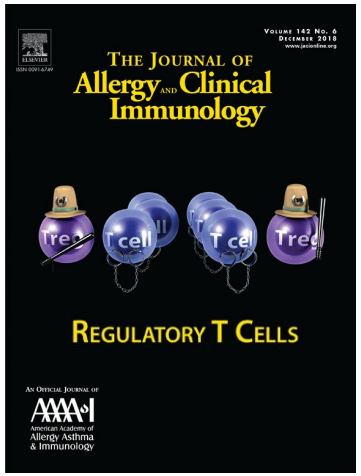
"for discoveries relating to regulatory T cells, which counteract harmful immune reactions in arthritis and other autoimmune diseases"



May 20-22, 2019
Boston, MA

Treg Summit

Treg Directed Therapy for Autoimmune Disorders



December 2018
Volume 142, Issue 6

MINI REVIEW

frontiers in Immunology

Chimeric Antigen Receptor (CAR) Treg: A Promising Approach to Inducing Immunological Tolerance

Front Immunol. 2018 Oct 12;9:2359

Pillars of Immunology — The Journal of Immunology

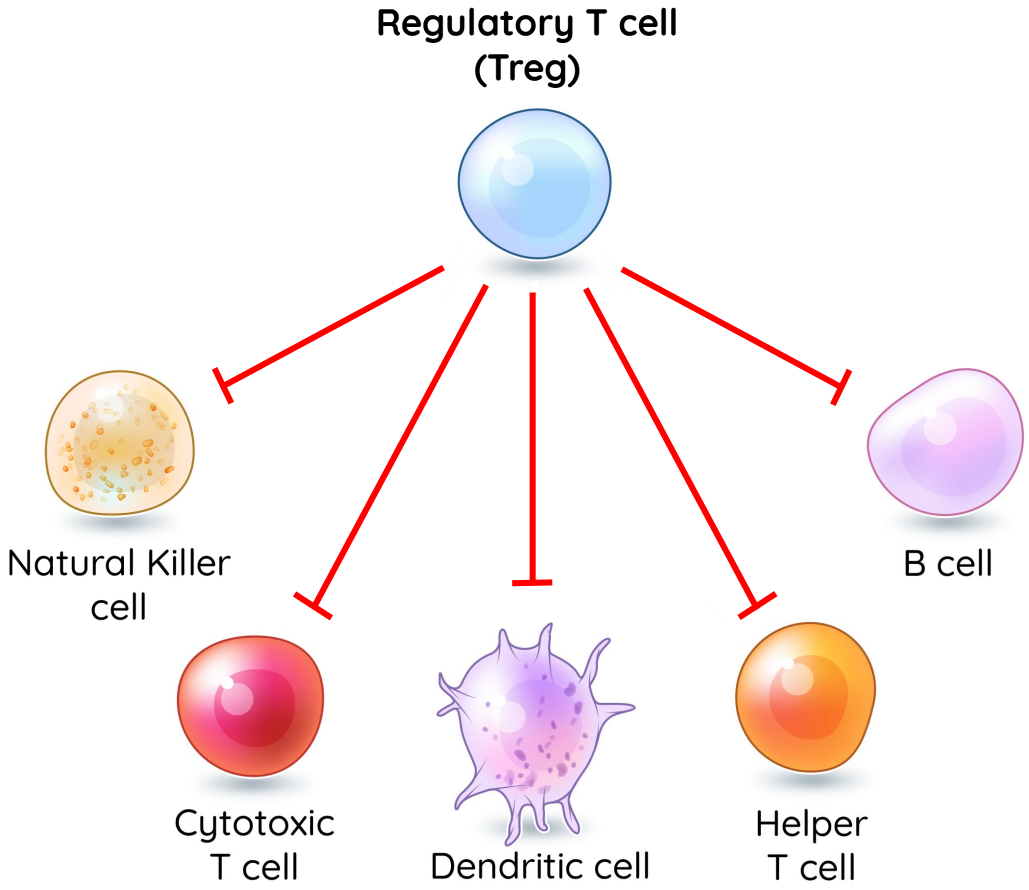
FOXP3, the Transcription Factor at the Heart of the Rebirth of Immune Tolerance

Jeffrey A. Bluestone

J Immunol. 2017 Feb 1;198(3):979-980

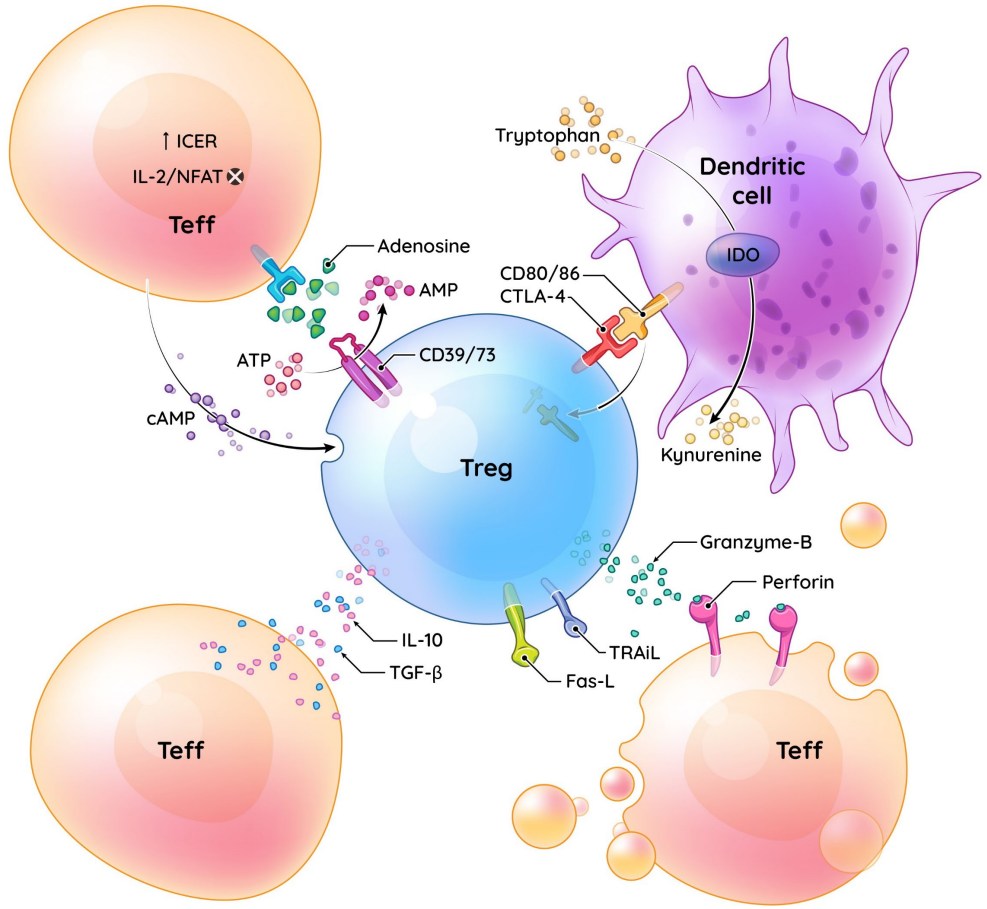
Regulatory T cells inhibit autoimmune disease

- 1-2% of circulating lymphocytes
- Specialized suppressor cells
- T_{REG} cells dominantly suppress immune activation
- T_{REG} cells actively prevent inflammatory and autoimmune disease
- Genetic deficiency in T_{REG} cells results in lethal systemic autoimmune syndrome
- T_{REG} cells deficiency or dysfunction is described in multiple autoimmune diseases



T_{REG} cell therapy leverages complete T_{REG} biology

- T_{REGS} act through multiple molecular mechanisms
- No single molecular mechanism can account for immunosuppressive properties
- Immune inhibition is context dependent
- T_{REG} cell therapy leverages complete T_{REG} biology

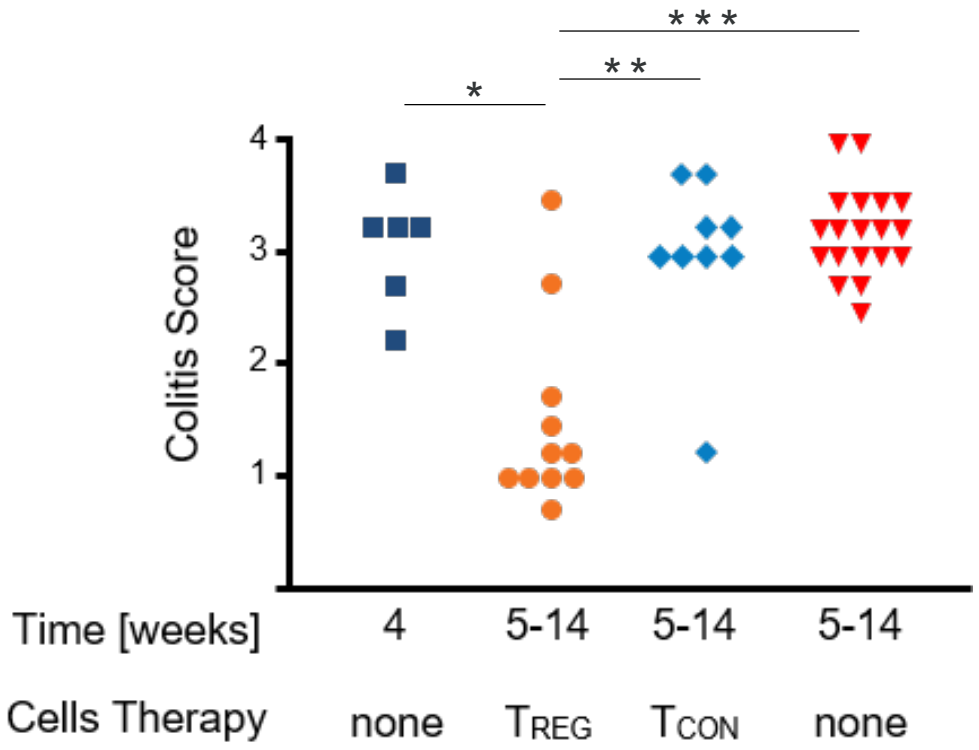


Adapted from Front Immunol. 2015 Aug 31;6:438

T_{REGS} reverse established disease in mouse IBD model

Cure of Colitis by CD4+CD25+ Regulatory T cells

Powrie and colleagues, J Immunol. 2003 Apr 15



Transfer of 10^6 Treg 4 weeks after disease induction
Figure adapted from publication

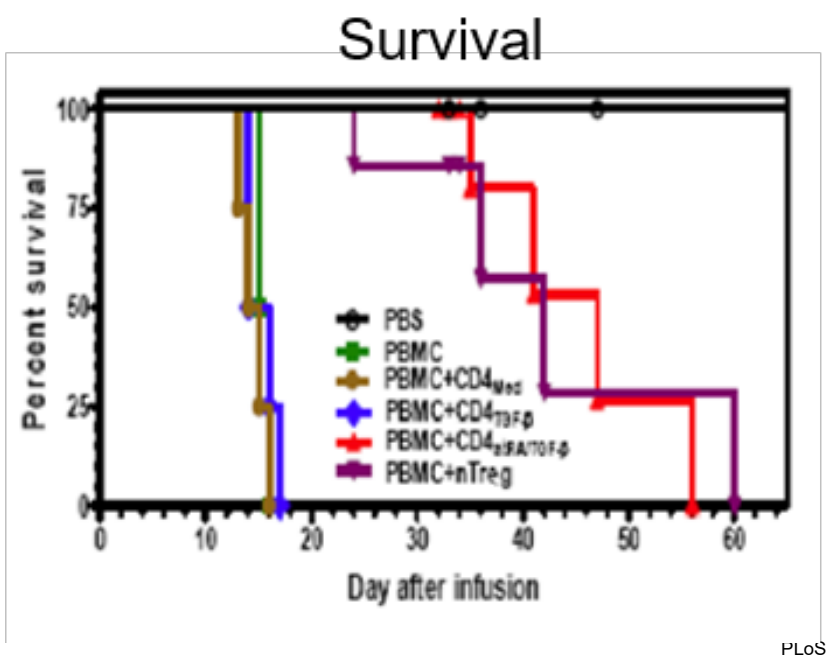
* P=0.009 * * P=0.0039 * * * P=0.0002

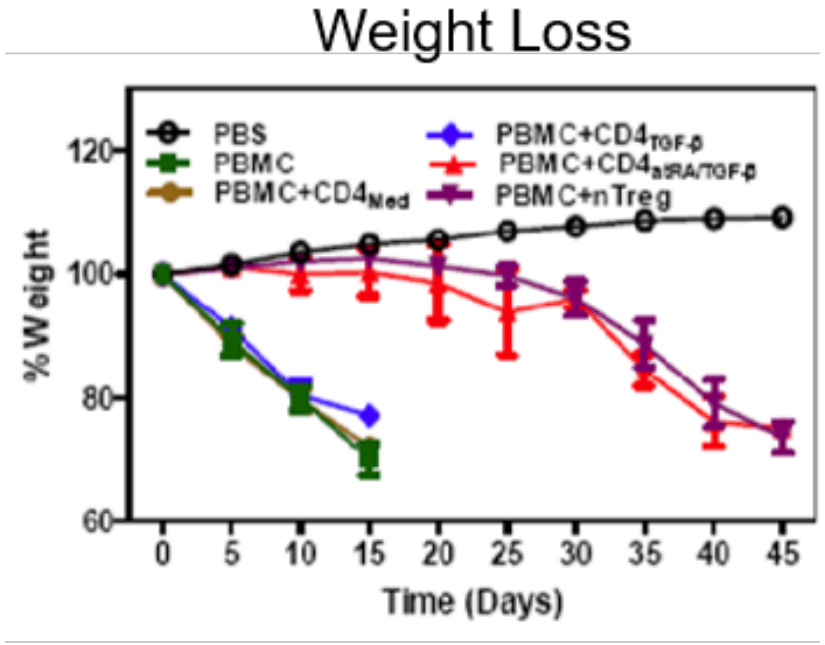
- T_{REG} cells can be efficiently expanded *ex vivo* and retain function
- T_{REG} cells can dominantly suppress immune pathology
- T_{REG} cell therapy conveys therapeutic benefit in numerous animal models of autoimmune disease

Sangamo THERAPEUTICS

Human T_{REGS} prevent xenogeneic GvHD

A rapidly fatal xenogeneic GvHD was induced by the transfer of $2x10^7$ CD25-depleted human PBMC into sublethally irradiated NSG mice. $5x10^6$ of indicated human T_{REG} populations or control $CD4^+$ T cells were combined with the human PBMC and transferred IV





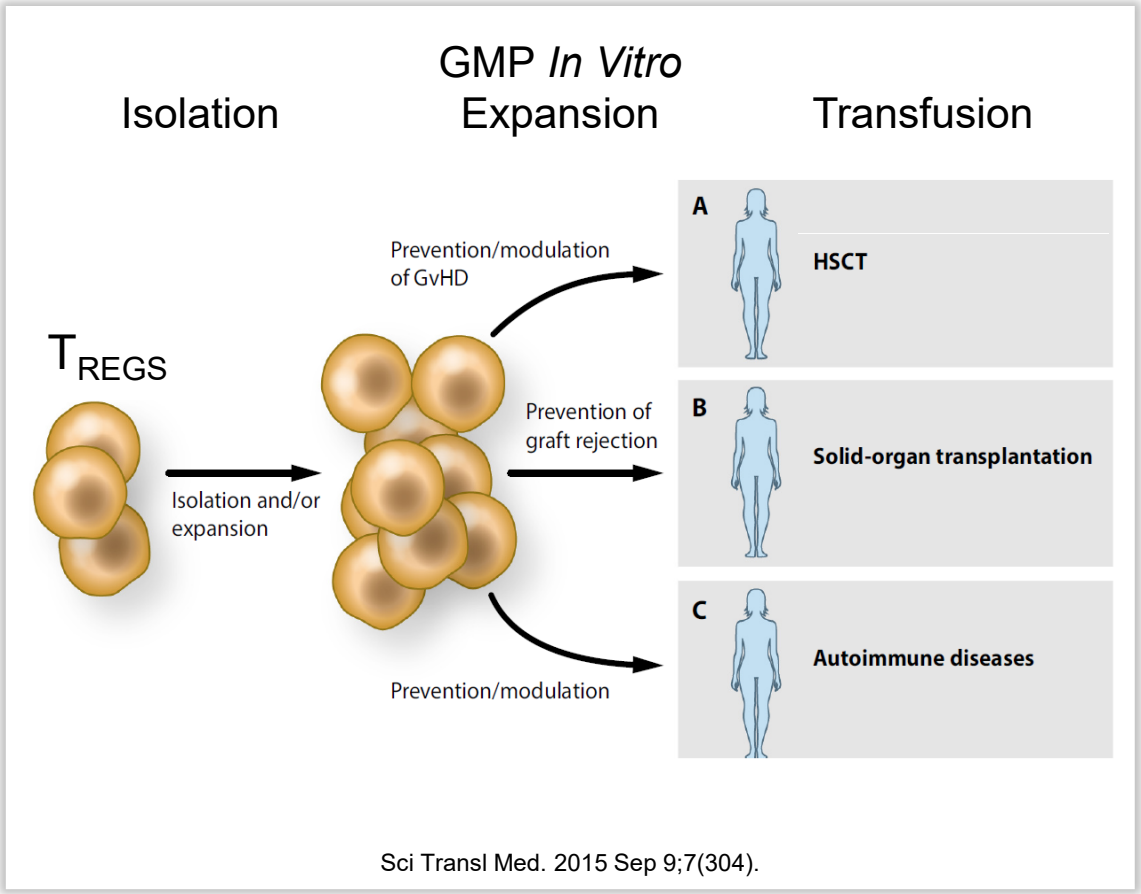
PLoS One. 2010 Dec 17;5(12):e15150

- Human T_{REG} cells can be expanded *ex vivo* and retain function
- Human T_{REG} cells can dominantly suppress aggressive immune pathology

PLoS One. 2010 Dec 17;5(12):e15150

Human T_{REG} cells have therapeutic potential

Autologous polyclonal T_{REG} cell therapy in humans



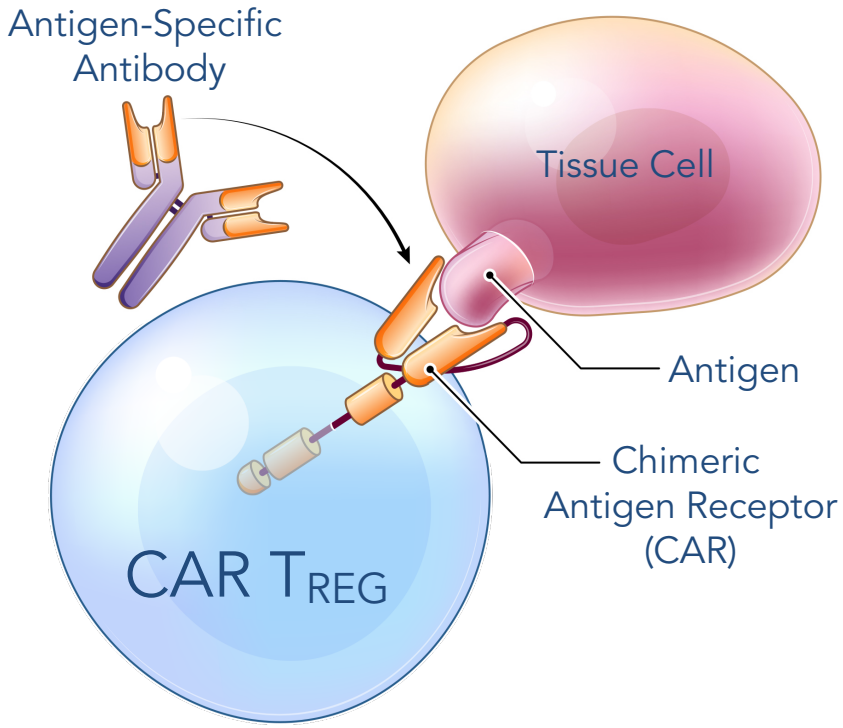
Sci Transl Med. 2015 Sep 9;7(304).

- Human T_{REG} cells can be efficiently expanded *ex vivo* at clinical scale
- Human T_{REG} cells retain functional properties upon *ex vivo* expansion
- Human T_{REG} cell therapy is safe
- Hints of therapeutic benefit
- No meaningful *in vivo* expansion or persistence
- No tissue targeting

Sangamo THERAPEUTICS

Harnessing T_{REG} Function with CAR-T_{REG} Therapy

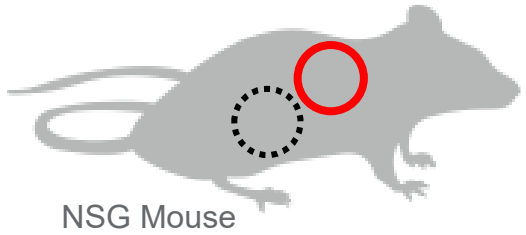
CAR-T_{REGS} overcome limitations of polyclonal T_{REG} Therapy



- Ex vivo engineered and expanded
- Tissue targeted
- Antigen activated & expanded
- Multiple mechanisms of immune regulation

CAR-mediated T_{REG} tissue targeting

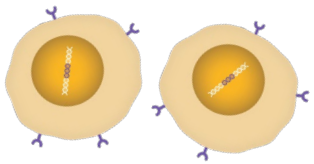
Skin Transplants



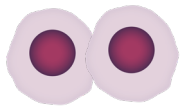
— **HLA–A2(–)**

····· **HLA–A2(+)**

I.V. Injection

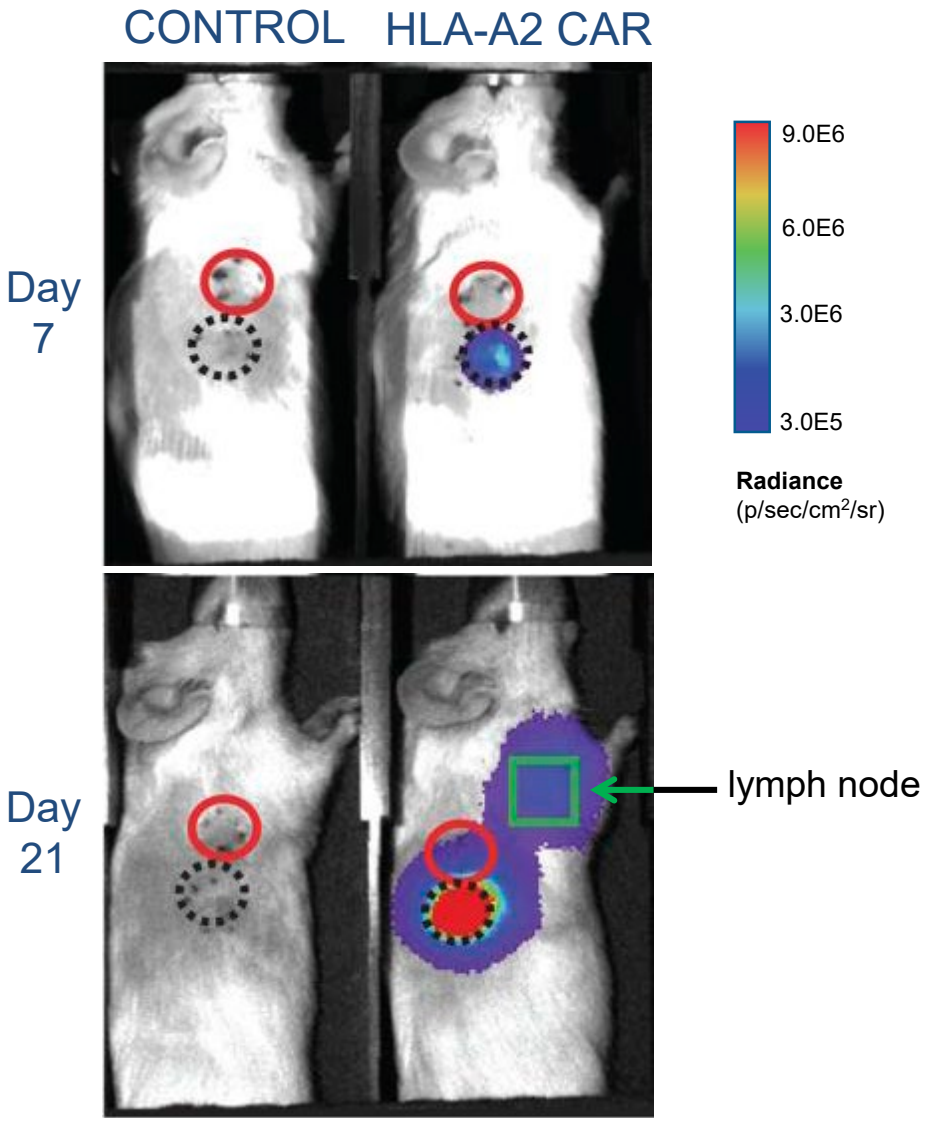


Luciferase^{+}
HLA-A2 CAR T_{REG} Cells or
Control CAR T_{REG} Cells



Peripheral Blood
Mononuclear Cells

Imaging

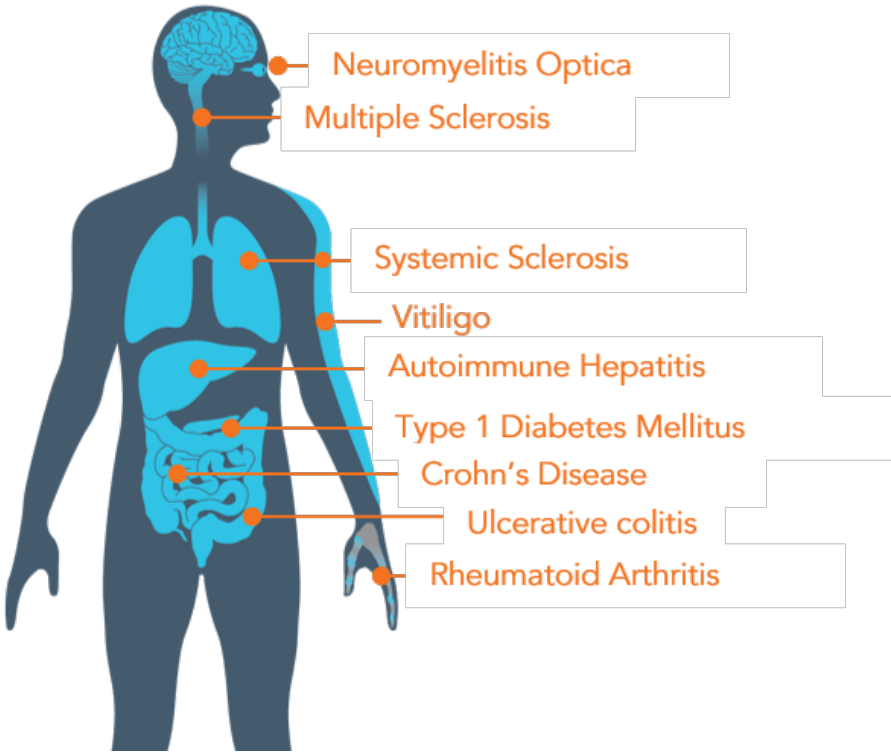


Dawson NA, Lamarche C et al. JCI Insight 2019;4(6):e123672.

TX200: Gateway to major autoimmune indications

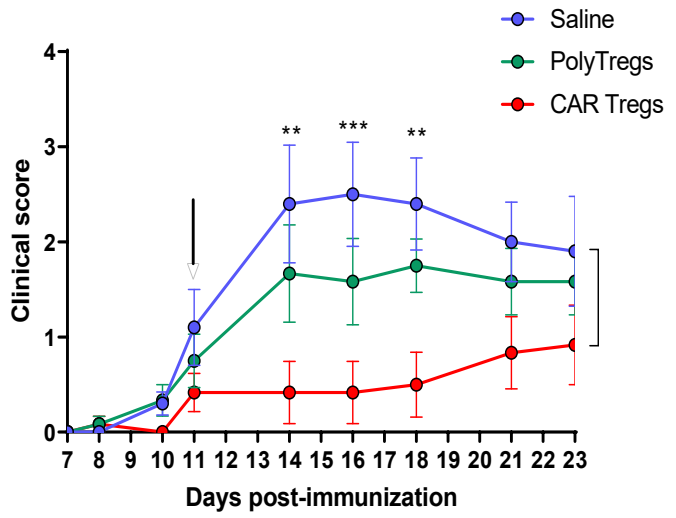
Key outcomes from TX200 CAR-T_{REG} program

- Provides data on safety and proof of concept
- Answers critical questions on CAR-T_{REG} pharmacology and biology in patients
- Establishes CAR-T_{REG} cell therapy process development know how and manufacturing infrastructure
- Gateway to multiple autoimmune indications with large patient populations and high unmet need



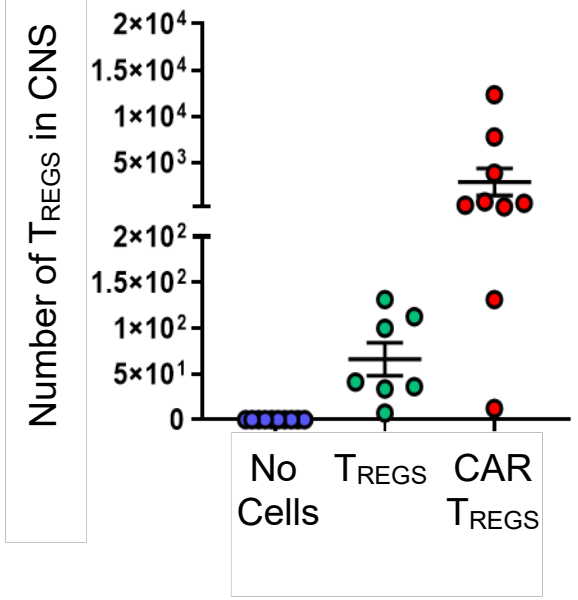
CNS-targeted CAR-T_{REG} for Multiple Sclerosis

CNS-Targeted CAR-T_{REGS} Reduces EAE

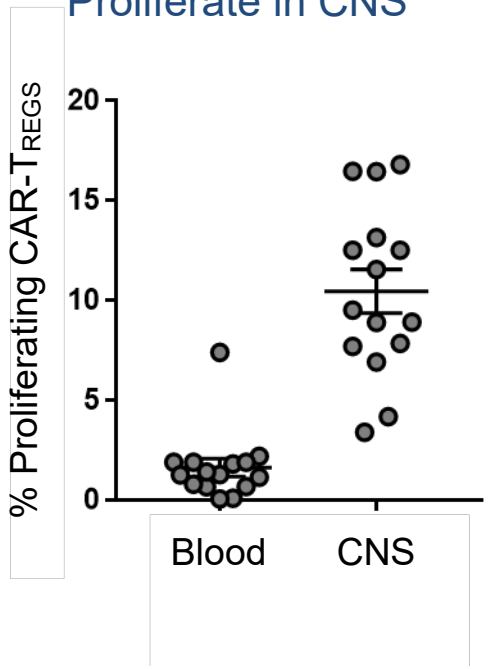


two-way ANOVA
n=5 for saline, n=6 for Poly nTregs and MOG CAR
**:p<0.05; **:p<0.001; ***:p<0.0005*

CNS-Targeted CAR-T_{REGS} Accumulate in CNS



CNS-Targeted CAR-T_{REGS} Proliferate in CNS



Sangamo engineered T_{REG} therapy 2.0

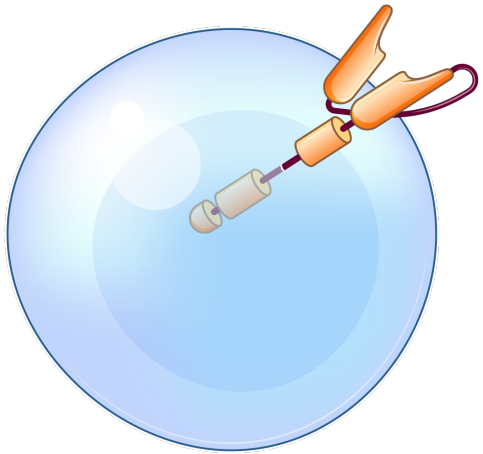
Sangamo ZFN Multiplexed Genomic Engineering

Allogeneic Off-the-Shelf

- Healthy donor-derived allogeneic T_{REG}
- iPSC-derived allogeneic T_{REG}
- Hypoimmunogeneic editing

Improved Function

- Increased Persistence
- Enhanced localization
- Improved potency



Sangamo T_{REG} Platform Investments

- T_{REG} Manufacturing
- scFv T_{REG} CAR screening platform

Sangamo cell therapy pipeline

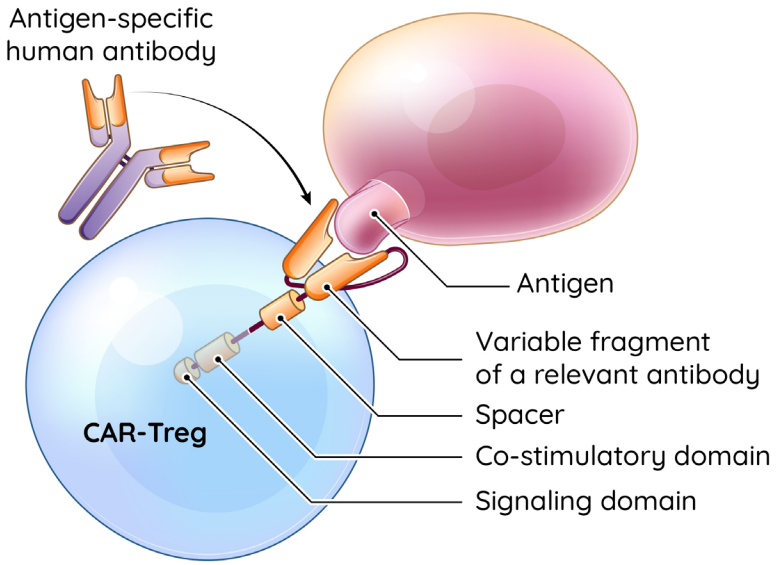
Cell Therapy	Research	Preclinical	Phase I/II	Phase III	
Hemoglobinopathies (ST-400, BIVV003)					+ SANOFI
Allogeneic anti-CD19 CAR-T (KITE-037)					+ Kite A GILEAD Company
Solid organ transplant CAR-T_{REG} (TX200)					Sangamo THERAPEUTICS
CAR-T_{REG} in Inflammatory Bowel Disease					Sangamo THERAPEUTICS
CAR-T_{REG} in Multiple Sclerosis					Sangamo THERAPEUTICS

TX200: CAR-T_{REG} cell therapy for renal transplantation

Essra Ridha, Medical Director

Sangamo is pioneering the next frontier in cell therapy

- Autologous HLA-A2 specific CAR-T_{REG} cell therapy
- Initial target indication: Prevention of immune mediated rejection in living donor renal transplantation
  - The STEADFAST Study will evaluate the safety and mechanism of action of TX200 in renal transplant recipients
- Therapeutic hypothesis and goals
  - Regulate the immune system in a targeted manner
  - Promote immunological tolerance to the renal transplant
  - Help preserve graft function and reduce graft loss



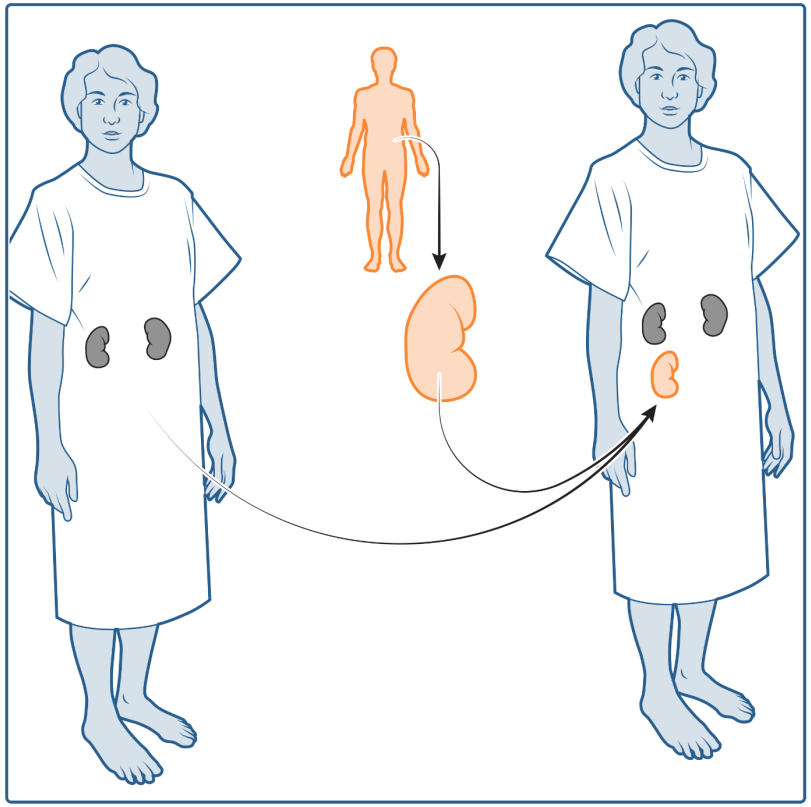
Sangamo's first step towards evaluation of CAR-T_{REGS} in autoimmune diseases

End stage renal disease and renal transplantation

End stage renal disease, the last stage of chronic kidney disease, affects an estimated 7.4 million worldwide

Renal transplantation is the treatment of choice:

- Results in a longer life expectancy and better quality of life than long-term dialysis treatment
- 80,000 renal transplantations are performed per year (US and EU)
- Requires lifelong immunosuppressive medications to prevent immune mediated rejection
- Immunosuppression is associated with infectious complications, de novo malignancies and drug toxicities

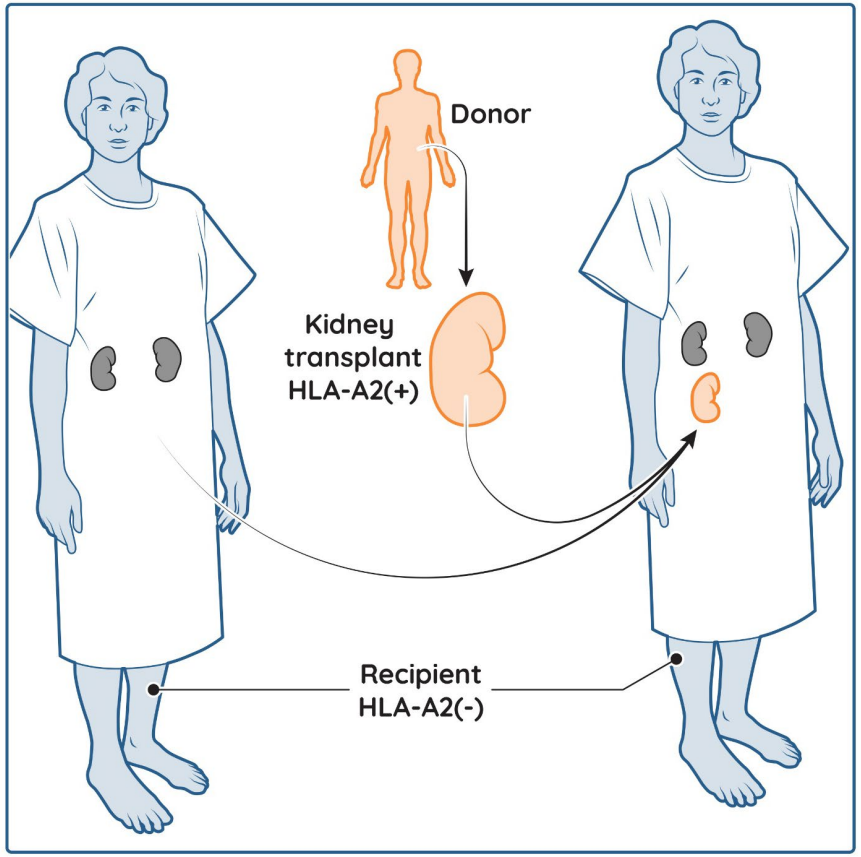


1. Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int 2015;88:950-7.
2. Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One 2016;11:e0158765.
3. Evans RW, Manninen DL, Garrison LPJr, et al. The quality of life of patients with end-stage renal disease. N Engl J Med 1985;312:553-9.

Sangamo THERAPEUTICS

HLA-A2: A rational target for solid organ transplantation

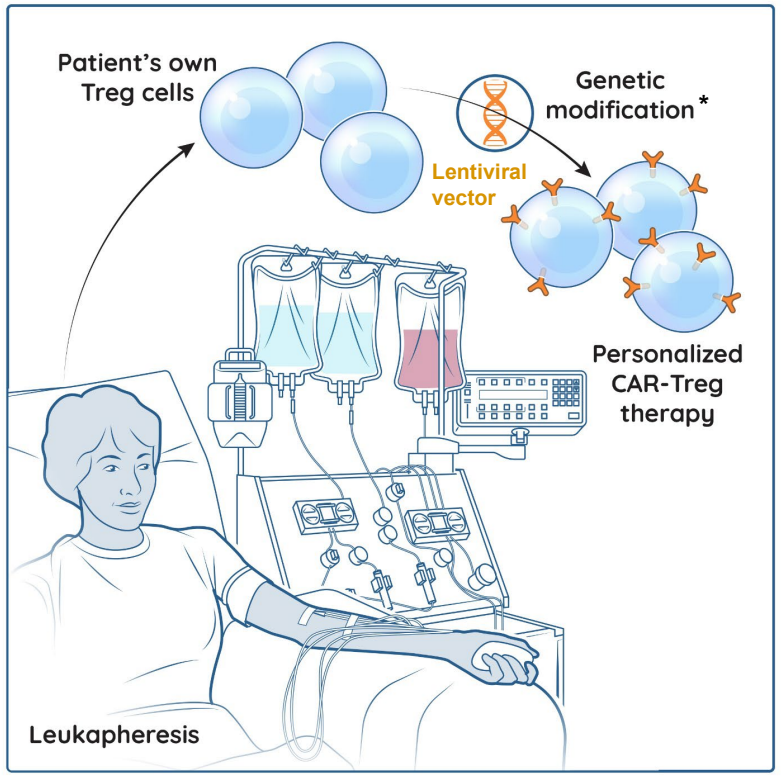
- HLA's: Initial and most important barrier to successful transplantation after ABO incompatibility
- Function: Presentation of peptides to T cells
- High HLA-A2 expression level: Robust induction of CAR-T_{REG} activity
- High allelic frequency: Approximately 21(1)-25%(2) of transplanted organs are HLA-A2 mismatched



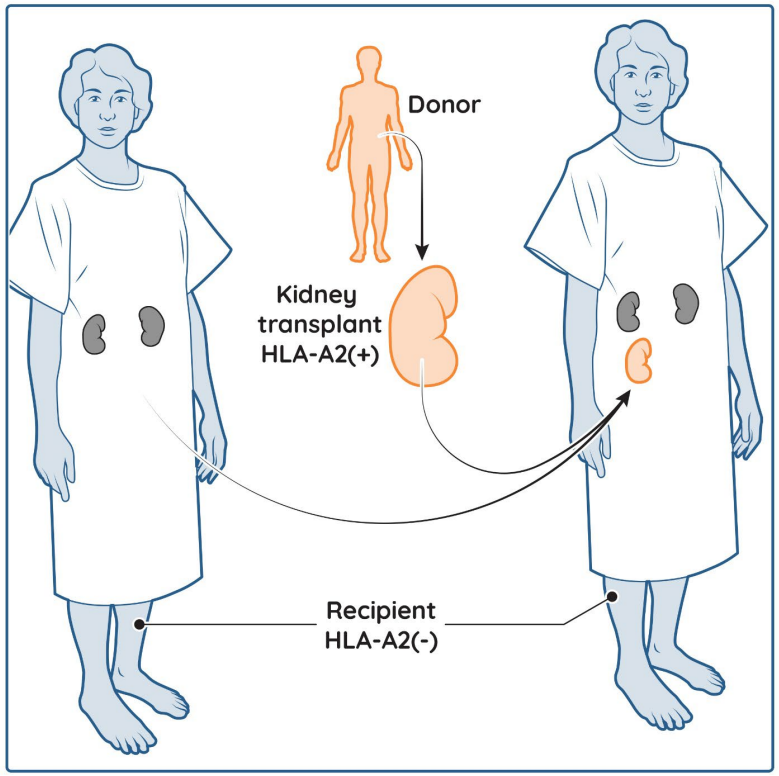
1. Noyan F, Zimmermann K, Hardtke-Wolenski M, Knoefel A, Schulde E, Geffers R, Hust M, Huehn J, Galla M, Morgan M, Jokuszies A, Manns MP, Jaeckel E. Am J Transplant. 2017 Apr;17(4):917-930.
2. Collins MM, Tang T, Slack R, Sintasath D, Hartzman RJ, Ng J, Hurley CK, Ng J, Hurley CK. Tissue Antigens. 2000 Jan;55(1):48-52.

HLA-A2 CAR-T_{REG} for solid organ transplantation

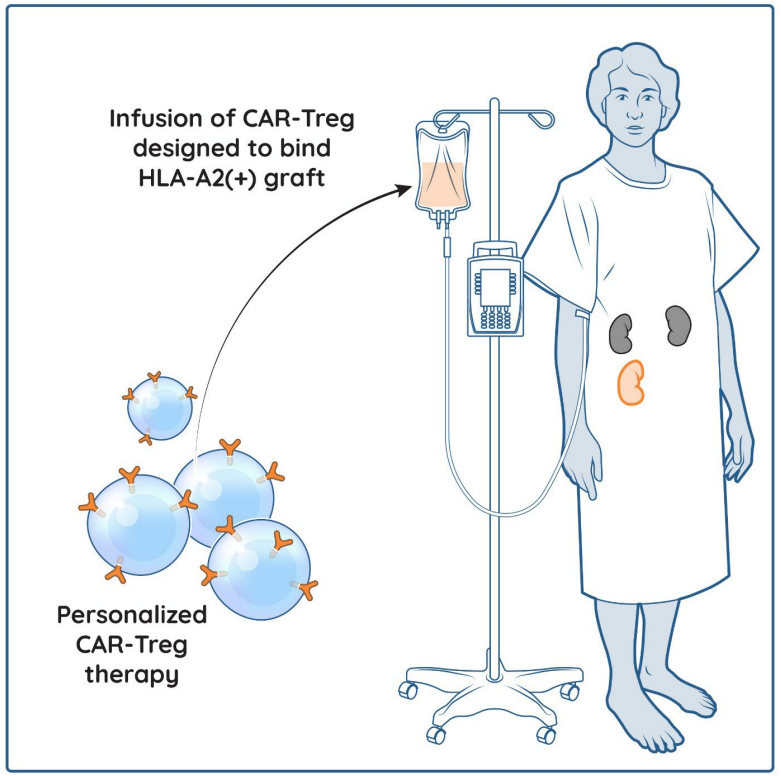
Pre-transplant
Preparation of personalized cell therapy



Transplant



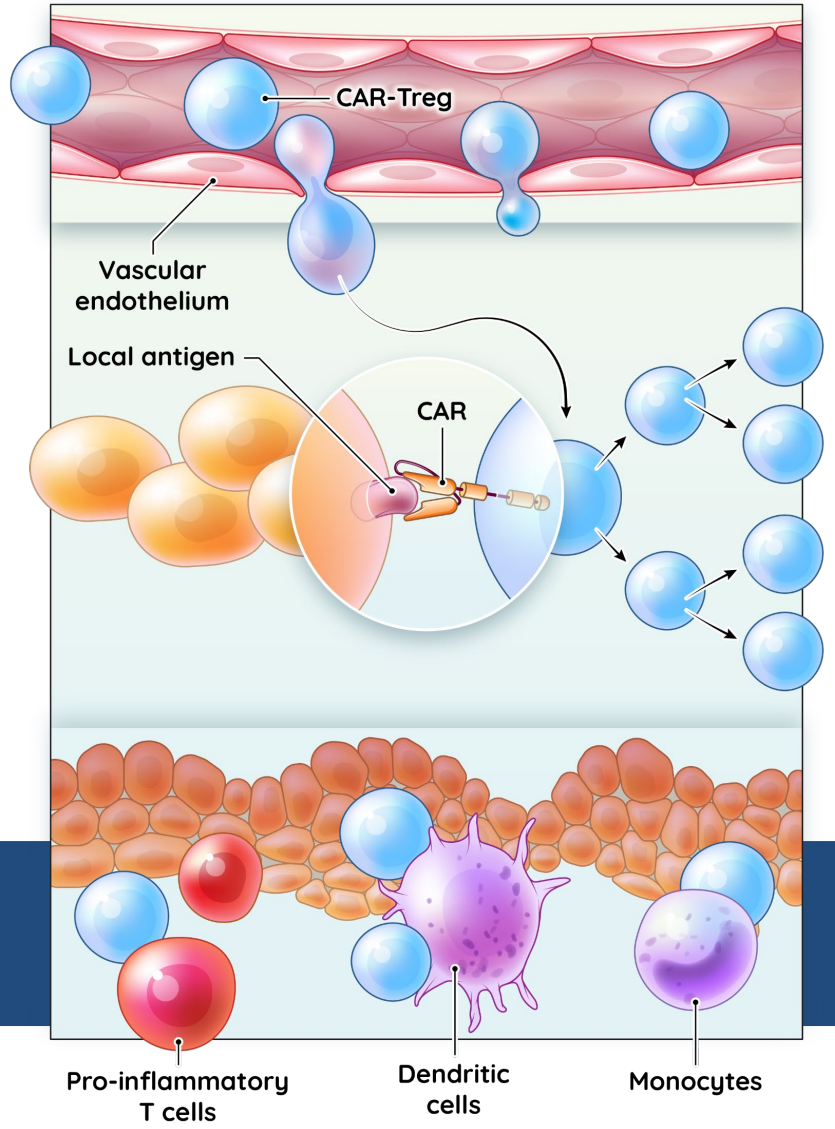
Post-transplant
Cell therapy infusion



* Transduction with a lentiviral vector encoding a CAR to recognise HLA-A*02

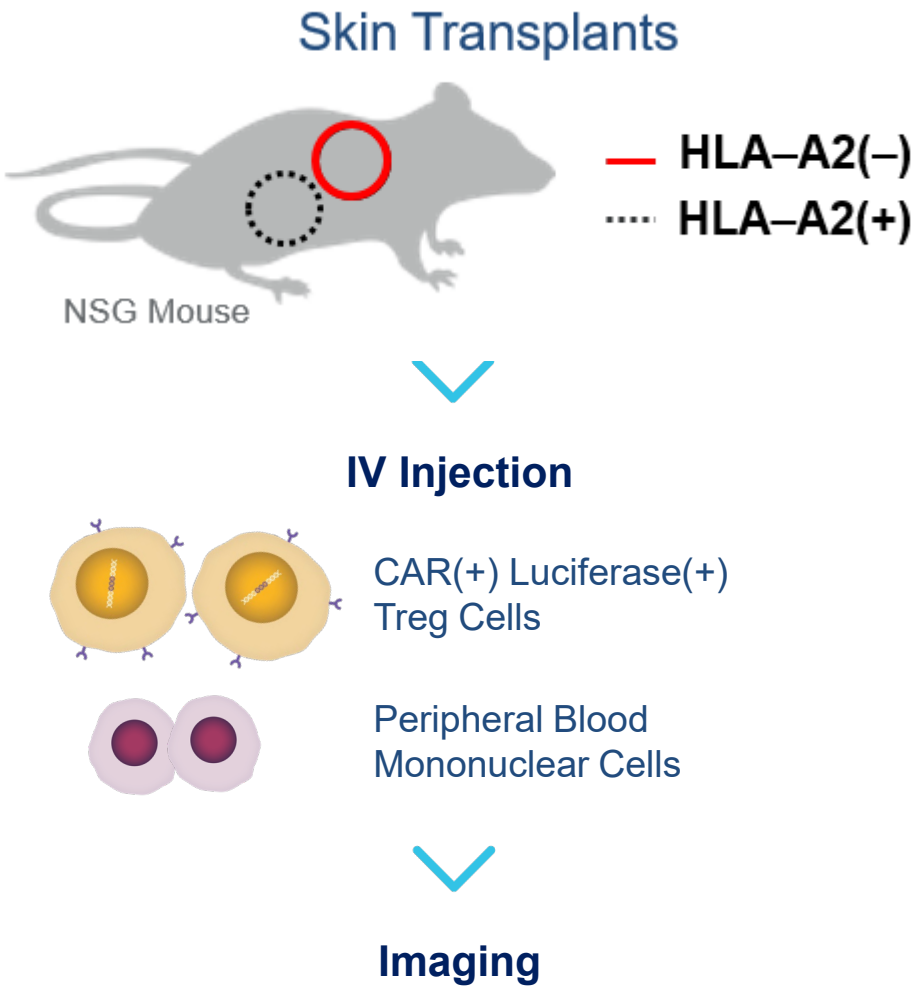
HLA-A2 CAR-T_{REGS} to induce targeted immune tolerance

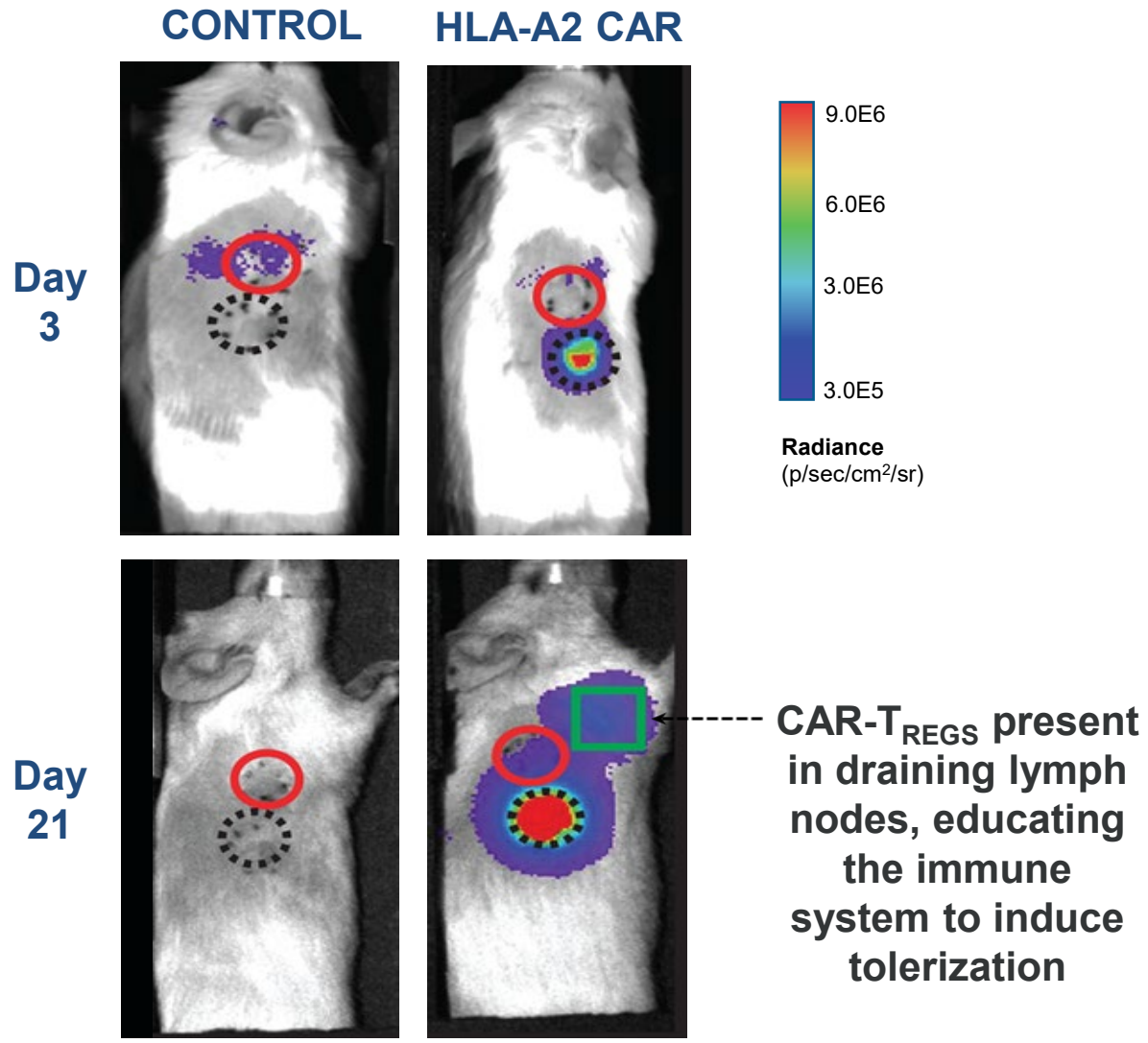
- HLA-A2 CAR-T_{REG} cells are administered intravenously
- They are expected to migrate to the HLA-A2 positive graft
- Upon binding to the antigen expressed by the graft, the CAR-T_{REGS} are expected to activate
- Upon activation, the cells are expected to proliferate and acquire their full immunosuppressive capacities



STEADFAST study will allow first evaluation of CAR-T_{REG} mechanism of action in humans

HLA-A2 CAR-T_{REGS} achieve precise targeting

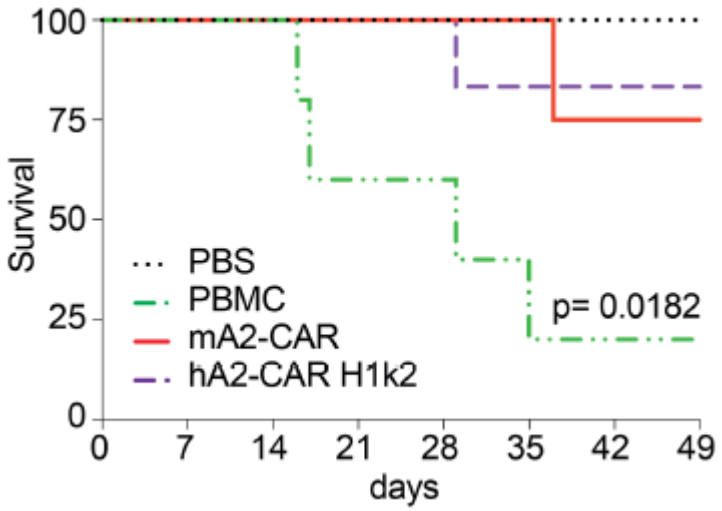




Dawson NA, Lamarche C et al. JCI Insight 2019;4(6):e123672.

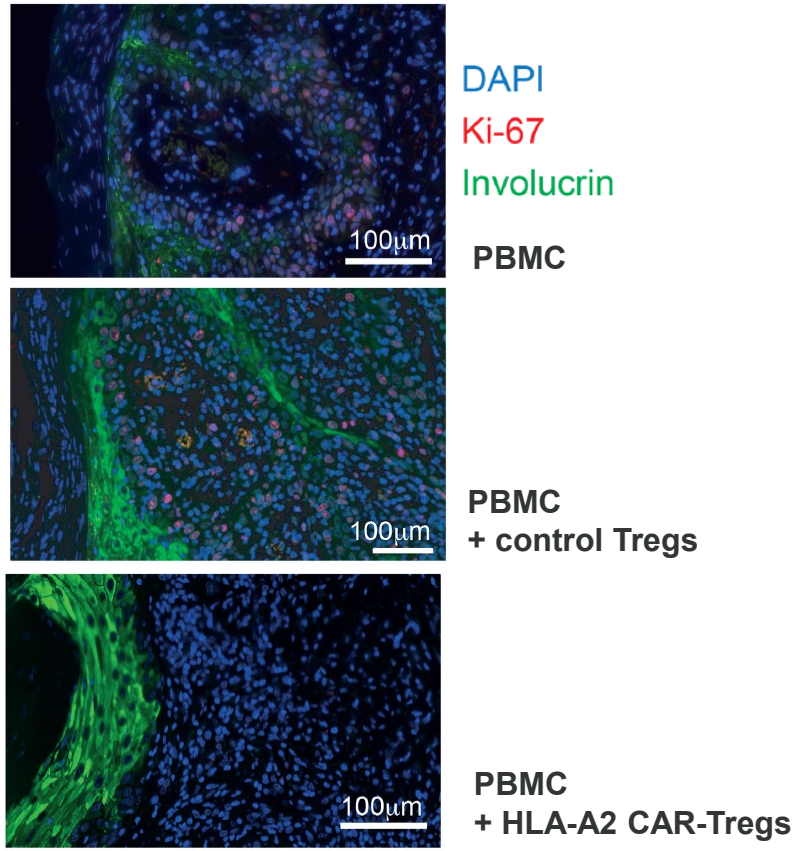
HLA-A2 CAR-T_{REGS} are suppressive in transplantation models

GvHD transplantation model
Survival rate



HER2-CAR: CAR-Tregs with an irrelevant CAR (HER2)
mA2-CAR: murine HLA-A2 CAR-Tregs
hA2-CAR: humanized HLA-A2 CAR-Tregs

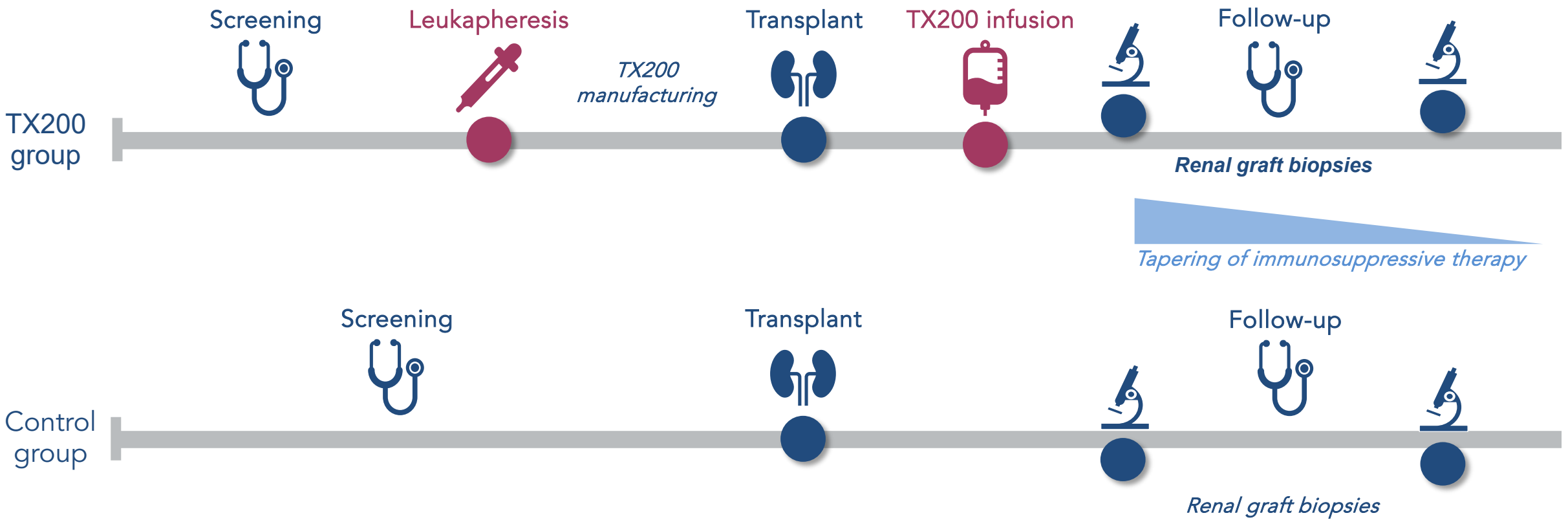
Skin graft model
PBMC proliferation



Dawson NA, Lamarche C et al. JCI Insight 2019;4(6):e123672.

STEADFAST TX200 Phase I/II Study

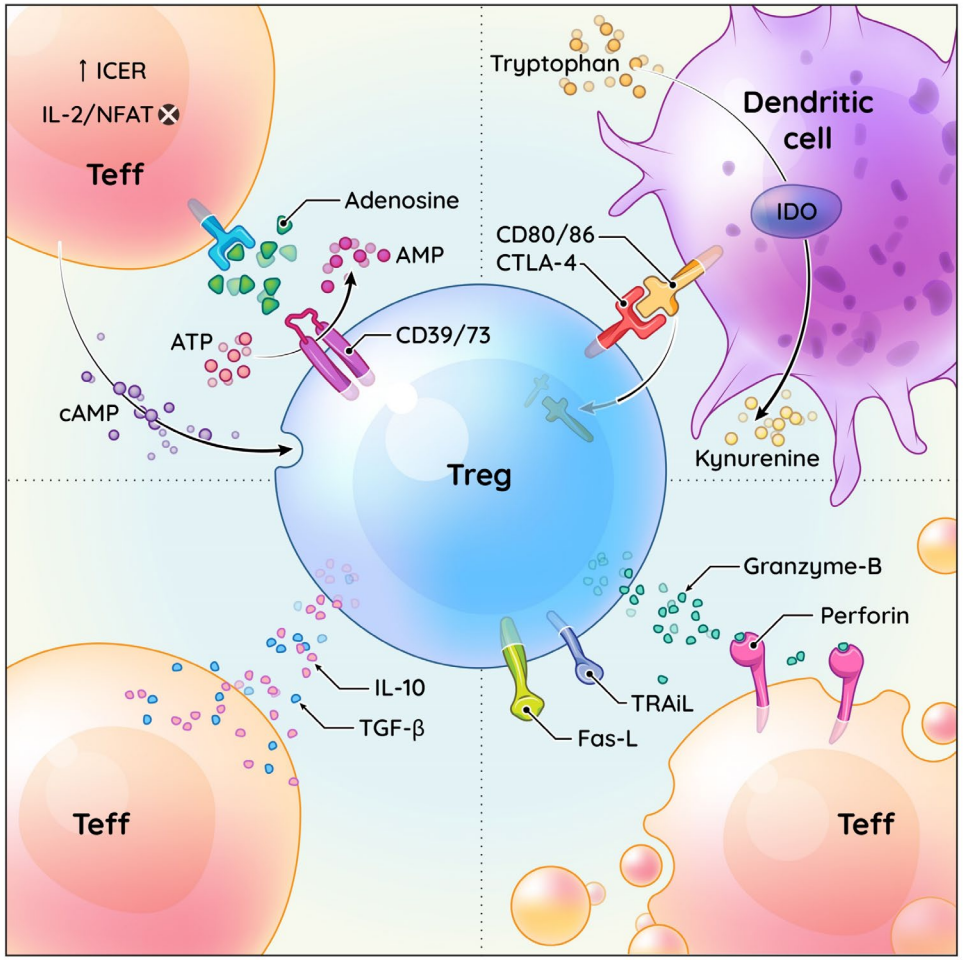
- Multicenter (UK, FR, DE, NL, BE), open-label, single ascending dose, dose-ranging study
- CTA approved November 2019 and first patient expected to be enrolled in 2020



What we expect to learn from the **ST**EADFAST study

Beyond transplantation, the STEADFAST study will bring invaluable knowledge about antigen-specific CAR-T_{REGS}:

- Safety & tolerability
- Proof of mechanism in patients
  - Localization
  - Activation
  - Phenotypic stability
  - Multiple mechanisms of action for immune regulation
  - Impact on immune cell composition



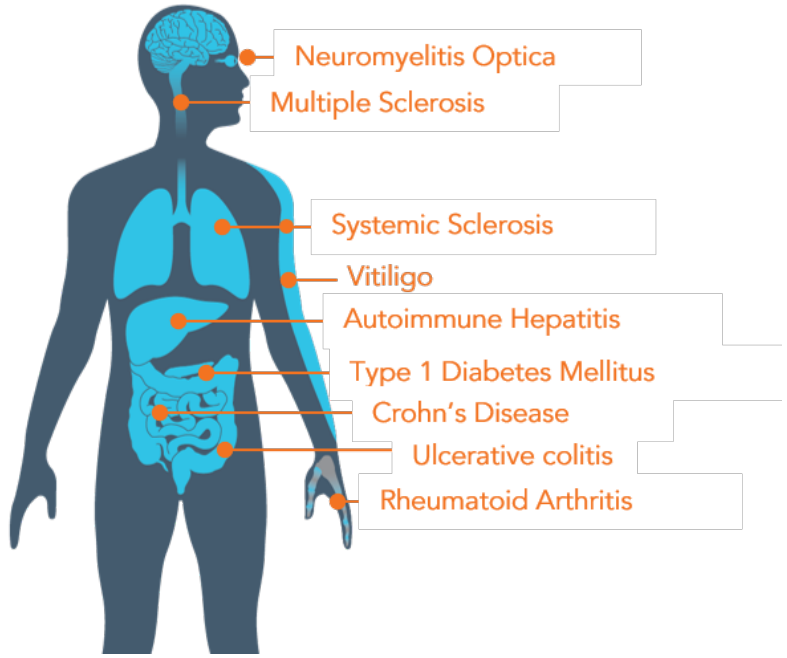
Sangamo CAR-T_{REG} Pipeline

Key outcomes expected from TX200 CAR-T_{REG} program:

- Provide data on safety and proof of mechanism
- Build critical understanding of CAR-T_{REG} in patients
- Pioneer CAR-T_{REG} cell therapy know-how
- Establish manufacturing platform

Projected 1Q 2020 CAR-T_{REG} Pipeline

CAR-T_{REG} Program	Research	Preclinical	Phase I/II
TX200: Anti-HLA-A2 CAR-T_{REG} In Solid Organ Transplant			
CAR-T_{REG} in Inflammatory Bowel Disease			
CAR-T_{REG} in Multiple Sclerosis			
Allogeneic T_{REG} Platform			



CAR-T_{REG} cell therapies can address:

- Multiple autoimmune diseases
- Large patient populations
- High unmet needs

Key takeaways

- TX200 is an innovative personalized cell therapy with potential to induce immunological tolerance
- Potential for significant improvement outcomes in transplantation medicine
- Preclinical work is promising and shows specificity and selectivity of CAR-T_{REGS} to their target as well as suppressive activity in GvHD and skin transplantation models of disease
- UK CTA approval granted in November 2019
- TX200 will provide a proof of concept for Sangamo to evaluate CAR-T_{REGS} in autoimmune diseases

AAV engineering

David Ojala, Scientist

Delivery is key to clinical success

- Sangamo is devoted to improving our delivery capabilities to support our pipeline for liver and CNS targeted therapies
- We have established an internal AAV engineering platform over the past 2.5 years. We also actively evaluate delivery technologies for in-licensing
- Pre-clinical and clinical results continue to support AAV6 as an effective serotype for delivery to the liver in non-human primates and humans

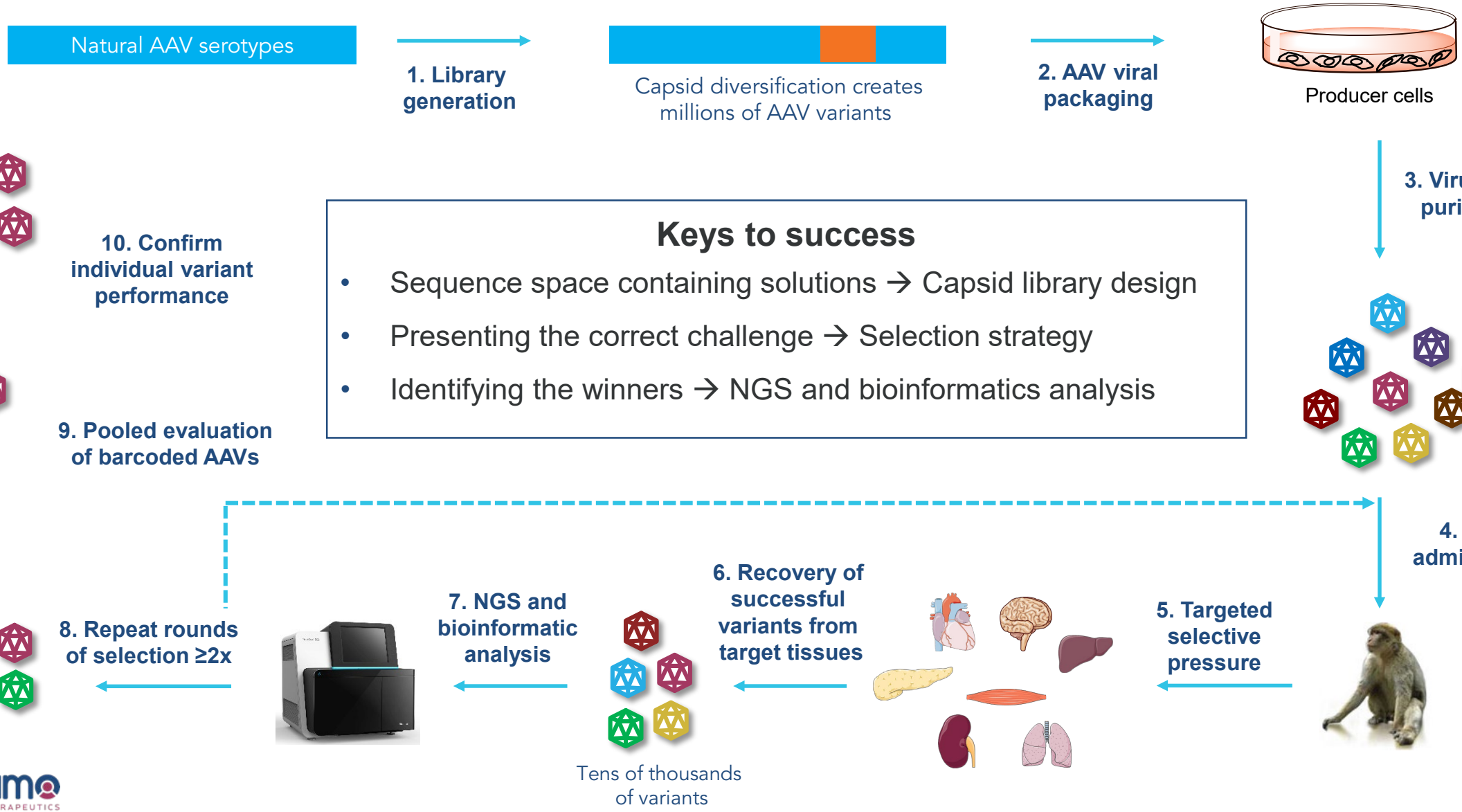
Natural AAV serotypes are versatile templates for protein engineering

Evolution of the AAV capsid has resulted in diverse receptor binding and tissue tropisms

	AAV1	AAV2	AAV3B	AAV4	AAV5	AAV6	AAV8	AAV9	AAVrh.10
Primary Receptor	N-linked sialic acid	HSPG	HSPG	O-linked sialic acid	N-linked sialic acid	N-linked sialic acid and HSPG	Unknown	N-linked galactose	Sulfated LacNAc
Prominent tissue tropisms	Heart, skeletal muscle	Brain (direct injection), Eye	Liver	Eye	Liver Lung	Liver, heart, skeletal muscle	Liver	CNS, heart, skeletal muscle	CNS Liver

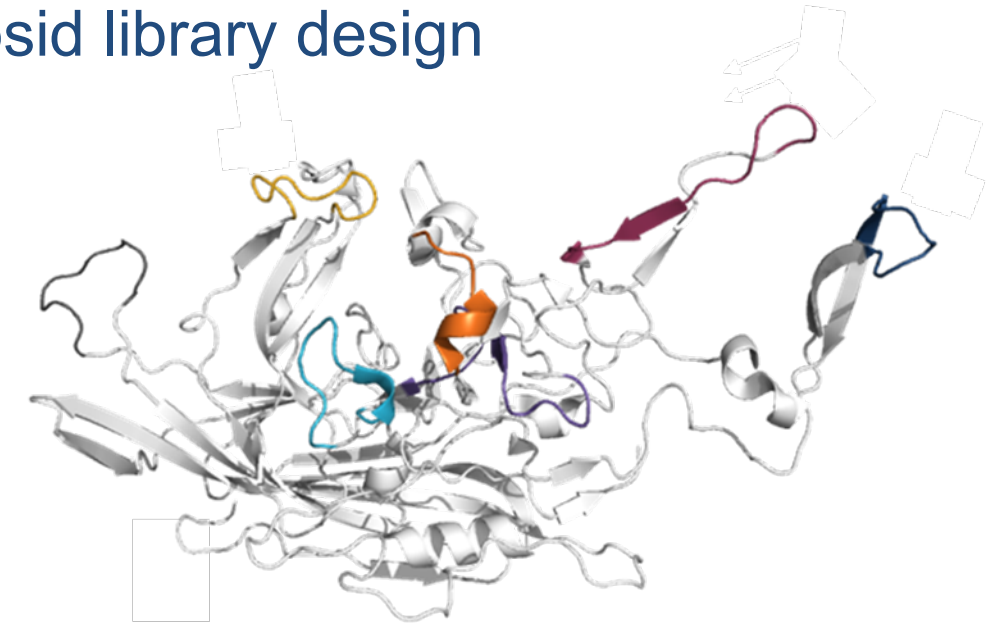
AAV did not evolve to meet all our therapeutic needs

AAV capsid engineering through directed evolution



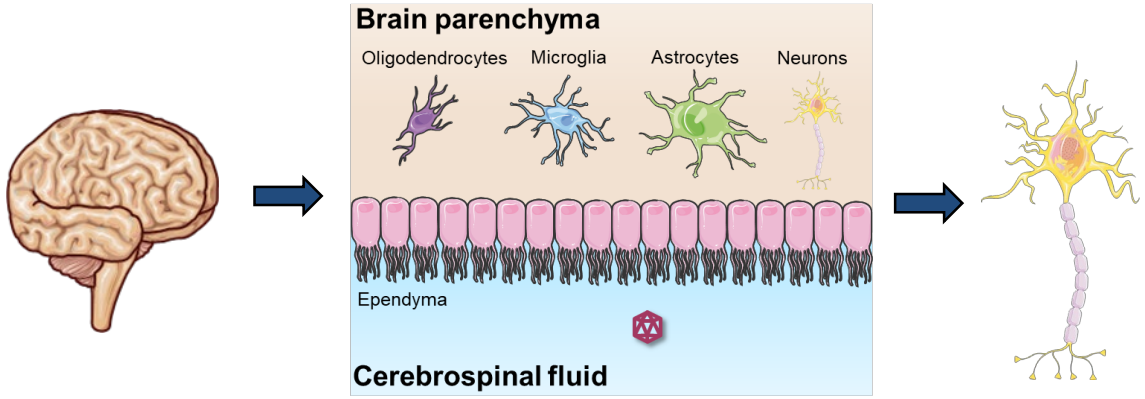
Key design choices for AAV library selections

Capsid library design



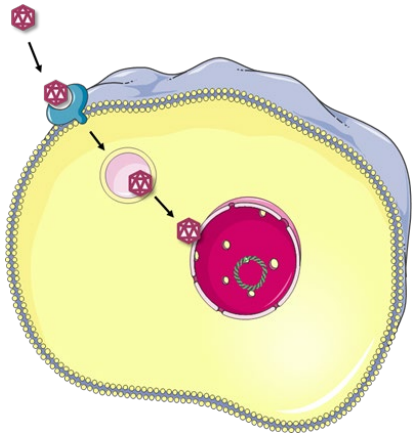
- Peptide insertions of various lengths were introduced into surface exposed loops of seven parental AAV serotypes
- Exogenous peptide sequences can impart novel function and/or modify affinity for receptors
- Each parent serotype represents a unique starting point in sequence space, different clinical challenges may favor different starting points

Functional selection strategy



Selective pressure for AAV variants that:

1. Bypass biological barriers to reach the target cell type
2. Engage cell surface receptors, escape the endosome, and traffic to the nucleus
3. Enter the nucleus, uncoat, and establish transgene expression

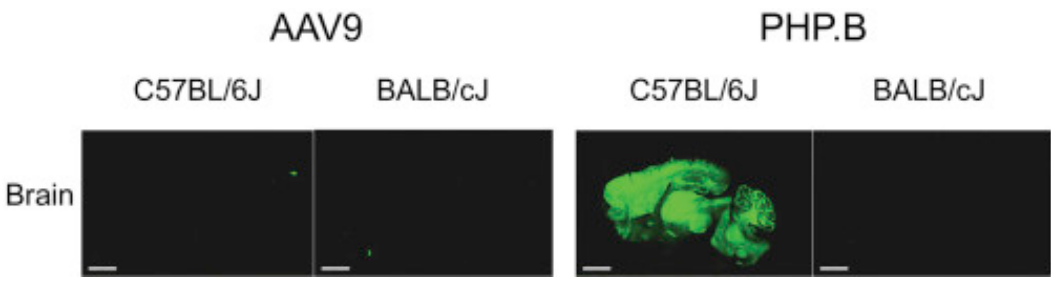


Innovation of a functional selection strategy and successful application in non-human primates

- A functional selection strategy was key to the development of PHP.B, a breakthrough serotype for gene delivery to the mouse CNS that **failed to translate to non-human primate**
- A limitation of this strategy is the requirement for selection in transgenic mice which are genetically distant from humans

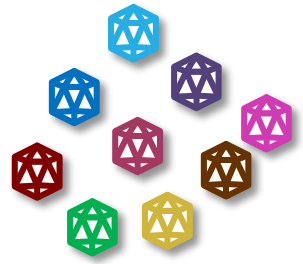
Cre-dependent selection yields AAV variants for widespread gene transfer to the adult brain

Benjamin E Deverman[1], Piers L Pravdo[1], Bryan P Simpson[1], Sripriya Ravindra Kumar[1], Ken Y Chan[1], Abhik Banerjee[1], Wei-Li Wu[1], Bin Yang[1], Nina Huber[2], Sergiu P Pasca[2] & Viviana Gradinaru[1]



- Sangamo has developed and applied a functional selection strategy for AAV library selections in non-human primates
- Non-human primates were used for library selections to best model the genetics and CNS anatomy of humans

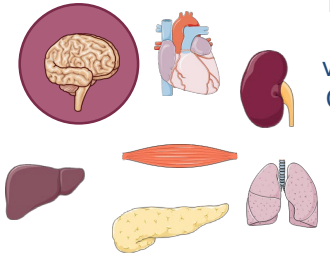
Path from selections to clinical candidates for the CNS



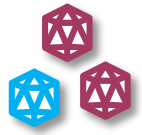
Library of AAV variants

Administration into CSF

2 rounds of selection



Recovery of successful variants from CNS tissues



Next-generation sequencing identifies variants with greatest fold enrichment

Round 1 Selection ✓
Millions of variants

Large sequence space probes many possible solutions

Round 2 Selection ✓
Tens of thousands of variants

Smaller, focused sequence space confirms variant performance

Pooled evaluation
Dozens of variants

High confidence head to head evaluation of top variants and natural serotypes

Individual candidates
Top hits

Evaluation of single serotype expressing a clinically relevant transgene

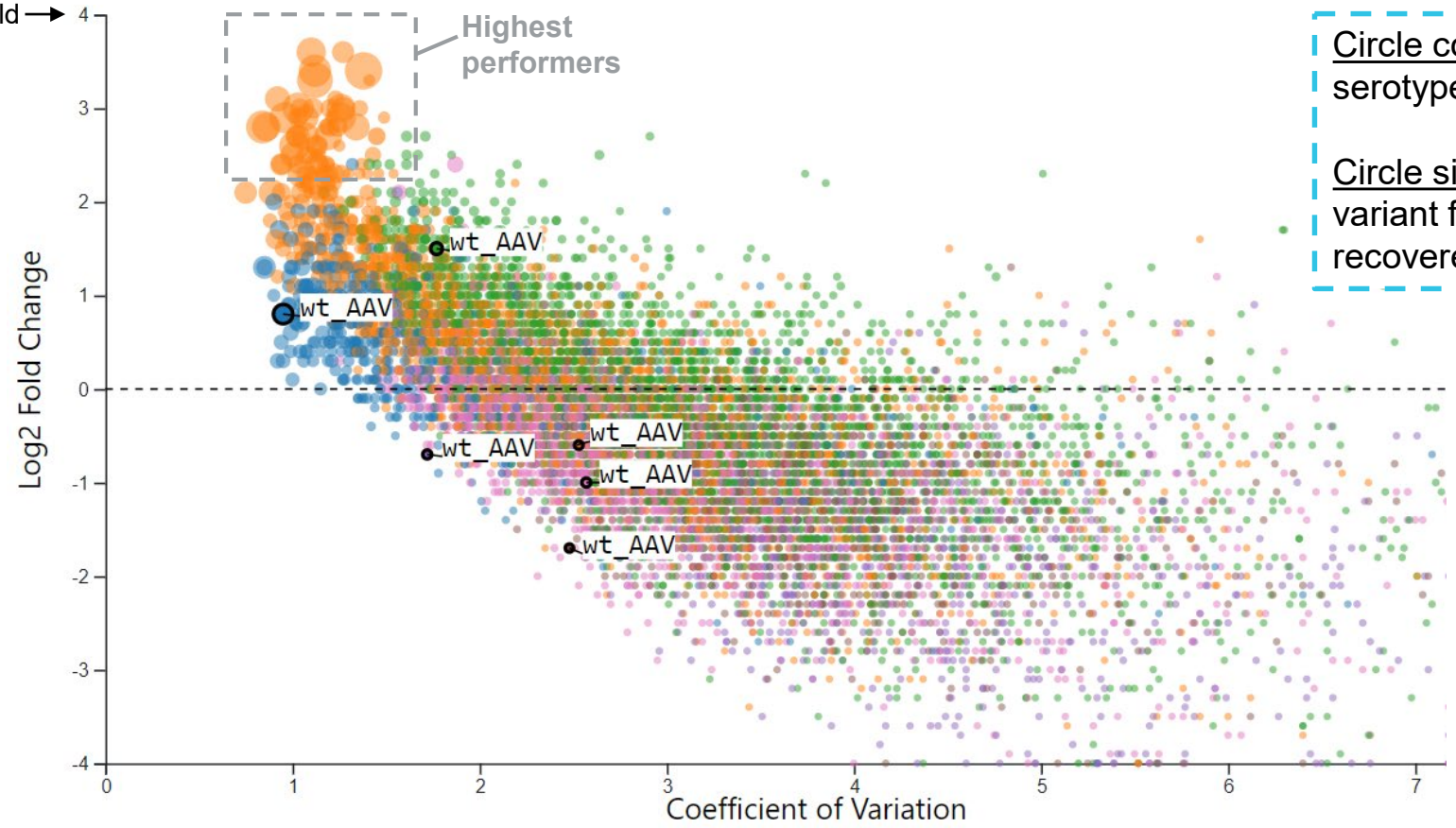
In progress

Sangamo THERAPEUTICS

Assessment of AAV library in key Alzheimer's disease brain regions

- The performance of wild type serotypes is annotated and 34 of the highest performing novel AAVs have been selected for further evaluation
- Consistently high enrichment across many brain and spinal cord regions is a promising indicator of efficacy

Fold enrichment is relative to the frequency of each variant in the administered library

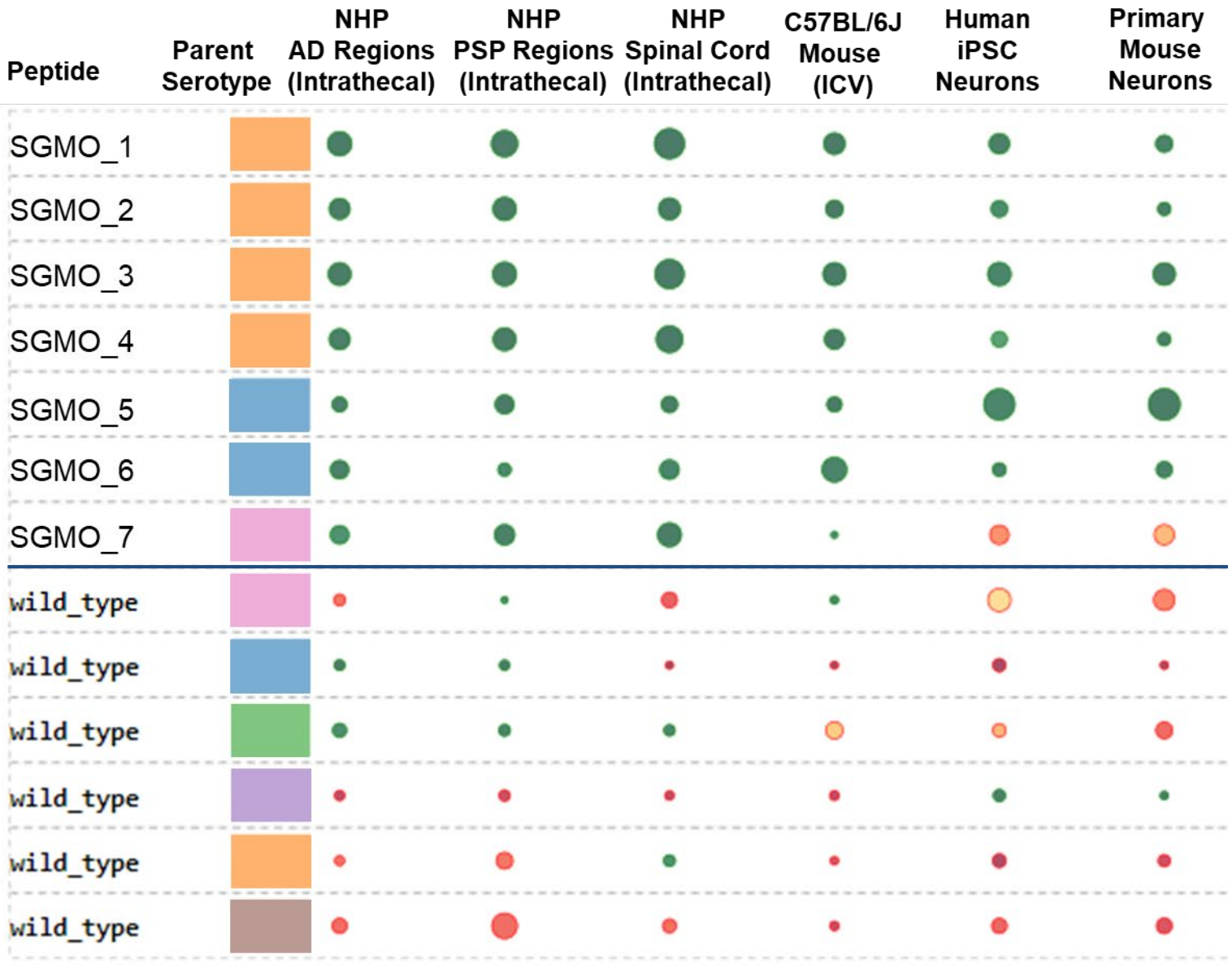


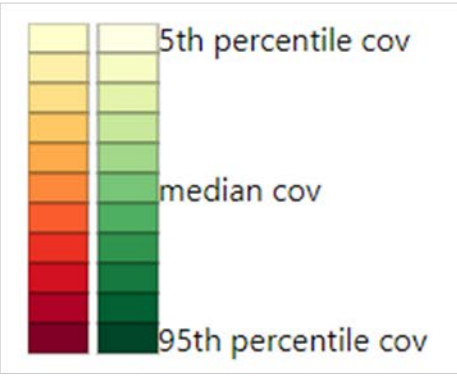
Circle color indicates parent serotype

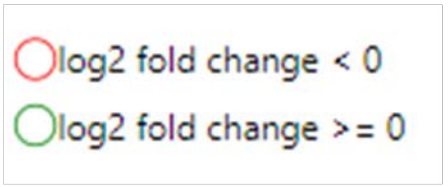
Circle size is proportional to the variant frequency in the recovered library

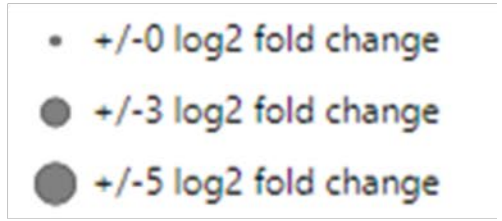
Coefficient of variation describes the consistency of variant performance across multiple non-human primates and brain regions

Performance of lead AAV variants and natural serotypes across different CNS regions and species







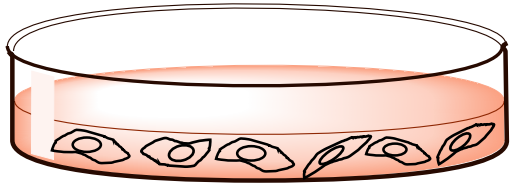


AD = Alzheimer's disease
PSP = Progressive supranuclear palsy
ICV = Intracerebroventricular

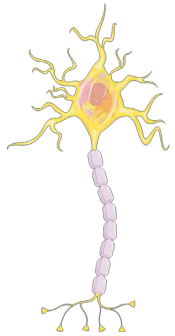
Evaluation of CNS-tropic AAV variants identified from library screen

Library data suggests improved performance of engineered serotypes. We are currently conducting follow-up evaluations of these lead candidates to quantify performance across multiple metrics that are important for clinical translation

Manufacturing yield



Neuro2A
(mouse neuroblastoma cell line)



Primary mouse neurons and
iPSC-derived human neurons

C57BL/6J Mice

Sprague-Dawley rat

Cynomolgus macaque

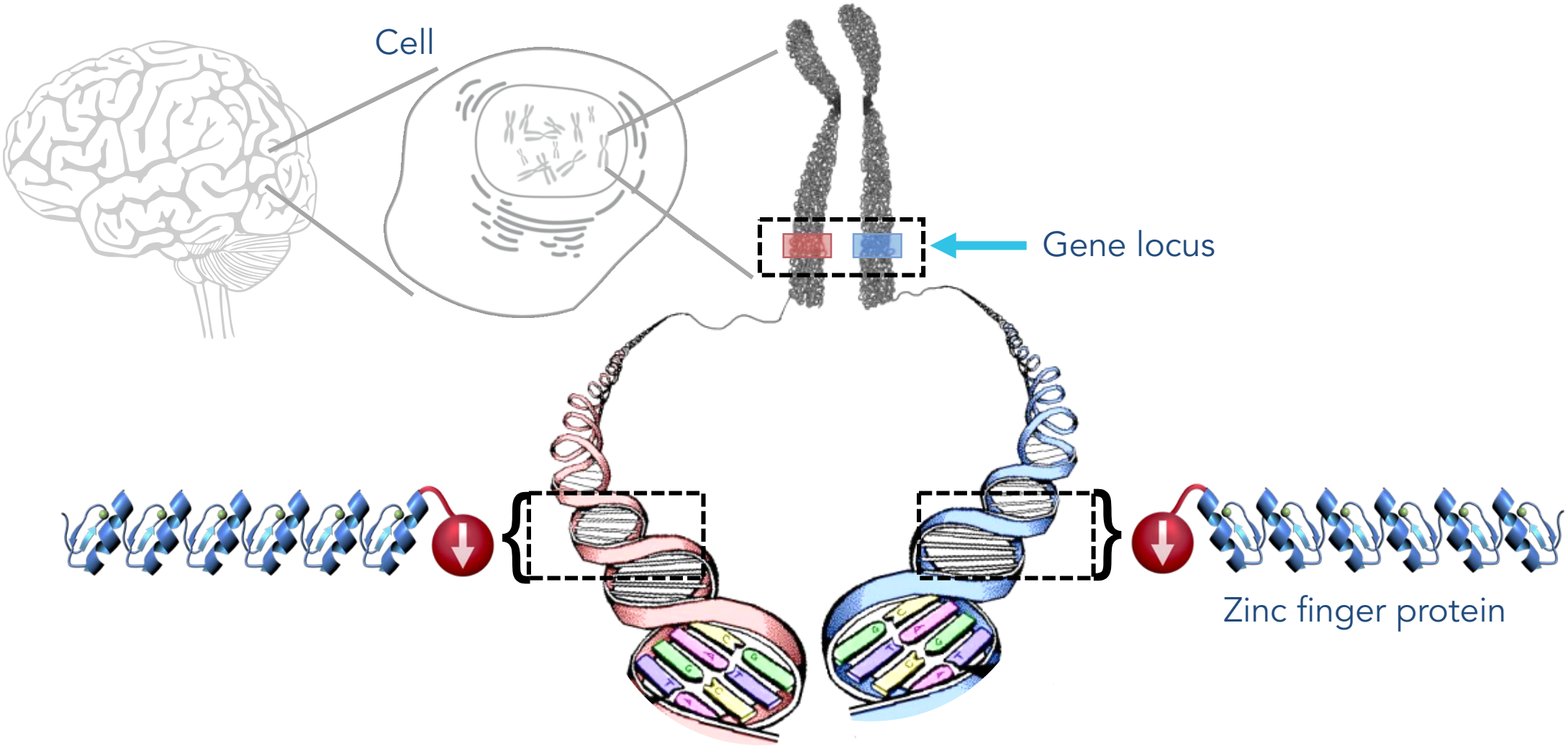
Key takeaways

- Innovative AAV engineering effort focused on design of a rich AAV library sequence space, application of a functional selection strategy in non-human primates, and analysis through a custom bioinformatics pipeline to separate true winners from noise
- Leveraged in-house AAV manufacturing and next-generation sequencing to create and vet high quality AAV library material
- Significant time and resources were invested to develop platform tools that can be directed towards any delivery challenge
- Completed two rounds of selection targeting the CNS in non-human primates, evaluation of novel AAV serotypes is underway

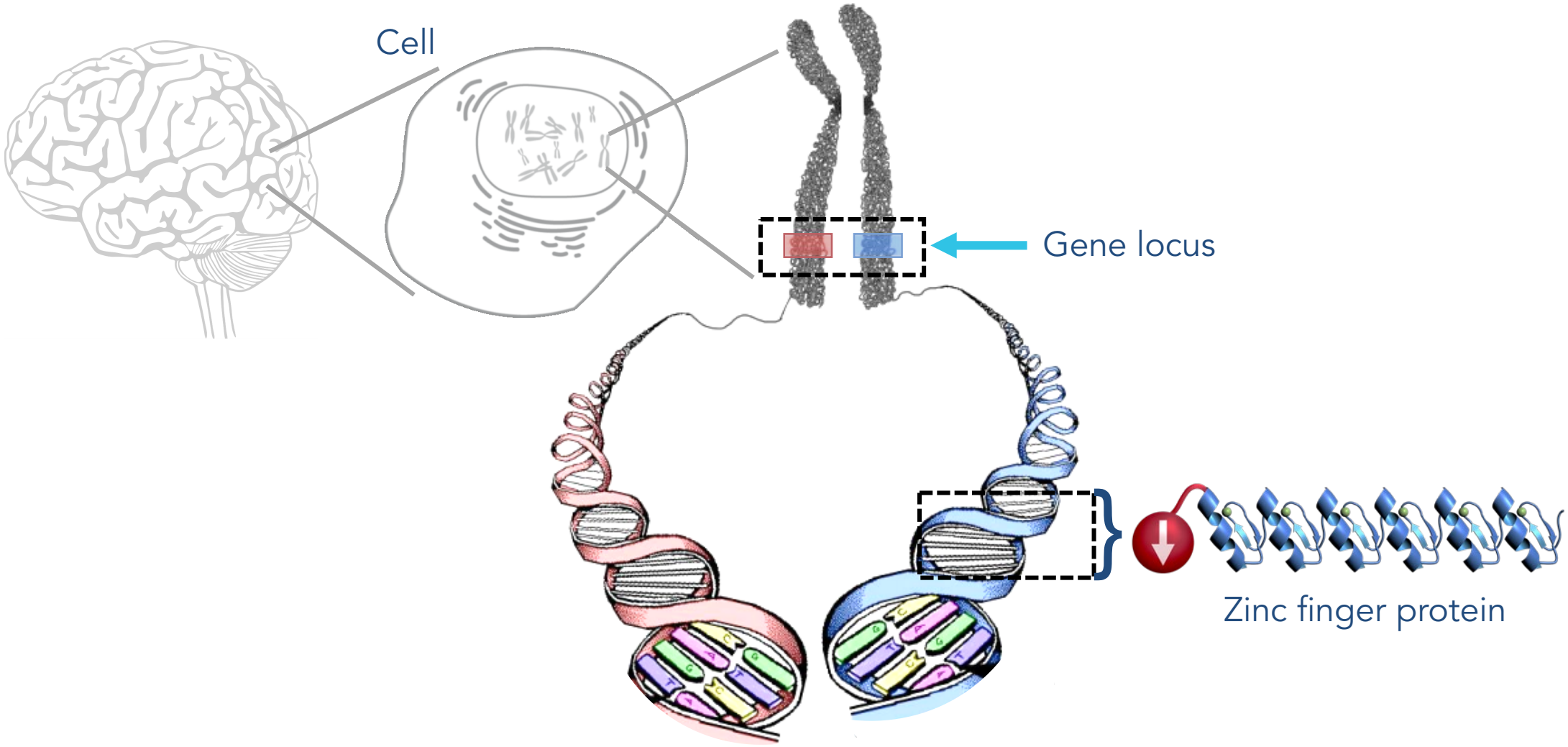
Regulating gene expression in the CNS with the ZFP-TF platform

Amy Pooler, Neuroscientist

Zinc finger proteins specifically and powerfully repress key genes involved in brain diseases



Zinc finger proteins are engineered to specifically repress expression of key genes



Potential CNS applications for Sangamo's zinc finger protein transcription factors (ZFP-TFs) and ZFNs

ZFP-TF genome regulation

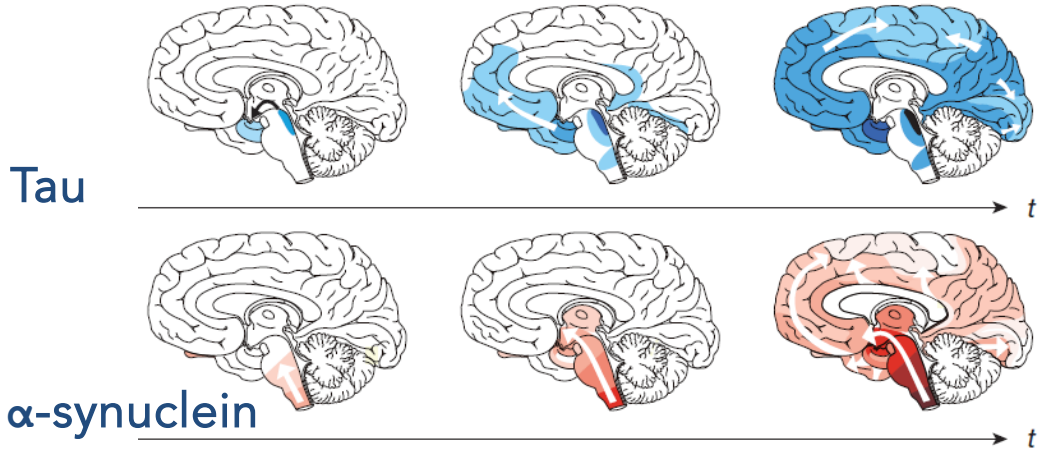
Pan-Allele	ZFP-TFs for single gene repression	• Tauopathies (IND 2021) • α-synuclein (IND 2022) • Prion
Allele-Selective	ZFPs target disease allele repeats selectively	• Huntington's Disease • C9ORF72-linked ALS
Epigenetic editing	ZFP-Epi to demethylate select sites	• Rett Syndrome • Fragile X

ZFN genome editing

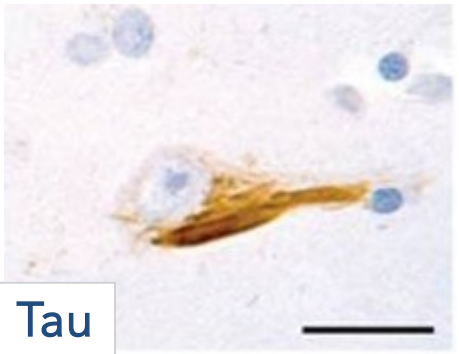
Inflammation	T_{REGS} for inhibition of neuroinflammation and remyelination	• Multiple Sclerosis • ALS
Mitochondrial	ZFNs for selective clearance of mutant mitochondrial genomes	• Cerebellar Ataxia • Leigh Syndrome

Sangamo THERAPEUTICS

ZFP-TFs may slow or prevent spread of neurodegeneration

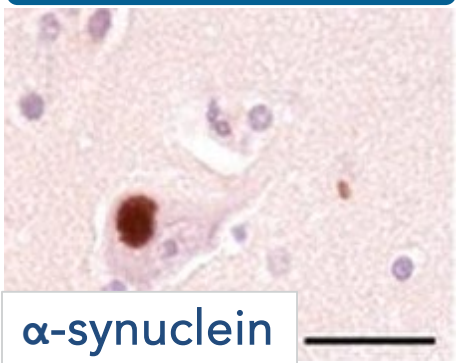


ALZHEIMER'S DISEASE



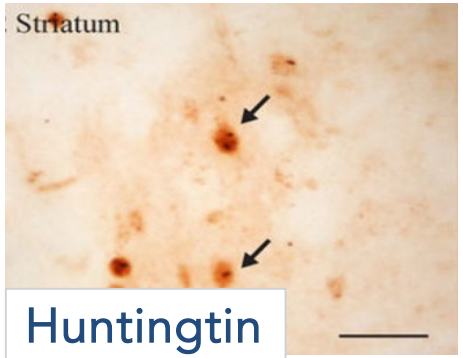
Tau

PARKINSON'S DISEASE



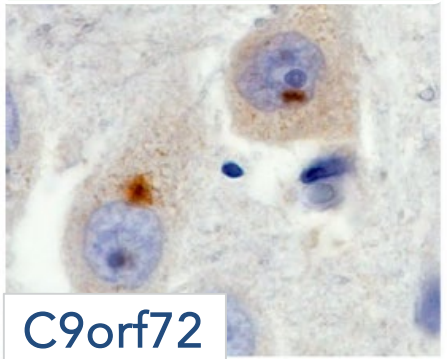
α-synuclein

HUNTINGTON'S DISEASE



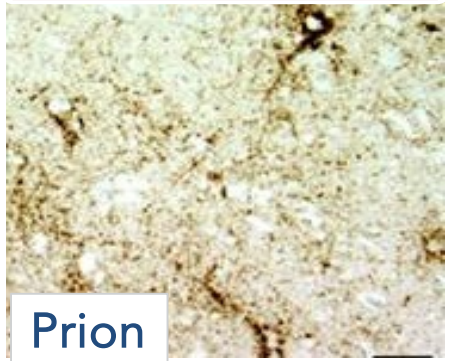
Huntingtin

ALS



C9orf72

PRION DISEASE

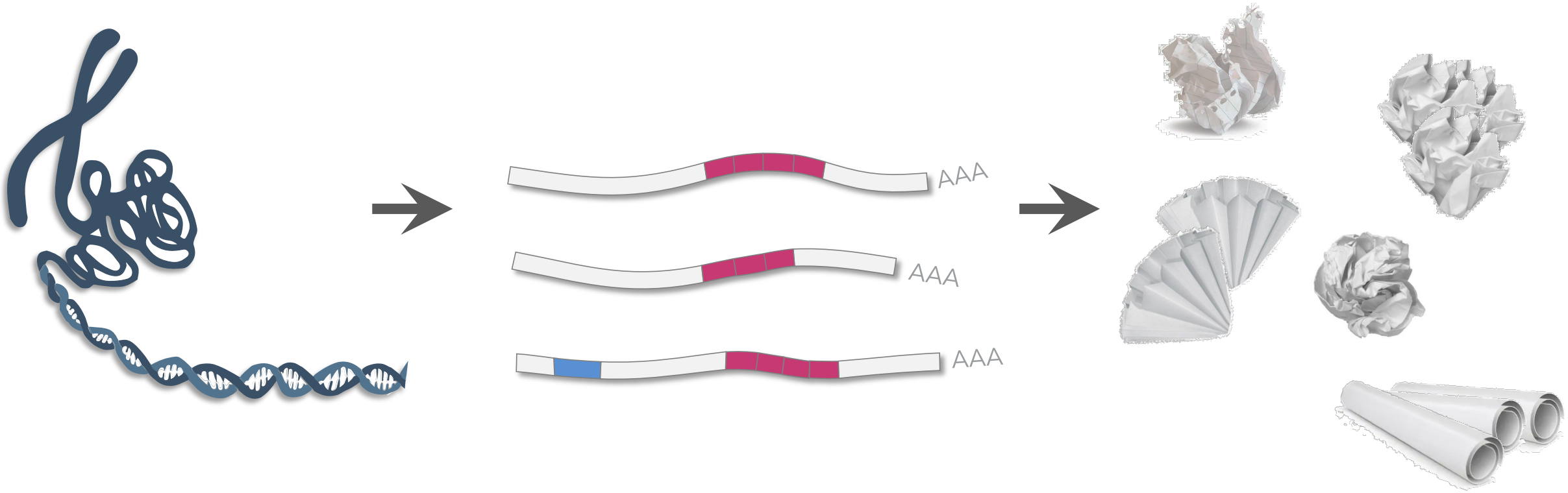


Prion

Sangamo THERAPEUTICS

Hill et al., 2003
Irwin et al., 2015
Jucker & Walker 2013
Waldvogel et al., 2014

ZFP-TFs lower all disease-causing RNA and protein forms



DNA

1 mutant allele

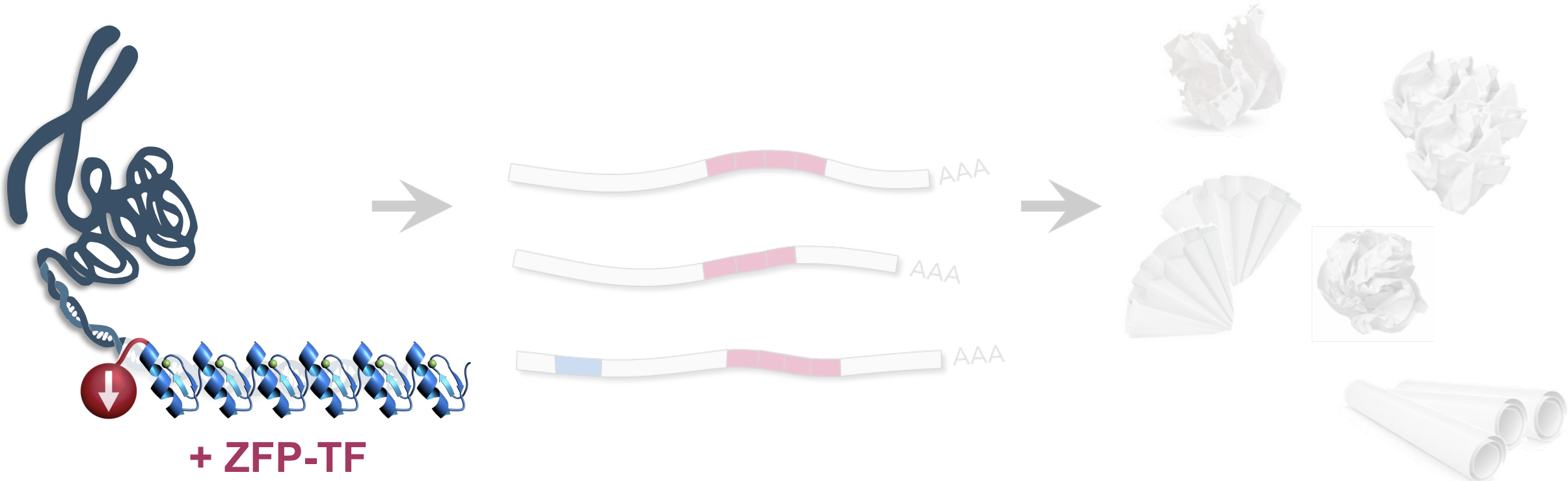
RNA

Sense, antisense, mis-spliced

Protein

Varied and complex

ZFP-TFs lower all disease-causing RNA and protein forms



DNA

1 mutant allele

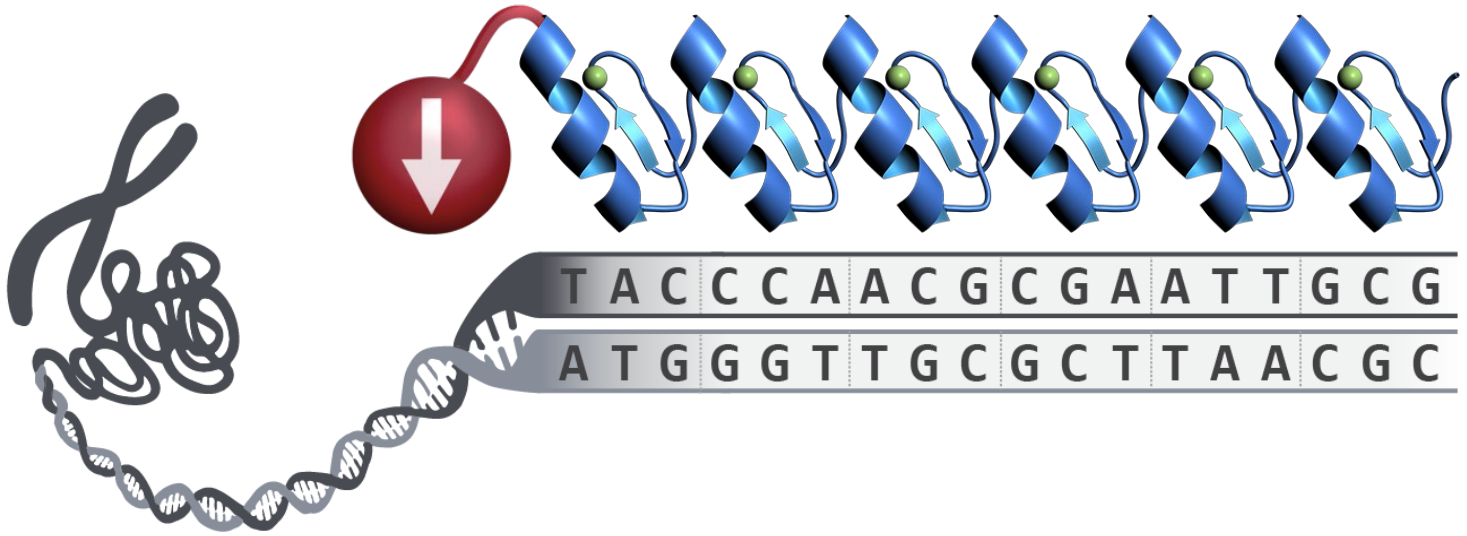
RNA

Sense, antisense, mis-spliced

Protein

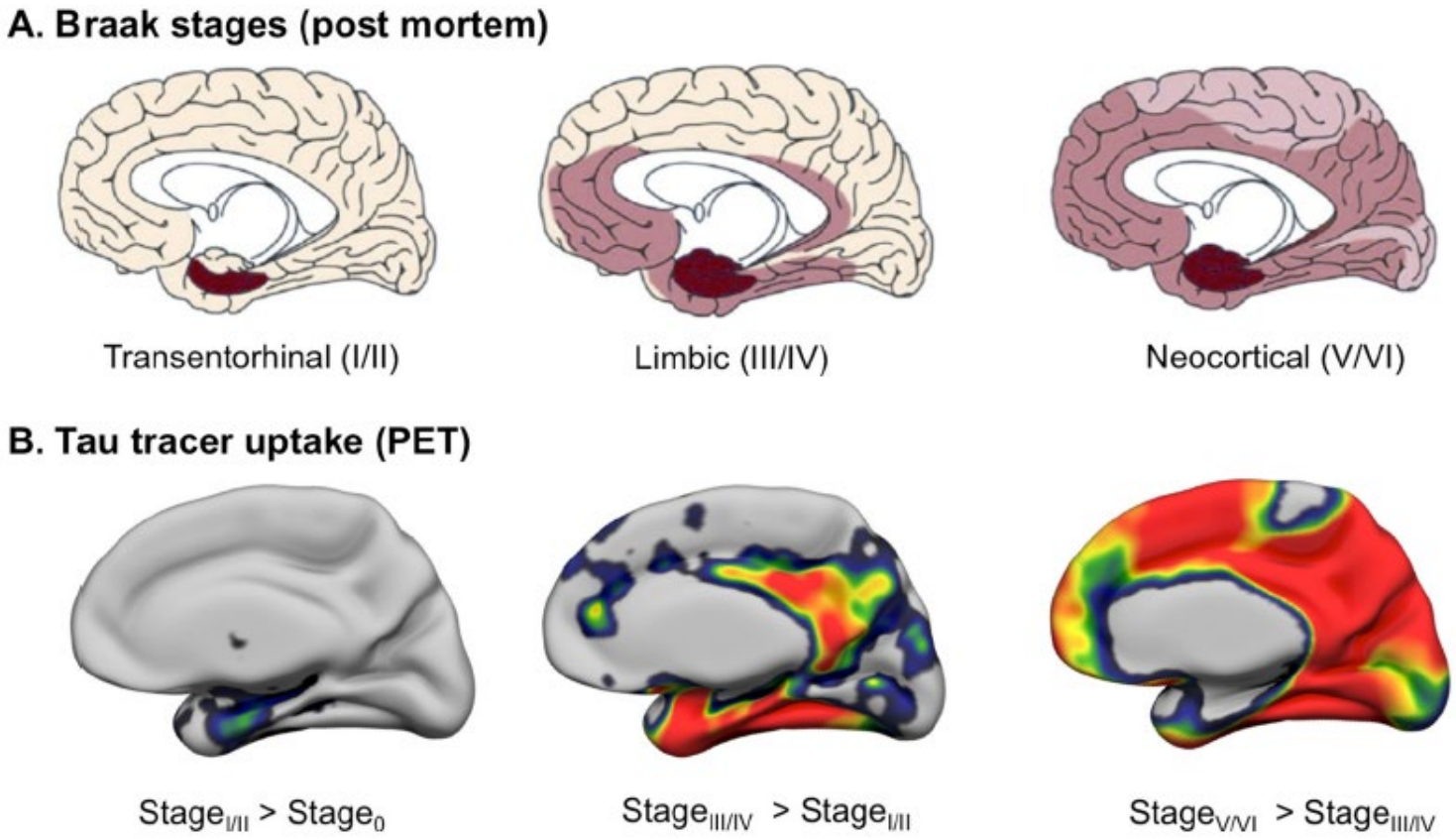
Varied and complex

ZFP-TFs can be engineered to regulate any gene



- **Compact**
  Easily packaged into AAV
- **High potency**
  2 targets per cell
- **Human origin**
  ZFP and KRAB come from human genes

Tau: accumulation tracks closely with AD progression



Tau pathology associated with several other diseases, including PSP, FTD, CTE and CBS

Progressive supranuclear palsy, Frontotemporal dementia, Chronic traumatic encephalopathy, Corticobasal syndrome

Figure: Schöll et al., 2018. Mol Cell Neurosci

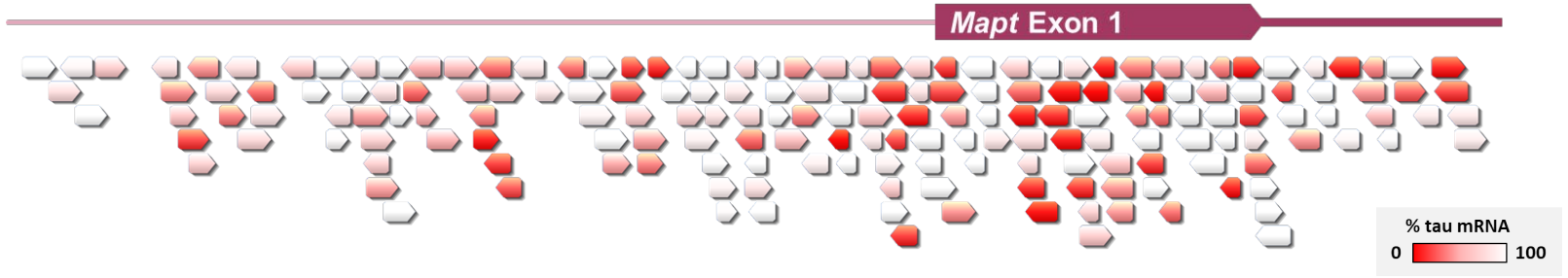
Potent, long-lasting, specific repression of tau by ZFP-TFs

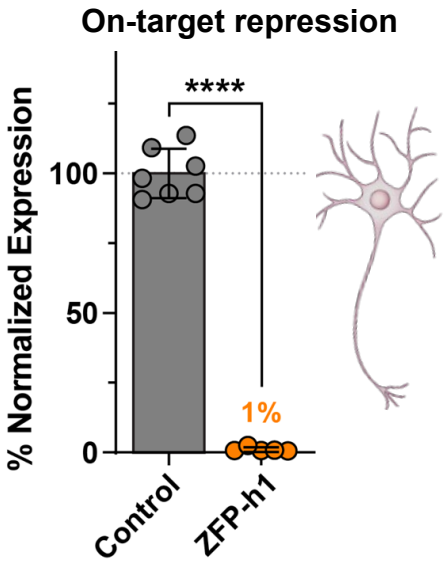
Pan-Allele

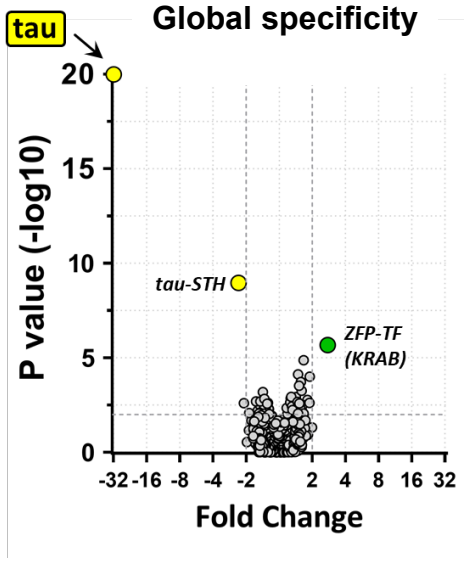
ST-501 – ALZHEIMER'S DISEASE AND OTHER TAUOPATHIES

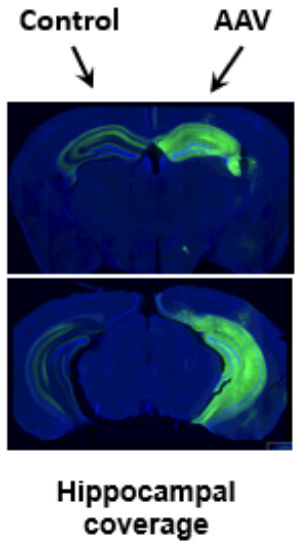
Abnormal tau is toxic to brain cells and leads to neurodegeneration in Alzheimer's disease

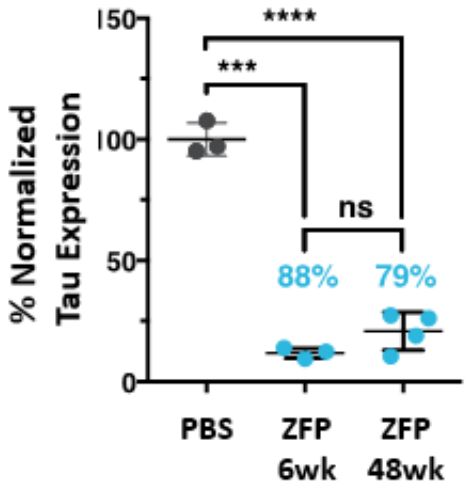
Tau reduction is a therapeutic strategy for targeting these diseases











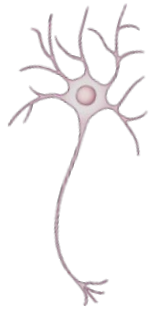
Tuning gene expression with ZFP-TFs to target disease pathology

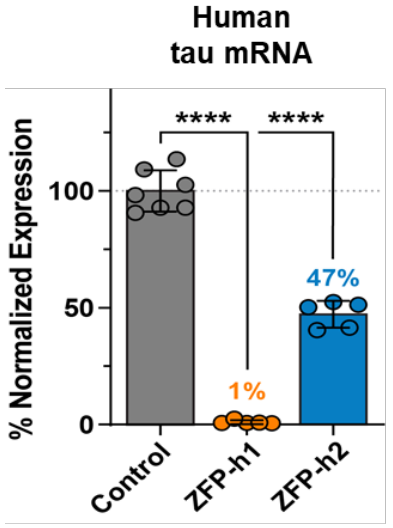
Pan-Allele

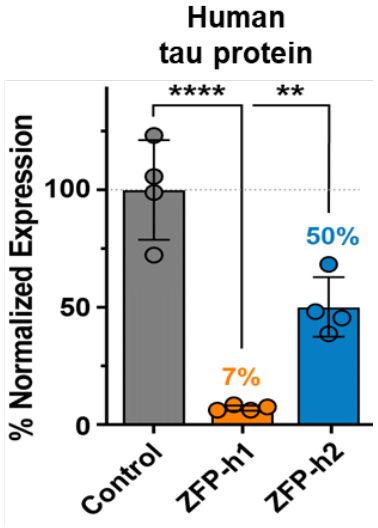
ST-501 – ALZHEIMER'S DISEASE AND OTHER TAUOPATHIES

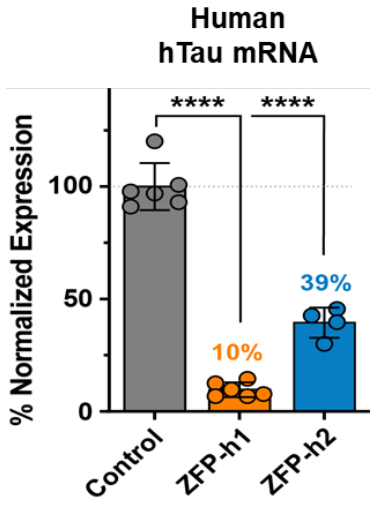
ZFP-TFs reduce expression of tau in a highly specific, tunable manner

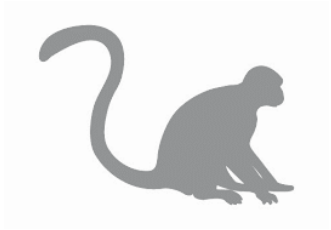
ZFP-TFs therefore represent a *novel therapeutic strategy for treating tauopathies*

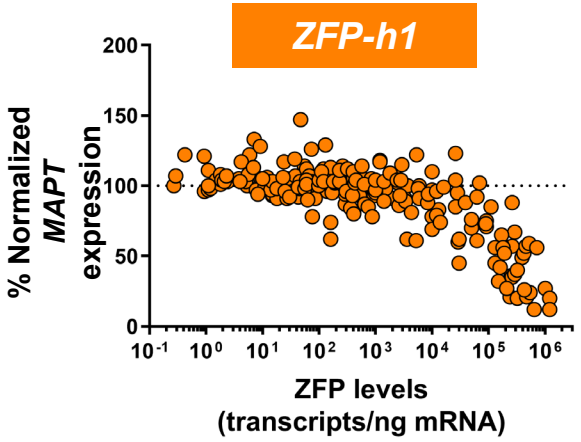


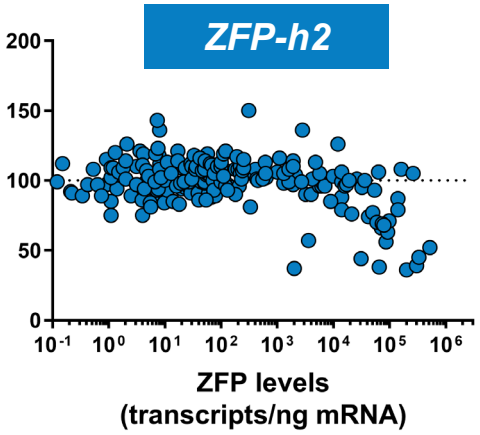












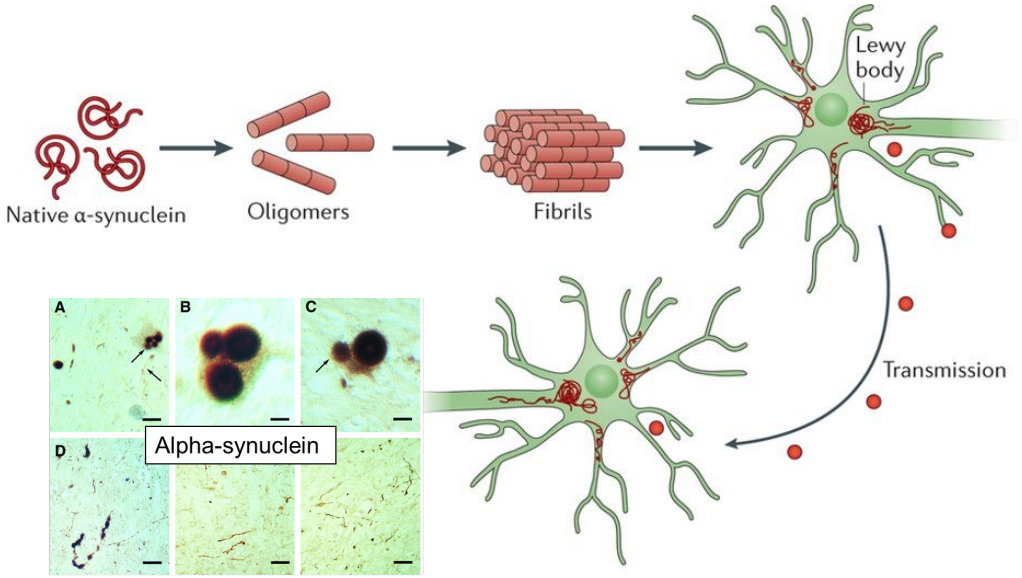
Sangamo THERAPEUTICS

Reducing gene expression with ZFP-TFs to target disease pathology

Pan-Allele

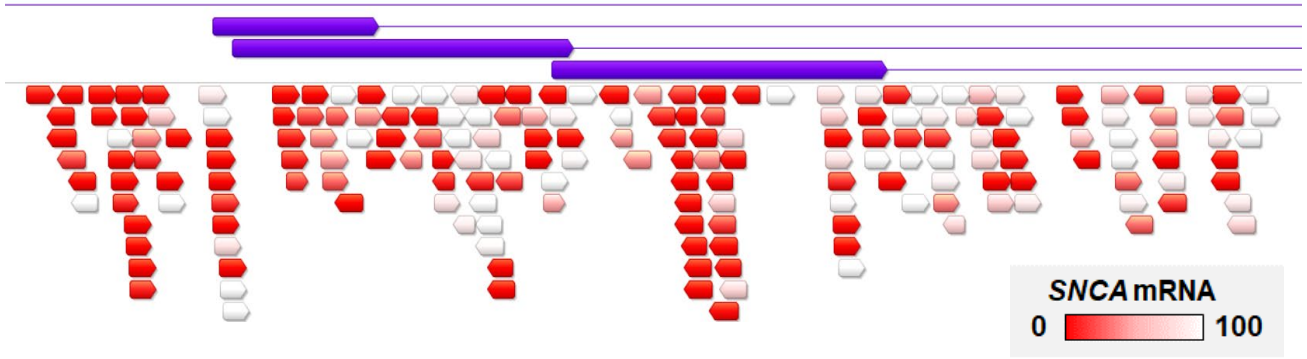
ST-502 – PARKINSON'S DISEASE

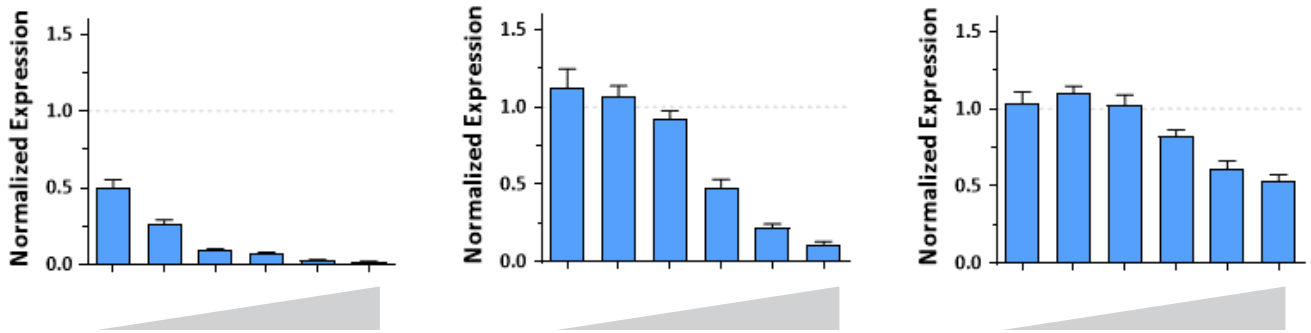
α-synuclein pathology tracks with disease progression in PD



Alpha-synuclein fibrils identified as major components of Lewy bodies and Lewy neurites (Goedert and Spillantini, 1998)

Kingwell 2017





55% of ZFP-TFs reduced total *SNCA* by ≥ 50%

3 / 10 / 30 / 100 / 300 / 1000
ng ZFP mRNA

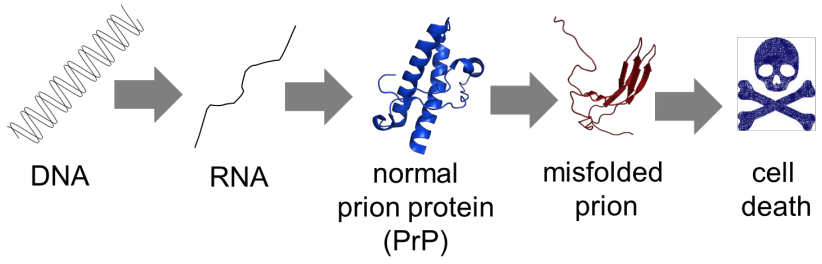
Sangamo THERAPEUTICS

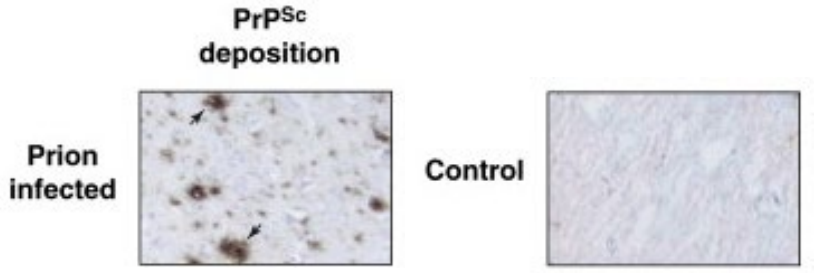
Reducing gene expression with ZFP-TFs to target disease pathology

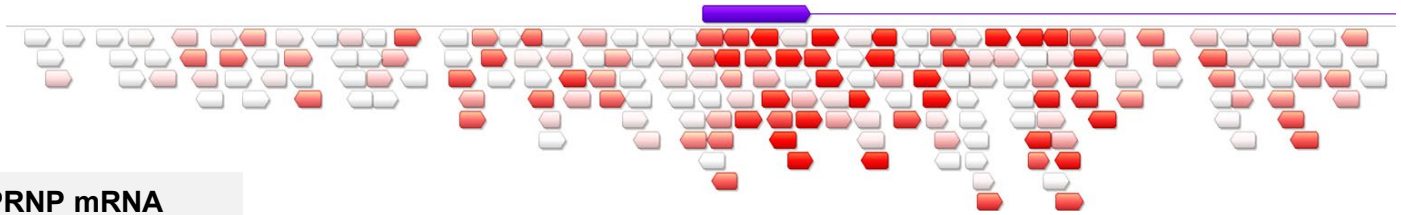
Pan-Allele

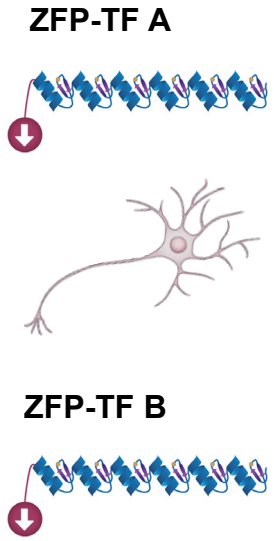
PRION DISEASE

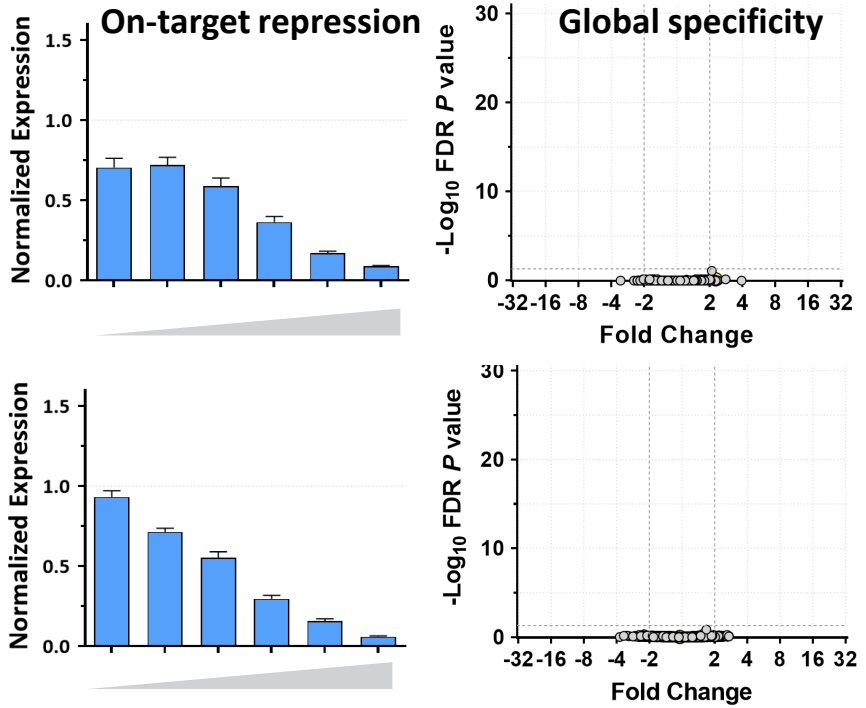
Misfolded prion protein leads to neurodegeneration in familial and sporadic forms of prion disease











Sangamo THERAPEUTICS

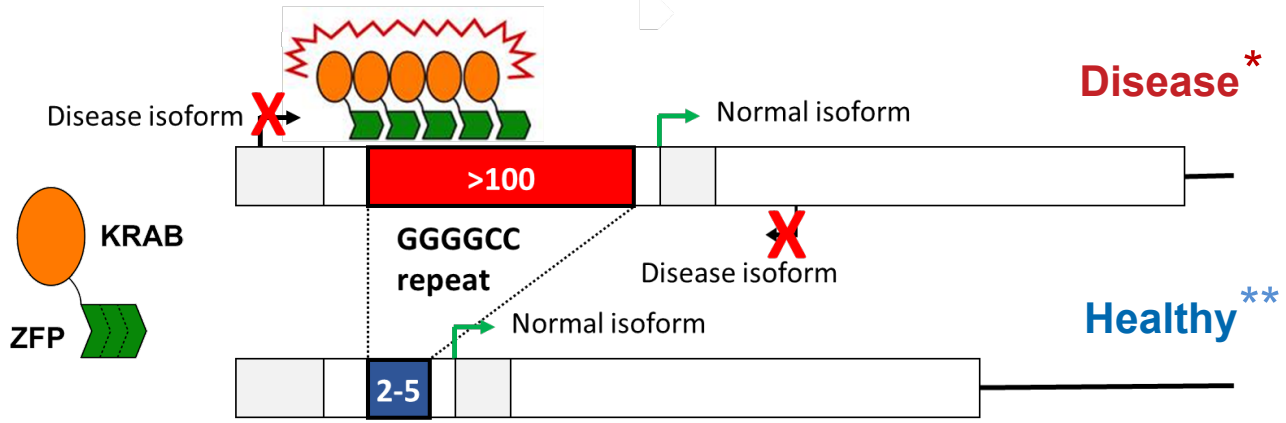
BROAD INSTITUTE

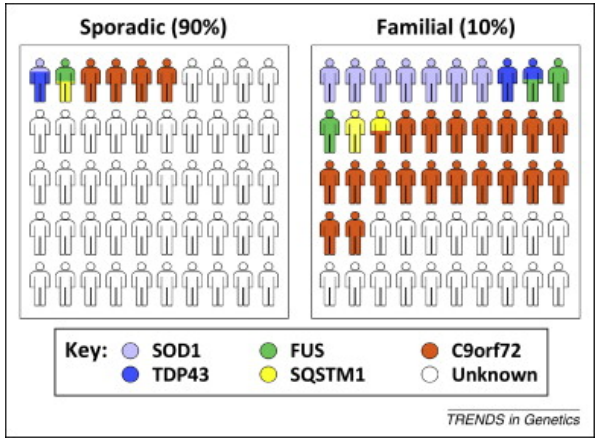
Reducing gene expression with ZFP-TFs to target disease pathology

Allele-selective

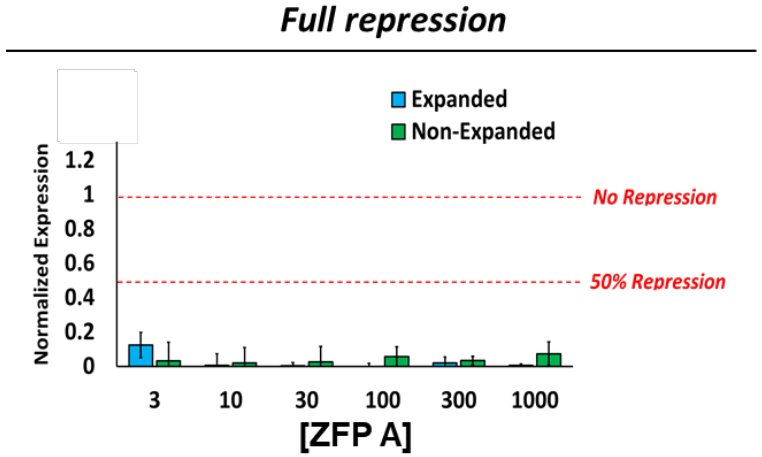
AMYOTROPHIC LATERAL SCLEROSIS (ALS)

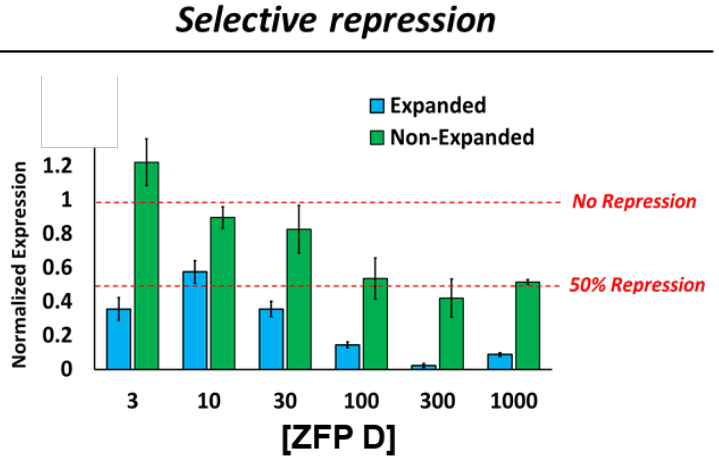
- Expansion of the GGGCC six base pair repeat causes neuronal degeneration in ALS/FTD
- Repeat-targeted ZFP-TFs selectively repress disease isoforms while preserving expression of normal C9ORF72





Lattante et al 2015





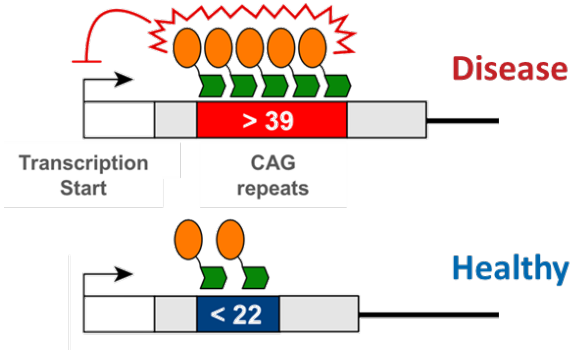
*Expanded repeat **Non-expanded

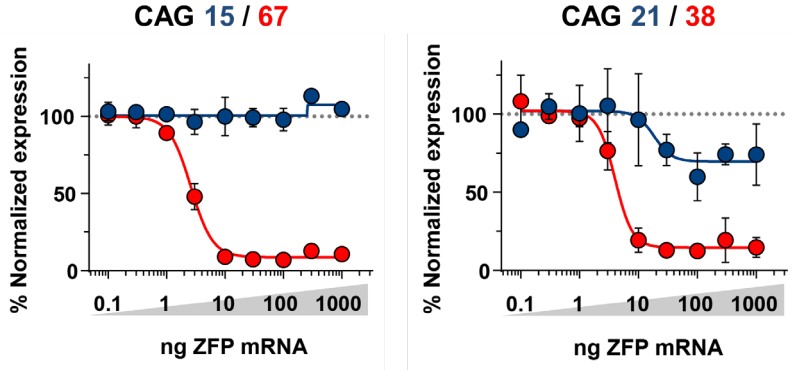
Reducing gene expression with ZFP-TFs to target disease pathology

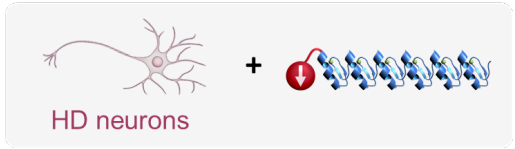
Allele-selective

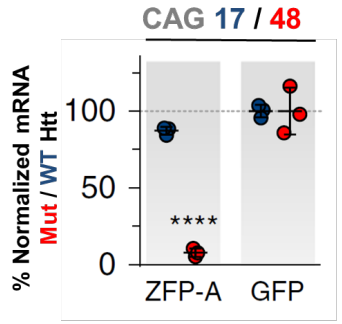
HUNTINGTON'S DISEASE

- Normal huntingtin protein has essential cellular functions
- Ideal therapy: Eliminate mutant, preserve normal
- ~90% of HD patients: **CAG15-22** and **CAG38-48**









Sangamo THERAPEUTICS + Takeda

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HUNTINGTON'S DISEASE

Astrocyte molecular signatures in Huntington's disease

Blanca Diaz-Castro[1], Mohitkumar R. Gangwani[1], Xinzhu Yu[1], Giovanni Coppola[2,3,4], Baljit S. Khakh[1,5]*

Diaz-Castro *et al., Sci. Transl. Med.* **11**, eaaw8546 (2019) 16 October 2019

Mutant huntingtin enhances activation of dendritic Kv4 K^+ channels in striatal spiny projection neurons

Luis Carrillo-Reid[1,2], Michelle Day[1], Zhong Xie[1], Alexandria E Melendez[1], Jyothisri Kondapalli[1], Joshua L Plotkin[1,3], David L Wokosin[1], Yu Chen[1], Geraldine J Kress[1,4], Michael Kaplitt[5], Ema Ilijic[1], Jaime N Guzman[1], C Savio Chan[1], D James Surmeier[1]*

eLIFE elifesciences.org

Carrillo-Reid *et al.* eLife 2019;8:e40818. DOI: https://doi.org/10.7554/eLife.40818

Faulty neuronal determination and cell polarization are reverted by modulating HD early phenotypes

P. Conforti[a,b], D. Besusso[a,b,1], V. D. Bocchi[a,b,1], A. Faedo[a,b,1,2], E. Cesana[c], G. Rossetti[b], V. Ranzani[b], C. N. Svendsen[d], L. M. Thompson[e,f], M. Toselli[c], G. Biella[c], M. Pagani[b,g], and E. Cattaneo[a,b,3]

www.pnas.org/cgi/doi/10.1073/pnas.1715865115

nature medicine ARTICLES

https://doi.org/10.1038/s41591-019-0478-3

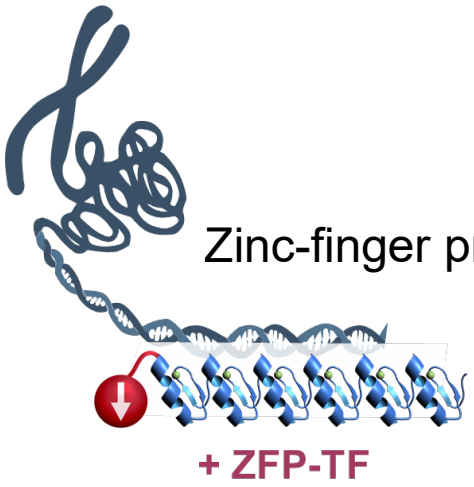
Allele-selective transcriptional repression of mutant *HTT* for the treatment of Huntington's disease

Bryan Zeitler[1]*, Steven Froelich[1], Kimberly Marlen[1], David A Shivak[1], Qi Yu[1], Davis Li[1], Jocelynn R Pearl[1], Jeffrey C Miller[1], Lei Zhang[1], David E Paschon[1], Sarah J Hinkley[1], Irina Ankoudinova[1], Stephen Lam[1], Dmitry Guschin[1,8], Lexi Kopan[1], Jennifer M Cherone[1], Hoang-Oanh B Nguyen[1], Guijuan Qiao[1], Yasaman Ataei[1], Matthew C Mendel[1], Rainier Amora[1], Richard Surosky[1], Josee Laganiere[1,9], B Joseph Vu[1], Anand Narayanan[1], Yalda Sedaghat[2], Karsten Tillack[2], Christina Thiede[2], Annette Gärtner[2], Seung Kwak[3], Jonathan Bard[3], Ladislav Mrzljak[3], Larry Park[3], Taneli Heikkinen[4], Kimmo K Lehtimäki[4], Marie M Svedberg[5], Jenny Häggkvist[5], Lenke Tari[5], Miklós Tóth[5], Andrea Varrone[5], Christer Halldin[5], Andrea E Kudwa[6], Sylvie Ramboz[6], Michelle Day[7], Jyothisri Kondapalli[7], D James Surmeier[7], Fyodor D Urnov[1,10], Philip D Gregory[1], Edward J Rebar[1], Ignacio Muñoz-Sanjuán[3]* and H Steve Zhang[1,11]

NATURE MEDICINE | VOL 25 | JULY 2019 | 1131–1142 | www.nature.com/naturemedicine

July 2019

Key takeaways



Zinc-finger protein transcription factors

Potent repression gene expression

Exquisitely specific repression of target gene

Tunable to desired level of repression

Optimized and reliable platform for gene repression

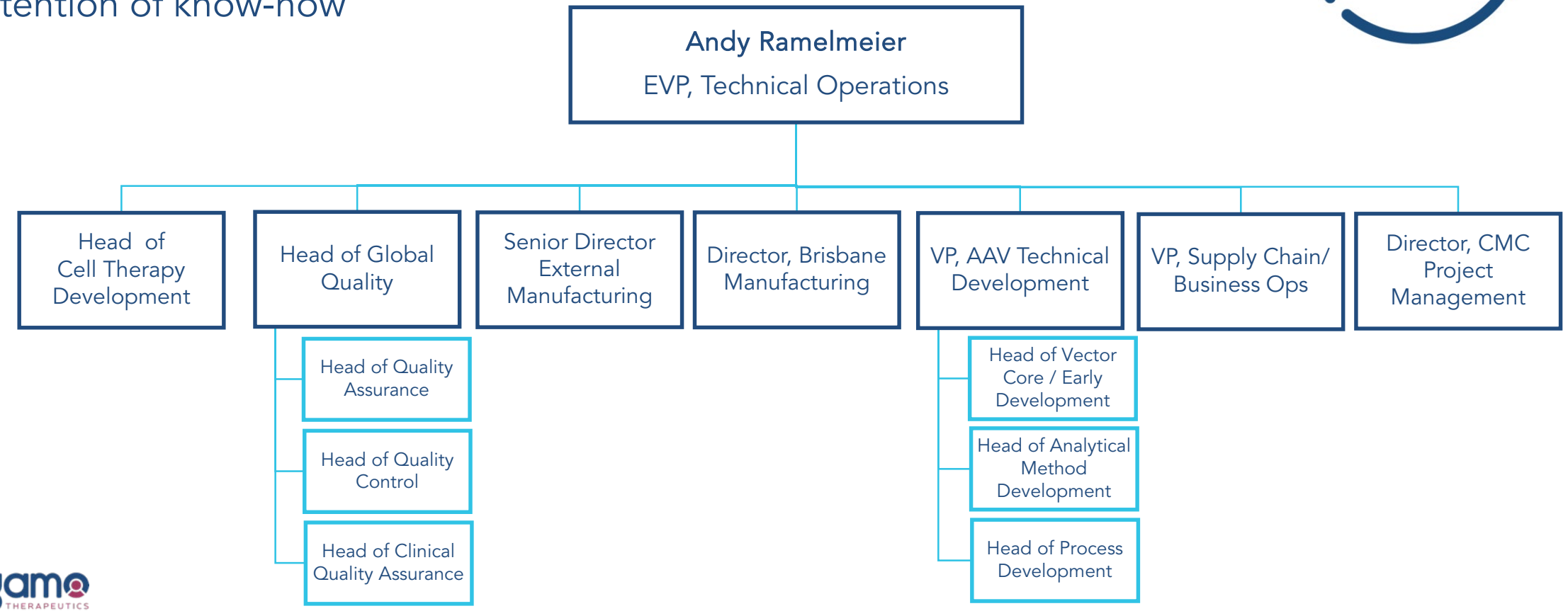
ZFP-TFs represent a universal and powerful platform for targeting neurodegenerative diseases

Manufacturing Strategy

Andy Ramelmeier,
Head of Technical Operations

Sangamo is building world class GMP manufacturing up to scale

- Investment in right people is key; 1/3 of Sangamo's headcount
- Substantial internal resources invested to develop unique capabilities
- Greater control over manufacturing and supply
- Retention of know-how



Rethinking cell and gene therapy manufacturing strategy

Traditional outsourcing Rule # 1

- Use CDMOs for expertise and capabilities you don't have

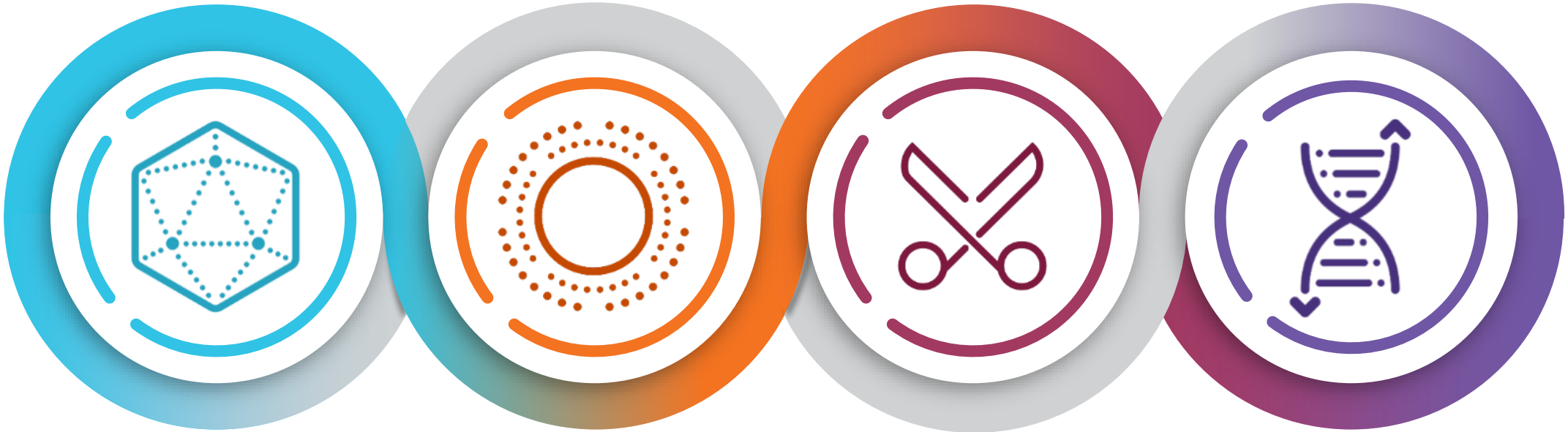
Current reality

- Industry is growing so quickly
- Innovators and CDMOs are learning as they go
- Complex early stage processes are a challenge for CDMOs
- Innovator companies want more control

Sangamo's manufacturing strategy

- Best fit for our pipeline is balance of in-house and CDMO manufacturing
- Phase 1/2: Manufacture AAV & cell therapy in-house to obtain the required capability, control & flexibility
- Leverage ThermoFisher for Ph3 and commercial AAV manufacturing, expertise & capacity optionality
- Late stage cell therapy manufacturing plans under development

Sangamo's platform technologies



Gene Therapy AAV	Gene-Edited Cell Therapy ZFN; AAV; LV	Genome Editing AAV; ZFN	Genome Regulation AAV; ZFP-TF
SB-525: Hemophilia A ST-920: Fabry disease ST-101: PKU	ST-400: Beta thalassemia BIVV003: Sickle cell disease TX200: Solid organ transplant KITE-037: Allo-CD19 CAR-T Undisclosed targets	SB-913: MPS II	ST-501: Tauopathies ST-502: α-synuclein C9ORF72-linked ALS/FTLD Huntington's disease Undisclosed targets

Sangamo is planning for manufacturing success

Balanced approach to manufacturing capacity

Investments in process development and analytics

Building a strong supply chain

Sangamo is planning for manufacturing success

Balanced approach to manufacturing capacity

- In-house: investing in two flexible and cost effective GMP facilities for early-stage pipeline and commercial
- Partnership with experienced CDMO for late-stage AAV products

Investments in process development and analytics

Building a strong supply chain

In-house cGMP facility and dedicated CDMO capacity provide scale for clinical and commercial supply

Ensuring control of quality, cost and timelines

In-house Phase 1/2 cGMP Facilities

Brisbane, US:

- Cell therapy (late 2020)
- Gene therapy (early 2021)

Valbonne, France:

- Cell therapy (late 2021)

CDMO ThermoFisher – dedicated access to AAV capacity up to 2000-L bioreactor scale

- Leveraging ThermoFisher AAV manufacturing know-how
- Enables seamless transition from early to late-stage development
- Provides late-stage clinical and large-scale commercial grade supply

ThermoFisher SCIENTIFIC

Building on Sangamo's strong track record of AAV and cell therapy manufacturing

Six AAV clinical trials supplied (>20 GMP runs)

- Up to 2000L scale

Extensive regulatory experience

- >30 regulatory meetings
- >15 regulatory submissions

Cell therapy clinical trials supplied

- HIV T cell studies (96 patients)
- ST-400 (5 patient runs & 28 healthy donor GMP runs to date)
- 7 GMP mRNA lots
- 10 GMP plasmid lots

Upcoming key manufacturing milestones

- AAV: Ph3 lots for ST-920 planned in 2020; position for PPQ/commercial readiness in 2022
- AAV: PKU, Tau & others to advance to Ph 1/2
- Cell therapy: T_{REGS} production for Ph 1/2 clinical trial


MEDICAL NITROGEN


DANGER
CAUSTIC

Sangamo is planning for manufacturing success

Balanced approach to manufacturing capacity

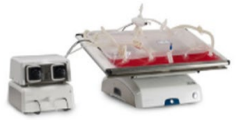
- In-house: investing in two flexible and cost effective GMP facilities for early-stage pipeline and commercial
- Partnership with experienced CDMO for late-stage AAV products

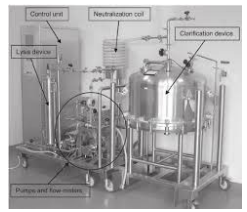
Investments in process development and analytics

- Utilizing top talent in-house with Phase 3 and commercial experience
- New labs in Brisbane HQ & Valbonne
- Robust and highly productive processes
- More potent AAV vectors and cell products

Building a strong supply chain

Sangamo AAV manufacturing process platform via Sf9





AAV Vector Drug Substance

Upstream

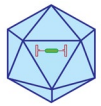
- Working Cell Bank
- Thaw WCB
- Start Cell Expansion
- End of Cell Expansion
- Infect with WBIICs
- Harvest
- Lysis & Clarified Harvest
- Filtration

Helper WBIIC Bank

Transgene WBIIC (ZFP-TF, cDNA)

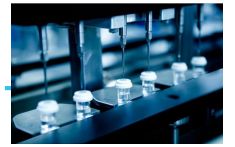
Downstream

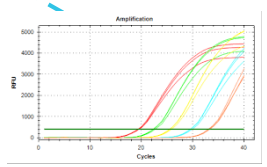
- Detergent Treatment
- Affinity Chromatography
- Ion Exchange Chromatography
- Nanofiltration
- Concentration
- Formulation & Sterile Filtration
- Bulk Fill & Freeze
- AAV Vector Drug Substance



AAV Vector Drug Substance

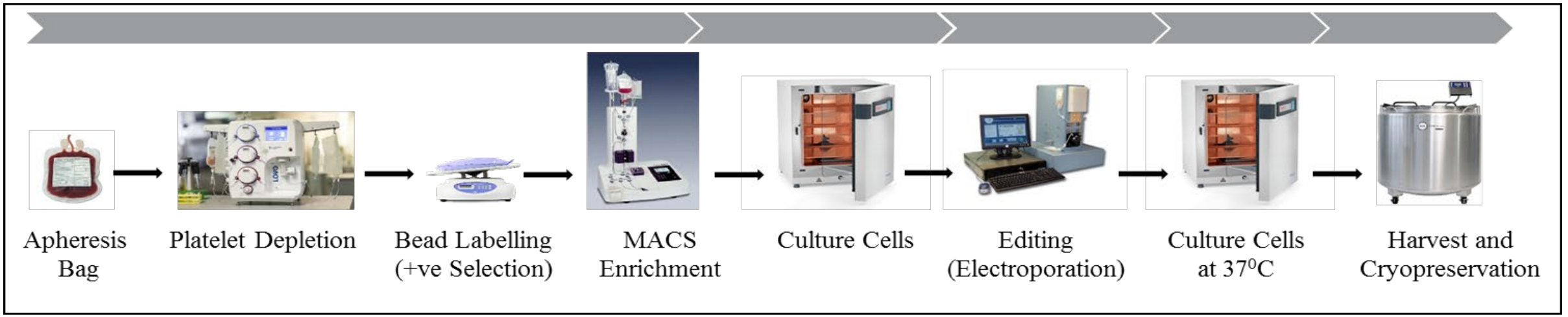
- AAV Vector Drug Substance
- Thaw
- Sterile Filtration
- Fill & Freeze
- Test & Release
- AAV Vector Drug Product





Master Baculovirus Infected Insect Cells (MBIIC), Working Baculovirus Infected Insect Cells (WBIIC), Drug Substance (DS) and Drug Product (DP) take approximately 11-12 months to manufacture, test and release

Continuous innovation in our cell therapy manufacturing



Develop a genetically-modified T_{REG} manufacturing process

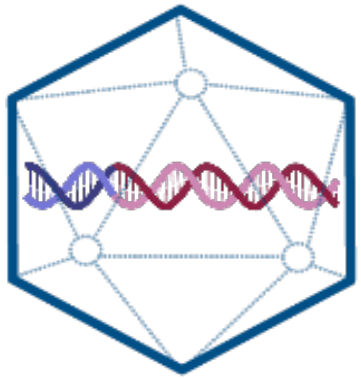
- Significant cell therapy experience from HIV projects, ST-400 and allogeneic CD-19

To establish a cost-effective, universal cell product we are investing in:

- Process and analytics development (better and more data)
- New technology and automation, including closed-system technology
- Novel and robust cell manufacturing processes from renewable cell source for our allogeneic platform

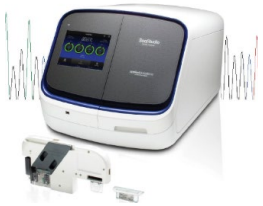
Sangamo THERAPEUTICS

AAV vector analytics and proprietary process development



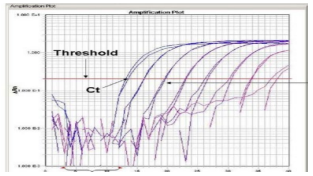
rAAV

Identity



Molecular identity by sequencing

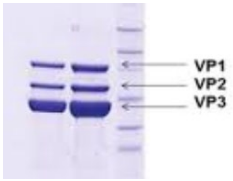
Vector genome (vg) titer



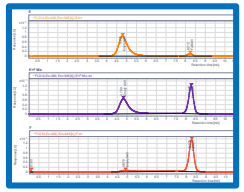
Vg titer by qPCR (CV% 10-20%)

Vg titer by ddPCR (CV% ~5%)

Purity

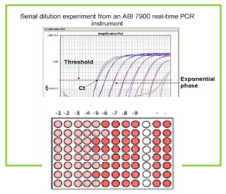


AAV purity by SDS PAGE gel



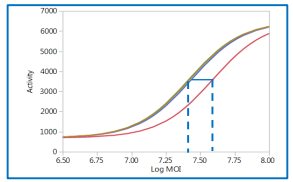
Proprietary HPLC assay
empty vs. full vector ratio

Infectivity



TCID50 assay for infectivity

Potency



Transduction/ELISA, RP

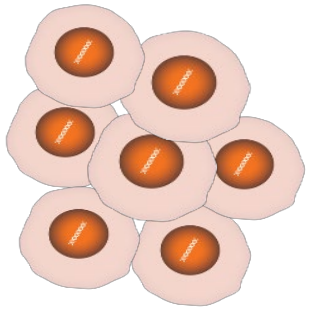
Relative potency transgene expression and enzyme activity

Gene modification, %Indel

Gene editing efficiency by MiSeq/NGS

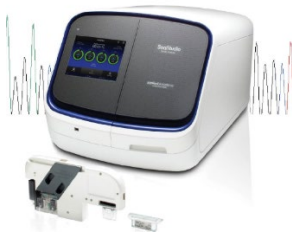
Sangamo THERAPEUTICS

Key analytics for Cell Therapy

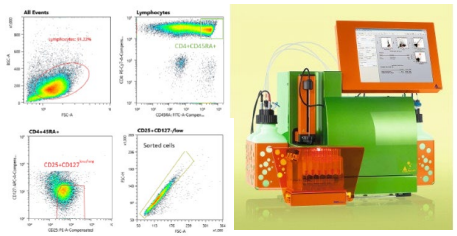


Genome-Edited Cell

Identity

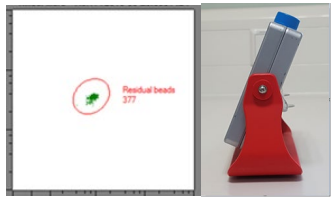


Sequencing genotyping



Cell phenotyping

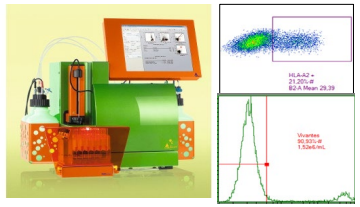
Purity



Residual beads count

FoxP3 hypomethylation status

Potency



Transduction efficiency
Cell quantity & viability

Gene Modification %Indel

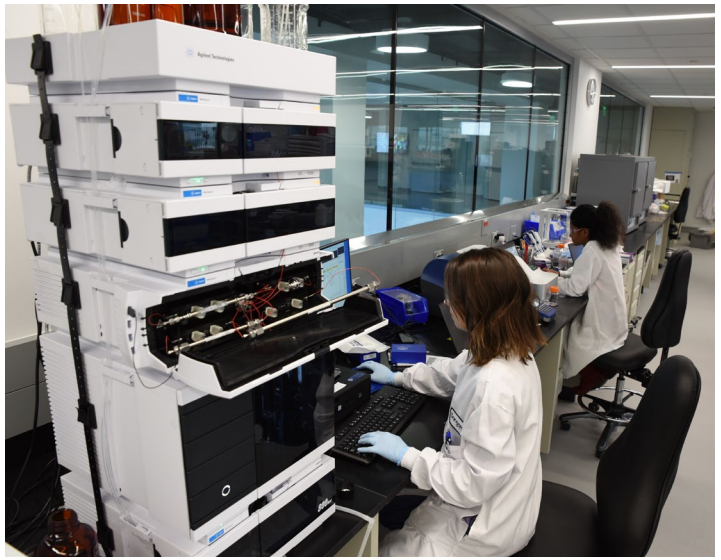
Safety

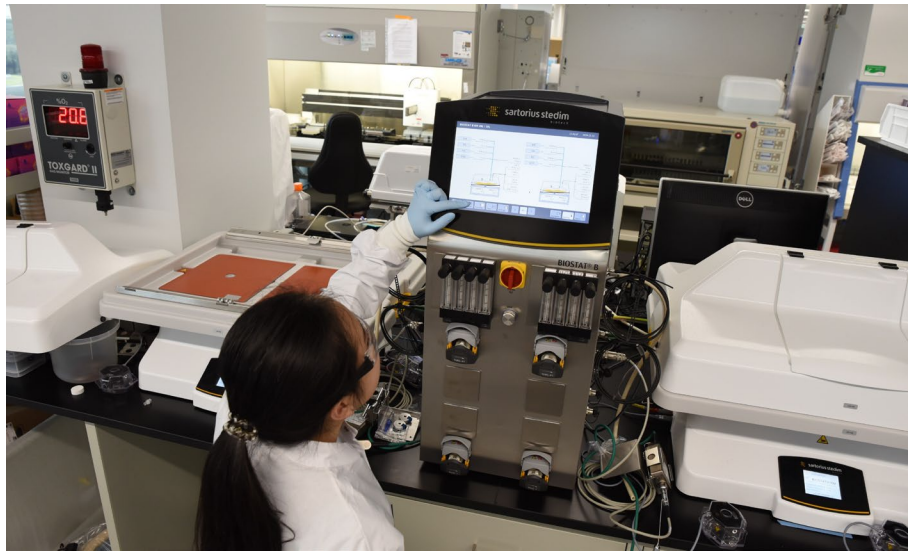
Mycoplasma
VCN / transdued cell

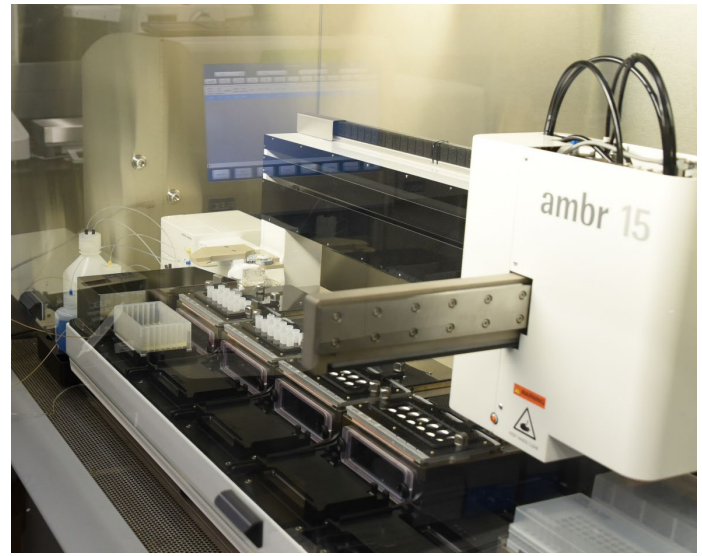
Sterility
Endotoxins
Adventitious Agents

Sangamo THERAPEUTICS

Investments in our process development labs







Sangamo is planning for manufacturing success

Balanced approach to manufacturing capacity

- In-house: investing in two flexible and cost effective GMP facilities for early-stage pipeline and commercial
- Partnership with experienced CDMO for late-stage AAV products

Investments in process development and analytics

- Utilizing top talent in-house with Phase 3 and commercial experience
- New labs in Brisbane HQ & Valbonne
- Robust and highly productive processes
- More potent AAV vectors and cell products

Building a strong supply chain

- Ability to handle clinical trial complexity, late stage activities, and launch

Securing the supply chain and critical raw materials

Strategically position suppliers and investments in new technologies to reduce risk to ongoing clinical supply

- Build supply chain to handle clinical trial complexity, late stage activities, and launch
- Invest in technology to better manage (track/trace) autologous and allogeneic cell therapies

Maintain inventory of critical materials

- Full materials management strategy
- Robust warehouse and inventory management for in-house operations

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Closing Remarks

Sandy Macrae, CEO

Strategy for therapeutic development and commercialization

Innovation

Platform

Delivery

LNP
AAV

Retain

- Assets with breakthrough potential
- Development and commercialization is financially and operationally feasible
- Synergies across programs and platforms

Therapeutic Area

Inherited Metabolic Diseases (IMDs), such as Fabry

Externalize

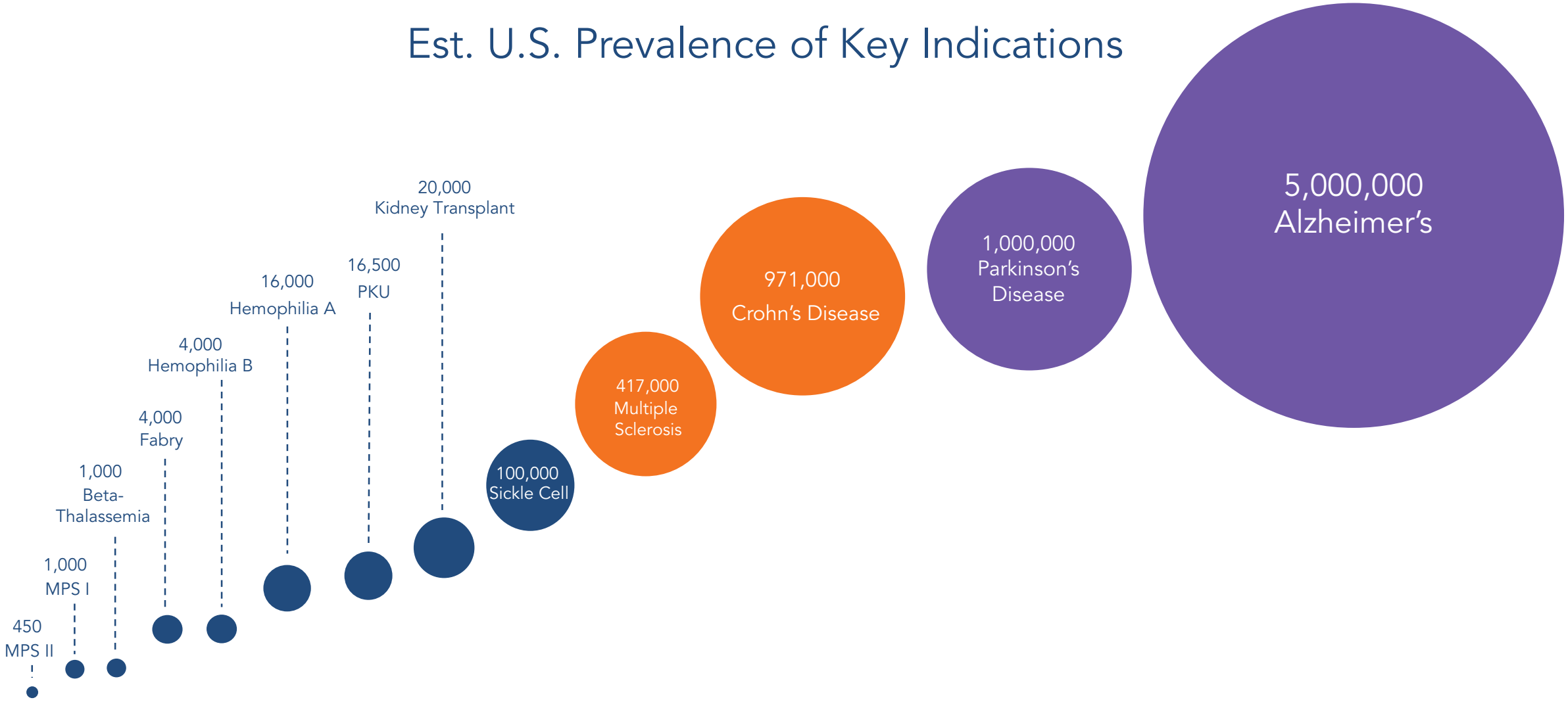
- Therapeutic areas with several competing franchises
- Very significant investment required
- Requires special disease area expertise and/or complementary assets

Therapeutic Area

Large CNS diseases, such as Alzheimer's

Sangamo THERAPEUTICS

Sangamo's technology will address large markets with serious unmet need



Note: The size of the spheres presented are adjusted for visual representation and may not be proportional

Collaborations will continue to be integral to Sangamo's strategy

Partnerships are a means to pursue the vast opportunity set of Sangamo's genomic medicines platform

- Therapeutic class leadership
- Clinical science expertise
- Financial and human resources

Key themes for R&D day

1. Core capabilities and talent enable transition to late-stage biotech
2. Clinical data yields useful new insights across platforms
3. Leading innovation in editing, cell therapy, and genome regulation
4. Advancing genomic medicines for larger patient populations

Thank you.