Sangamo THERAPEUTICS

ZINC FINGER NUCLEASES FOR PRECISION GENOME EDITING

SANDY MACRAE, CEO,
SANGAMO THERAPEUTICS

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, as amended. These forward-looking statements include, but are not limited to, the therapeutic potential of Sangamo's product candidates; the design of clinical trials and expected timing for initiation, enrollment and presentation of data; anticipated clinical development and other milestones; the expected benefits of Sangamo's collaborations; the anticipated capability 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 CAR-T and CAR-Tregs 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 Sangamo's dependence on the success of clinical trials of its lead programs; 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 Sangamo's product candidates; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; Sangamo's limited experience in conducting later stage clinical trials and the potential inability of Sangamo and its partners to advance any of Sangamo's 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; and the potential for technological developments by Sangamo's competitors that will obviate Sangamo's gene therapy technology. Further, there can be no assurance that the necessary regulatory approvals will be obtained or that Sangamo and its partners will be able to develop commercially viable gene-based therapeutics. Actual results may differ from those projected in forward-looking statements due to risks and uncertainties that exist in Sangamo's operations. 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 June 30, 2019 that it filed on or about August 7, 2019. Forward-looking statements contained in this presentation are made as of the date hereof, and Sangamo undertakes no obligation to update such information except as required under applicable law.

Sangamo's genomic medicines encompass a breadth of technical approaches and diverse pipeline assets

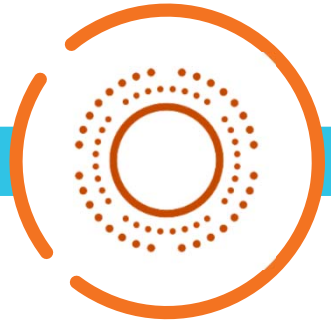
Ex vivo

In vivo

Gene Therapy

SB-525: Hemophilia A
ST-920: Fabry disease
Undisclosed targets

Gene-Edited Cell Therapy



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

Genome Editing

SB-913: MPS II
SB-318: MPS I
SB-FIX: Hemophilia B
Undisclosed targets

Gene Regulation

Tauopathies
C9ORF72-linked ALS/FTLD
Huntington's disease
Undisclosed targets

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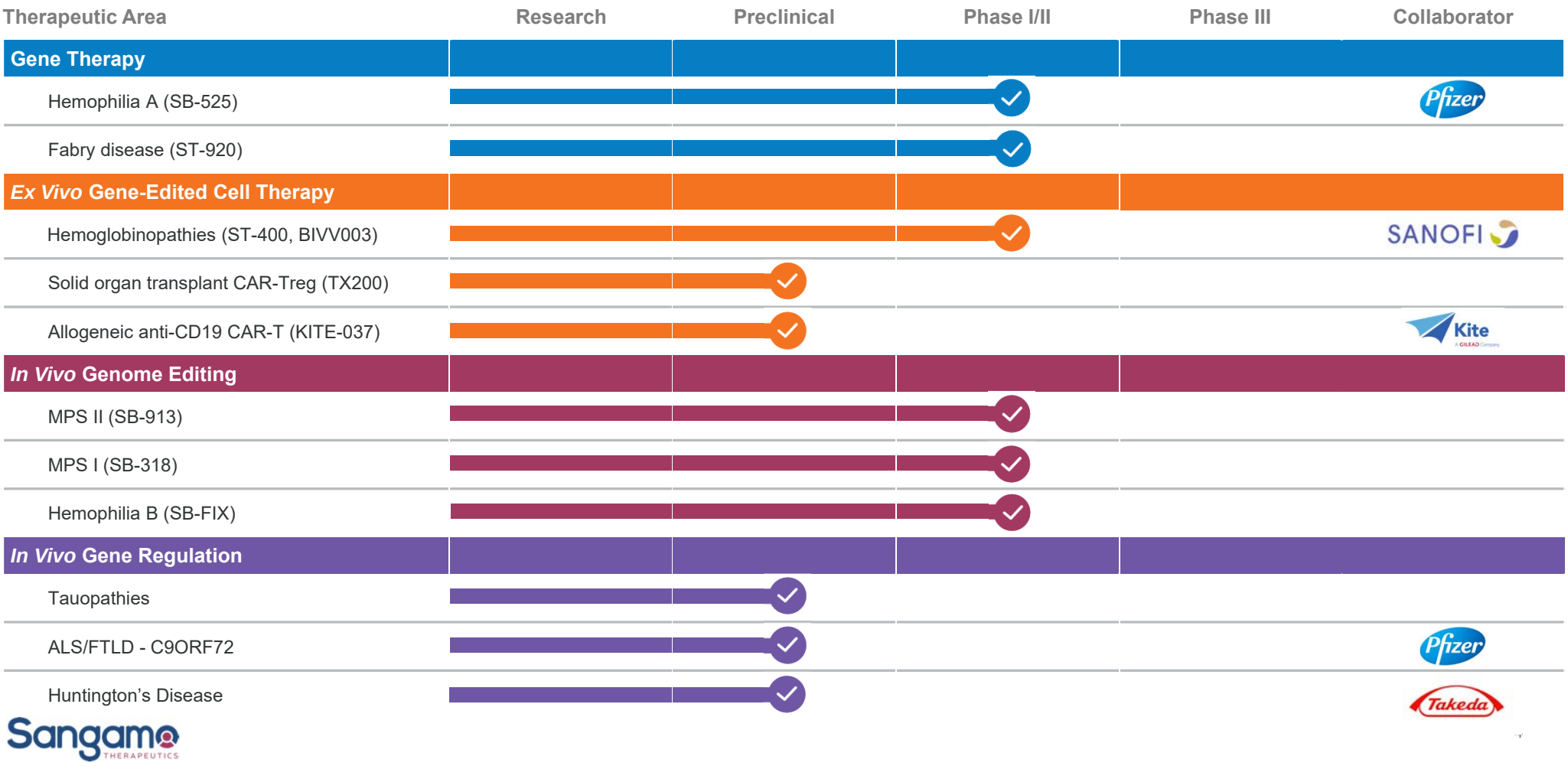
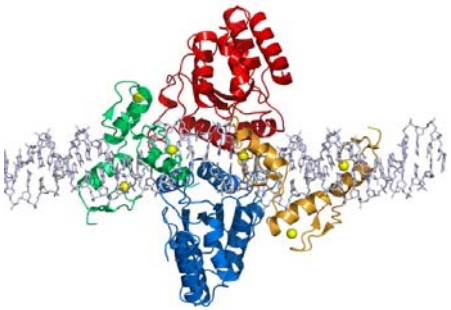
Robust pipeline of genomic medicines in clinical and preclinical stages of development



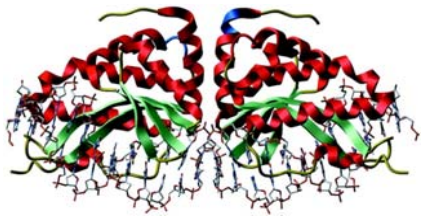
ZFN Overview

Gene editing reagents

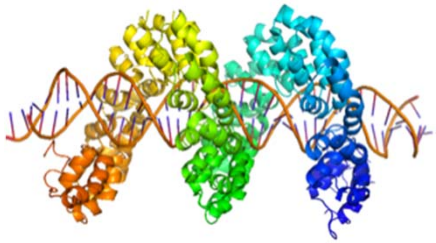
Zinc Finger Nucleases



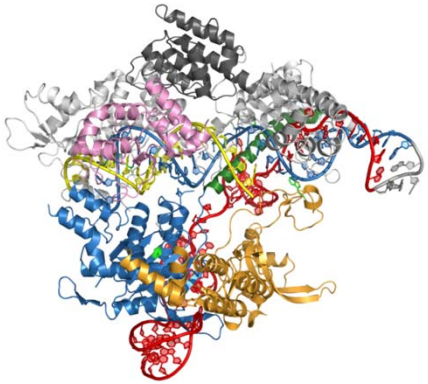
Meganucleases



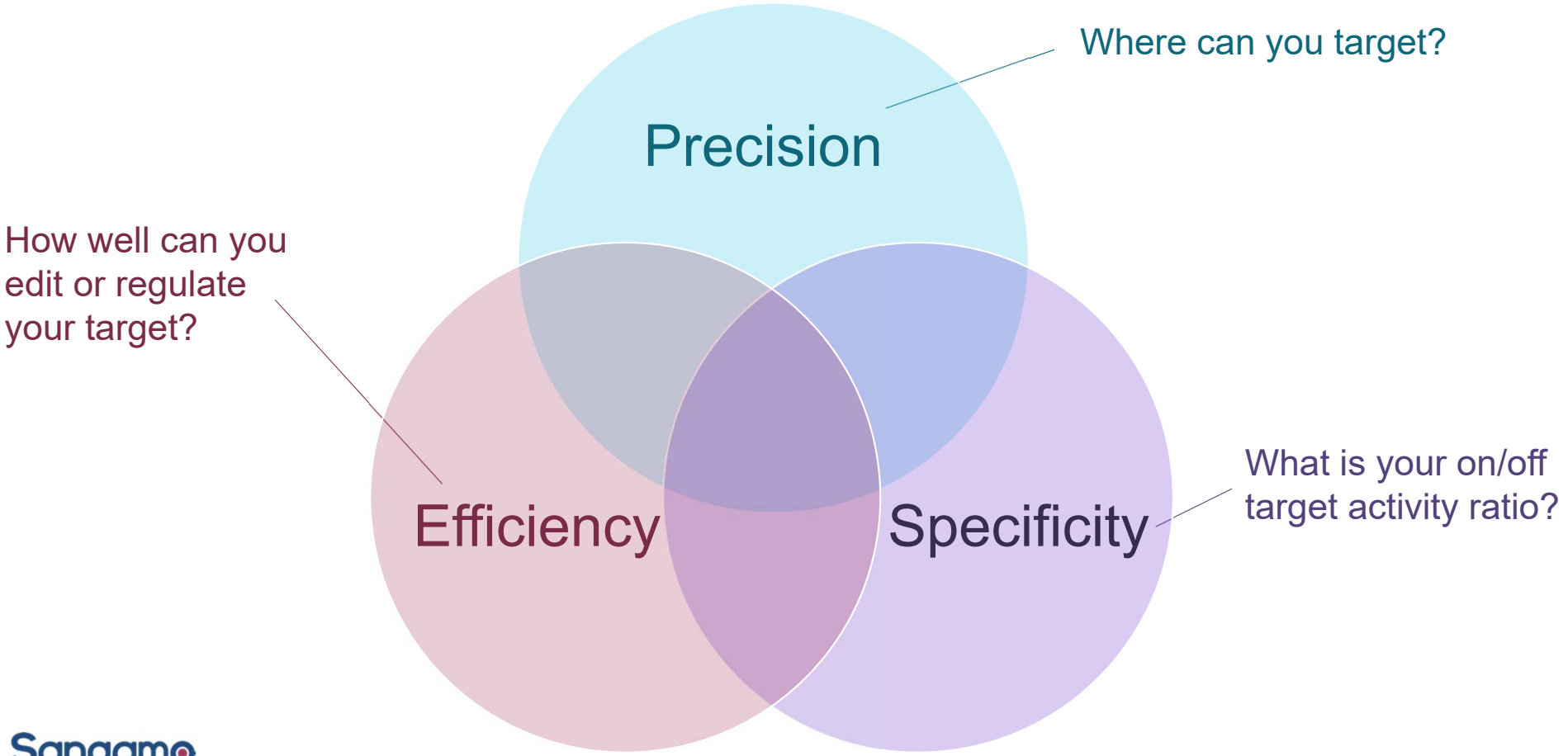
TALE Nucleases (TALENs)



CRISPR/Cas9 and CRISPR/Cpf1



Three key dimensions to performance



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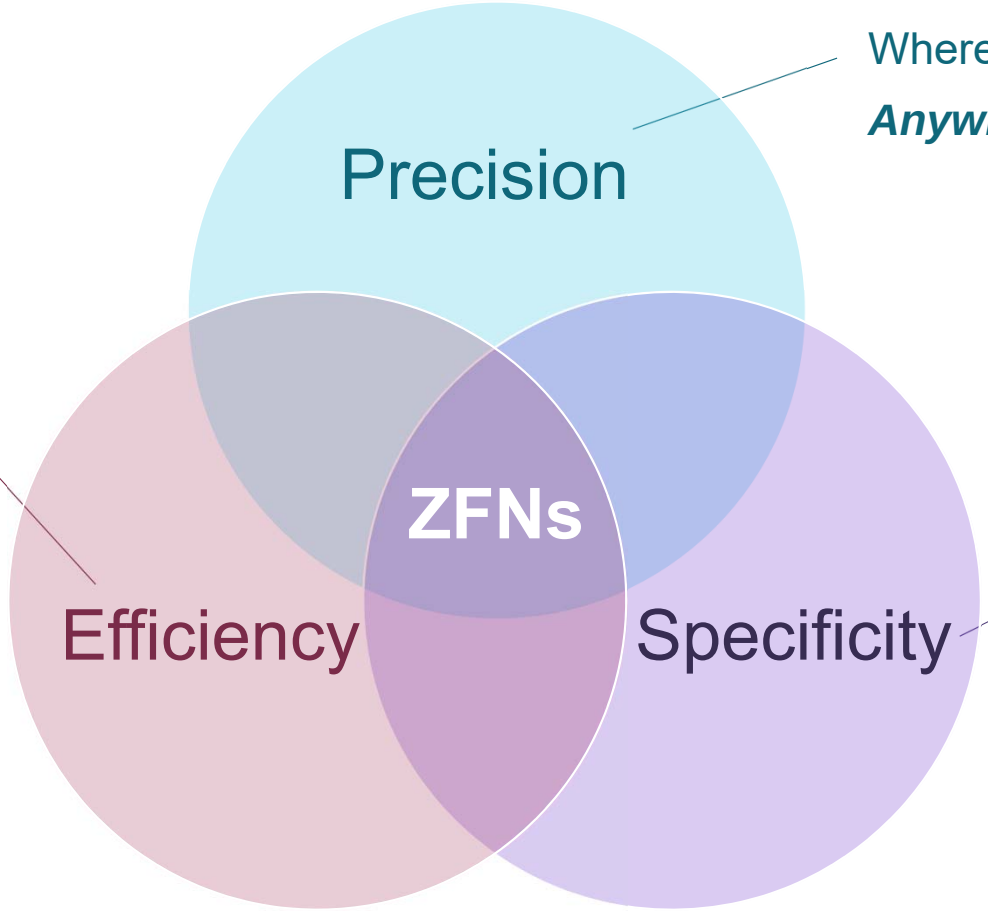
ZFNs offer unmatched performance



Where can you target?

Anywhere

How well can you edit or regulate your target?

>98% editing
>99% repression

What is your on/off target activity ratio?

Extremely high

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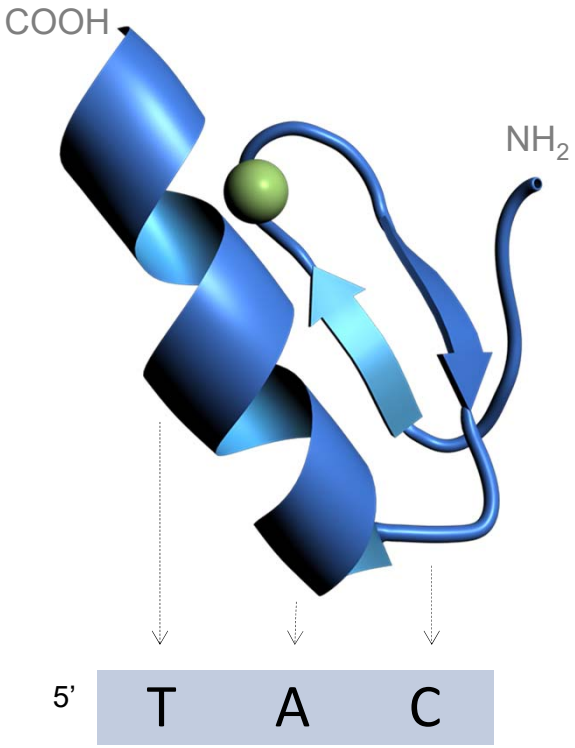
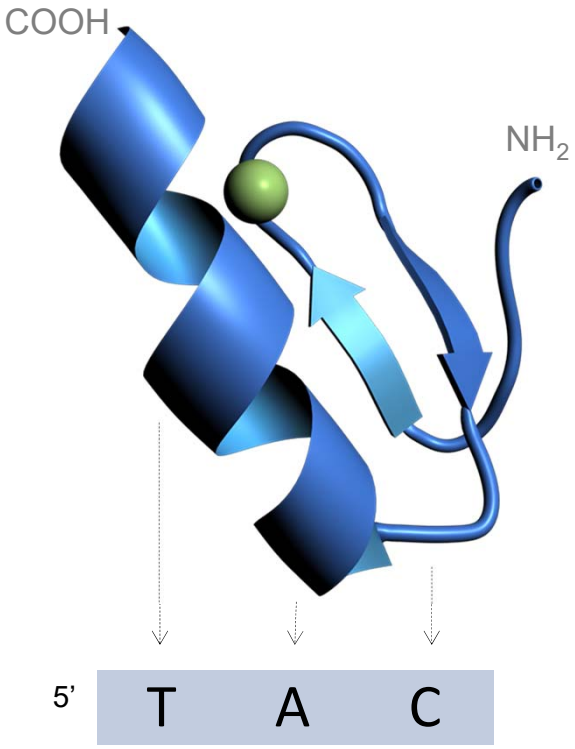
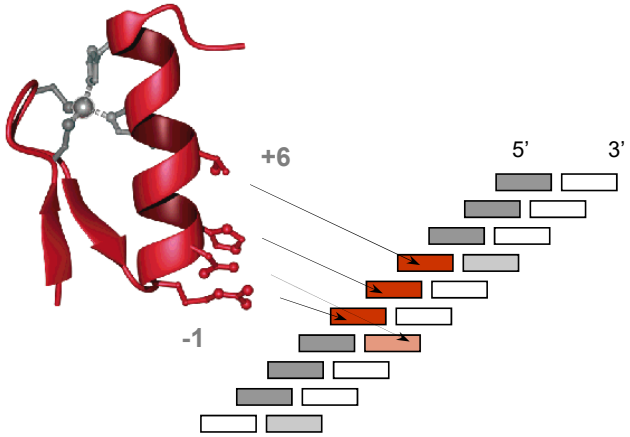
A single finger provides the fundamental DNA binding unit



- 28 amino acid peptide
- Binds 3-4 bp of DNA
- Contacts DNA from amino terminal half of α-helix

Alpha helix sequence determines base preference





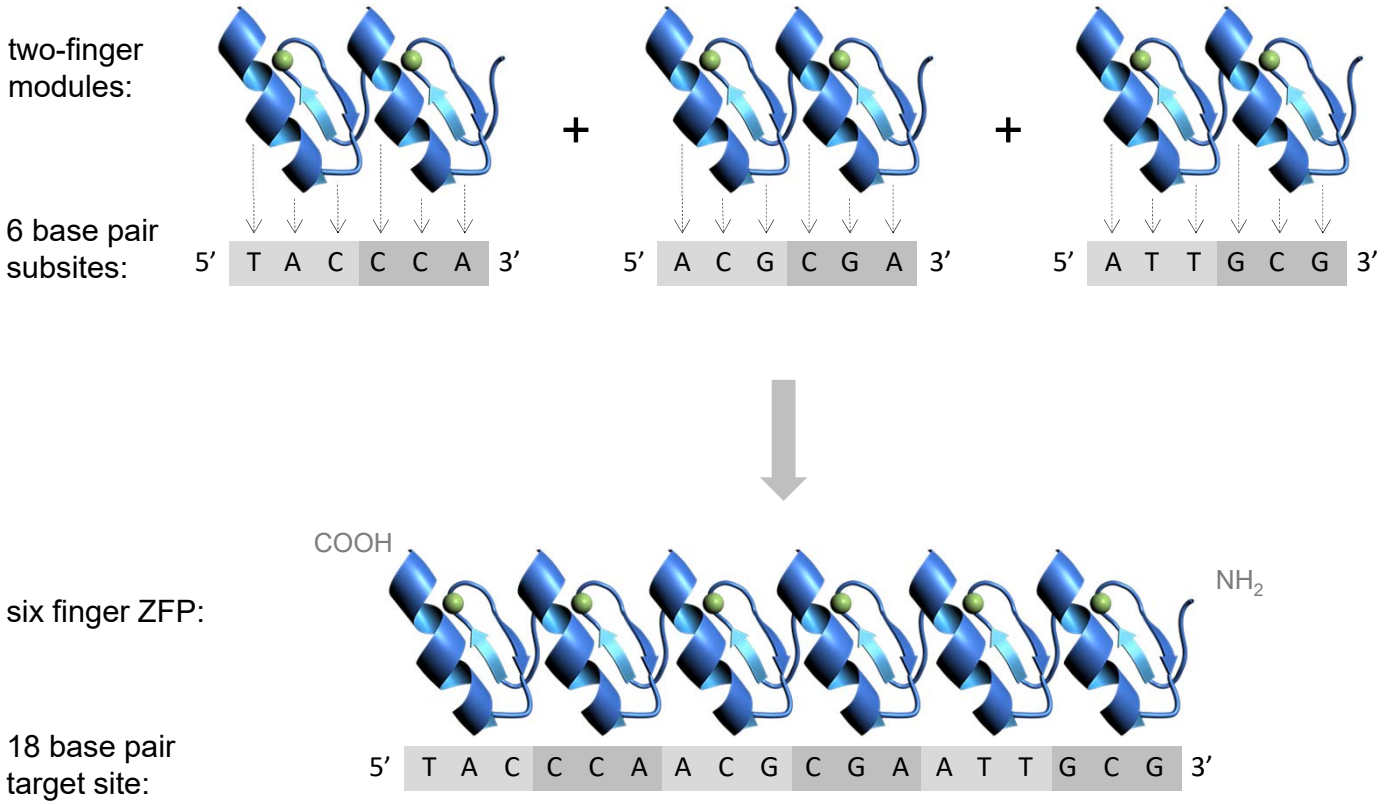
Helix sequence -1 +6	Binding preference
LKQNLCM	CAT
AQCCLFH	AGC
DQSNLRA	AAC
RSDELTR	GCGG
… etc	…

With distinct DNA recognition events, each ZFN has a unique efficiency and specificity profile

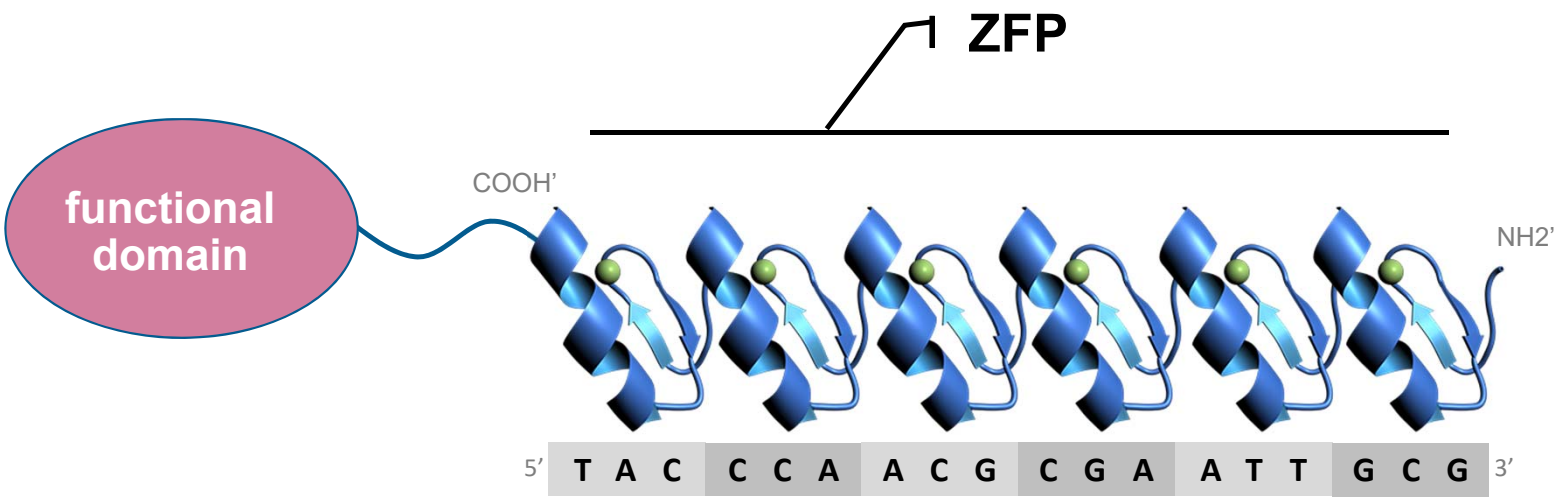
ZFP Design Options		DNA Recognition Helix Protein Sequences	ZFP Design Options	
QSADRTK	QKATRTT		DRSNRTK	RSDNLSQ

An analogy from the English language: Homonyms, e.g., whole and holes, sound the same but have very different meanings

Modular function enables facile design of new ZFPs

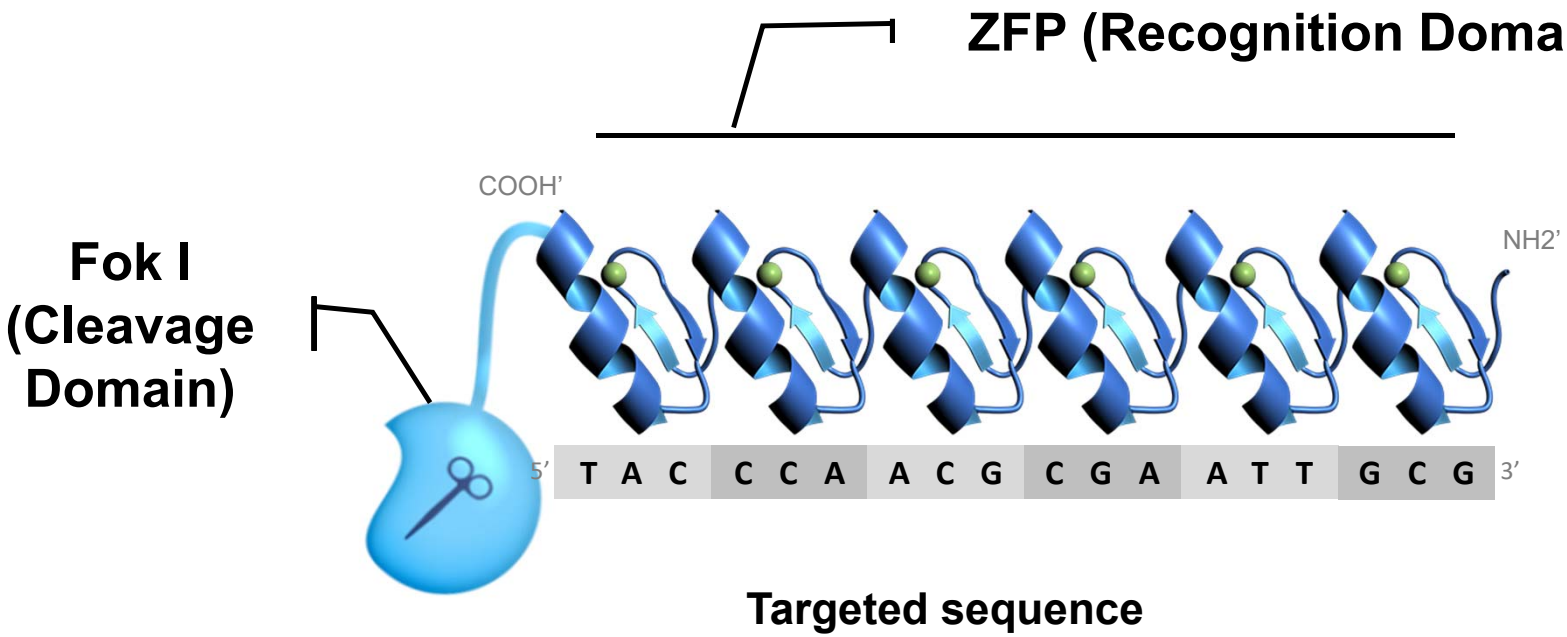


ZFPs can link any domain to any chosen genome locus

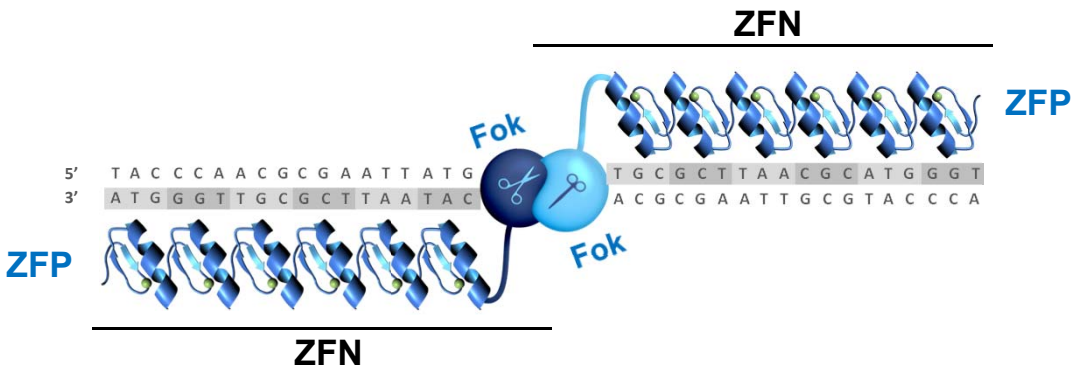


Targeted genome sequence

Attaching a nuclease enables targeted DNA cleavage



Zinc Finger Nuclease (ZFN)

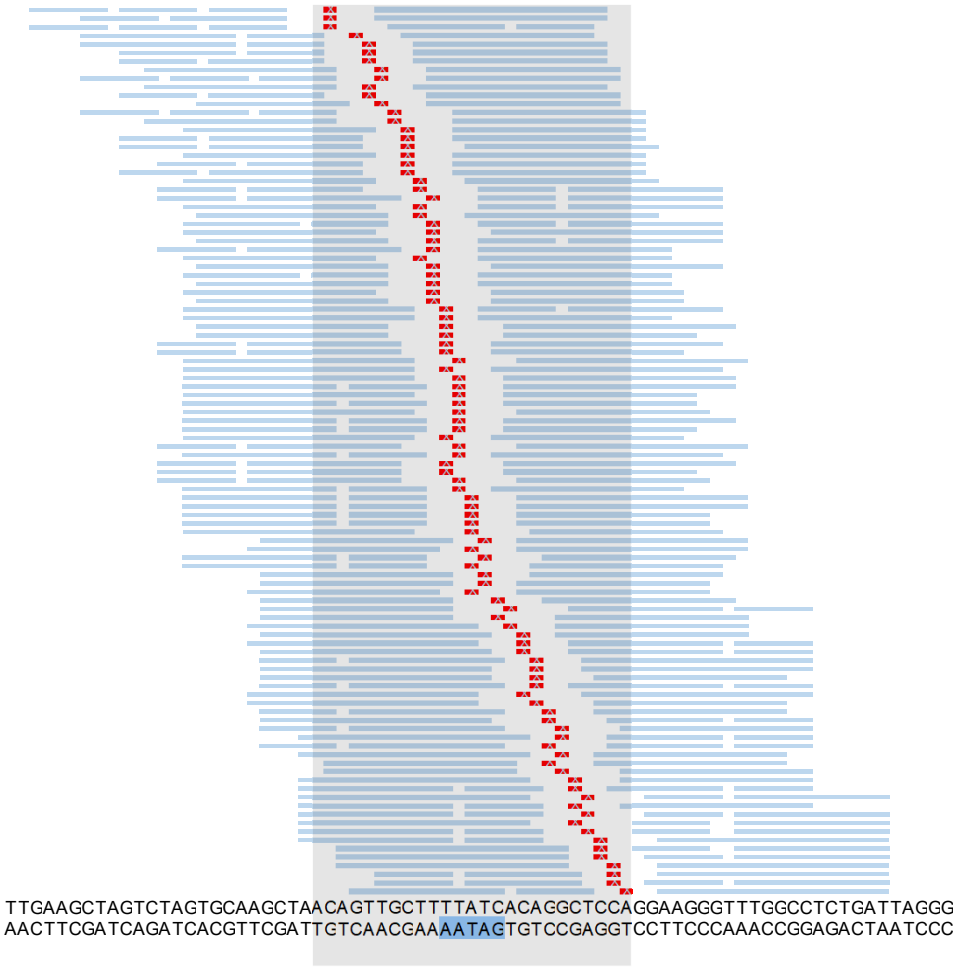


- Programmable nuclease
- Contains two domains:
  - **nuclease domain of FokI**
  - **zinc finger protein (ZFP)**
- Cleaves only when dimerized
- Specifies an extended target (36bp)

Platform enables dense tiling of targeted regions

***Example*: erythroid-specific enhancer of BCL11A**

104 ZFN architectures available for GATAA ± 10bp



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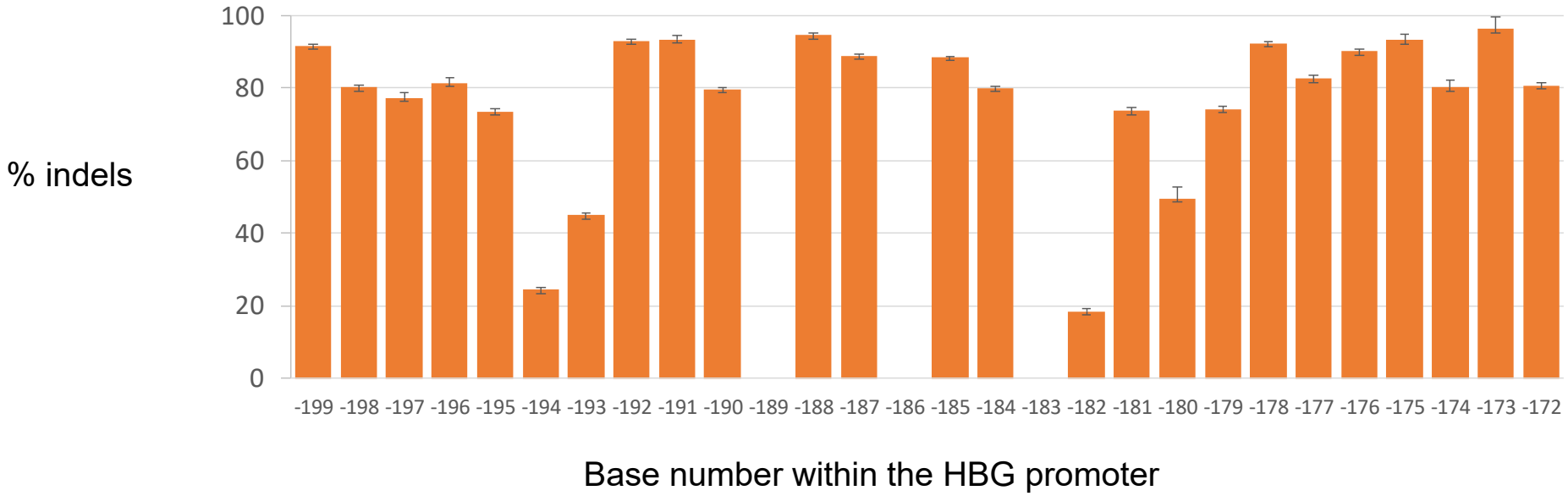
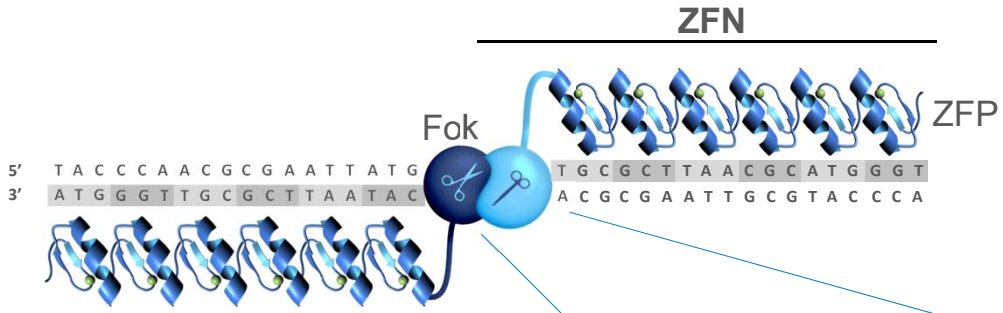
Highly active ZFNs available for almost every base step

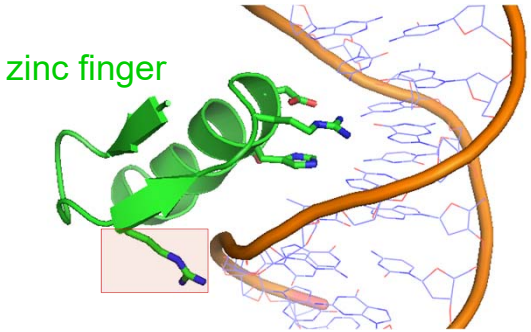


- Target region: 28 bp window in the HBG promoter spanning key HPFH mutations
- Screened via transient RNA delivery in K562 cells

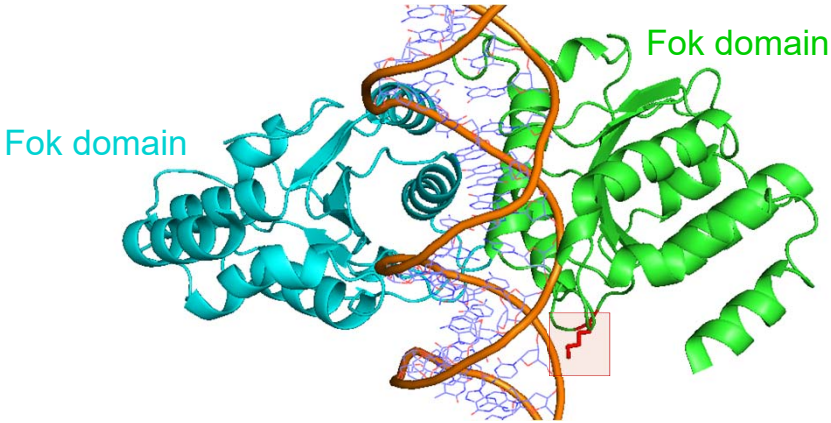
Two complementary approaches for engineering specificity



1) Removing Arg-phosphate contacts



2) Substituting key FokI residues



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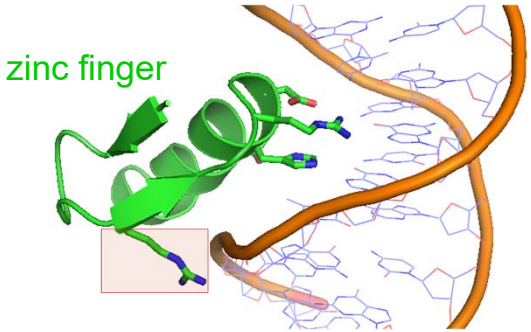
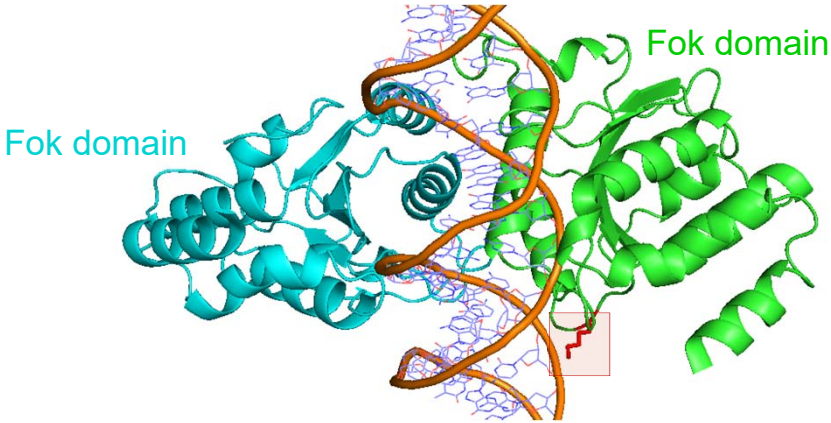
Independent tuning of dissociation and catalysis

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

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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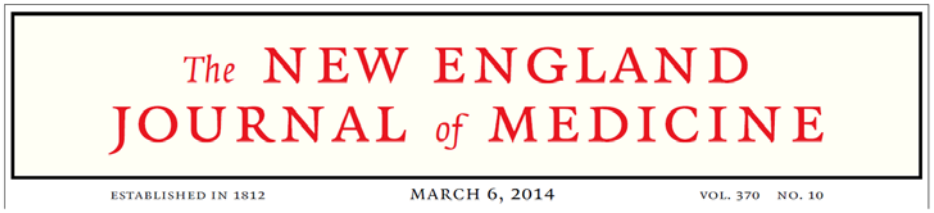
More than a decade of gene editing experience beginning with HIV



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale A. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

Sangamo, along with academic collaborators, pioneered the use of *ex vivo* gene edited cell therapy to treat HIV

UPenn	Carl June, Jim Hoxie, Jim Riley, Bruce Levine
Case Western	Rafick Sekaly
Fred Hutch	Hans-Peter Kiem
UCSF	Steven Deeks, Joseph Wong
USC	Paula Cannon
City of Hope	John Zaia
UCLA	Ronald Mitsuyasu
Univ de Montréal	Nicolas Chomont

NIH amfAR AIDS RESEARCH CIRM CALIFORNIA'S STEM CELL AGENCY defeatHIV

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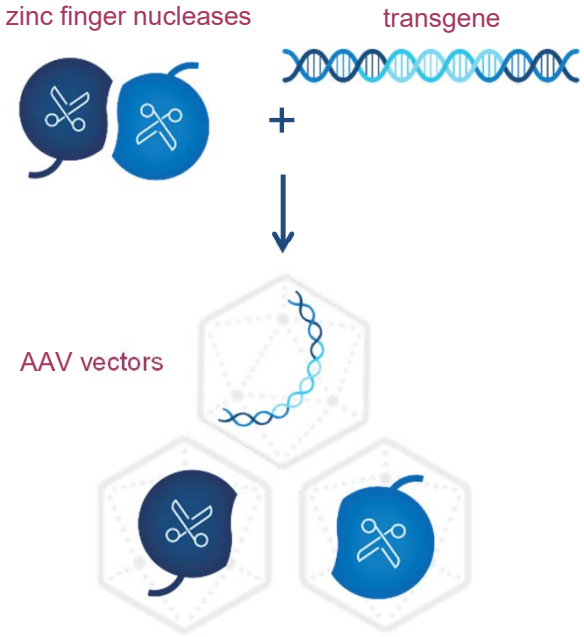
Experience with gene-edited cell therapy for HIV

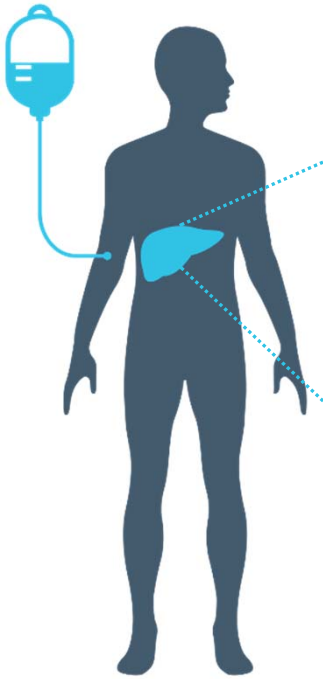
Area of Expertise	Achievements
T Cell Editing	**Robust GMP manufacturing of genome edited T cells** ▪ Growth and expansion of genome edited T cells for clinical use
Engraftment and Persistence	**Engraftment and persistence of edited T cells observed in every treated subject for the duration of observation (3+ yrs)** ▪ Significant improvement of CD4 count in HIV infected subjects
Safety of T Cell Therapy	**~100 HIV infected patients treated with autologous ZFN mediated (CCR5KO) T cells** ▪ Safe and well-tolerated – no product related serious adverse events ▪ No observation of ZFN immunogenicity
Viral Reservoir Reduction	**CCR5 edited T-cell persistence led to continual reduction of HIV reservoir over 3 yrs** ▪ Only intervention to demonstrate significant reduction of HIV reservoirs in chronically infected subjects
Impact HIV Viremia During TI	**Reduction of HIV viremia from historical viral set-point during treatment interruption**

In Vivo genome editing: harnessing the albumin locus in the liver

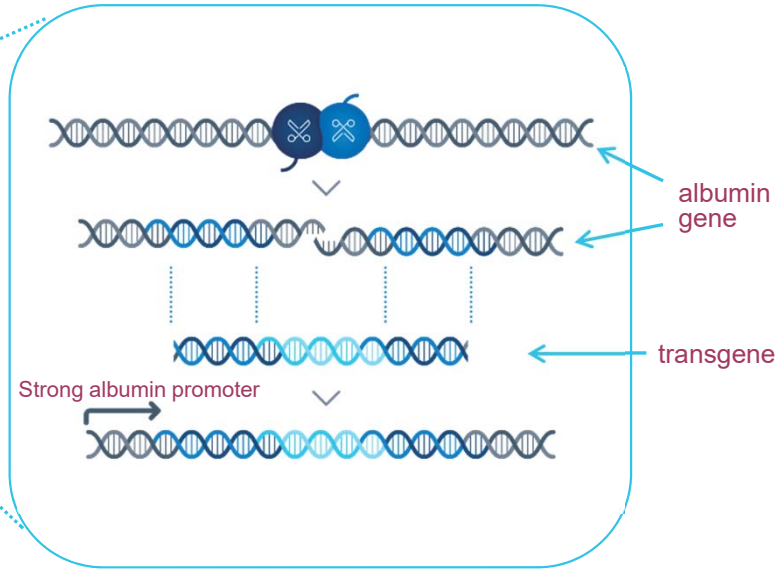
Packaging into AAV vectors



Delivery



In the liver



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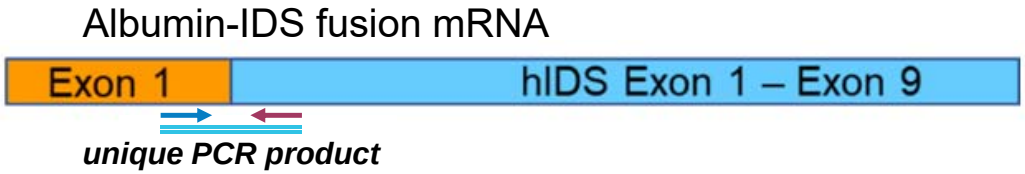
CHAMPIONS: Liver Biopsy to Assess Genome-Editing



- An RT-qPCR assay has been developed to identify the unique albumin-IDS mRNA transcript in liver biopsy tissue that is made after integration of the IDS gene into the targeted albumin locus
- Results were positive in both Cohort 2 subjects who received 1e13vg/kg dose, Cohort 3 results are pending

Week 24 Results	Cohort 1		Cohort 2		Cohort 3	
Subject	**1**	**2***	**3**	**4**	**5***	**6**
Integration Assay	-	*n/a*	+	+	*n/a*	pend

*no results available as liver biopsy procedure contraindicated due to anticoagulation therapy

- A less sensitive genomic DNA assay using MiSeq to detect insertions/deletions (“indels”) at target site in the albumin gene was negative in all samples tested (lower limit of quantitation ~ 1 in 1,000 genomes)

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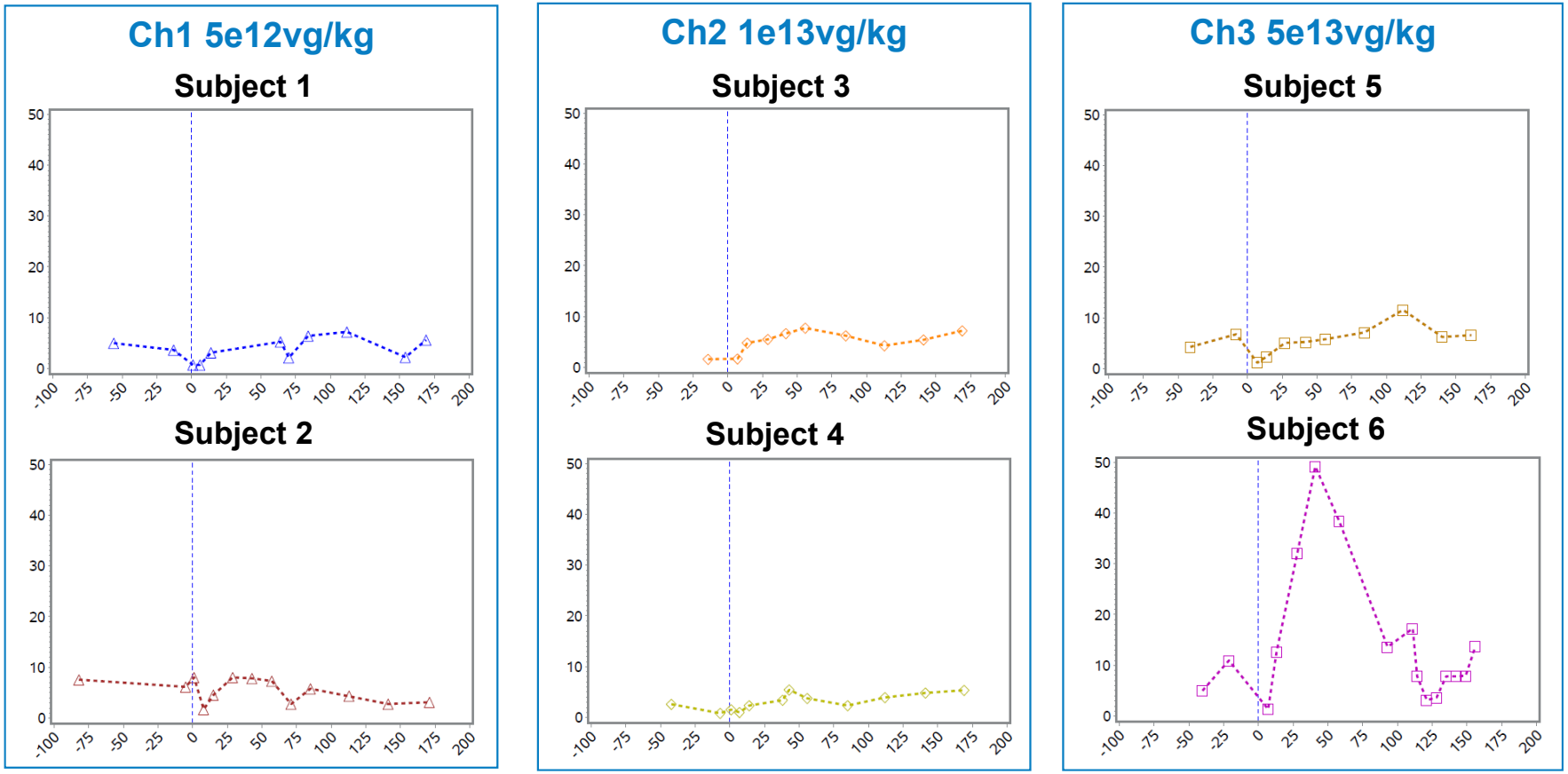
Data cut-off date: 10 JAN 2019

CHAMPIONS: Plasma IDS Activity up to Week 24



Highly-sensitive qualified fluorometric assay with lower limit of quantitation=0.78, samples obtained <96h post-ERT excluded
Reference ranges (nmol/mL/hr): Unaffected: 82-200 Baseline MPS II (>96h post-ERT): estimated 0-10

CHAMPIONS: Study Drug-Related Adverse Events (AEs)

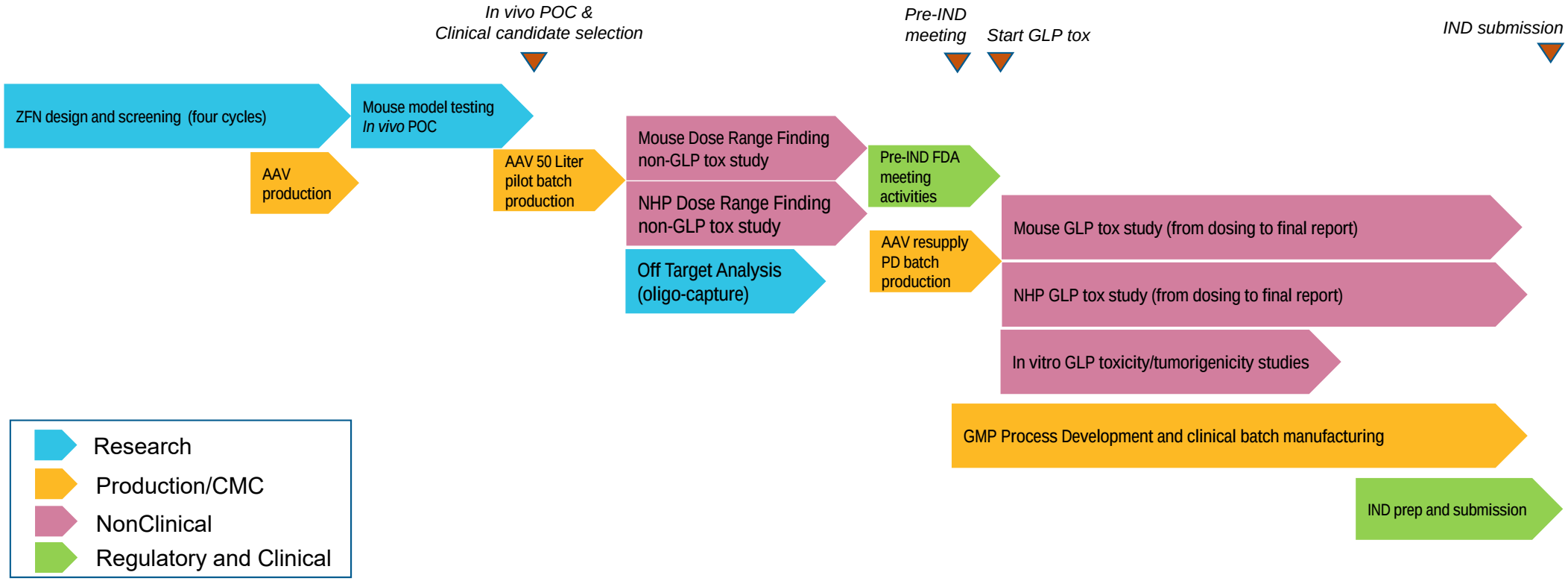
- Study drug-related AEs were mild or moderate and all resolved

MedDRA Preferred Term Severity	Cohort 1 (N=2) n [T]	Cohort 2 (N=2) n [T]	Cohort 3 (N=4) n [T]	Overall (N=8) n [T]
Any Event	2 [5]	1 [5]	2 [8]	5 [18]
Grade 1-Mild	2 [5]	1 [5]	2 [6]	5 [16]
Grade 2-Moderate	-	-	1 [2]	1 [2]
Pruritus	1 [2]	-	1 [1]	2 [3]
Flushing	-	1 [1]	1 [1]	2 [2]
Erythema	-	1 [2]	-	1 [2]
Transaminases increased	-	-	1 [3]	1 [3]
Alanine aminotransferase increased	-	1 [1]	-	1 [1]
Aspartate aminotransferase increased	-	1 [1]	-	1 [1]
Asthenia	1 [1]	-	-	1 [1]
Cold sweat	1 [1]	-	-	1 [1]
Dizziness	1 [1]	-	-	1 [1]
Dysgeusia	-	-	1 [1]	1 [1]
Headache	-	-	1 [1]*	1 [1]
Pyrexia	-	-	1 [1]*	1 [1]

N= Total number of subjects in each treatment group, n= number of subjects in each SOC, [T]= total number of adverse events. *Grade 2 event reported

Data cut-off date: 20 DEC 2018

Pathway to *in vivo* genome editing IND



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The ultimate goal is to edit any gene in any tissue

Enzyme Replacement Therapy

- Burden of disease
- Expensive chronic Infusions
- Does not address key symptoms / stop disease progression

Gene Therapy

- Stable production of missing enzyme
- Non-integrating approach, risk of wash-out
- Limited by current delivery capabilities

Genome Editing

- Stable production of missing enzyme
- Integration into genome, permanent solution
- Treat pediatric patients (best benefit)
- Limited by current delivery capabilities

Gene Editing

The ultimate goal for genomic medicines:

To precisely and specifically edit the disease at the point of origin

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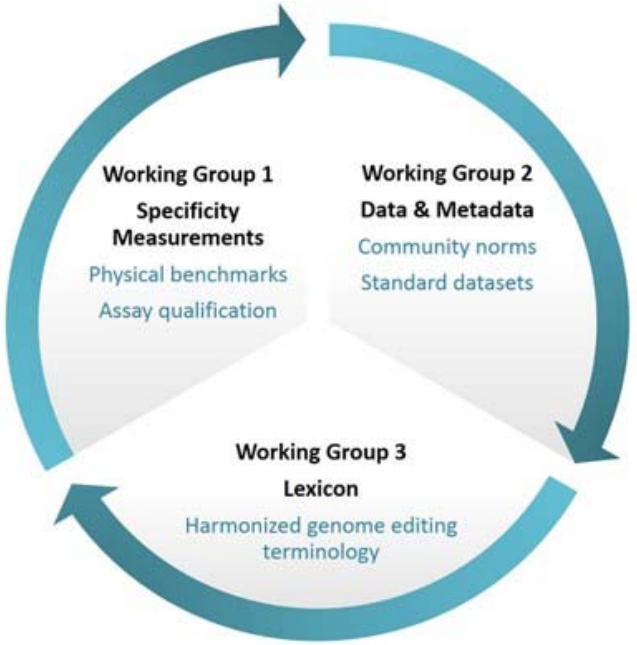
NIST Genome Editing Consortium: an opportunity to inform industry & regulatory standards for the evaluation of genome editing

1. Specificity measurements
   - Evaluate existing methods of on- & off-target quantification.
   - Physical DNA controls to benchmark & validate NGS pipelines.
2. Data & Metadata
   - Consistent data formats. Tools to benchmark data analysis.
   - Types of experimental details needed to evaluate NGS assays.
3. Lexicon
   - Uniform terminology for genome editing.



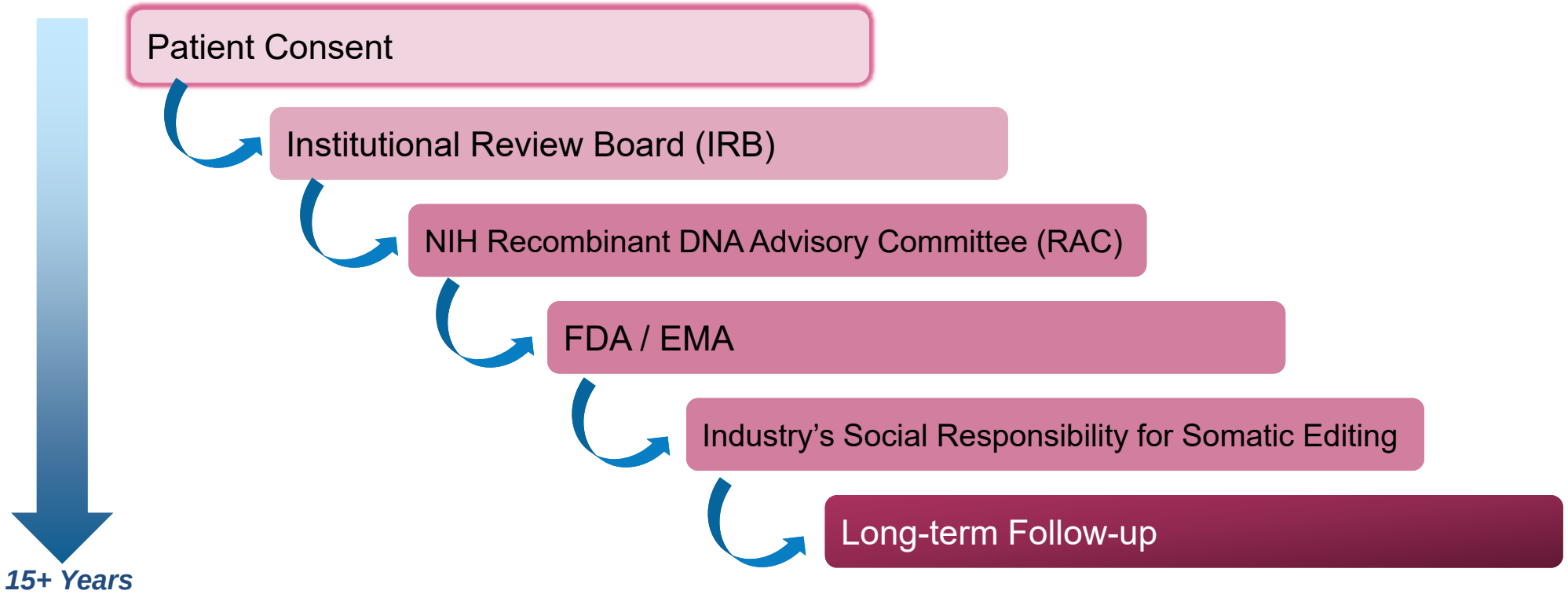
Focus on safety

- Acute safety issues: Viral reactions, hepatitis, etc.
- Long-term safety issues: Unknown and potentially oncogenic effects
  off-target cleavage
  - Sangamo applies state-of-the-art analyses to identify any potential off-targets
  - Technologists have discovered new approaches to reduce or eliminate potential off-targets

Focus on ethics

- Sangamo sponsoring bioethics forum with NYAS and ge^{2}p^2 global foundation
- In-house Fellows program
  - Somatic, *in utero,* germline
  - Long-term follow-up (consent for life)
  - Registries and transparency
  - Challenges of informed consent in pediatric rare disease clinical trials

Layers of protection in the development of genomic medicines

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