Engineering Genome Edited Cellular Therapies: A Biologic Biologic

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Potential Conflicts of Interest

CRISPR Therapeutics:	Equity
Allogene Therapeutics:	Equity and SAB
Graphite Bio:	Equity and BoD
Versant Ventures:	Advisor
Ziopharm:	SAB

Managed through Stanford in accordance with their conflict of interests policy.

History of Medicine: Innovative Medicines Result in New Cures

Sanitation/Clean Water

Antisepsis/Anesthesia

Vaccines

Small Molecules

Biologics
(Enzymes and Antibodies)

Cell and Gene Medicines

Microbiome Manipulation

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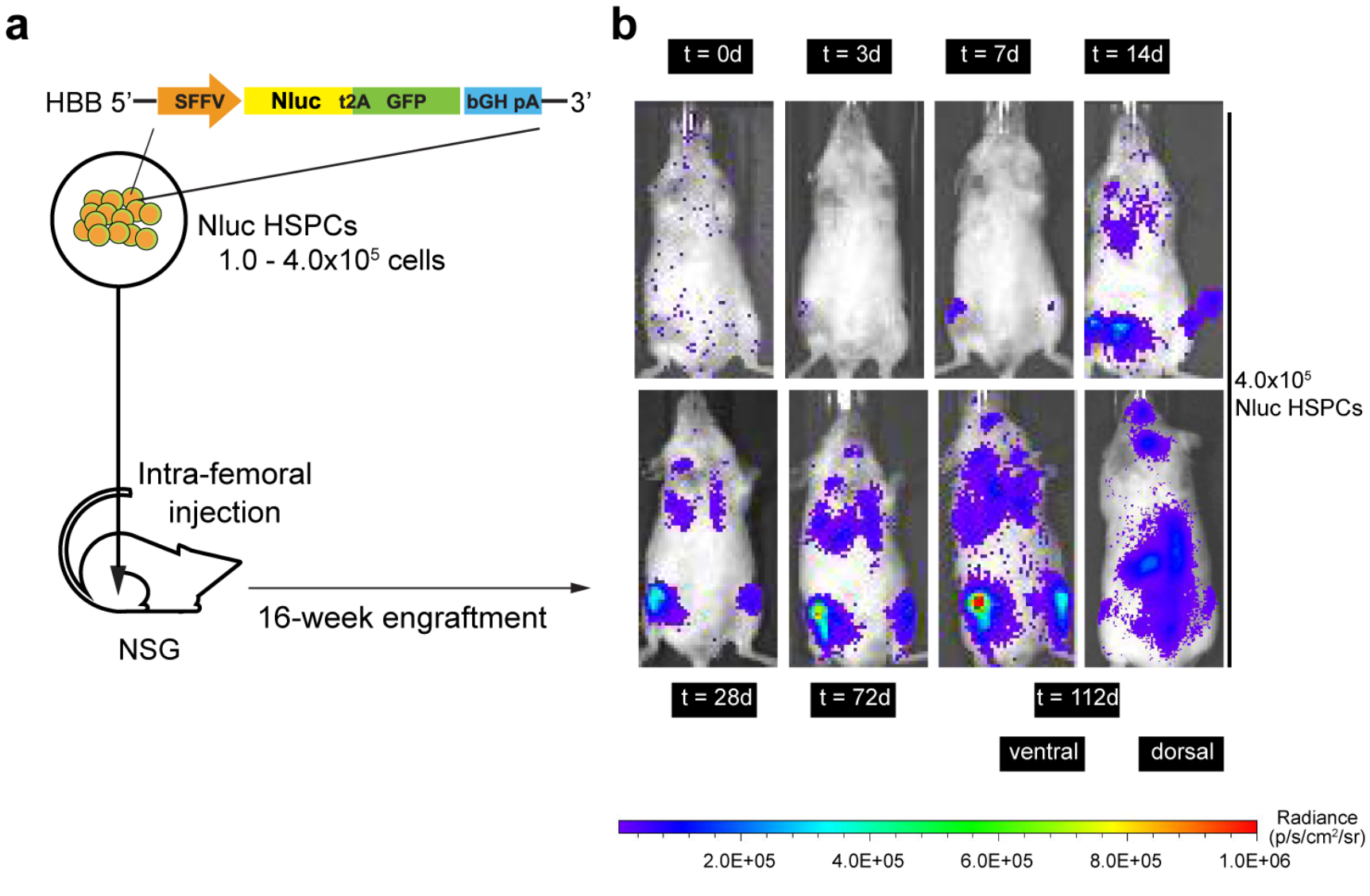
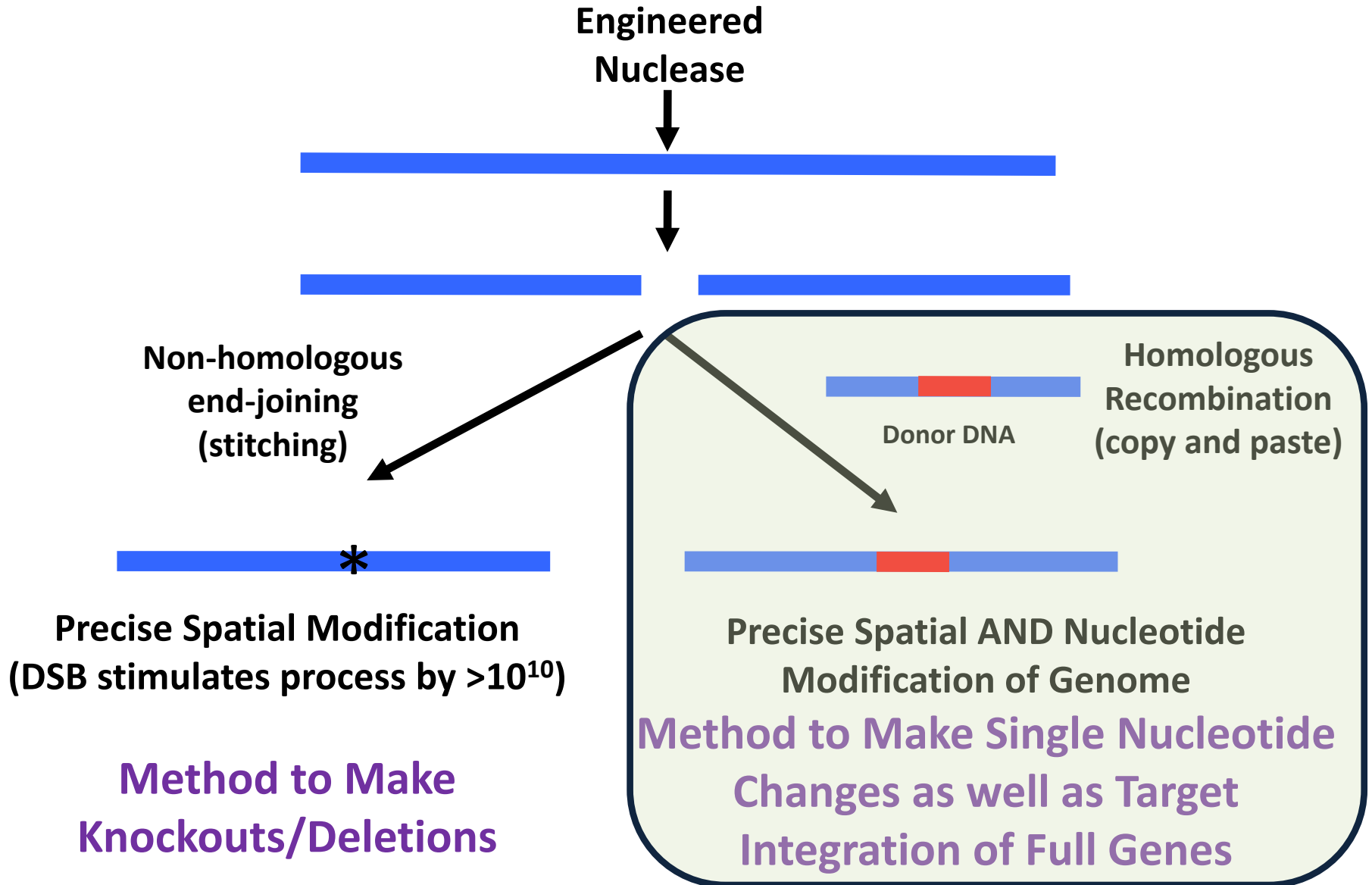
"Living Drugs"
Different PK/PD
Migrate, Divide,
Respond…

A Visual Example of the Different PK/PD of Genome Edited Engineered Hematopoietic Stem Cells

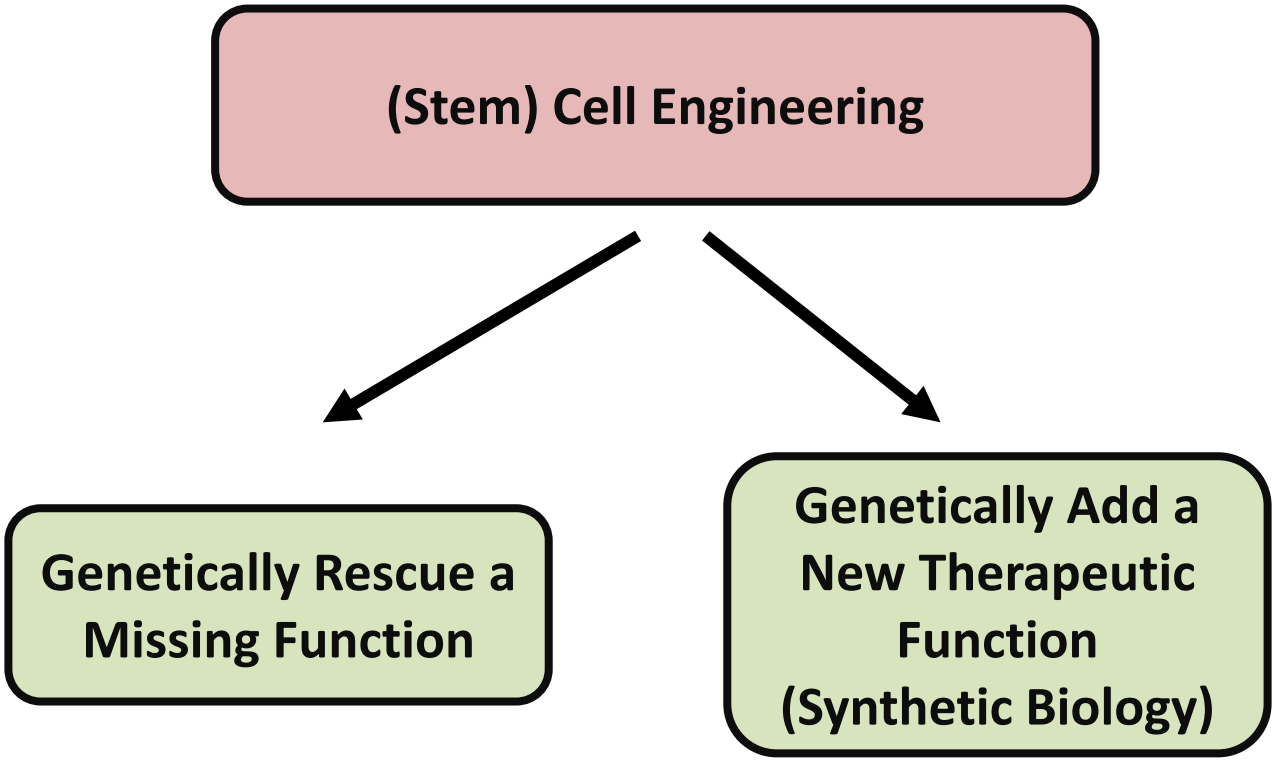


Hypothesis: Precision engineering will enable more effective, safer cellular therapies which will enable more patients with a wider variety of diseases to be treated or even cured

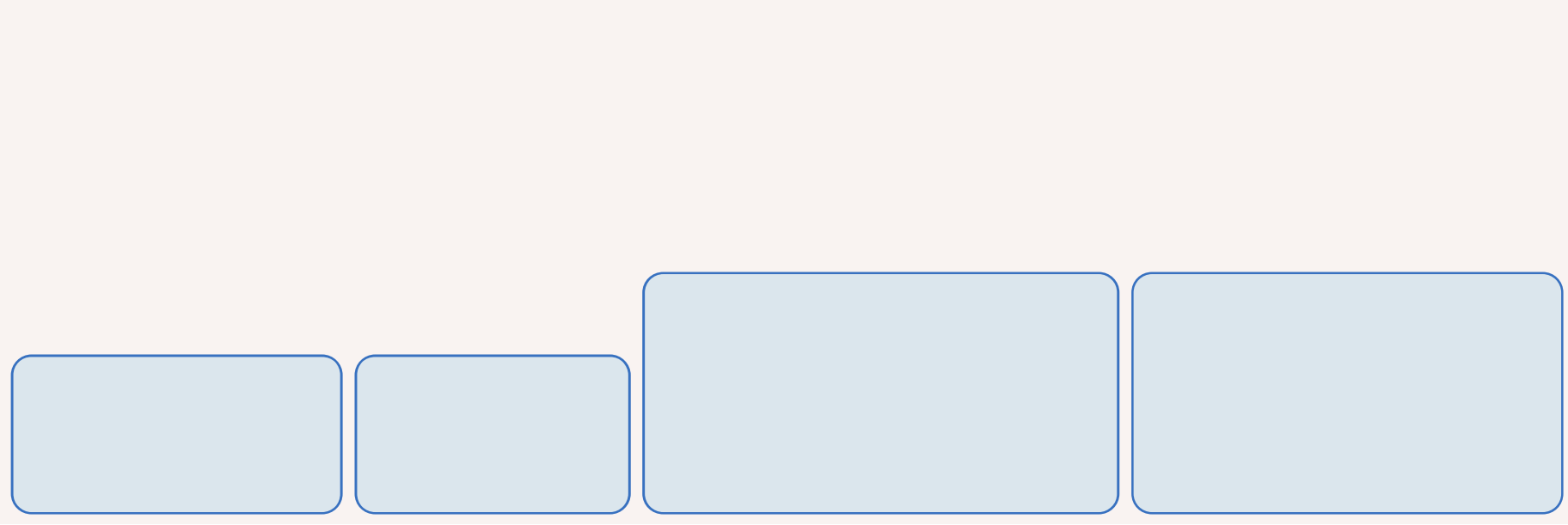
Genome Editing Provides a Precise Method of Genetically Engineering Cells



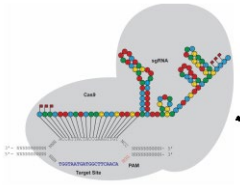
Genome Engineering to Engineer Therapeutic Cells

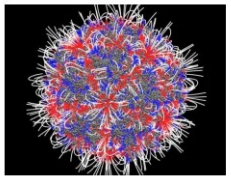


Multiple Uses of Homologous Recombination Based Editing

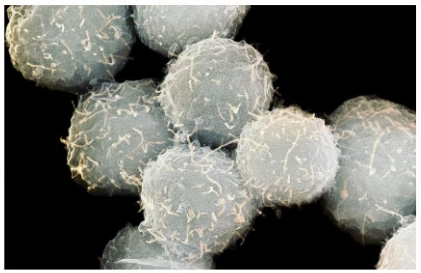


Gene Correction for Sickle Cell Disease

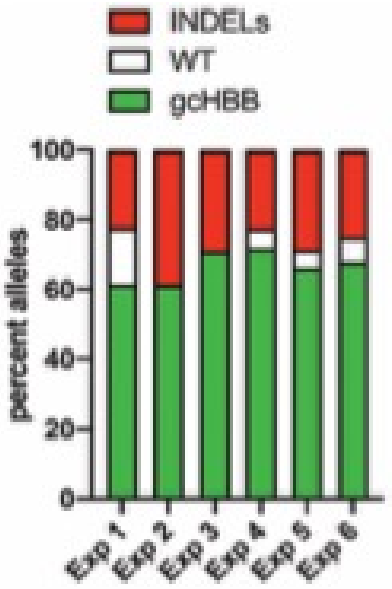


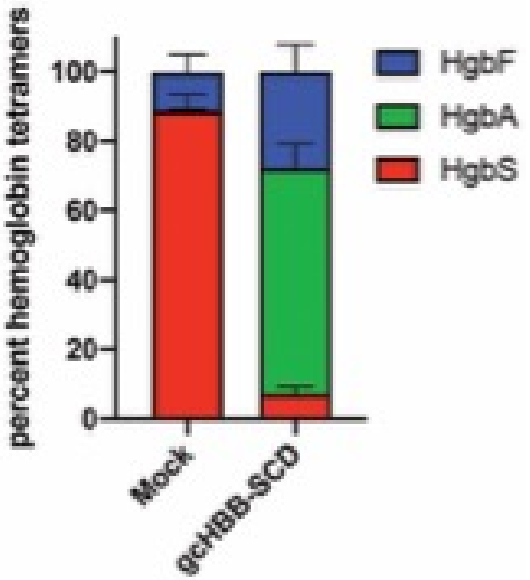


Recombinant Adeno-Associated Virus (AAV6) (non-integrating)

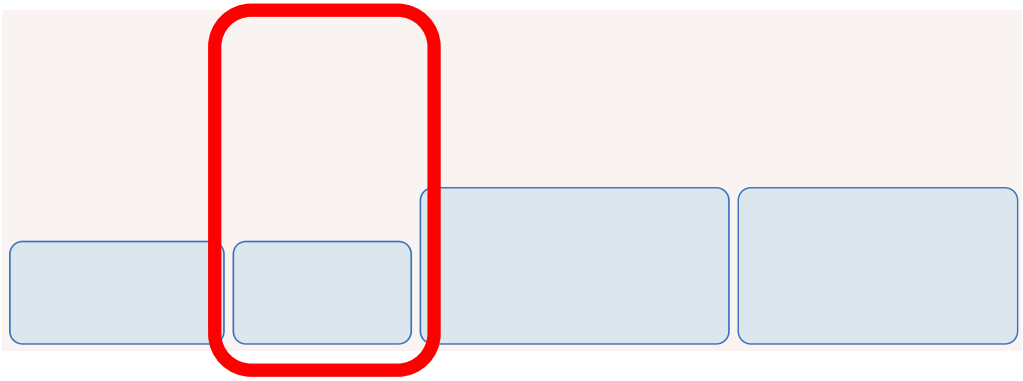


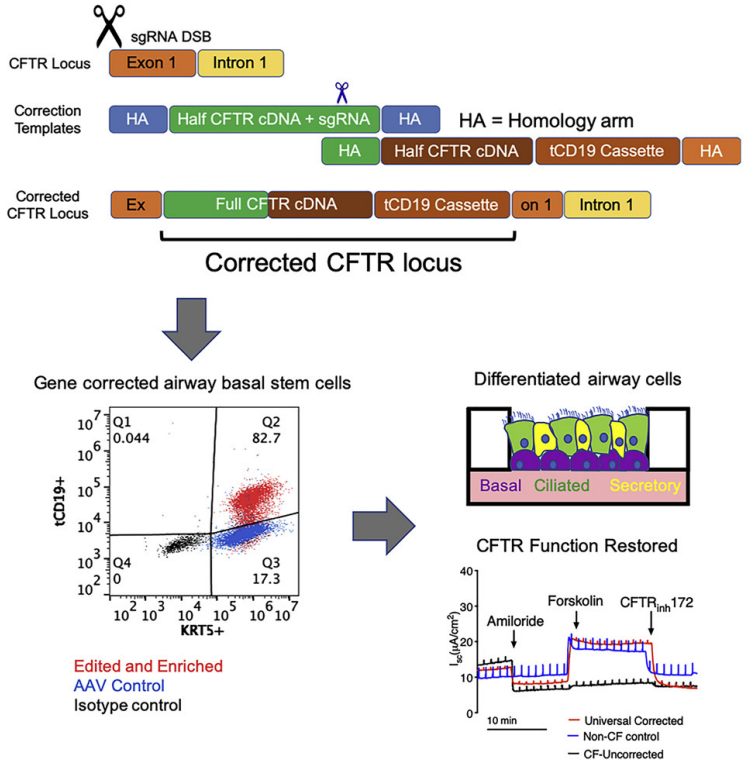
Bak, Dever et al Nature Protocols (2018)





Functional Gene Correction: Near Universal Gene Correction Strategy for Genetic Diseases Caused by Multiple Mutations





Molecular Therapy, 2021

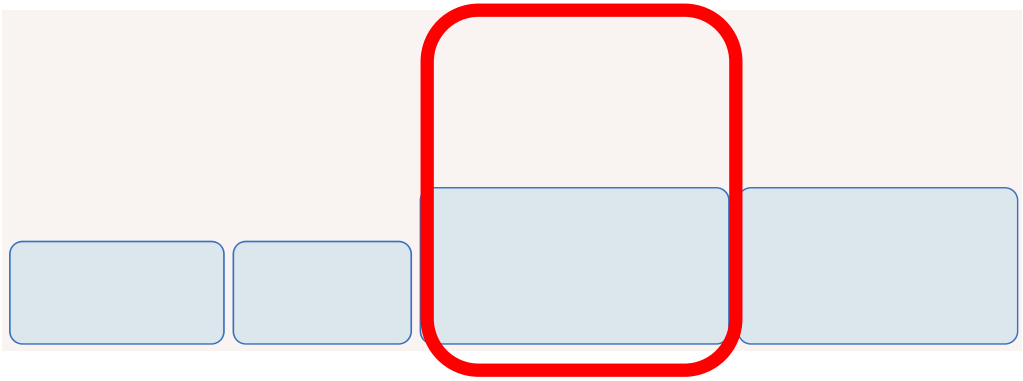
Targeted replacement of full-length CFTR in human airway stem cells by CRISPR-Cas9 for pan-mutation correction in the endogenous locus

Sriram Vaidyanathan,[1] Ron Baik,[1] Lu Chen,[2,8,9] Dawn T. Bravo,[3] Carlos J. Suarez,[4] Shayda M. Abazari,[1] Ameen A. Salahudeen,[2] Amanda M. Dudek,[1] Christopher A. Teran,[3] Timothy H. Davis,[5] Ciaran M. Lee,[5] Gang Bao,[5] Scott H. Randell,[6] Steven E. Artandi,[2,8,9] Jeffrey J. Wine,[7] Calvin J. Kuo,[2] Tushar J. Desai,[2] Jayakar V. Nayak,[3] Zachary M. Sellers,[1] and Matthew H. Porteus[1]

Other Examples:

- SCID-X1
- RAG2
- WAS
- CGD
- PKD
- EB

Engineering Cells to Deliver Therapeutic Proteins to All Tissues of the Body (including the brain)

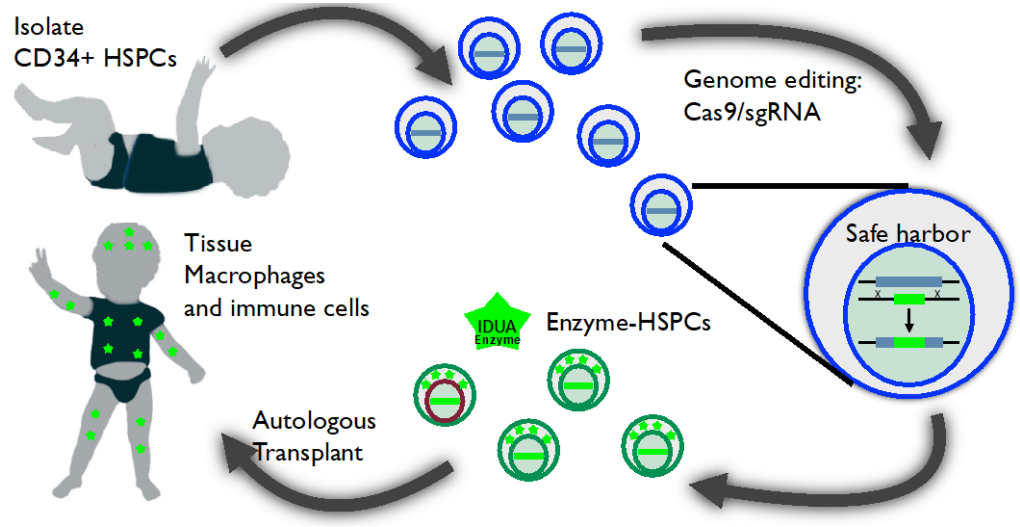


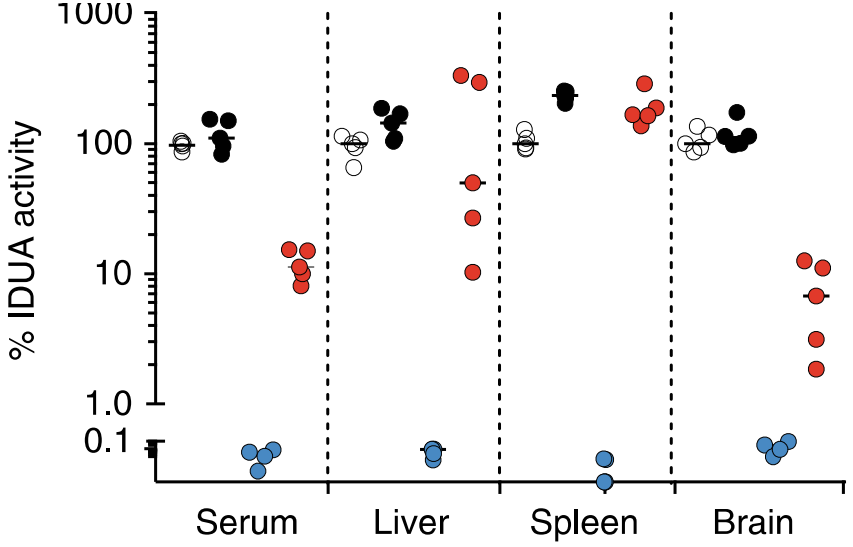
ARTICLE

https://doi.org/10.1038/s41467-019-11962-8 OPEN

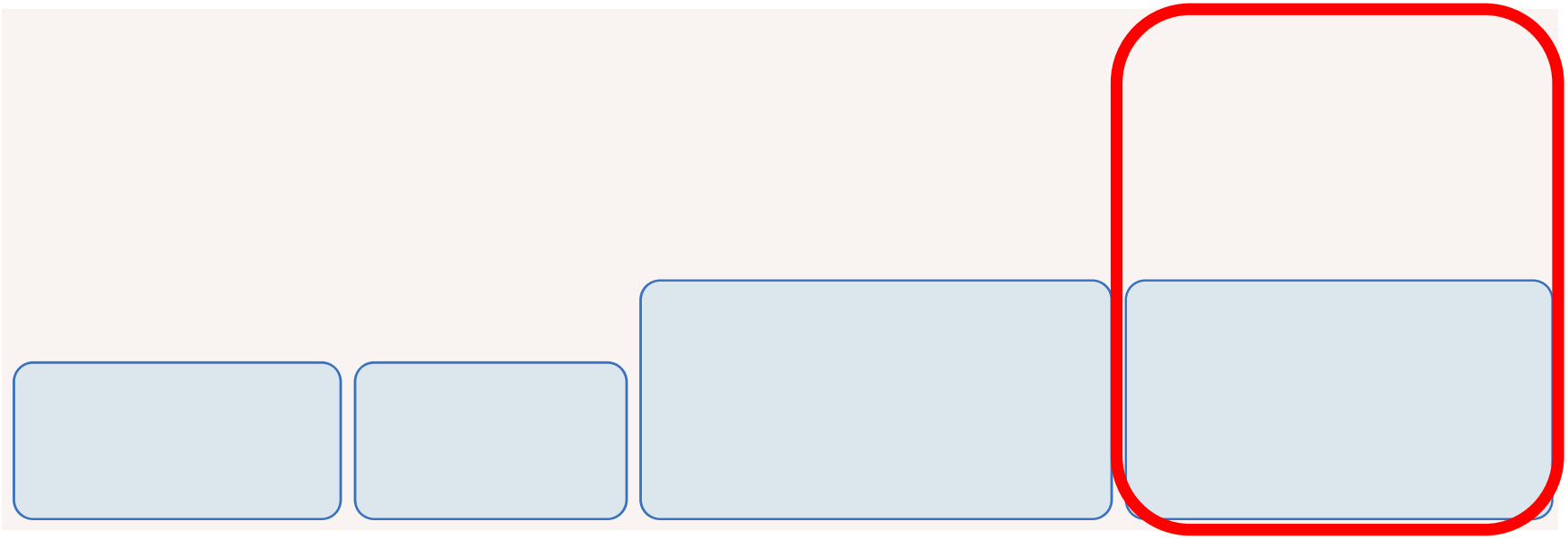
Human genome-edited hematopoietic stem cells phenotypically correct Mucopolysaccharidosis type I

Natalia Gomez-Ospina[1], Samantha G. Scharenberg[1], Nathalie Mostrel[1], Rasmus O. Bak[2,3], Sruthi Mantri[1], Rolen M. Quadros[4], Channabasavaiah B. Gurumurthy[4,5], Ciaran Lee[6], Gang Bao[6], Carlos J. Suarez[7], Shaukat Khan[8], Kazuki Sawamoto[8], Shunji Tomatsu[8], Nitin Raj[9], Laura D. Attardi[9,10], Laure Aurelian[11,12] & Matthew H. Porteus[1]





Repurposing the Genome: Knocking a Therapeutic Gene into Another Gene



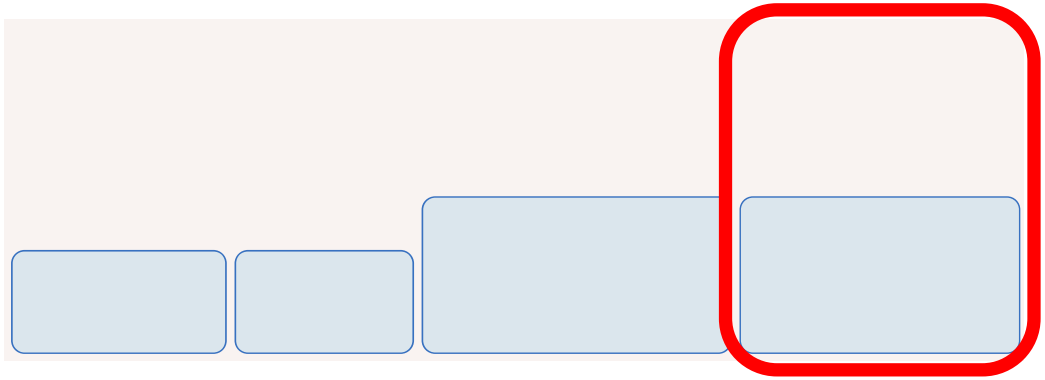
Targeting a CAR to the *TRAC* locus with CRISPR/Cas9 enhances tumour rejection

Justin Eyquem[1]*, Jorge Mansilla-Soto[1]*, Theodoros Giavridis[1], Sjoukje J. C. van der Stegen[1], Mohamad Hamieh[1], Kristen M. Cunanan[2], Ashlesha Odak[1], Mithat Gönen[2] & Michel Sadelain[1]

Gene replacement of α-globin with β-globin restores hemoglobin balance in β-thalassemia-derived hematopoietic stem and progenitor cells

M. Kyle Cromer[1,9], Joab Camarena[1,9], Renata M. Martin[1], Benjamin J. Lesch[1], Christopher A. Vakulskas[2], Nicole M. Bode[2], Gavin Kurgan[2], Michael A. Collingwood[2], Garrett R. Rettig[2], Mark A. Behlke[2], Viktor T. Lemgart[1], Yankai Zhang[3], Ankush Goyal[3], Feifei Zhao[4,5], Ezequiel Ponce[1], Waracharee Srifa[1], Rasmus O. Bak[6,7], Naoya Uchida[8], Ravindra Majeti[4,5], Vivien A. Sheehan[3], John F. Tisdale[8], Daniel P. Dever[1]✉ and Matthew H. Porteus[1,5]✉

Creating Lineage Specific Control for Enhanced Safety



ARTICLE

>5-log kill of Pluripotent Cells

No effect on differentiated progeny

Optimism about Genome Edited Cells As the Next Generation Biologics

Precision of Genome Editing Can Enhance Potency and Safety and Potentially Allow Use in More Diseases and More Patients

Thank You!

(for your attention and the opportunity to present our work)

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Gang Bao/Ciaran Lee (Rice)
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