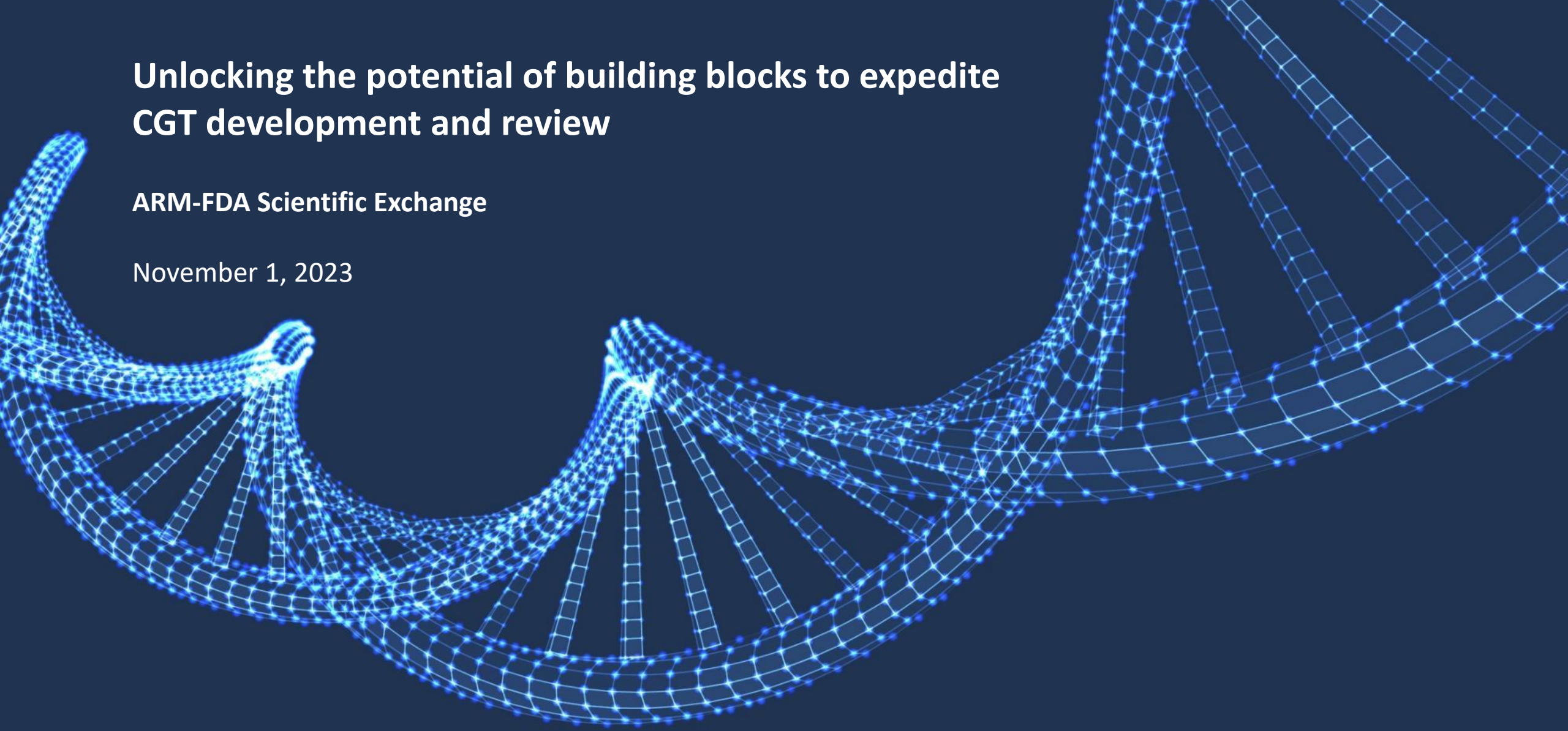
Unlocking the potential of building blocks to expedite CGT development and review

ARM-FDA Scientific Exchange

November 1, 2023



SHAPING MARKETS

GALEN ATLANTICA

CO-CREATING HEALTH

Agenda (I)

Set up
9 – 9:30

- **Galen/Atlantica opening:** Introductions, objectives, ground rules
- **Peter Marks (FDA):** Pursuing the long tail of rare diseases, FDA objectives
- **Mike Lehmicke (ARM):** Opening remarks
- **Tim Charlebois (NIIMBL):** Opening remarks

Problem definition & impact
9:30-10:30

Phillip Kurs (FDA)

- Statutory considerations shaping the Designation Program for Platform Technologies

Fyodor Urnov

- Development approaches and risk-benefit for an ‘n of 1’ therapy

Galen/Atlantica synthesis of opportunities from pre-meeting discussions

- Introducing building blocks
- Vehicles to deliver building blocks, and evidentiary requirements

What are the limitations of cell and gene therapy without building blocks? What is the role of every stakeholder in promoting standardization?

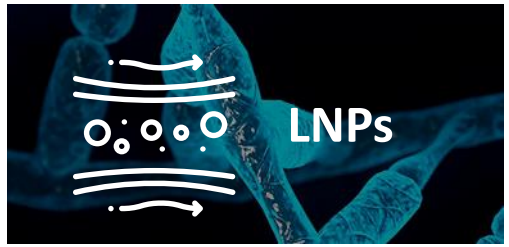
- *Group discussion*

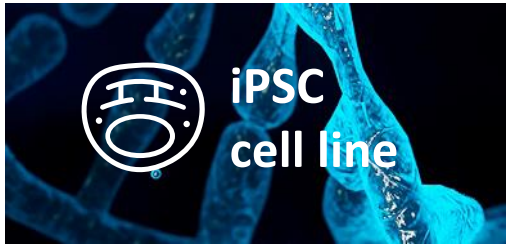
Break

Consideration of building blocks
10:30 – 1:00

Technology-specific breakout groups to test potential building blocks

- ***Describe****:* What element of development, manufacture or delivery can be re-used across programs?
- ***Defend:*** What is the case for this element as a building block? Contrarian views?
- ***Define:*** What are the measurable parameters that define that building block?
- ***Bound:*** What specific elements (e.g., mfg’ing) of a building block must be fixed across applications?
- ***Disseminate:*** What is the vehicle for the developer or industry to reference a building block?
- ***Value:*** What steps in development can be omitted or done more efficiently? What is the value?





Agenda (II)

Lunch (1:00 pm)

Case study outcomes, implications
1:45 – 3:30

Individual case study teams present findings back to group

- Developer perspectives
- FDA evidence requirements
- Discussion

Common themes across cases studies

- What defines a robust building block?
- On what aspects of drug development should companies compete, and where are pre-competitive approaches needed?
- What do developers need to do differently to introduce and validate building blocks? What does the FDA need to do differently?

Break (if needed)

Next steps and closing
3:30 – 4:00

- **Peter Marks:** Closing reflections and take-aways
- **Galen/Atlantica:** Roadmap for progress
- **Close**

Platform Technologies Designation Program

CBER Regulated Products

Phillip Kurs, J.D.

Introduction in Prevent Pandemics Act

- Designation program created as part of 2022 PREVENT Pandemics Act
- Section 2503 of the PREVENT Pandemics Act amended the Federal Food Drug, and Cosmetic Act to add “Sec 506K Platform Technologies”

Platform Technology Designation Criteria

- "A platform technology incorporated within or utilized by a . . . biological product is eligible for designation as a designated platform technology under this section if—
  - (1) the platform technology is incorporated in, or utilized by, . . . a biological product licensed under section 351 of the Public Health Service Act;
  - (2) preliminary evidence . . . demonstrates that the platform technology has the potential to be incorporated in, or utilized by, more than one drug without an adverse effect on quality, manufacturing, or safety; and
  - (3) data or information . . . indicates that incorporation or utilization of the platform technology has a reasonable likelihood to bring significant efficiencies to the drug development or manufacturing process and to the review process."

Platform Technology definition

- "Definitions.—For purposes of this section:
  - (1) The term 'platform technology' means a well-understood and reproducible technology . . . that the Secretary determines to be appropriate, that the sponsor demonstrates—
    - (A) is incorporated in or utilized by a drug or biological product and is essential to the structure or function of such drug or biological product;
    - (B) can be adapted for, incorporated into, or utilized by, more than one drug or biological product sharing common structural elements; and
    - (C) facilitates the manufacture or development of more than one drug or biological product through a standardized production or manufacturing process or processes."

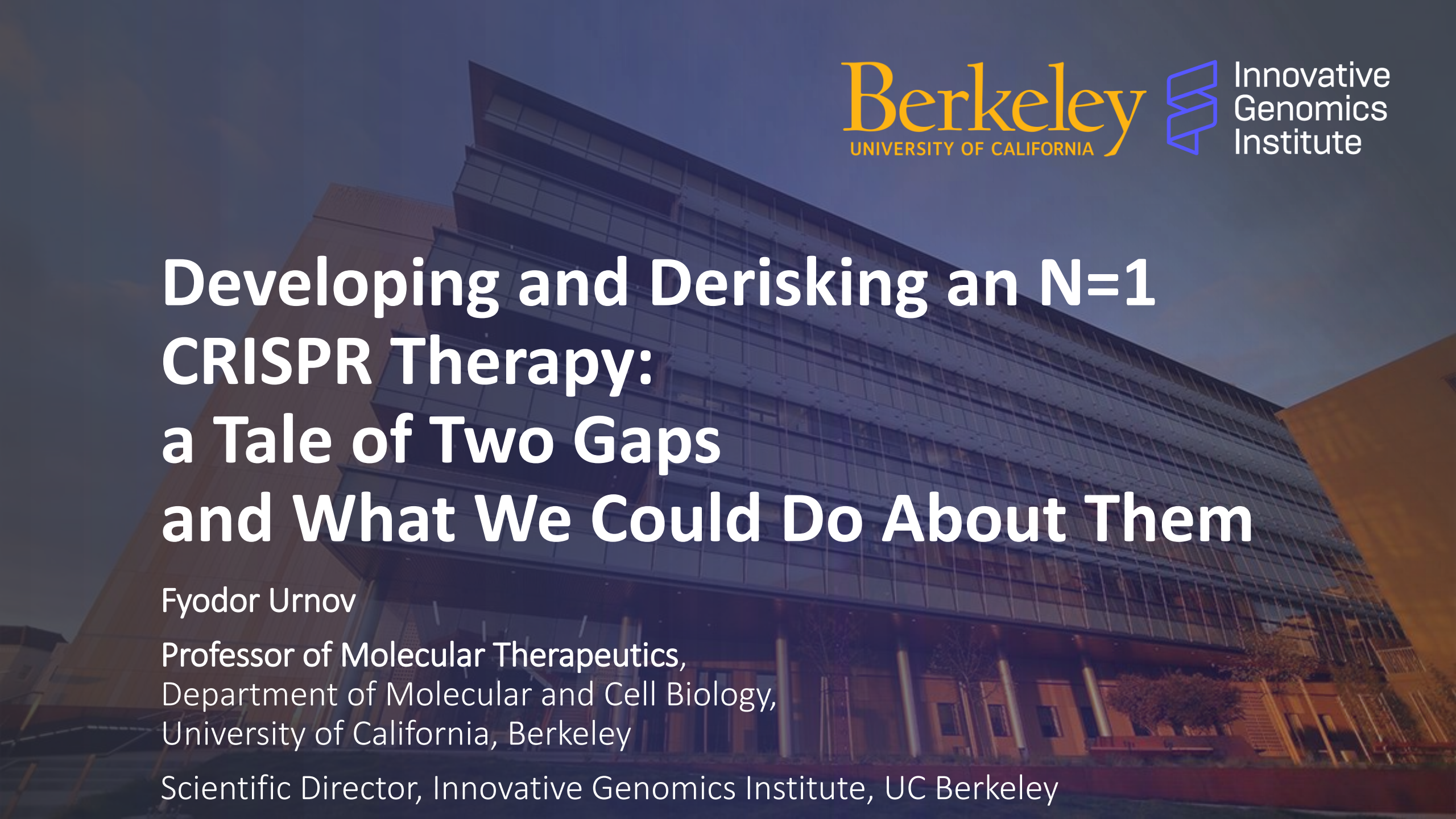
Rule of Construction

- "Nothing in this section shall be construed to—
  - alter the authority of the Secretary to ... license biological products pursuant to section 351 of the Public Health Service Act, including standards of evidence and applicable conditions for approval or licensure under the applicable Act; or
  - confer any new rights with respect to the permissibility of a sponsor of an application for a . . . biological product referencing information contained in another application submitted by the holder of . . . a license under section 351(a) of the Public Health Service Act.''

Knowledge and Control of Manufacturing Process

- "As a scientific matter [for 351(a) BLAs] . . . a license holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license."
  - Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry (April 2015)


FDA
U.S. FOOD & DRUG
ADMINISTRATION



Developing and Derisking an N=1 CRISPR Therapy: a Tale of Two Gaps and What We Could Do About Them

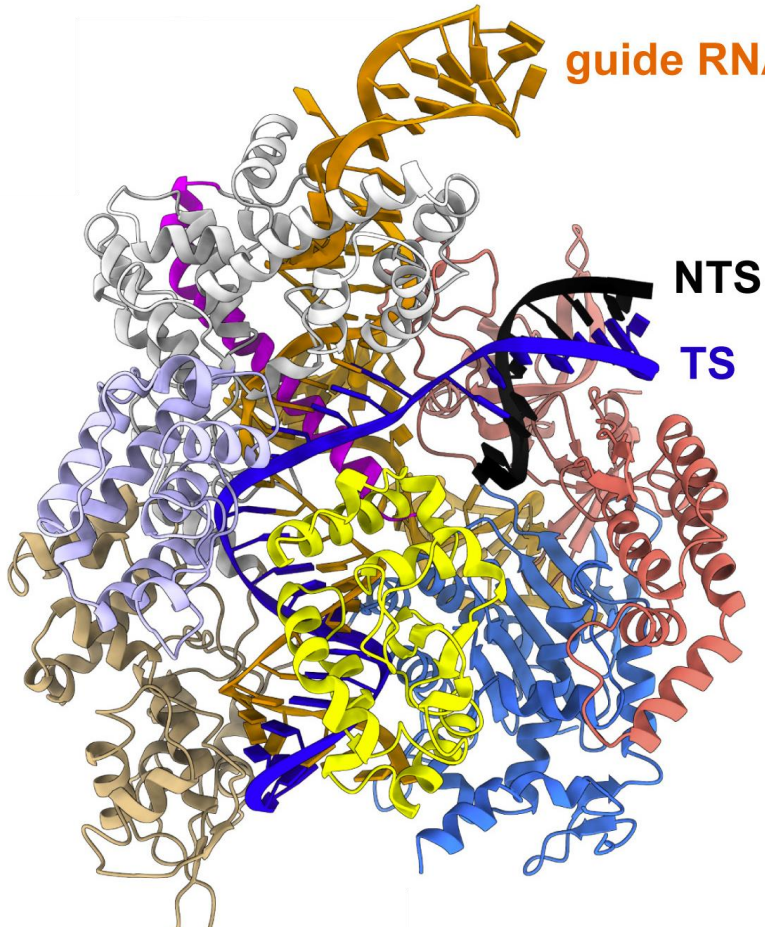
Fyodor Urnov

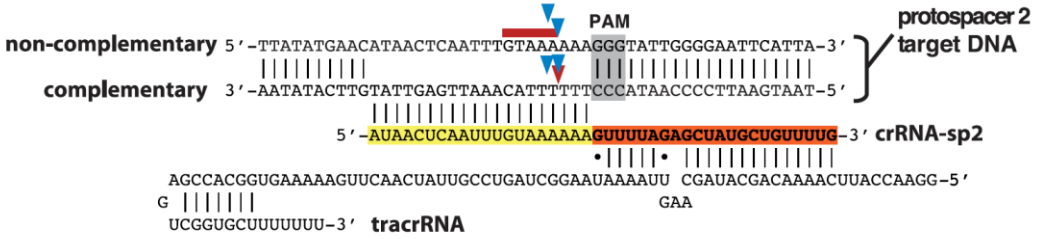
Professor of Molecular Therapeutics,
Department of Molecular and Cell Biology,
University of California, Berkeley

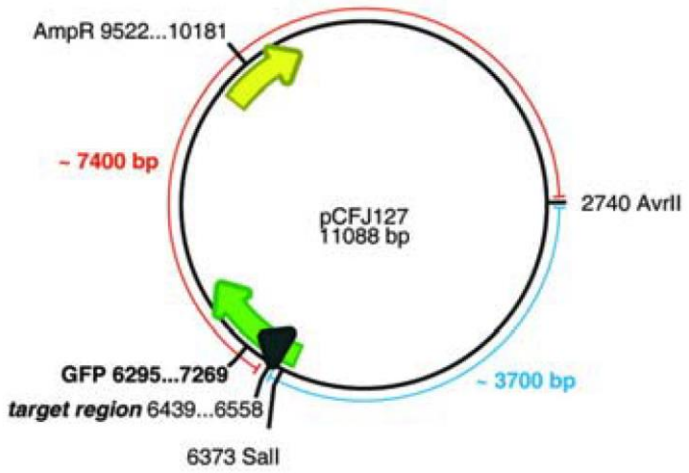
Scientific Director, Innovative Genomics Institute, UC Berkeley

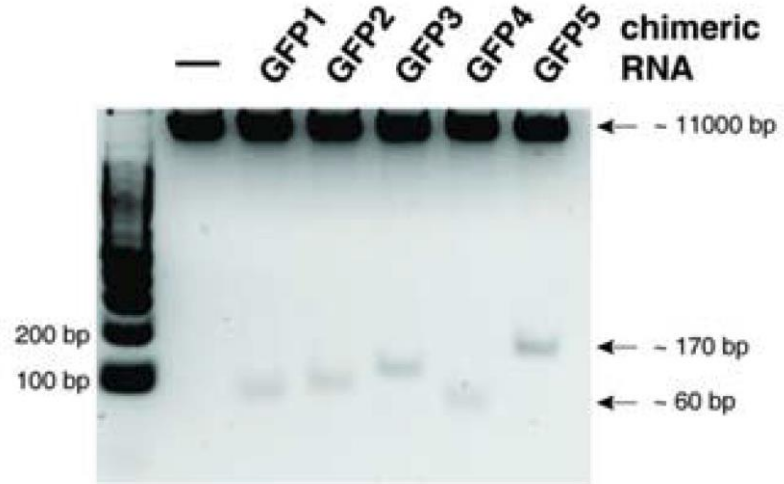
Fyodor Urnov: disclosures

- Cimeio Therapeutics: SAB chair, paid advisor, hold equity
- Ionis Pharmaceuticals: paid advisor
- Tune Therapeutics: scientific co-founder, paid advisor, hold equity
- Vertex Pharmaceuticals: paid consultant on exa-cel program









Jinek et al *Science* (2012) 337: 816-821 | Pacesa et al *Cell* (2022) 185: 4067-4081.

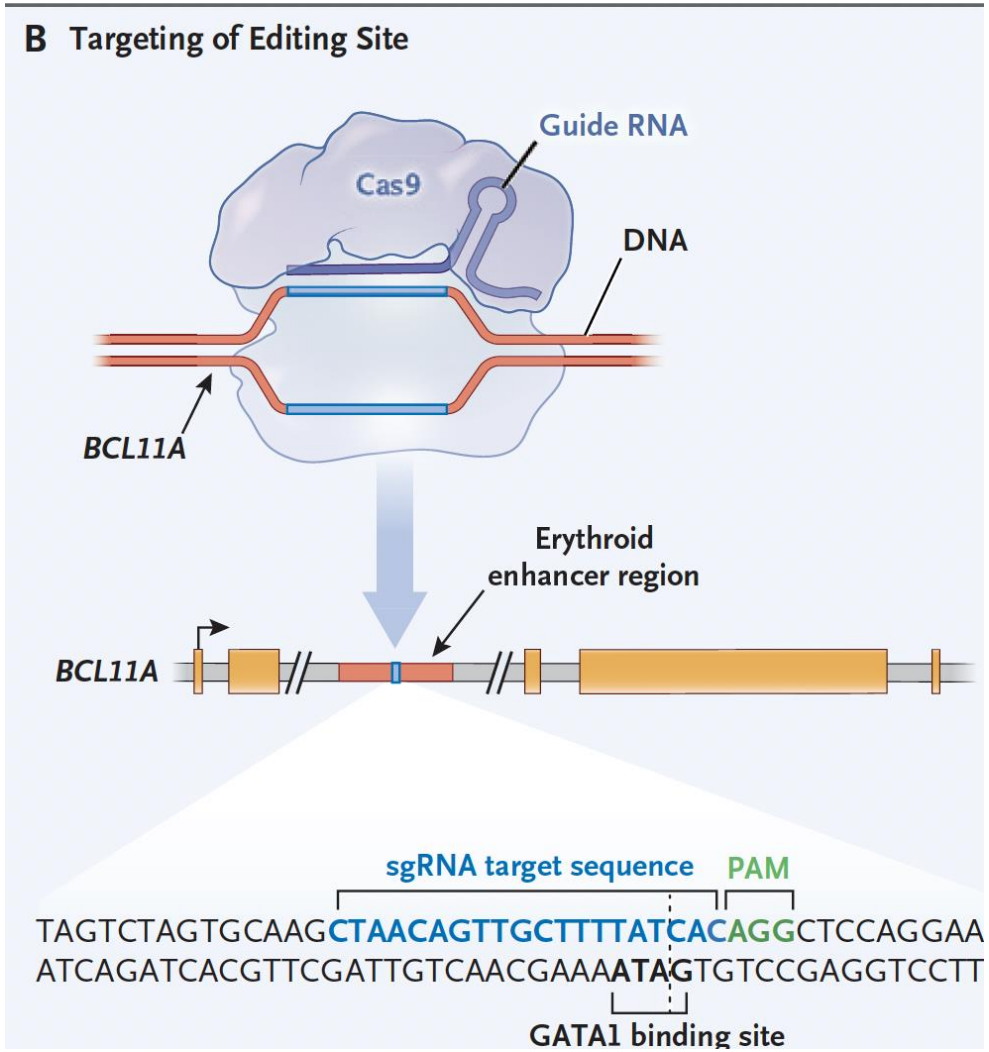
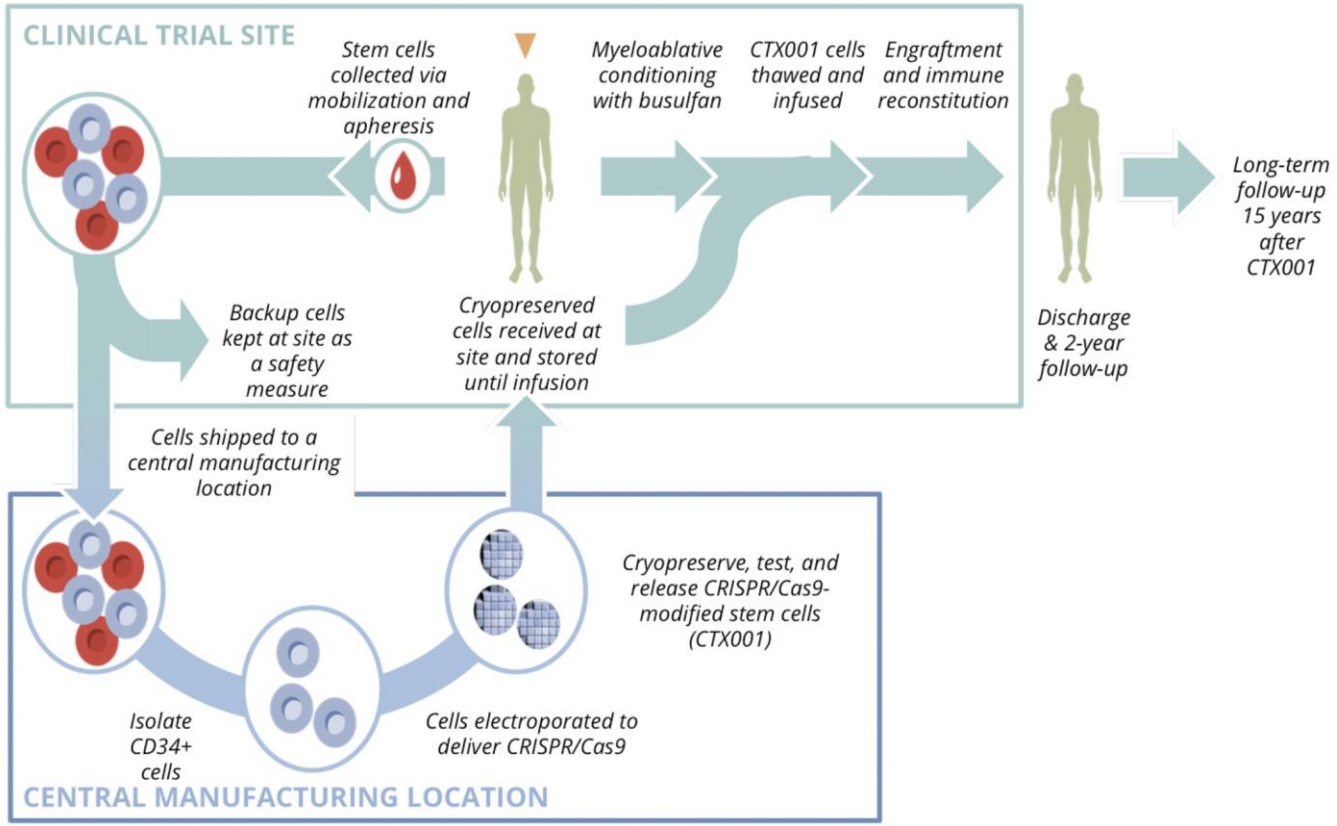
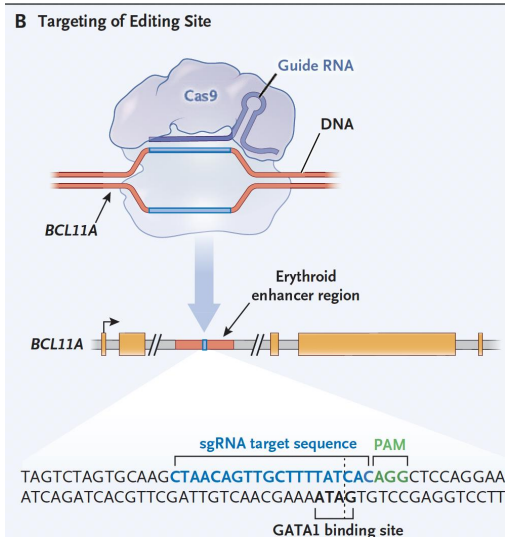


Figure S2. Schematic Representation of the CTX001 Manufacturing and Infusion Process



Frangoul et al NEJM 2021



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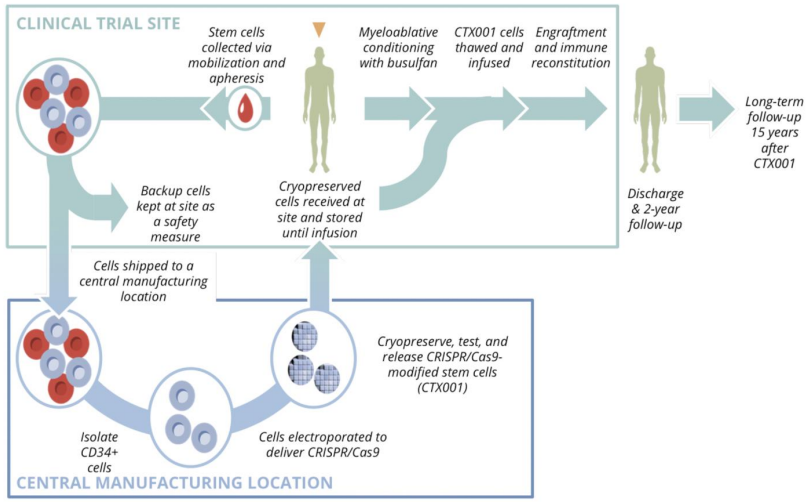
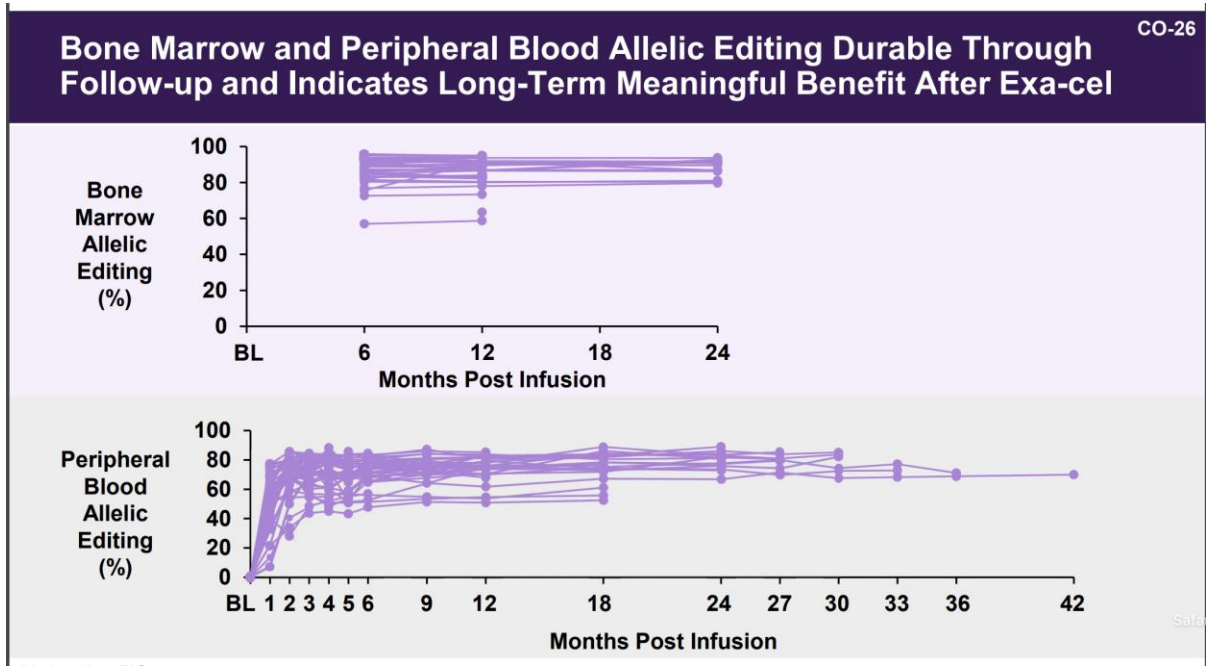
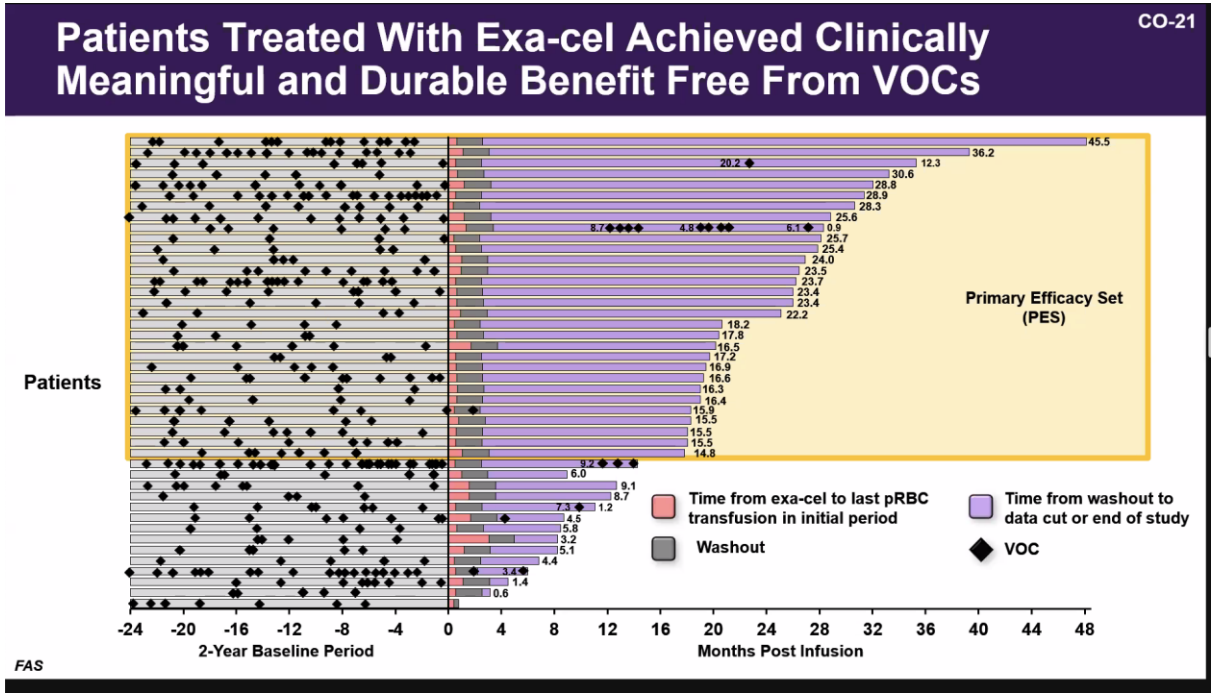


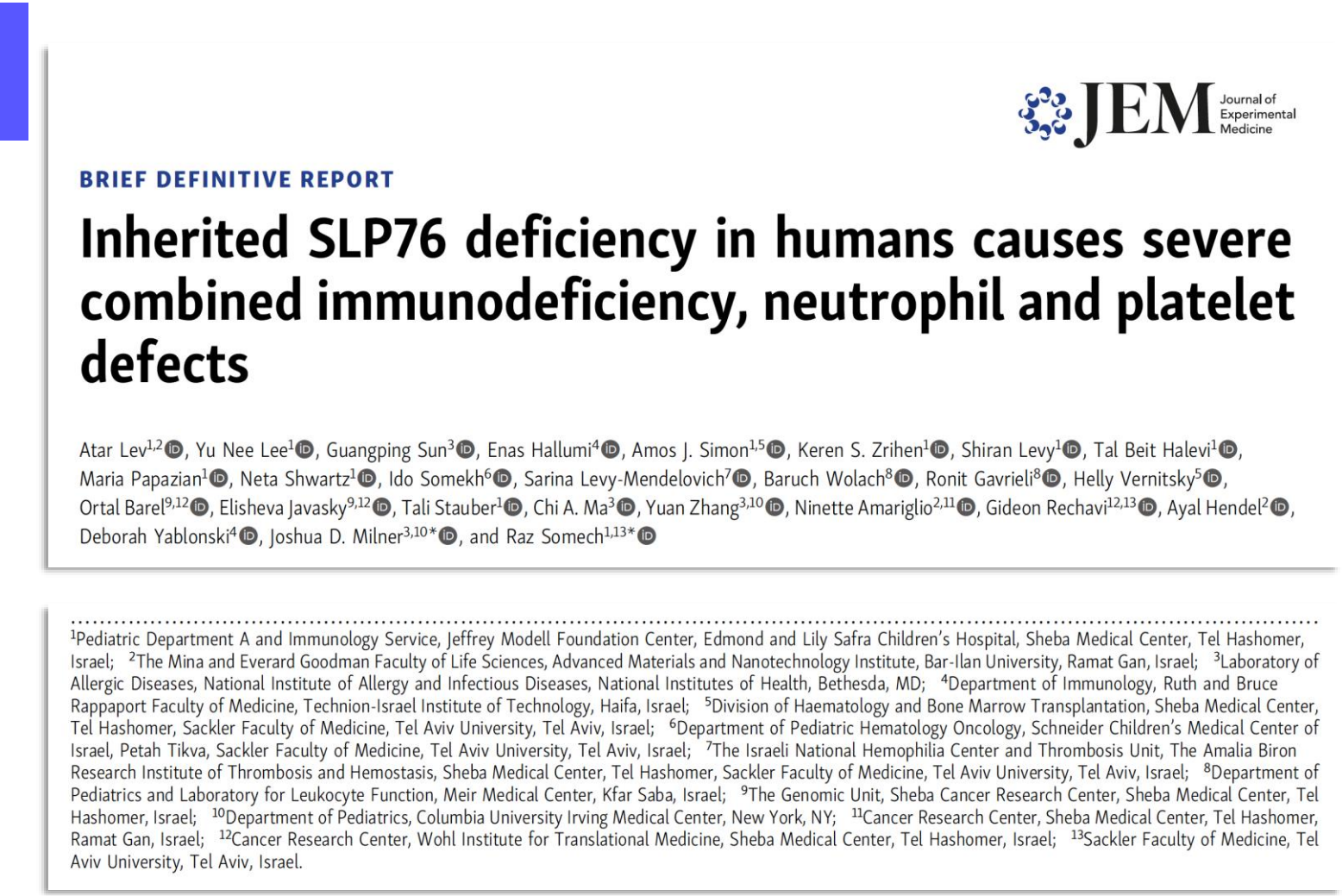




Frangoul et al NEJM 2021 | Vertex FDA AdCom 2023

Gap #1:

Rapid progress in genome-editing two blood diseases (SCD+TDT) has, at present, no path to affecting 112,000 patients with editable blood disease



JEM Journal of Experimental Medicine

BRIEF DEFINITIVE REPORT

Inherited SLP76 deficiency in humans causes severe combined immunodeficiency, neutrophil and platelet defects

Atar Lev[1,2], Yu Nee Lee[1], Guangping Sun[3], Enas Hallumi[4], Amos J. Simon[1,5], Keren S. Zrihen[1], Shiran Levy[1], Tal Beit Halevi[1], Maria Papazian[1], Neta Shwartz[1], Ido Somekh[6], Sarina Levy-Mendelovich[7], Baruch Wolach[8], Ronit Gavrieli[8], Helly Vernitsky[5], Ortal Barel[9,12], Elisheva Javasky[9,12], Tali Stauber[1], Chi A. Ma[3], Yuan Zhang[3,10], Ninette Amariglio[2,11], Gideon Rechavi[12,13], Ayal Hendel[2], Deborah Yablonski[4], Joshua D. Milner[3,10]*, and Raz Somech[1,13]*

[1]Pediatric Department A and Immunology Service, Jeffrey Modell Foundation Center, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [2]The Mina and Everard Goodman Faculty of Life Sciences, Advanced Materials and Nanotechnology Institute, Bar-Ilan University, Ramat Gan, Israel; [3]Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD; [4]Department of Immunology, Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [5]Division of Haematology and Bone Marrow Transplantation, Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [6]Department of Pediatric Hematology Oncology, Schneider Children's Medical Center of Israel, Petah Tikva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [7]The Israeli National Hemophilia Center and Thrombosis Unit, The Amalia Biron Research Institute of Thrombosis and Hemostasis, Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [8]Department of Pediatrics and Laboratory for Leukocyte Function, Meir Medical Center, Kfar Saba, Israel; [9]The Genomic Unit, Sheba Cancer Research Center, Sheba Medical Center, Tel Hashomer, Israel; [10]Department of Pediatrics, Columbia University Irving Medical Center, New York, NY; [11]Cancer Research Center, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel; [12]Cancer Research Center, Wohl Institute for Translational Medicine, Sheba Medical Center, Tel Hashomer, Israel; [13]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

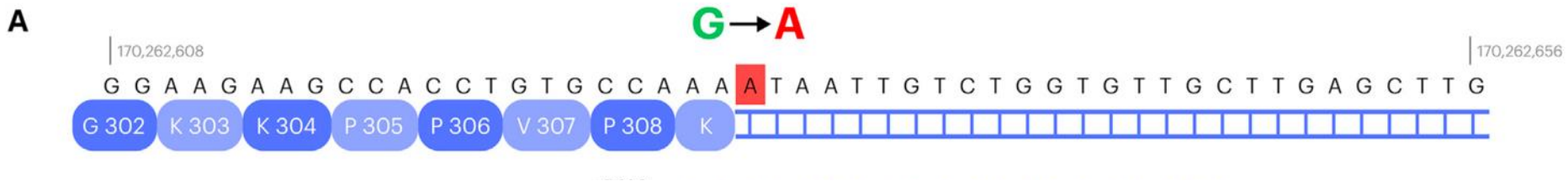
"[Patient] presented at the age of 2 mo with recurrent skin abscesses and skin rash.

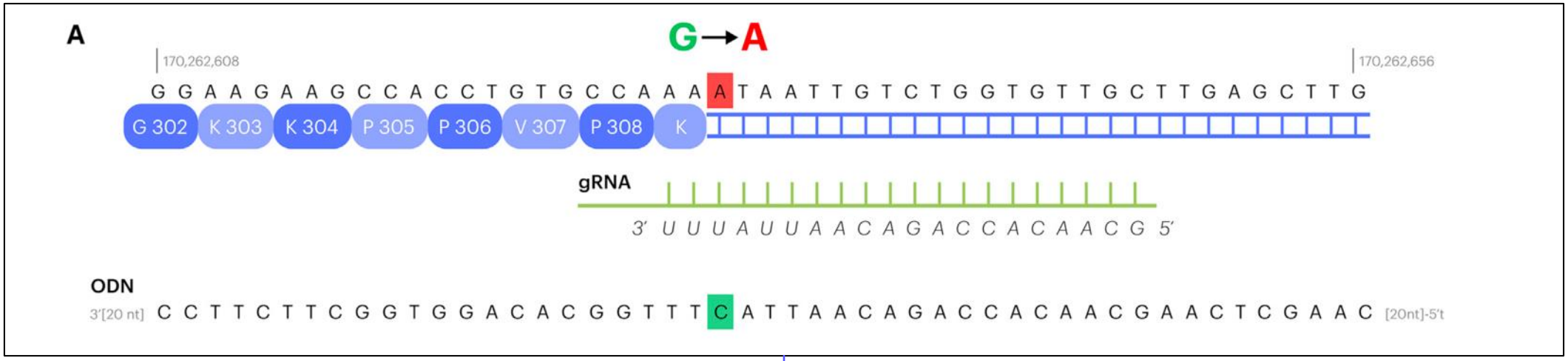
The patient died of transplant-related complications [at 10 months of age]."

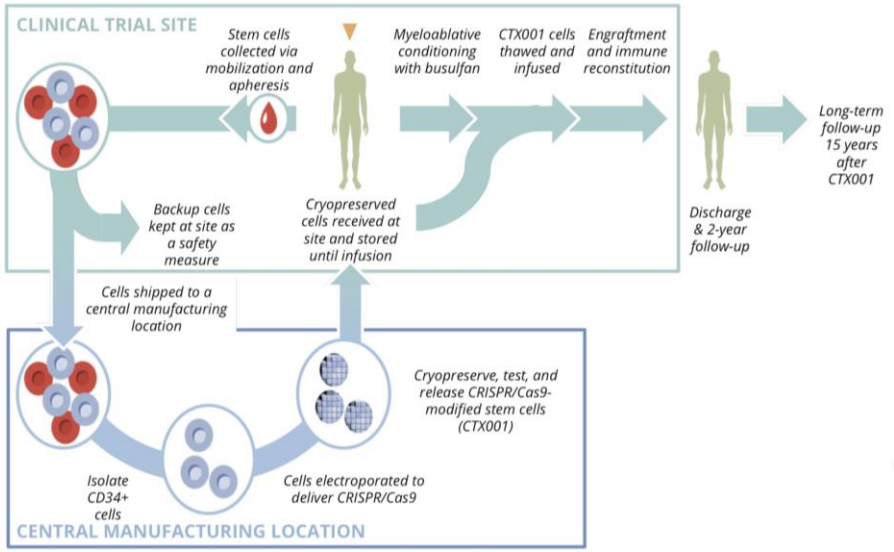
What killed this child?

a novel mutation in the *SLP76* gene

The mutation that killed this child was actionably editable





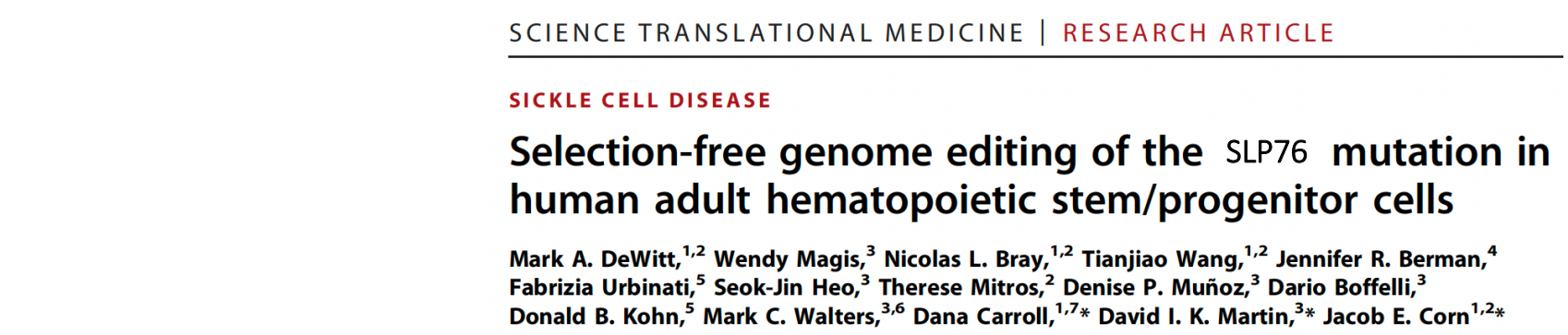


TWO MONTHS from mutation to clinical lead ready to go

ONE MONTH to make+release cell product

3 months to clinical outcome

If you change something – eg the gRNA and the ssODN – it's a new product, so back to square 1



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

SICKLE CELL DISEASE

Selection-free genome editing of the SLP76 mutation in human adult hematopoietic stem/progenitor cells

Mark A. DeWitt,[1,2] Wendy Magis,[3] Nicolas L. Bray,[1,2] Tianjiao Wang,[1,2] Jennifer R. Berman,[4] Fabrizia Urbinati,[5] Seok-Jin Heo,[3] Therese Mitros,[2] Denise P. Muñoz,[3] Dario Boffelli,[3] Donald B. Kohn,[5] Mark C. Walters,[3,6] Dana Carroll,[1,7]* David I. K. Martin,[3]* Jacob E. Corn[1,2]*

Patient → Cause → Effector → Efficacy → Safety → CMC → Regulatory → Trial

~ 4 years, $7m (academic pricing)

~ 4 years, $7m (academic pricing)

2020-2021 Global Survey on Primary Immunodeficiencies

GLOBAL TOTALS

1. Total number of patients being followed	256,153
2. Total number of patients identified with a specific PI defect	112,337
3. Total number of patients receiving IgG:	
A) IVIG - Clinic	18,913
B) IVIG - Home	3,344
C) SCIG	13,548
D) Other	256
4. Total number of patients treated by Gene Therapy	248
5. Total number of patients treated with PEG-ADA	126

6. Total number of patients treated by Transplant	6,991
Donor Type:	
A) MRD	1,908
B) MUD	2,012
C) mMUD	462
D) Parental Haplo	1,106
Stem Cell Source:	
A) BM	3,312
B) PBSC	1,334
C) Cord	661
D) Other (please specify)	127

For Tables I - X, please enter the number of patients followed in the box to the right of the specified gene. Available OMIM numbers are provided and linked within each table.

TABLE I. IMMUNODEFICIENCIES AFFECTING CELLULAR AND HUMORAL IMMUNITY

1.	ADA (Adenosine deaminase deficiency), AR	OMIM 608958	575	31.	LIG4 (DNA ligase IV deficiency), AR	OMIM 601837	60
2.	AK2 (AK2 Defect), AR	OMIM 103020	42	32.	MALT1 (MALT1 deficiency), AR	OMIM 615468	23
3.	B2M (MHC class I deficiency), AR	OMIM 109700	11	33.	MAP3K14 (NIK deficiency), AR	OMIM 604655	1
4.	BCL10 (BCL10 deficiency), AR	OMIM 616098	4	34.	MSN (Moesin deficiency), XL	OMIM 300988	11
5.	CARD 11 (CARD11 deficiency), AR LOF	OMIM 615206	31	35.	NHEJ1 (Cernunnos/XLF deficiency), AR	OMIM 611290	27
6.	CD3D (CD3$_{d}$ deficiency), AR	OMIM 186790	54	36.	POLD 1 (Polymerase δ deficiency), AR	OMIM 174761	5
7.	CD3E (CD3ε deficiency), AR	OMIM 186830	26	37.	POLD 2 (Polymerase δ deficiency), AR	OMIM 600815	2
8.	CD3G (CD3γ deficiency), AR	OMIM 186740	13	38.	PRKDC (DNA PKcs deficiency), AR	OMIM 615966	17
9.	CD3Z (CD3ζ deficiency), AR	OMIM 186780	6	39.	PTPRC (CD45 Deficiency), AR	OMIM 151460	6
10.	CD40 (CD40 deficiency), AR	OMIM 606843	104	40.	RAC2 (Activated RAC2 defect), AD GOF	OMIM 602049	13
11.	CD40LG (CD40 ligand (CD154) deficiency), XL	OMIM 308230	686	41.	RAG1 (RAG deficiency), AR	OMIM 179615	513
12.	CD8A (CD8 deficiency), AR	OMIM 186910	18	42.	RAG2 (RAG deficiency), AR	OMIM 179616	325
13.	CIITA (MHC class II deficiency group A, B, C, D), AR	OMIM 600005	97	43.	REL (c-Rel deficiency), AR	OMIM 164910	2
14.	CORO1A (Coronin-1A deficiency), AR	OMIM 605000	15	44.	RELA (RelA haploinsufficiency), AD	OMIM 618287	7
15.	DCLRE1C (Artemis deficiency), AR	OMIM 605988	268	45.	RELB (RelB deficiency), AR	OMIM 604758	15
16.	DOCK2 (DOCK2 deficiency), AR	OMIM 603122	21	46.	RFX5 (MHC class II deficiency group A, B, C, D), AR	OMIM 601863	61
17.	DOCK8 (DOCK8 deficiency)), AR	OMIM 243700	509	47.	RFXANK (MHC class II deficiency group A, B, C, D), AR	OMIM 603200	156
18.	FCHO1 (FCHO1 deficiency), AR	OMIM 613437	10	48.	RFXAP (MHC class II deficiency group A, B, C, D), AR	OMIM 601861	16
19.	ICOS (ICOS deficiency), AR	OMIM 604558	28	49.	RHOH (RHOH deficiency), AR	OMIM 602037	3
20.	ICOSLG (ICOSL deficiency), AR	OMIM 605717	3	50.	STK4 (MST1 deficiency), AR	OMIM 614868	17
21.	IKBKB (IKBKB deficiency), AR	OMIM 615592	32	51.	TAP1 (MHC class I deficiency), AR	OMIM 170260	22
22.	IKZF1 (IKAROS deficiency), AD DN	OMIM 603023	35	52.	TAP2 (MHC class I deficiency), AR	OMIM 170261	6
23.	IL21 (IL-21 deficiency), AR	OMIM 615767	2	53.	TAPBP (MHC class I deficiency), AR	OMIM 601962	0
24.	IL21R (IL-21R deficiency), AR	OMIM 615207	21	54.	TFRC (TFRC deficiency), AR	OMIM 616740	15
25.	IL2RG ($_{g}$c Deficiency, γc SCID, CD132 deficiency), XL	OMIM 308380	818	55.	TNFRSF4 (OX40 deficiency), AR	OMIM 615593	0
26.	IL7R (IL7R$_{a}$ deficiency), AR	OMIM 146661	208	56.	TRAC (TCR$_{a}$ deficiency), AR	OMIM 615387	9
27.	ITK (ITK deficiency), AR	OMIM 186973	34	57.	ZAP70 (ZAP-70 combined mutations), AR (LOF/GOF)	OMIM 617006	8
28.	JAK3 (JAK3 deficiency), AR	OMIM 600173	250	58.	ZAP70 (ZAP-70 deficiency (ZAP70 LOF)), AR	OMIM 269840	103
29.	LAT (LAT deficiency), AR	OMIM 602354	1	59.	Other Immunodeficiencies Affecting Cellular and Humoral Immunity:		2,160
30.	LCK (LCK deficiency), AR	OMIM 615758	3			TOTAL	7,528

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D) Parental Haplo	1,106
Stem Cell Source:	
A) BM	3,312
B) PBSC	1,334
C) Cord	661
D) Other (please specify)	127

505 different inborn errors of immunity

>112,000 patients

ZERO gene editing trials for them

ONE approved gene therapy product

Lenardo, Michael (NIH/NIAID) [E] <mlenardo@niaid.nih.gov>
to me

Dear Fyodor,

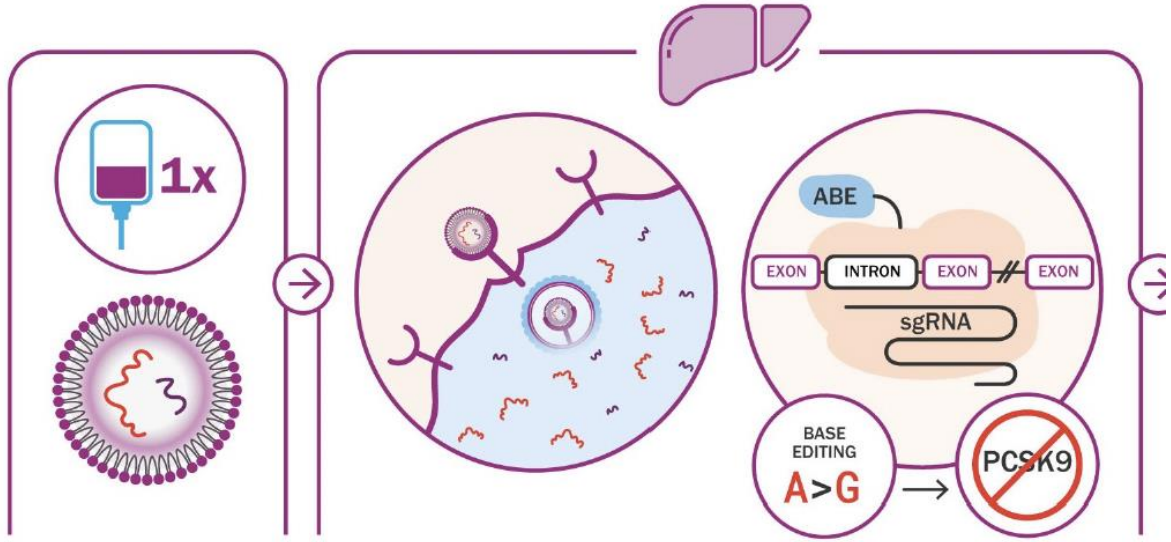
About 100-200 patients and roughly 10 diseases.

Happy New Year,

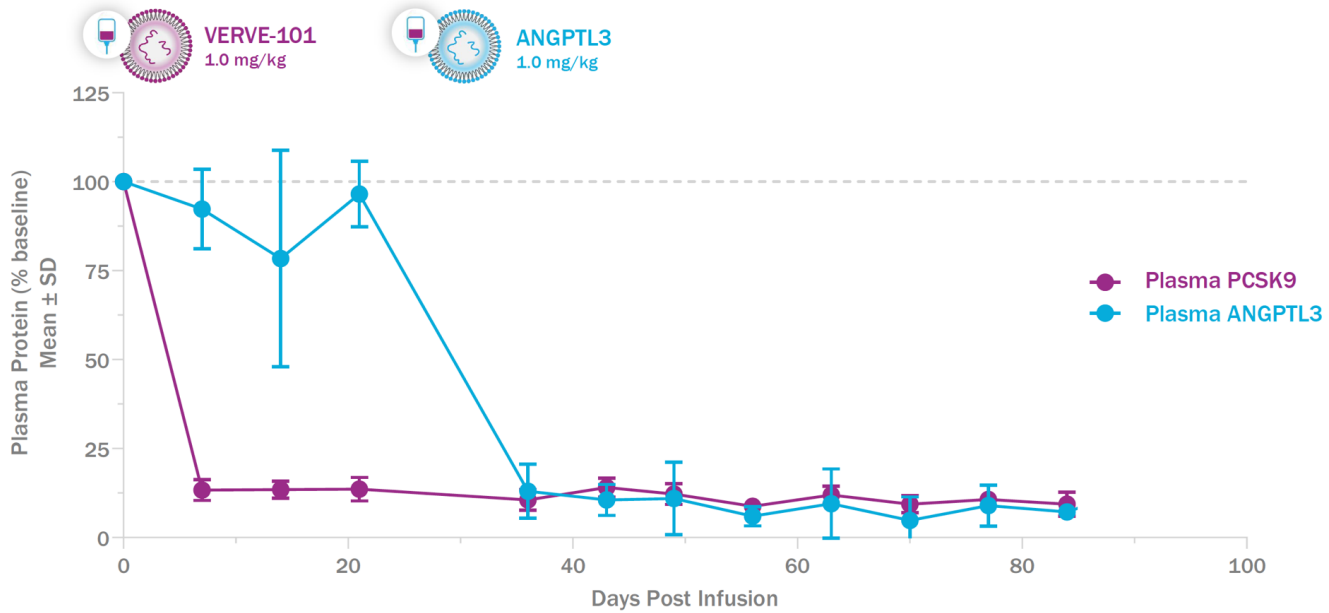
Mike

Michael Lenardo M.D.
NIH Distinguished Investigator
Chief, Molecular Development of the Immune System Section
Laboratory of Immune System Biology,
Director, Clinical Genomics Program,
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Building 10, Room 11D14
10 Center Drive, MSC 1892
Bethesda, MD 20892-1892 USA

The current nonclinical pharmtox, CMC, and regulatory framework need an upgrade to align with the clinically established platform nature of CRISPR-Cas genome editing AND the unmet medical need in “rare” diseases.



Sequential dosing in NHPs: >90% reduction of plasma PCSK9 protein followed by >90% reduction observed of plasma ANGPTL3 protein



Oct 31, 2023

Verve and Lilly Relationship Expands to Include Verve's In Vivo Gene Editing Programs Targeting PCSK9 and ANGPTL3

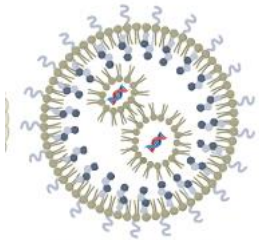
Oct 23, 2023

Verve Therapeutics Announces Clearance of Investigational New Drug Application by the U.S. FDA for VERVE-101 in Patients with Heterozygous Familial Hypercholesterolemia

Gap #2:

Rapid progress in genome-editing the liver (Verve, Intellia, soon others) has, at present, near no path to affecting >2,500 US newborns per year with inborn errors of metabolism

Phenylketonuria:



Lipid nanoparticle

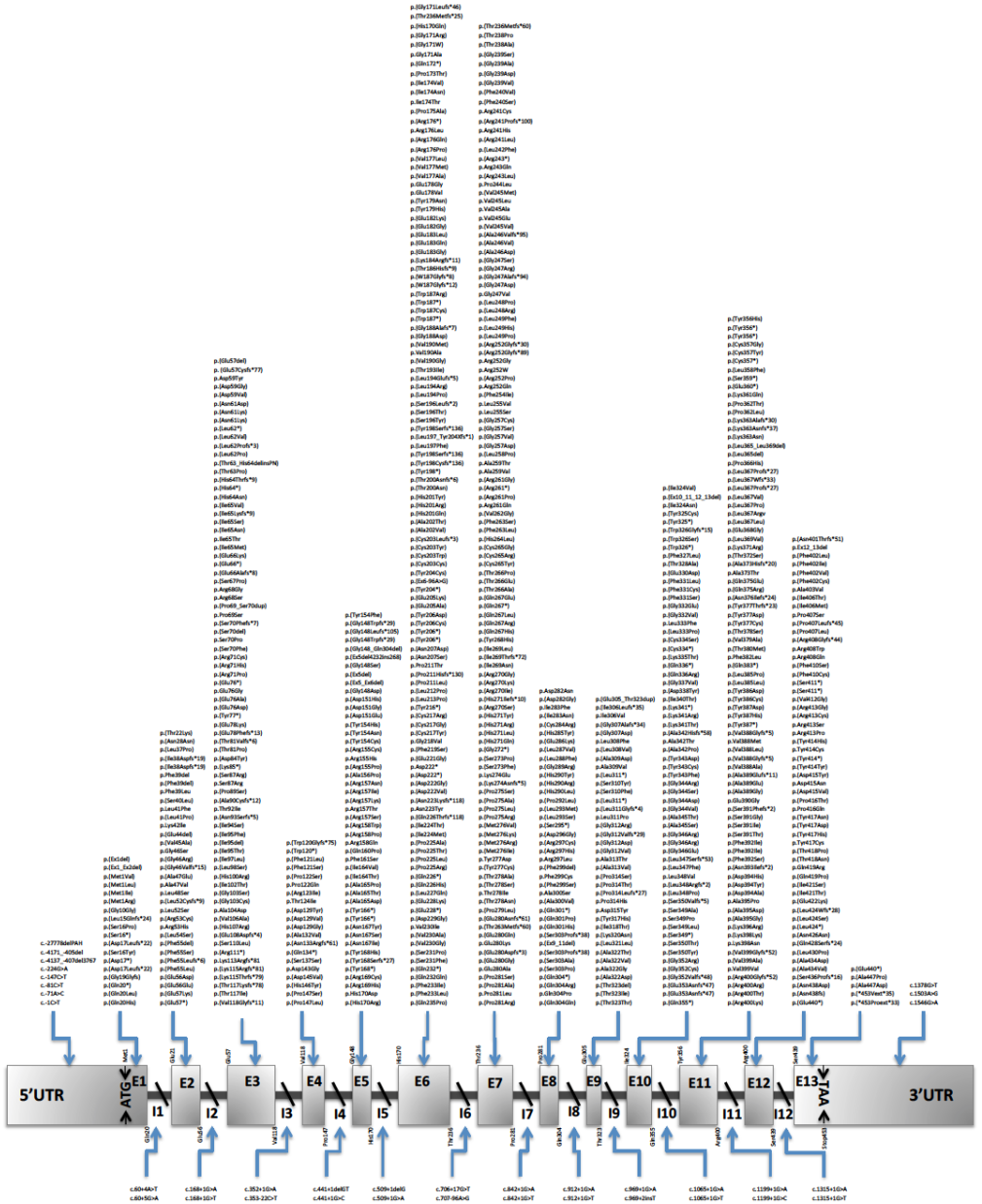
1 in 15,000 live births in the US

Universal screening at birth

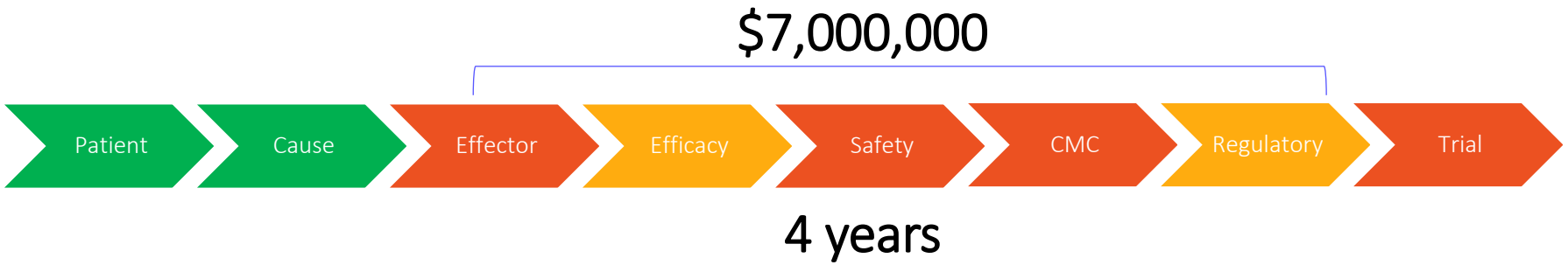
Over 90% of the newborns could be CRISPR-gene-edited to health in their first year of life.

Same for 2,500 newborns with other IEMs.

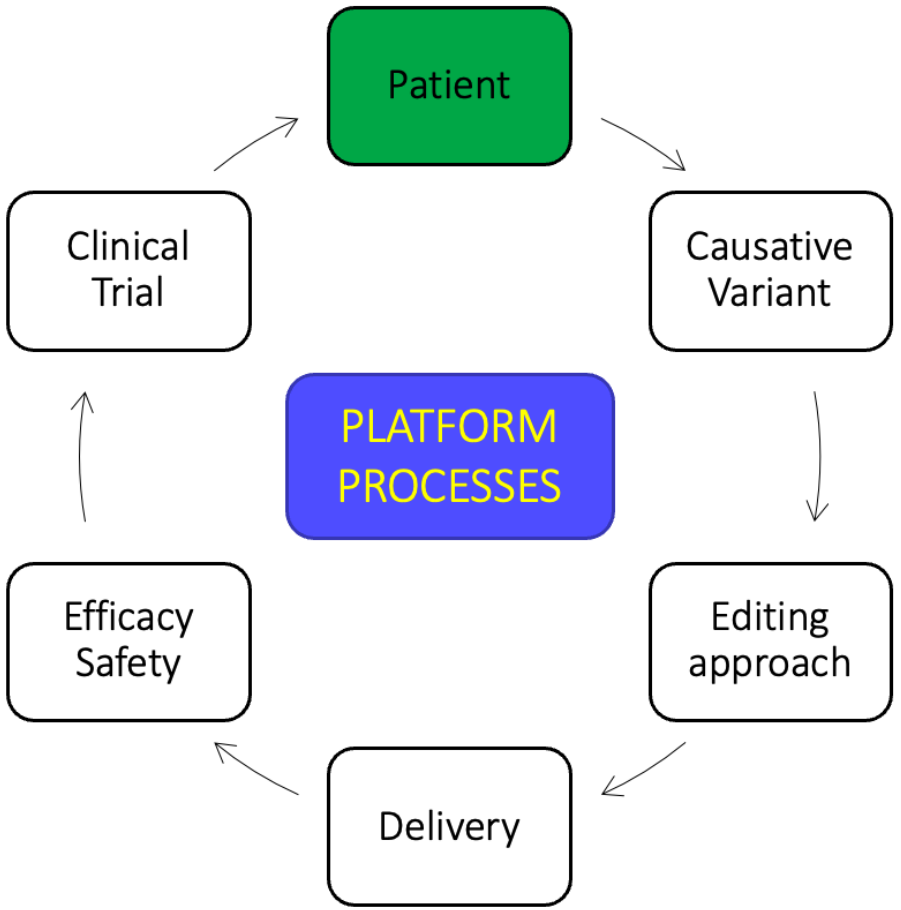
100% of the relevant technologies – CRISPR and LNP delivery – exist.



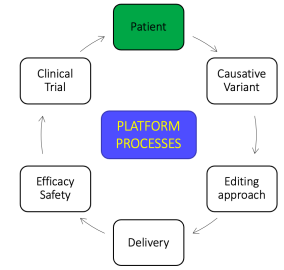
http://www.biopku.org/home/docs/variants_all.pdf
https://depts.washington.edu/pku/about/diet.html


$7,000,000
Patient
Cause
Effector
Efficacy
Safety
CMC
Regulatory
Trial
4 years


Patient
Cause
Effector
Efficacy
Safety
CMC
Regulatory
Trial

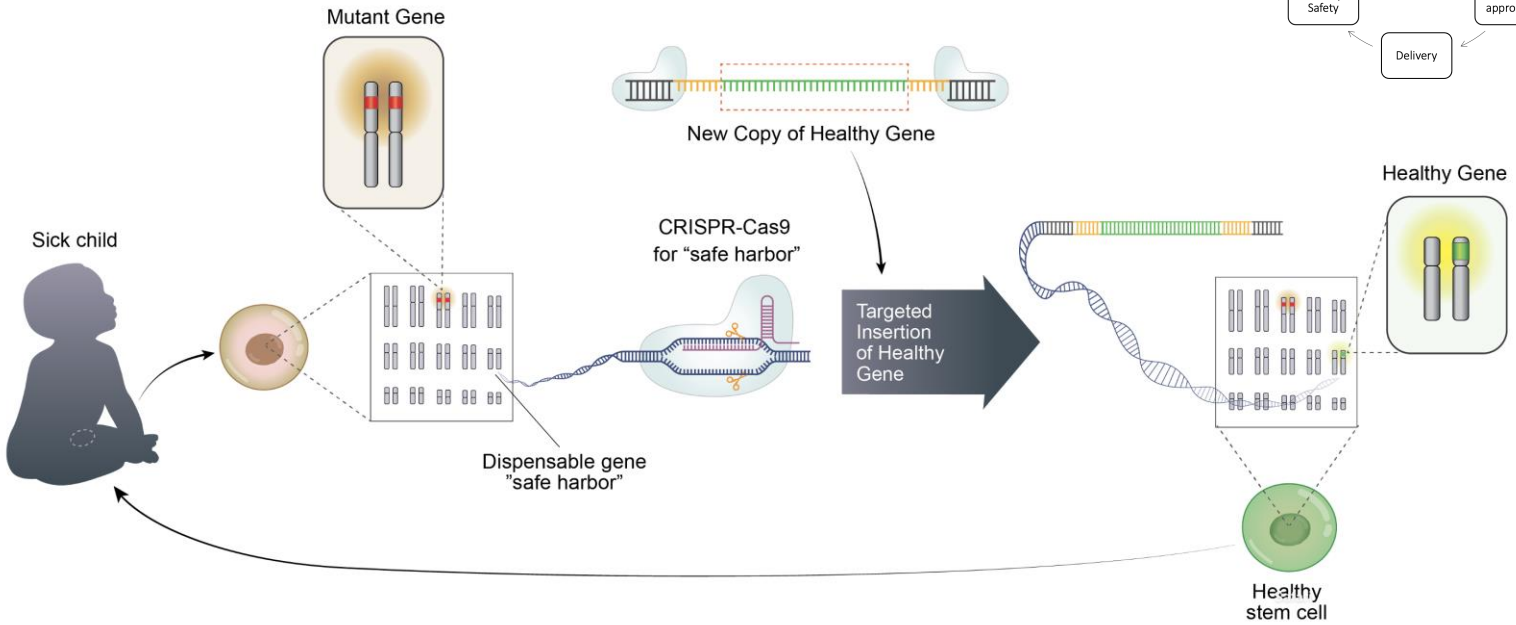

Patient
Causative Variant
Editing approach
Delivery
Efficacy Safety
Clinical Trial
PLATFORM PROCESSES

IGI-Originated Reductions of This To Practice



Same nuclease, same manufacture

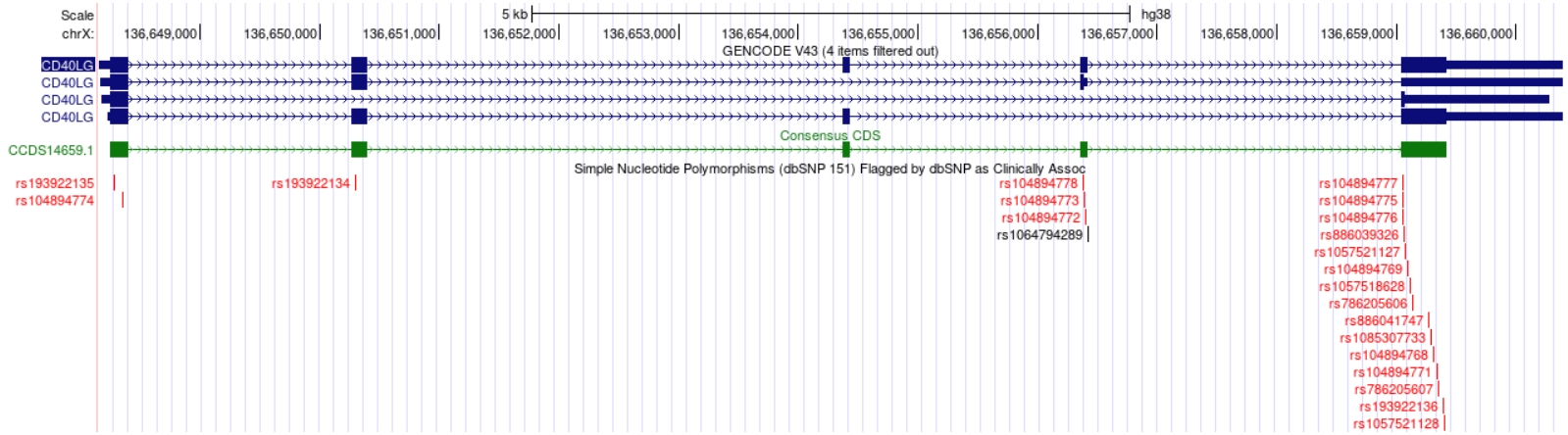
<u>Different</u> nonviral templates for different IEIs



With Jennifer Puck, Mort Cowan, Matt Kan, Don Kohn

Same nuclease, same manufacture, same disease

<u>Different</u> guide RNAs for different mutations



With Michelle Hermiston, Brian Shy, Jeff Goldberg, Carlo Condello

A key way to find out how to safely edit people is to edit more people.

“Academic” INDs for ”N=rare” will dose a small number of subjects but will yield ”rising tide lifts all boats” data on what matters and what does not matter in preclinical space AND WILL HELP INFORM AGENCY THINKING.

CRISPR Catch-2023:

A key way to find out how to safely and efficiently genome-edit people is to

edit more people.

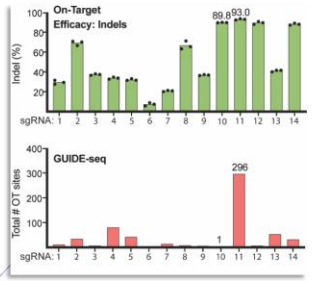
This requires new nonclinical frameworks to take editing to clinic.

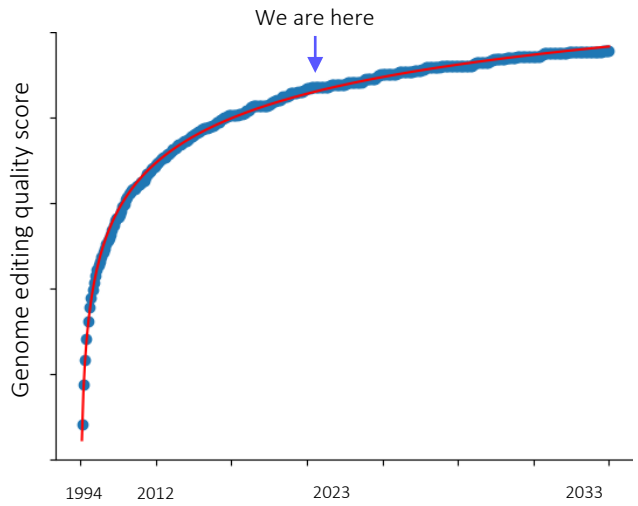
This, in turn, requires more clinical data on what matters and what does not

at the nonclinical stage.

Not enough clinical data because current path to IND is long and expensive. If there were more clinical data we'd improve it.
But we cannot improve it because that current path is, itself, an obstacle to improving it.

!!!





Introduction of Double-Strand Breaks into the Genome of Mouse Cells by Expression of a Rare-Cutting Endonuclease

PHILIPPE ROUET, FATIMA SMIH, AND MARIA JASIN*

Cell Biology and Genetics Program, Sloan-Kettering Institute and Cornell University Graduate School of Medical Sciences, New York, New York 10021

DSB drives edits

Genome editing native genes

A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

Genome editing with Cas9

1994 2001-2005 2012 2023 2033

Maria Jasin | Dana Carroll, Matthew Porteus, David Baltimore, Sangamo, others | Jennifer Doudna, Emmanuelle Charpentier | Lazzarotto et al *Nature Biotechnology* (2022) 38: 1317-1327

CRISPR Cures 2033?

2020-2021 Global Survey on Primary Immunodeficiencies

GLOBAL TOTALS

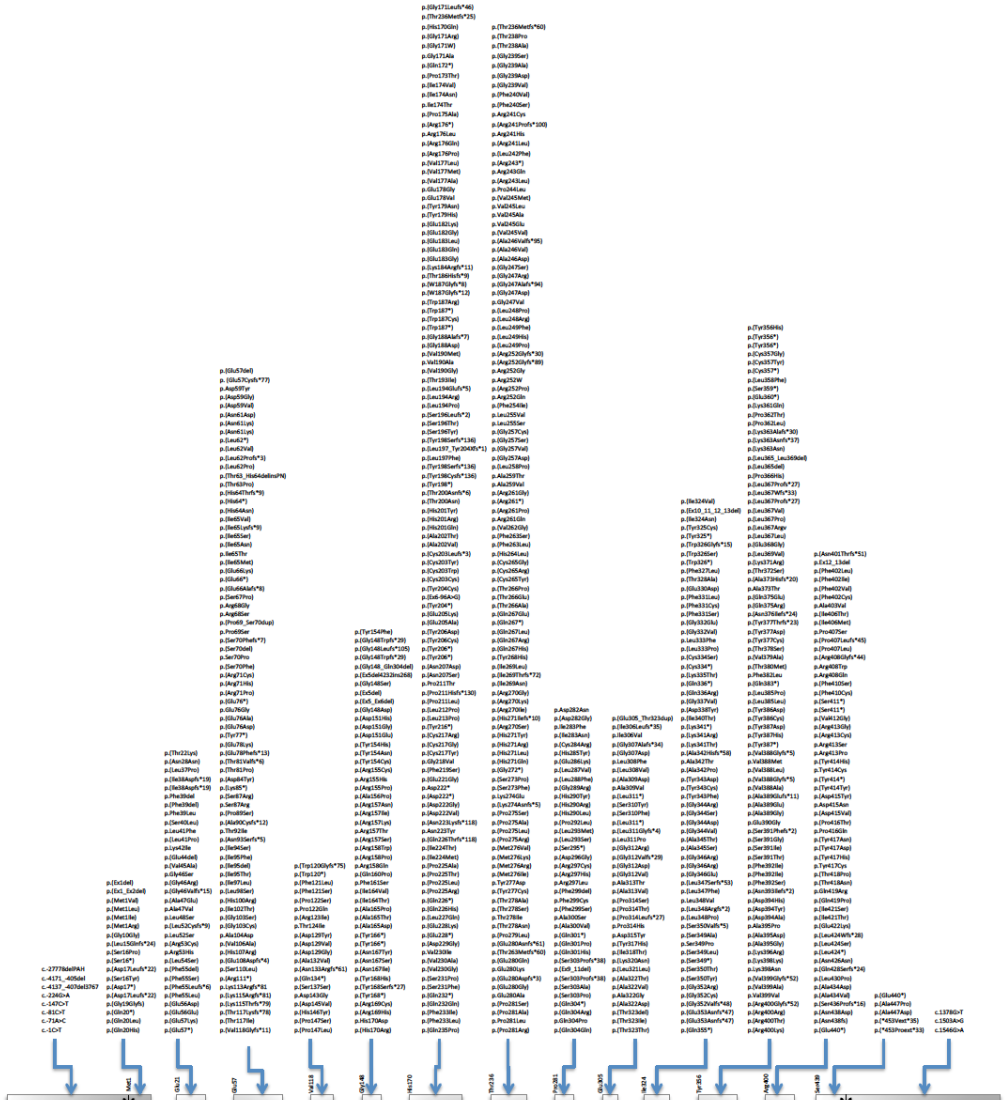
Jeffrey Modell Centers Network

1. Total number of patients being followed	256,153	6. Total number of patients treated by Transplant	6,991
2. Total number of patients identified with a specific PI defect	112,337	Donor Type:	
3. Total number of patients receiving IgG:		A) MRD	1,908
A) IVIG - Clinic	18,913	B) MUD	2,012
B) IVIG - Home	3,344	C) mMUD	462
C) SCIG	13,548	D) Parental Haplo	1,106
D) Other	256	Stem Cell Source:	
4. Total number of patients treated by Gene Therapy	248	A) BM	3,312
5. Total number of patients treated with PEG-ADA	126	B) PBSC	1,334
		C) Cord	661
		D) Other (please specify)	127

For Tables I - X, please enter the number of patients followed in the box to the right of the specified gene. Available OMIM numbers are provided and linked within each table.

TABLE I. IMMUNODEFICIENCIES AFFECTING CELLULAR AND HUMORAL IMMUNITY

1. ADA (Adenosine deaminase deficiency), AR	OMIM 608958	1.	575	31. LIG4 (DNA ligase IV deficiency), AR	OMIM 601837	31.	60
2. AK2 (AK2 Defect), AR	OMIM 103020	2.	42	32. MALT1 (MALT1 deficiency), AR	OMIM 615468	32.	23
3. B2M (MHC class I deficiency), AR	OMIM 109700	3.	11	33. MAP3K14 (NIK deficiency), AR	OMIM 604655	33.	1
4. BCL10 (BCL10 deficiency), AR	OMIM 616098	4.	4	34. MSN (Moesin deficiency), XL	OMIM 300988	34.	11
5. CARD 11 (CARD11 deficiency), AR LOF	OMIM 615206	5.	31	35. NHEJ1 (Cernunnos/XLF deficiency), AR	OMIM 611290	35.	27
6. CD3D (CD3$_\delta$ deficiency), AR	OMIM 186790	6.	54	36. POLD 1 (Polymerase δ deficiency), AR	OMIM 174761	36.	5
7. CD3E (CD3$_\varepsilon$ deficiency), AR	OMIM 186830	7.	26	37. POLD 2 (Polymerase δ deficiency), AR	OMIM 600815	37.	2
8. CD3G (CD3$_\gamma$ deficiency), AR	OMIM 186740	8.	13	38. PRKDC (DNA PKcs deficiency), AR	OMIM 615966	38.	17
9. CD3Z (CD3$_\zeta$ deficiency), AR	OMIM 186780	9.	6	39. PTPRC (CD45 Deficiency), AR	OMIM 151460	39.	6
10. CD40 (CD40 deficiency), AR	OMIM 606843	10.	104	40. RAC2 (Activated RAC2 defect), AD GOF	OMIM 602049	40.	13
11. CD40LG (CD40 ligand (CD154) deficiency), XL	OMIM 308230	11.	686	41. RAG1 (RAG deficiency), AR	OMIM 179615	41.	513
12. CD8A (CD8 deficiency), AR	OMIM 186910	12.	18	42. RAG2 (RAG deficiency), AR	OMIM 179616	42.	325
13. CIITA (MHC class II deficiency group A, B, C, D), AR	OMIM 600005	13.	97	43. REL (c-Rel deficiency), AR	OMIM 164910	43.	2
14. CORO1A (Coronin-1A deficiency), AR	OMIM 605000	14.	15	44. RELA (RelA haploinsufficiency), AD	OMIM 618287	44.	7
15. DCLRE1C (Artemis deficiency), AR	OMIM 605988	15.	268	45. RELB (RelB deficiency), AR	OMIM 604758	45.	15
16. DOCK2 (DOCK2 deficiency), AR	OMIM 603122	16.	21	46. RFX5 (MHC class II deficiency group A, B, C, D), AR	OMIM 601863	46.	61
17. DOCK8 (DOCK8 deficiency), AR	OMIM 243700	17.	509	47. RFXANK (MHC class II deficiency group A, B, C, D), AR	OMIM 603200	47.	156
18. FCHO1 (FCHO1 deficiency), AR	OMIM 613437	18.	10	48. RFXAP (MHC class II deficiency group A, B, C, D), AR	OMIM 601861	48.	16
19. ICOS (ICOS deficiency), AR	OMIM 604558	19.	28	49. RHOH (RHOH deficiency), AR	OMIM 602037	49.	3
20. ICOSLG (ICOSL deficiency), AR	OMIM 605717	20.	3	50. STK4 (MST1 deficiency), AR	OMIM 614868	50.	17
21. IKBKB (IKBKB deficiency), AR	OMIM 615592	21.	32	51. TAP1 (MHC class I deficiency), AR	OMIM 170260	51.	22
22. IKZF1 (IKAROS deficiency), AD DN	OMIM 603023	22.	35	52. TAP2 (MHC class I deficiency), AR	OMIM 170261	52.	6
23. IL21 (IL-21 deficiency), AR	OMIM 615767	23.	2	53. TAPBP (MHC class I deficiency), AR	OMIM 601962	53.	0
24. IL21R (IL-21R deficiency), AR	OMIM 615207	24.	21	54. TFRC (TFRC deficiency), AR	OMIM 616740	54.	15
25. IL2RG ($_{\gamma c}$ Deficiency, γc SCID, CD132 deficiency), XL	OMIM 308380	25.	818	55. TNFRSF4 (OX40 deficiency), AR	OMIM 615593	55.	0
26. IL7R (IL7R$_\alpha$ deficiency), AR	OMIM 146661	26.	208	56. TRAC (TCR$_\alpha$ deficiency), AR	OMIM 615387	56.	9
27. ITK (ITK deficiency), AR	OMIM 186973	27.	34	57. ZAP70 (ZAP-70 combined mutations), AR (LOF/GOF)	OMIM 617006	57.	8
28. JAK3 (JAK3 deficiency), AR	OMIM 600173	28.	250	58. ZAP70 (ZAP-70 deficiency (ZAP70 LOF)), AR	OMIM 269840	58.	103
29. LAT (LAT deficiency), AR	OMIM 602354	29.	1	59. Other Immunodeficiencies Affecting Cellular and Humoral Immunity:		59.	2,160
30. LCK (LCK deficiency), AR	OMIM 615758	30.	3			TOTAL	7,528




AAV
LNP-mRNA
LNP-Cas9
Lenti
iPSC

Objective and guardrails

Objective

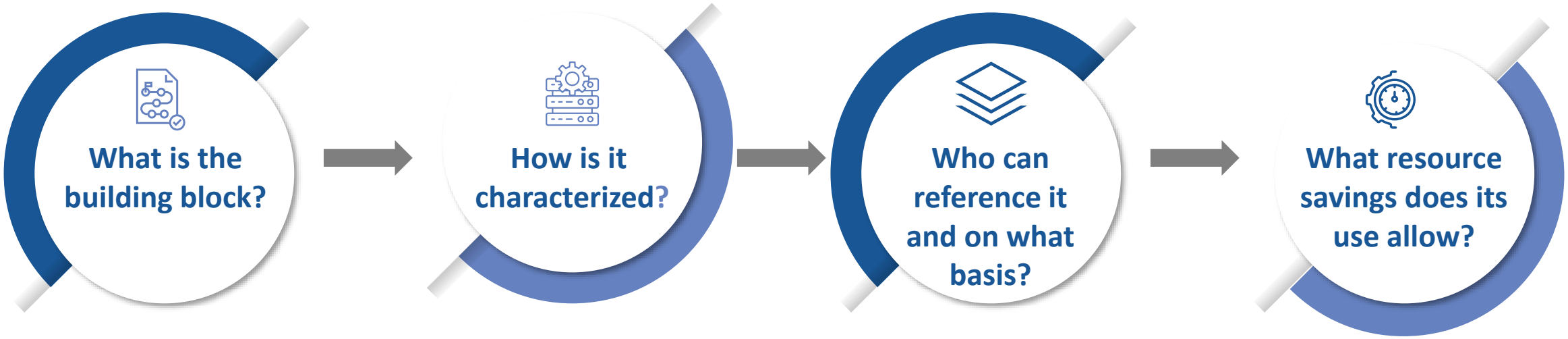
Improve time and resource efficiency of CGT development and regulatory review by leveraging elements that can serve as **building blocks** across programs

Guardrails

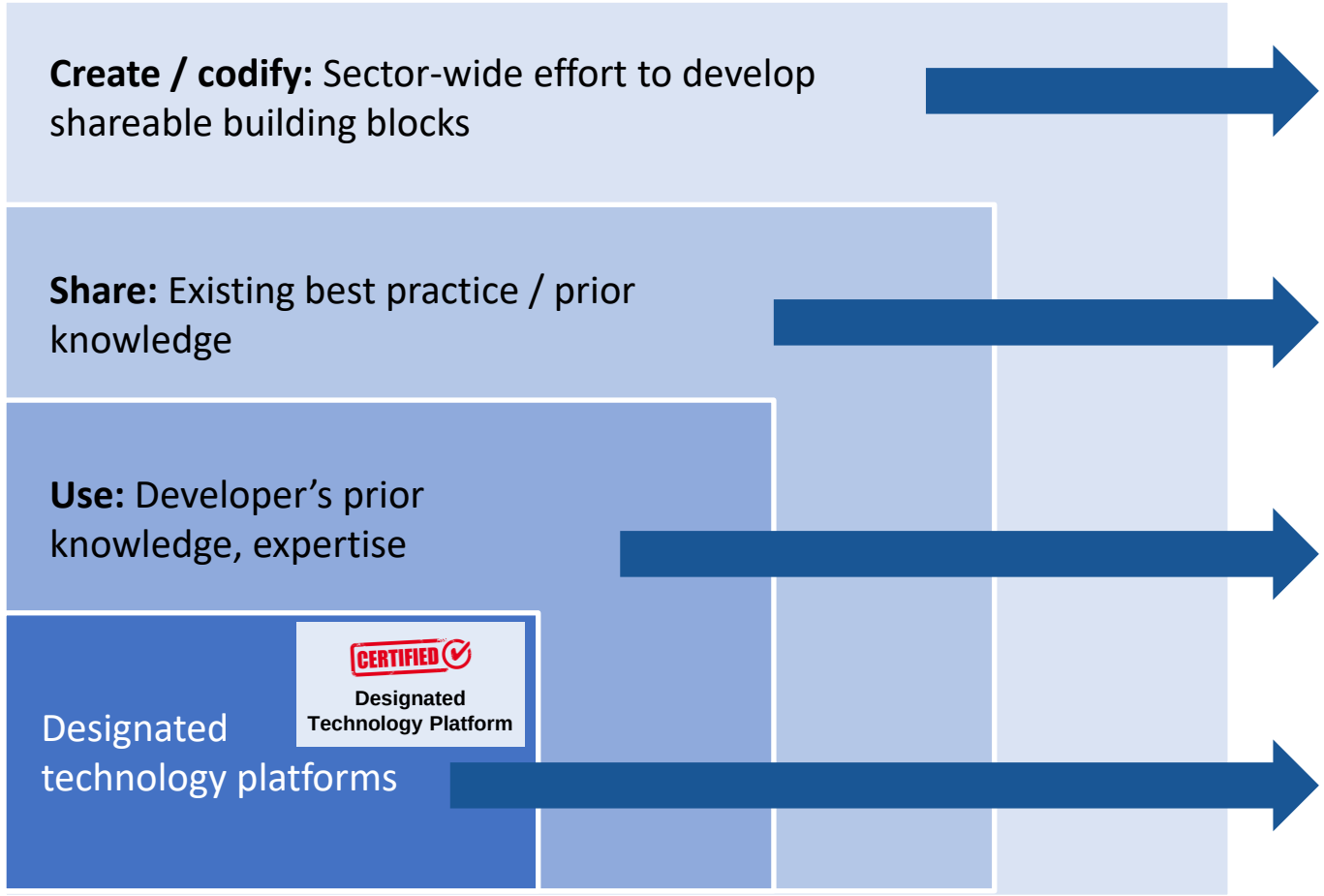
The objective should be pursued subject to the following guardrails:

- Maintain patient safety
- Avoid freezing in place the state of the art in CGT innovation
- Allow dissemination and use of productive platforms

Building blocks framework



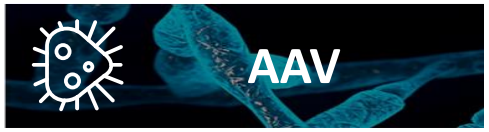
How to create and disseminate building blocks



Who develops	Needed for use	Vehicle for dissemination
▪ Coalition ▪ Association	▪ Publication	▪ Any developer or CDMO
▪ Coalition ▪ Association	▪ Regulatory clarity ▪ Voluntary info sharing	▪ Any developer or CDMO (?)
▪ Medicine sponsor ▪ CDMO	▪ Meet guidance ▪ Review decision	▪ Regulatory guidance, historic reviews
▪ Medicine sponsor	▪ Approved drug ▪ FDA-designated platform	▪ Original developer ▪ Licensee

Specific examples of potential building blocks: Case studies for technology-specific breakout groups to consider

4 case studies



4 case studies

3 case studies