Innovative Genomics Institute

Equitable Access to CRISPR-Cas Treatments for Severe Disease

Fyodor Urnov

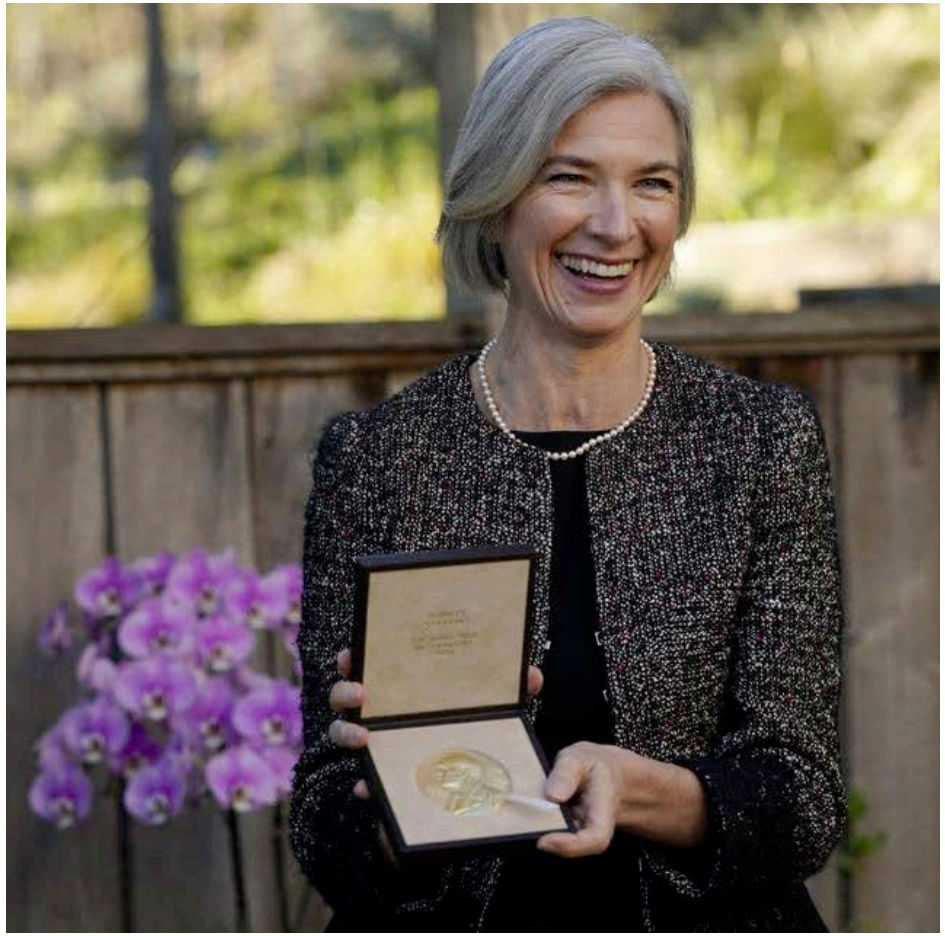
Scientific Director, Technology and Translation, IGI

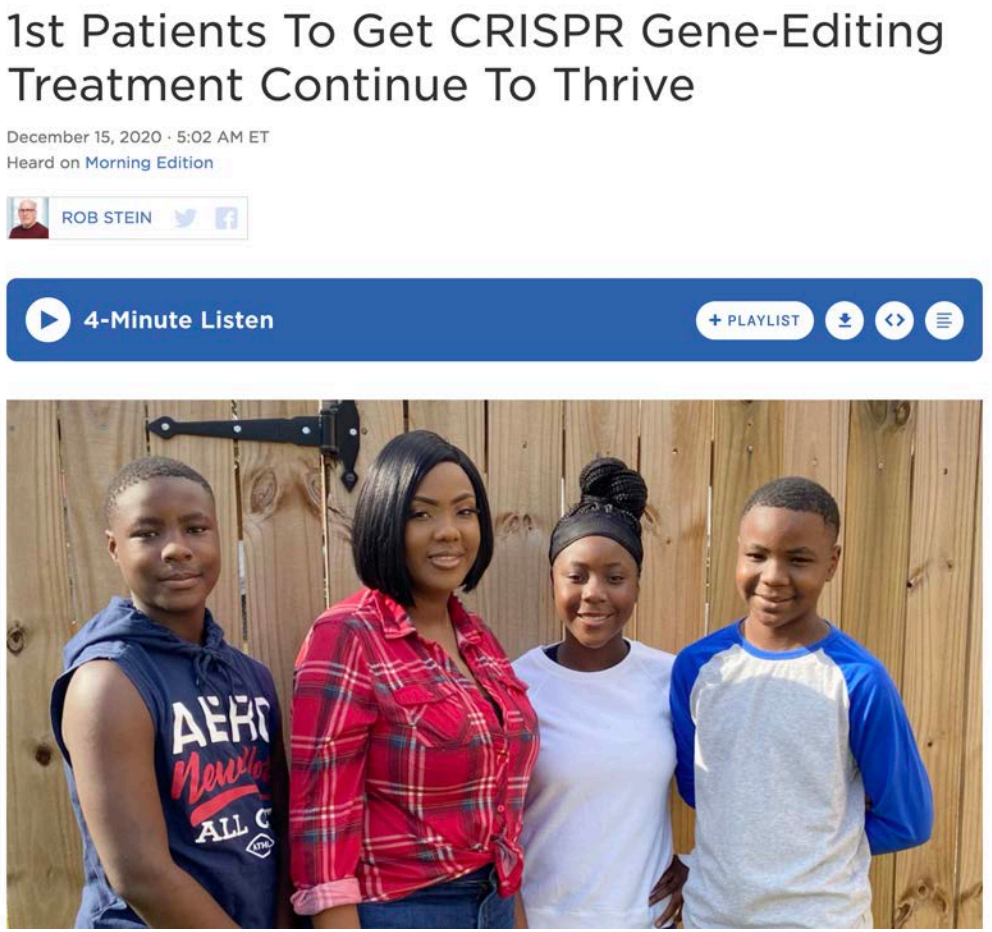
Professor, MCB Department, UC Berkeley

2020:

Nobel Prize – Jennifer Doudna – CRISPR genome editing
CRISPR cure – Victoria Gray

https://www.npr.org/sections/health-shots/2020/12/15/944184405/1st-patients-to-get-crispr-gene-editing-treatment-continue-to-thrive





JAD (April 2018): “CRISPR as the standard of medical care” – unique opportunity to make this reality

1

Genome editing as a therapeutic:

2005 – 2021

2030

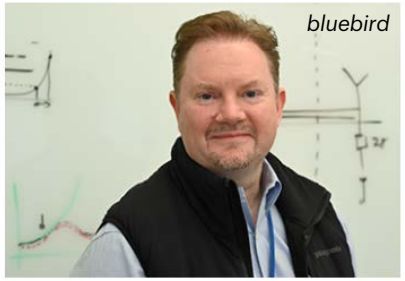
2030

Sana

Ed Rebar, PhD

Chief Technical Officer

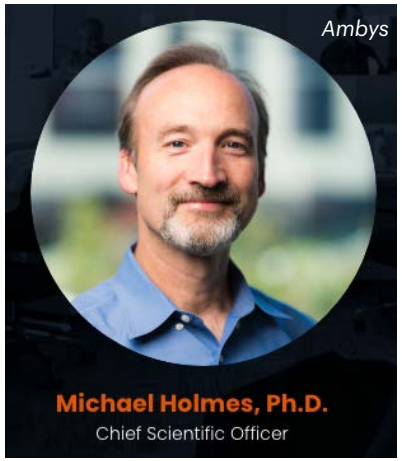
bluebird



Philip D. Gregory, D. Phil.

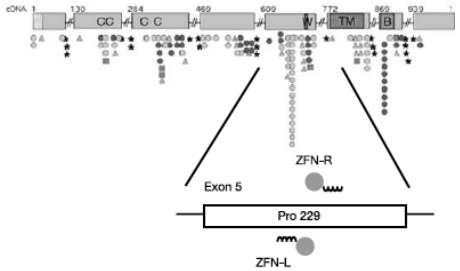
CHIEF SCIENTIFIC OFFICER

Ambys



2002: gamma-retro SAE for X-SCID

2005: *Nature*

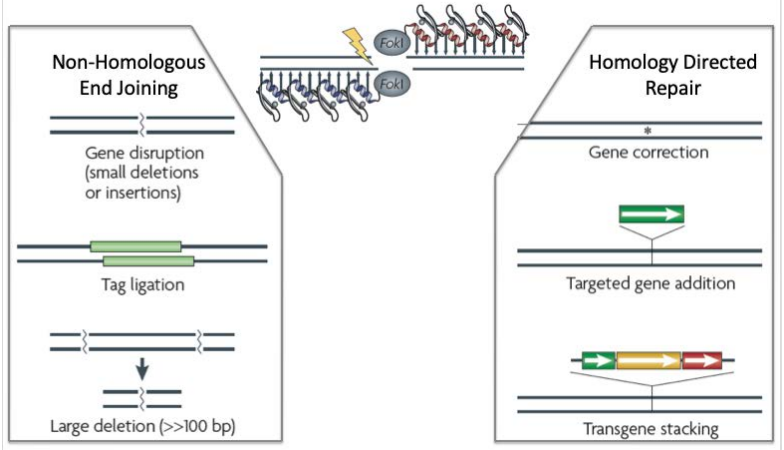


20% IL2Rγ mutation correction

2010: *Nature Reviews Genetics*

Genome editing with engineered zinc finger nucleases

Fyodor D. Urnov, Edward J. Rebar, Michael C. Holmes, H. Steve Zhang and Philip D. Gregory

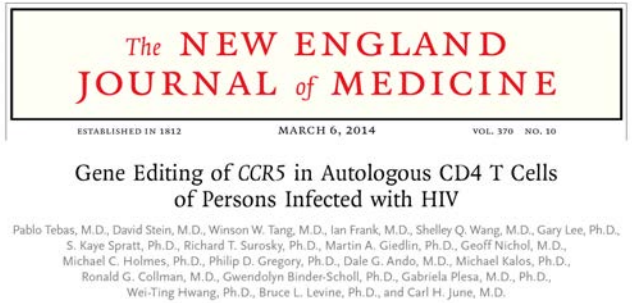


Senti

Gary Lee, Ph.D.

Chief Scientific Officer

2009: first subject dosed with ex vivo gene-edited T cells



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

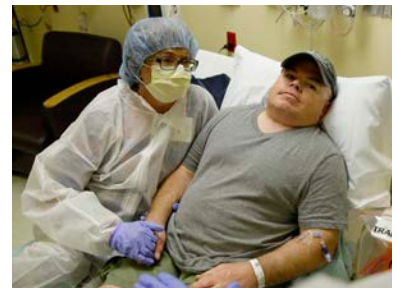
Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., 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.

>100 subjects dosed, no tmt-related SAEs

2010: first subject dosed with ex vivo gene-edited HSPCs

2017: first subject dosed *in vivo*

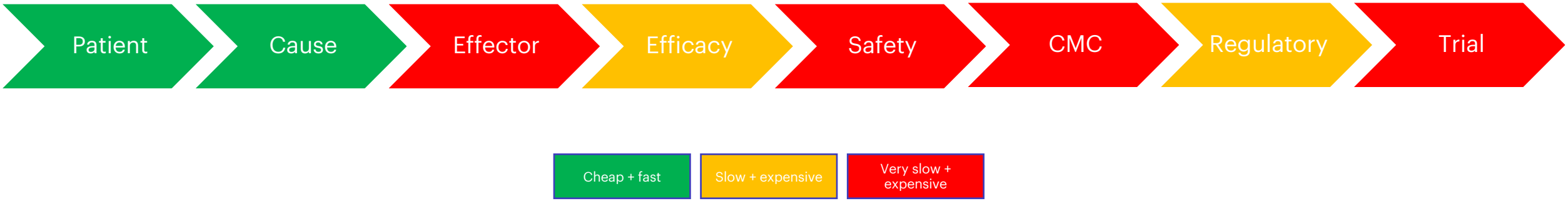
Clinical trials for:
MPS1
MPS2
Hemophilia B



2018: first IND for genome editing in the hemoglobinopathies

2008-2018:

Charted preclinical path for *ex vivo* and *in vivo*



Hbopathies, cancer, and *some* rare disesase

Table 1. Genome Editing Clinical Trials in the Hemoglobinopathies with IND Applications Received by the U.S. FDA

Indication	*Goal*	*Nuclease/target*	*Sponsor, collaborator*	*Clinical trial ID, reference*	*# Subjects dosed*	*Notes, references*
SCD	Elevate HbF	Cas9/BCL11A enhancer	Vertex Pharmaceuticals, CRISPR Therapeutics	NCT03745287	4	[19]
TDT	Elevate HbF	Cas9/BCL11A enhancer	Vertex Pharmaceuticals, CRISPR Therapeutics	NCT03655678	6	[19]
SCD	Elevate HbF	ZFN/BCL11A enhancer	Sangamo Therapeutics, Sanofi	NCT03653247	—	[20,38,39]
TDT	Elevate HbF	ZFN/BCL11A enhancer	Sangamo Therapeutics, Sanofi	NCT03432364	4	[20,38,39]
SCD	Elevate HbF	Cas9/HBG1/2 promoter	Editas Medicine	—	—	IND submitted 12/9/2020
TDT	Elevate HbF	Cas9/HBG1/2 promoter		—	—	Guided to IND submission in 2021
SCD	Elevate HbF	Cas9/not disclosed	Intellia Therapeutics, Novartis	—	—	Novartis has not disclosed precise strategy
TDT	Elevate HbF	Cas9/not disclosed	Intellia Therapeutics, Novartis	—	—	Novartis has not disclosed precise strategy
SCD	Repair HbS mutation	Cas9 HBB correction	Graphite Bio	—	—	Developed and taken to IND by M. Porteus (Stanford) and then transferred to Graphite[36]
SCD	Repair HbS mutation	Cas9 HBB correction	UCSF Benioffs, UCLA, IGI	—	—	Developed at the IGI, UCSF, and UCLA,[37] taken to IND Nov 2020 by same team

Editas: LCA Intellia: ATTR CRISPR Tx: CD19 CAR-T Cellectis: CARs Allogene: CARs

On approach: Exonics/Vertex, Verve, Beam, Sana, …

CRISPR 2030: if current trends continue ...

There will be approved editing medicines (CRISPR-based and using other nuclease platforms) for:

- Cancer (allo CAR-T)
- Sickle and thal
- A **small number** (< 10) of genetic diseases such as TTR or LCA or familiar hypercholesterolemia

It is certain that, in the US, they will be priced in the > $2 million / patient range.

It is also certain that the VAST majority of “rare” genetic disease will remain unaddressed.

2

The vision of “CRISPR cures for all” is under threat

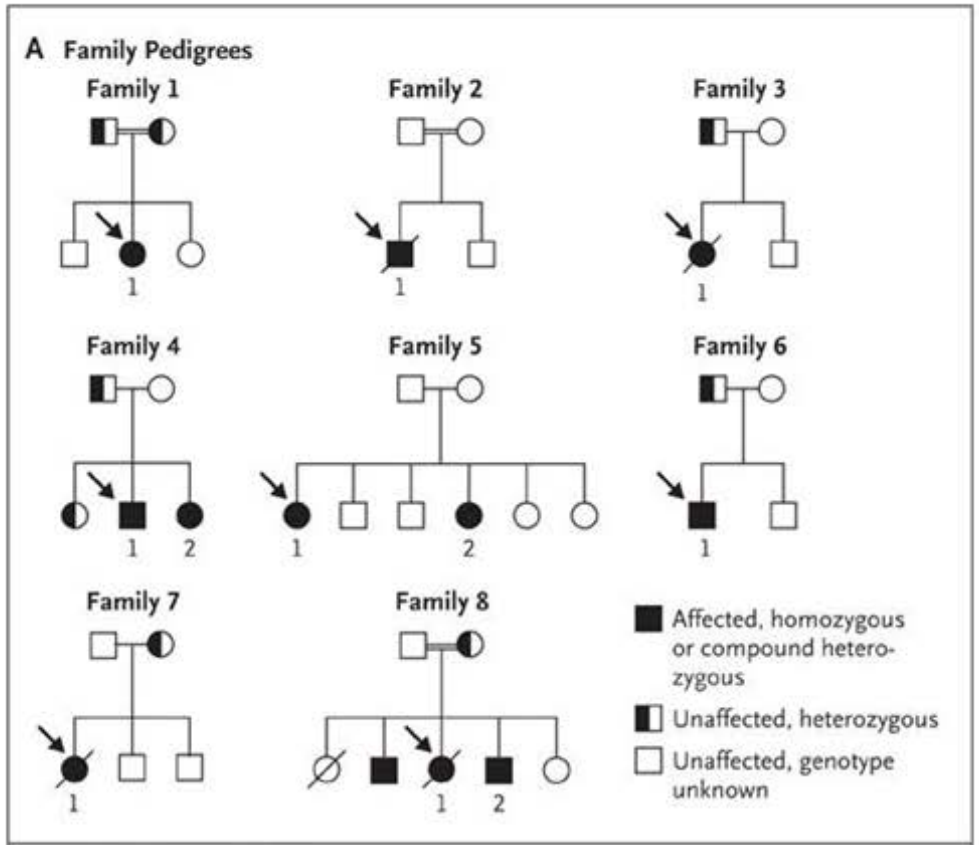
https://well.blogs.nytimes.com/2015/03/28/teen-advance-directive-end-of-life-care/

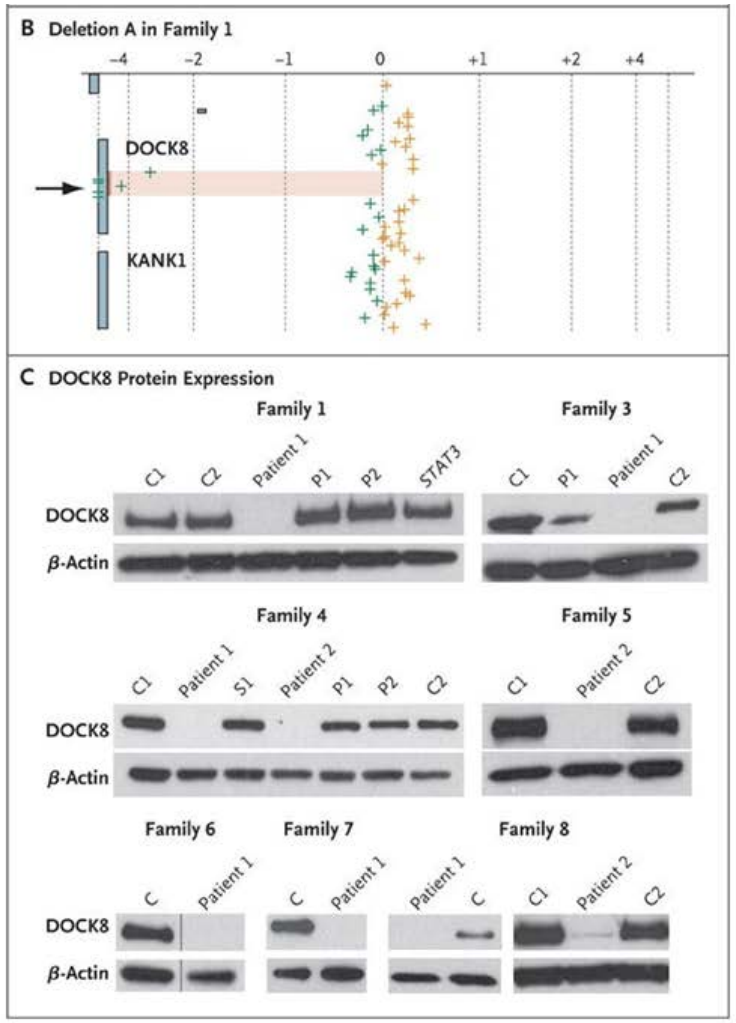
Karly Koch, 20, Muncie, Ind.

“She has a rare genetic immune disorder, and has written about her end-of-life plans”

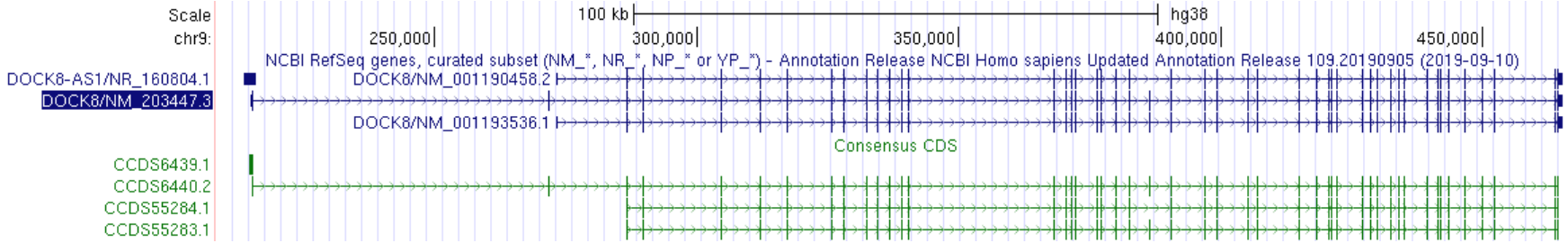
Why didn’t *someone* edit Karly?

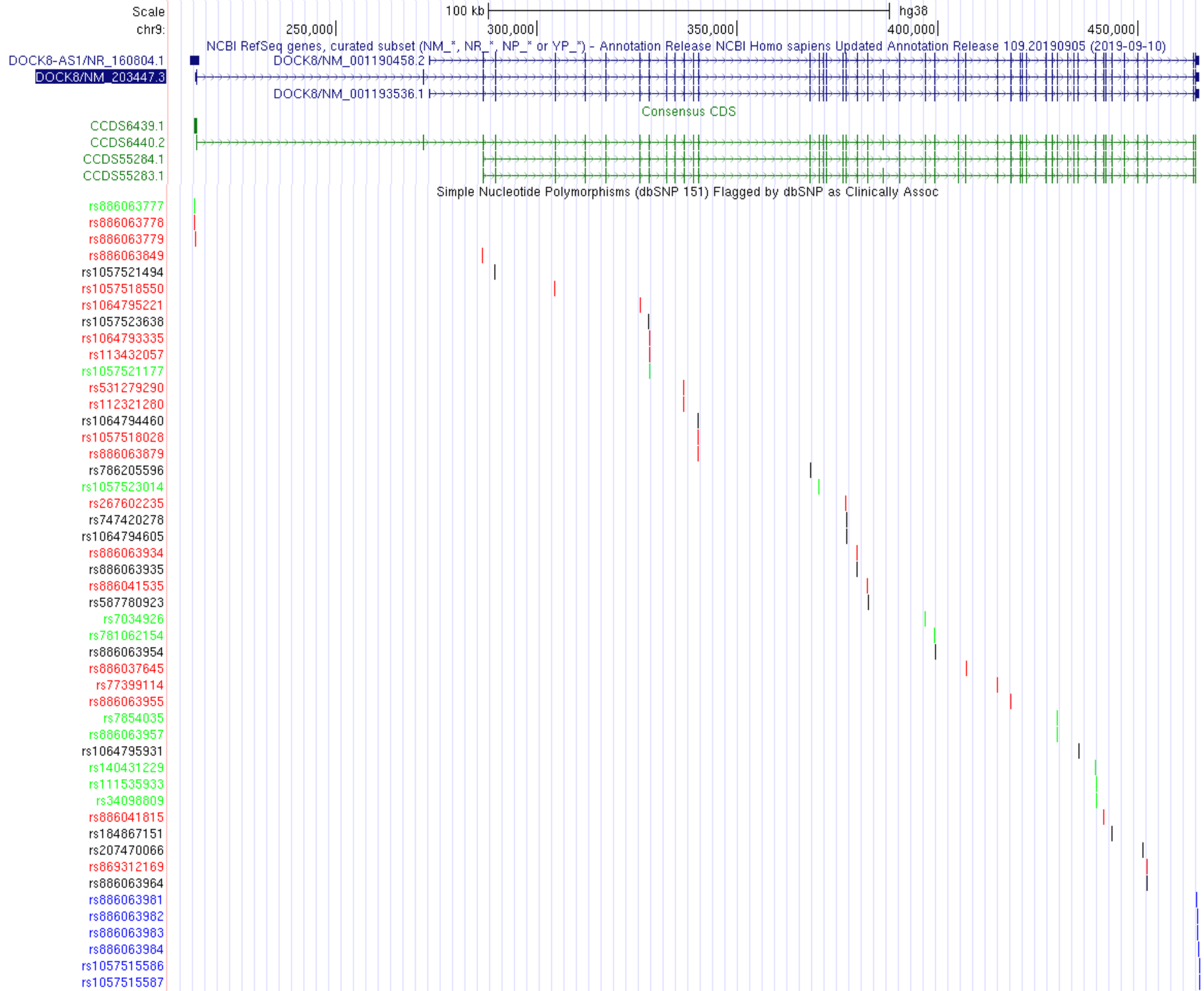
Karly had an immunodeficiency due to loss-of-function mutations in DOCK8 (chr 9p)

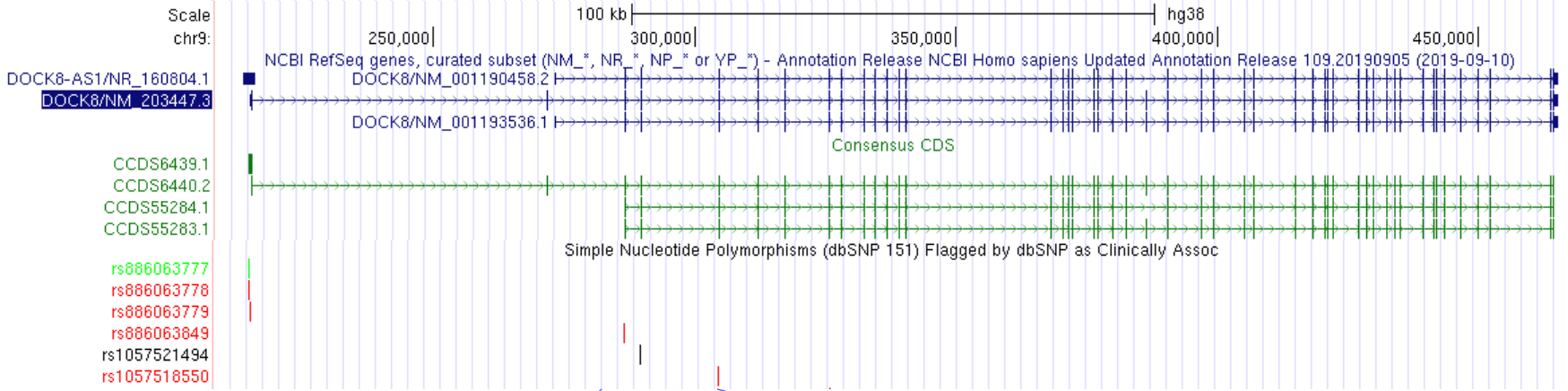


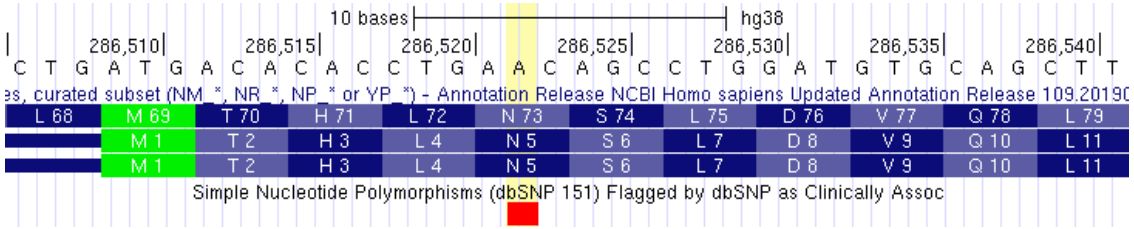


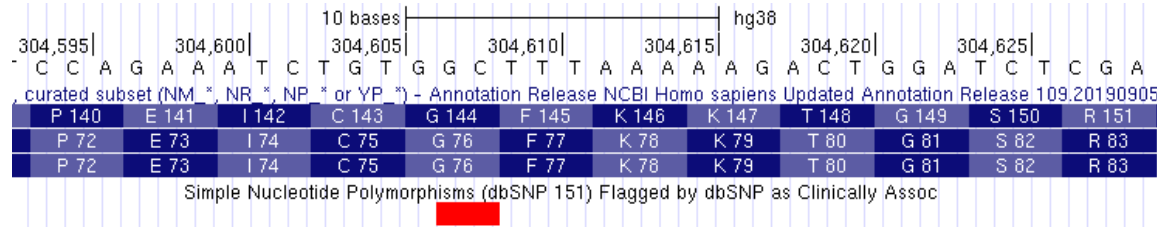
Zhang et al NEJM 2009


Scale
100 kb
hg38
chr9:
250,000
300,000
350,000
400,000
450,000
NCBI RefSeq genes, curated subset (NM_*, NR_*, NP_* or YP_*) - Annotation Release NCBI Homo sapiens Updated Annotation Release 109.20190905 (2019-09-10)
DOCK8-AS1/NR_160804.1
DOCK8/NM_203447.3
DOCK8/NM_001190458.2
DOCK8/NM_001193536.1
Consensus CDS
CCDS6439.1
CCDS6440.2
CCDS55284.1
CCDS55283.1


Scale
100 kb
hg38
chr9:
250,000
300,000
350,000
400,000
450,000
NCBI RefSeq genes, curated subset (NM_*, NR_*, NP_* or YP_*) - Annotation Release NCBI Homo sapiens Updated Annotation Release 109.20190905 (2019-09-10)
DOCK8-AS1/NR_160804.1
DOCK8/NM_203447.3
DOCK8/NM_001190458.2
DOCK8/NM_001193536.1
Consensus CDS
CCDS6439.1
CCDS6440.2
CCDS55284.1
CCDS55283.1
Simple Nucleotide Polymorphisms (dbSNP 151) Flagged by dbSNP as Clinically Assoc
rs886063777
rs886063778
rs886063779
rs886063849
rs1057521494
rs1057518550
rs1064795221
rs1057523638
rs1064793335
rs113432057
rs1057521177
rs531279290
rs112321280
rs1064794460
rs1057518028
rs886063879
rs786205596
rs1057523014
rs267602235
rs747420278
rs1064794605
rs886063934
rs886063935
rs886041535
rs587780923
rs7034926
rs781062154
rs886063954
rs886037645
rs77399114
rs886063955
rs7854035
rs886063957
rs1064795931
rs140431229
rs111535933
rs34098809
rs886041815
rs184867151
rs207470066
rs869312169
rs886063964
rs886063981
rs886063982
rs886063983
rs886063984
rs1057515586
rs1057515587





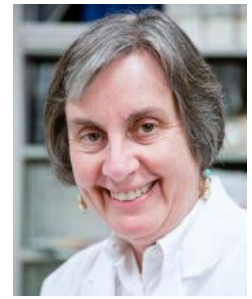


IND #1

IND #2

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

… and now multiply that by 416



Jennifer Puck (UCSF)

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-019-00737-x

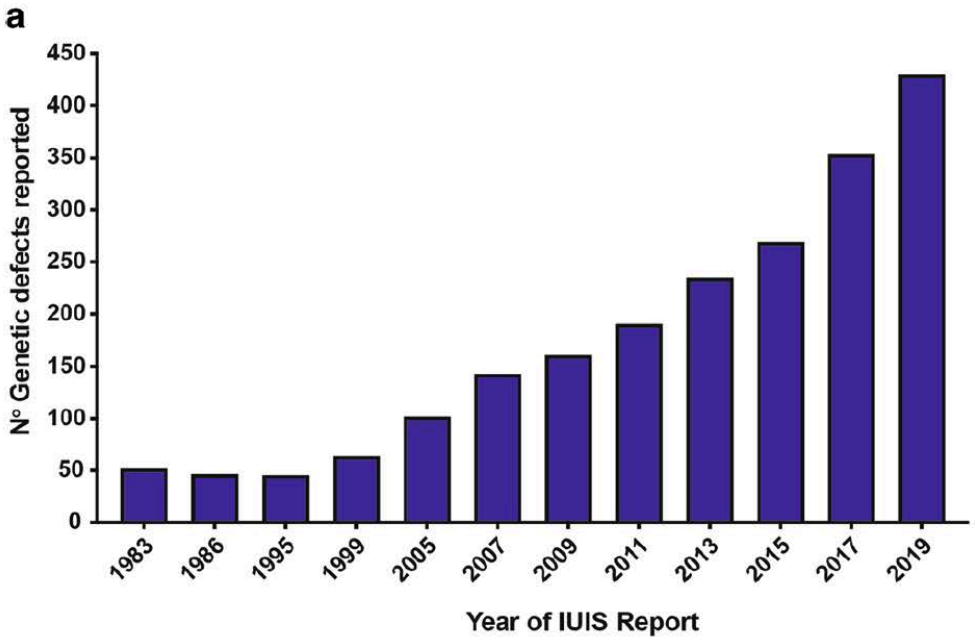
ORIGINAL ARTICLE

Check for updates

Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee

Stuart G. Tangye[1,2] · Waleed Al-Herz[3] · Aziz Bousfiha[4] · Talal Chatila[5] · Charlotte Cunningham-Rundles[6] · Amos Etzioni[7] · Jose Luis Franco[8] · Steven M. Holland[9] · Christoph Klein[10] · Tomohiro Morio[11] · Hans D. Ochs[12] · Eric Oksenhendler[13] · Capucine Picard[14,15] · Jennifer Puck[16] · Troy R. Torgerson[12] · Jean-Laurent Casanova[17,18,19,20] · Kathleen E. Sullivan[21]

Received: 4 November 2019 / Accepted: 18 December 2019



Tangye et al *JCI* 2019

The fact that editing represents an approach to the majority of primary immunodeficiences *in principle* does not mean that some biotech will take on disease #314 *in practice*.

We need a fundamentally new N=1 framework.

And it has to be a public-sector one.

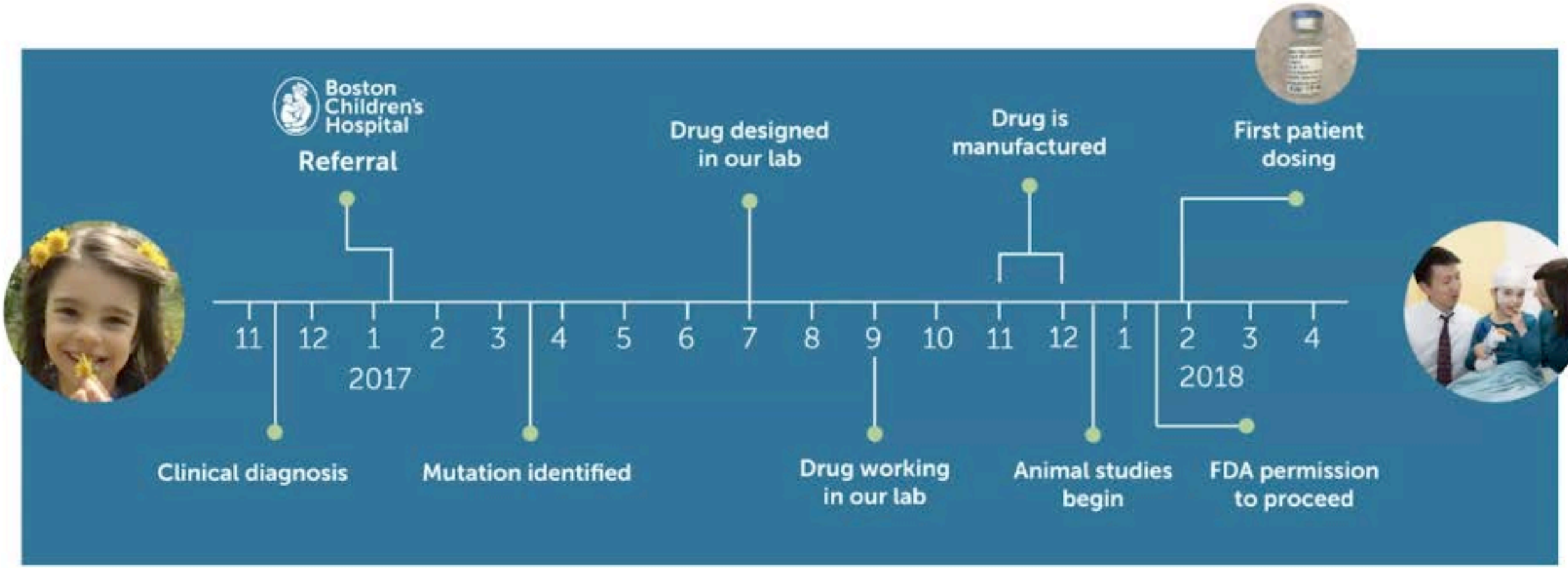
There is a giant gap between commercially viable products (eg allo CAR-T, SCD/TDT, hemophilia), and N=1 indications where the NPV is such that it makes no commercial sense for a for-profit-entity to take it on.

3

A once-in-a-generation moment in biotechnology

Slide courtesy of Timothy Yu, Boston Childrens

A patient-customized ASO for Batten disease



Kim & Hu et al, NEJM 2019
Boston Children's Hospital
Mila's Miracle Foundation

Slide courtesy of Peter Marks, FDA CBER

Bespoke Gene Therapy Consortium

Non-profit umbrella organization

FDA to streamlining of regulatory requirements: master files/templates

Idea for Gene Therapy Target

Vector generation

Manufacture of therapeutic

Clinical ability to treat patients

Therapies for patients

Standard vector menu

Standard process menu

Standard delivery menu

All results from treatments are reported back to the consortium for iterative learning

Broad Area of Opportunity:

Enabling Equitable Access to CRISPR-Cas Treatments for Severe Disease

The Gladstone-UCSF Institute of Genomic Immunology

GLADSTONE INSTITUTES UCSF

Innovative Genomics Institute

4

From N=1 to N=many

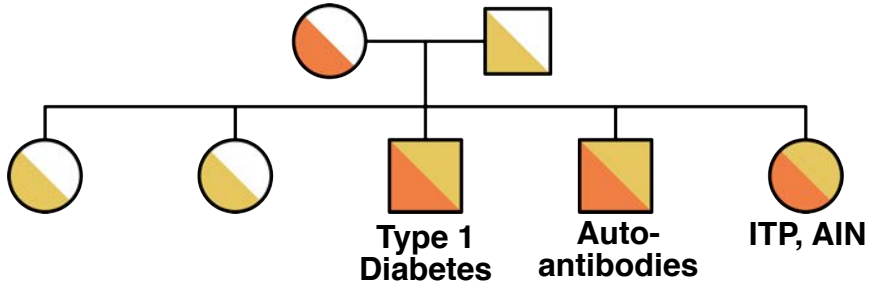
A case study

Not merely a line on page 19 out of 41 …

Disease	Genetic defect	Inheritance	OMIM	Circulating T cells	Circulating B cells	Functional defect	Associated features
1. Familial hemophagocytic lymphohistiocytosis (FHL syndromes)							
Perforin deficiency (FHL2)	*PRF1*	AR	170280	Increased activated T cells	Normal	Decreased to absent NK and CTL activities cytotoxicity	Fever, HSM, hemophagocytic lymphohistiocytosis (HLH), cytopenias
UNC13D/Munc13–4 deficiency (FHL3)	*UNC13D*	AR	608897	Increased activated T cells	Normal	Decreased to absent NK and CTL activities (cytotoxicity and/or degranulation)	Fever, HSM, HLH, cytopenias,
Syntaxin 11 deficiency (FHL4)	*STX11*	AR	605014				
STXBP2/Munc18–2 deficiency (FHL5)	*STXBP2*	AR or AD	601717				
FAAP24 deficiency	*FAAP24*	AR	610884	Increased activated T cells	Normal	Failure to kill autologous EBV transformed B cells. Normal NK cell function	EBV-driven lymphoproliferative disease
SLC7A7 deficiency	*SLC7A7*	AR	222700	Normal	Normal	Hyper-inflammatory response of macrophages Normal NK cell function	Lysinuric protein intolerance, bleeding tendency, alveolar proteinosis
2. FHL syndromes with hypopigmentation							
Chediak-Higashi syndrome	*LYST*	AR	606897	Increased activated T cells	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, recurrent infections, fever, HSM, HLH, giant lysosomes, neutropenia, cytopenias, bleeding tendency, progressive neurological dysfunction
Griscelli syndrome, type 2	*RAB27A*	AR	603868	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, fever, HSM, HLH, cytopenias
Hermansky-Pudlak syndrome, type 2	*AP3B1*	AR	603401	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia, HLH
Hermansky-Pudlak syndrome, type 10	*AP3D1*	AR	617050	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Oculocutaneous albinism, severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay
3. Regulatory T cell defects							
IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked	*FOXP3*	XL	300292	Normal	Normal	Lack of (and/or impaired function of) $CD4^+$ $CD25^+$ $FOXP3^+$ regulatory T cells (Tregs)	Autoimmune enteropathy, early onset diabetes, thyroiditis hemolytic anemia, thrombocytopenia, eczema, elevated IgE and IgA
CD25 deficiency	*IL2RA*	AR	147730	Normal to decreased	Normal	No CD4 + C25+ cells with impaired function of Tregs cells	Lymphoproliferation, autoimmunity, impaired T cell proliferation in vitro

Jeff Bluestone, PhD

Kevan Herold, MD



Tangye J Clin Immunol 2019

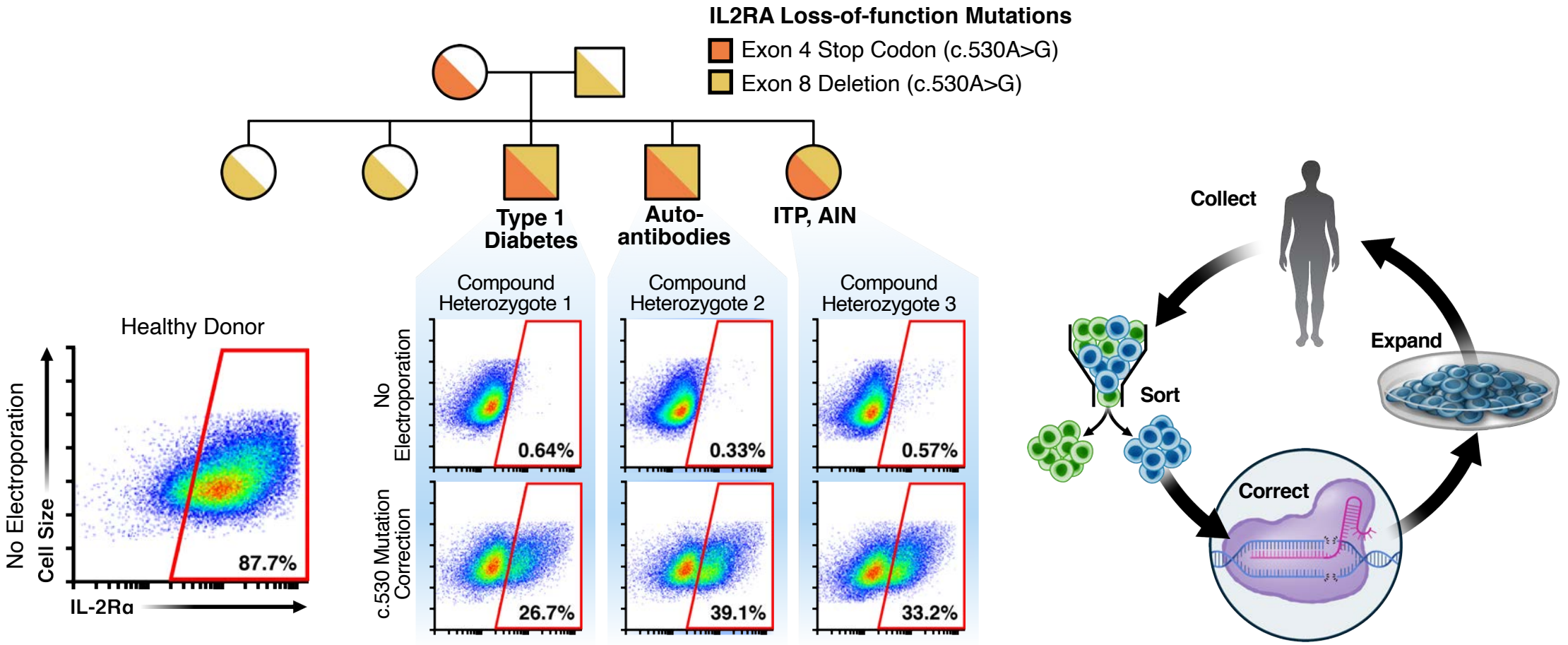
Jennifer Doudna

Alex Marson

Jonathan Esensten

Brian Shy

2015: T cell editing w Cas9 RNP -> 2018: **all-nonviral** T cell mutation repair (*Nature*)



Wrapping up for a 2021 N=1 IND

California has a vibrant cell/gene therapy/editing ecosystem in its research universities

Maria Grazia Roncarolo

Matthew Porteus
(both Stanford)

ARTICLES
https://doi.org/10.1038/s41591-018-0137-0
nature medicine

A high-fidelity Cas9 mutant delivered as a ribonucleoprotein complex enables efficient gene editing in human hematopoietic stem and progenitor cells

Christopher A. Vakulskas[1,7], Daniel P. Dever[2,7], Garrett R. Rettig[1], Rolf Turk[1], Ashley M. Jacobi[1], Michael A. Collingwood[1], Nicole M. Bode[1], Matthew S. McNeill[1], Shuqi Yan[1], Joab Camarena[2], Ciaran M. Lee[3], So Hyun Park[3], Volker Wiebking[2], Rasmus O. Bak[4,5], Natalia Gomez-Ospina[2], Mara Pavel-Dinu[2], Wenchao Sun[6], Gang Bao[3], Matthew H. Porteus[2*] and Mark A. Behlke[1*]

Open IND for editing in SCD Nov 2020

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

SICKLE CELL DISEASE

Selection-free genome editing of the sickle 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*]

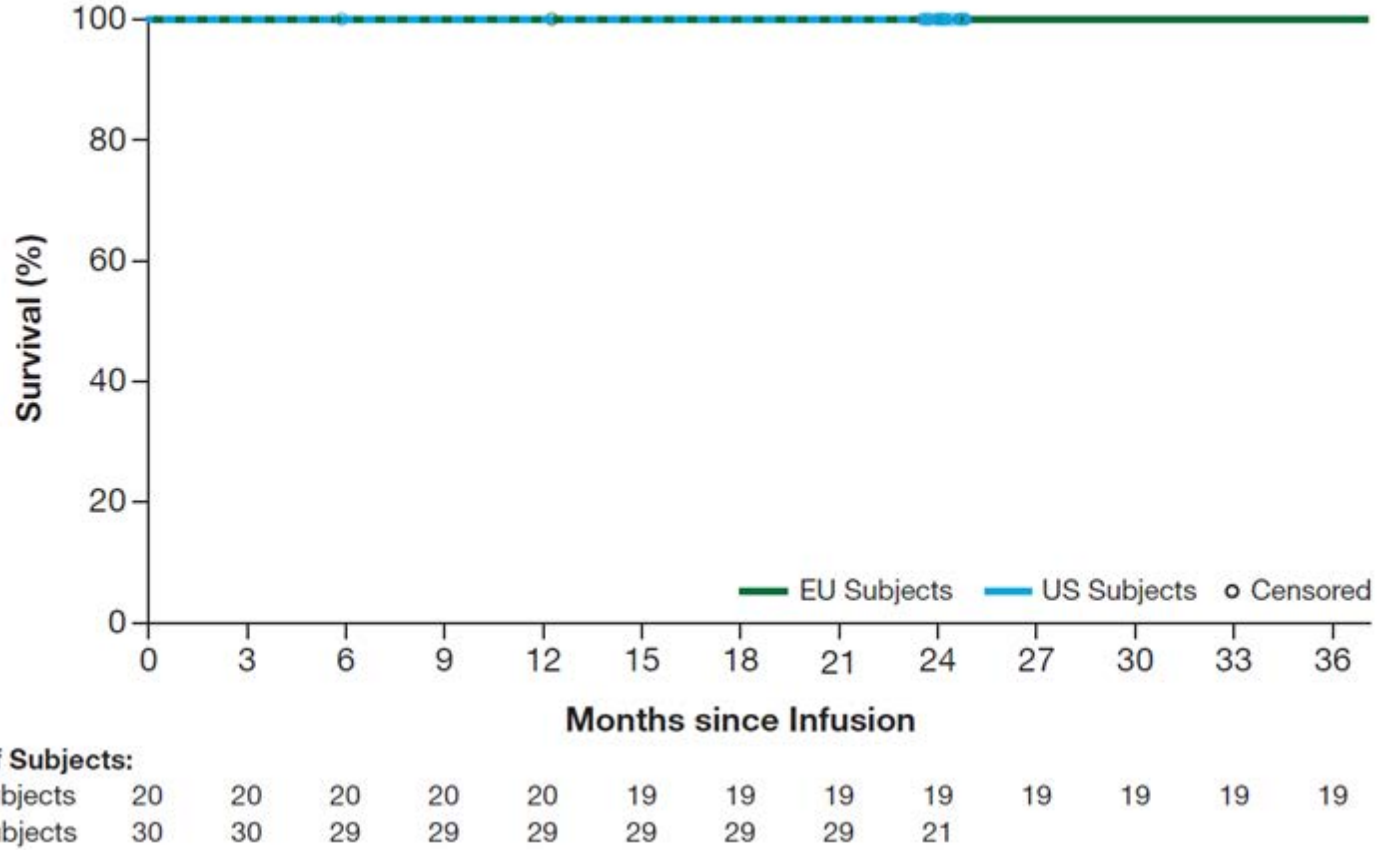
Open IND for editing in SCD Nov 2020

Don Kohn (UCLA)

Mark Walters (UCSF)

Autologous *Ex Vivo* Lentiviral Gene Therapy for the Treatment of Severe Combined Immunodeficiency due to Adenosine Deaminase Deficiency

50
PEDIATRIC
SUBJECTS



No. of Subjects:													
EU Subjects	20	20	20	20	20	19	19	19	19	19	19	19	19
US Subjects	30	30	29	29	29	29	29	29	21				

Don Kohn (UCLA)

Kohn, Booth et al, NEJM, In Press

C4

A CIRM Consortium for CRISPR Cures

Team up (“Avengers”)

Existing strengths -> core hubs

“Maniatis mindset”: standardize!

Key partners: FDA + industry

Patient

Causative Variant

Effector

Efficacy, safety

CMC

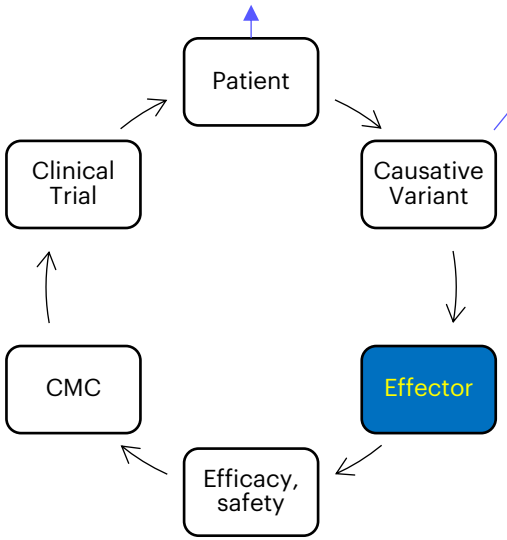
Clinical Trial

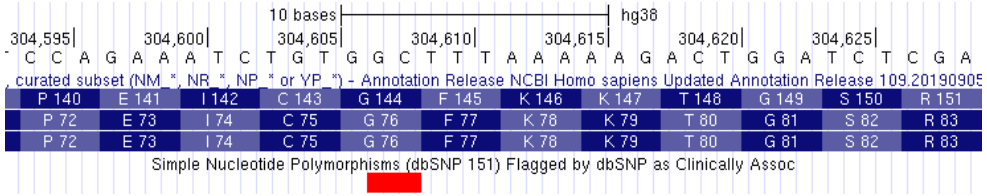
CIRM
CALIFORNIA'S STEM CELL AGENCY

FDA

UCSF Innovative Genomics Institute UCLA

GLADSTONE INSTITUTES UCSF
Gladstone-UCSF Institute of Genomic Immunology





Editing strategy

KO, repair, TI, new?

Editing mode:

Cutting, base, prime, epi, new?

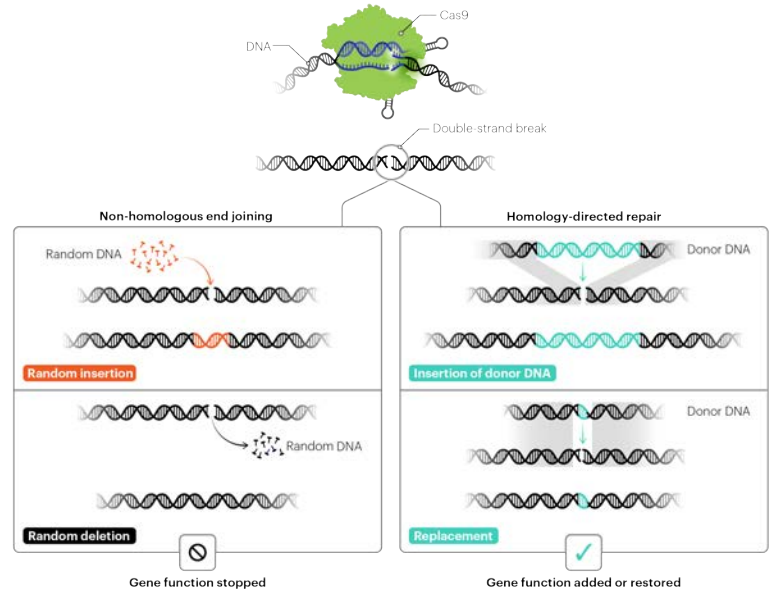
Which Cas?

Evergreen “Library of CRISPR”

Design

CMC

In-house vs industry CRO



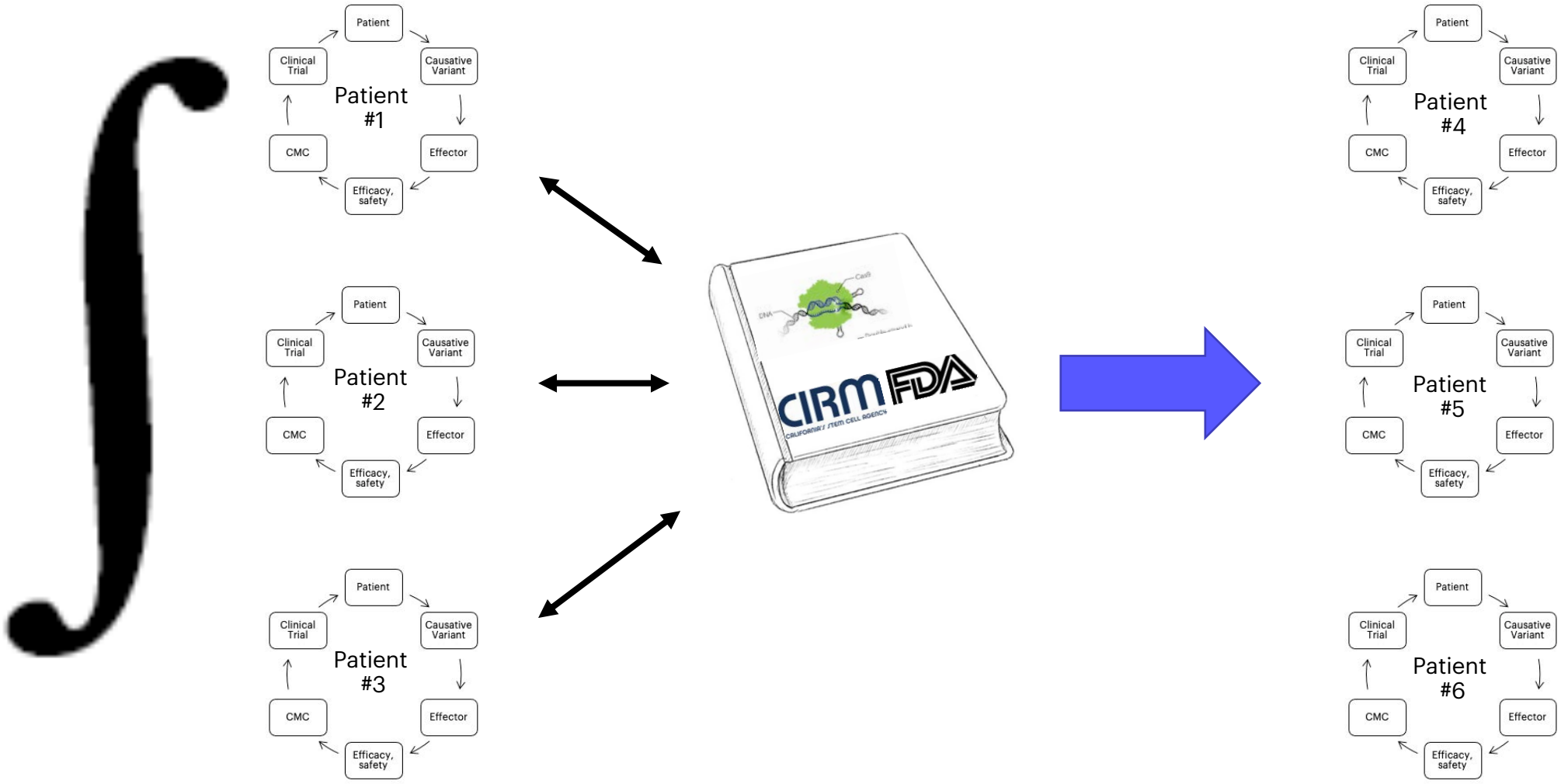
Research lead (1 week) – max. efficiency – transfer to Team PD for pilot runs and Team Biology

Clinical lead (6-8 weeks) – maximal efficiency, FDA-grade specificity – Team PD eng. Runs

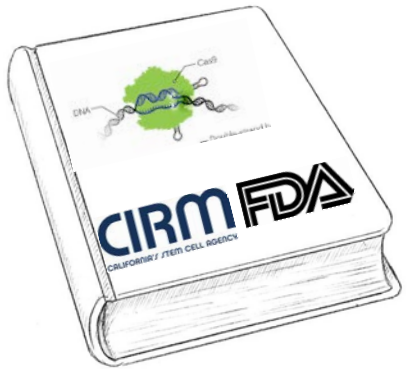
Team Tox – maximal focus on ex vivo – scientific + regulatory innovation

+1 Kevin Eggan, Peter Marks, Cat Jamieson re innovation in tox and LTFU!!! +1 Chris re PM!

An FDA-grade CRISPR Cures Cookbook
continuously upgraded by clinical experience



"On-ramp for training next generation of translational scientists and clinician-scientists"

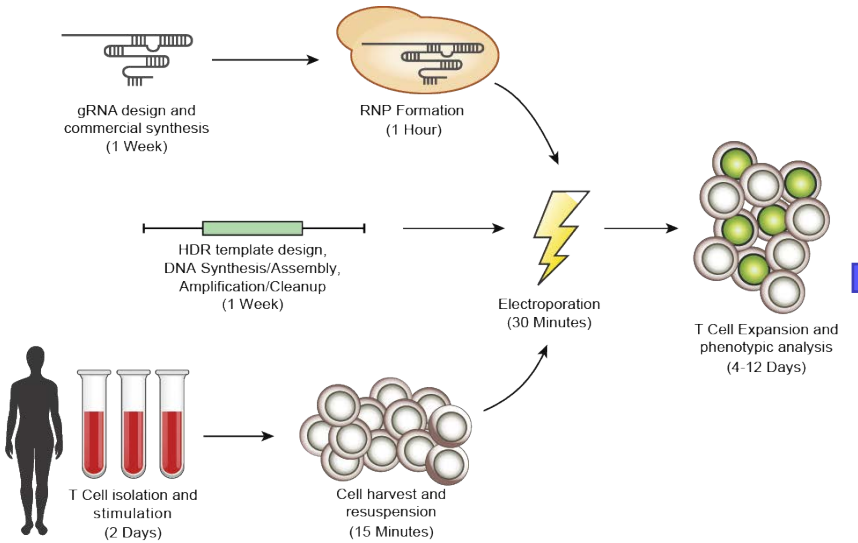


Beyond Blood – Leveraging Nonviral Cell Engineering / Screening Into Oncology

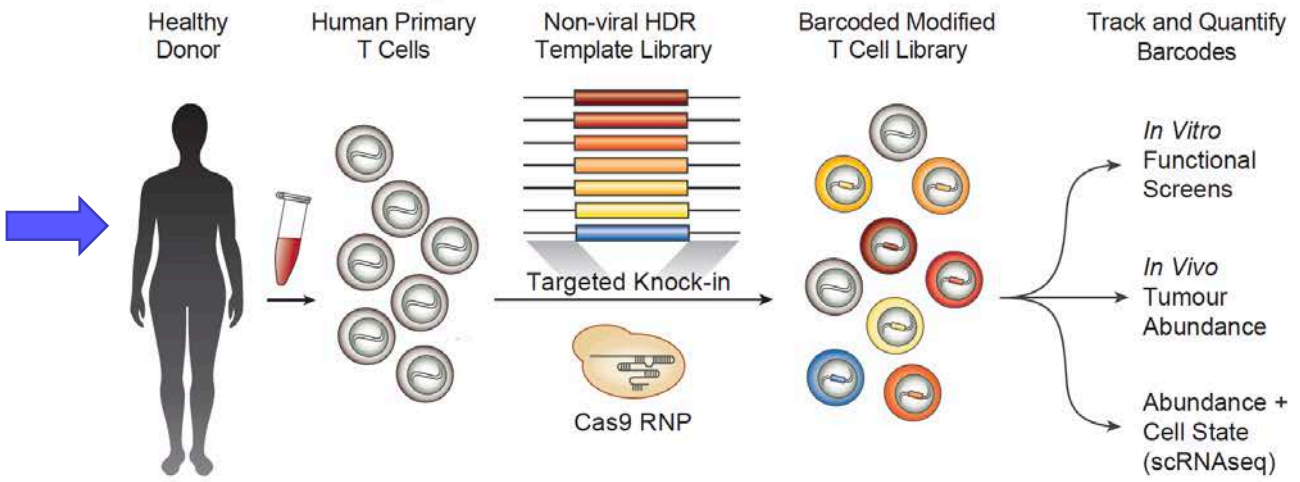
Alex Marson

Toni Ribas

Nature 2018: nonviral T cell editing



Cell 2018, 2020: nonviral T cell functional genomics for CART



PANEL OF INDs

Multiplex all-nonviral cell editing / epiediting for cancer therapeutics

But what about Allogene, Sangamo, Lyell, CRISPR Tx, Beam, Cellectis, Sana, T-munity, Poseida, Senti and a formidable number of other companies? -> not a zero sum game!

“A rising tide lifts all boats” – JFK 1963

Why build a dam in Arkansas?

“These projects produce wealth, they bring industry, they bring jobs, and the wealth they bring brings wealth to other sections of the United States. This State had about 200,000 cars in 1929. It has a million cars now. They weren't built in this State. They were built in Detroit. As this State's income rises, so does the income of Michigan. As the income of Michigan rises, so does the income of the United States. A rising tide lifts all the boats and as Arkansas becomes more prosperous so does the United States and as this section declines so does the United States.”

https://www.presidency.ucsb.edu/documents/remarks-heber-springs-arkansas-the-dedication-greers-ferry-dam