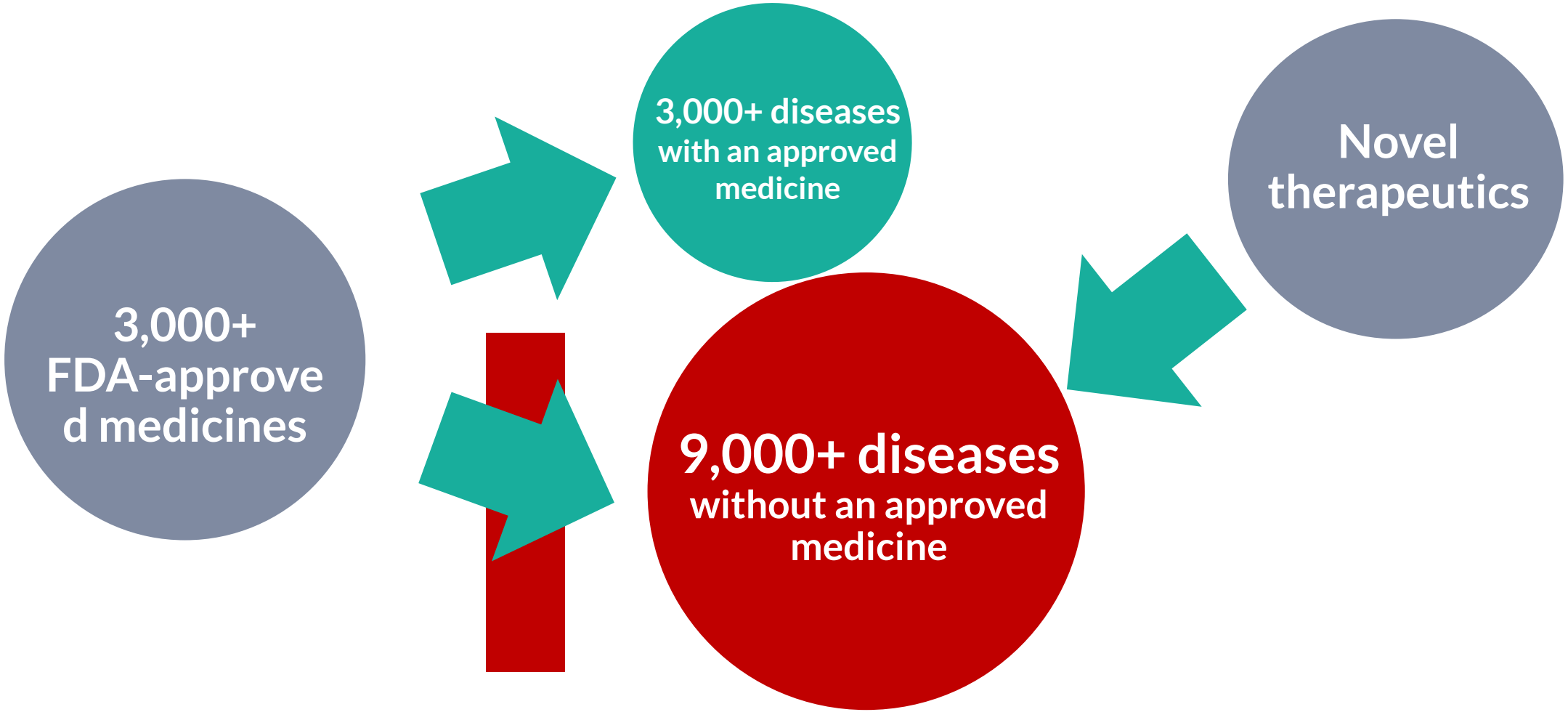
From Chasing My Cure to Every Cure:
Unlocking the full potential of available medicines

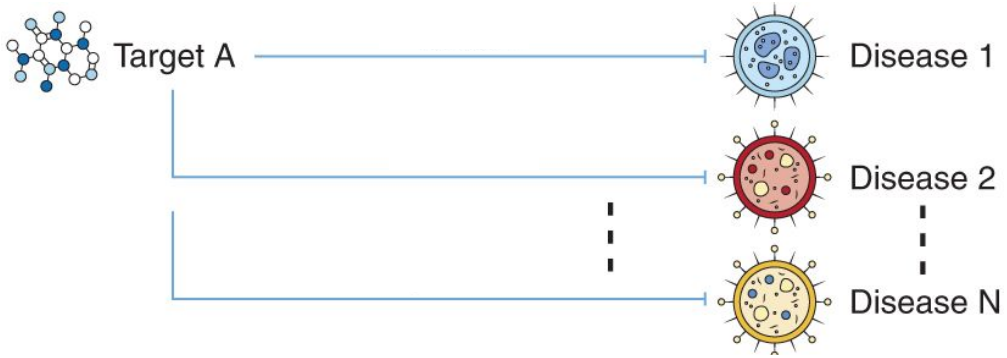
DAVID FAJGENBAUM, MD, MBA, MSc
Founding Director, Center for Cytokine Storm Treatment & Laboratory
Associate Director, Orphan Disease Center, University of Pennsylvania
Co-Founder & President, Castleman Disease Collaborative Network
Co-Founder & President, Every Cure

March 7, 2024

3,000 medicines are approved for 3,000 diseases, but 9,000+ diseases don't have a single approved therapy



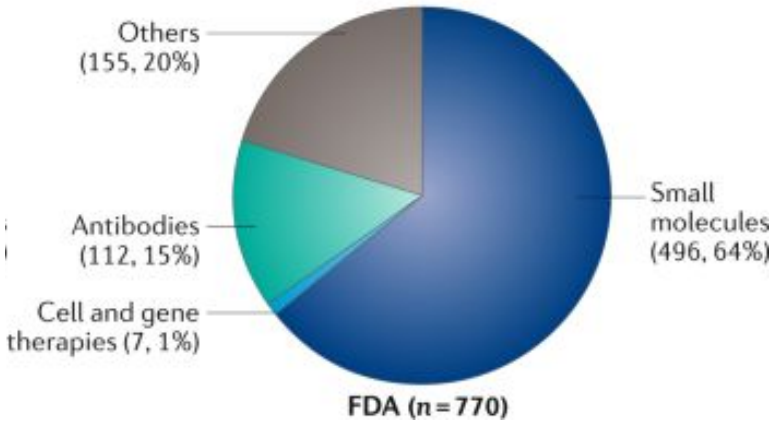
Many diseases share mechanisms and many drugs have multiple targets, highlighting the potential of repurposing



Korsunska & Fajgenbaum, Nat Mach Intell, 2021.

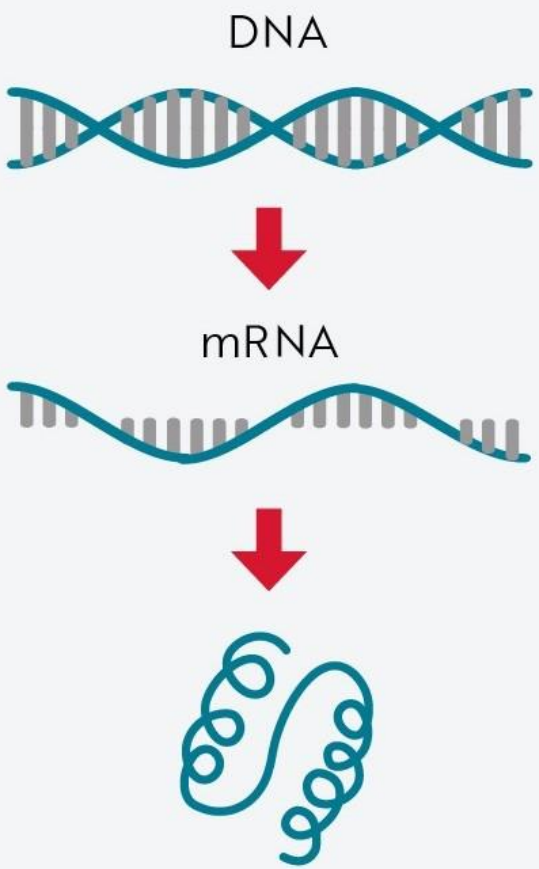
Novel treatment modalities are advancing to patients faster than ever

Modality	Cause of disease at the protein level		Molecular target			Protein target localization			Delivery		
	Reduction or loss of function	Excessive or detrimental function	DNA	RNA	Protein	Extracellular	Plasma membrane	Intracellular	Oral	Injection	Inhaled
Small molecule	●	●	●	●	●	●	●	●	●	●	●
Protein replacement	●				●	●		●		●	
Antibody		●			●	●	●			●	
Oligonucleotide therapy	●	●		●		●	●	●		●	
Cell and gene therapy*	●		●			●	●	●		●	

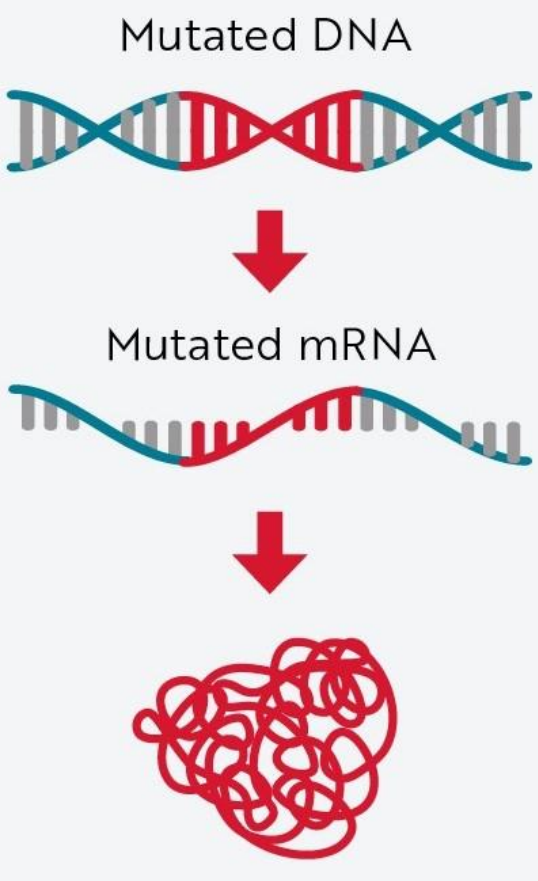


Tambuyzer et al. Nature Reviews Drug Discovery. 2019.

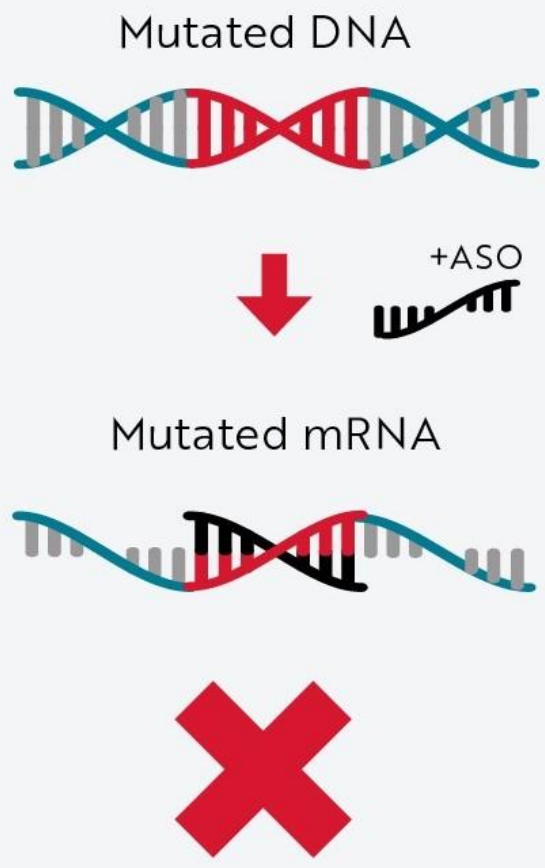
NO MUTATIONS



DISEASE-LINKED GENE MUTATIONS



DISEASE-LINKED GENE MUTATIONS + ASO



Knockdown ASOs work to eliminate the mutated, toxic protein by preventing it from being produced.

Even gene therapies and cellular therapies have potential beyond their initial indication

F.D.A. Approves Sickle Cell Treatments, Including One That Uses CRISPR

People with the genetic disease have new opportunities to eliminate their symptoms, but the treatments come with obstacles that limit their reach.

By Gina Kolata
Gina Kolata has reported on gene therapy for nearly 30 years and on sickle cell disease since 2018.

Dec. 8, 2023 Updated 12:27 p.m. ET

On Friday, the Food and Drug Administration approved the first gene editing therapy ever to be used in humans, for sickle cell disease, a debilitating blood disorder caused by a single mutated gene.

The agency also approved a second treatment using conventional gene therapy for sickle cell that does not use gene editing.

FDA NEWS RELEASE

FDA approval brings first gene therapy to the United States

Share | Post | Linkedin | Email | Print

For Immediate Release: August 30, 2017

First gene editing therapy to treat beta thalassemia and severe sickle cell disease

Share

15 December 2023

EMA has recommended approval of the first medicine using CRISPR/Cas9, a novel gene-editing technology. Casgevy (exagamglogene autotemcel) is indicated for the treatment of transfusion-dependent beta thalassemia and severe sickle cell disease in patients 12 years of age and older for whom haematopoietic stem cell transplantation is appropriate and a suitable donor is not available.

CAR T-Cell Therapy Shows Promise in Autoimmune Diseases in Early Study Presented at ASH

Dec 10, 2023 | Jessica Kim Cohen

Premium

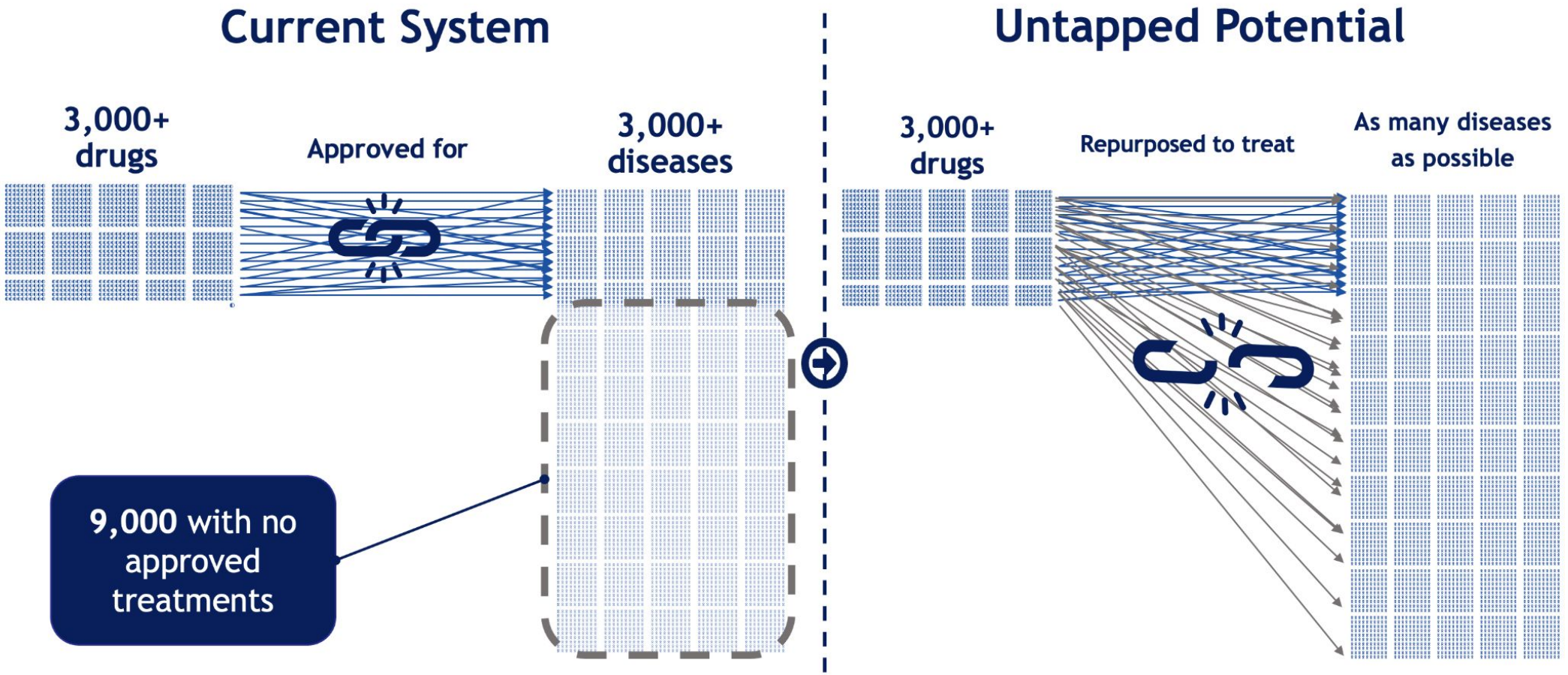
NEW YORK – An autologous CAR T-cell therapy originally designed for cancer led to complete drug-free remission in patients with lupus and other autoimmune diseases, according to a small study presented on Saturday at the American Society of Hematology's annual meeting in San Diego.

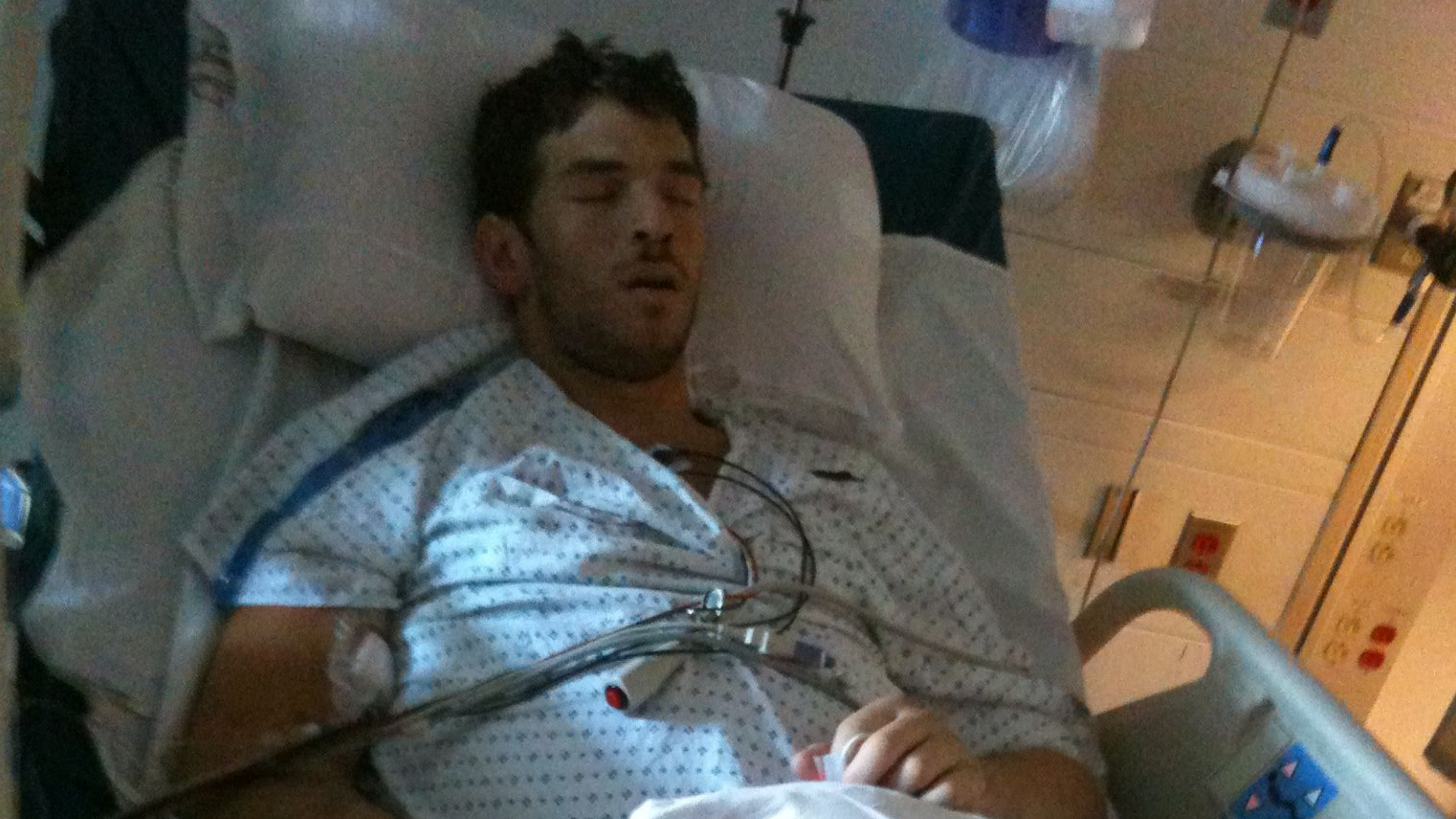
Pornpak Khunatorn / Getty Images

A team of researchers in Germany sought to establish whether a CD19-targeting CAR T-cell therapy, dubbed MB-CART19.1, that has previously been used to treat B-cell malignancies could also treat autoimmune diseases triggered by autoreactive B cells, such as systemic lupus erythematosus (SLE), idiopathic inflammatory myositis (IIM), and systemic sclerosis (SSc).

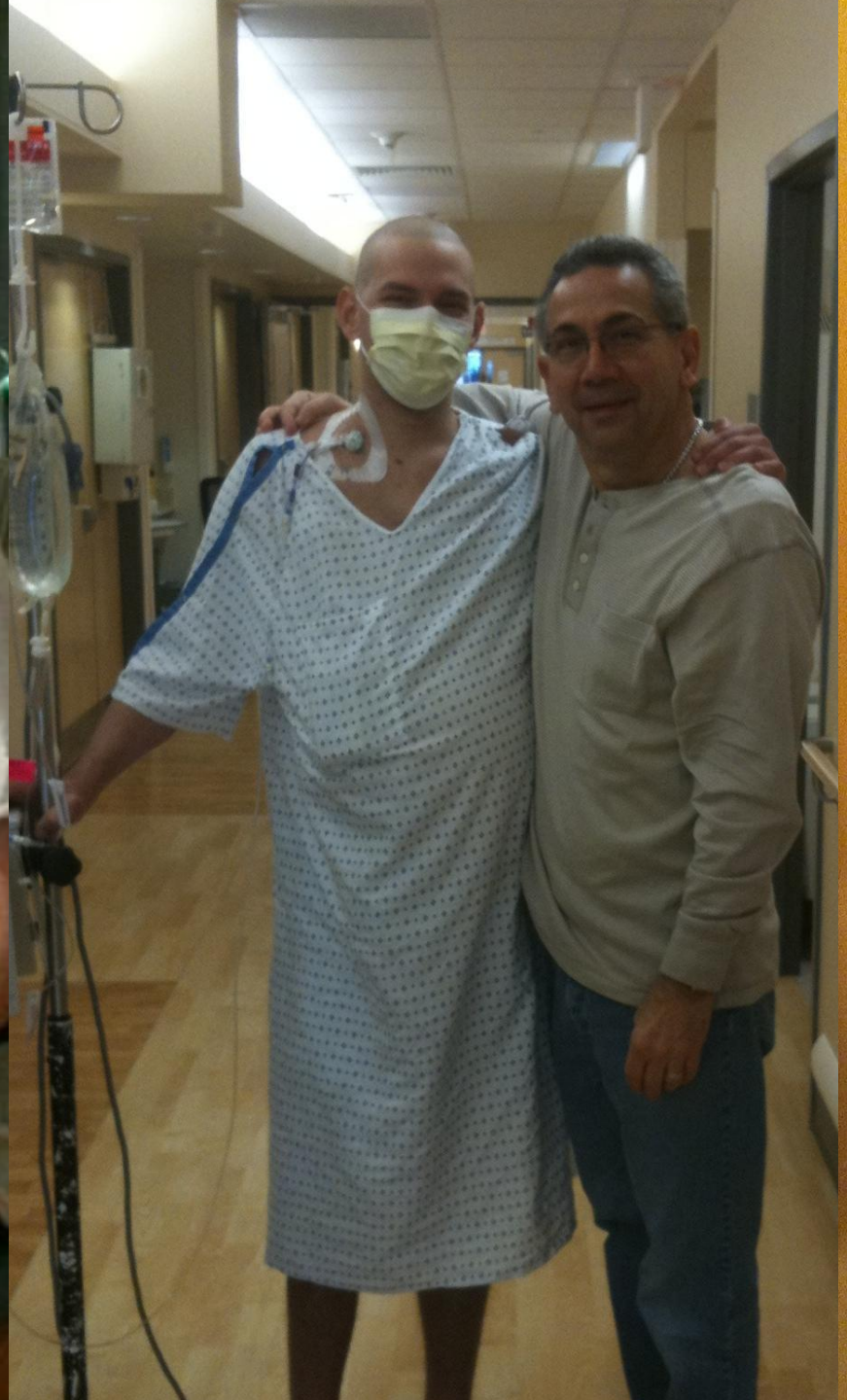
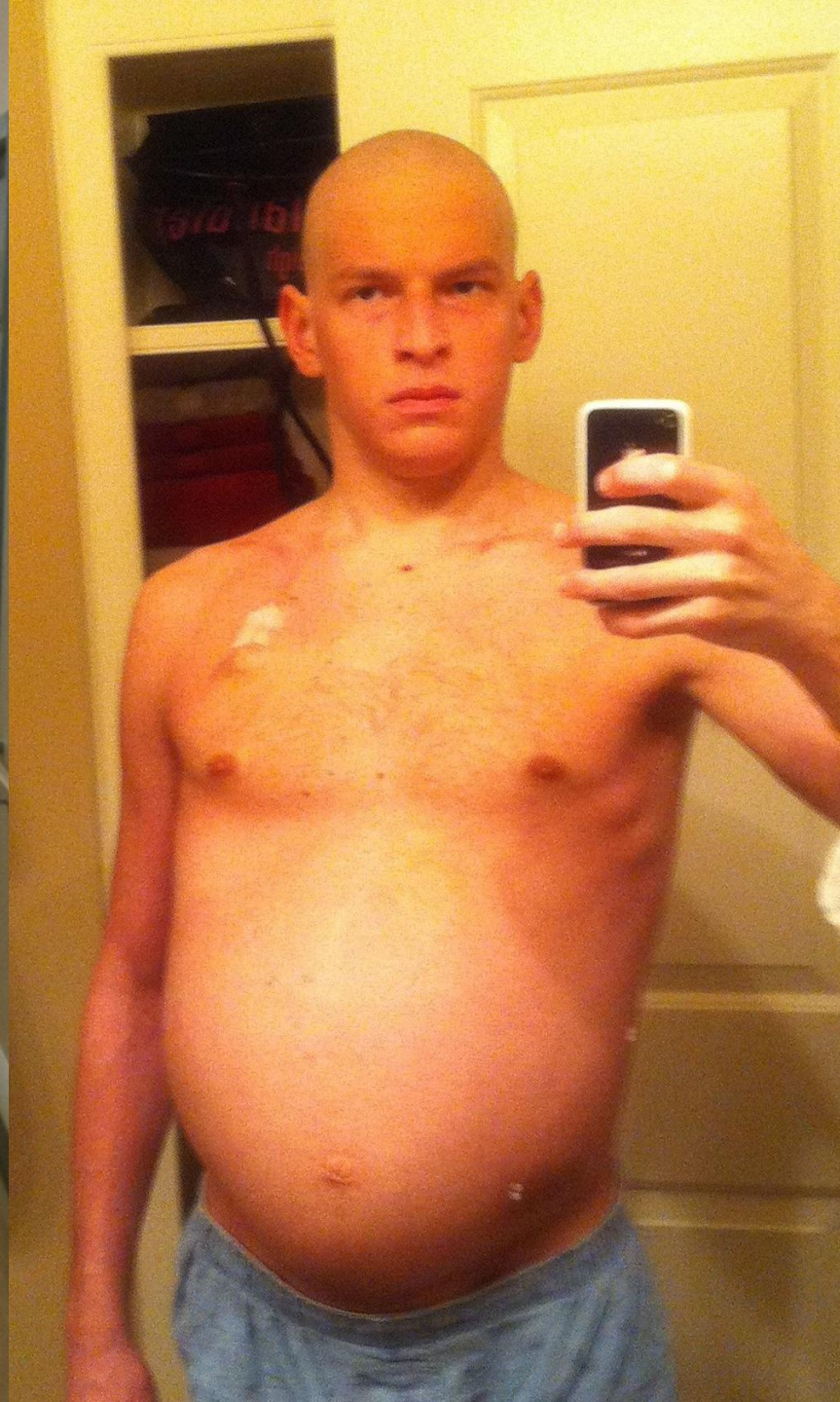
Tambuyzer et al. Nature Reviews Drug Discovery. 2019.

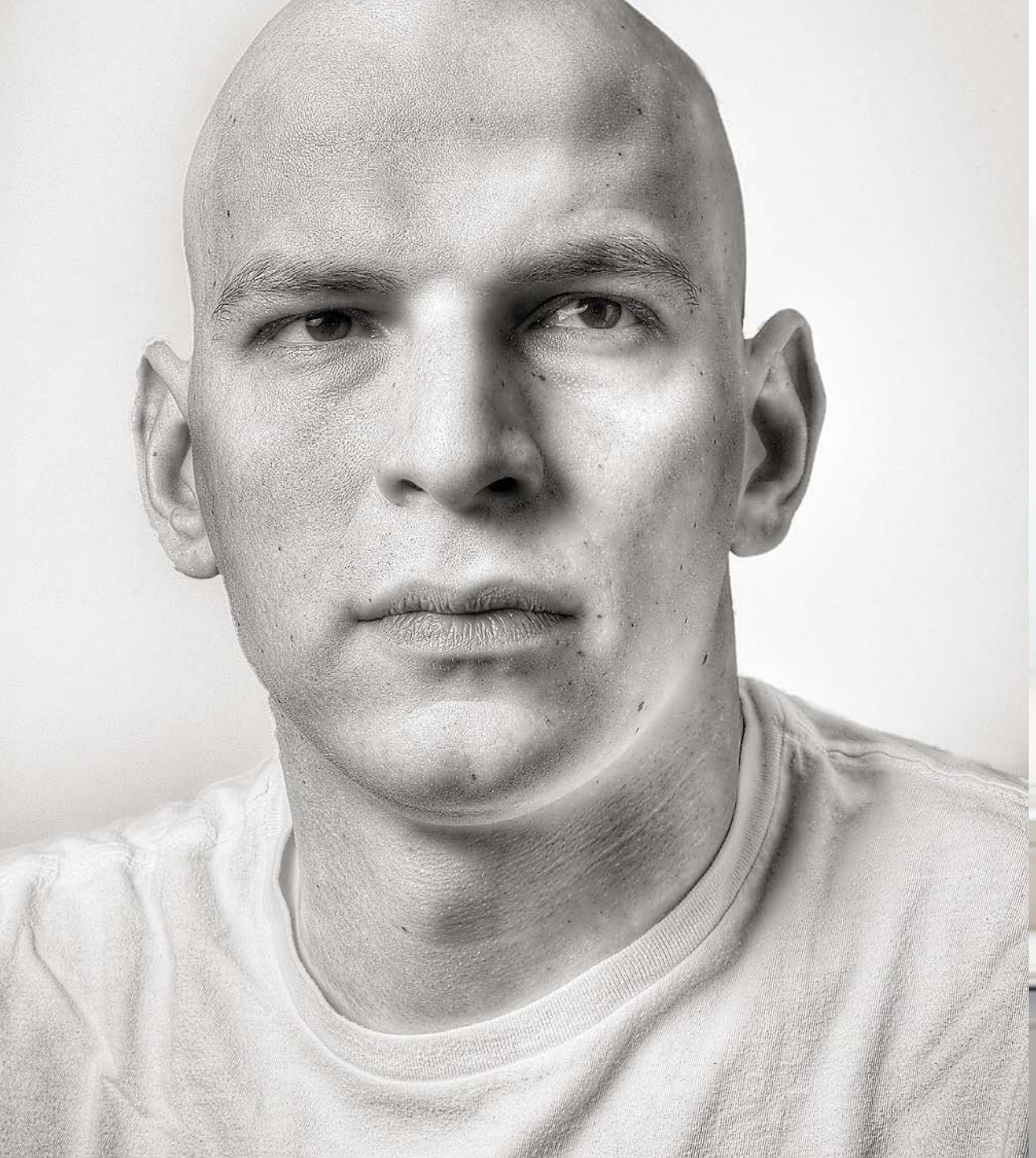
There is tremendous untapped potential within our FDA-approved medicines



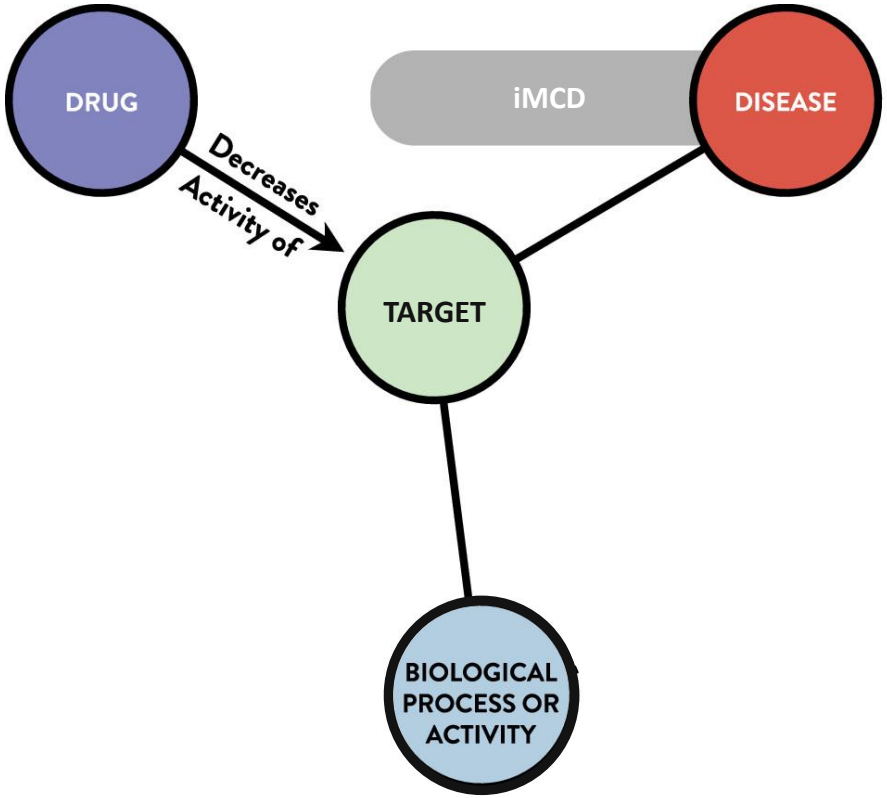



EXIT

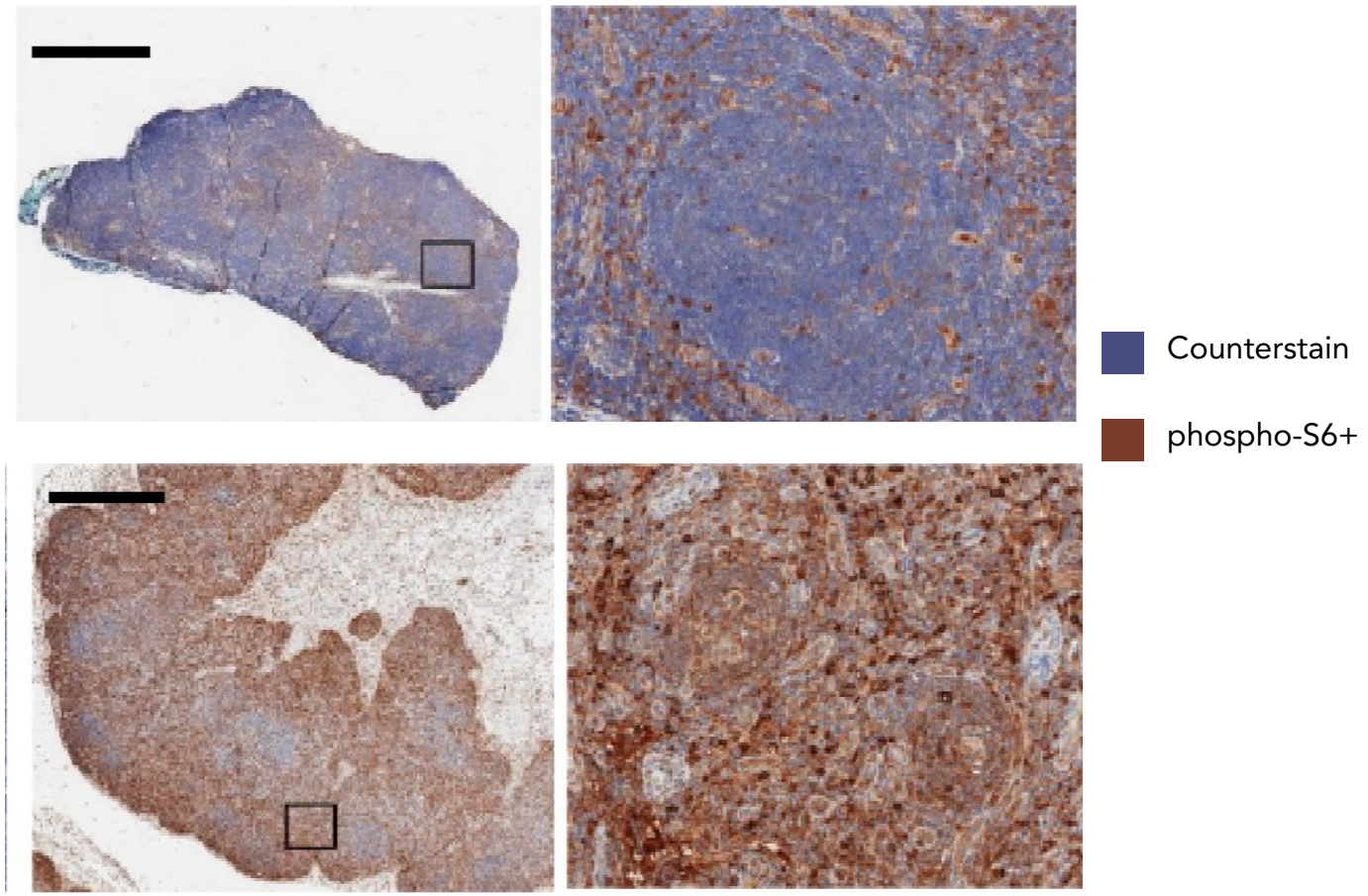






Sirolimus identified for iMCD by uncovering mechanistic insights

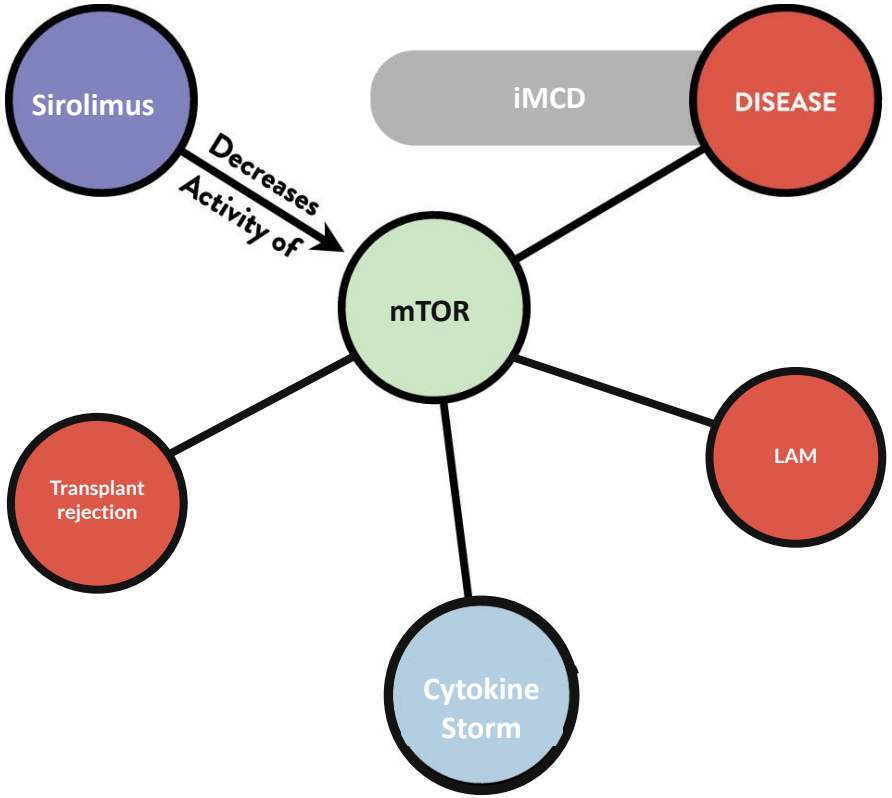


Immunohistochemistry for pS6, a marker of mTOR activation



Fajgenbaum et al. JCI, 2019.

Sirolimus identified for iMCD by uncovering mechanistic insights



Fajgenbaum et al. JCI, 2019.

"An extraordinary memoir . . . It belongs with Atul Gawande's writings and *When Breath Becomes Air*." —Adam Grant, *New York Times* bestselling author of *Originals*

NATIONAL BESTSELLER

CHASING MY CURE

A Doctor's Race to Turn Hope into Action

A MEMOIR

David Fajgenbaum

Above, Clarice Maggio, a nurse
port on Dr. David Fajgenbaum
through which he will receive t
the Hospital of the University o
Pennsylvania. Left, the doctor,
Castleman disease, with his wi
home in Philadelphia.

Doctor, Cure Thyself

On the brink of death, a physician with a rare disease decides to become his own test subject.

By KATIE THOMAS

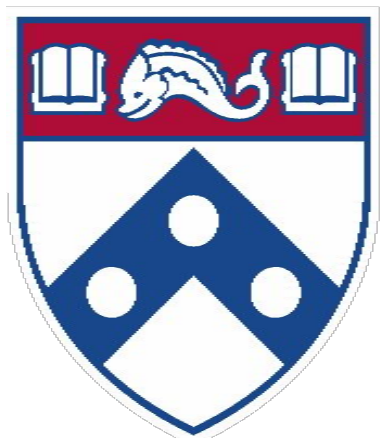
They called him the Beast.

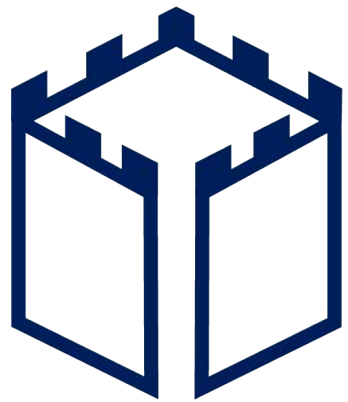
David Fajgenbaum was the fittest of his friends at the University of Pennsylvani
medical school, a 6-foot-3 gym
former quarterback
mammoth

his former roommate, Gran
used to walk to
would

The New York Times

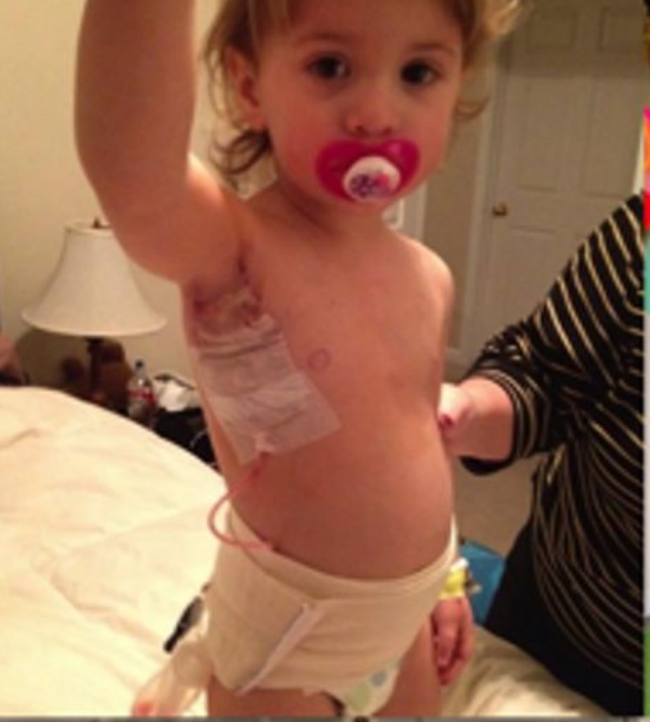
SUNDAY, FEBRUARY 5, 2017





CSTL

Center *for* Cytokine Storm
Treatment & Laboratory

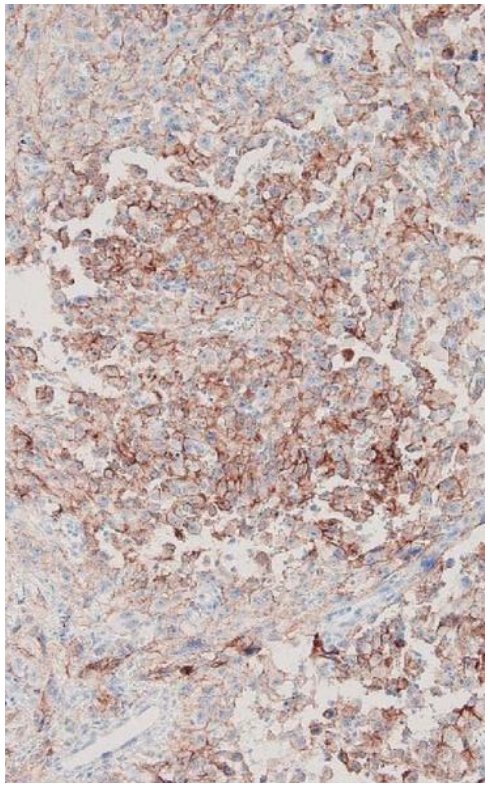


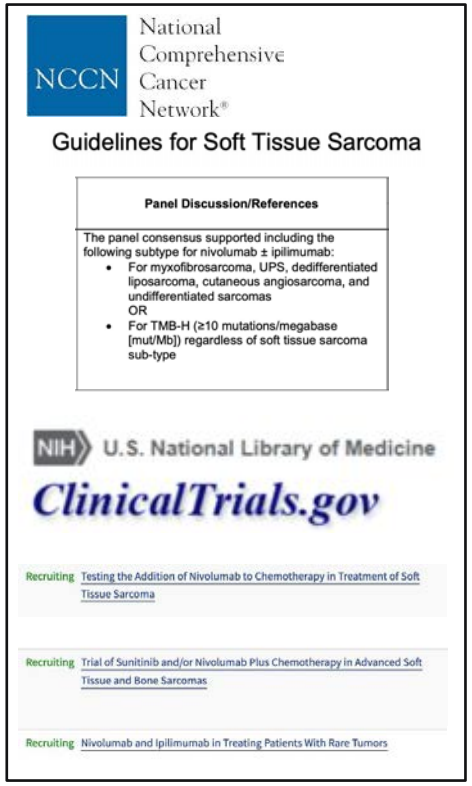





Treatment identified for AS by uncovering published link

AS — PDL1 — PD1-i





2013 paper links PD1/PDL1 and angiosarcoma (AS)

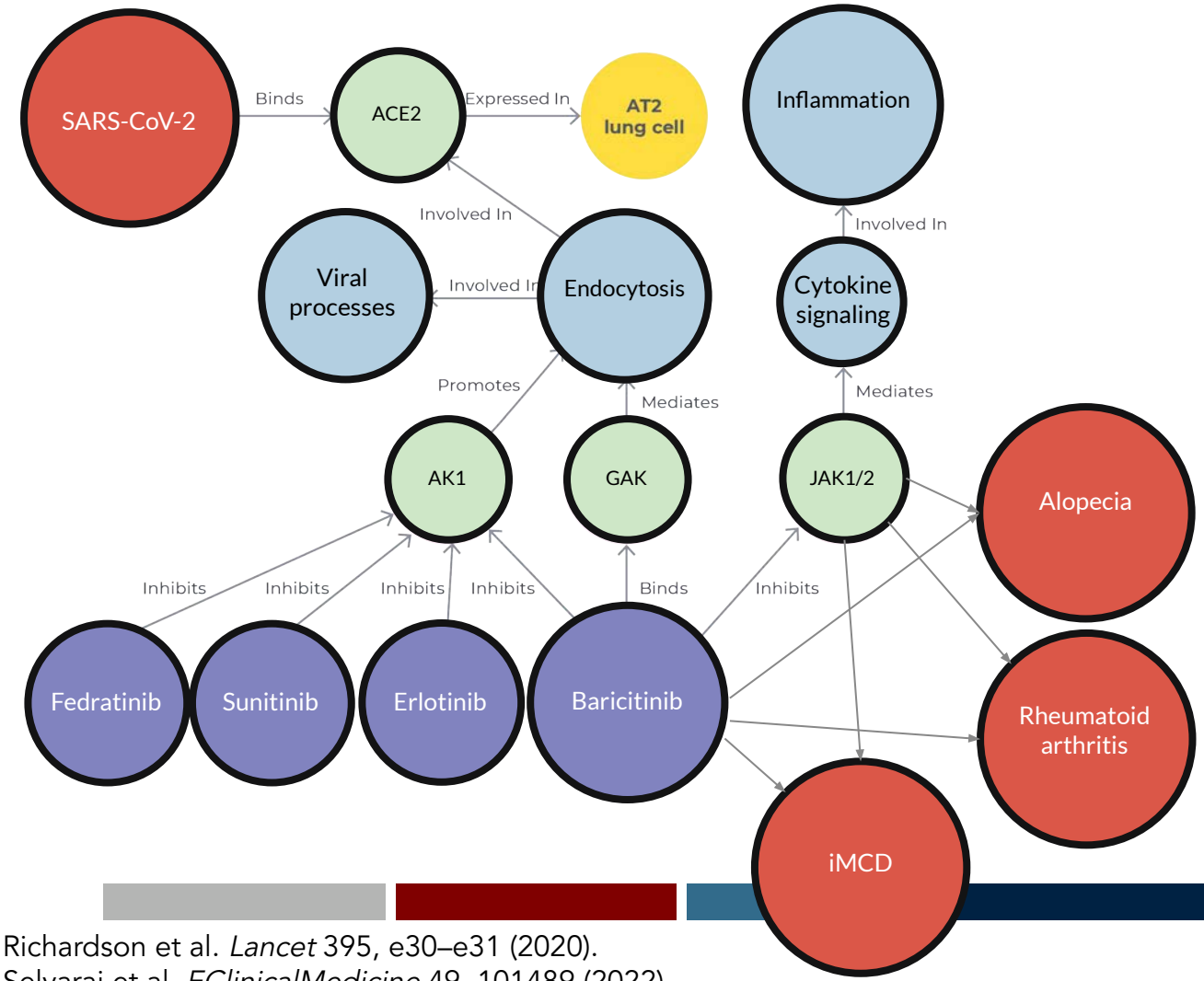
Testing confirmed increased PDL1 in 2016

First AS patient treated with PD1 inhibitor in remission >7 years

Recommended by NCCN and clinical trials underway

Kim et al. PLOS ONE. 2013.

Baricitinib identified for COVID by applying AI to KGs and NCATS building critical data infrastructure



TRANSLATOR
Funded by NIH's National Center for Advancing Translational Sciences

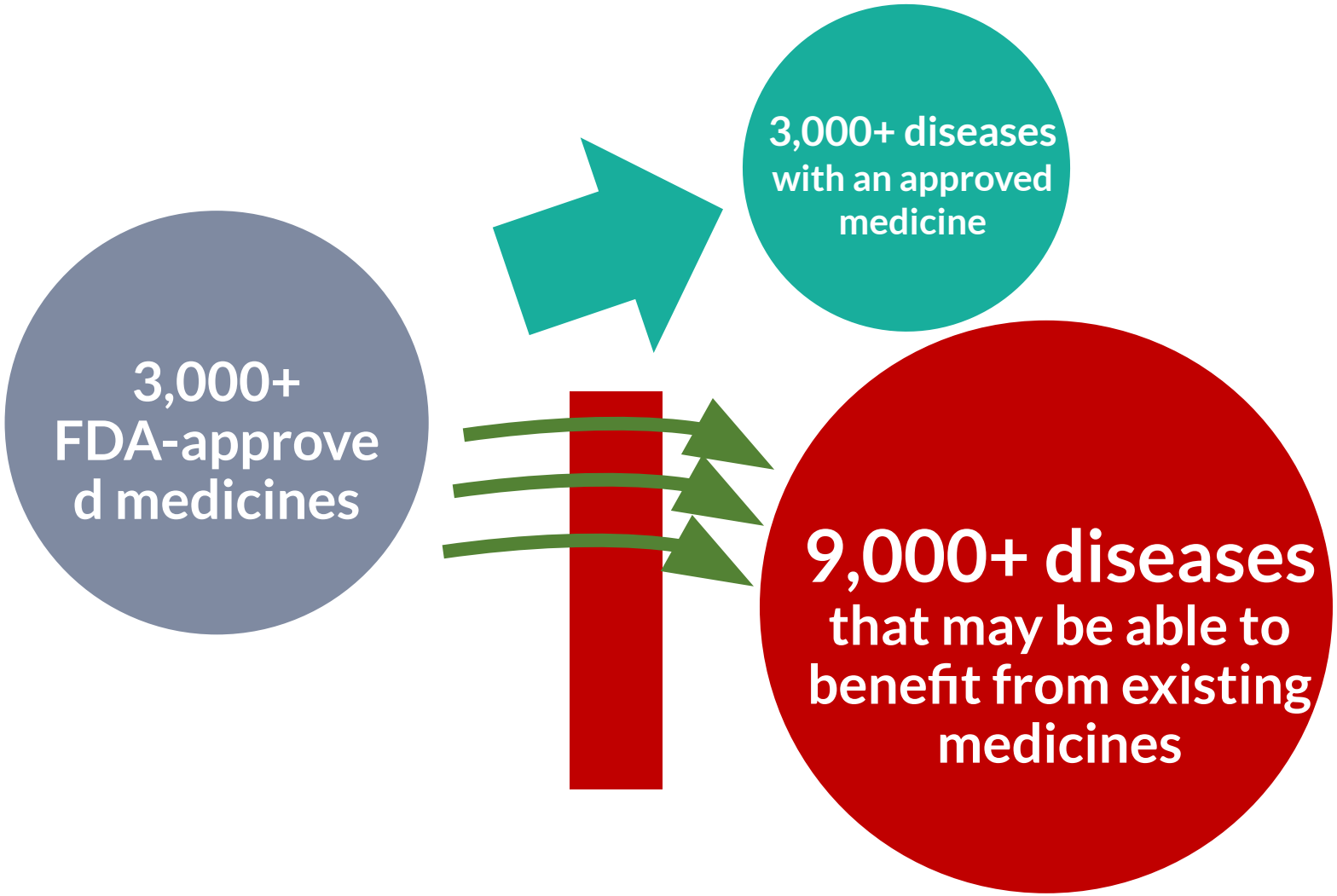
NIH National Center for Advancing Translational Sciences

Richardson et al. *Lancet* 395, e30–e31 (2020).
Selvaraj et al. *EClinicalMedicine* 49, 101489 (2022).
Marconi et al. *Lancet Respir Med* 9, 1407–1418 (2021).

EVERY CURE · CSTL Center for Cytokine Storm Treatment & Laboratory


Acne Medication
5
ALBUTEROL SULFATE
align
Calcium
Centrum
ANUCORT-HC

Many existing medicines already have data supporting their use in other diseases, but they aren't being pursued due to systemic barriers



Systemic barriers

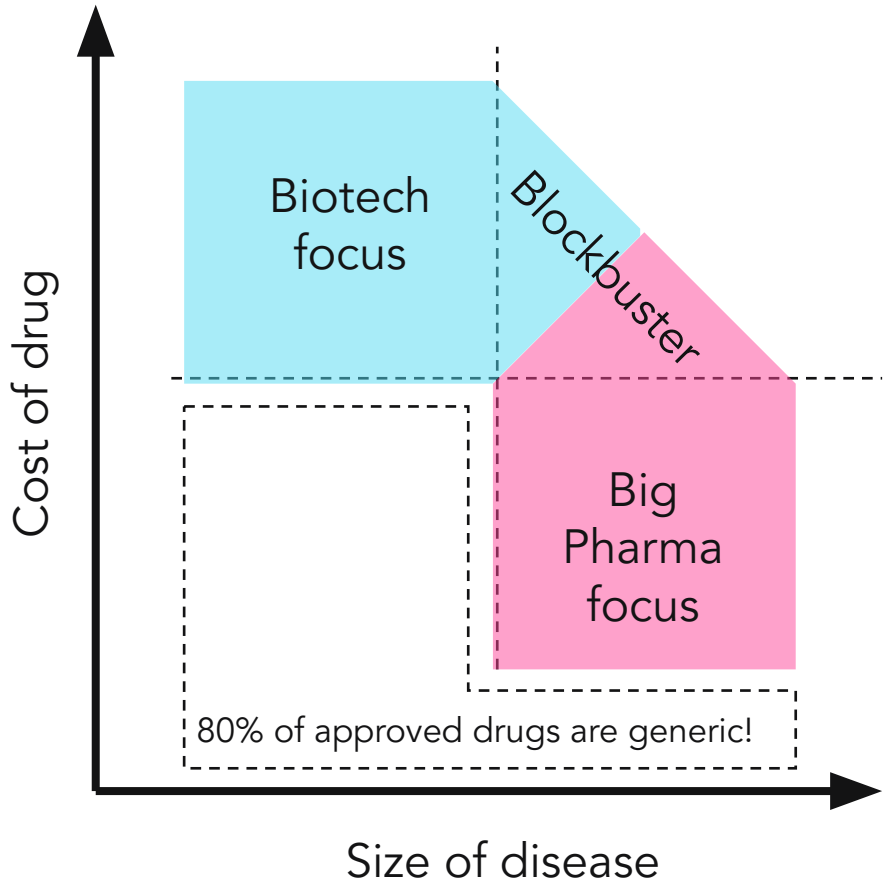
No central database or scoring system

Public data

Private data

Government data

Insufficient incentives for 80% of approved drugs



Systemic barriers

ResearchAmerica. Estimated U.S. Medical and Health R&D Investments, by Source, 2020.

“

There is a missing link in the system that isn't filled by NIH, FDA, or pharma...
No one is responsible for making sure that drugs are fully utilized across diseases.

— JANET WOODCOCK, MD
PRINCIPAL DEPUTY COMMISSIONER, FDA

EVERY CURE

Unleashing the potential of *every* approved medicine to treat *every* disease and *every* patient possible

Advancing a new field of therapeutic crosspurposing

Traditional Drug Repurposing

Disease — Drugs

+

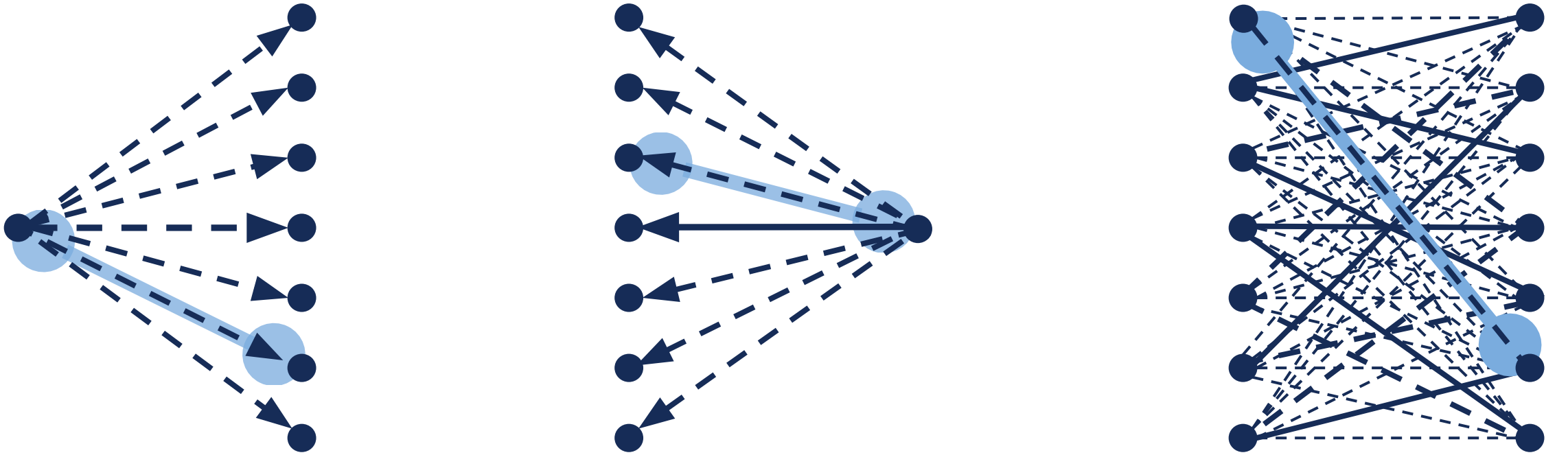
Drug Repurposing: Indication Expansion

Diseases — Drug

=

Therapeutic Crosspurposing / Pharmacophenomics

Diseases — Drugs



Korsunska, et al. 2024 (in submission).

Penn
University of Pennsylvania

EVERY CURE

Identify drug-disease links

Grade links

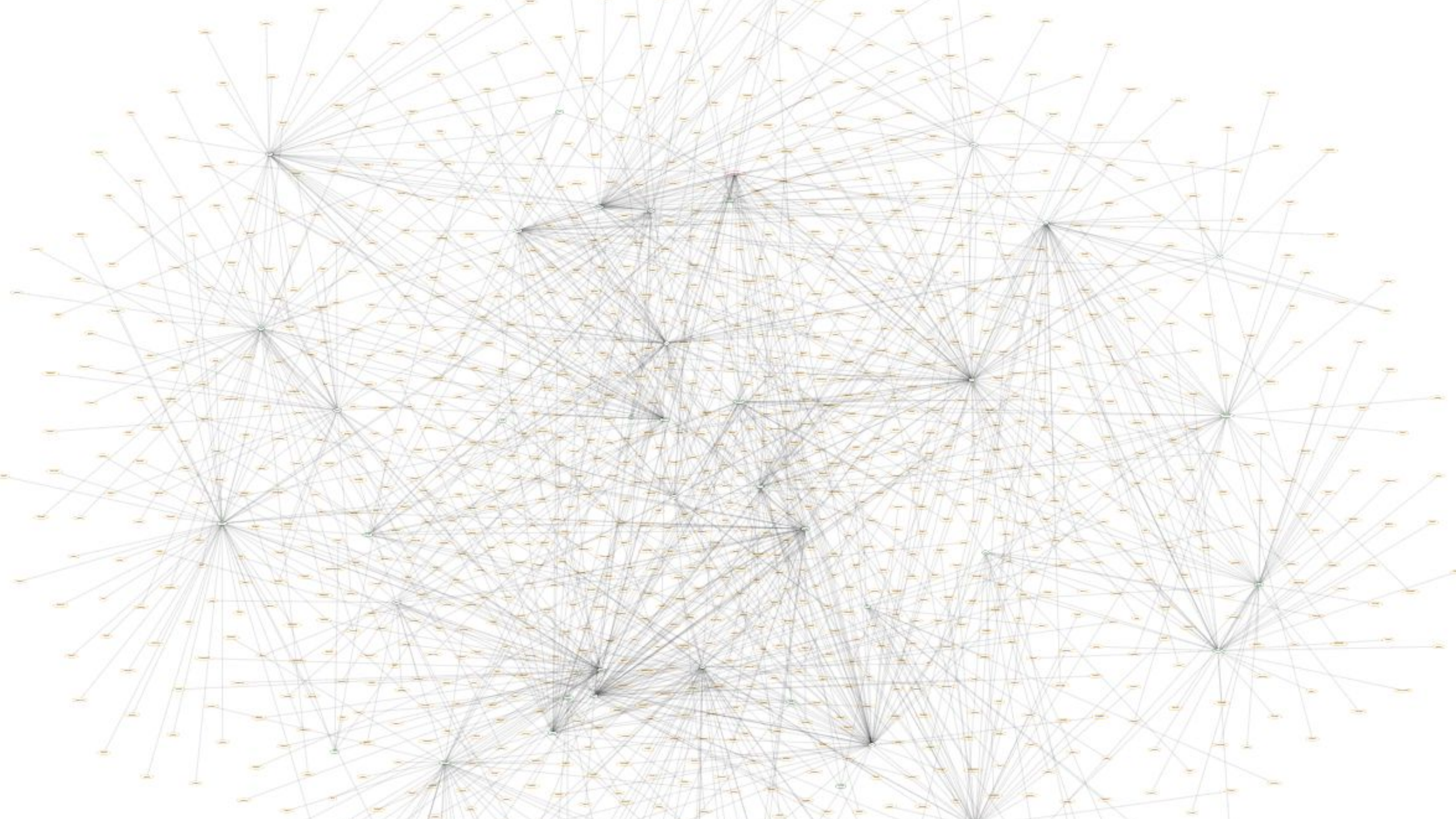
Study in clinical trials

Ensure equitable access

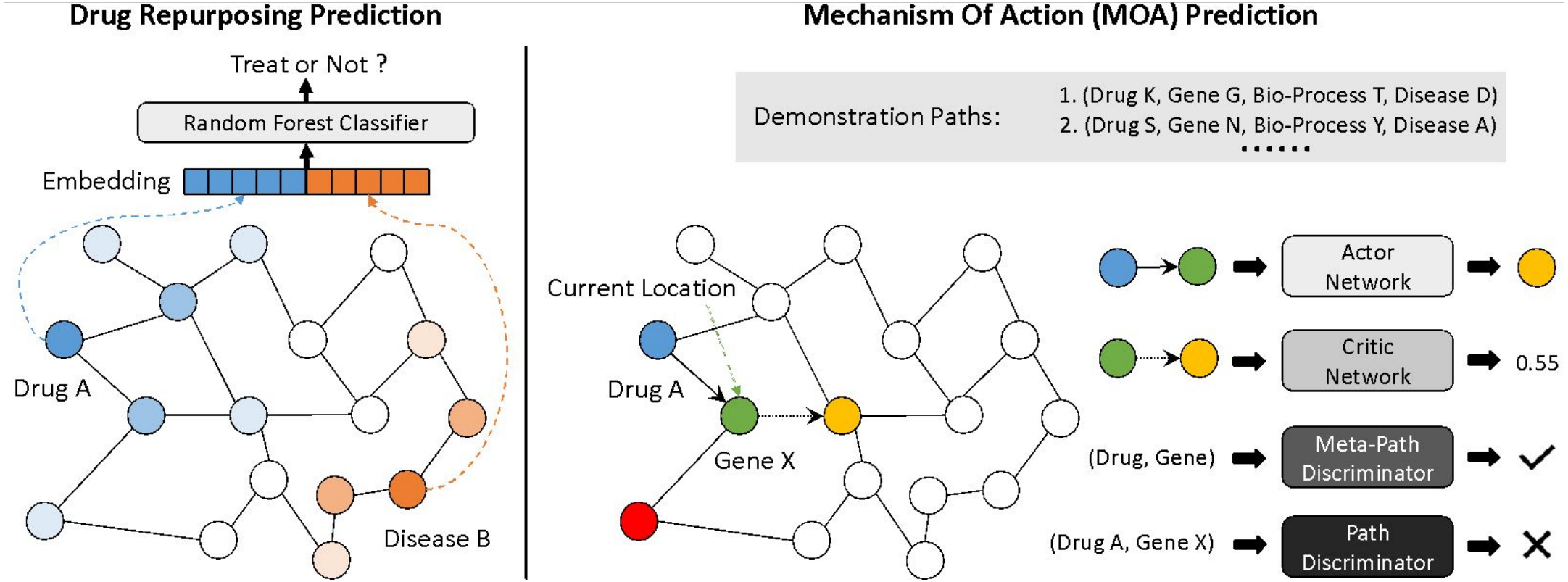
NIH National Center for Advancing Translational Sciences

FDA

CDRC
CURE DRUG REPURPOSING COLLABORATORY



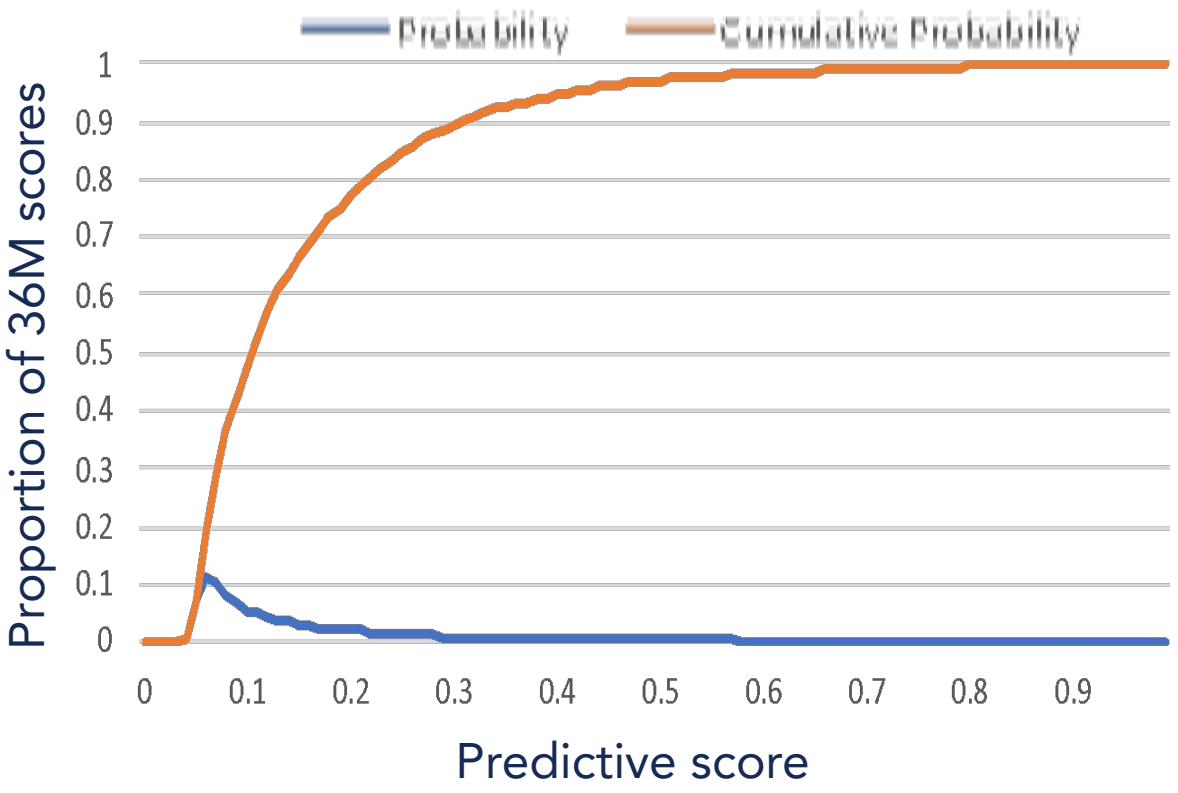
Using AI to generate scores for all drugs vs all diseases



Mu et al. KGML-xDTD. bioRxiv. 2022.

Using AI to generate scores for all drugs vs all diseases

Pilot: Majority of scores are less than 0.1

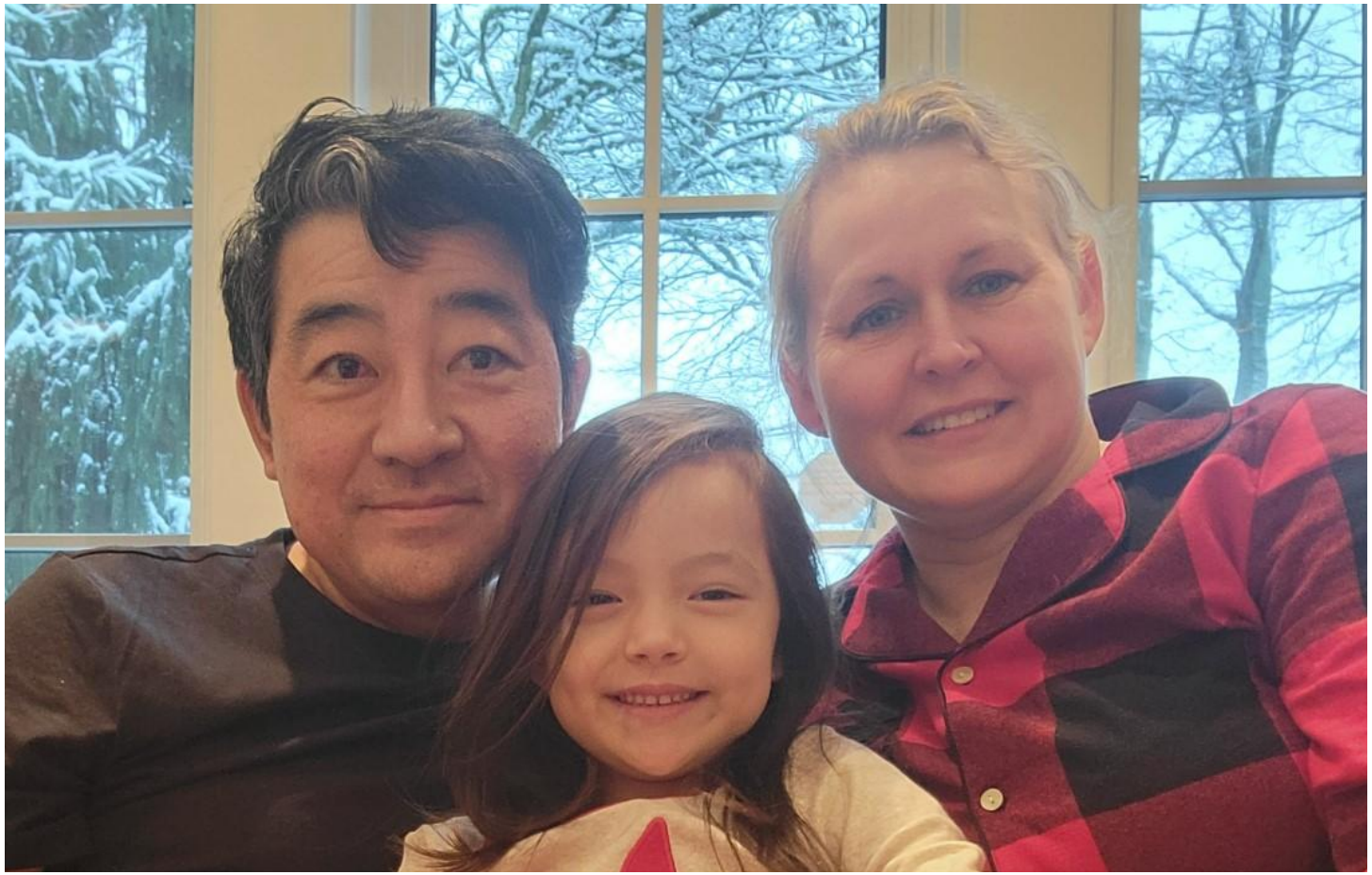


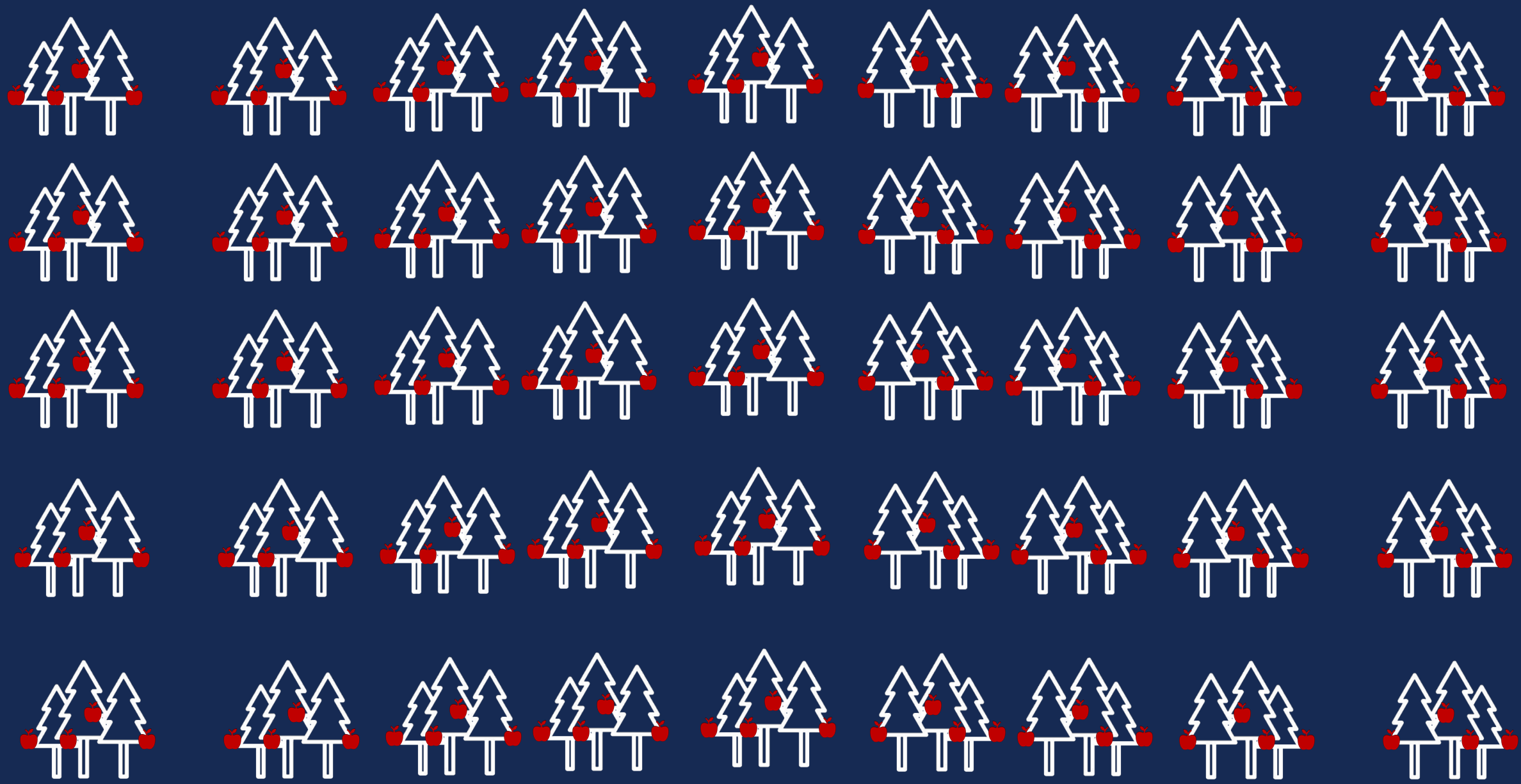
Pilot: adalimumab was #1 drug for Castleman's

Rank	Drug	Mechanism	Score
1	ADALIMUMAB	Anti-TNF	0.83735989
2	RITUXIMAB	B cell depletion	0.83385483
3	CERTOLIZUMAB PEGOL	Anti-TNF	0.82613921
4	CYCLOPHOSPHAMIDE	cytotoxic	0.81639938
5	METHYLPREDNISOLONE	corticosteroid	0.81590714
6	PREDNISONE	corticosteroid	0.80920972
7	SECUKINUMAB	Anti-IL17A	0.80650303
8	TRASTUZUMAB	Anti-HER2	0.80566249
9	TRIAMCINOLONE	corticosteroid	0.80365282
10	CISPLATIN	cytotoxic	0.80064139
63	Ruxolitinib	JAK1/2	0.77005478
177	Temsirolimus	mTOR	0.75333104
253	Sarilumab	IL-6	0.74729794

Unpublished.
Mu et al., bioRxiv. 2022.

Top hit for CD was a drug that recently saved a patient's life





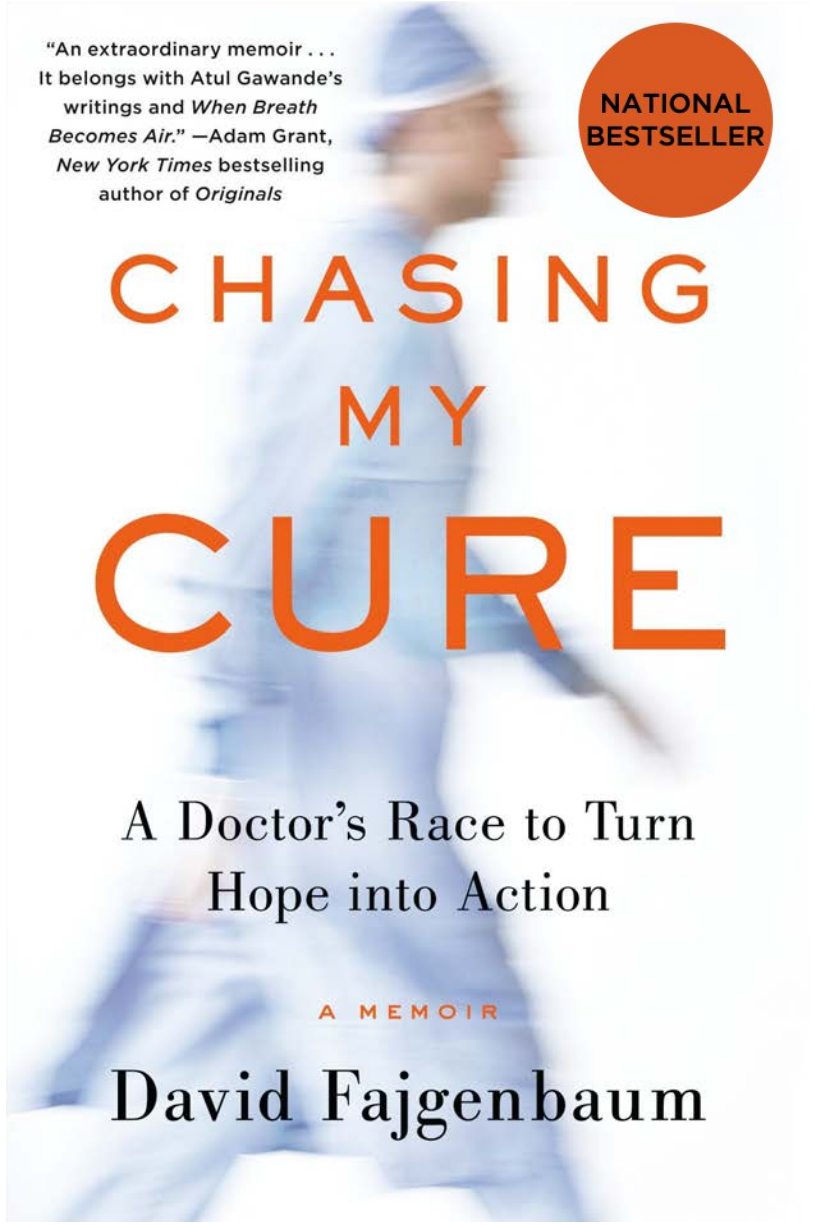
Future directions

We need your help to unlock more uses for existing FDA-approved medicines

- Support Every Cure with obtaining datasets from private data sources (eg, Elsevier), biopharma companies, and government agencies (eg, VA and FDA)
- Contribute cutting-edge AI/ML algorithms
- Support Every Cure with prioritization of top hits
- Perform *in vitro* and *in vivo* validation studies
- Partner on clinical trials of top hits

We need your help to advance more novel therapies!

David@everycure.org



@DavidFajgenbaum
@dfajgenbaum

ChasingMyCure.com
CDCN.org

Everycure.org
davidfa@pennmedicine.upenn.edu

Thank you!

CSTL/CDCN

Josh Brandstadter (Assoc Director, Clinical Research)
Michael Gonzalez (Assoc Director, Computational Res)
Tracey Sikora (Assoc Director, Repurposing)
Melanie Mumau (Assoc Director, Translational Res)
Martin Romeon (Assoc Director, Laboratory Res)
Joe Zinsky (SRI)
Amber Cohen (Exec Admin)
Bridget Austin (Biobank Coordinator)
Criswell Lavery (Research Coordinator)
Mateo Sarmiento (Data Analyst)
Sai Shyamsundar (Data Analyst)
Abiola Irvine (Research Specialist)
Ira Miller (Research Specialist)
Daniel Korn (Data Scientist)
Sally Nijim (MD student)
Mary Zuccato (CDCN Executive Director)
CDCN Board, Advisory Council, & SAB
Mentors: Dan Rader, Arthur Rubenstein

Partners/Funders:

A few collaborators

Frits van Rhee (UAMS)
Thomas Uldrick (FHCC)
Taku Kambayashi
Megan Lim
Kojo Elenitoba-Johnson
Adam Cohen
Sunita Nasta
Dan Martinez
Mike Betts
Alberto Japp
John Wherry
Ivan Maillard
Josh Brandstadter
Jason Ruth
Chris Nabel (MGHCC)
Alexander Fossa (Oslo)
Yasuharu Sato (Okayama)
Mark Bower (ICL)
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Yasufumi Masaki (Kanazawa)
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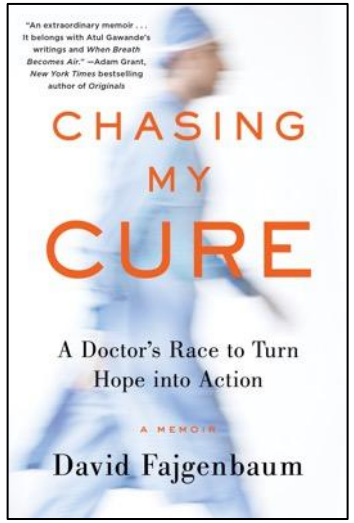

davidfa@pennmedicine.upenn.edu

Thank you to our Every Cure team and partners!

Every Cure

Grant Mitchell, MD, MBA; CEO
Tracey Sikora, CIO
Mary Zuccato, MBA; COO
Adam Green, MS; COS
Matej Macak, PhD
Daniel Korn, PhD
Charlie Hempstead, MBA
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Pascal Brokmeier, PhD
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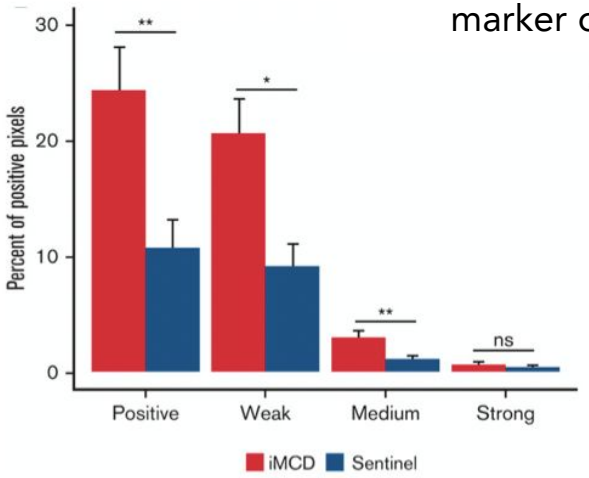
ELSEVIER
REAGAN-UDALL FOUNDATION for the Food and Drug Administration
Penn Medicine
medidata
WORLDWIDE CLINICAL TRIALS

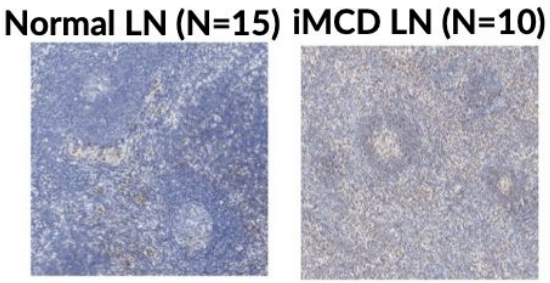
Ruxolitinib identified for iMCD by uncovering mechanistic insights

Table 1. Hallmark pathways significantly enriched in the discovery dataset among cluster 1 anti–IL-6 responders and in all siltuximab nonresponders

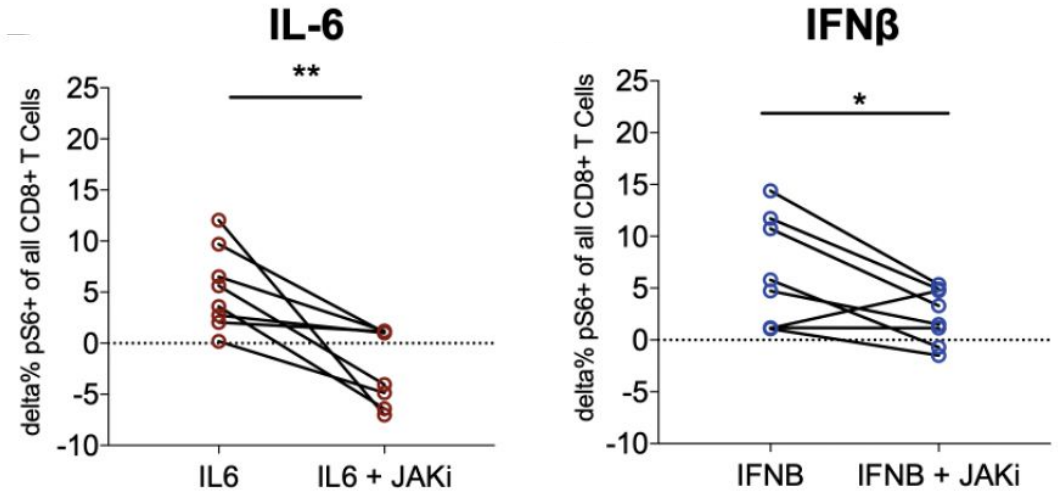
Pathway	Nominal *P* value	FDR q value
Enriched pathways in cluster 1 siltuximab responders vs HDs		
TNFα signaling via NF-κB	.004	0.090
Estrogen response early	.013	0.137
IFN-γ response	.033	0.149
Allograft rejection signature	.033	0.167
IL-6-JAK STAT3 signaling	.020	0.184
Enriched pathways in siltuximab nonresponders vs HDs		
KRAS signaling up	.029	0.118
IL-6-JAK STAT3 signaling	.031	0.144
TNFα signaling via NF-κB	.006	0.173
Allograft rejection signature	.043	0.177
IL2 STAT5 signaling	.018	0.179

Immunohistochemistry for pSTAT3, a marker of JAK1/2 activation



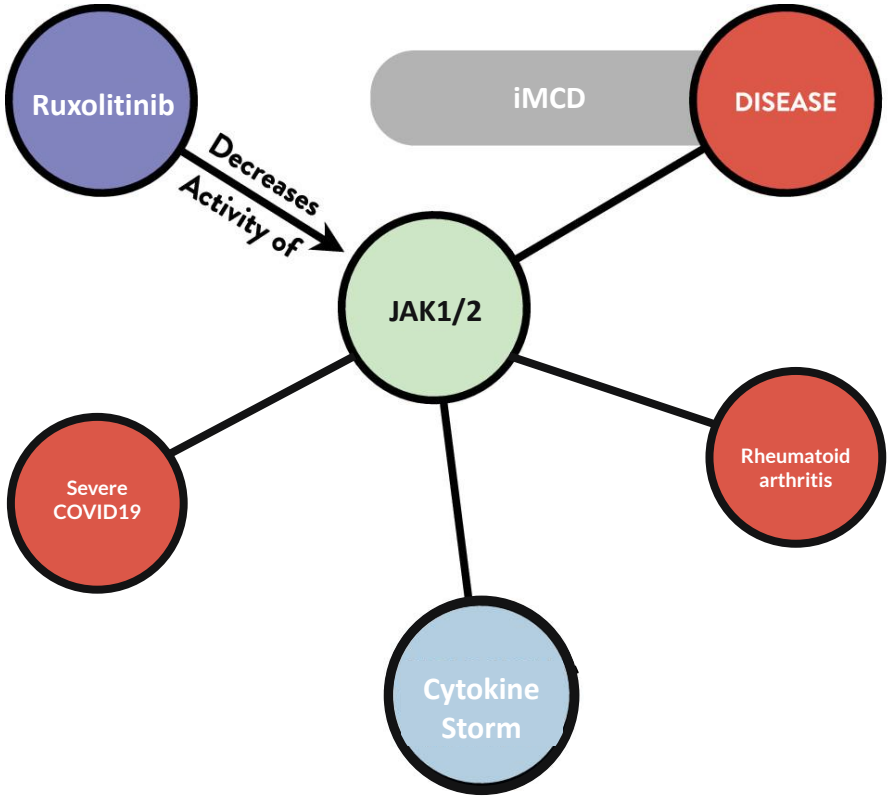


pFlow reveals JAK1/2 inhibition abrogates excess signaling



Pierson & Fajgenbaum. Blood Adv, 2020.
Pai & Fajgenbaum, JCI Insight, 2020.

Ruxolitinib identified for iMCD by uncovering mechanistic insights



Fajgenbaum et al. JCI, 2019