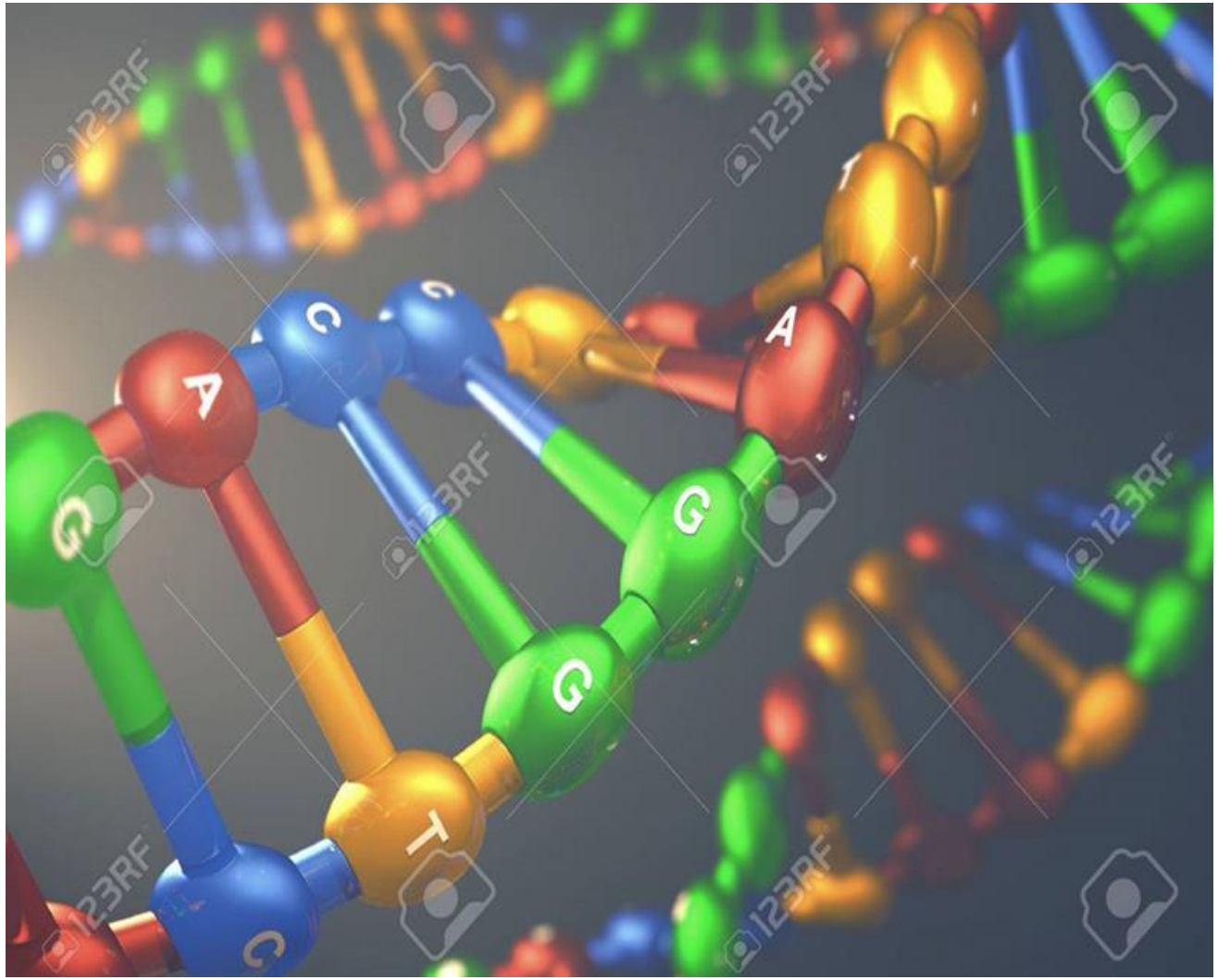


OPPORTUNITIES FOR GENE THERAPY IN UGANDA

5th Annual National Biosafety Forum

23rd June 2022

Dr. Cissy Kityo Mutuluuza
Executive Director, Joint Clinical Research Centre

GENE THERAPIES:

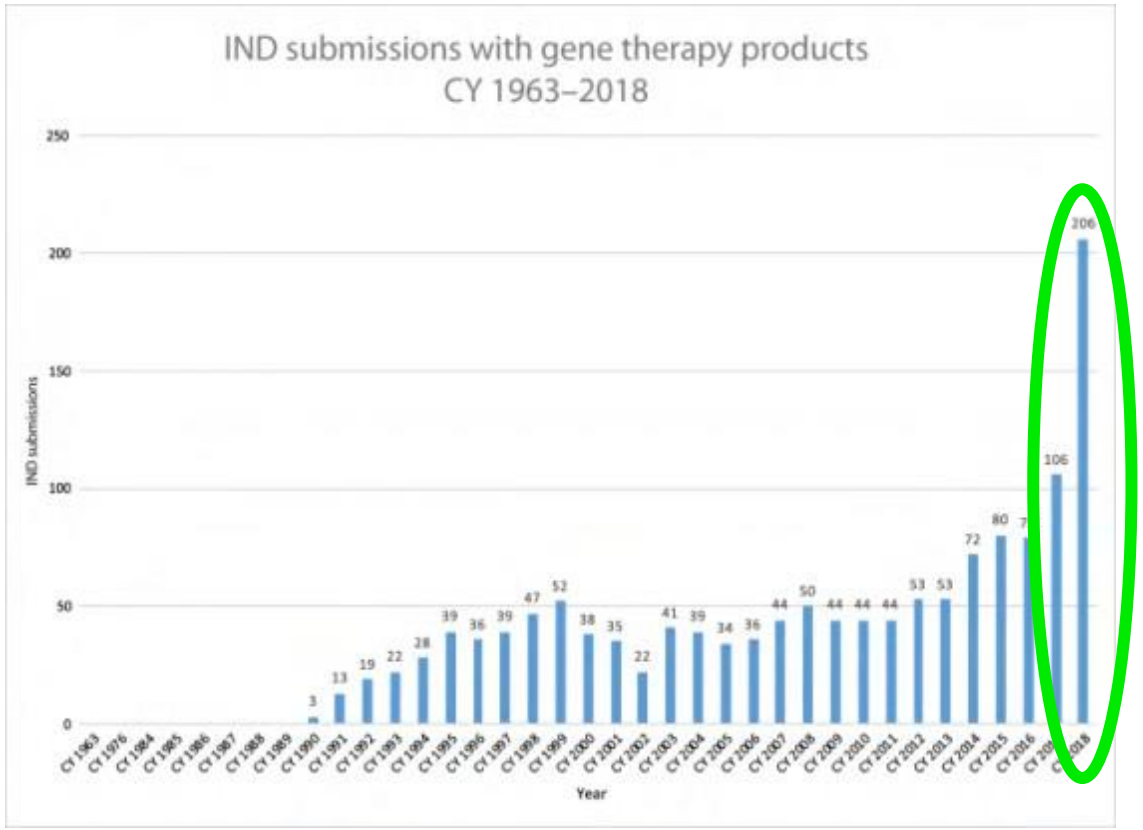
The Next Generation of Medicine

CURE Prospects using Gene Therapy presents a promising new paradigm for management of HIV and SCD

√ **Curative**	Acutely focused and locally targeted on the biology of the disease
√ **One-time**	Administered in just a single dose
√ **Durable**	Sustained, life-long benefits
√ **Potent**	Transformative efficacy improvements over standard of care
√ **Safe**	Improved safety profile, avoiding adverse events and challenging medical procedures
√ **Valuable**	High impact on quantity and quality of life, with great clinical, economic, and social value

Gene & cell therapy is “booming”

- As of 2021, **536 gene therapy developers**[1]
- As of 2020, **373 gene therapy trials**[1]
- In 2020, **$19.9 billion in financing**[2]



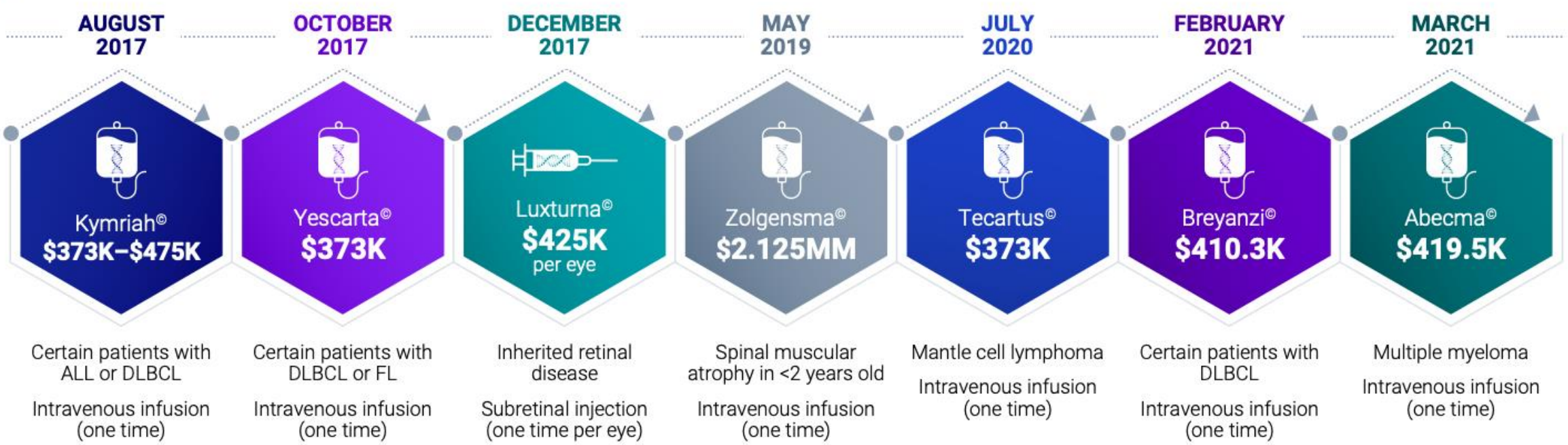
“By 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year based on an assessment of the current pipeline and the clinical success rates of these products.”[4]

Dr. Scott Gottlieb

FDA Commissioner, 2017 - 2019

1 Alliance for Regenerative Medicine 2020; 2 Alliance for Regenerative Medicine 2021; 3 High 2020; 4 FDA 2019

Current FDA approved gene therapies.

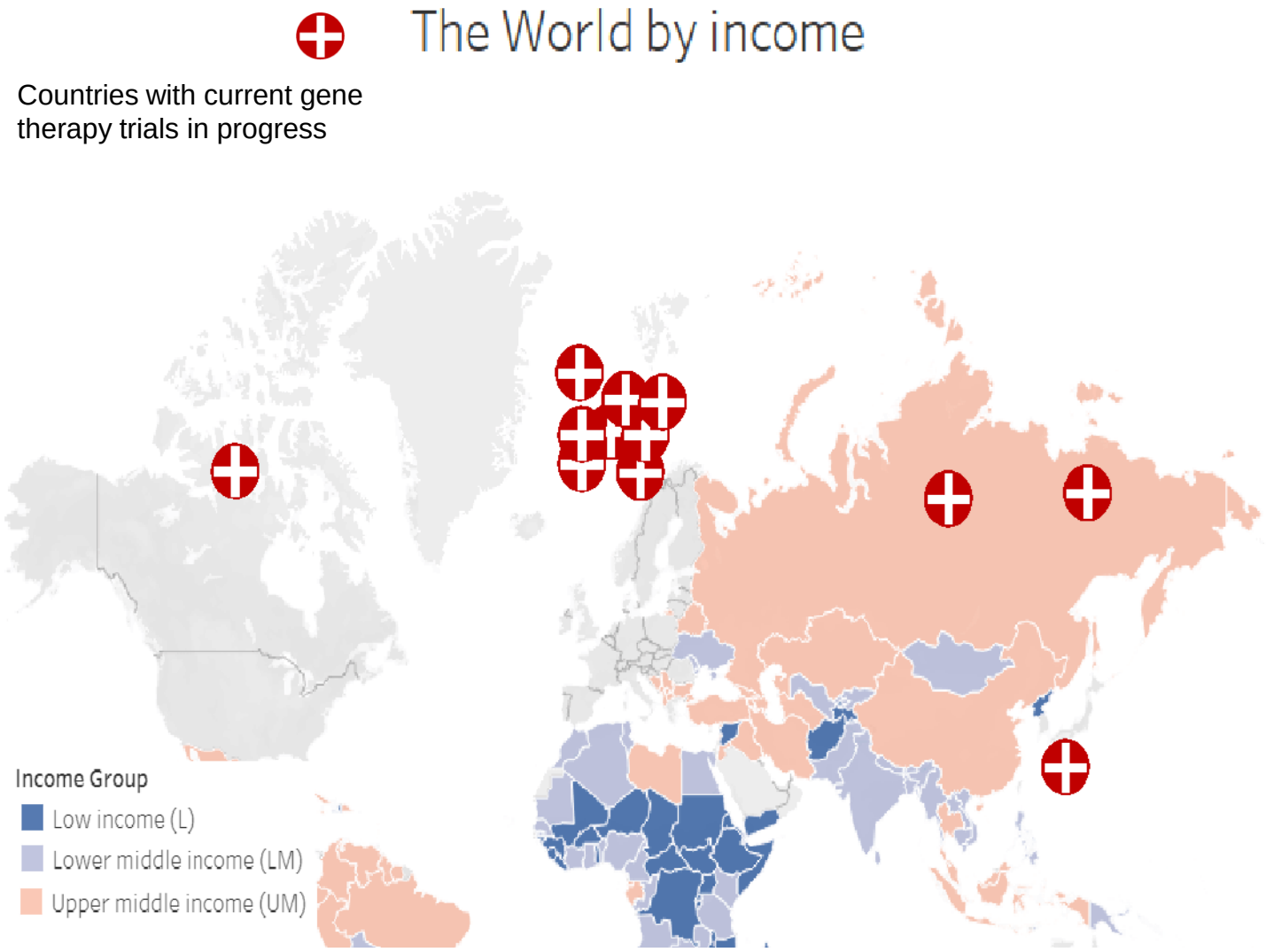


https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

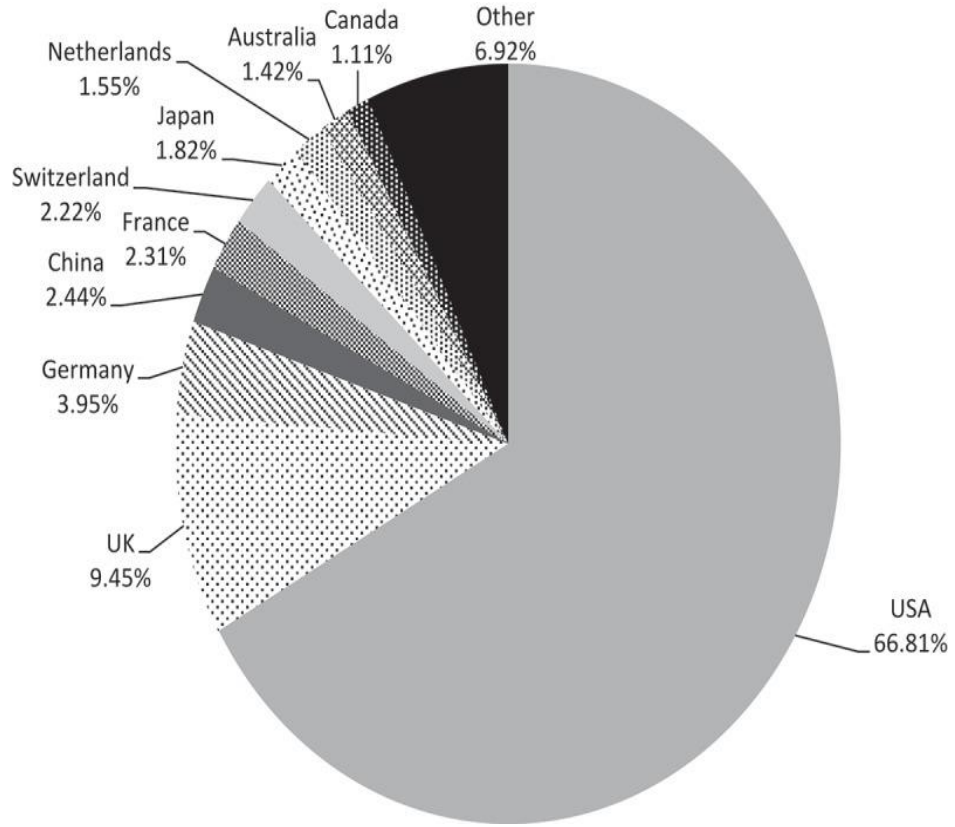
truveris

LMICs are Currently Excluded from Gene Therapy Development

Countries with current gene therapy trials in progress



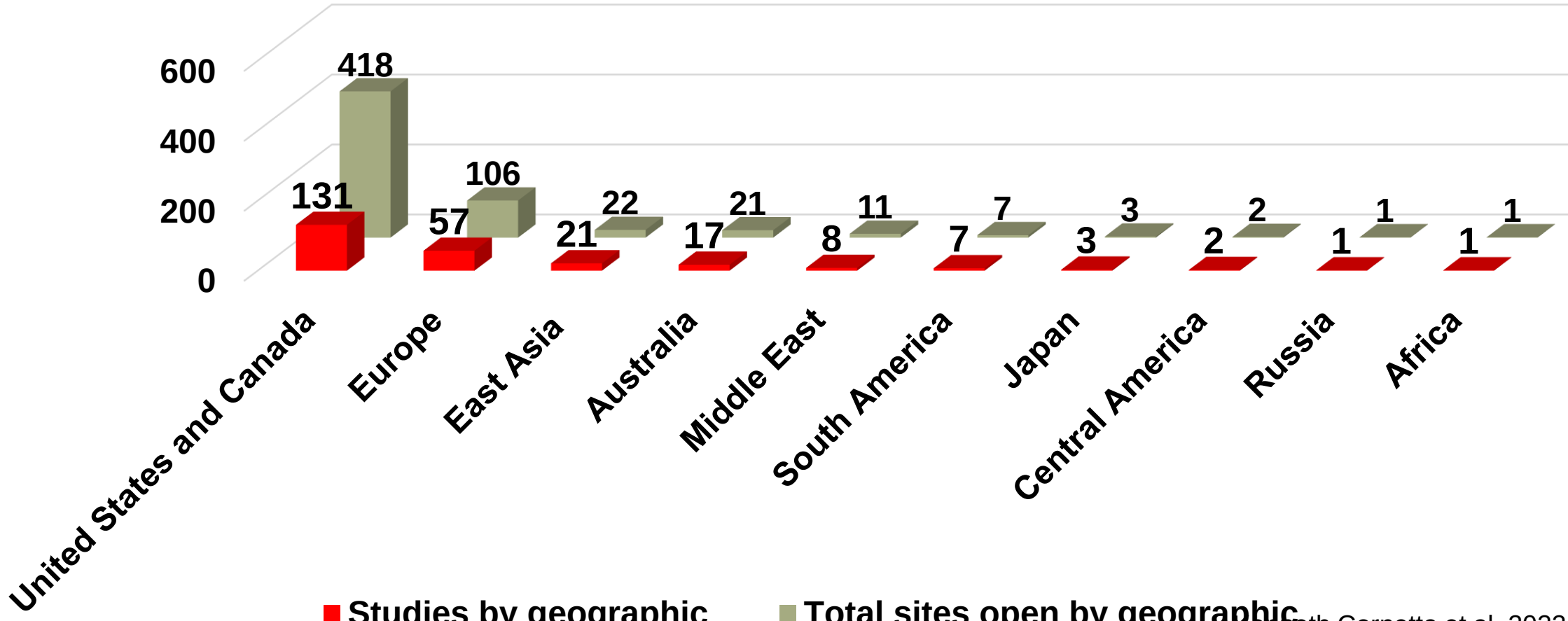
World Bank 2021



Distribution of gene therapy trials by country

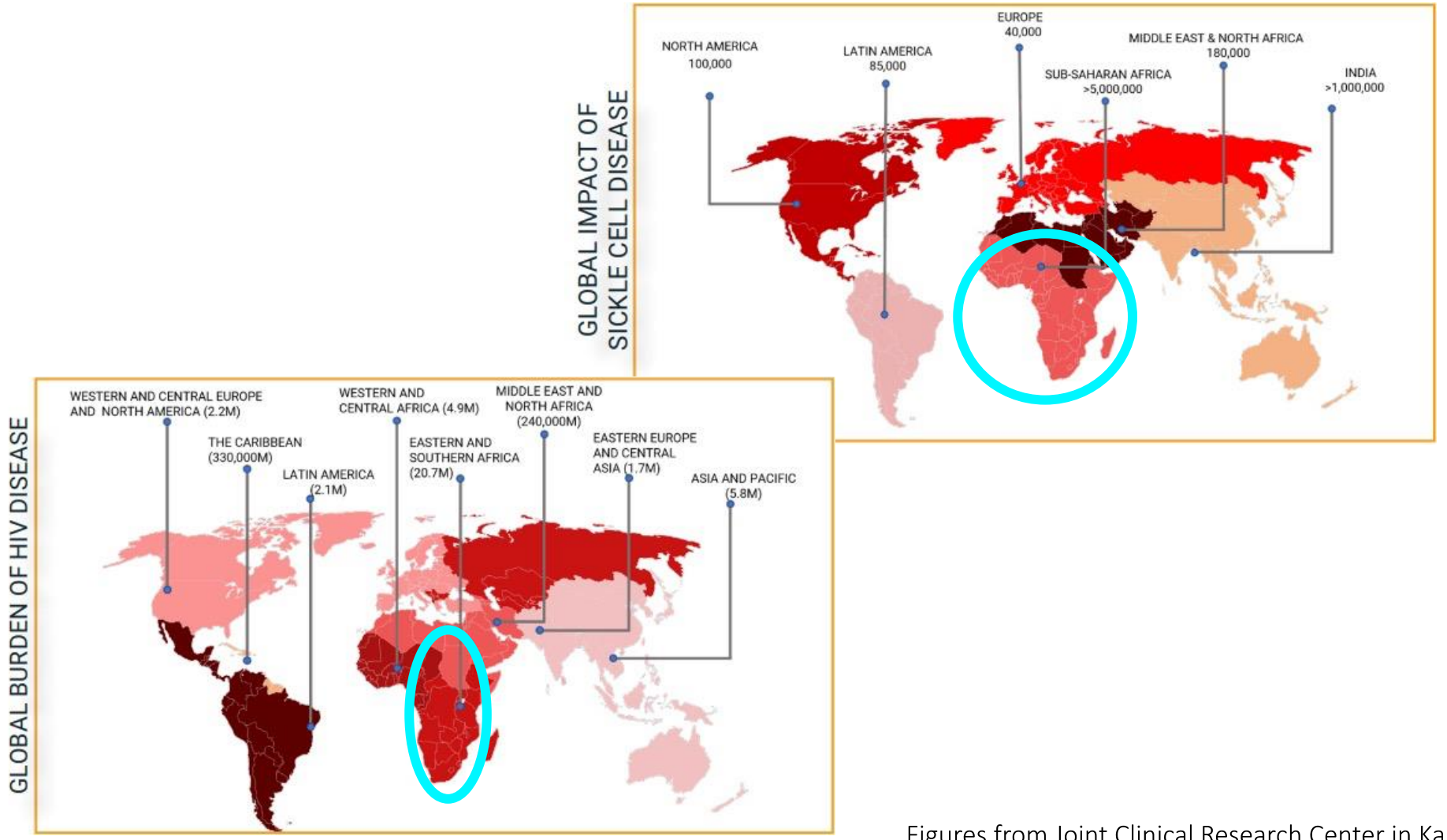
Gene therapies development: slow progress and promising prospect. Hanna E, et al. J Mark Access Health Policy, 2017

Gene Therapy Trials (accessed November 22, 2021 in ClinicalTrials. gov) by region



Kenneth Cornetta et al, 2022

The Global majority of HIV & sickle cell disease (SCD) patients reside in low- and middle-income countries (LMIC)

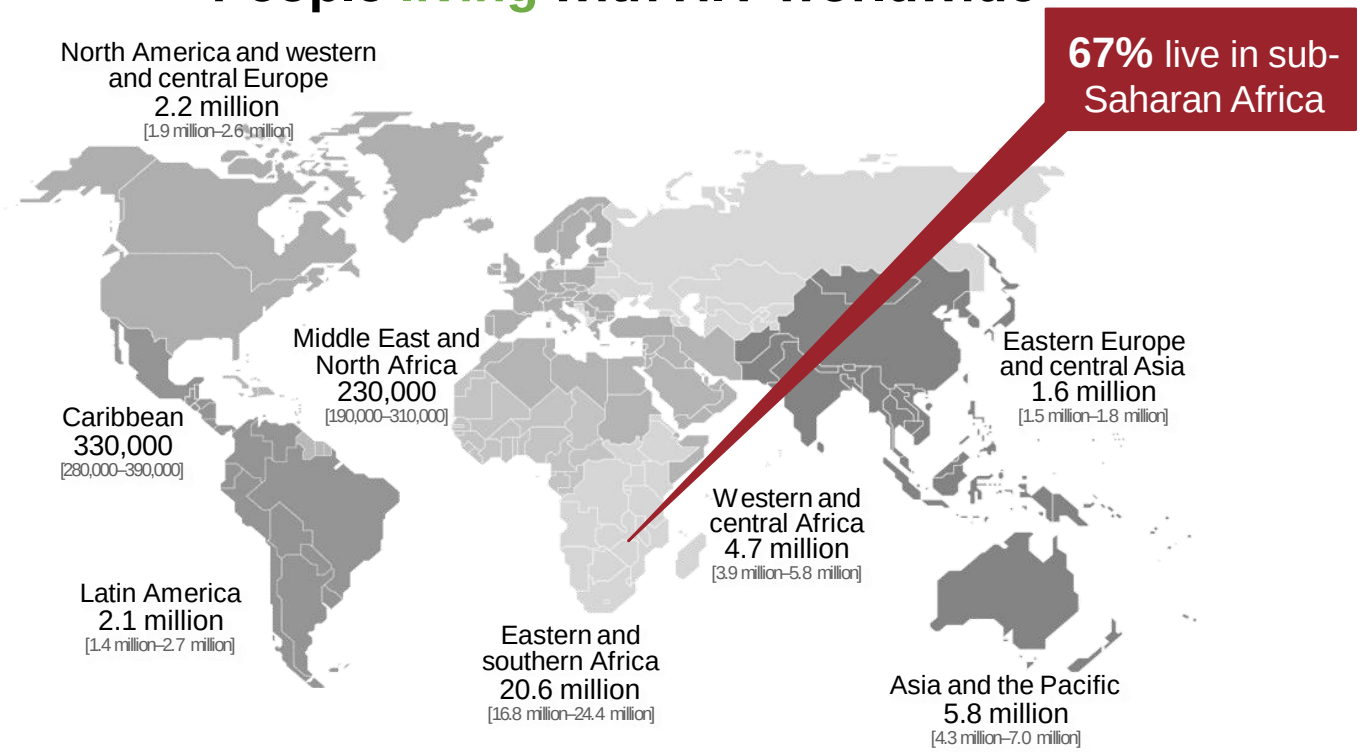


Figures from Joint Clinical Research Center in Kampala

34 Years after ART was developed, HIV/AIDS remains a leading cause of death

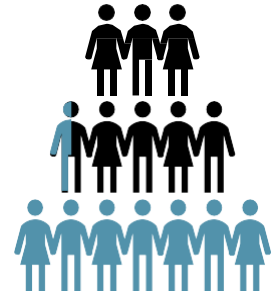
38M

People living with HIV worldwide



Global rates are projected to remain steady through 2030[1]

47% of people living with HIV **(17.8M)** are unable to access effective antiretroviral therapy (ART)



… **11.6M** live in sub-Saharan Africa

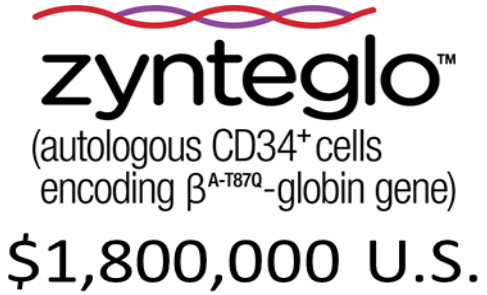
Hard-fought progress is threatened by stagnant funding and donor fatigue

A cure could benefit 38M people living with HIV today

1. Goalkeepers Report, HIV. Map source: UNAIDS 2021 epidemiological estimates.

One of the first ten FDA approvals included a gene therapy relevant to SCD

Regulatory approval of Zynteglo™: a gene therapy for beta-thalassemia, which could also be used to treat SCD



Part of our progress includes gene & cell therapy to treat HIV and sickle cell disease (SCD)

7 clinical trials of gene therapy to treat **SCD** opened between 2014 and 2021

Since 1994, **36 clinical trials** using some kind of gene therapy to treat **HIV** infection have been registered

The number of gene & cell therapy trials for HIV or SCD which have taken place in Africa:

0

NEWS OF CURES SPARKS HOPE…

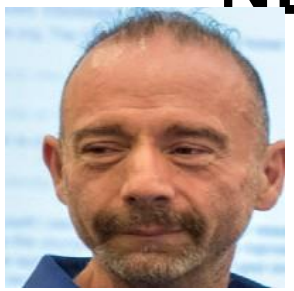


Photo credit: Fred Hutch

Timothy Ray Brown

The Berlin Patient

1st person cured of HIV.

There are now 4 people cured from HIV

Photo credit: POZ

Adam Castillejo

The London Patient

2nd person cured of HIV

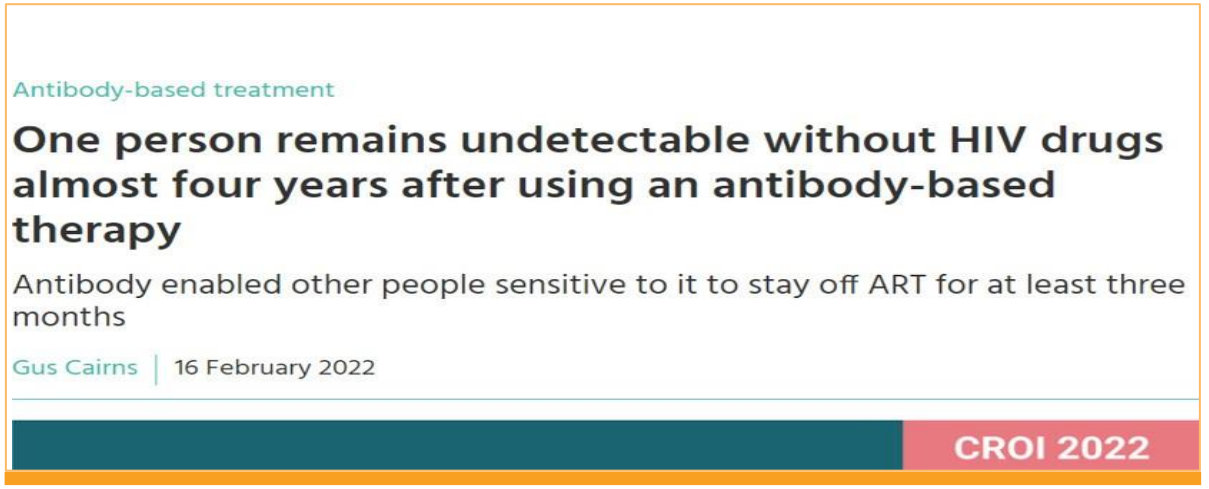
Photo credit: NPR

Victoria Gray

First patient with sickle cell disease to be treated with cells modified using one of the fastest gene editing tools called CRISPR cas-9

Third person apparently cured of HIV using novel stem cell transplant

Patient is mixed-race woman treated in New York using umbilical cord blood, in technique raising chances of finding suitable donors



Antibody-based treatment

One person remains undetectable without HIV drugs almost four years after using an antibody-based therapy

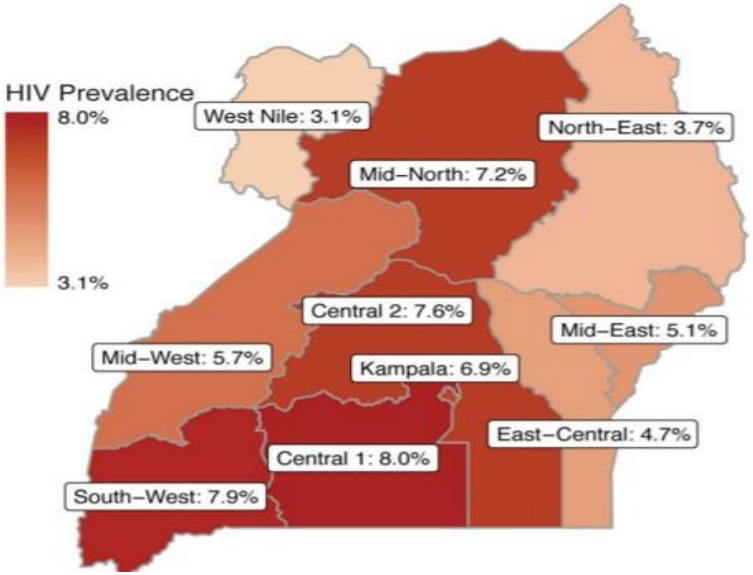
Antibody enabled other people sensitive to it to stay off ART for at least three months

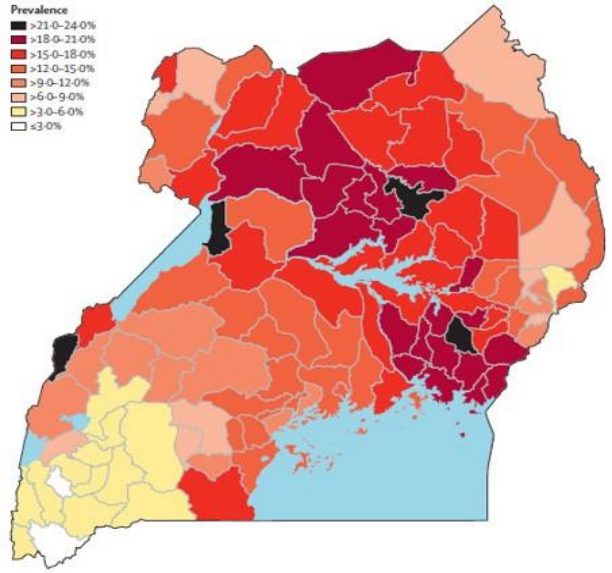
Gus Cairns | 16 February 2022

CROI 2022

WHY GENE THERAPY IS IMPORTANT FOR UGANDA

HIGH PREVALENCE OF BOTH HIV AND SICKLE CELL DISEASE IN UGANDA





- Despite expanded access to treatment, HIV remains a leading cause of death
- Pills need to be taken daily and patients get fatigued
- HIV resistant viral variants have emerged and threaten effectiveness of HIV treatment programs
- Hard-fought progress is threatened by stagnant funding and donor fatigue
- Adherence to ART regimens is inconsistent

- SCD is the most common blood disorder; Uganda has the 5th highest burden of Sickle Cell Disease in Africa
- Stigma and denial are common and lead to delayed diagnosis
- There is limited funding to support management of SCD
- Hydroxyurea is the current long-term treatment, is very expensive, about $0.5 per tablet/day, not affordable by over 90% of patients and there are no pediatric formulations
- Diagnostic capacity is limited

OPPORTUNITIES FOR GENE THERAPY IN UGANDA

PROMISING CURE

Gene therapies are the most promising cure strategy with the greatest potential for accessibility because they do not require a donor.

REGIONAL CENTRE OF CARE AND TREATMENT

Uganda is leading in efforts to make Gene Therapy accessible; positions us to be a Regional Centre for care & treatment translating into economic gains

INTELLECTUAL PROPERTY RIGHTS

Stronger stake in Intellectual Property Rights & Patenting

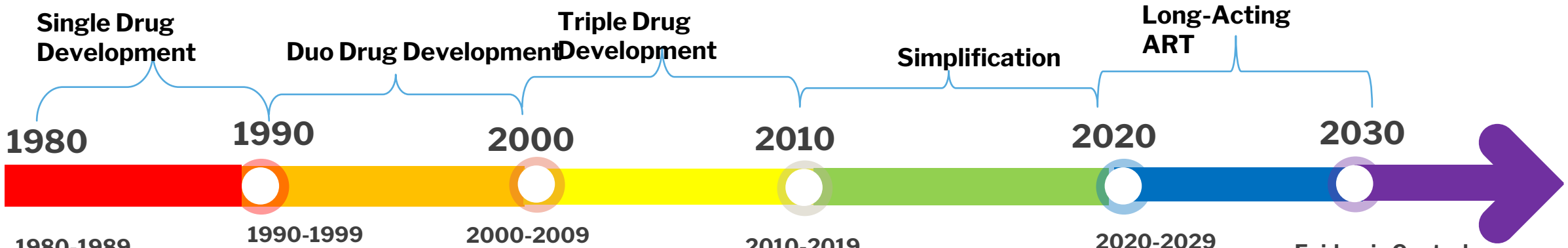
IMPROVED LIFE EXPECTANCY AND QUALITY OF LIFE

Targeting these two diseases first will significantly improve the life expectancy & quality of life of affected individuals, families & the nation translating into increased productivity

TRANSFER OF TECHNOLOGY

Presents opportunity for technology transfer for local manufacturing of gene therapy products for local use & export

cART DEVELOPMENT TIMELINE: 17 YEARS TO ACCESS IN UGANDA



1980-1989
1981- AIDS epidemic officially begins
1987- AZT

1990-1999
1990 -Didanosine
1992 -Zalcitabine
1994-Stavudine
1995 -Lamivudine
-Saquinavir
1996 -Nevirapine
-Indinavir
-Ritonavir
1997-Combivir

(zidovudine/3TC)
-Delavirdine
-Nelfinavir
1998 -Abacavir
-Efavirenz

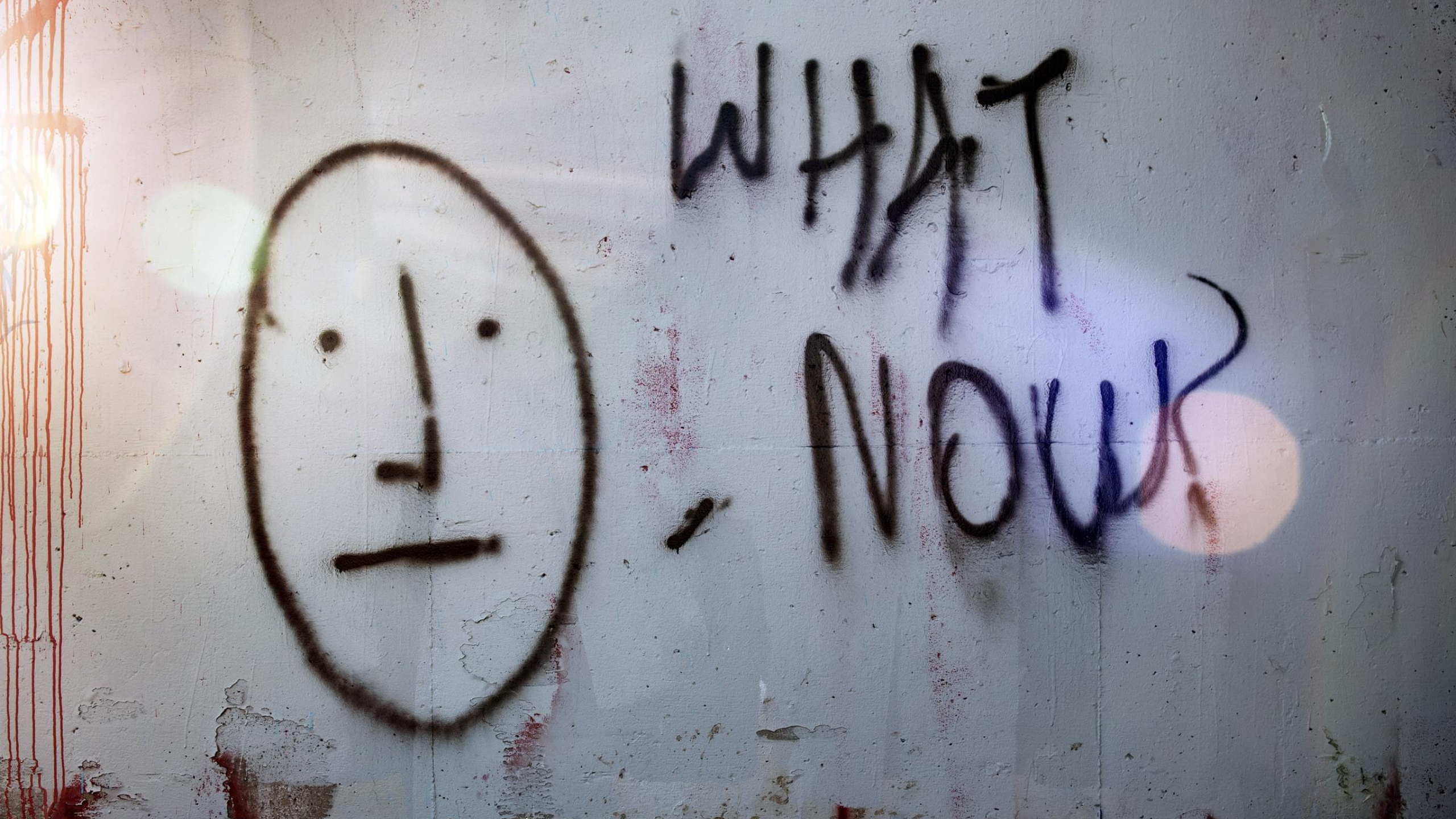
2000-2009
2000 -Trizivir (ABC/ZDV/3TC)
-Videx EC
-Kaletra (LPV/r)
2001 -Viread (TDF)
2003 -Emtricitabine
-Fosamprenavir
-ATV
-enfuvirtide
2004 -Epzicom (ABC/3TC)
-Truvada (TDF/FTC)
2005 -tipranavir
2006 -Atripla (EFV/TDF/FTC)
-darunavir
2007- raltegravir
- Maraviroc
2008- Etravirine

2010-2019
2011-Complera (RPV/TDF/FTC)
-Edurant (RPV)
2012 -Stribild (FTC/COBI/FTC/TDF)
2013 -Dolutegravir
2014 -Triumeq (DTG/ABC/3TC)
-Tybost
-Vitekta
2015 -Genvoya (EVG/COBI/FTC/TAF)
-Prezcoix (DRV/COBI)
-Evotaz (ATV/COBI)
2016 -Odefsey (FTC/RPV/TAF)
-Descovy (FTC/TAF)

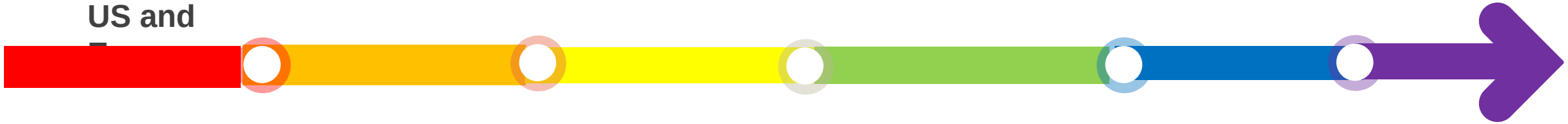
2020-2029
2020-Cabenuva (RPV LA+CAB LA)

Epidemic Control:
95-diagnosed
95-on treatment
95- virally suppressed

HIV CURE


WHAT
NOW?

Gene Therapy Development: How Long Before Access in LMICs ?



Global Gene Therapy Initiative (GGTI) Working Group was formed in 2020 to work towards enabling access and implementation of gene therapies as curative medicines in LMICs initially focusing on HIV and SCD.

GGTI works by advocating for appropriate research, clinical development, capacity-building, training, community adoption, regulatory pathway approval and sustainability

2024
Goal to have first Phase 1 trials initiated

GGTI
GLOBAL GENE THERAPY INITIATIVE

Cofounders of GGTI

Prof Jennifer Adair, FredHutch, Seattle

Dr Cissy Kityo Mutuluuza, Joint Clinical Research Centre, Uganda


BLACK SEA
BULGARIA
ALBANIA
Istanbul
Ankara
TURKEY
ANATOLIA
Barcelona
Rome
Naples
Vesuvius
Sardinia
Cagliari
TYRRHENIAN SEA
IONIAN SEA
Palermo
Sicily
Messina
Catania
Athens
AEGEAN SEA
Izmir
Antalya
Lisbon
SPAIN
Madrid
Balearic Is.
Palma
Alger
Annaba
Oran
Constantine
Tunis
MEDITERRANEAN
CRETE
CYPRUS
Nicosia
LEBANON
Beirut
Damascus
SYRIA
IRAQ
JORDAN
Jerusalem
Benghazi
Derna
Gulf of Sidra
Sirte
El Agheila
Socna
Marada
Ouargla
El Goléa
ALGERIA
Zillah
LIBYA
Kufra
Rebiana
OASIS
EGYPT
El Kharga
Aswan
Medina
Riyadh
PERSIAN GULF
Wadi Halfa
Nubian Desert
Port Sudan
SAHARA
TIBESTI MTS
Tummo
MAURITANIA
MALI
Araouane
Tombouctou
SENEGAL
GAMBIA
Agadem
N'Guigmi
L. Chad
Zinder
Hadejia
El Fasher
Umm Keddada
El Obeid
Omdurman
Khartoum
Ed Damer
Massawa
Gondar
N'Djamena
Hadjer
Sarh
Ndélé
CENTRAL
Kaka
Akelo
Bor
Conakry
SIERRA LEONE
Freetown
Monrovia
LIBERIA
IVORY COAST
Bouaké
Kumasio
GHANA
Tamale
TOGO
BENIN
Ibadan
Ilorin
Makurdi
Boulai
Kandi
Ouagadougou
Gaoua
Bobo Dioulasso
Ségou
Séguéla

Emphasis: patients and advocates at the table

Michael Louella
Community Engagement Project Manager defeatHIV Community Advisory Board, Co-Chair, DARE

Olabimpe Olayiwola
Research Assistant, NIH NHLBI Grant Recipient, Case Western Reserve University

Moses Supercharger
Chair, Joint Clinical Research Centre's Community Advisory Board

Evelyn Harlow Mwesigwa
Program Officer, Uganda MoH; Director, Sickle Cell Network Uganda

Jeff Sheehy
Consultant
Former: CIRM Executive Board
District 8 Representative, San Francisco

Lynda Dee
Attorney
Founder: AIDS Action Baltimore

GGTI
GLOBAL GENE THERAPY INITIATIVE

JCRC

Joint Clinical Research Centre Kampala, Uganda

CaringCross
CREATING ACCESS TO CURES

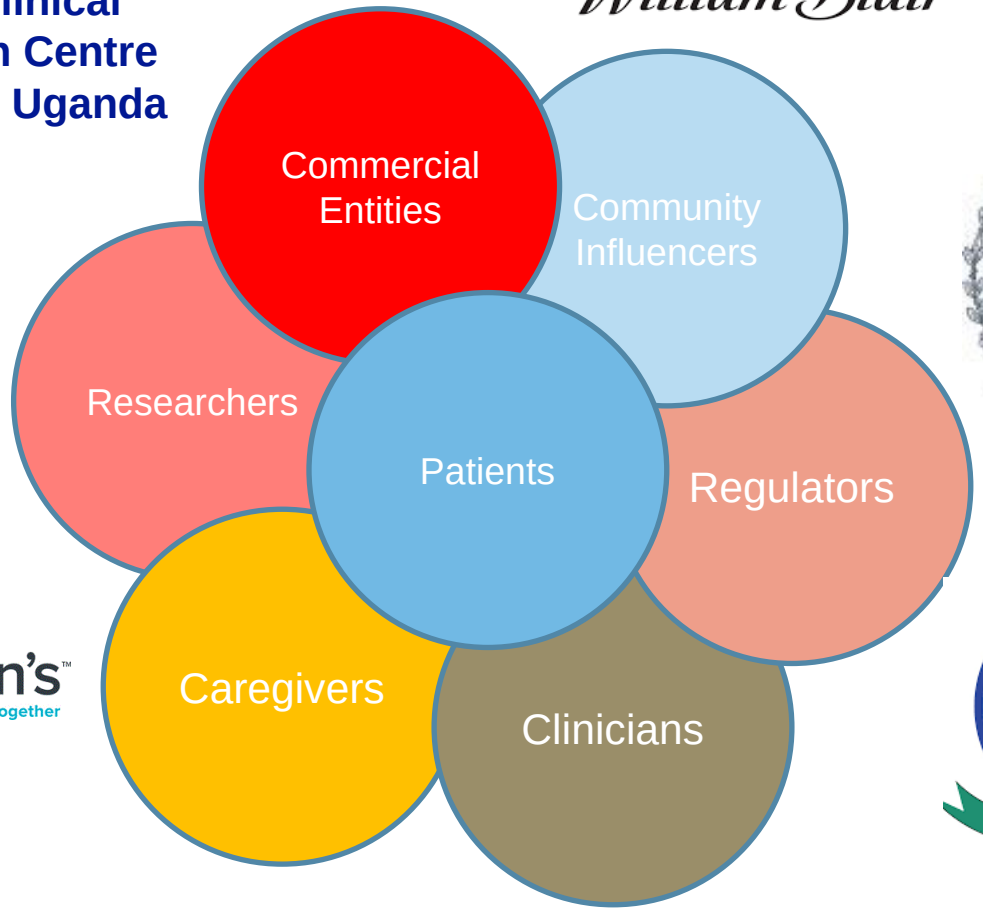
William Blair

Christian Medical College Vellore, India

UCSF

The African Academy of Sciences

Yale University



UW Medicine
UW SCHOOL OF MEDICINE

PITTSBURGH HEART, LUNG, AND BLOOD VMI
VASCULAR MEDICINE INSTITUTE
VITALANT • HCWP • UNIVERSITY OF PITTSBURGH • UPMC

GEORGETOWN UNIVERSITY
Georgetown University Medical Center

NIH National Heart, Lung, and Blood Institute

Cell And Gene Therapy Center | IQVIA

Inserm

Cincinnati Children's
changing the outcome together

MUHAS

BILL & MELINDA GATES foundation

CASE WESTERN RESERVE UNIVERSITY EST. 1826

UC San Diego

NOVARTIS

ROIVANT SOCIAL VENTURES

HOW ARE WE DOING IT ?

Clinical Readiness & Implementation

Training & Capacity Building

Regulation & Policy

Infrastructure for Commercialization

New Technology Development

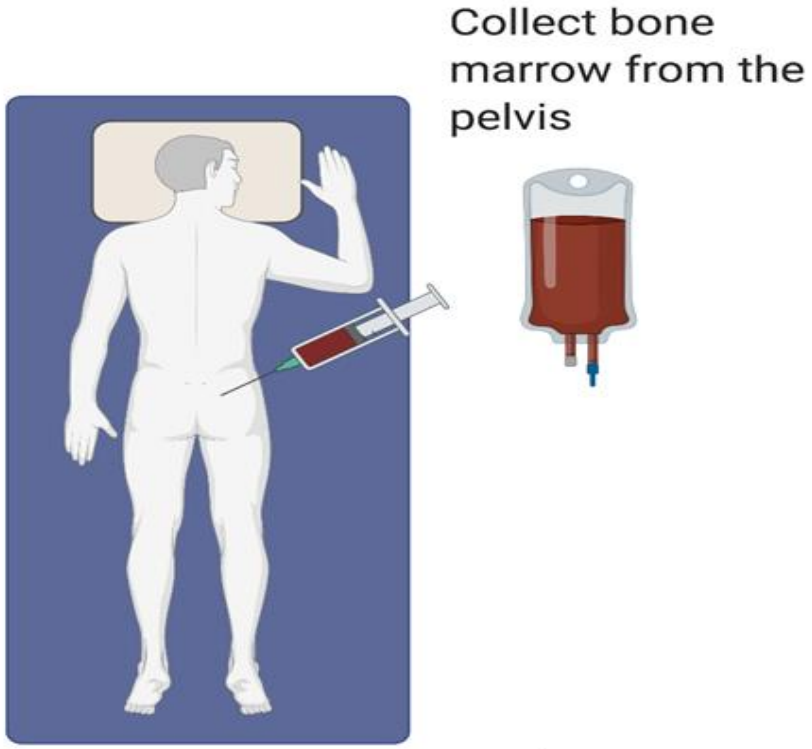
Sustainability

Community Outreach & Education

Adoption

Collection of Blood Stem Cells for Gene Therapy

A From the bone marrow directly



B From the blood stream through the apheresis procedure

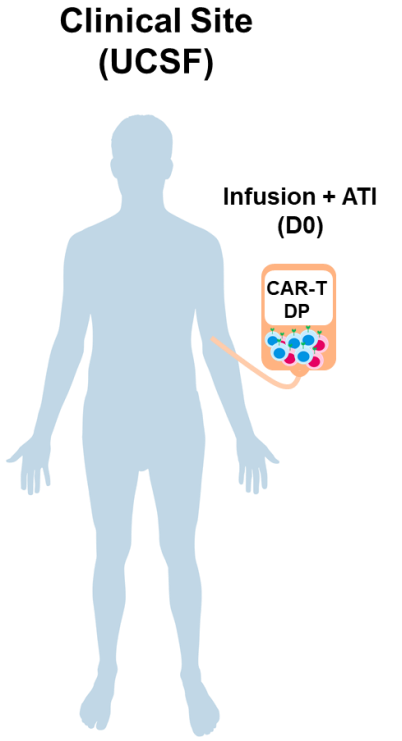
Blood stem cells are moved or “mobilized” out of the bone marrow into circulation with drugs like plerixafor, followed by apheresis.

Apheresis is a procedure that involves removing whole blood from a donor or patient and separating the blood into individual components so that one particular component, in this case blood stem cells can be removed.

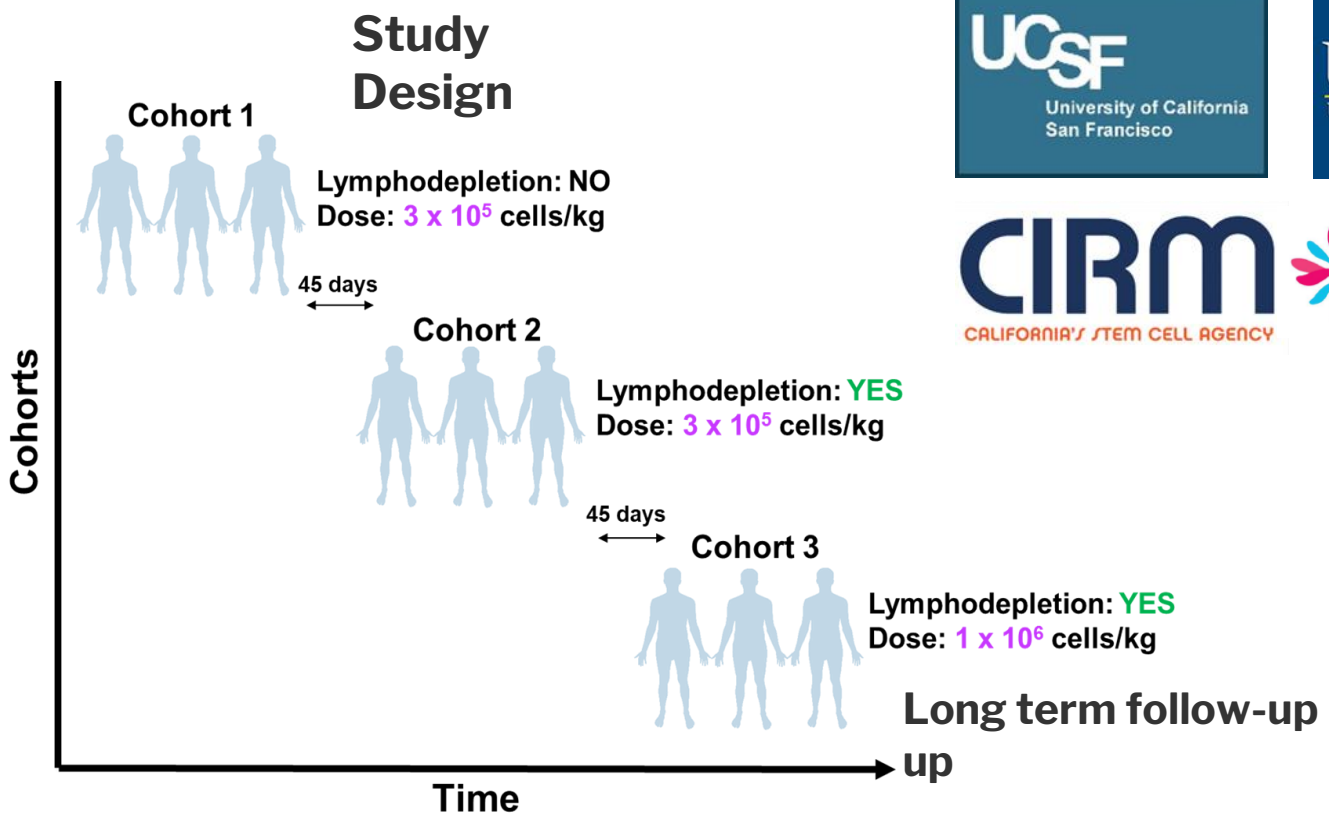
PRODUCT DEVELOPMENT:

Clinical trial design: Translating anti-HIV duoCAR-T cell therapy to PWH

- First-in-human phase I/II study to evaluate the **safety** and **efficacy** of duoCAR-T cell therapy in ART-suppressed PLWH (NCT04648046, PI: Dr. Steven Deeks)



ATI = Analytic Treatment Interruption
PLWH = people living with HIV



UCSF University of California San Francisco

UC DAVIS UNIVERSITY OF CALIFORNIA

CIRM CALIFORNIA'S STEM CELL AGENCY

CaringCross

GGTI Access to Gene Therapy Products for HIV and SCD

GGTI
GLOBAL GENE THERAPY INITIATIVE

CaringCross

NIH National Heart, Lung, and Blood Institute

Multispecific anti-HIV duoCAR-T cells display broad in vitro antiviral activity and potent in vivo elimination of HIV-infected cells in a humanized mouse model

KIM ANTHONY-GONDA, ARIOLA BARDHI, ALEX RAY, NINA FLERIN, MENGYAN LI, WEIZAO CHEN, CHRISTINA OCHSENBAUER, JOHN C. KAPPES, WINFRIED KRUEGER, [...]
BORO DROPULIĆ +7 authors Authors Info & Affiliations

SCIENCE TRANSLATIONAL MEDICINE • 7 Aug 2019 • Vol 11, Issue 504 • DOI: 10.1126/scitranslmed.aav5685

Article | Open Access | Published: 02 October 2019

Development of a forward-oriented therapeutic lentiviral vector for hemoglobin disorders

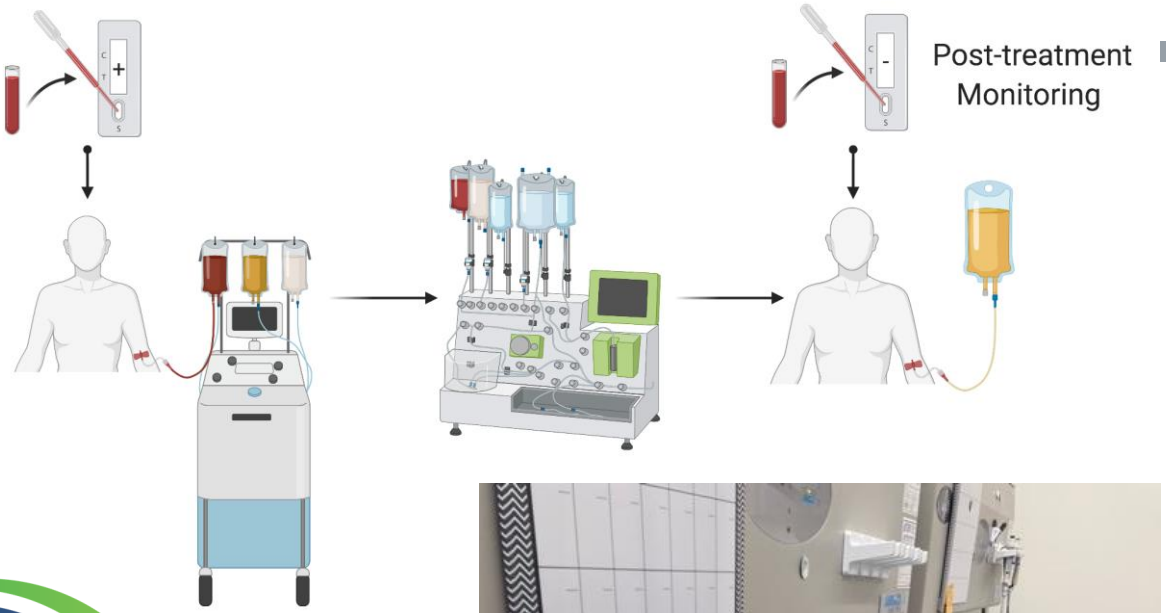
Naoya Uchida ✉, Matthew M. Hsieh, Lydia Raines, Juan J. Haro-Mora, Selami Demirci, Aylin C. Bonifacino, Allen E. Krouse, Mark E. Metzger, Robert E. Donahue & John F. Tisdale

Nature Communications **10**, Article number: 4479 (2019) | Cite this article

Funding Success: Training the 1st Generation of Ugandan Gene Therapists

Clinical Readiness & Implementation

Training & Capacity-building



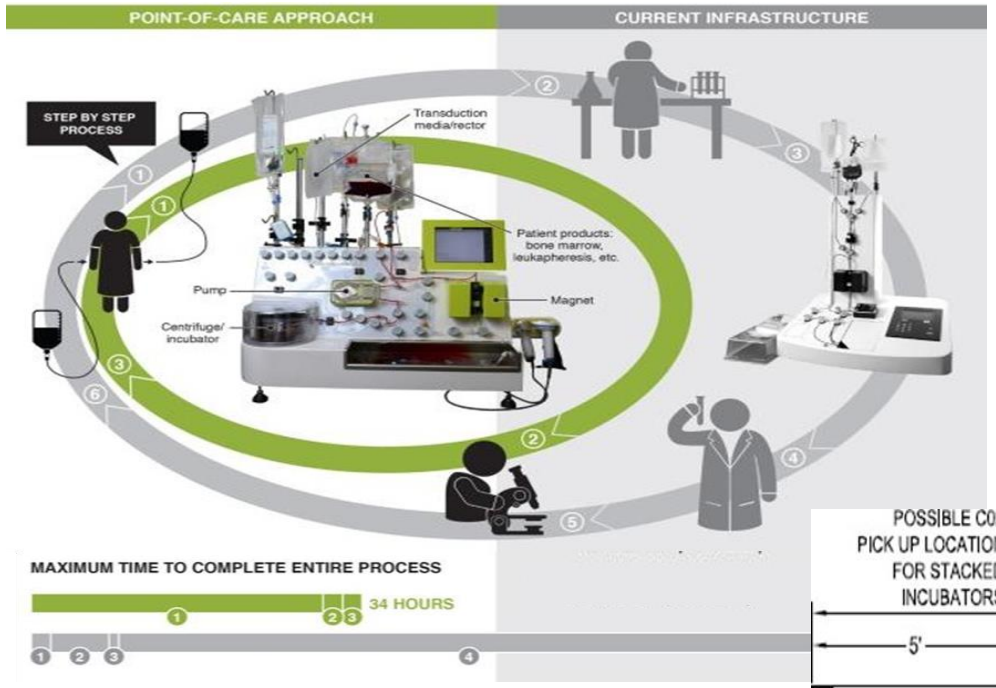
CaringCross
CREATING ACCESS TO CURES

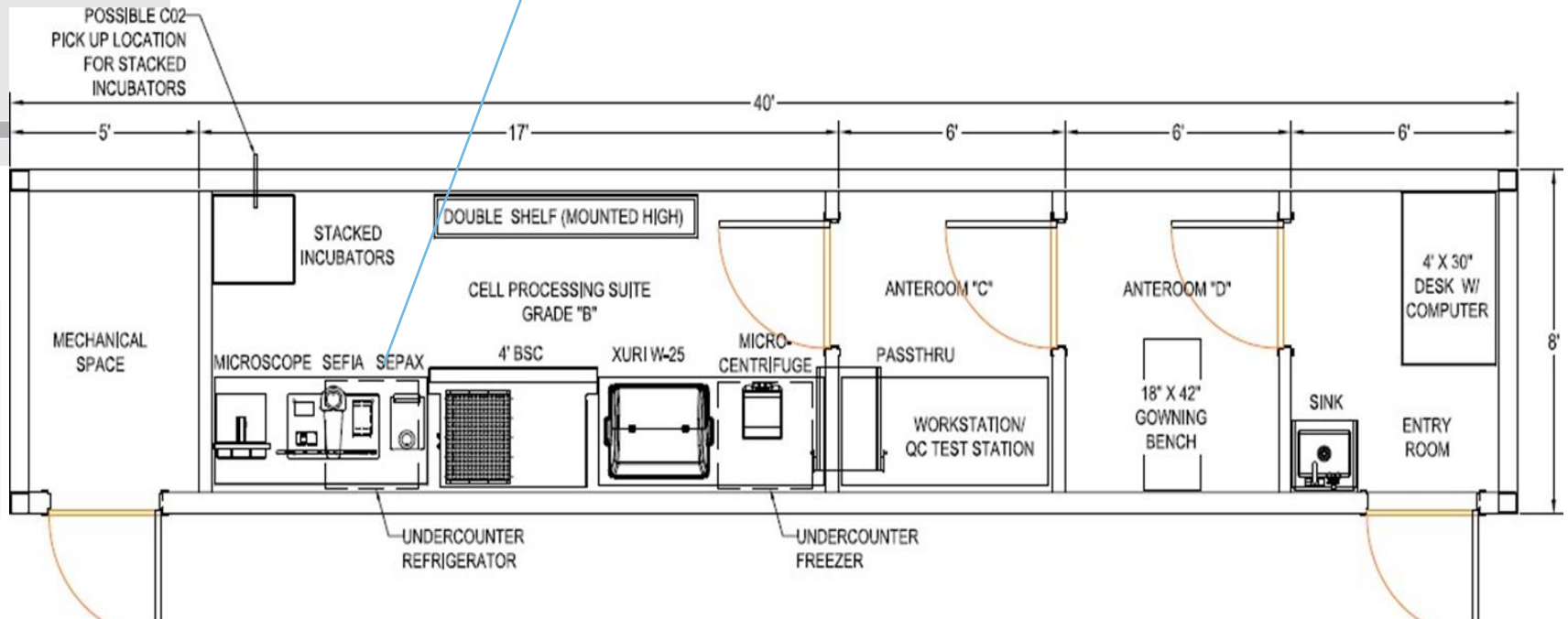
GGTI
GLOBAL GENE THERAPY INITIATIVE

BILL & MELINDA GATES foundation

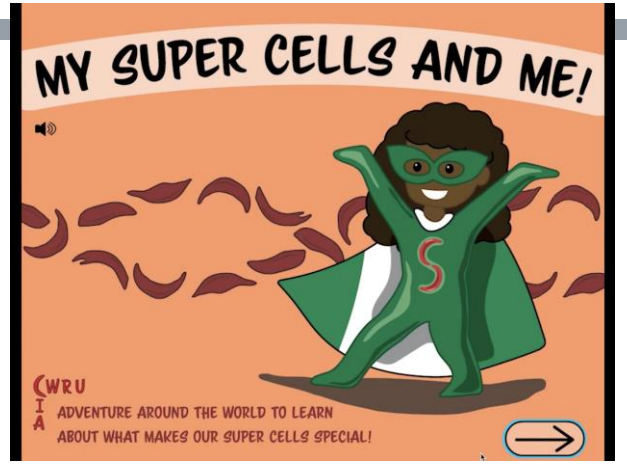
Dr. Lois Bayigga, JCRC as she learns the process of blood stem cell transduction in the Adair Lab.

Production and Manufacturing: Place-of-Care





Decentralized Manufacturing Container Facility
cGMP Cell Therapy Processing Suite



GGTI
GLOBAL GENE THERAPY INITIATIVE

defeatHIV
COMMUNITY ADVISORY BOARD
MEETING

Community Outreach & Education

Adoption

Regulation & Policy

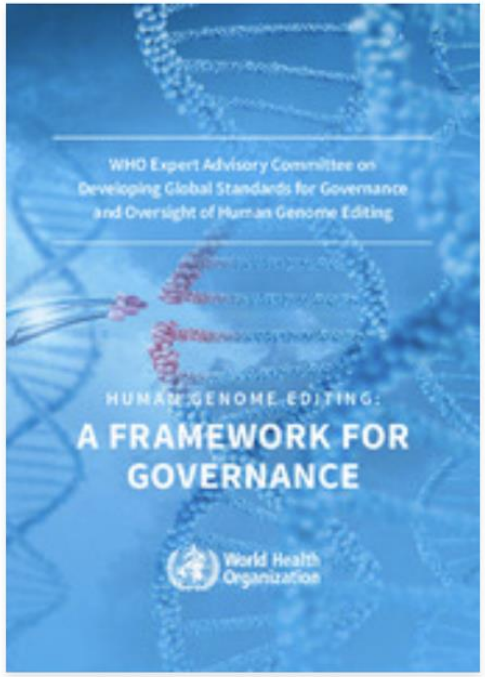
Infrastructure for Commercialization

GGTI
GLOBAL GENE THERAPY INITIATIVE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

World Health Organization

THREE DOCUMENTS:



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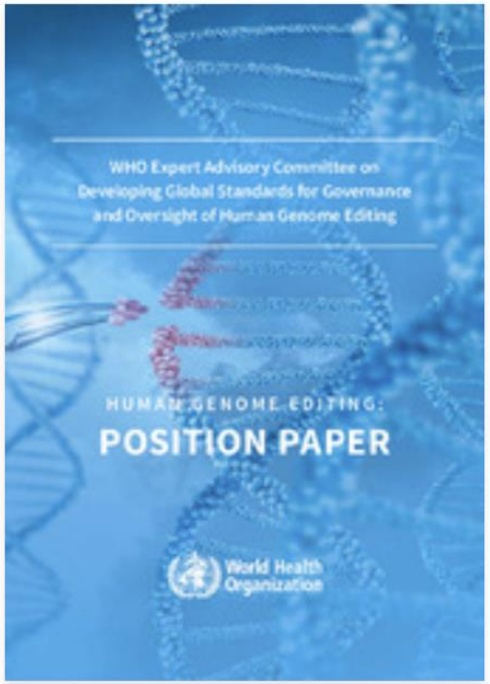
https://www.who.int/publications/i/item/9789240030060

Download (919.5 kB)

https://www.who.int/publications/i/item/9789240030381



Download (225.6 kB)

https://www.who.int/publications/i/item/9789240030404

CONCLUSION

- Gene-editing tools are fast evolving and their applications are vast- require domesticated governance and regulatory frameworks for research, clinical care, community engagement, infrastructural and capacity development
- Uganda will serve as a Test Case for implementation of the WHO Governance Framework for Human Genome Editing
- JCRC in collaboration with experts within the GGTI and with support from government institutions, regulatory authorities, Ethics & Biosafety Committees is pioneering the development of Gene Therapy products in-country to address public health problems

THANK YOU FOR YOUR ATTENTION

GGTI

GLOBAL GENE THERAPY INITIATIVE

FLY with GGTI

Supported by Ardent Funder

Joint Clinical Research Centre (JCRC)

GENE THERAPY FOR THE – HEALTH & WELLBEING – OF UGANDANS

MARCH 2022

What is

DNA?

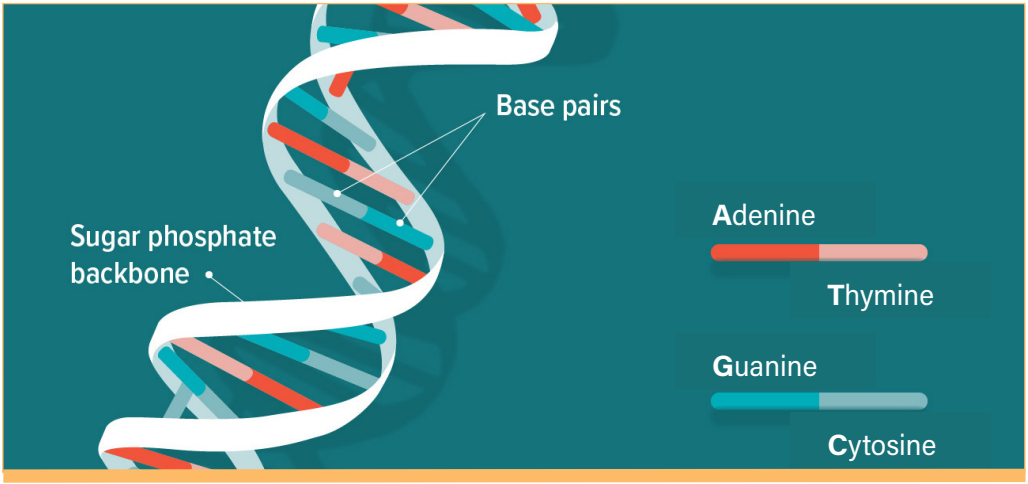
DNA is the material that carries all the information about how a living thing will look and function. It supplies the genetic instructions that tell the body how to develop, live and reproduce.

1. DNA is made up of chemical substances that are linked together to form a shape like a ladder

2. DNA also has chemicals called bases - A, T, G, C. Each base on one strand is joined to a base on the other strand

3. These four chemicals are repeated in different orders over and over again in each strand of DNA

The Structure of DNA

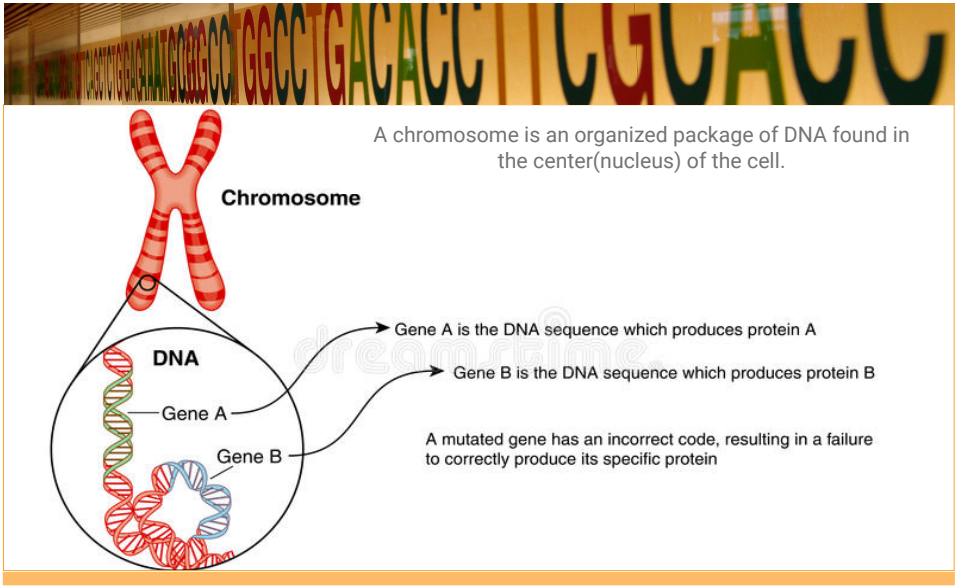


What are

GENES?

Similar to the way that letters in the alphabet can be arranged to form words, the order of the bases (A, T, G, C) in a DNA sequence forms genes which in the language of the cell, tell the cell how to make a specific protein leading to a particular characteristic or function.

Proteins perform most life functions and make up almost all cellular structures. Genes control everything from hair color to blood sugar by telling cells which proteins to make, how many of them, when to make them, and where.



What is

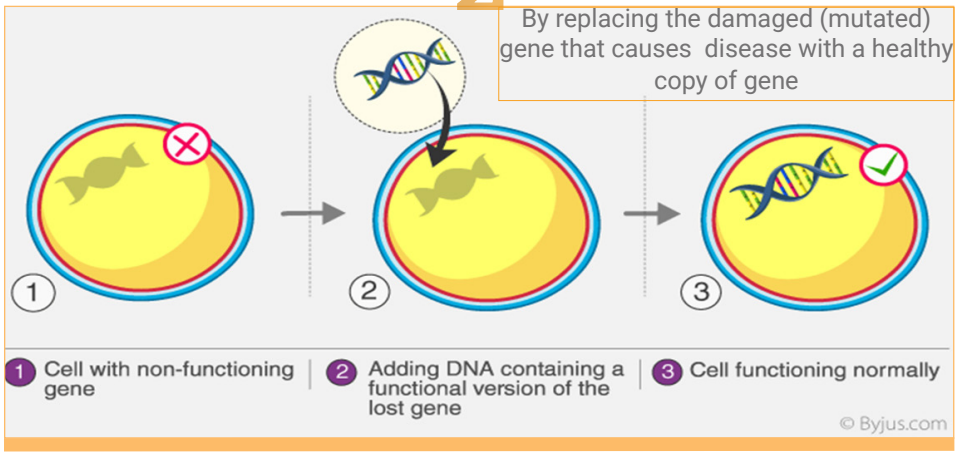
GENE THERAPY?

Gene Therapy is the **alteration of genes inside the organisim's cells** to treat or CURE disease. **Sometimes it is called Genetic Engineering.** Researchers are testing several approches to gene therapy, including;

1. Knocking out or "inactivating" a damaged gene that is not functioning properly

2. By replacing the damaged (mutated) gene that causes disease with a healthy copy of gene

3. Introducing a new gene into the body to help fight a disease

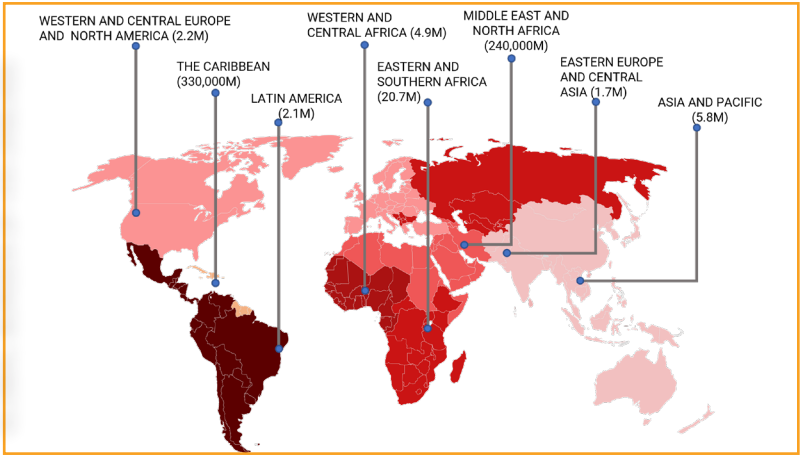


Our proposed activities do not include alteration of sperm or egg (germ) cells but rather body cells and therefore the changes are not heritable

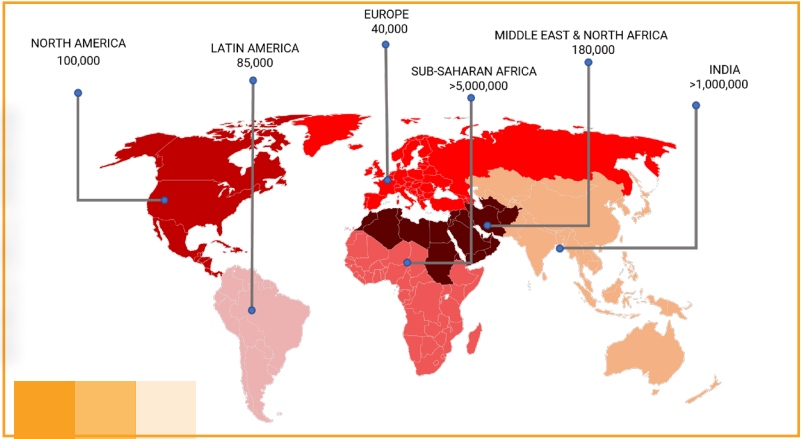
Why is

GENE THERAPY IMPORTANT FOR UGANDA

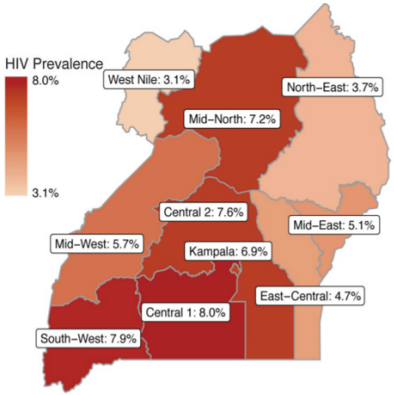
GLOBAL BURDEN OF HIV DISEASE



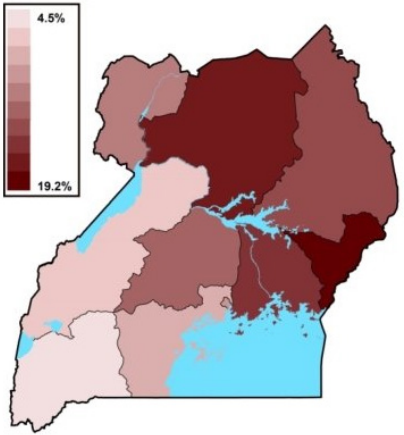
GLOBAL IMPACT OF SICKLE CELL DISEASE



BURDEN OF HIV DISEASE IN UGANDA



BURDEN OF SICKLE CELL DISEASE IN UGANDA



Why is

GENE THERAPY IMPORTANT FOR UGANDA

GENE THERAPIES:

The Next Generation of Medicine

- Despite expanded access to treatment, HIV remains a leading cause of death
- Pills need to be taken daily and patients get fatigued
- Adherence to ART regimens is inconsistent

1.4m

A cure could benefit 1.4m people living with HIV and **400,000** people living with Sickle Cell Disease, today!

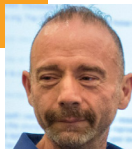
- HIV resistant viral variants have emerged and threaten effectiveness of HIV treatment programs
- Hard-fought progress is threatend by stagnant funding and donor fatigue
- Sickle Cell Disease (SCD) is the most common blood disorder
- Uganda has the 5th highest burden of Sickle Cell
- Diagnostic capacity is low
- Stigma and denial are common
- There is limited funding to support management of SDC

News of

CURES SPARKS HOPE

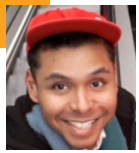
Victoria Gray
First patient with sickle cell disease to be treated with cells modified using one of the fastest gene-editing tools called CRISPR cas-9

Photo credit: NPR



Timothy Ray Brown
The Berlin Patient
1st person cured of HIV. There are now 4 people cured from HIV

Photo credit: Fred Hutch

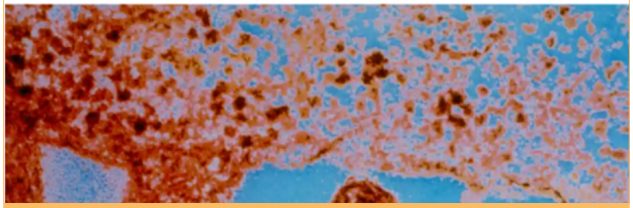


Adam Castillejo
The London Patient
2nd person cured of HIV

Photo credit: POZ

Third person apparently cured of HIV using novel stem cell transplant

Patient is mixed-race woman treated in New York using umbilical cord blood, in technique raising chances of finding suitable donors



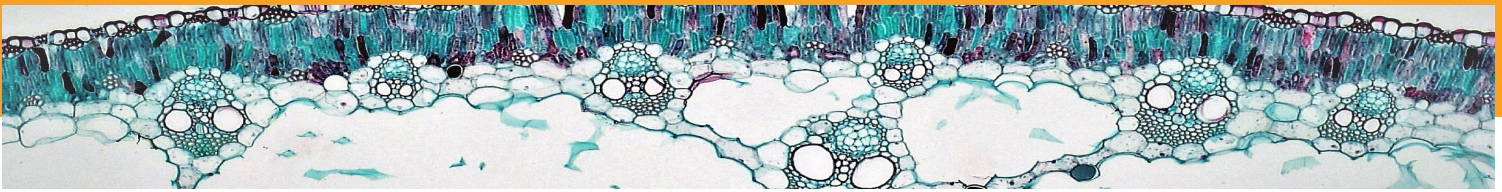
Antibody-based treatment

One person remains undetectable without HIV drugs almost four years after using an antibody-based therapy

Antibody enabled other people sensitive to it to stay off ART for at least three months

Gus Cairns | 16 February 2022

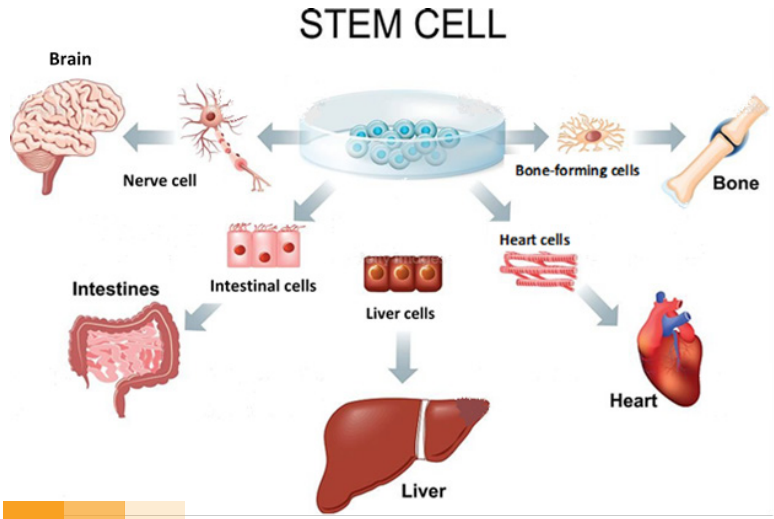
CROI 2022



What are

STEM CELLS?

These are cells in the body that are able to produce all of the other cell types that are needed. They are present in all of us from birth throughout life.



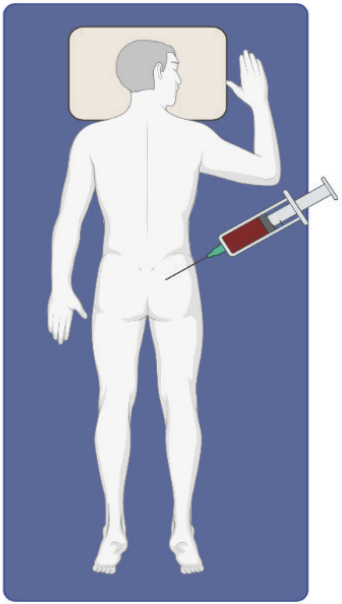
They can **reproduce themselves** to make many more cells

OR

Develop into special cells that carry out special functions in the body such as the skin, blood, muscles and nerves

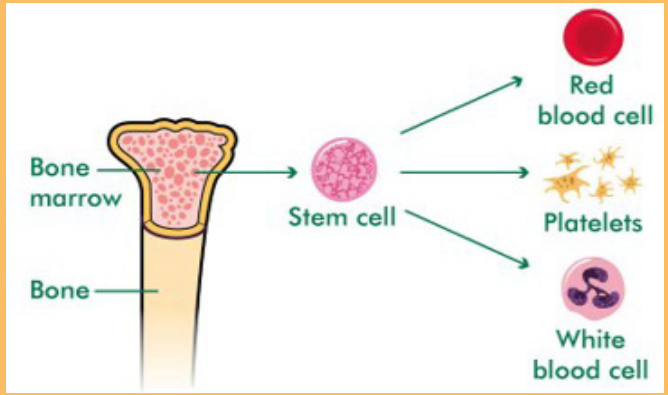
Which blood

CELLS COME FROM STEM CELLS?



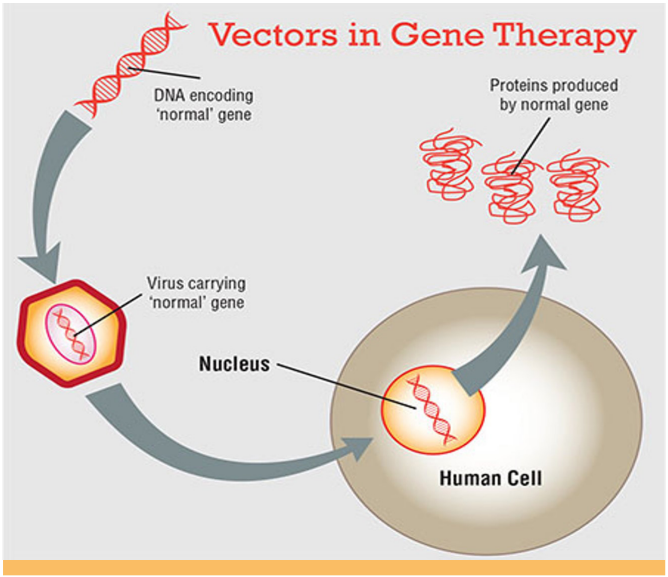
Patient

Blood-forming cells also known as blood stem cells are produced in the bone marrow. There are 3 main types of blood cells: red blood cells, white blood cells and platelets



How is

GENE THERAPY DELIVERED TO BLOOD STEM CELLS?



Gene therapies require carriers to deliver the gene of interest to the nucleus of the cell

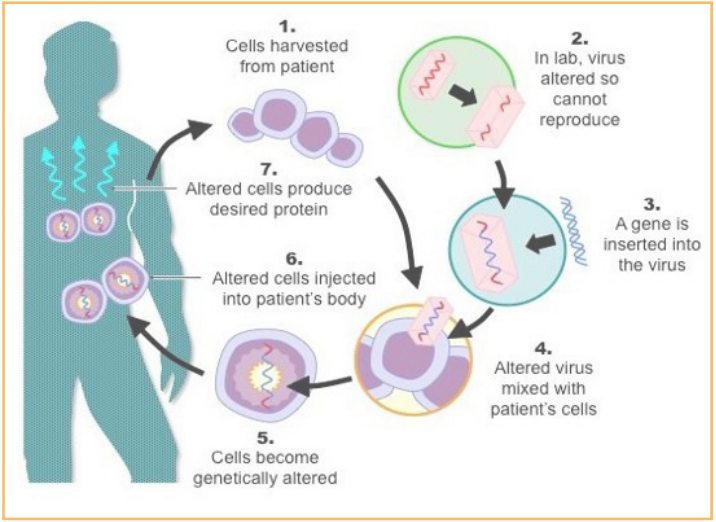
Vectors carry the healthy gene (gene of interest) to the nucleus of the target cell

Virus vectors are the most common type of carriers used to deliver gene therapy to blood stem cells

How

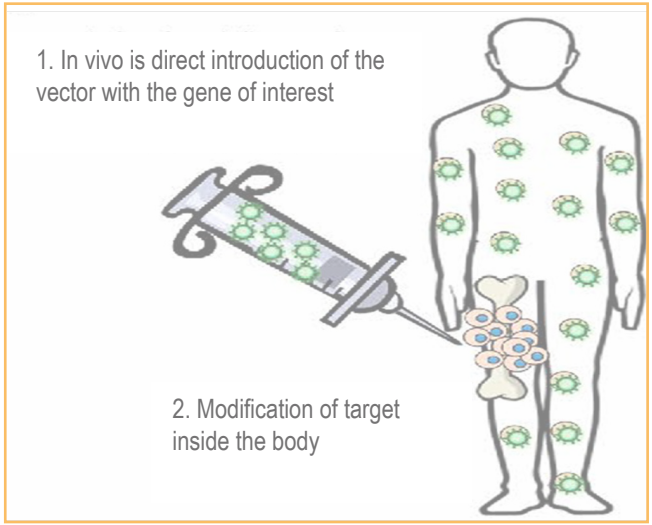
GENE THERAPY IS PERFORMED?

Outside the body (Ex-vivo)

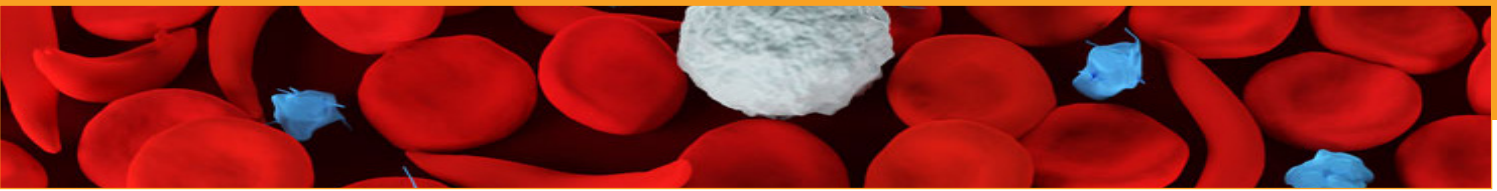


- Patient's blood cells are collected from the bone marrow or blood
- A vector/carrier with the gene of interest is introduced to these cells in a laboratory
- The cells with gene of interest are multiplied to produce more copies
- These copies are introduced into the patient's body

Inside the body (In-vivo)



- A vector/carrier with the gene of interest is directly introduced into the patient's body via a syringe.
- The introduction of the gene of interest into the blood cells is done directly in the body.



How do we

GET BLOOD STEM CELLS FOR GENE THERAPY

Directly from the bone marrow

A

Bone marrow is collected from the pelvis

From the blood stream through the apheresis procedure

B

Blood stem cells are moved or "mobilized" out of the bone marrow into circulation with drugs like plerixafor

The Apheresis procedure involves separation of blood components:

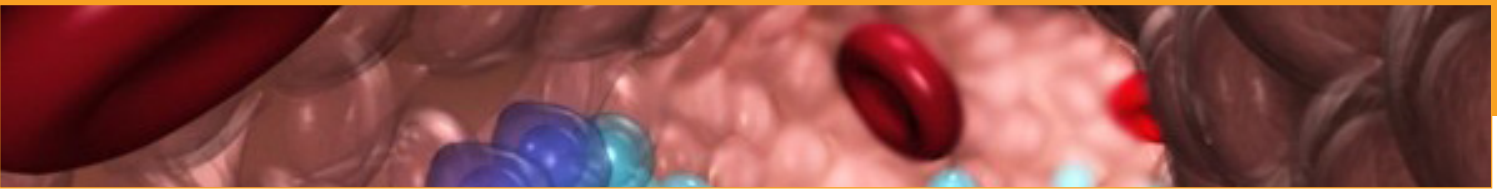
1. Removing whole blood from a donor or patient themselves
2. Separating/filtering that blood into individual components so that one particular component is removed
3. Re-introducing the remaining blood components to the patient's blood stream

How are

GENETICALLY ENGINEERED BLOOD CELLS PREPARED?

This table-top device can automate the whole process for gene transfer-also called **"Gene therapy in a box"**

It has potential to make these innovative treatments accessible to countries like Uganda



How will

GENE THERAPY BENEFIT UGANDANS?

PROMISING CURE

Gene therapies are the most promising cure strategy with the greatest potential for accessibility because they do not require a donor.

REGIONAL CENTRE OF CARE AND TREATMENT

Uganda is leading in efforts to make Gene Therapy accessible; positions us to be a Regional Centre for care & treatment translating into technology and economic development.

IMPROVED LIFE EXPECTANCY AND QUALITY OF LIFE

Targeting these two diseases first will significantly improve the life expectancy & quality of life of affected individuals, families & the nation translating into increased productivity.

TRANSFER OF TECHNOLOGY

Presents opportunity for technology transfer for local manufacturing of gene therapy products for local use & export.

INTELLECTUAL PROPERTY RIGHTS

Stronger stake in Intellectual Property Rights & Patenting.

Possible risks of

GENE THERAPY

- Unwanted immune system reaction: however, we have developed Quality Management Tools & Expertise pool
- Off-Target response: therapy gets into other cells of the body but this risk is minimized because the cells are purified before they are given back to the patient
- Cancer: this is still a theoretical possibility as no patient on this therapy to date has reported
- New infections because the carrier (viral vector) used to deliver the gene therapy recovered its original infectious capability or combined with another virus the patient was exposed to

The vision for

HIV & SICKLE CELL DISEASE MANAGEMENT

These treatments could be:

ONE-TIME

Administered in just a single dose

CURATIVE

Acutely focused and locally targeted on the biology of the disease

VALUABLE

High impact on quantity and quality of life, with great clinical, economic, and social value

SAFE

Improved safety profile, avoiding adverse events and challenging medical procedures

POTENT

Transformative efficacy improvements over standard of care

DURABLE

Sustained, life-long benefits

Questions?

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