Gene Therapy:

Blood and Immune Disorders

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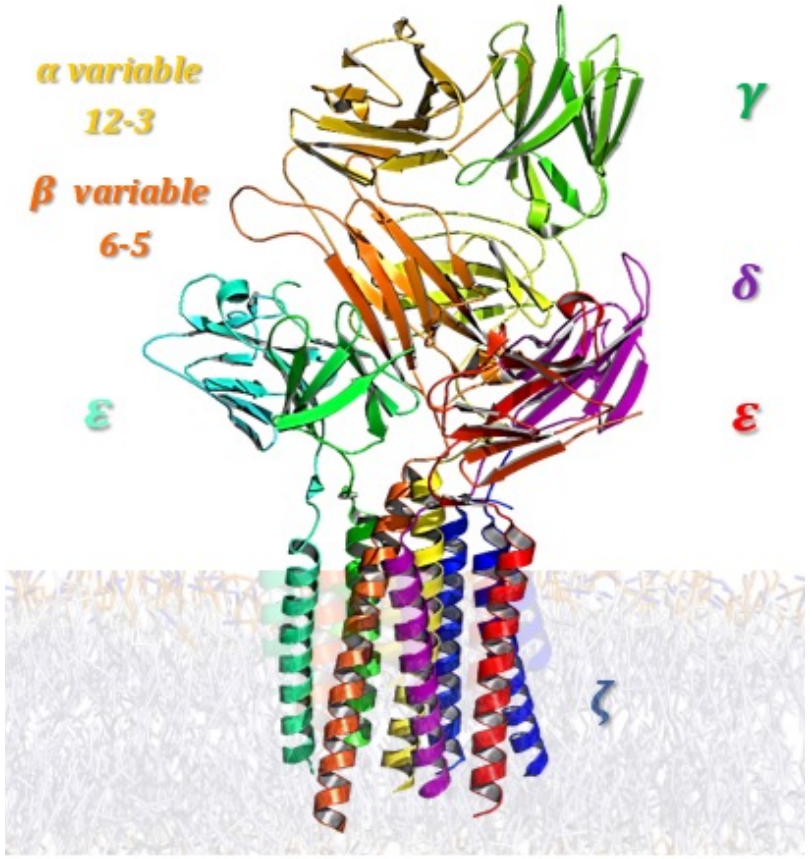


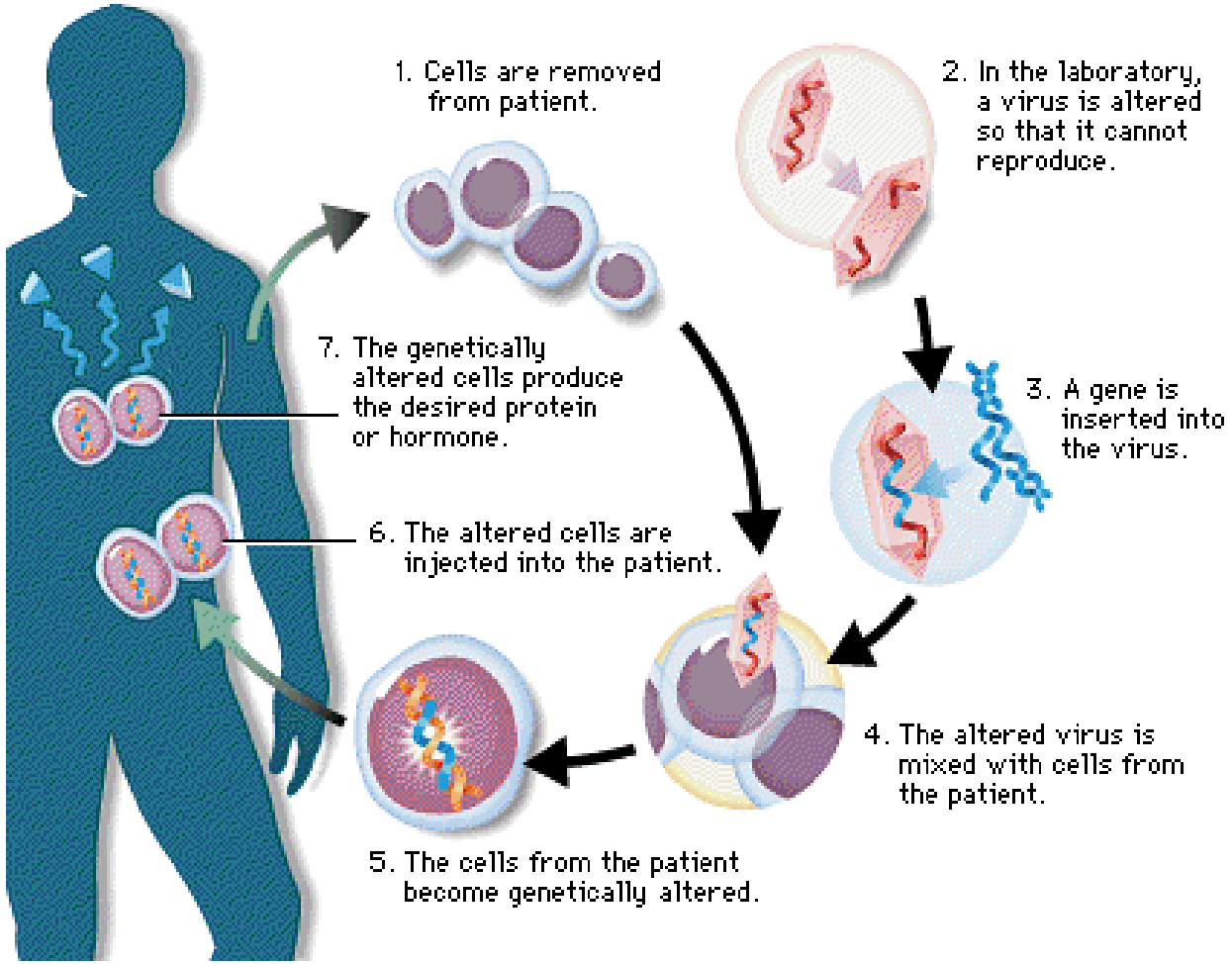
Gene therapy for blood & immune disorders

- Only curative treatment is hematopoietic stem cell transplant or bone marrow transplant
- Gene Therapy advantages over transplant:
  - No need to find a donor
  - Conditioned with less chemotherapy, lower treatment-related toxicity
  - No risk of graft vs host disease
  - No need for immune suppressive medications post transplant
  - Could be more cost effective?*
- Proven to be safer and more effective for some types of immune disorders
  - 50 pt with ADA SCID had 100% survival and adequate immune reconstitution in 96%

Kohn et al JACI 2019;143:852
Kohn et al NEJM 2021, 384:2002-2013

Gene Therapy strategies: Viral Vector

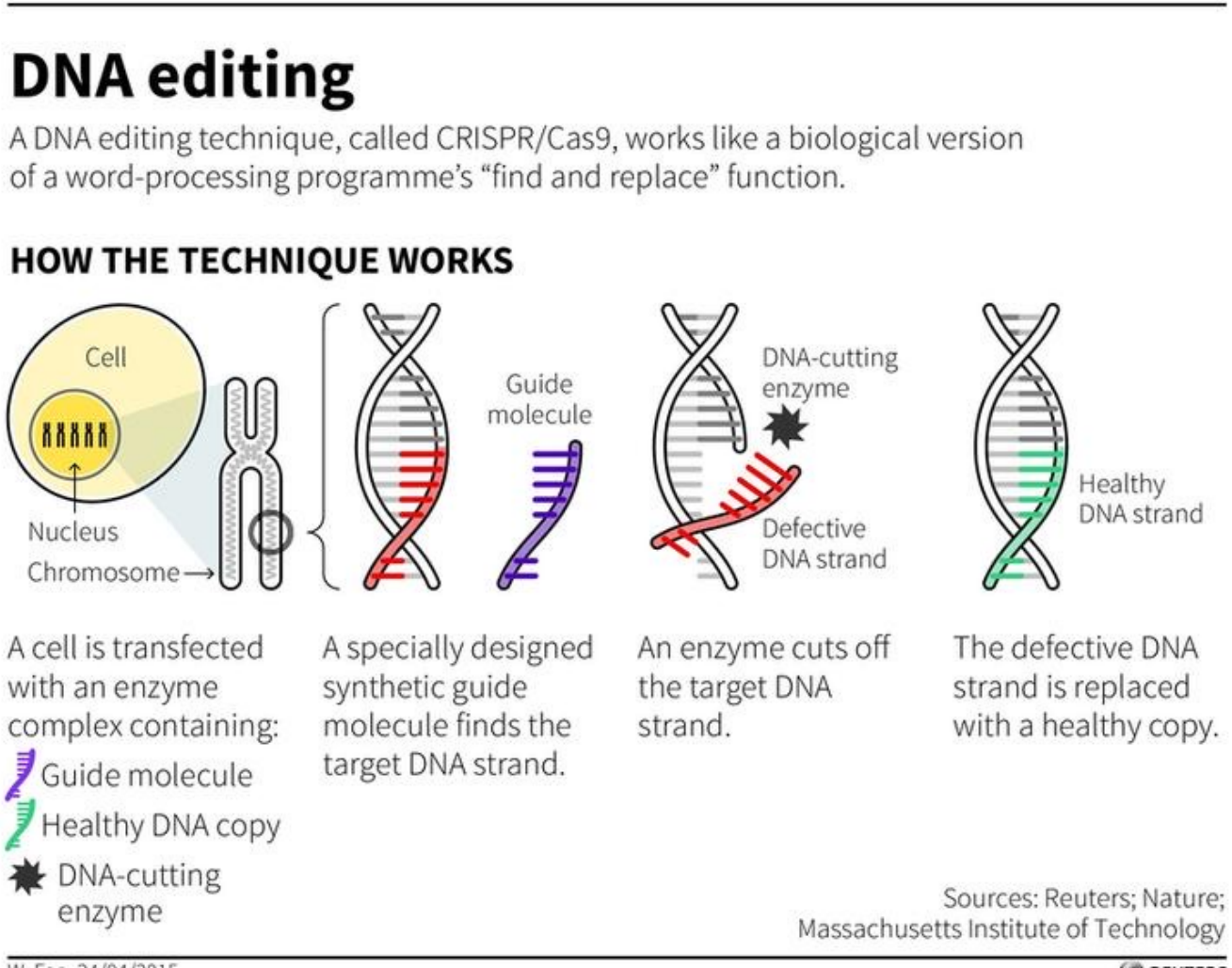
- Initial trials used gamma retrovirus
  - Complicated by insertional mutagenesis
- Newer trials use a lentivirus or adenovirus
- Commercialization/scaling up of viral vector production is difficult and expensive
- **Commercialized therapies:**
  - **Strimvelis for ADA SCID (gamma-retro)**
  - **Zynteglo for B thalassemia (lenti)**
  - **Hemgenix for Hemophilia B (AAV5)**



Shinde, N World J Pharm Res 2014; 3(2):1861

Gene editing: spellcheck for DNA

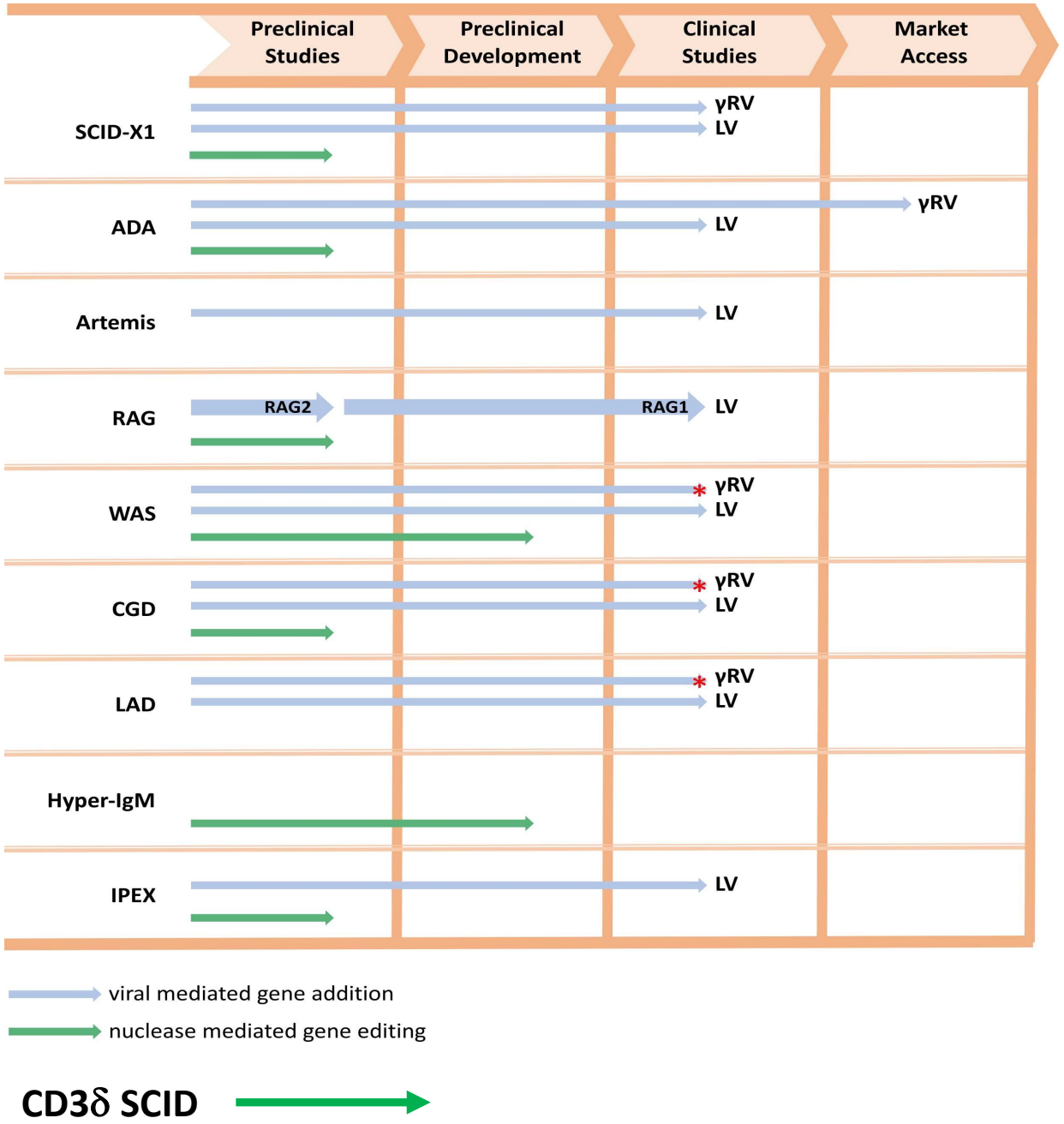
- Delivers the spellchecker/correcting machinery into the cell
- CRISPR/Cas9 and base editing: delivers a guide RNA and editing enzyme



CRISPR/Cas9

- edits a small piece of DNA

- Base editing corrects just one letter



Current therapies for Inborn Errors of Immunity

ADA-SCID Gene Therapy Strimvelis

- Uses a gamma-retro virus
- Only commercially available gene therapy for immune disorders
- Only available in Milan, Italy
- Costs ~$2.4 million
- Considered standard of care for ADA-SCID in Europe and the UK
- Have reported leukemia

Gene Therapy for Blood Diseases

- **Sickle Cell Disease**
- **Beta Thalassemia**
- **Hemophilia A & B**

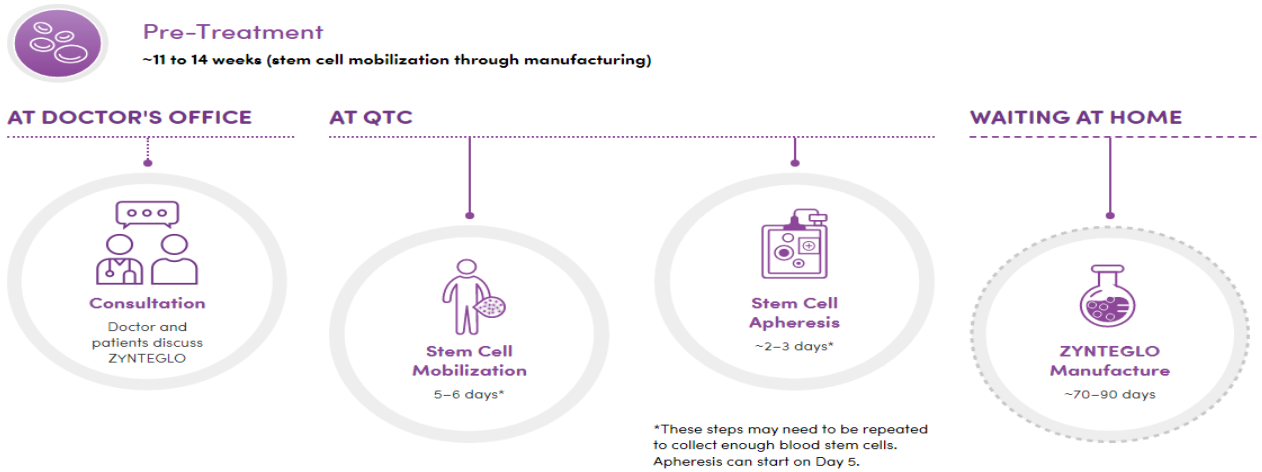
Other Diseases:

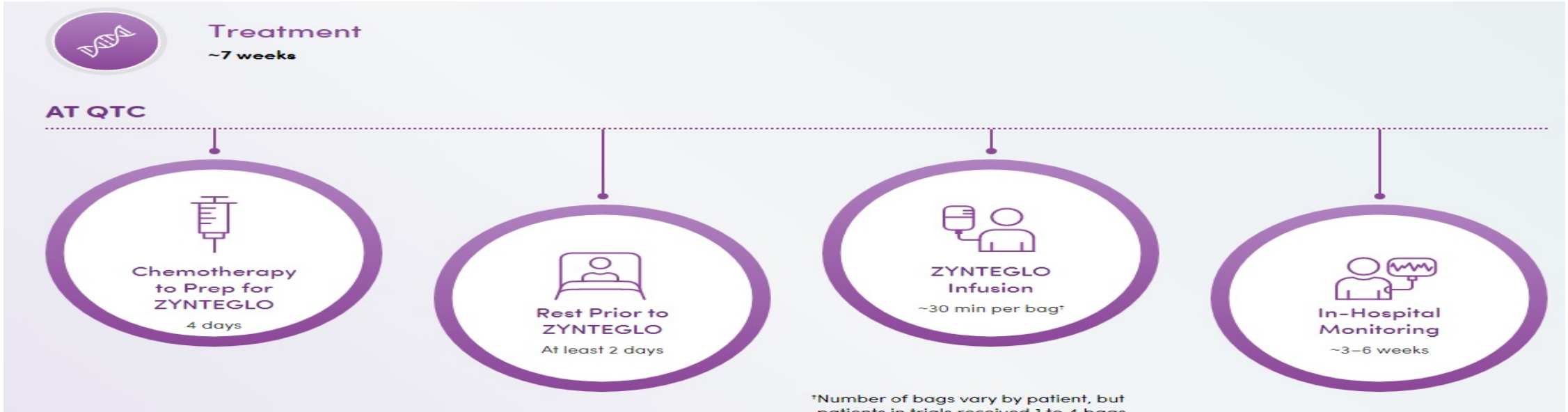
- Gaucher
- X-linked adrenoleukodystrophy
- Metachromiatic leukodystrophy

Beta Thalassemia: Viral Vector

Zynteglo – betibeglogene autotemcel, Bluebird Bio

- Lentivirus expressing a modified human β-globin, $\beta^{A\text{-}T87Q}$ – globin
- FDA approved, commercially available
  - 89% achieve transfusion independence
  - Only available at 10 US centers





VERTEX

FORBES > INNOVATION > HEALTHCARE

UK Approves Groundbreaking CRISPR-Based Gene Therapy For Sickle Cell Disease And Thalassemia

William A. Haseltine Contributor ⓘ

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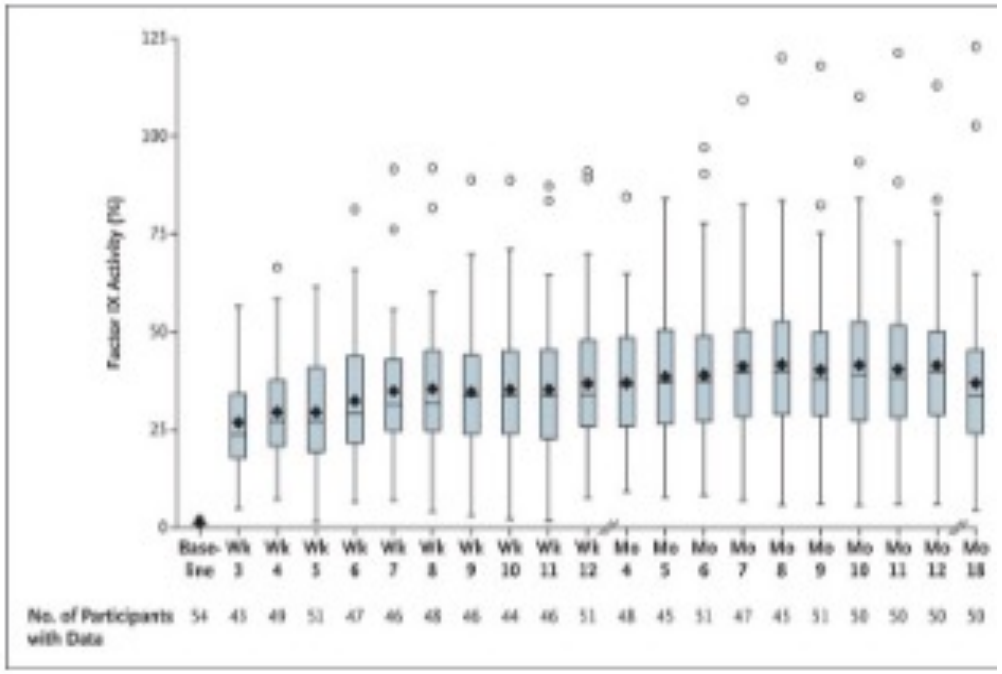
Nov 18, 2023, 09:00am EST

Hemophilia B Gene Therapy: Hemgenix
etranacogene dezaparvovec-drlb, CSL Behring

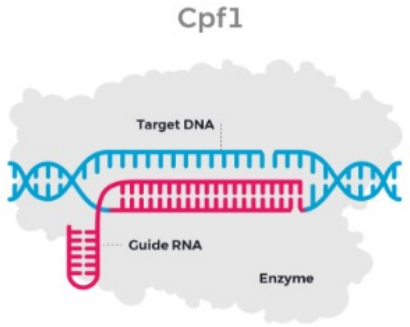
- FDA approved 2022, undergoing expedited approval through Health Canada
- Adeno-associated virus (AAV5) carrying Padua gene variant of FIX
  - Targets liver cells
  - Padua variant has 6-8 x activity as wild type FIX
- Only approved for adults
- Single IV infusion



Endogenous Factor IX Activity over 18 Months after Treatment (Full Analysis Population).

Pipe et al NEJM 2023;388:706

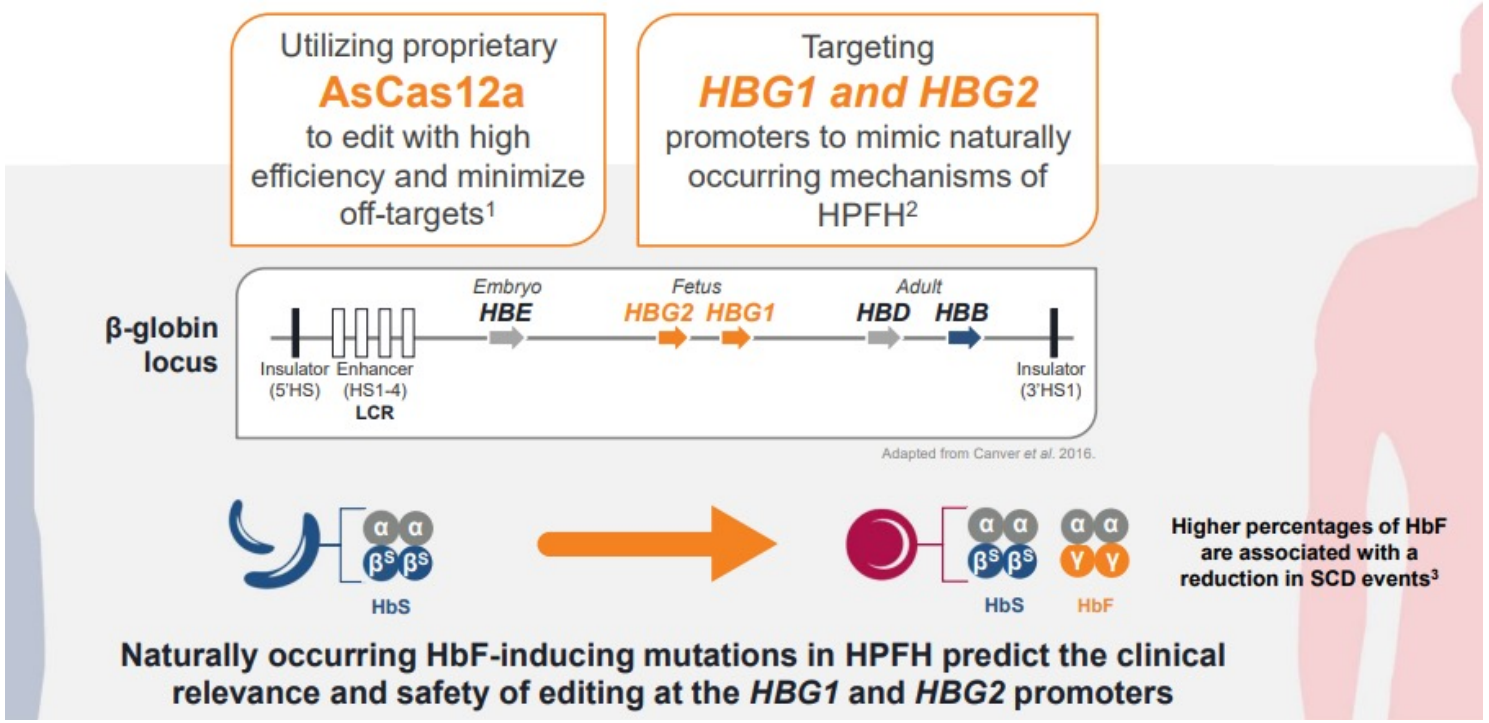
Clinical Trials open in Canada



- Ruby Trial: EDIT-301, Editas Medicine
  - γ-globin gene editing with CRISPR/Cas12a
    - Increases Hgb F, decreases Hgb S

- Ottawa Hospital Research Institute; Princess Margaret Cancer Center, TO; Ste. Justine, QC
- 18-50 yo

Preliminary results:
- 4 SCD, 1 thal pt treated
- Normal Hgb, HgbF >40% in first 2
- No VOC

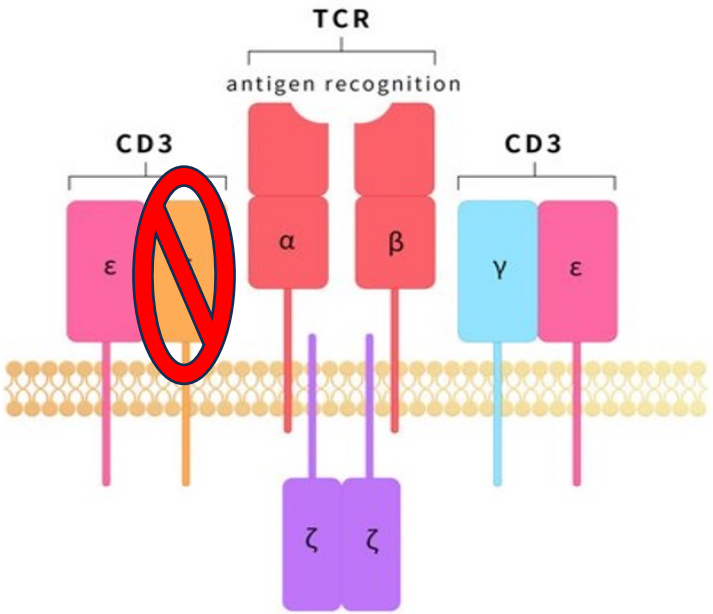


Upcoming Trial:
CD3δ SCID: Exemplary candidate for GT

- Excellent prototype for a Canadian gene therapy trial
  - Majority of patients are in Canada and Mexico
  - **If we don't do it, no one else will**

- Patients have the same point mutation
  - Amenable to adenine base editing
  - Will be one of the first trials to use base editing

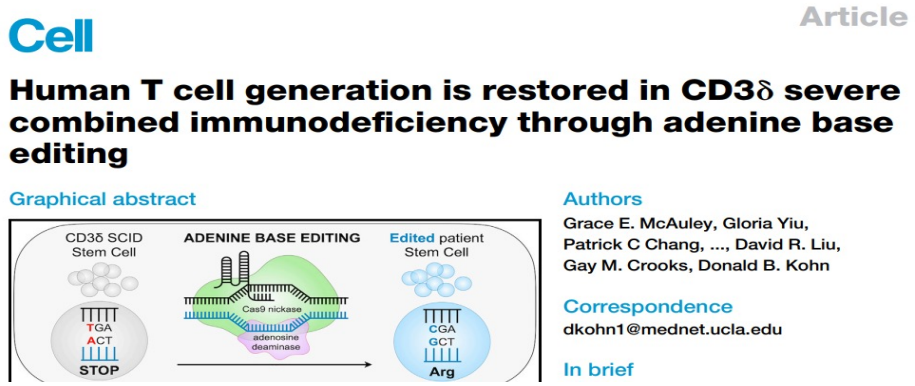
- Pilot project to develop a pipeline for other gene therapy trials in Canada



CAHN EDIT CD3δ SCID

Gene editing for CD3δ SCID

- Collaboration:
  - Nicola Wright, University of Calgary
  - Don Kohn, UCLA
  - Geoff Cuvelier and Tamar Rubin, University of Manitoba
  - Eyal Grunebaum, Toronto SickKids



Cell

Article

Human T cell generation is restored in CD3δ severe combined immunodeficiency through adenine base editing

Graphical abstract

Authors
Grace E. McAuley, Gloria Yiu, Patrick C Chang, ..., David R. Liu, Gay M. Crooks, Donald B. Kohn

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In brief

- Dr. Kohn performing preclinical work

- Proceeding to regulatory approvals
  - Need to complete toxicity experiments and manufacturing for FDA and Health Canada

- Clinical trial will begin once regulatory approval obtained (1-2 years)
  - Awarded $2.4 million CIHR grant and $5.9 million CIRM grant

Operational Challenges

- Preclinical models are expensive, time consuming
- Specific regulatory needs
- Challenges with large scale production
- Need financial support, infrastructure, people investment in R&D for rare diseases
- Investment in clinical trials
  - Few patients – difficult to get patient samples, difficult to recruit
- Need academic/health authority/industrial alliances
- High cost of commercialization

Commercialization Challenges

Orchard Therapeutics Restructures, Cuts Rare Disease Programs to Extend Runway into 2024

March 31, 2022

Rare Daily Staff

Gene therapy biotech Orchard Therapeutics said it will discontinue its rare primary immune deficiency programs, including about 30 percent of its workforce, to focus its hematopoietic stem cell gene therapy platform exclusively on severe neurometabolic diseases and early research programs.

The discontinued programs include OTL-103 for Wiskott-Aldrich syndrome, OTL-102 for X-linked chronic granulomatous disease, and Strimvelis, a gammaretroviral vector-based gene therapy approved in Europe for adenosine deaminase severe combined immunodeficiency (ADA-SCID).

DIVE BRIEF

Orchard abandons promising gene therapy for rare immune disorder

Published June 3, 2021

Orchard's decision is suggestive of the difficulty drugmakers can face in turning complex, but promising rare disease treatments into a sustainable business. The termination wasn't unexpected; Orchard said last May it was reducing staff and reordering its priorities, reducing investment in OTL-101 as a result.

Canadian challenges

- Pts need to go to other countries currently
- Researcher/company reluctance to obtain Health Canada approval
- Lack of infrastructure
- Lack of expertise
- Provincialized health care system
  - Difficult for pts to go to another province for trials, challenging to set up multiple sites
  - Need to integrate clinical care with research without barriers
  - Health authorities need to include development and access in their mandates

We have a great Opportunity!

- Goal should be to develop and offer gene therapies outside of the ‘for profit’ pharmaceutical model

- **Academic/health authority cooperation**

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