



Infusion of off-the-shelf *ex vivo* expanded cryopreserved progenitor cells to facilitate the engraftment of a single CCR5 Δ 32 homozygous or heterozygous cord blood unit in patients with HIV and hematological malignancies

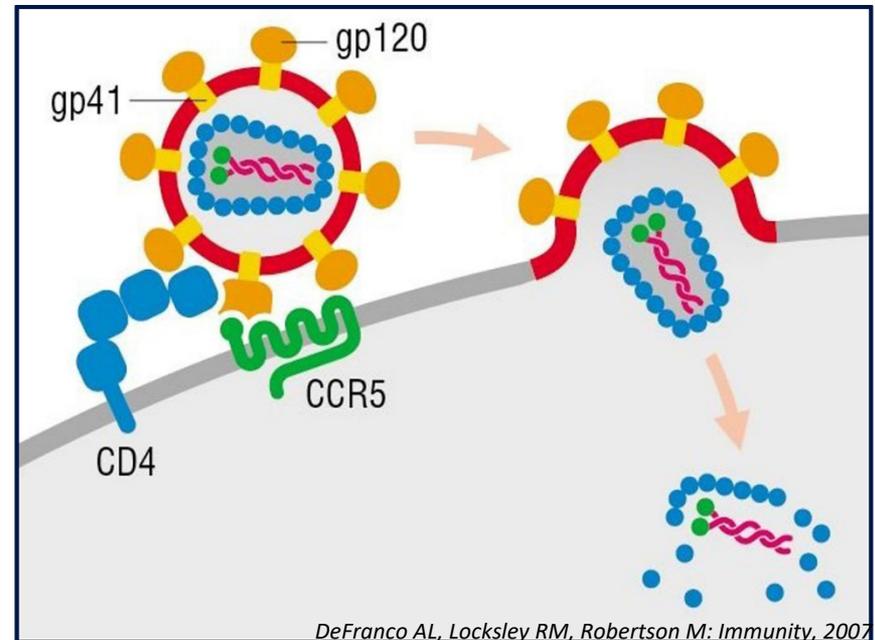
Background

- This is a Phase I/II prospective, open label, multi-site, non-randomized study in which patients with HIV & hematological malignancies will be enrolled.
- Objective will be to evaluate the safety of single unit homozygous or heterozygous CCR5 Delta32 cord blood transplant with a second non-matched off-the-shelf (OTS) *ex vivo* expanded cryopreserved UCB progenitor cells infused in patients with hematological malignancies and HIV infection in need of allogeneic stem cell transplant (alloSCT).
- AlloSCT has the potential for elimination of the HIV reservoir via GvH mechanism.
- Improbability of finding a CCR5 Δ 32 homozygous allogeneic marrow donor
 - *The feasibility to identify an HLA-matched homozygous CCR5 Δ 32 adult donor ranges only 0.1-0.4% for HIV infected hematology patients in need of alloSCT.*
- HLA mismatched UCB expands the likelihood of finding CCR5 Δ 32 homozygous donors. The prevalence of CCR5 Δ 32 homozygous units is estimated to be 0.8% with potentially over 5000 units carrying the mutation.

HIV entry into a host cell

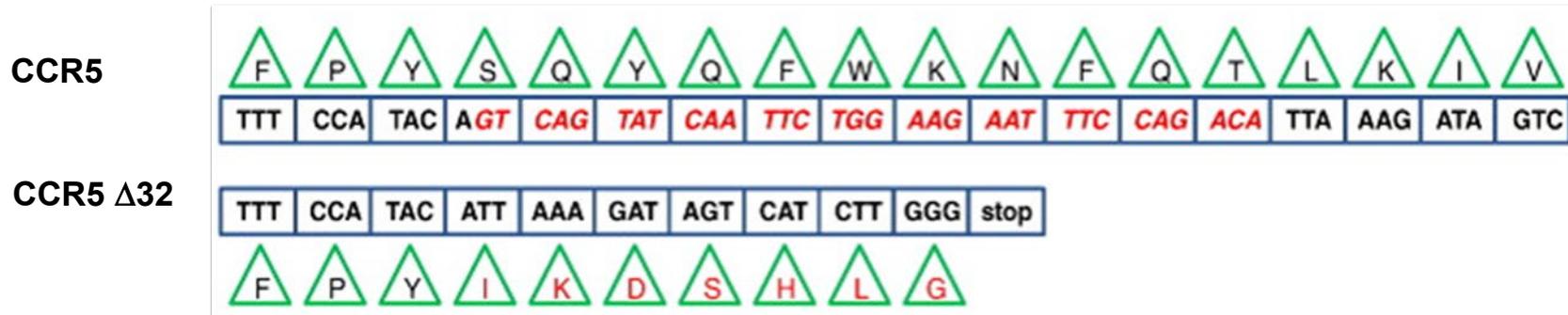
- HIV strains can be broadly classified based on their co-receptor usage.
- Viruses that use the chemokine receptor **CCR5** are termed **R5 HIV**, those that use **CXCR4** are termed **X4 HIV**, and viruses that can use both co-receptors are called **R5X4 HIV**.
- Interestingly, despite identification at earlier time points and despite high levels of CXCR4 expression on circulating HIV target cells, X4 or even R5X4 HIV rarely predominate until late in infection.
- Focus of this study is the R5 HIV virus, which targets human CD4 T cells by CCR5 binding.

R5 HIV virus targeting CD4 T cells by binding to CCR5



Wild-type CCR5 and CCR5 $\Delta 32$

The CCR5 protein undergoes a 32 base pair deletion, producing a non-functional protein, known as CCR5 Delta32



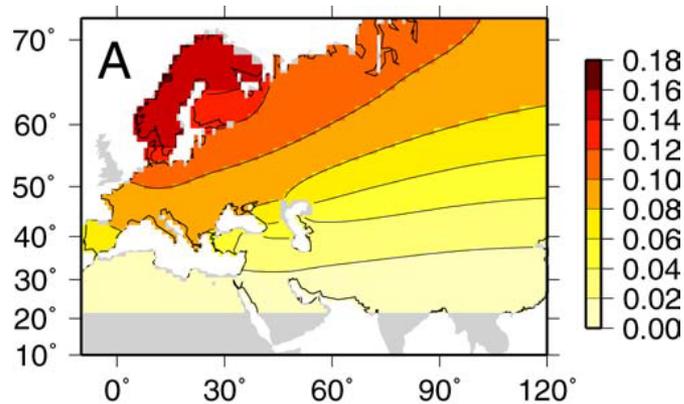
CCR5 $\Delta 32$ homozygotes are resistant to HIV-1 and the heterozygotes have a slower disease progression

The “Berlin patient”

- Case of allogeneic stem cell transplantation with HLA-matched adult donor homozygous for the CCR5 Δ 32 deletion
- Led to a stable engraftment of an HIV resistant immune system
- ART was discontinued from 2007, with no evidence of viral rebound over a period of 13 years
- No traces of residual replication competent virus found to date

ART: Antiretroviral therapy

The Geographic Spread of the CCR5 Δ 32 Allele



The Δ 32 mutation is found only in European, West Asian, and North African populations

The allele frequency exhibits a north–south decline with frequencies ranging from 16% in northern Europe to 6% in Italy and 4% in Greece

The broadest area of high frequency is located in north-eastern Europe, particularly the Baltic region, Sweden, Finland, Belarus, Estonia, and Lithuania

Probability of finding an adequately HLA-matched unit with a cell dose requirement of $\geq 1 \times 10^7$ TNC/kg is 85.6% for Caucasian pediatric patients and 82.1% for Caucasian adult patients

For members of minority ethnic groups, the projected probabilities are lower (e.g., 52.5% for Mexican American children, 34.1% for African American children, and 15.7% for Chinese American children)

Screening for CCR5-D32/D32 Cord Blood Grafts

- Once a HIV infected hematology patient requiring alloSCT is identified, preliminary search for potential allogeneic donors is performed via NMDP/WMDA including UCB grafts (approximately 600K global current inventory)
- This will be followed by screening blood spots of the identified, suitably HLA-matched UCB for CCR5 D32 homo/heterozygous deletions
- The screening process involves CCR5 genotypic analysis using a nested PCR based assay system, on DNA preparations extracted from cord blood spots

Clinical Trial Plan

- The patient will receive an adequately HLA matched CCR5 Delta32 homozygous or heterozygous un-manipulated cord blood unit.
- This unit will be given with off-the-shelf, NOTCH-1 based *ex-vivo* expanded second UCB graft to support the patient during the first 90 days and to facilitate engraftment of the CCR5 Delta32 homo-/heterozygous graft.
- **Immune Reconstitution** is monitored post transplant to determine optimal timing of planned ART interruption.
- During ART interruption (expected approximately 12 months after UCB alloSCT), viral load is monitored closely to determine any evidence of rebound.

Study Design



Estimated Accrual: 10 patients

Patients with hematological malignancies and HIV in need of allogeneic HSCT at 5 different Centers



CB searches should identify at least 15-25 potential grafts matched at 4 of 6 HLA loci or better with a **MINIMUM of 2.5×10^7 TNC/kg** and with a **MINIMUM of 1.7×10^5 CD34/kg**. CB searches results will be communicated to Cleveland Cord Blood Bank.



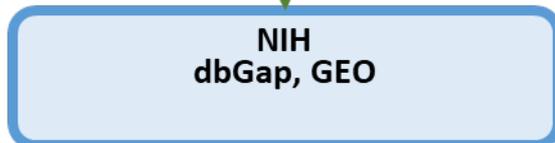
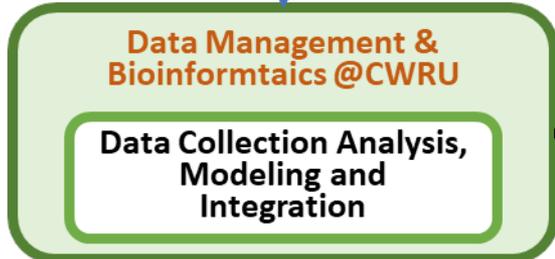
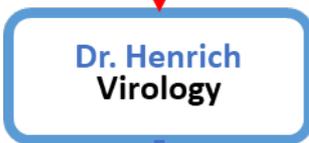
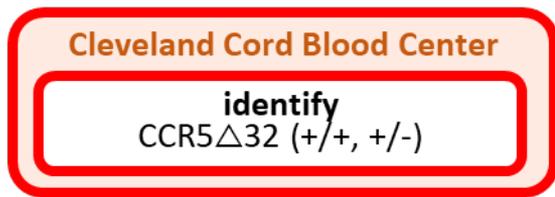
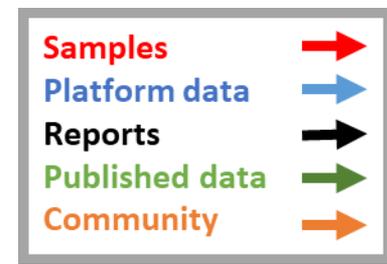
Cleveland Cord Blood bank will request blood spots or segments of the 15-25 potential CB units: Screening for CCR5 Δ 32 homozygous or heterozygous mutation.



If a CCR5 Δ 32 homozygous or heterozygous cord blood unit is identified then the patient will be enrolled. Screening failure log will be maintained

Study Sites:

- Fred Hutch/SCCA (Filippo Milano, PI)
- Case Western/University Hospitals (Rafick-Pierre Sékaly & Marcos de Lima, PI)
- Children's Research Institute/Children's National Medical Center (Blachy Davila-Saldana, PI)
- Memorial-Sloan Kettering Cancer Center (Juliet Barker, PI)
- University of California-San Francisco (Timothy Henrich, PI)
- Cleveland Cord Blood Center (Mary Laughlin, PI)



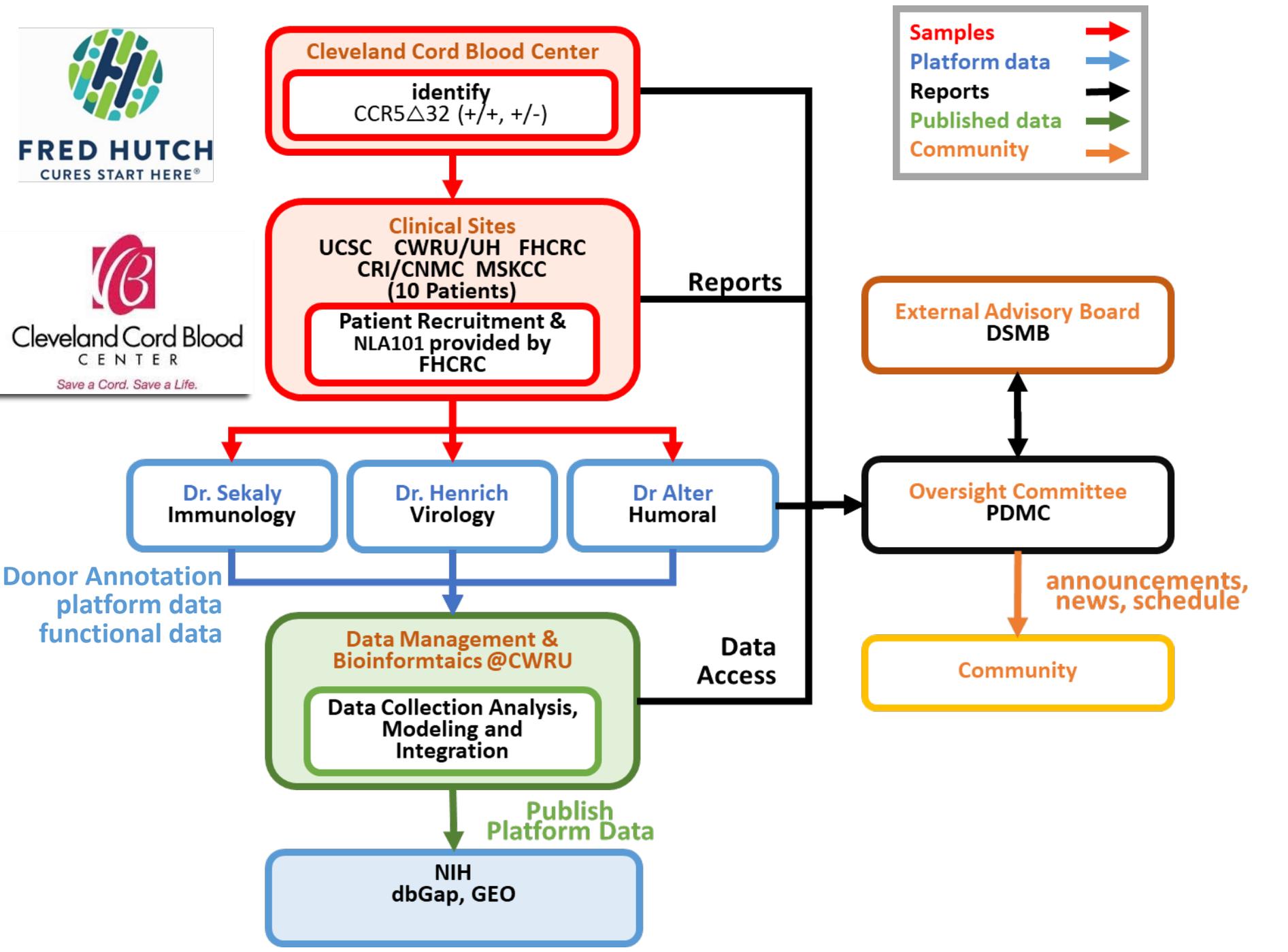
Donor Annotation
platform data
functional data

Publish
Platform Data

Reports

Data
Access

announcements,
news, schedule



Collaborators for the Phase I/II Clinical trial

Fred Hutchinson Cancer Research Center

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