Understanding the role of CCR5 Δ32 mutation, biomarkers for HIV resistance

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***THEME*: INFECTIOUS DISEASES: TRENDS AND THREATS**

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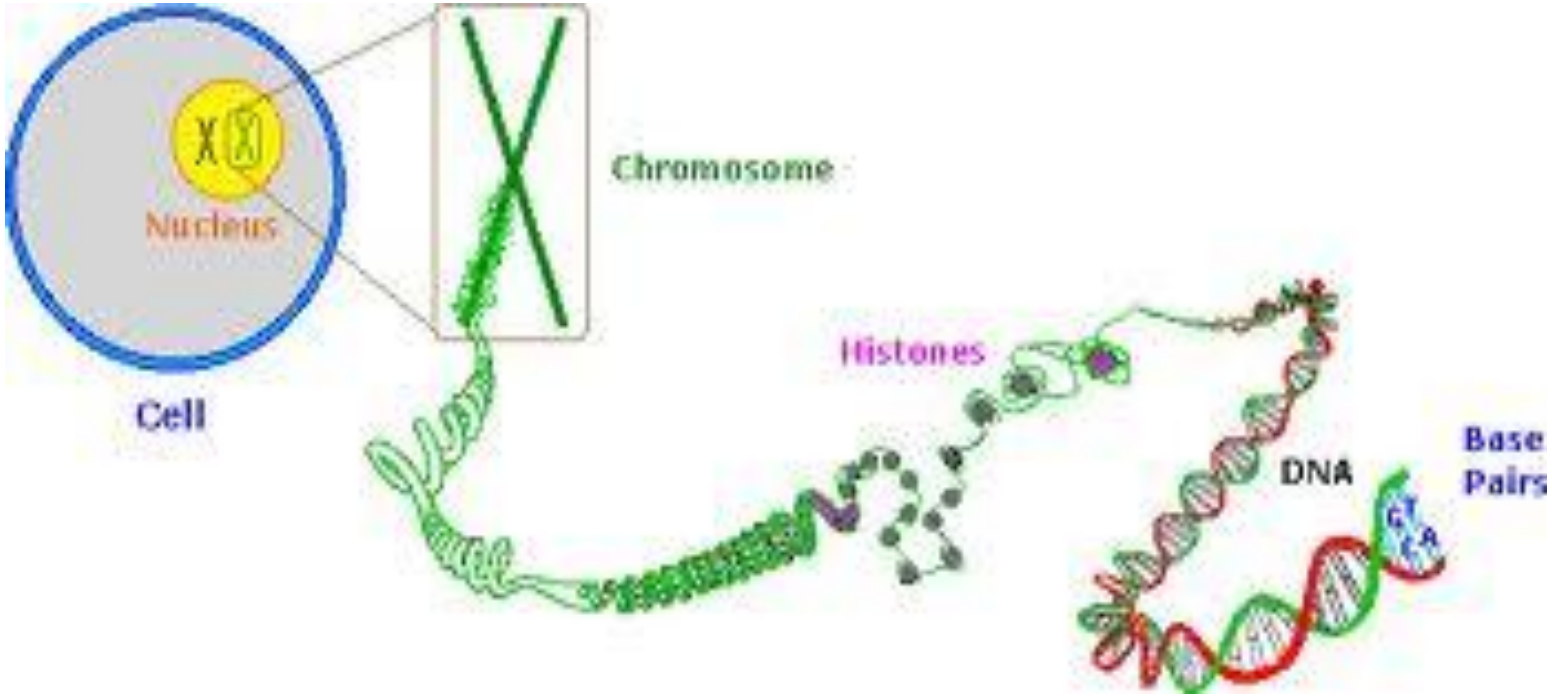
Introduction:

- Sequencer & HIV
- New insight on pharmacovigilance.
- Host genomics to Rx.
- Pharmacokinetics.
- Pharmacodynamics
- SNP
- Individual directed treatment plans

Then you will know the truth, and the truth will set you free (John 8:32) NIV

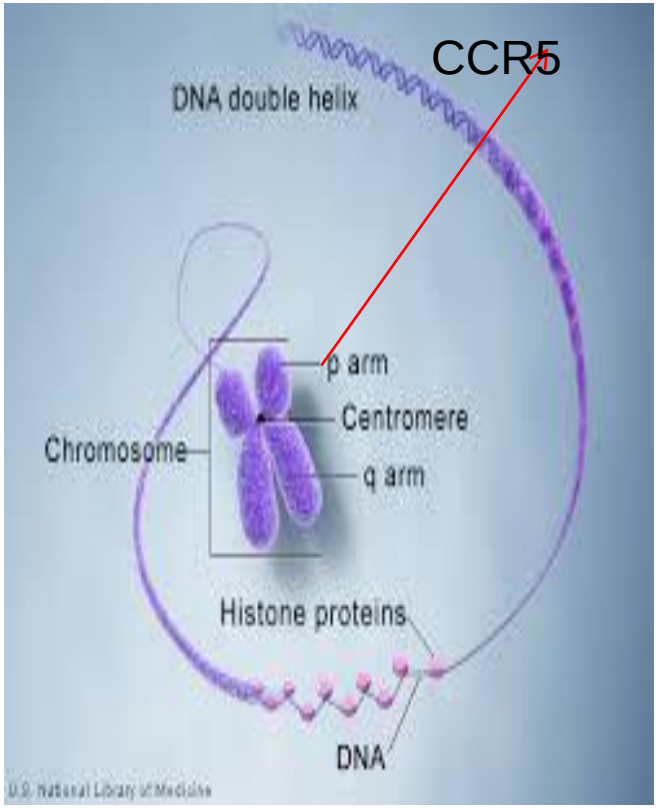
Introduction cont...



Cell - Nucleus- Chromosome-Histones- Ribonucleic acid- Bases

The ABC of Molecular Biology

About CCR5-delta32



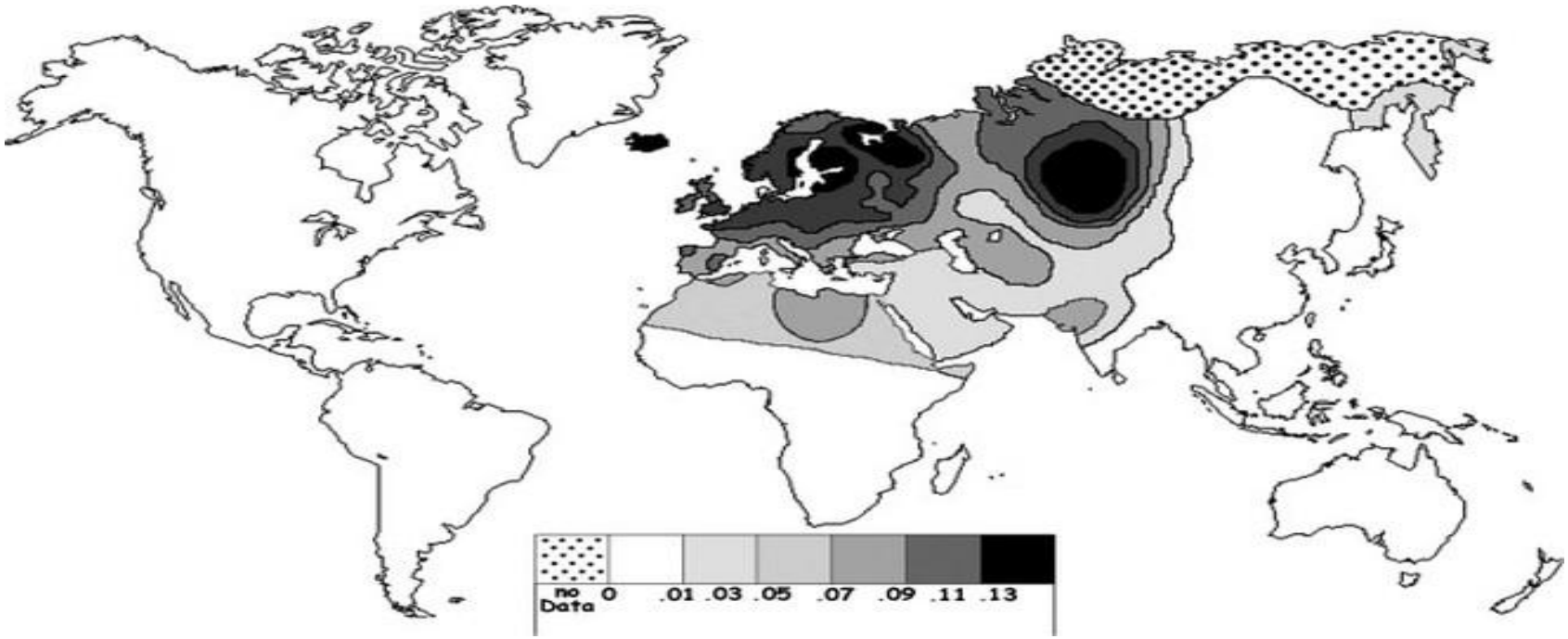
Located at the short arm at position 21 of Chromosome 3

- Chemokine receptor type 5 or CD195.
- Protein on WBC for immune system.
- *Delta 32* mutation resulting in the genetic deletion of a portion of the CCR5 gene.
- It is a G protein-coupled receptor.
- In HIV-1 gp120 V3 loop interact with CCR5.

CCR5-delta32

- CCR5-delta32 is a polymorphism in the gene encoding CCR5 in which a 32 base pair has been deleted.
- The distribution of CCR5-delta32 varies geographically.
- The frequency of the mutation is about 10% in Europe and nearly absent in Africans and East Asians.
- In the United States, about 1% of Caucasians have at least one copy of the gene.

About CCR-5 delta 32 (CD195) and its global distribution



USA, Canada and Australia, the frequency is 8% to 10% within the Caucasians.

Less than 1% in the Afro-American (www.delta-32.com).

Highly Exposed Seronegative commercial sex workers in Nairobi Kenya

- **Objectives**:

-To identify novel biomarkers for HIV-1 resistance.

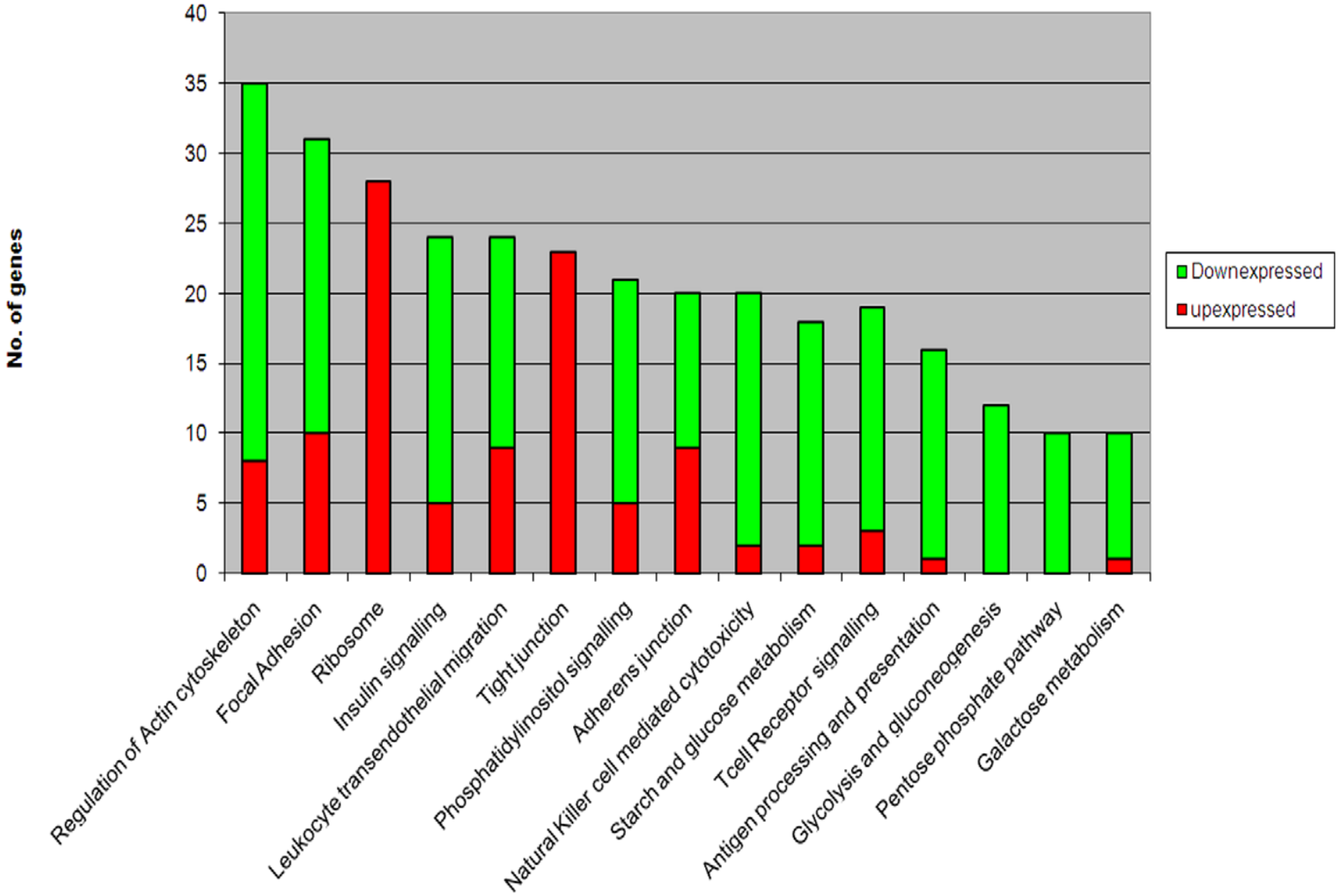
-To determine pathways that may be critical in anti-HIV-1 vaccine design.

- 43 HIV-1 resistant sex workers and a similar number of controls
- **Methods**: Total RNA was extracted and hybridized.

Highly Exposed Seronegative commercial sex workers in Nairobi Kenya

- **Results**: More than 2,274 probe sets were differentially expressed in the HESN Vs control
- Expressed genes readily distinguished HESNs from controls.
- KEGG signalling database revealed impacted pathways (13 of 15).,
- 87% participants had genes that were significantly down regulated.

Proportion of differentially expressed genes in significantly affected pathways.



Major Pathway affected to energy metabolism, cell adhesion, signal transduction and immune signalling categories

About 40 genes been documented to be involved in HIV-resistance

- Over the past 10 years, approximately 40 genes have been documented from HESN.
- These are TRIM5a ,specific KIR-HLA and APOBEC3G.
- HLA- cluster A was down-regulated, p value P=0.001.
- KIR3DL1 down-regulated, p value=0.001.
- Serpin B-13 family up-regulated p= 0.02.

The Black Death

- In 1665, the black plague hit a small village in England called Eyam. The town quarantined itself to keep the Black Death from spreading,
- A year later half of the people were dead.
- In 1996, researchers tracked down descendants of the half that lived.
- They found the mutation called CCR5-delta32.
- The mutation was already known to be the special component in mysteriously HIV resistant individuals.

The Black Death

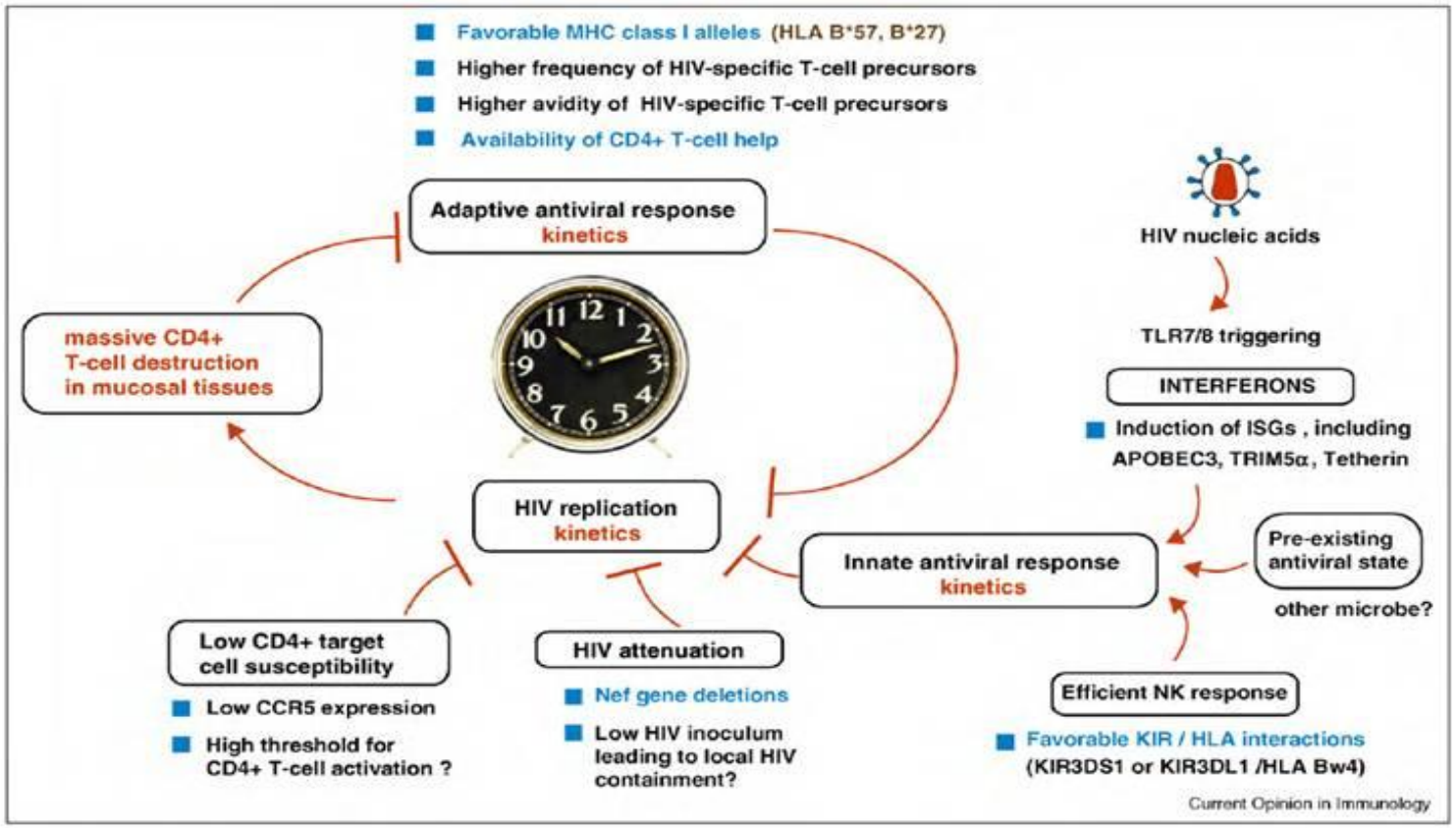
- The Black Death was one of the most deadly pandemics in human history, killing about 40% of the European population.
- Today, what we call the Bubonic plague is caused by the bacterium, *Yersinia pestis*.
- Black Death because in Europe the graves are crawling with *Yersinia pestis*.
- Allele was favored by natural selection during the Black Death or during small pox outbreaks.
- Two diseases evolved, and cause the CCR5 mutation.

HIV resistance?

- Why is the CCR5-delta32 mutation so frequent in Northern Europe?
- It is possible that this gene provided resistance to previous epidemics.
- If true, people with CCR5-delta32 mutation would have been more likely to survive and pass it down to their offspring.
- Immune activation play a big role toward epidemic sub-Saharan African.

Natural immune to HIV

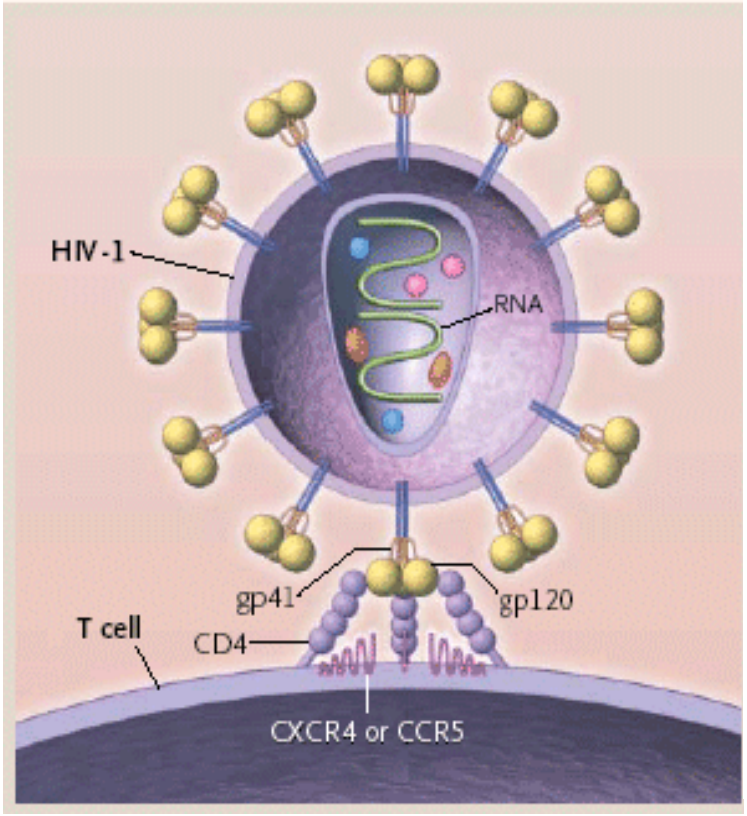
Figure 3

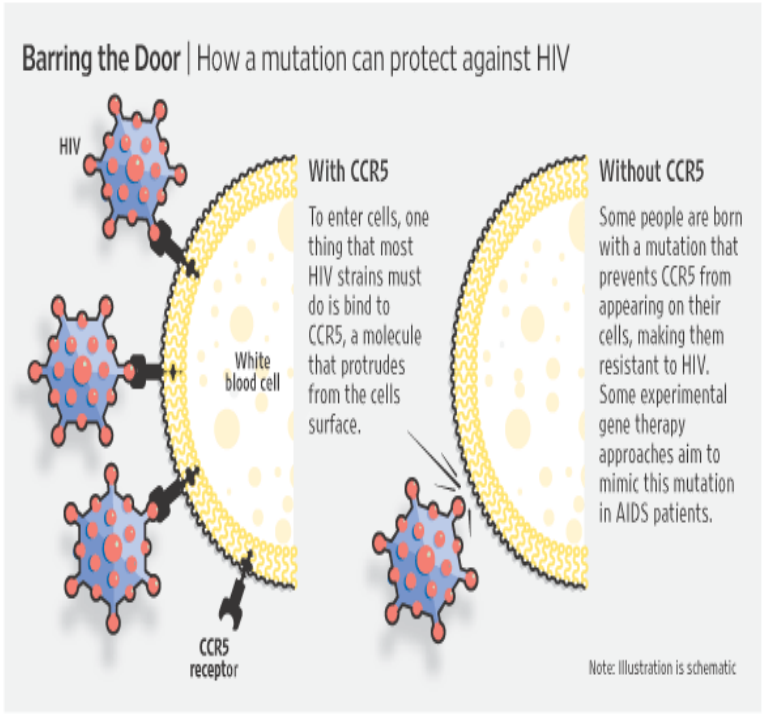


Very early events in HIV control. Proven (blue) and putative (black) factors involved in determining the outcome of the race between HIV replication and the early immune response. Multiple factors may slow the kinetics of HIV replication during the acute infection stage, thus avoiding a massive depletion of CD4+ T-cells within mucosal tissues, and preserving CD4+ T-cell help needed for the maintenance of an efficient adaptive antiviral response. HIV control can result from direct viral attenuation, though the occurrence of severe attenuation through gene deletion seems a very rare event. Experiments in the SIV model suggest that a low viral inoculum may also lead to viral control. Host factors include those that limit CD4+ target cell susceptibility, that accelerate or potentiate the innate response, and that favor the development of the adaptive response. Factors acting at these three levels may synergize in establishing HIV control.

www.sciencedirect.com **Current Opinion in Immunology** 2010, **22**:488–496

HIV entry into CD4 T lymphocytes is mediated by the chemokine CCR5 receptor





NATURE · VOL 381 · 20 JUNE 1996

Background: Genetic Mutations and HIV Immunity

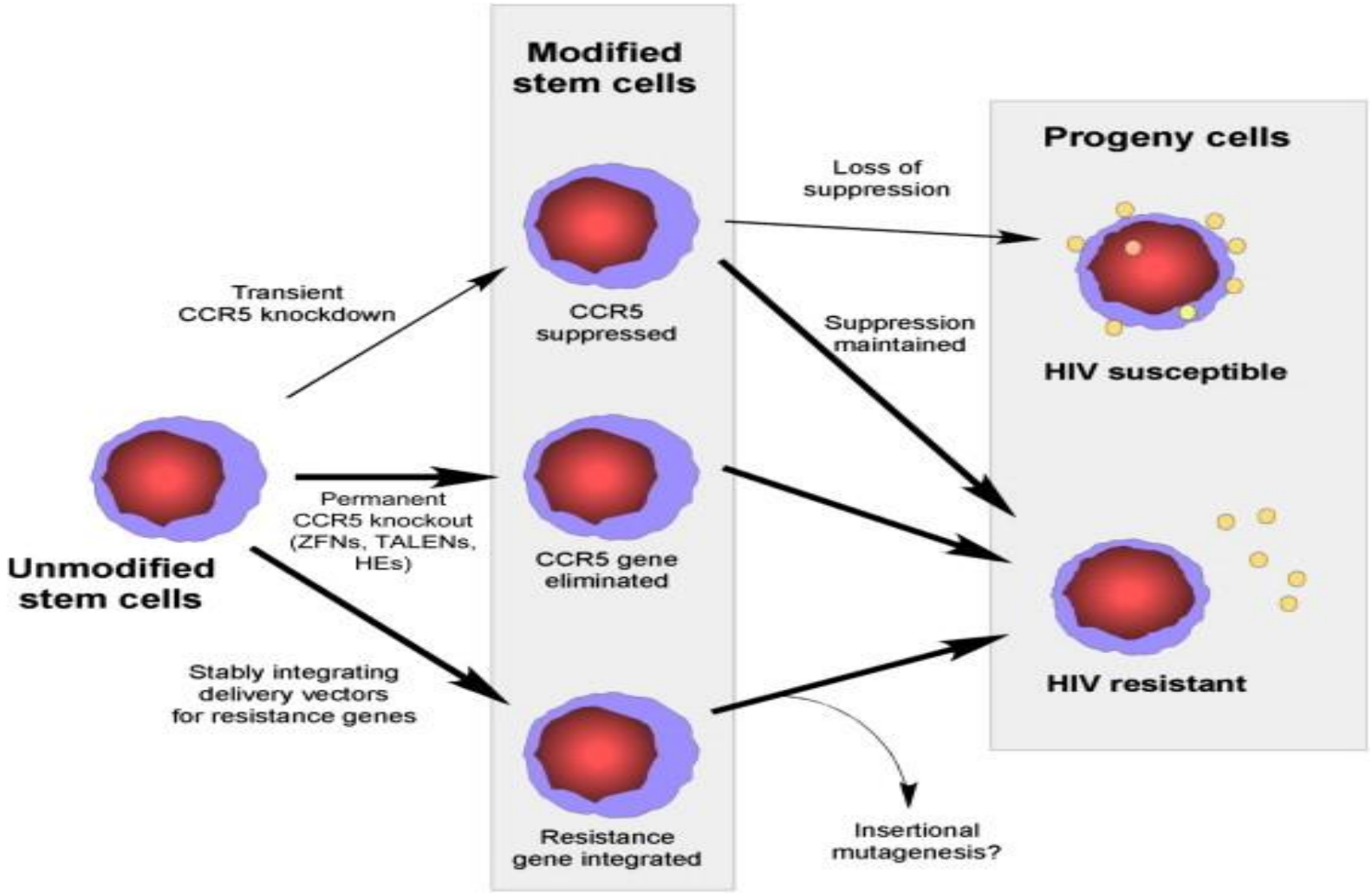
CCR5 co-receptor

- Required for macrophage-tropic HIV variants
- Mutated CCR5 gene with 32-nucleotide deletion from coding region→non-functional protein
- CCR5-delta 32 only present in Caucasians
  - 10% heterozygous
  - 1% homozygous

CXCR4 co-receptor

- Required for lymphocyte-tropic HIV variants
- Infect and destroy activated CD4 T cells
- CD4 T cell count less than 200 cells/mm^3 or less than 15% indicates disease has progressed to AIDS

Stem cell modification



Natural HIV resistance by CCR5Δ32/Δ32 mutation

CCR5 Δ32/Δ32 homozygous mutation

1% in Caucasian population

No CCR5 expression

Naturally protected from HIV-1 infection

WARNING:

Please do not partake in risky behavior and assume that you can not contract HIV just because your grandmother is British…You will be surprised!!!!

Success story in HIV treatment: Man Cured of AIDS

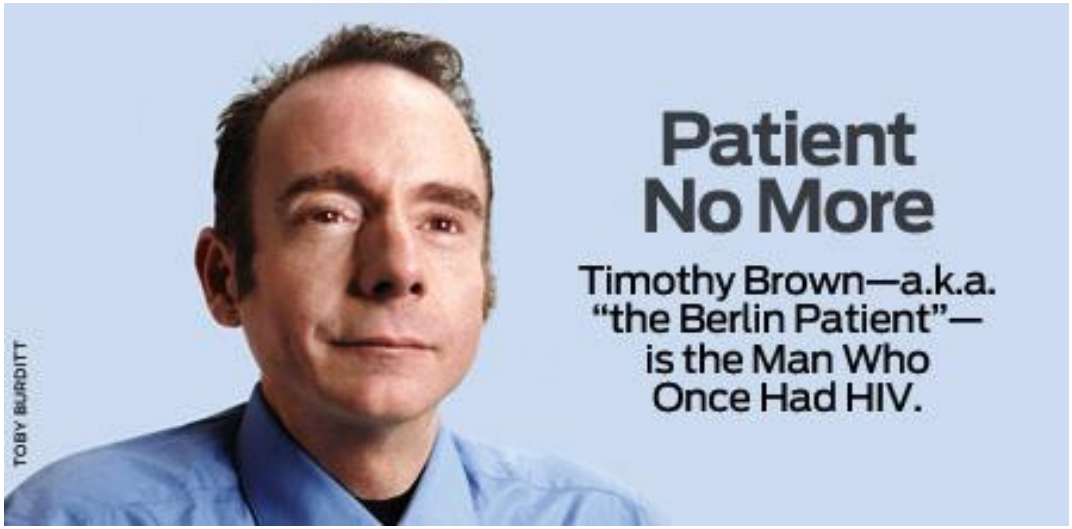


Photo Credit: http://pozmagazine.tumblr.com/

Challenges in the current treatment for HIV infection

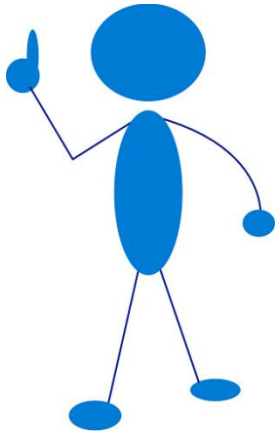
- No cure.
- Rapid rebound of viremia if patients stop medication.
- Everyday life long medication
- Treatment adherence is difficult.
- Side effects.
- Medication costs
- HIV-1 diversity
- Emergence of multi-drug resistant HIV.
- Limited treatment access world wide.
- No vaccine

Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation

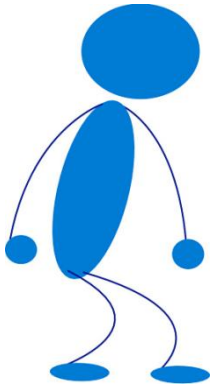
Hutter et.al. N Engl J Med. 2009 Feb 12;360(7):692-8.

CCR5-Δ32/ Δ32
BM Donor (HIV-)

Acute Myeloid Leukemia
Patient (HIV+)



Bone Marrow transplant



This "Berlin Patient" was cured from HIV.

Nearly 100% replacement with the CCR5 negative donor cells.
HAART was discontinued after BM transplant.
HIV RNA and DNA became undetectable at 68 days post-transplant and remained negative for 5 years.

http://www.nytimes.com/1998/06/21/magazine/the-berlin-patient.html?pagewanted=all

Conclusions

- There is a big gap between what is known and unknown about biomarkers and clinical disease outcomes.
- Therapies based on interfering with the CCR5 receptor could be achieved in the treatment of HIV.
- More research on biomarkers as surrogate endpoints of disease clinical course is mandatory.

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