Potential Role of Human Endogenous Retrovirus K102 (HERV-K102) Particles in Resistance to HIV-1 Transmission

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HERV-K102 is SPECIAL: It has Salient Features of Foamy Viruses

WHAT ARE FOAMY RETROVIRUSES (FV)?

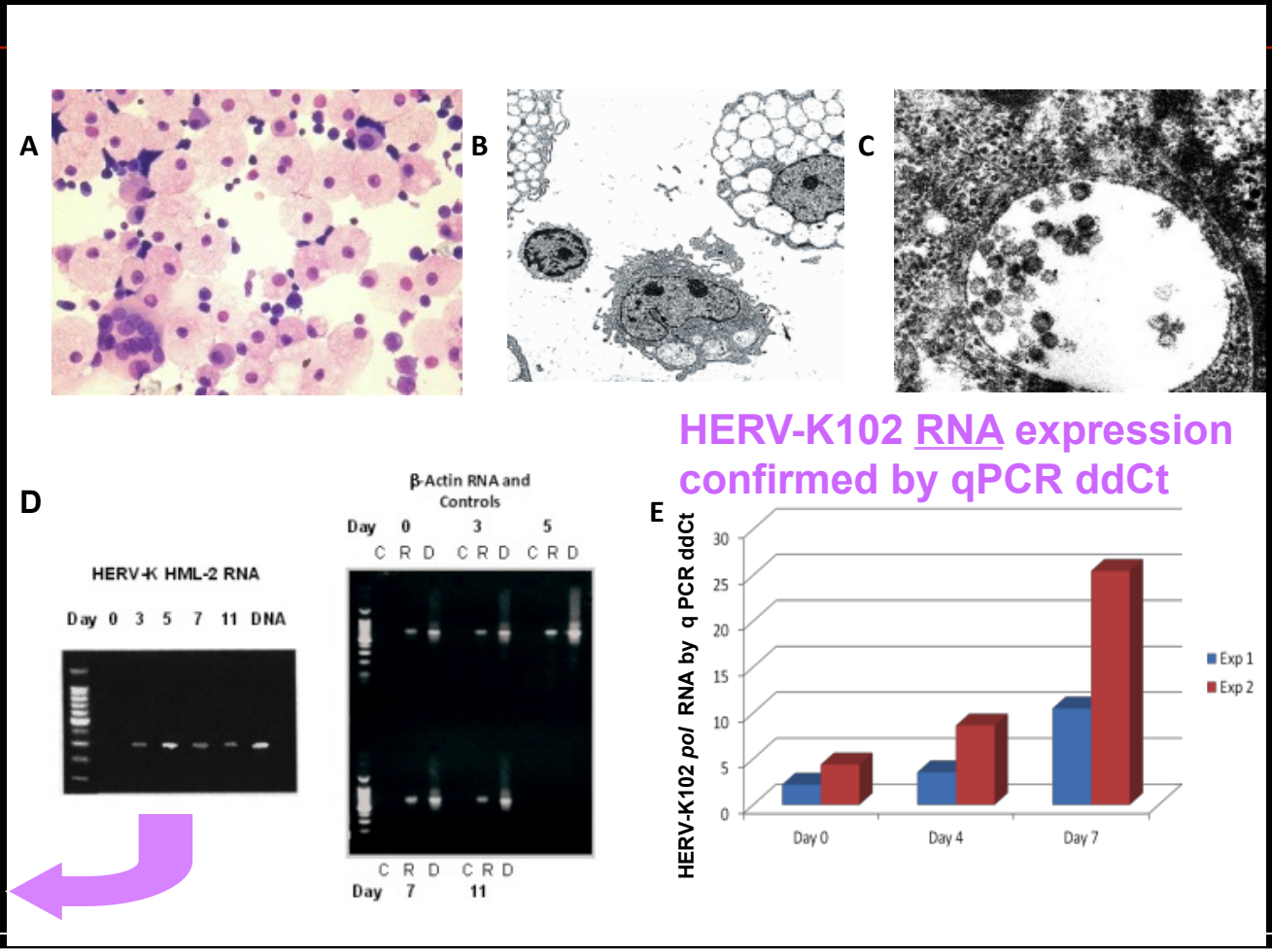
- Replication competent and fully infectious, but lack a Rec-like domain
- NON-PATHOGENIC yet can undergo lytic infections
- Get their name from immature particles budding into vacuoles which gives the cells a foamy appearance
- Require Env expression and processing for particle formation
- Unconventional, have a reversed life-cycle to HIV (reverse transcribe on leaving cell)
- Particle associated genomes are predominately cDNA Not RNA
- Present in many primate and other mammalian species but none yet identified in humans (well studied HFV renamed PFV as it was of chimp origin)
- PFV undergoes lytic infection in HIV-1 infected cells (Mikovits J, et al, 1996) and in tumor cells (Heinkelein M et al, 2005) raising the issue that FVs may be protective against viruses and tumors

Human Endogenous Retroviruses (HERVs)

- 8% of human genome involves HERVs
- HERV-K HML-2 proviruses are the most recent and biologically active
- HML-2 has two types: without (type 1) or with (type 2) a 292 bp Rec-like domain in *env*
- HERV-K102 is a HML-2 type 1 provirus and lacks the Rec-like domain like FV
- HERV-K102 has other genetic properties similar to PFV (see www.aminomics.com)
- HERV-K102 is unique to humans

An Inducible Endogenous Human FV from Normal Cord Blood (CB) : HERV-K102

Sequencing of excised ***pol*** bands revealed only HERV-K102 *pol* (6/6 CB samples)



In addition to RNA, HERV-K102 DNA was also replicating and integrating in the cultures

Table 1. Increased Genomic Copies (3.3)* of HERV-K102 *pol* Occurs *In Vitro*

	HERV-K102 *pol* DNA ddCt Ratios by Real Time PCR	
	No Digestion of cDNA	Digestion of cDNA (% signal representing genomic DNA)
CB Day 0	0.74 (+/- .01)	-
CB Day 4	3.68 (+/- .02)	1.78 (35%)
CB Day 7 (after lysis of about 30% of cells)	2.87 (+/- .02)	2.45 (80%)

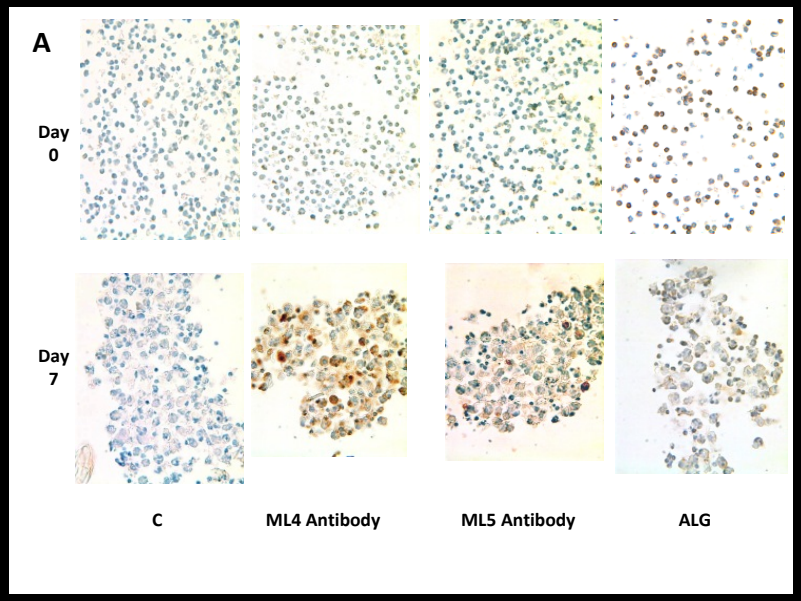
Mean Normal HERV-K102 pol ddCt ratio was 0.86 +/- 0.06 (n=31)

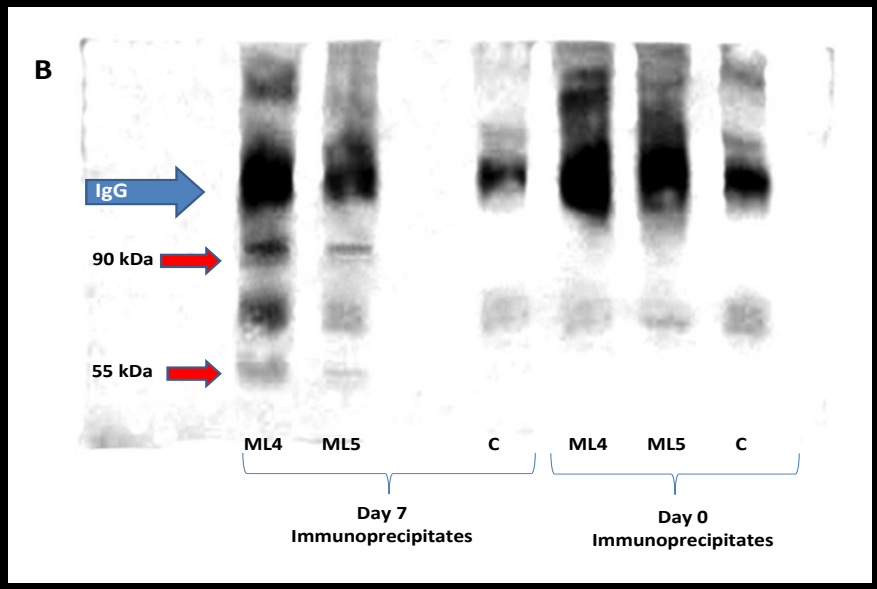
* $P<0.0001$

Methods: Laderoute MP et al, AIDS 2007

Isolated DNA (total) or cDNA was digested with UNG

and HERV-K102 Env Expression and Env Processing were Detected

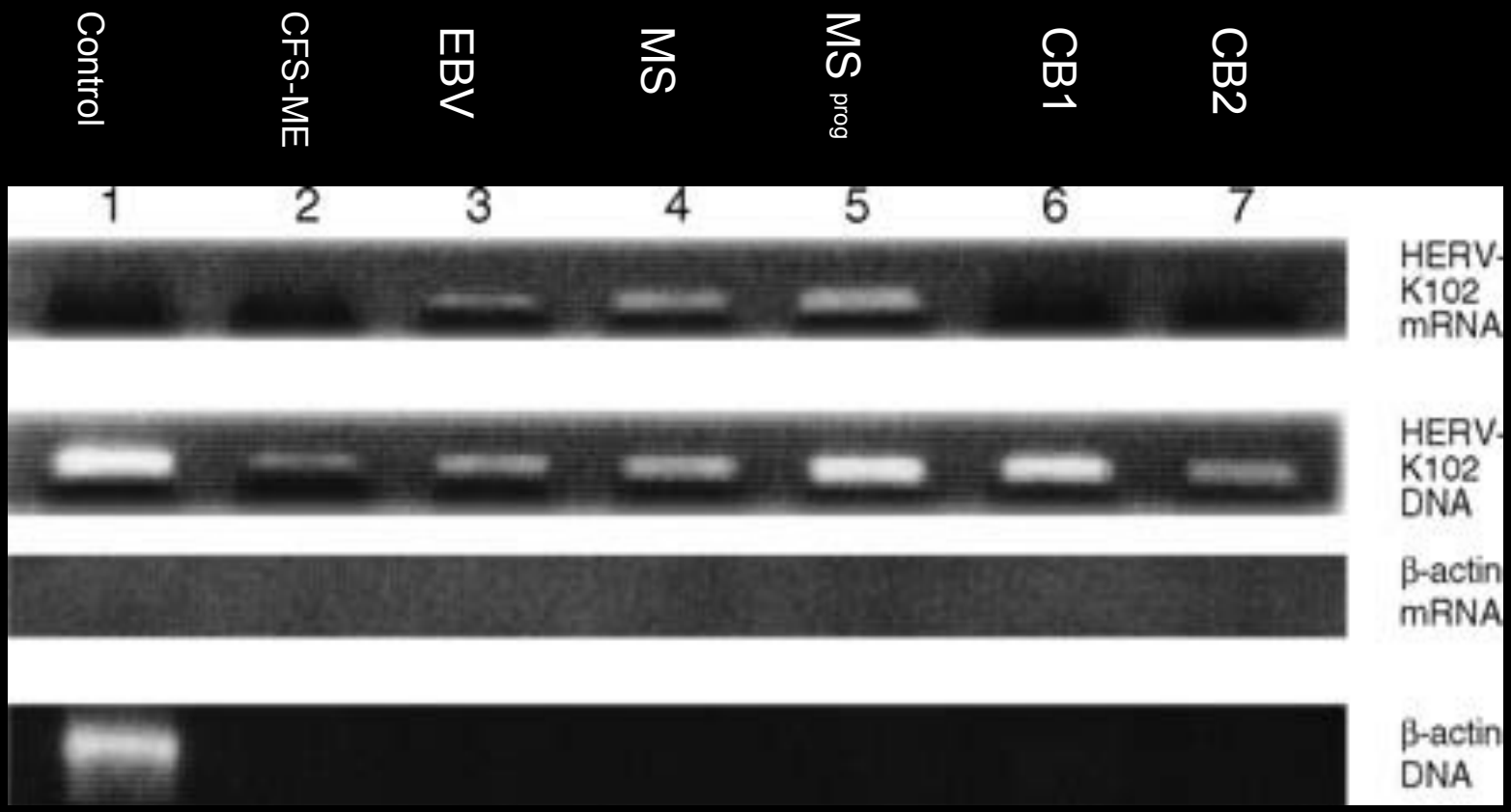




No membrane accentuation found in IH and confirmed by flow cytometry.
HERV-K102 Env is NOT on the cell surface of highly vacuolated normal cells.

Methods: Laderoute MP et al, AIDS 2007

DNA Genomes were identified in particles isolated from plasma [1]



1 Laderoute MP et al, AIDS 2007

OUR PREVIOUSLY published Work on HIV-1 Patients[1]

[About 75% had antibody to HERV-K102 Env and about 75% were positive for DNA by qPCR ddCt ratio in plasma].

96 % of HIV-1 samples were positive for HERV-K102 activity by qPCR ddCt ratio (DNA) and/or serology.

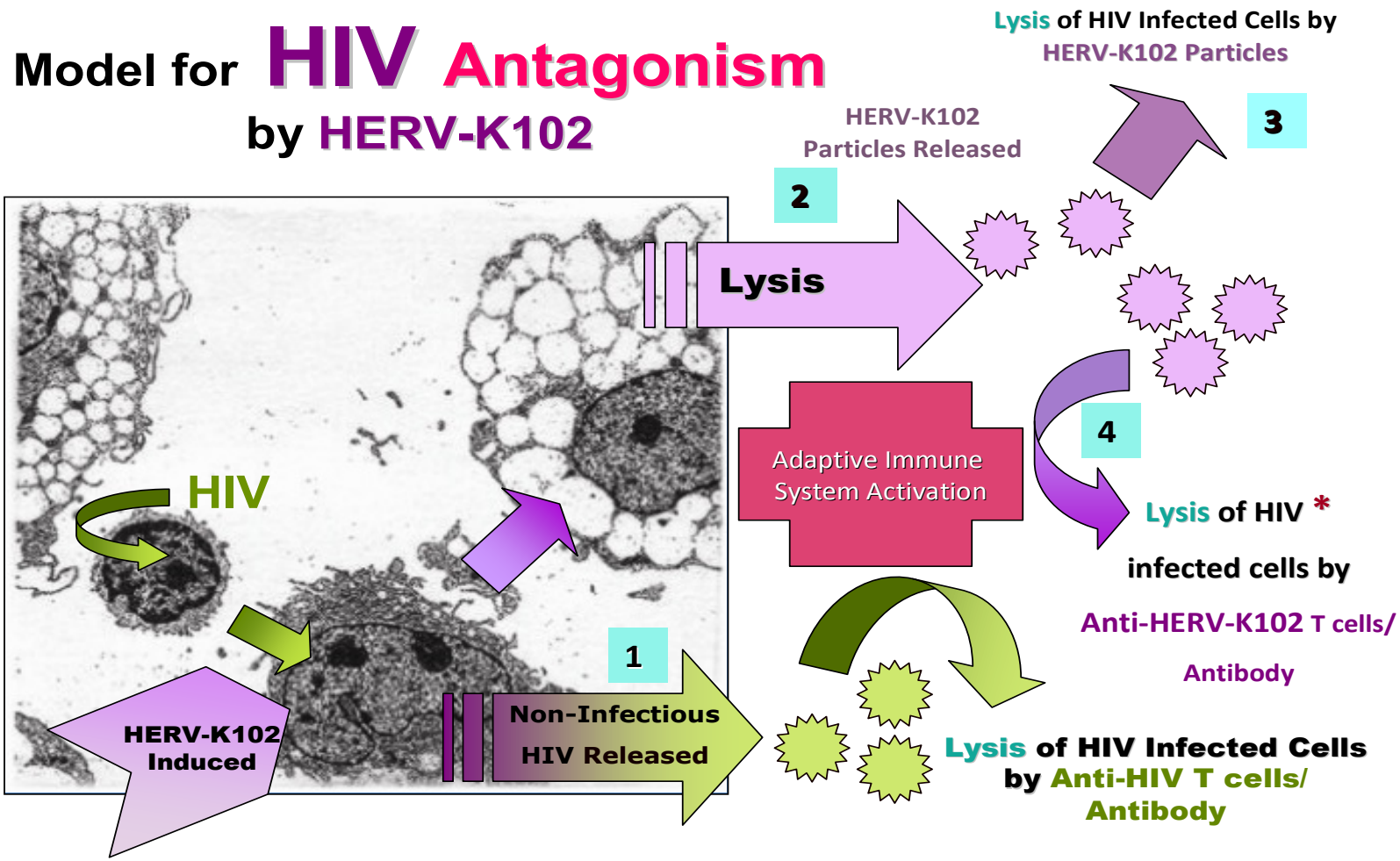
2-3% of normals showed only marginally positive reactions using the same criteria.

HERV-K102 activation induced with other bloodborne viral infections, but the maximal level of particle production was 7 logs lower in HIV-1 patients.

Confirmed it was in fact cDNA in all the HIV-1 patients.

Thus, HERV-K102 actively replicates in HIV-1 patients, but appears to be antagonized.

1 Laderoute MP et al, AIDS 2007



In the CFS-ME patient, no particles to 10^{11} per ml of plasma in 84 hours (all cDNA).

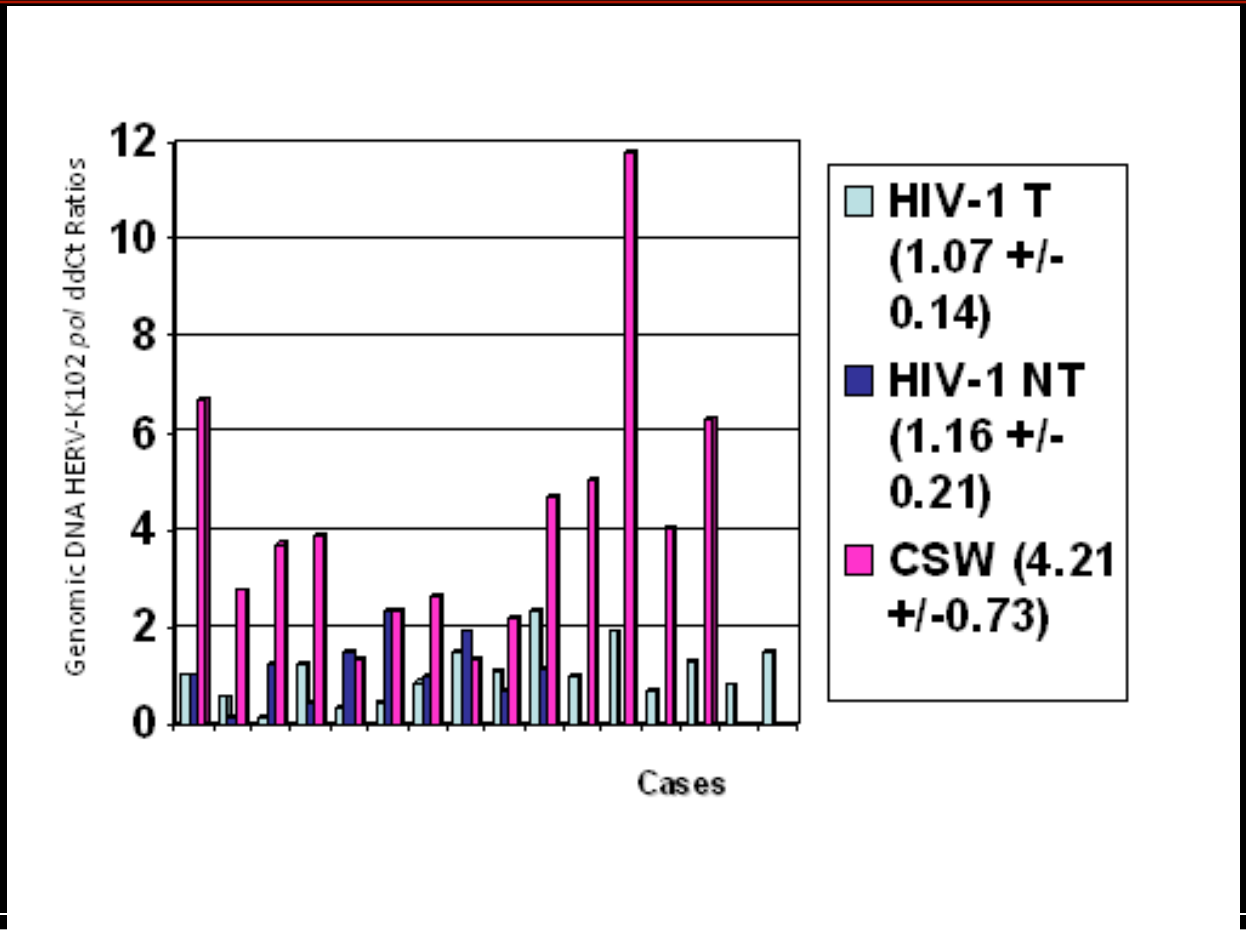
Other Research Groups (Douglas Nixon, David Markovitz, the Wang-Johannings) have validated our model including…

- Induction of HML-2 RNA by HIV-1 Tat, Vif
- HERV-K102 particles from HIV-1 plasma
- HML-2 type 1 B cell responses are protective against tumors (induce apoptosis) and anti-TM antibodies found at higher levels in elite controllers
- HML-2 T cell responses are protective against HIV-1, HML-2 Env found on cell surface of HIV infected cells, and T cells eliminate HIV infected cells

But is HERV-K102 particle production protective against HIV-1?

- Address recent-past replication by examining ddCt ratios on genomic DNA for HERV-K102 comparing groups:
  - resistant to HIV-1 transmission (HESN CSW Nairobi), and
  - non-resistant groups (HIV-1 patients +/-ART)
- By analyzing genomic DNA isolated from plasma, this would be from recently lysed cells and would enrich for cells of major interest.
- Care was taken to digest all the particle associated cDNA of plasma with UNG.

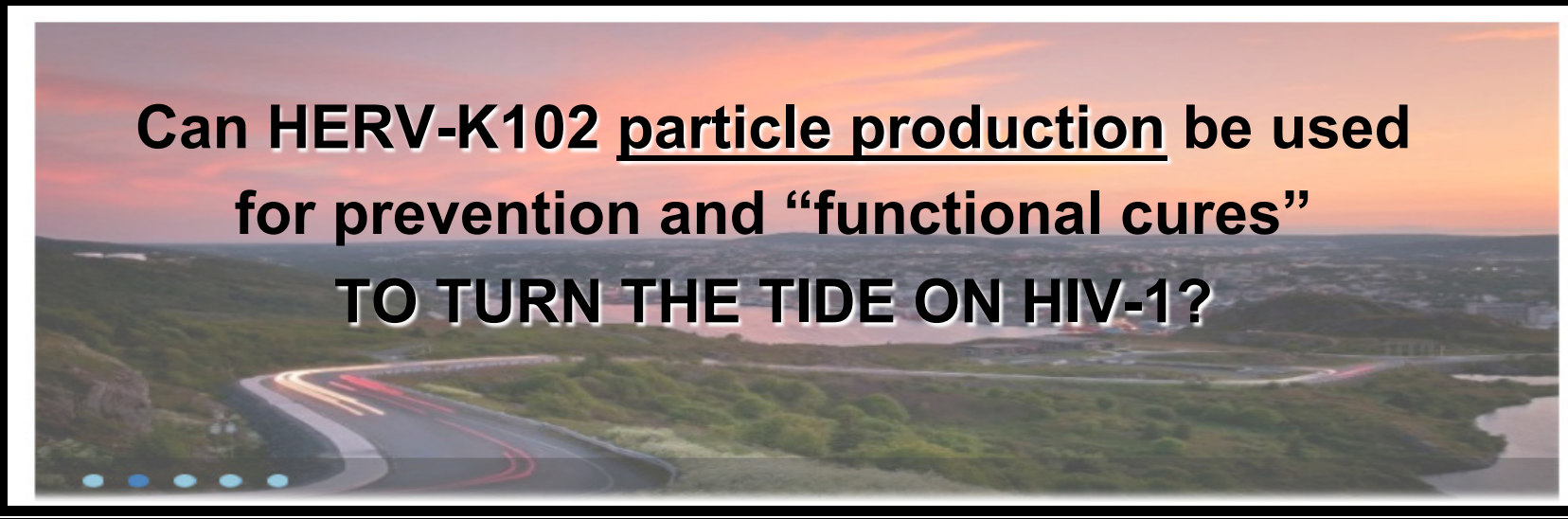
Mean Genomic ddCt ratio for HERV-K102 *pol* Appears to be Elevated Associated with Resistance to HIV-1 Infection



P <0.0005 (Normal control ddCt ratios =0.86 +/- 0.06

Results are preliminary as sex, age, and ethnicity not controlled, but this should be explored further on a larger sample size and different cohorts.

HERV-K102 particle production could be a plausible candidate innate resistance factor protecting against HIV-1 transmission.



Immune System Management

Thank you.