Mechanisms by Which the HERV-K102 Protector 'Trained Immunity'System Reduces Enveloped RNA Pandemic Virus Replication

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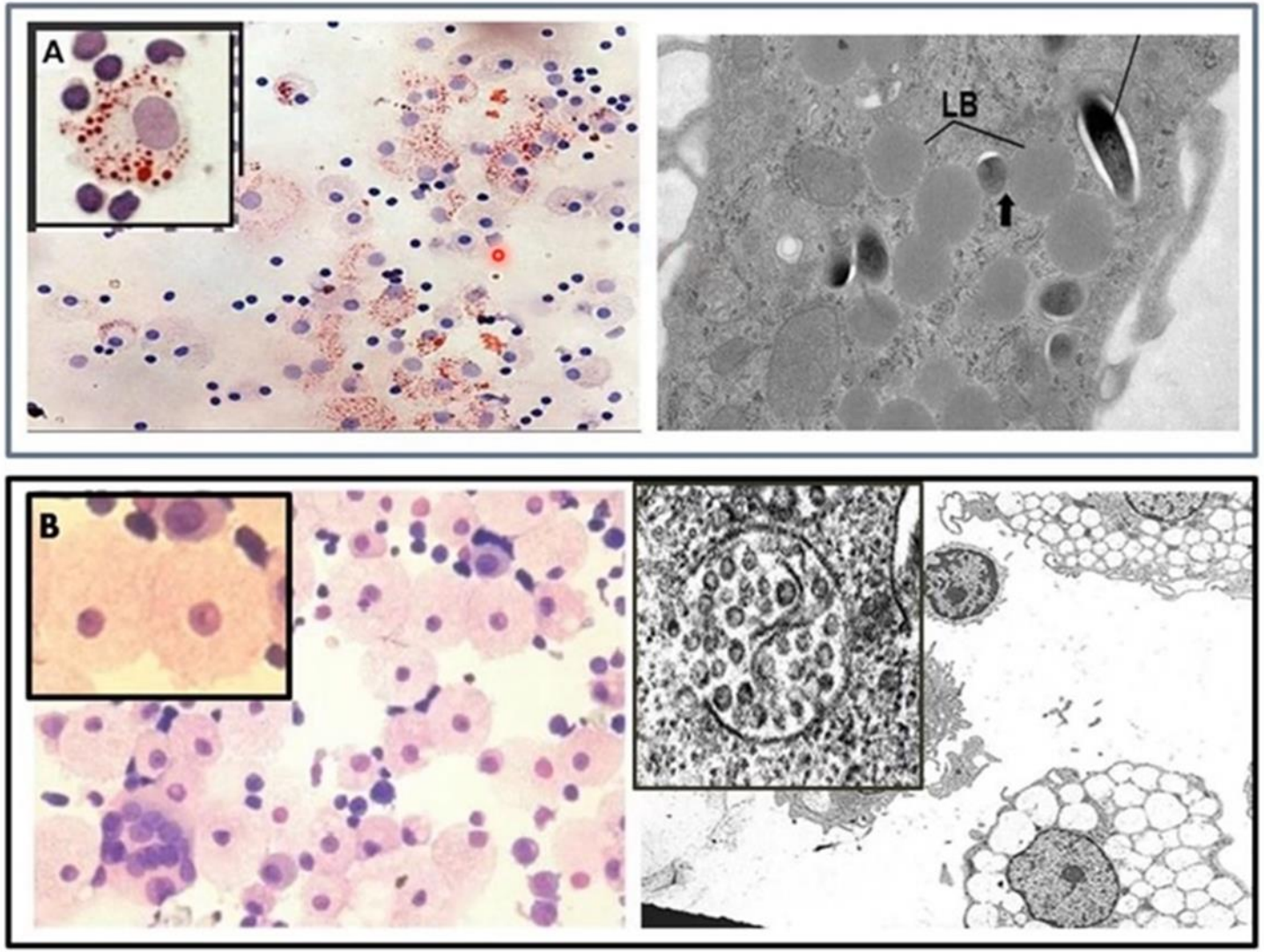
Mycobacterium tuberculosis Induces TWO Types of Foamy Macrophages (FM) *In Vitro* (see TOP Panel) (Peyron P *et al.*, PLoS Pathogens, 2008)

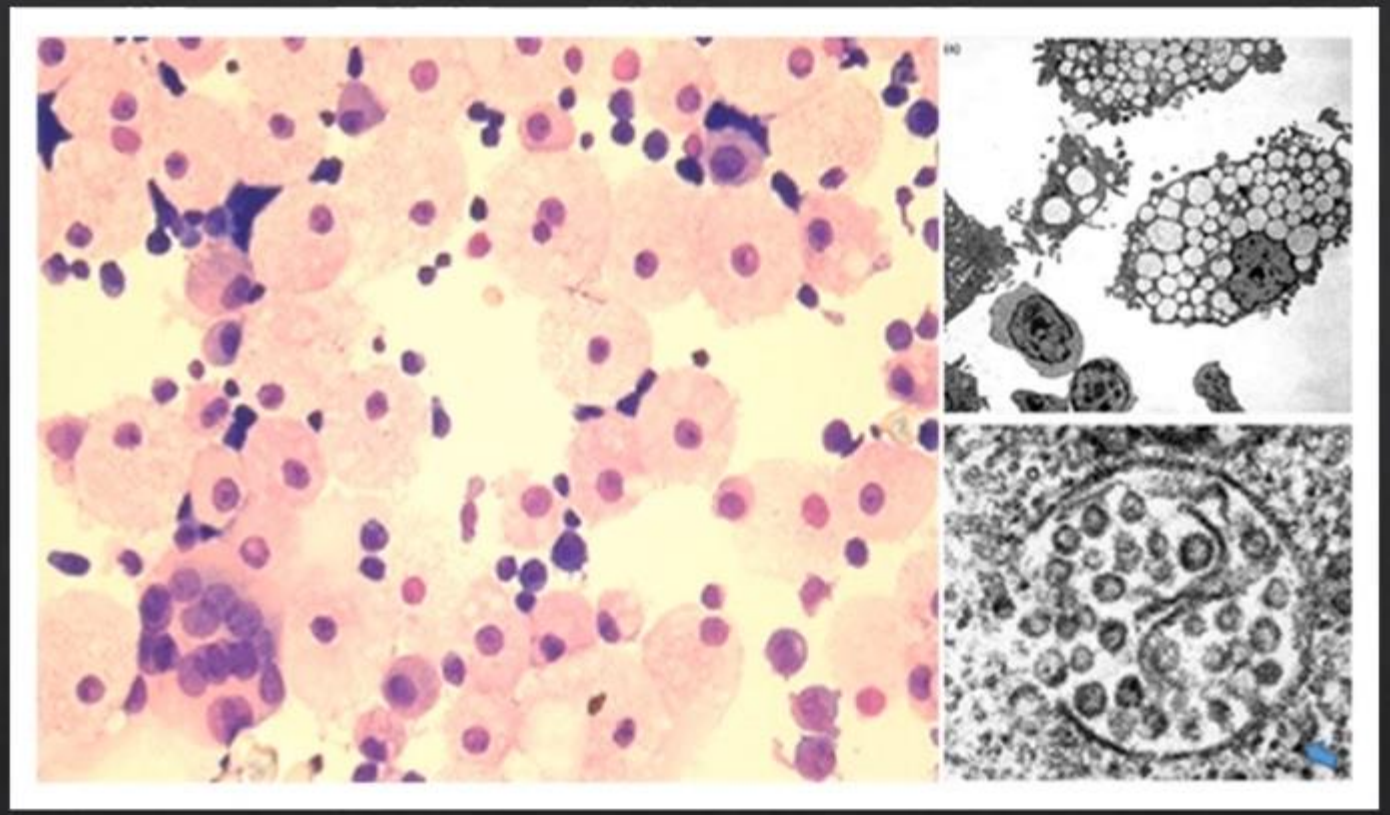
A (inset) are the 2 X larger lipid body positive (LB+) foamy macrophages (**anti-inflammatory**) with large diffuse oval nuclei (no prominent nucleolus) which strongly take up Oil Red O, a stain for esterified cholesterol of lipid bodies (Peyron P *et al.*, 2008)

B (inset) are the 2 X smaller lipid body negative (LB-) foamy macrophages (**pro-inflammatory**) with small round nuclei (and prominent nucleolus) which do not stain well for Oil Red O. This image is of human cord blood mononuclear cells cultured in IMDM (not RPMI) and the vacuolation is due to HERV-K102 particle production (Laderoute M *et al.*, 2007; 2015).



Human endogenous retrovirus K102 (HERV-K102) present on chromosome 1, is a protector foamy virus found in all humans but not in other animals (foamy viruses induce foam and coevolve with the host).

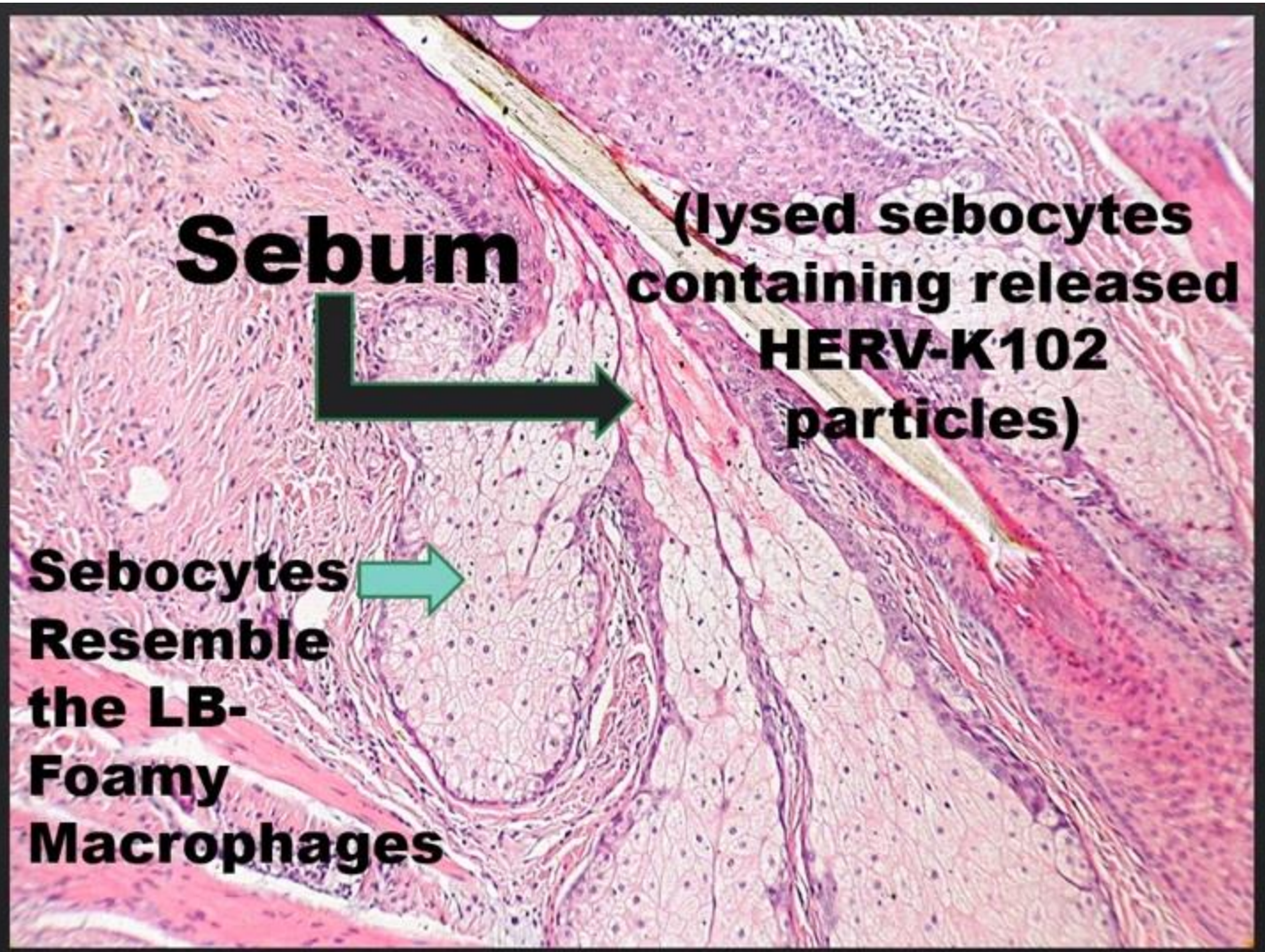
HERV-K102 appears to provide innate immunity against emerging pathogens and pandemic viruses (such as HIV-1). Therefore, its activation and release from foamy macrophages is very relevant to the current COVID-19 pandemic caused by SARS-CoV-2.



HERV-K102 virus particle production induces foam in macrophages and generates the highly vacuolated foamy macrophages. (Laderoute M *et al.*, AIDS 2007, Open AIDS J 2015). Once sufficient particles have built up inside the cell, release of the protective particles is by cell lysis (apoptosis), which is uniquely sensed in the cytoplasm (Fisher H *et al.*, 2017 and see comments by Zouboulis CC, 2017).

Sebocytes in sebaceous glands appear to be *specialized* foamy macrophages *constitutively* producing HERV-K102 (ERVK-7) particles [*interpretation of data from:* Nelson AM *et al.*, J Clin Invest. 2008]. The protector particles are released by cell lysis (apoptosis) and is called sebum (holocrine secretion).

Sebaceous glands line mucosal tissues such as the oral and nasopharyngeal cavities providing the first line of defence against respiratory pandemic viruses like SARS-CoV-2.



A sebaceous gland.

From: https://simple.wikipedia.org/wiki/Sebaceous_gland#/media/File:Insertion_of_sebaceous_glands_into_hair_shaft_x10.jpg

HERV-K102 Antibodies to HERV-K102 Env and HERV-K102 Particles Are Found in Response to Viral Infections*

Table 1. Serology for antibodies to HERV-K102 envelope peptides by ELISA.

Serum sample cohort	ML4 (% positive)	ML5 (% positive)
Normal controls	1/51 (2%)[a]	1/51 (2%)[b]
HIV viremia	8/10 (80%)*	7/10 (70%)*
Herpes viremia	3/17 (18%)	3/17 (18%)

[a]Marginal reactivity to ML4 in an apparently healthy farm worker.
[b]Marginal reactivity to ML5 in an apparently healthy laboratory worker.
*$P < 0.0001$ Fisher exact test when compared to normal controls.

Table 2. Testing for particle-associated HERV-K102 *pol* cDNA templates in plasma samples by the ddCt ratio qPCR method.*

Cohort	% Positive Ratios (positive/total)	Range
Normal[a]	3.3% (1/30)	0.41 to 1.74
Hepatitis B and C viremia	78.6% (22/28)*	0.81 to 4.32×10^9
Herpes viremia	61.9% (13/21)*	0.24 to 2.02×10^9
HIV viremia	75.7% (28/37)*	0.49 to 121.9

[a]The HERV-K102 *pol* to 18 sRNA ddCt qPCR ratio for the 30 samples from serologically negative, normal healthy controls was 0.88 ± 0.37.
*$P < 0.0001$ Fisher exact test when compared to normal by nonparametric proportions.

* From: Laderoute M *et al.*, AIDS 2007

* To estimate the number of HERV-K102 particles per ml of plasma multiply the ddCt value by 10^3 (*mean value* for patients with HIV-1 was low at 8,200 HERV-K102 particles per ml of plasma)

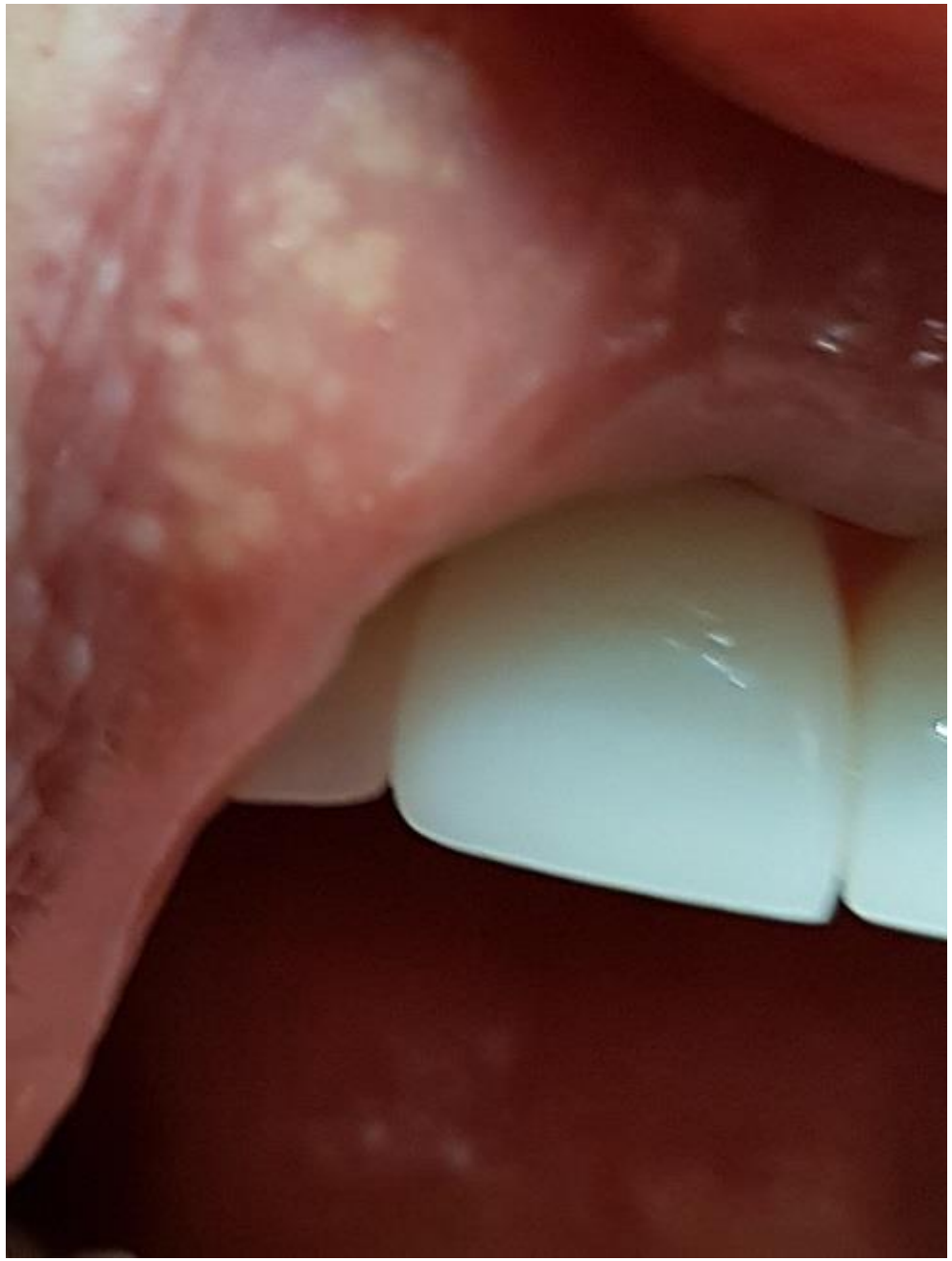
Fordyce Spots (Sebaceous Glands Under the Upper Lip) May be Prominent in Individuals With Active HERV-K102 Particle Production such as this Individual with Chronic Fatigue Syndrome (a post-viral syndrome) and with Familial Hypercholesterolemia

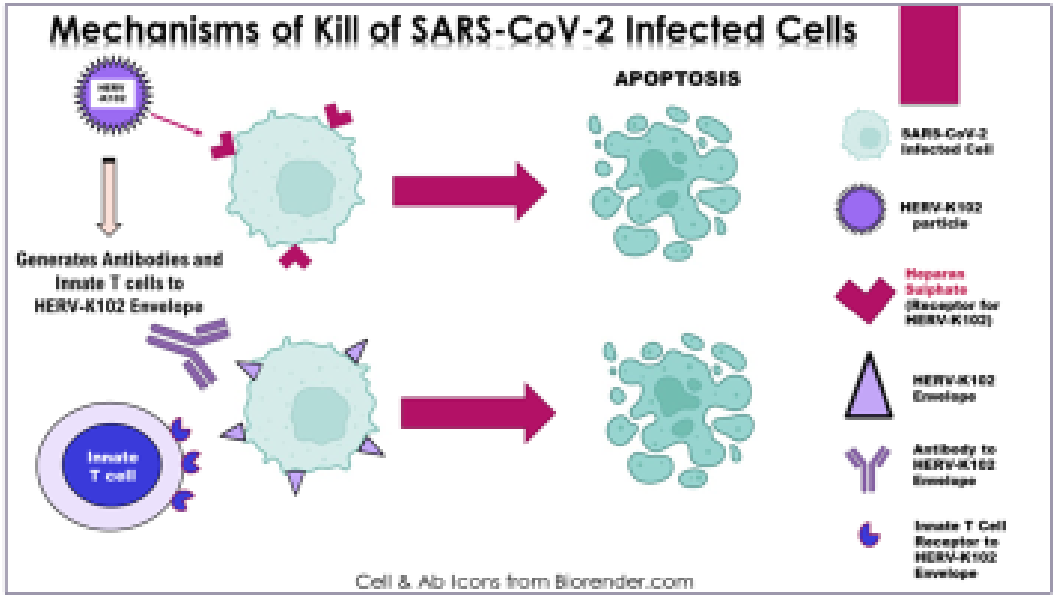
(patient had about 2.55 x 10^{11} HERV-K102 particles per ml of plasma)

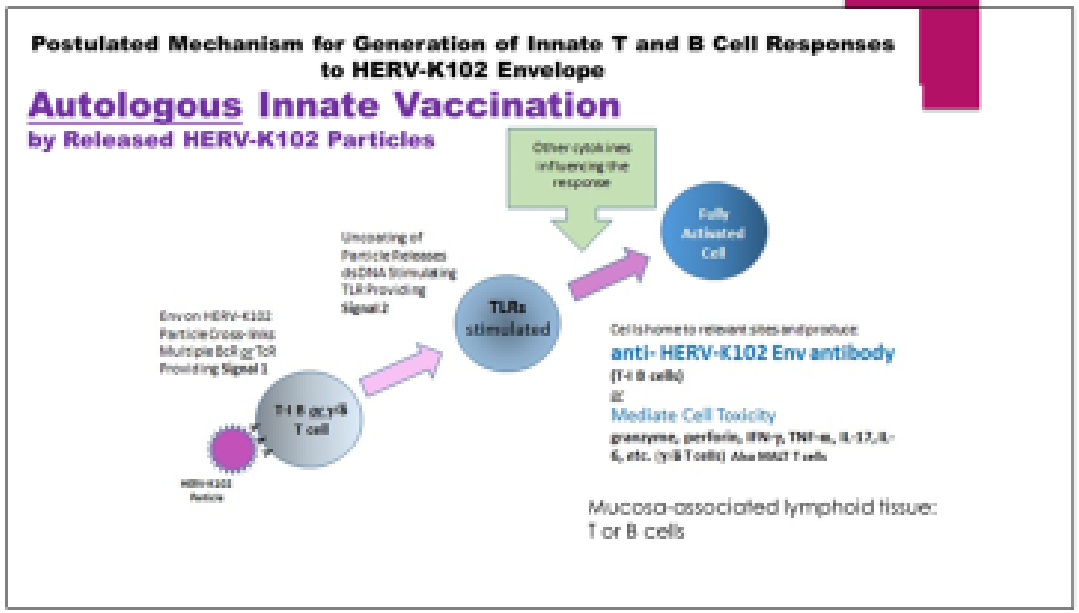
A putative SARS-CoV-2 infection acquired around January 22, **2020** yielded a uniform row of blisters across the entire under lip of this individual approximately at day 6. (Asymptomatic except for hematochezia on day 7 but husband came down with full-blown COVID-19 symptoms on day 8 and he was very sick in bed coughing until day 13.)

In response to the first Pfizer-BioNTech COVID-19 mRNA vaccination (April 9, **2021**), these Fordyce Spots blistered at day 6 (middle and edges) .

In response to the second Pfizer-BioNTech mRNA dose at 111 days after the first dose, the Fordyce Spots blistered at 6 hours (less apparent and mostly at edges).

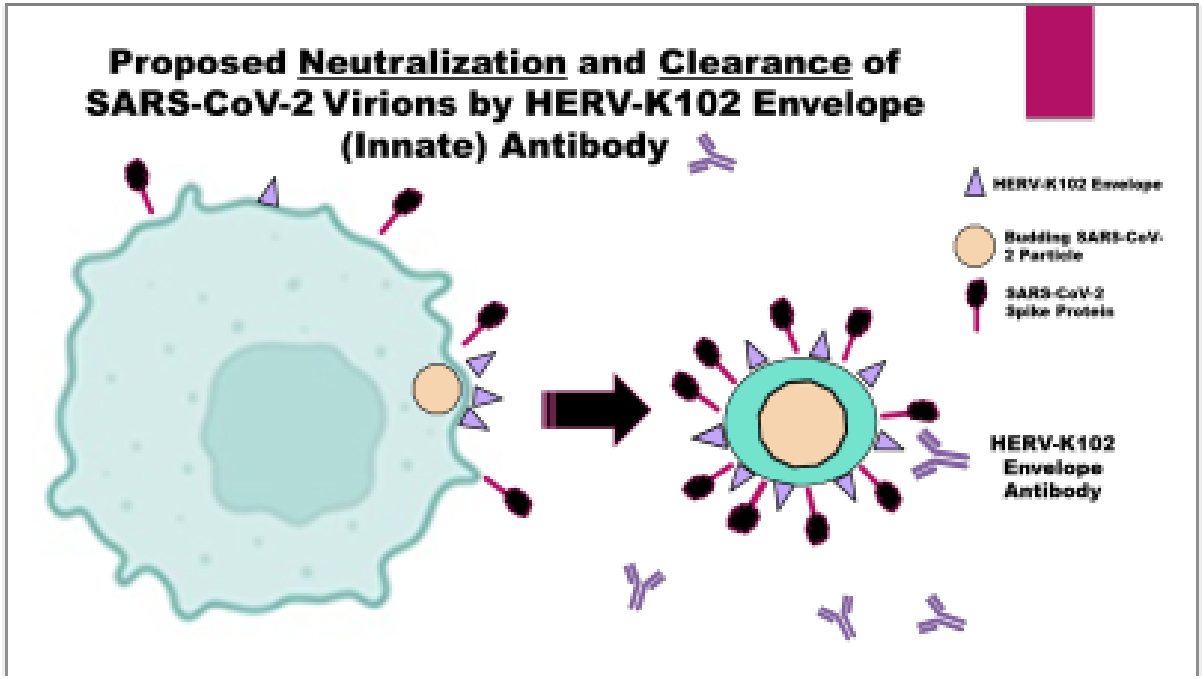




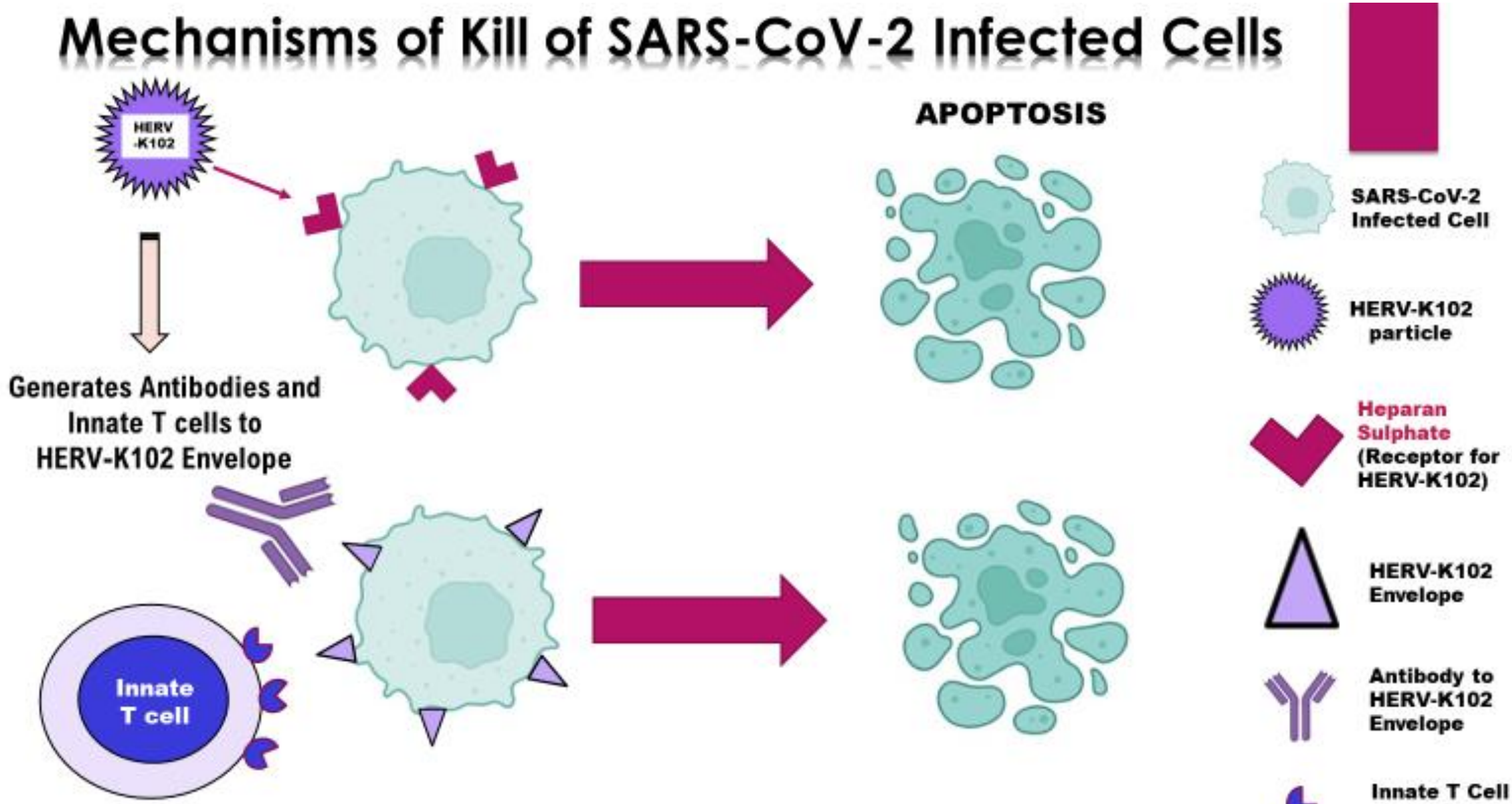


The HERV-K102 INNATE 'Trained Immunity' Protector System Includes the Ability to Neutralize and Clear SARS-COV-2 Virions Without Recognizing Virus Specific Antigens*

* Therefore there is no chance of selection pressure for emergence of SARS-CoV-2 variants. This protector system is ideal against enveloped RNA pandemic viruses. Neanderthals & Denisovans lost HERV-K102 at the orthologous position at 1q22 and went extinct.



Mechanisms of Kill of SARS-CoV-2 Infected Cells

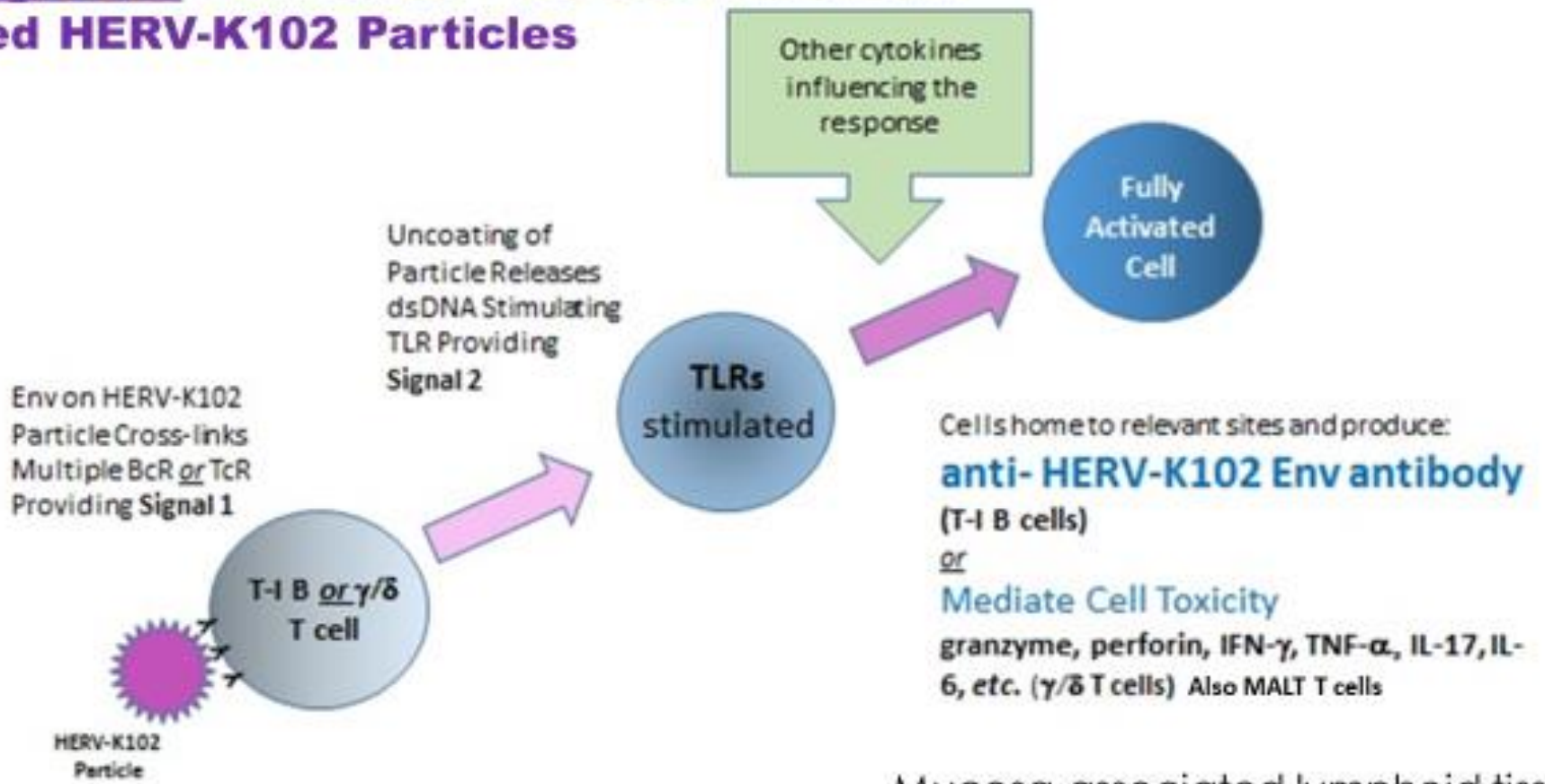


Cell & Ab Icons from Biorender.com

Postulated Mechanism for Generation of Innate T and B Cell Responses to HERV-K102 Envelope

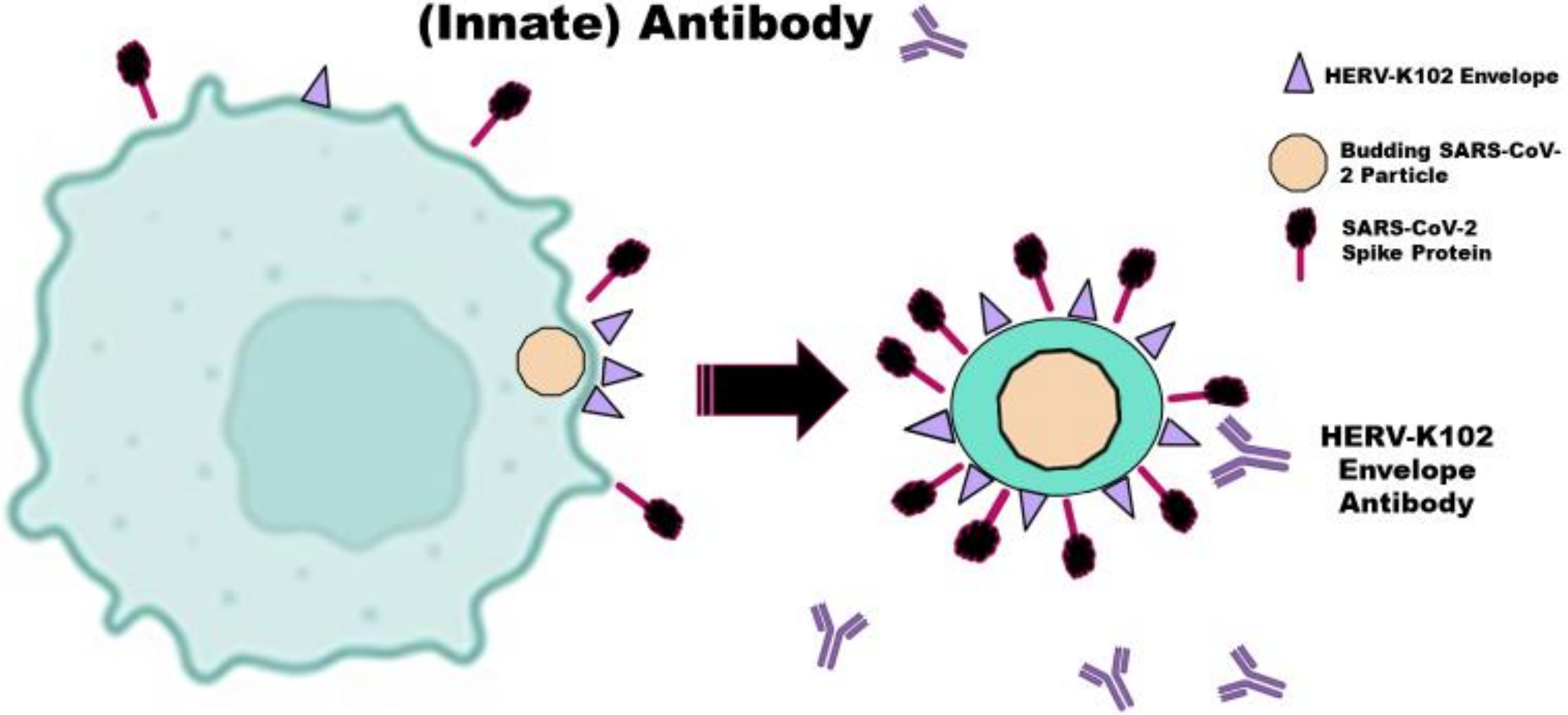
Autologous Innate Vaccination

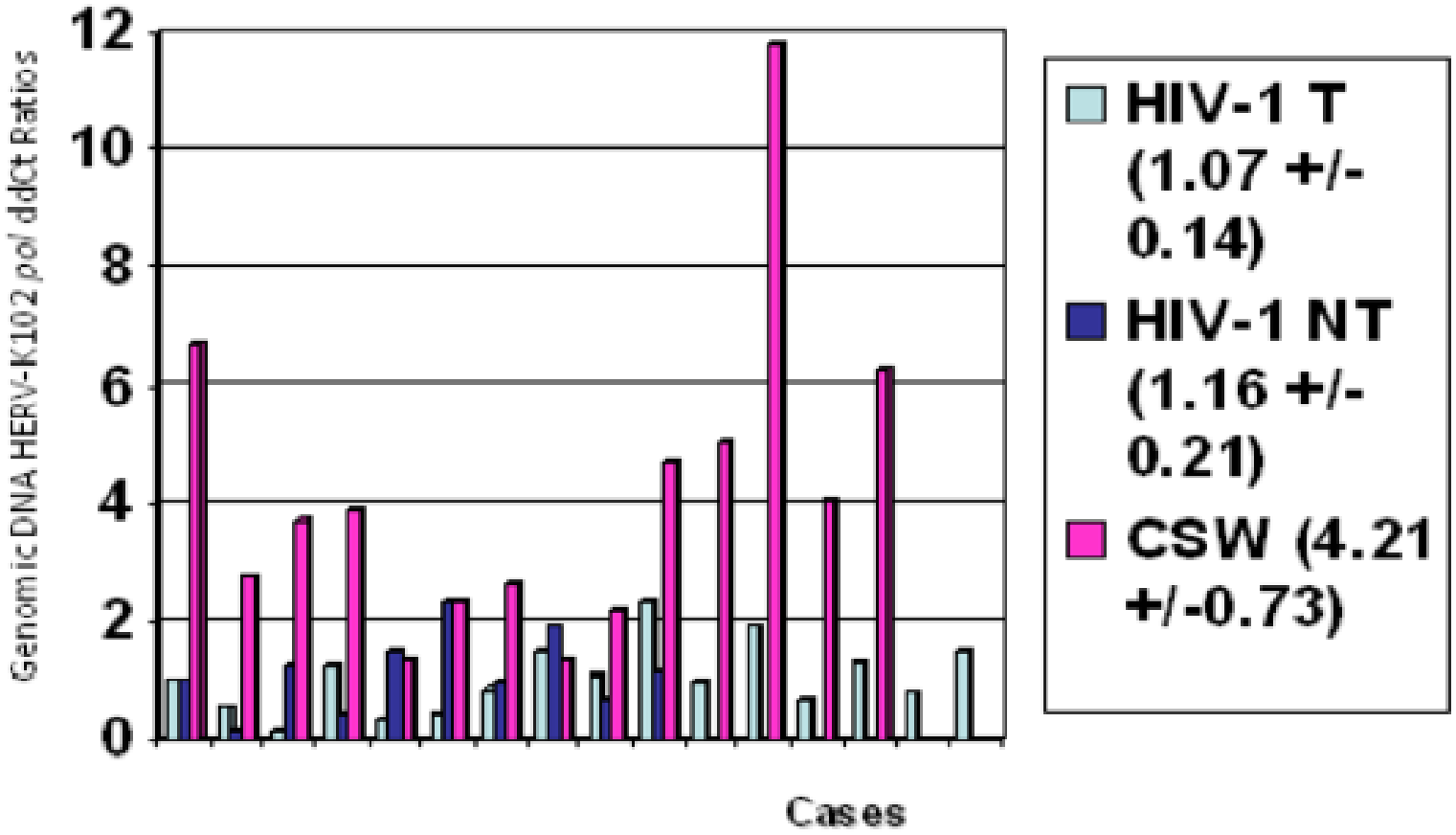
by Released HERV-K102 Particles



Mucosa-associated lymphoid tissue:
T or B cells

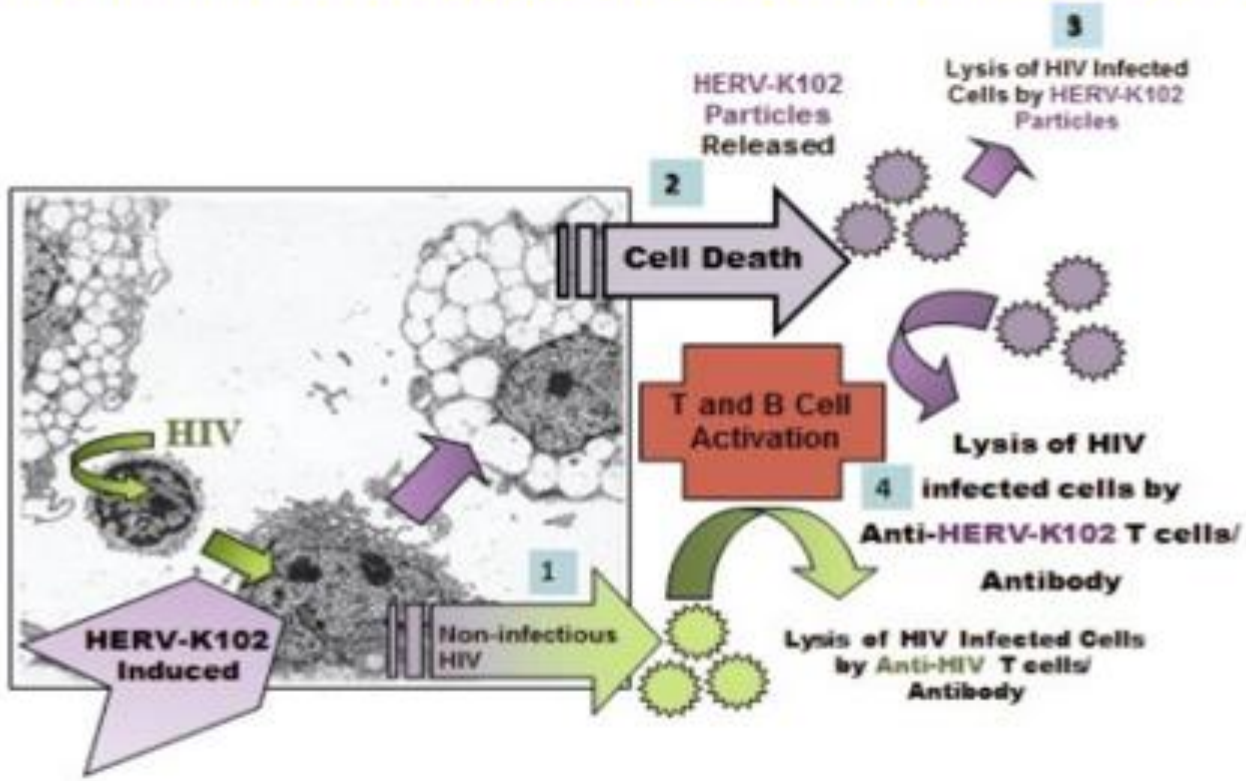
Proposed Neutralization and Clearance of SARS-CoV-2 Virions by HERV-K102 Envelope (Innate) Antibody





A Commercial Sex Worker (CSW) Cohort Defined as HIV-1 Exposed and Seronegative (HESN) with Resistance to HIV-1 Acquisition for at Least 3 Years Shows a 5-fold Increased HERV-K102 Genomic DNA Copy Number over Normal Healthy Adults (n=30, ddCt 0.88 +/- 0.37; p<0.0005) Not Detected in patients with HIV-1 Whether (T) or Not (NT) on Anti-retroviral Therapy [Laderoute M et al., Open AIDS J, 2015].

At least 4 general mechanisms by which HERV-K102 or the expression of HERV-K HML-2 group proteins may protect against HIV-1 [Laderoute M. Discovery Medicine, 2015].



1. Molecular interference (such as HK protease cutting HIV-1 proteins in the wrong places) yielding non-infectious HIV-1 particles.
2. Lytic release of HERV-K102 particles kills the HIV-1 infected cells.
3. Released particles undergo lytic infection in cells infected by HIV-1 but merely integrate into normal cells.
4. HERV-K102 particles autovaccinate innate T and B cells with receptors for HERV-K102 envelope (Env) which kill HIV-1 infected cells. Note that the HERV-K102 Env on the surface of HIV-1 infected cells directly induces apoptosis when triggered by the antibody with no need for complement or ADCC [Wang- Johanning F et al, JNCI, 2012].
5. NOT shown; antibodies to HERV-K102 Env likely neutralize and clear HIV-1 virions by two mechanisms: 1) since HIV-1 is enveloped it probably has HERV-K102 Env on the surface of its virions picked up during budding and 2) HERV-K18 but not HERV-K102 Envelope is able to pseudotype HIV-1 particles [Brinzevich D et al., J Virol 2014.]