AIDS Institute, Department of Microbiology
Li Ka Shing Faculty of Medicine, HKU

HKU AIDS Research Institute Discovers a New Immune Pathway Critical to Treatment of Gut Inflammation in HIV-1 Infection

Press Conference
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Speakers

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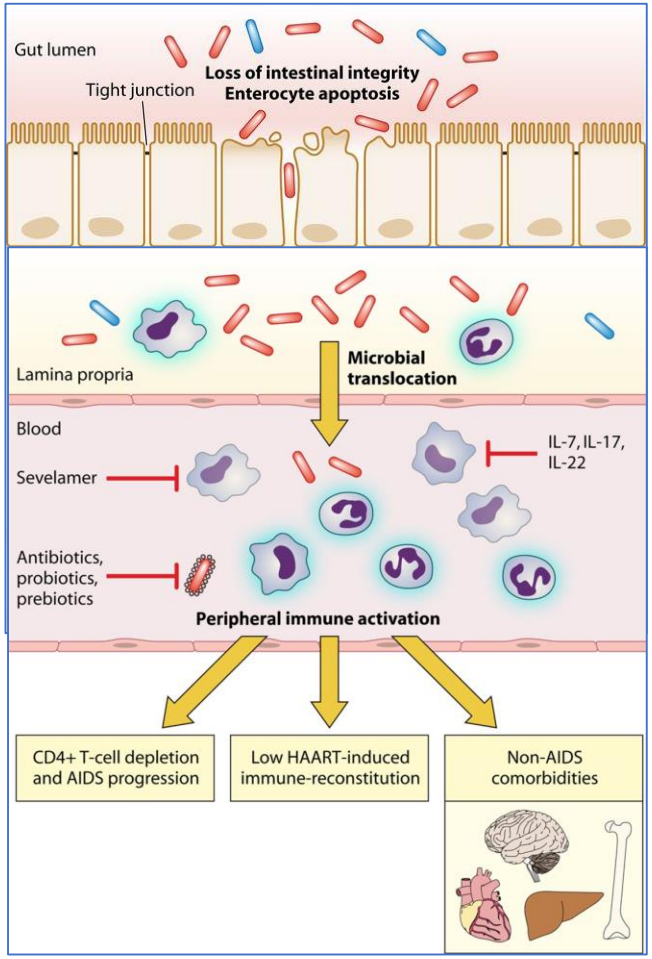
HIV / AIDS

- Human Immunodeficiency virus type 1 (HIV-1) causes AIDS
- Infects primarily CD4 T lymphocytes, integrates into the host genome and establishes chronic infection
- Diminishing CD4 T cell count over years
- Immune dysfunction
- Prone to opportunistic infections and other diseases such as gut enteropathy
- Highly active antiretroviral therapy (HAART) can prolong a patient's life
- No vaccine to date
- New understanding and therapy is required

HIV / AIDS



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Early HIV-1 infection

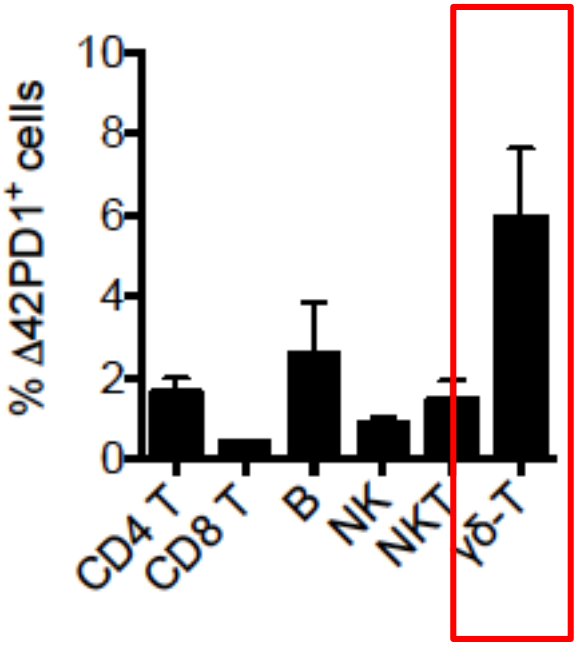
- Gut inflammation
- CD4 depletion
- Inflammatory cytokines
- Viral replication
- Viral setpoint

Difficulty to study

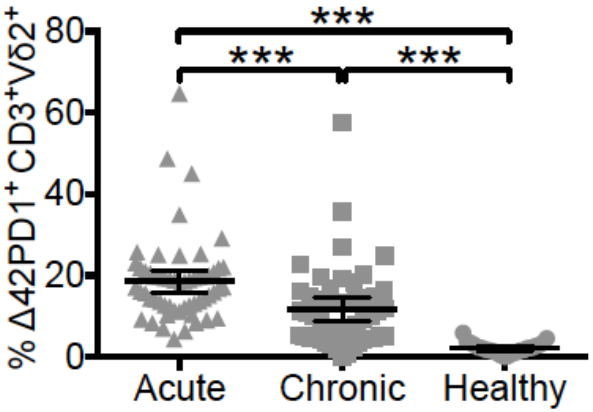
- Rare samples
- Window period <30 days
- Non-human models

Identification of Δ42PD1

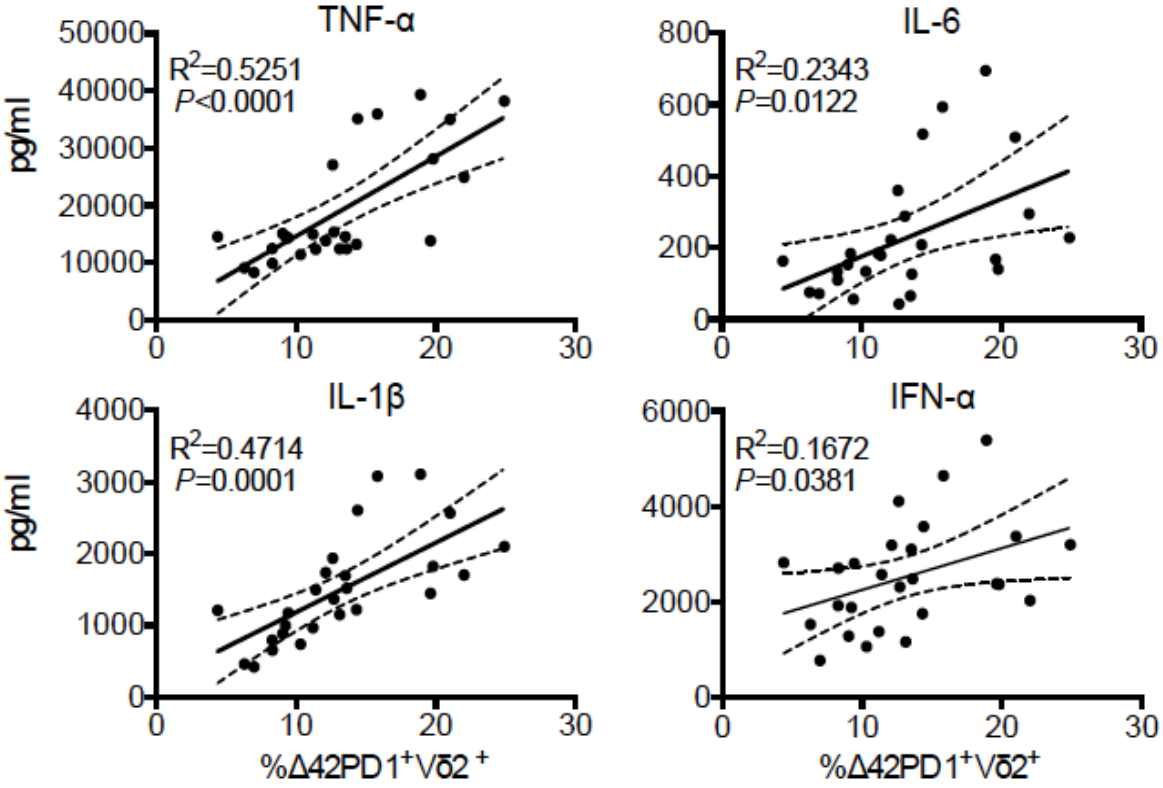
- Isoform of PD-1 (*Molecular Therapy 2013*)
- Expressed on a subset of T cells = γδ-T
- γδ-T comprise of 1-10% of peripheral blood lymphocytes
- Important in maintenance and activating immune response
- Readily migratory



High Δ42PD1+γδ-T cells in acute HIV-1 patients



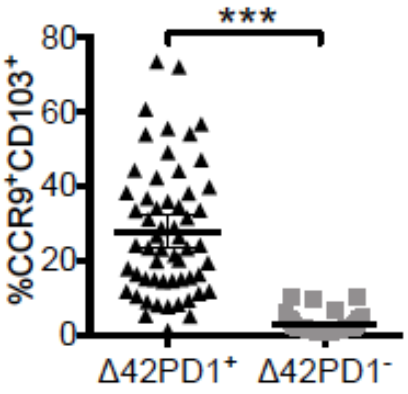
Plasma cytokines



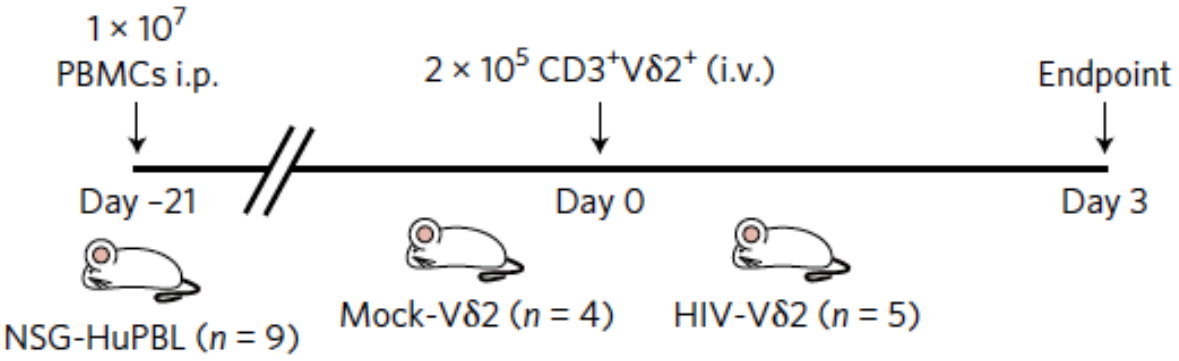
TNF-a, IL-6, IL-1b, IFN-a = pro-inflammatory cytokines

Δ42PD1+γδ-T cells are gut-homing

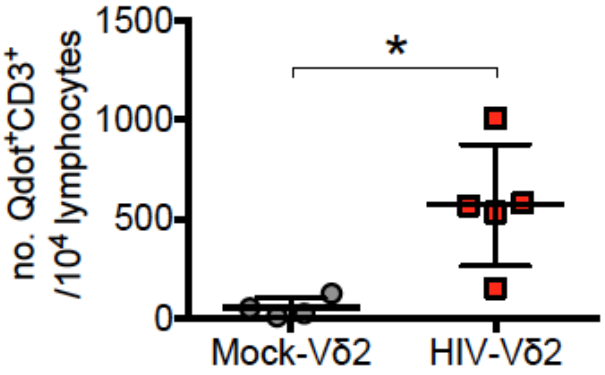
Acute HIV-1 patients

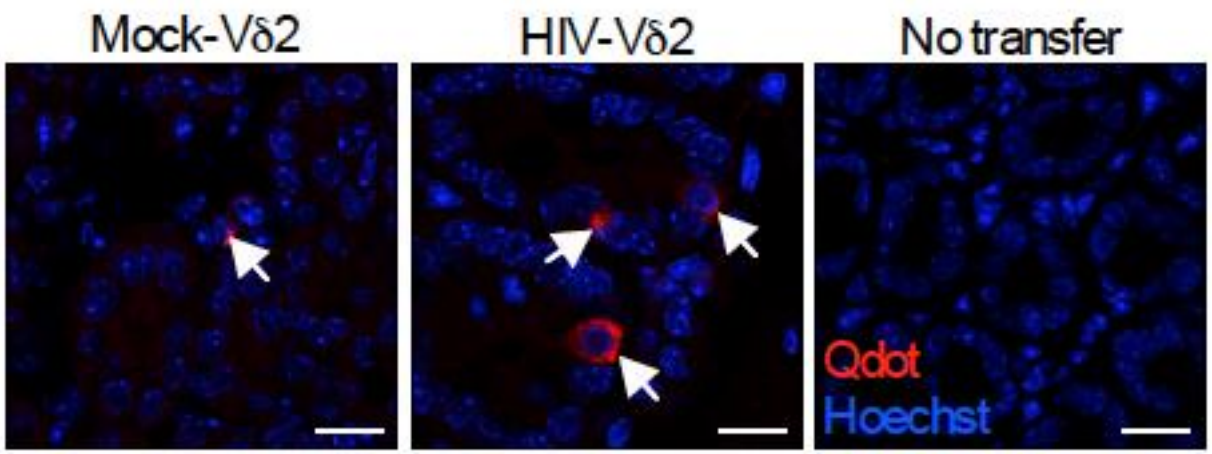


Humanized mice model – transfer of labelled cells



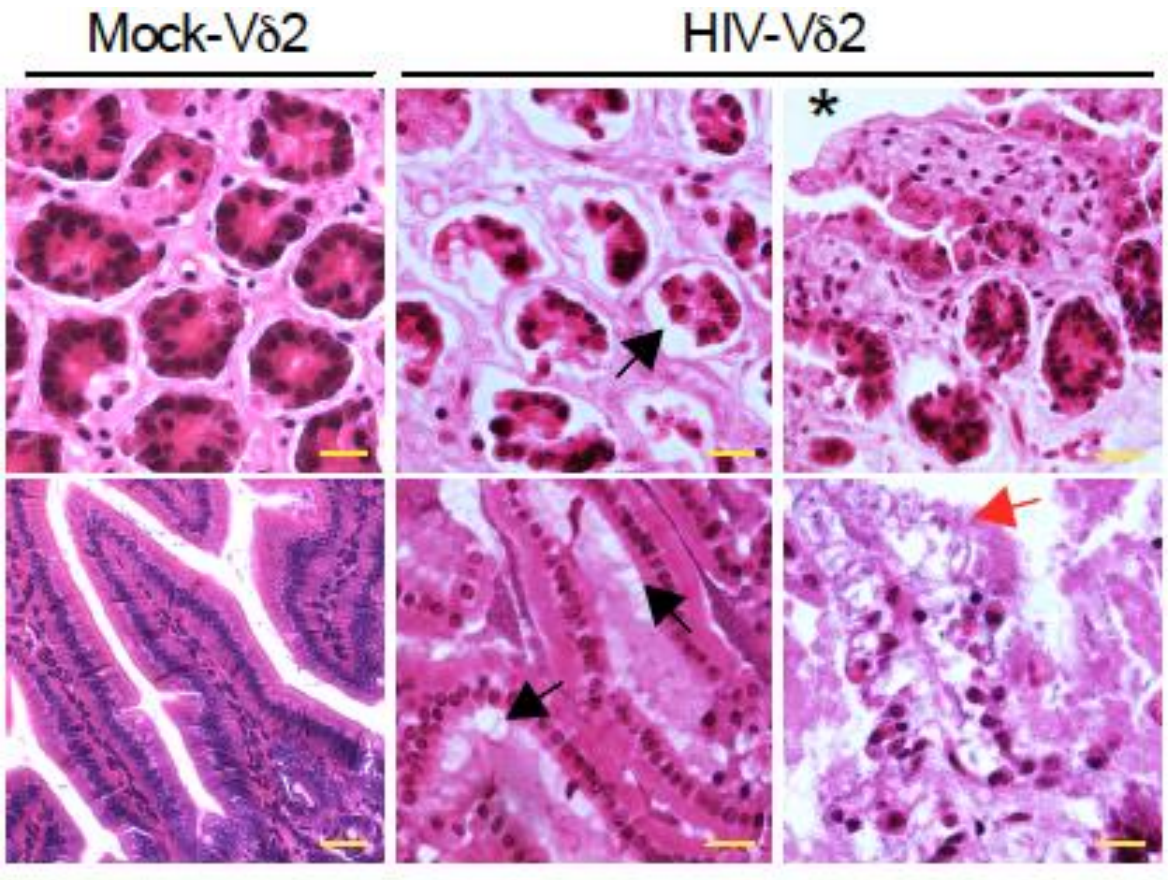
Detection of HIV-induced labelled γδ-T cells in small intestines





Δ42PD1+γδ-T cells causes gut inflammation

Small intestines after transfer



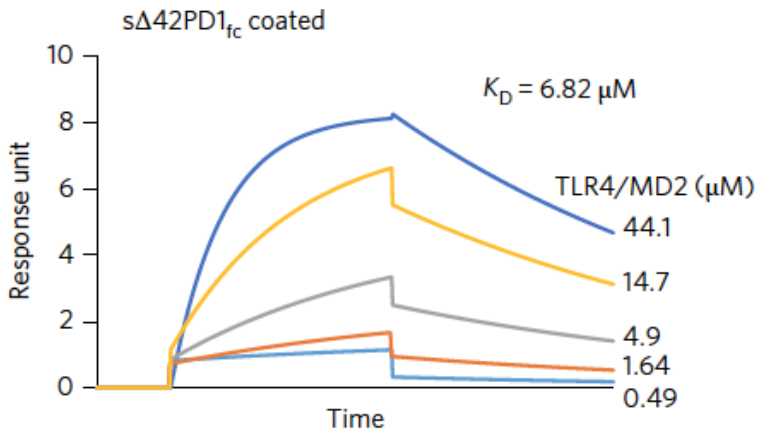
Normal villi

Inflammation

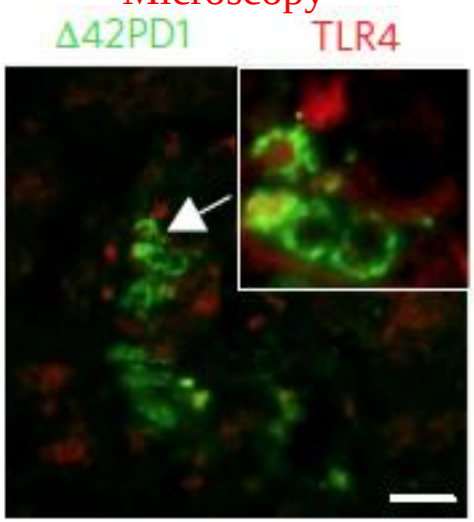
- Villous blunting
- Vacuolization
- Epithelial layer detachment
- Mucosal ulceration
- Disintegration of lamina propria

Δ42PD1-TLR4 interaction

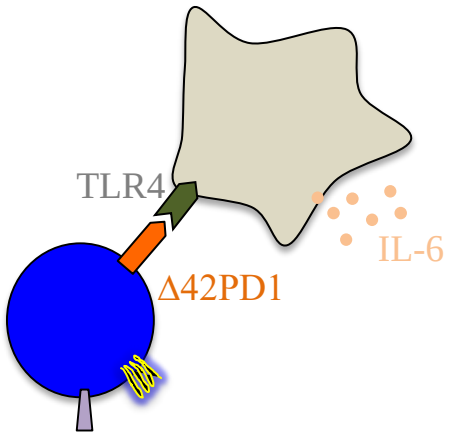
Protein-protein binding

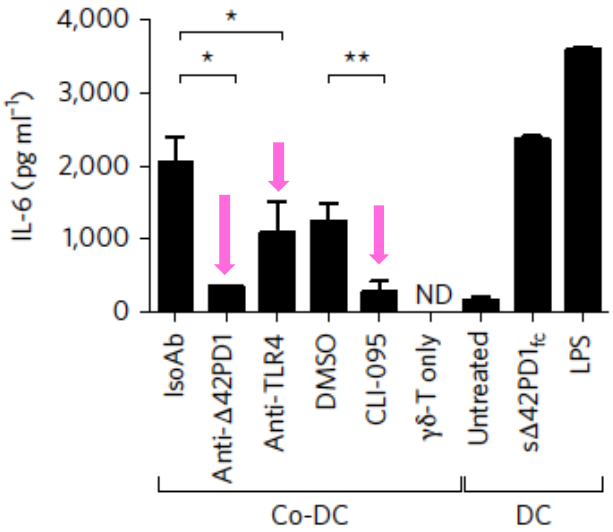


Microscopy

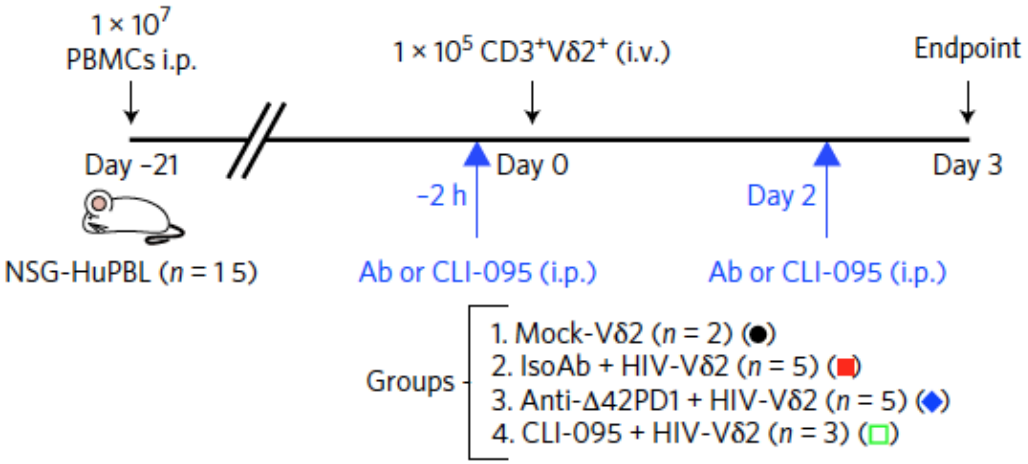


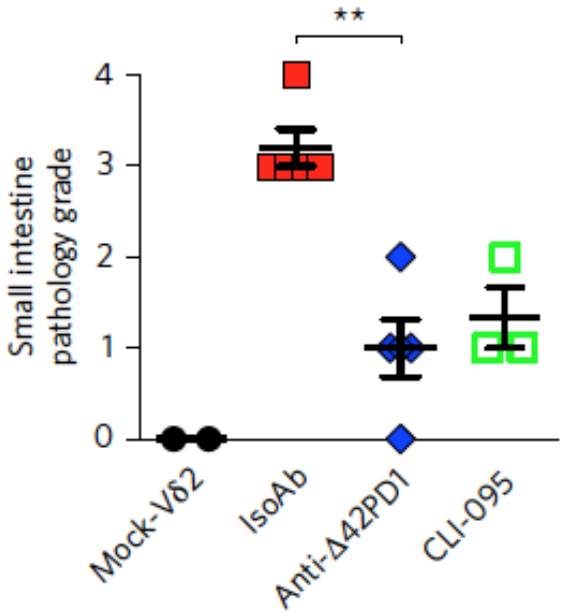
Cell experiments





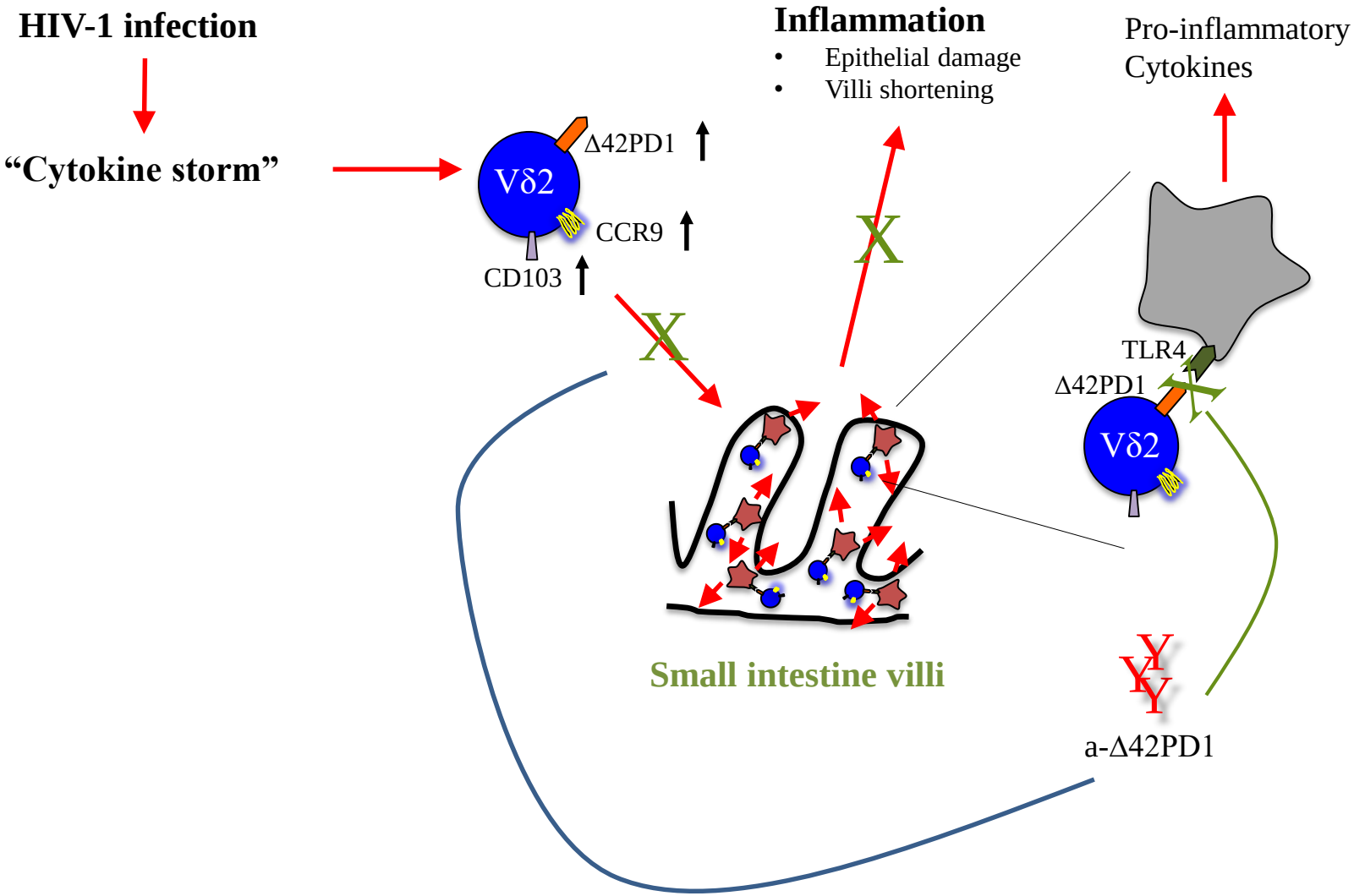
Blocking Δ42PD1-TLR4 pathway prevents gut inflammation





CLI-095 = TLR4 inhibitor

Summary


HIV-1 infection
"Cytokine storm"
Inflammation
• Epithelial damage
• Villi shortening
Pro-inflammatory Cytokines
Vδ2
Δ42PD1
CCR9
CD103
X
X
TLR4
Δ42PD1
Vδ2
Small intestine villi
Y
Y
Y
a-Δ42PD1

Conclusions

- Discovered a new Δ42PD1-TLR4 pathway important to understand early HIV-1 infection
- Generated an antibody to block it and prevent gut inflammation
- May be applicable to other mucosal inflammatory diseases
- Develop the antibody for clinical use

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Li Ka Shing Faculty of Medicine, HKU

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Q & A Session