ADCC and HVEM: Lessons from an HSV-2 ΔgD vaccine

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Herpes Simplex Viruses

- Predominantly infect epithelial cells; establish latency in peripheral nerves
- HSV-1 and HSV-2 cause painful recurrent oral or genital mucosal lesions
  - Both transmitted perinatally
  - HSV-2 associated with increased risk of HIV acquisition/transmission
- HSV-2: 400+ million people worldwide
- HSV-1: 3.7 billion people worldwide
  - Major cause of genital herpes in the developed world
  - Leading cause of fatal infectious encephalitis
  - Corneal blindness

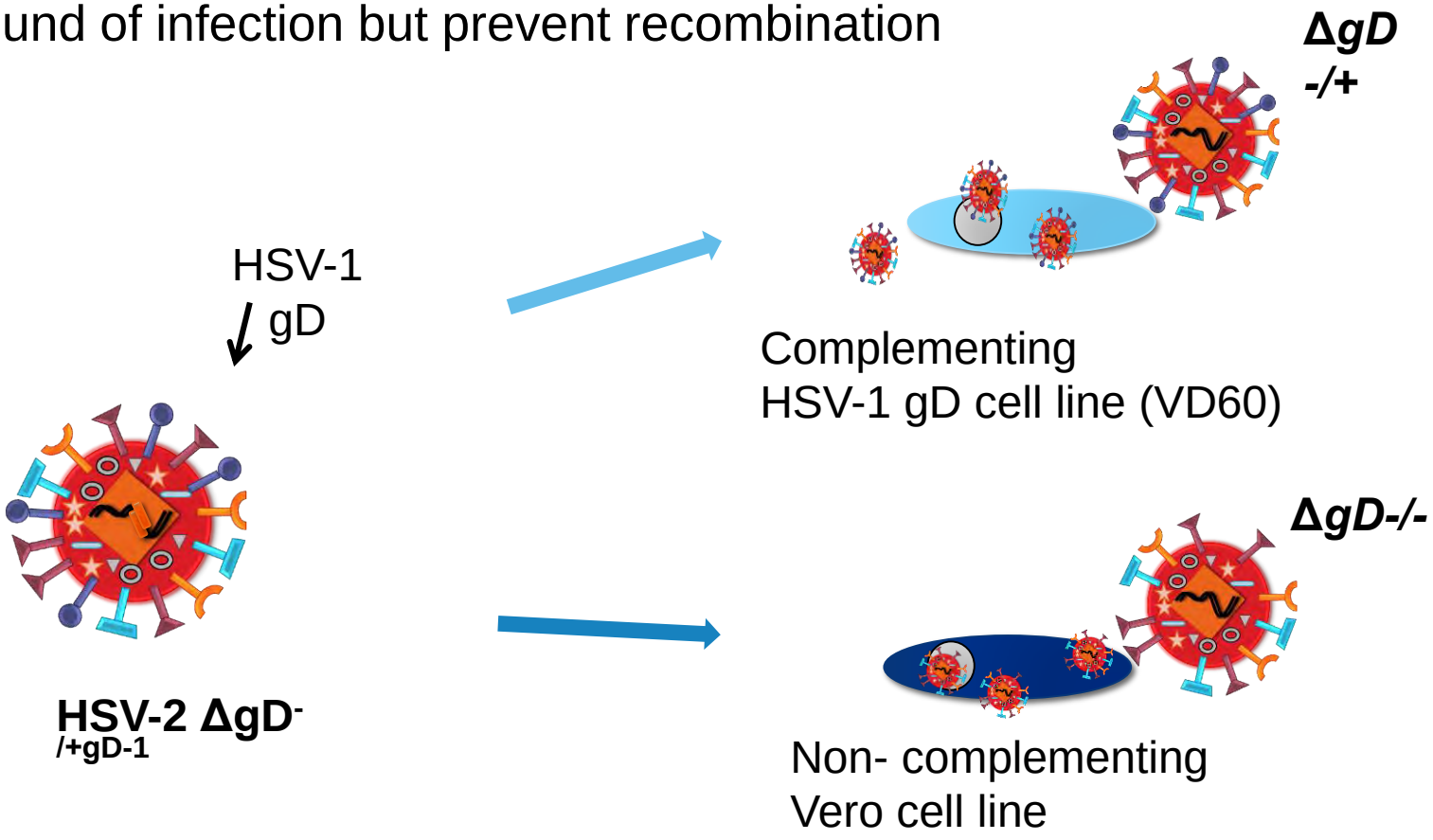
Looker et al, 2012

HSV vaccine trials

- Dominated by subunit vaccines targeting gB and gD that generate primarily a neutralizing antibody (nAb) response
- Clinical trial results:
  - gB/gD/MF59 (Chiron) elicited high titer nAbs, but did not protect
    - Overall vaccine efficacy 9% (95% CI, -29% to 36%) (JAMA, 1999)
  - rgD2/AS04 vaccine elicited high titer gD nAbs and CD4 T cell responses but failed to protect
    - In discordant partners, protective in ♀ who were seronegative for HSV-1 and 2, but not HSV-1+ (NEJM, 2002)
    - No efficacy against HSV-2 disease or infection in field study seronegative ♀ (-38% [95% CI, -167 to 29]
  - Dl5-29
    - Replication defective, deleted in 2 genes involved in viral replication (expresses gD)
    - Phase 1 completed, results pending

What if we try something different?

- HSV-2 single-cycle vaccine strain *deleted* in gD
  - Single cycle virus complemented with HSV-1 gD to allow initial round of infection but prevent recombination

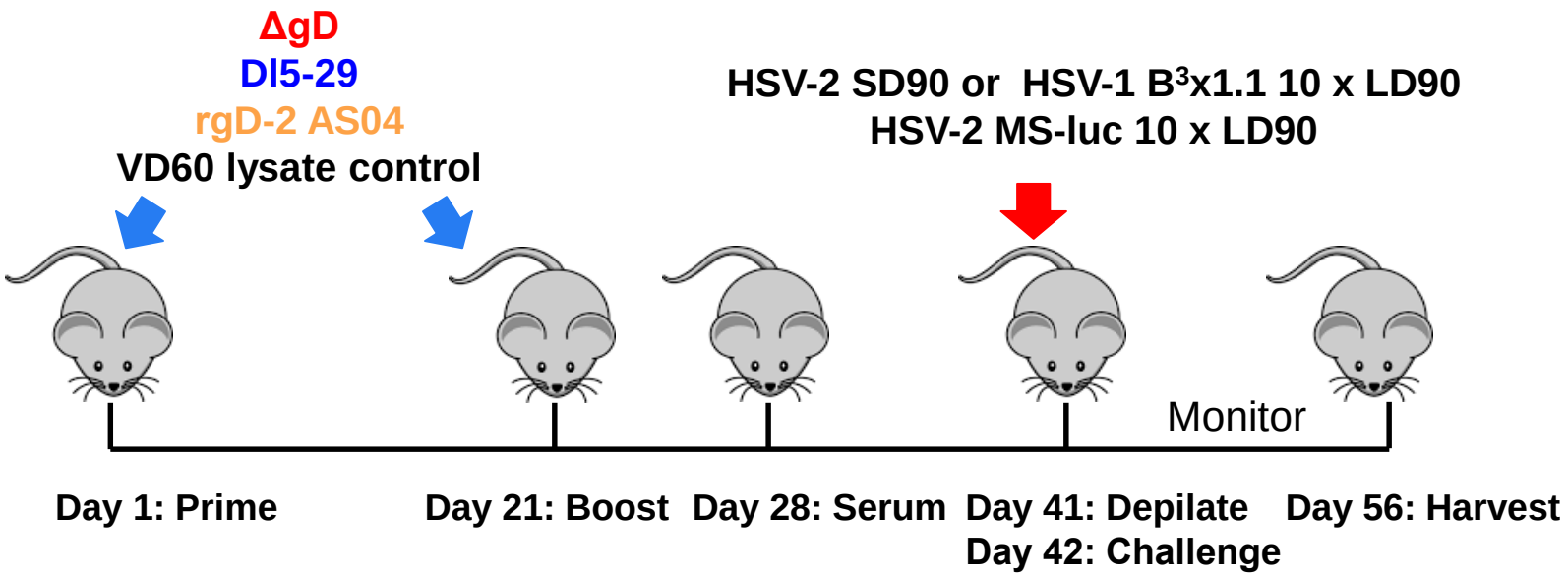


What we know about HSV-2 ΔgD

- Protected > 100 mice from lethal challenge (100%)
  - Male and female mice
  - Challenged intravaginally (female) or by skin scarification with different clinical isolates of HSV-2 and HSV-1
  - Prevents establishment of latency
  - Rapidly clears virus
  - Lasting protection (100% out to 6 months post-boost)
- Generates high titer HSV Ab response as well as CD4 and CD8 T cells
  - Abs alone are sufficient to passively protect naïve mice from challenge
  - Abs are NOT neutralizing but activate the FcR to induce ADCC and ADCP

Why does this vaccine do something different?

Approach: Compare different vaccines

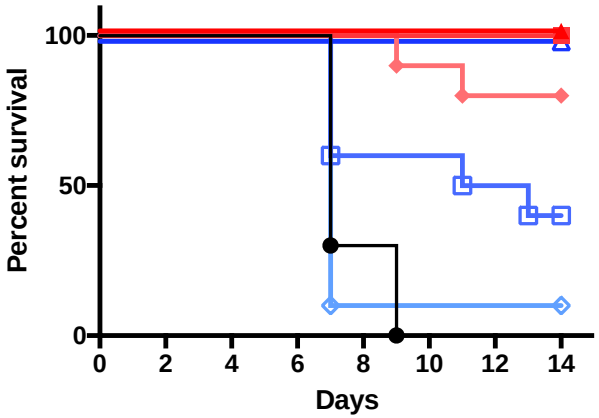


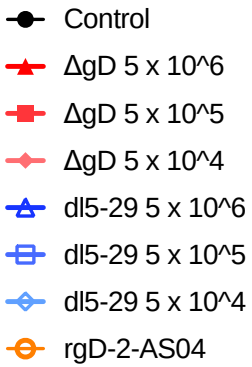
Dl5-29: replication defective; deleted in 2 genes involved in viral replication

Gift from David Knipe (Harvard)

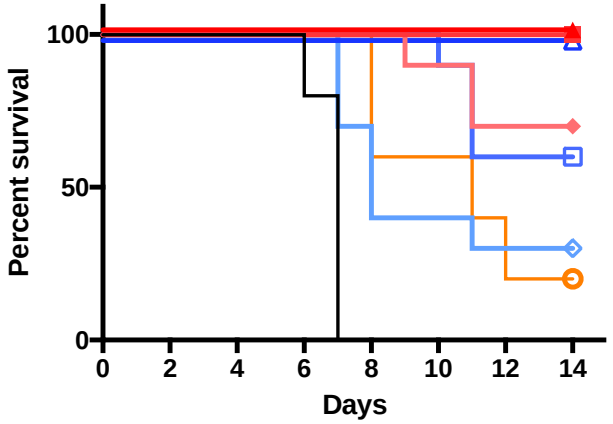
HSV-2 ΔgD rapidly clears virus & protects against 10xLD90 HSV-1 & HSV-2: dose dependence

HSV-1 survival



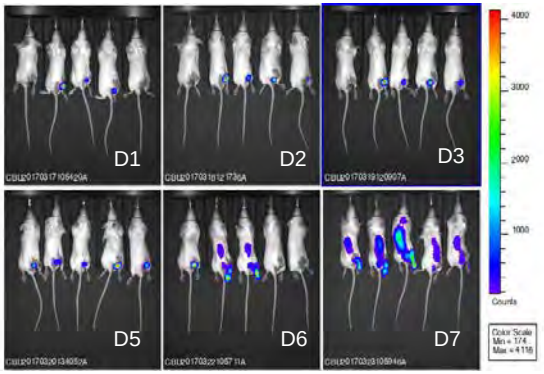


HSV-2 survival

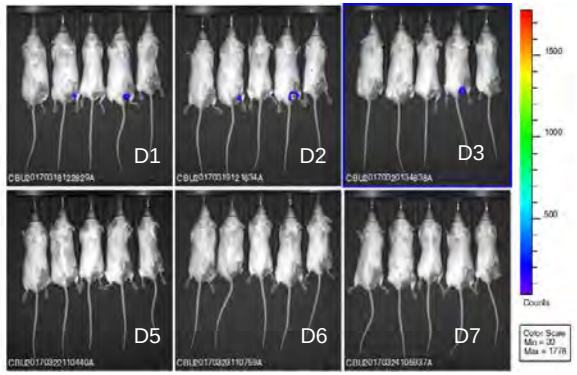


HSV-2 MS-luc

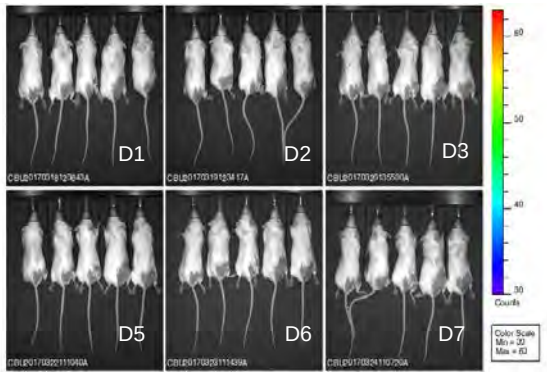
Control



Dl5-29



ΔgD



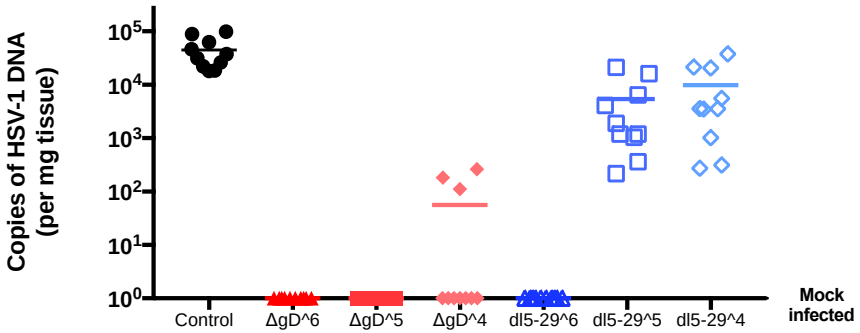
n = 5 - 10/group

Images representative of 2 independent experiments

Dose dependent differences in protection from latency and Ab responses

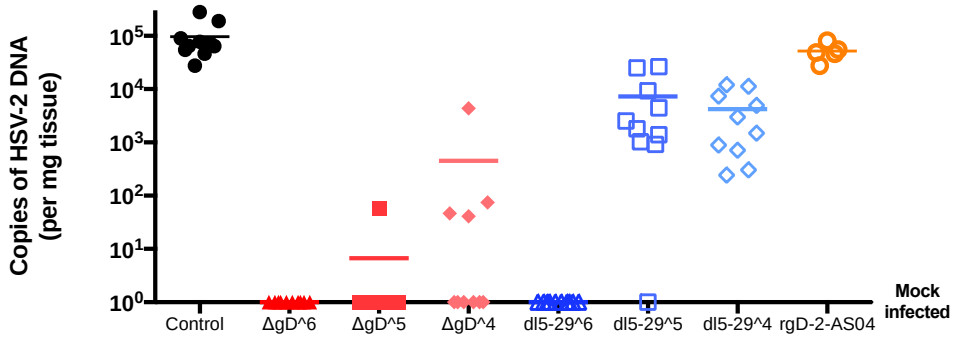
HSV-1 $B^3x1.1$

DNA in DRG

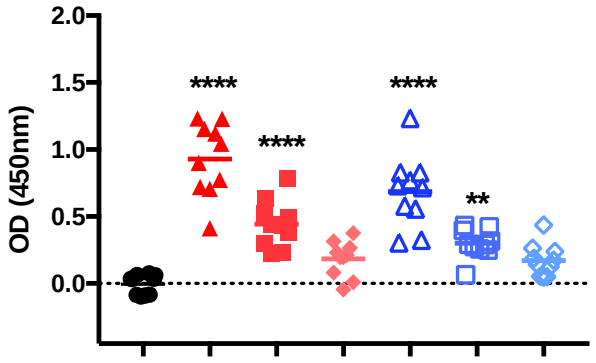


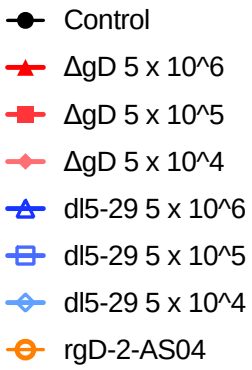
HSV-2 SD90

DNA in DRG

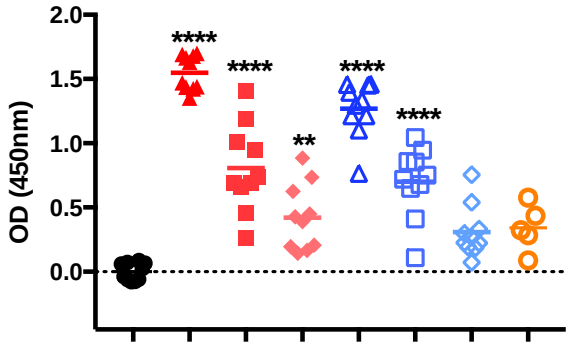


Total HSV-1 binding IgG



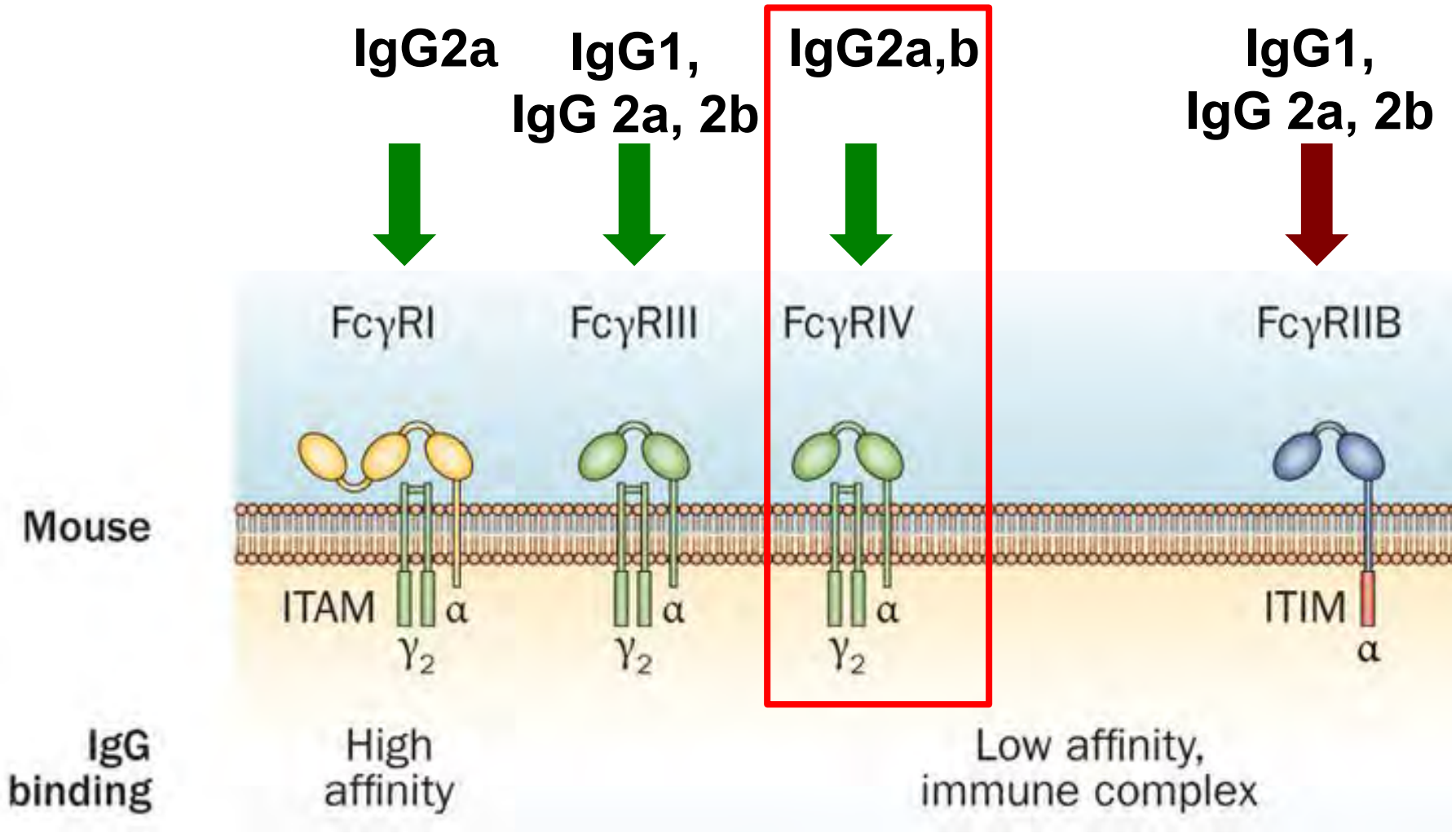


Total HSV-2 binding IgG



n = 10/group

Mouse Fc receptors

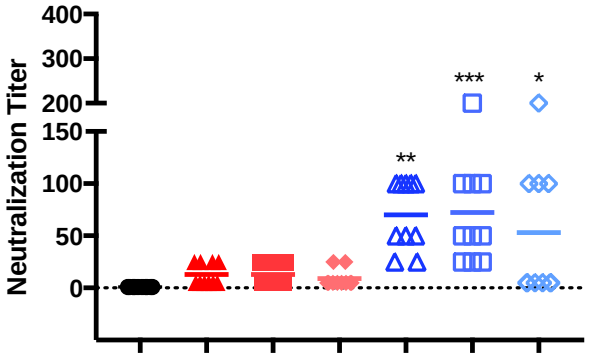


Lünemann et al, 2015

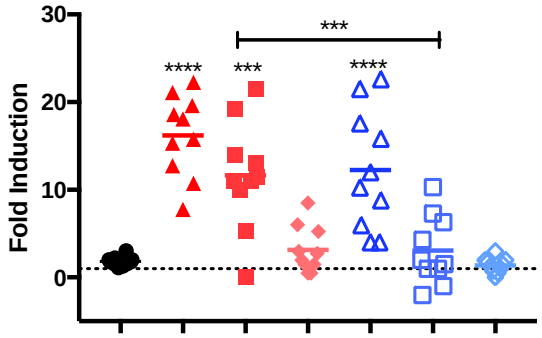
Antibody functionality differs by vaccination

HSV-1 $B^3x1.1$

Neutralizing titer

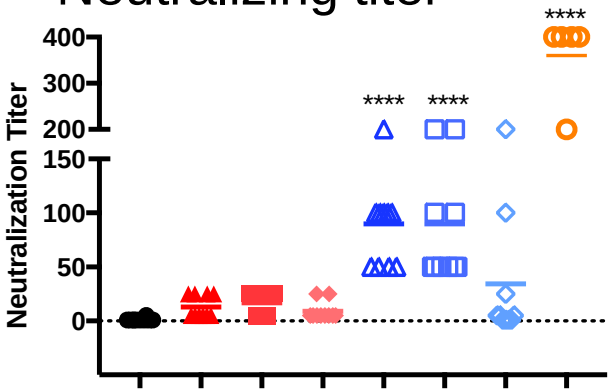


FcγRIV acitvation

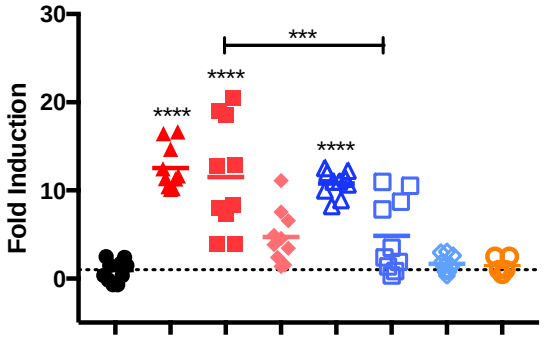


HSV-2 SD90

Neutralizing titer



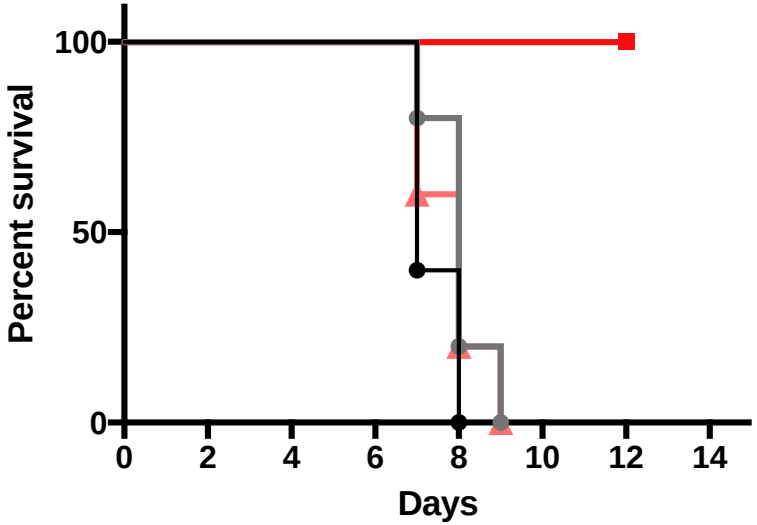
FcγRIV acitvation



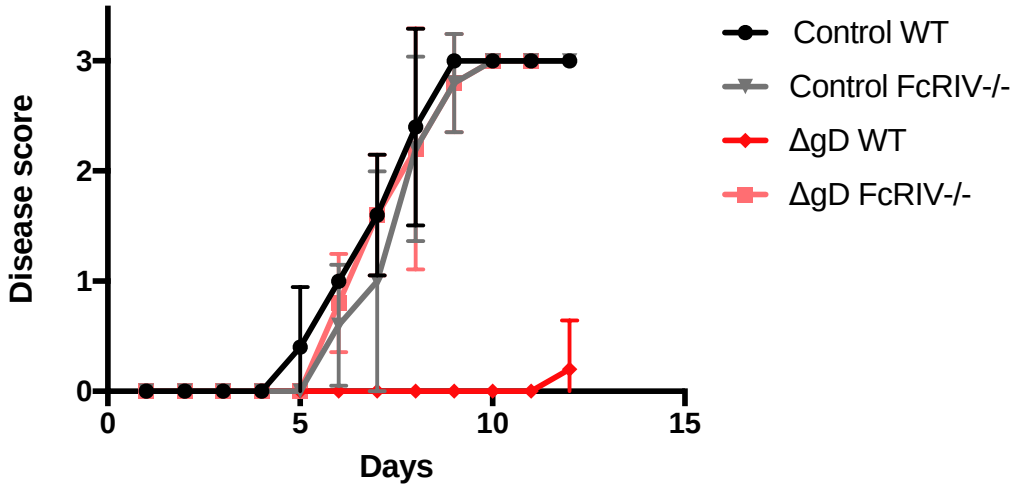
n= 10/group

FcγRIV is necessary for passive protection

Survival



Neurological Disease



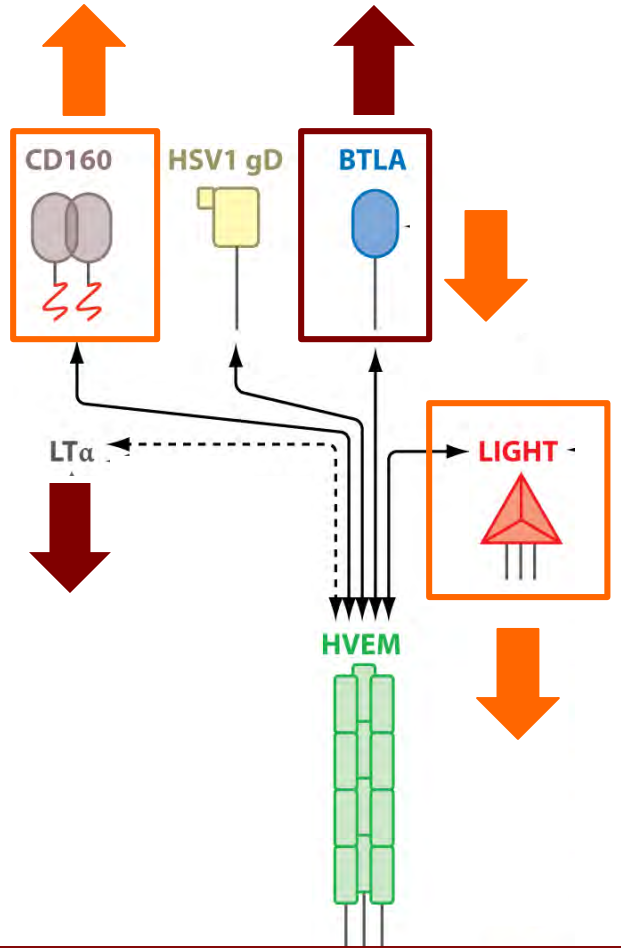
n= 5/group

Why does ΔgD evoke FcR response?

- **Unmasking other antigens?**
- **Loss of immunomodulatory effect?**
  - **gD binds HVEM?**

Skews the immune response leading to neutralizing Ab response?

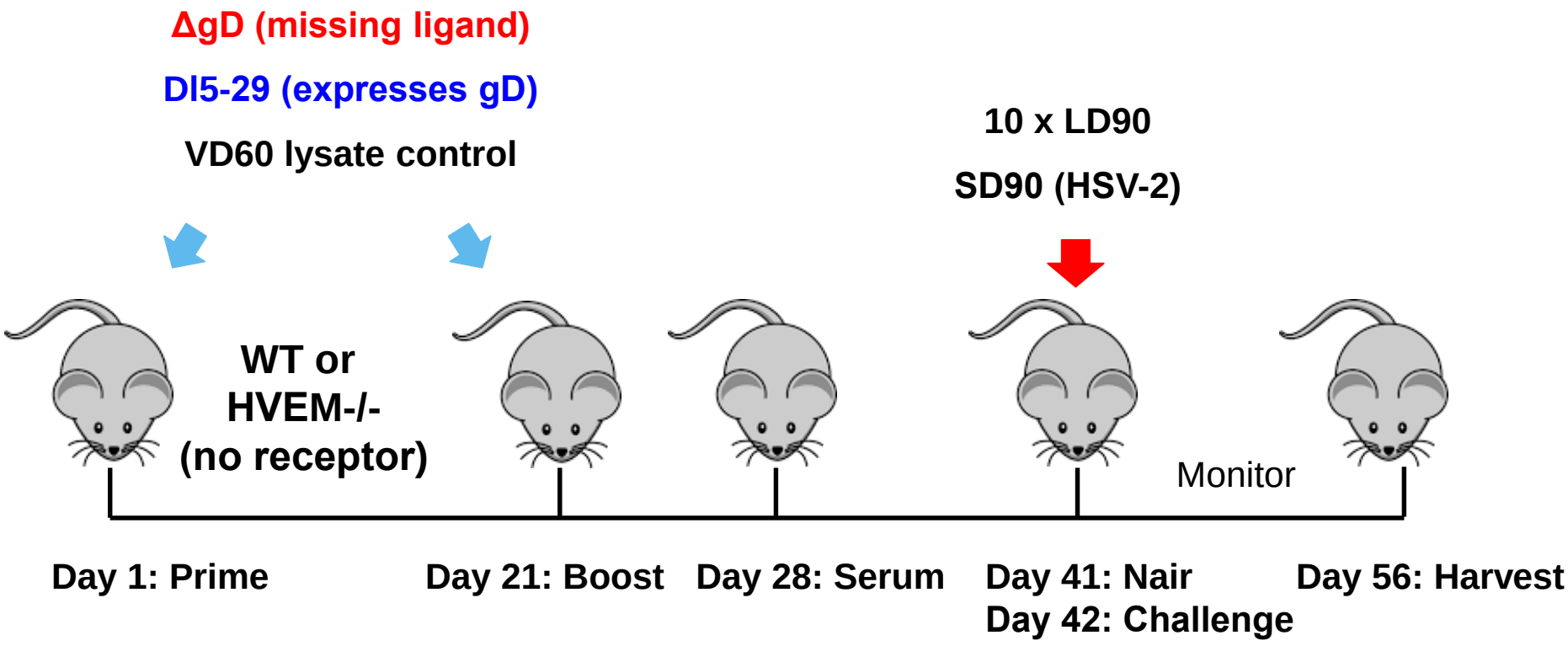
- Bidirectional **costimulatory**/**coinhibitory** signalling molecule
- **Activating** and **inhibitory** ligands
- Depends on cis/trans
- Broadly expressed on immune cells



gD is known to block some of the natural ligands of HVEM

Adapted from Murphy and Murphy, 2010

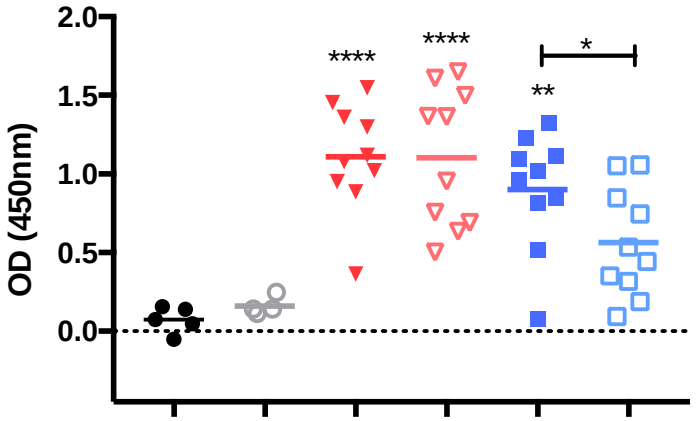
Do gD-HVEM interactions play a role in generating protective responses?



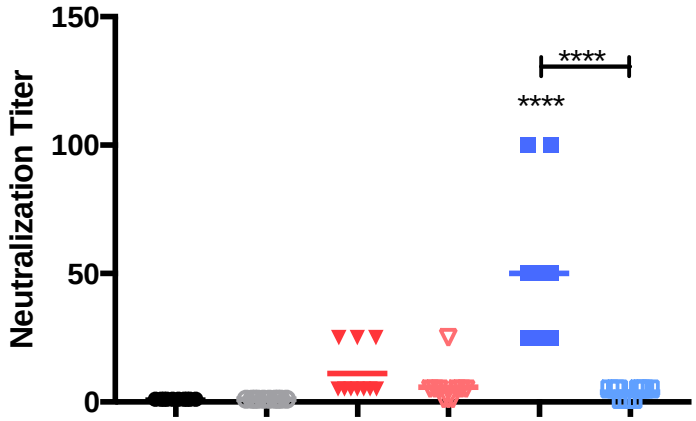
Expect that dl5-29 but NOT ΔgD will behave differently in HVEM-/-

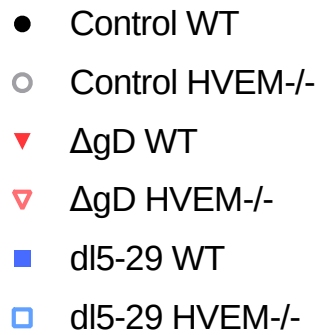
Changes to the antibody response in HVEM-/- mice

Total HSV-binding Ab

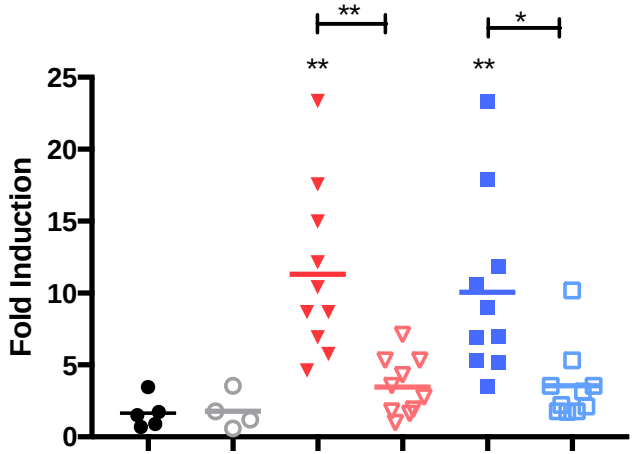


Neutralization titer

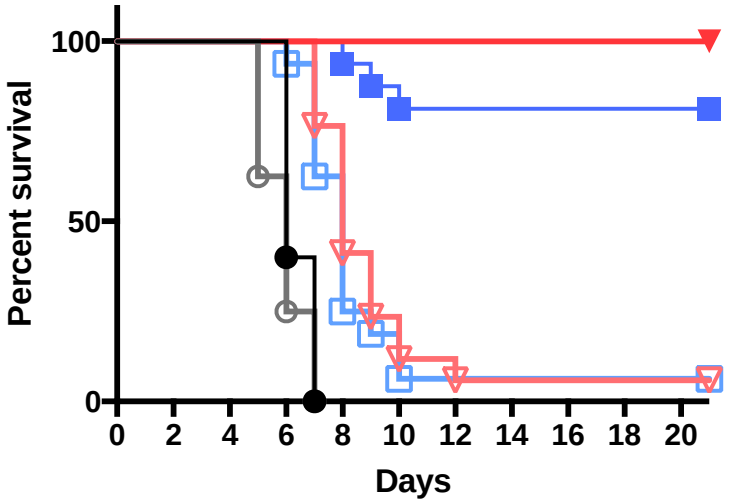




FcR activation

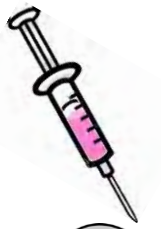


Survival



n = 10/group

Passive Transfer Experiments in HVEM KO Mice to Assess Effector Cell Function



Administer serum
ΔgD
Dl5-29
Control

WT or HVEM-/-

Monitor for disease

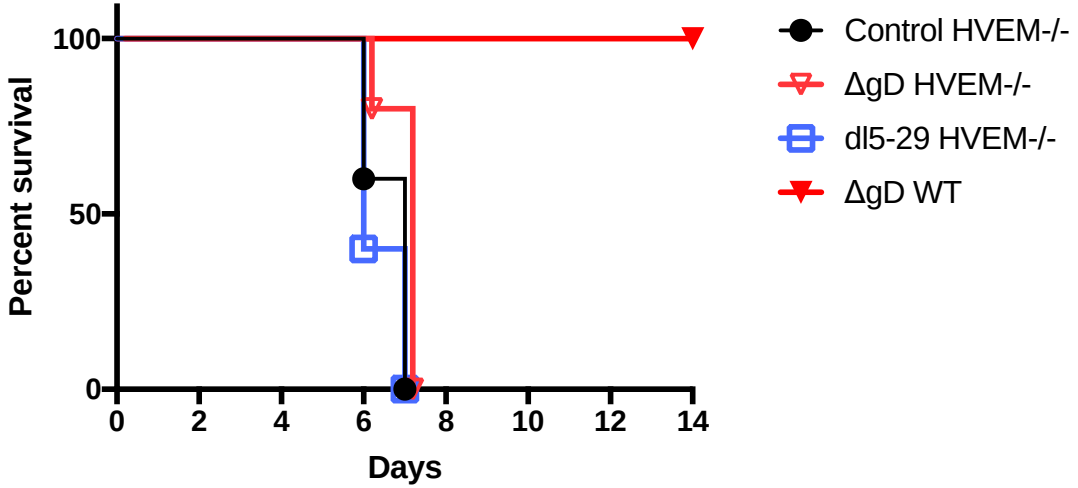
Day -1: Serum (i.p)

Day 0: HSV-2 challenge - skin (4674)

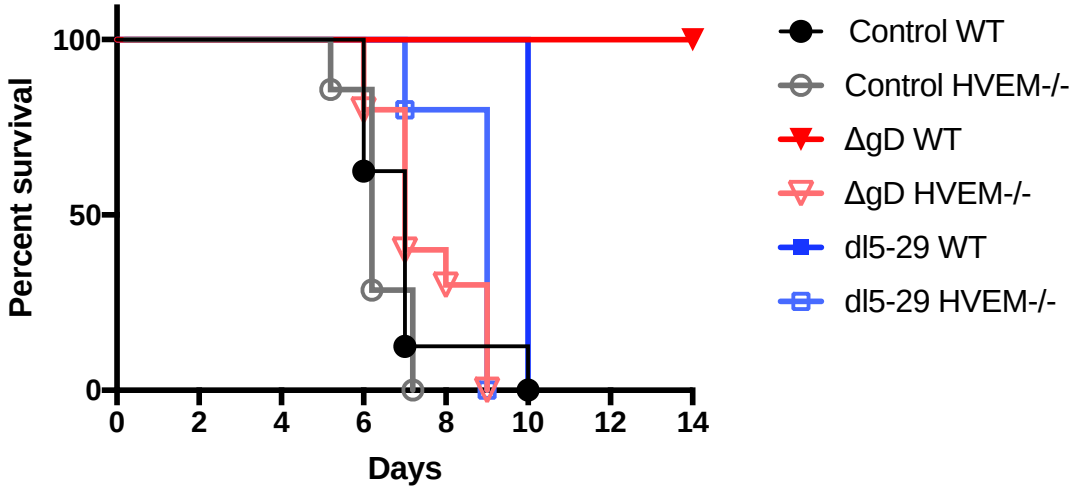
Day 14: Harvest

HVEM is involved in mounting Ab response AND effector response

Transfer immune serum from : HVEM-/- → WT



Transfer immune serum from : WT → HVEM-/-



n = 5-10/group

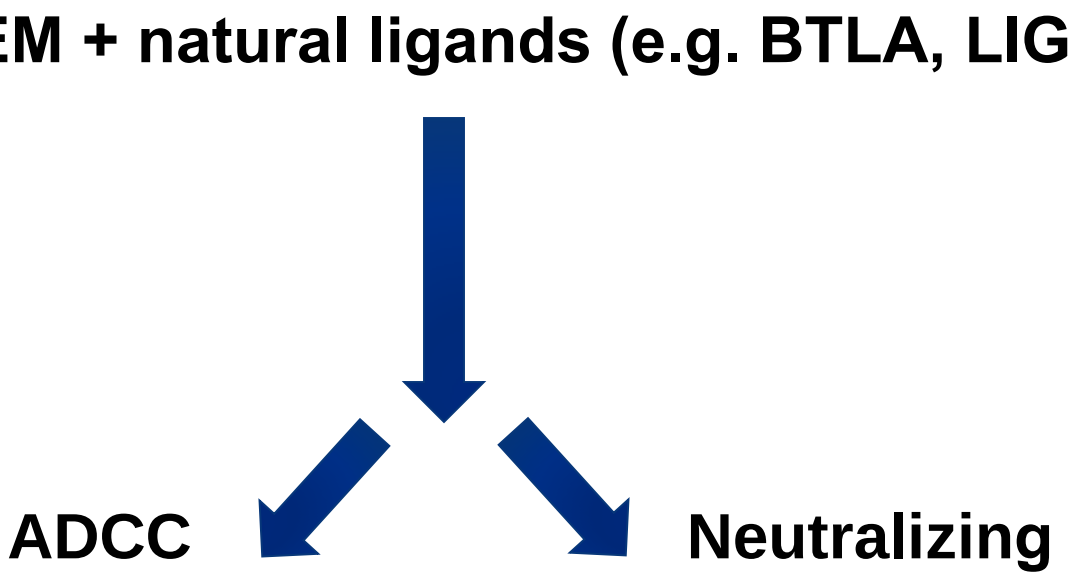
ΔgD Protection Summary

	HSV-1 Challenge (B^3x1.1)	HSV-2 Challenge (SD90)	Total
Protection	82/85*	146/152*	**228/237 (96.2%)**
Protection from DNA in DRG	56/60	110/117	**166/177 (93.8%)**

*all deaths (and all but 1 HSV+ DRG) at 8 months post-boost or 5 x10^4 vaccine dose

Conclusions

- FcR activating antibody is a correlate of protection for HSV-1 and HSV-2 clinical isolates in mice
  - High FcR titers (△gD) → greater active & passive protection
  - Little FcR activity (rgD or HVEM KO) → Little active or passive protection
- HVEM signaling modulates type of Ab response



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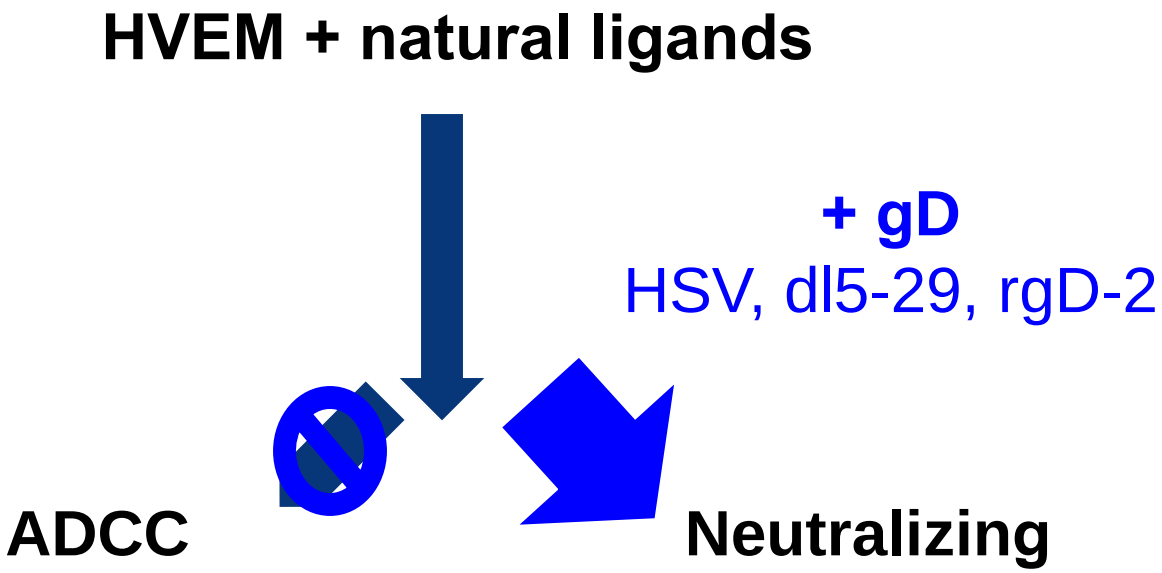

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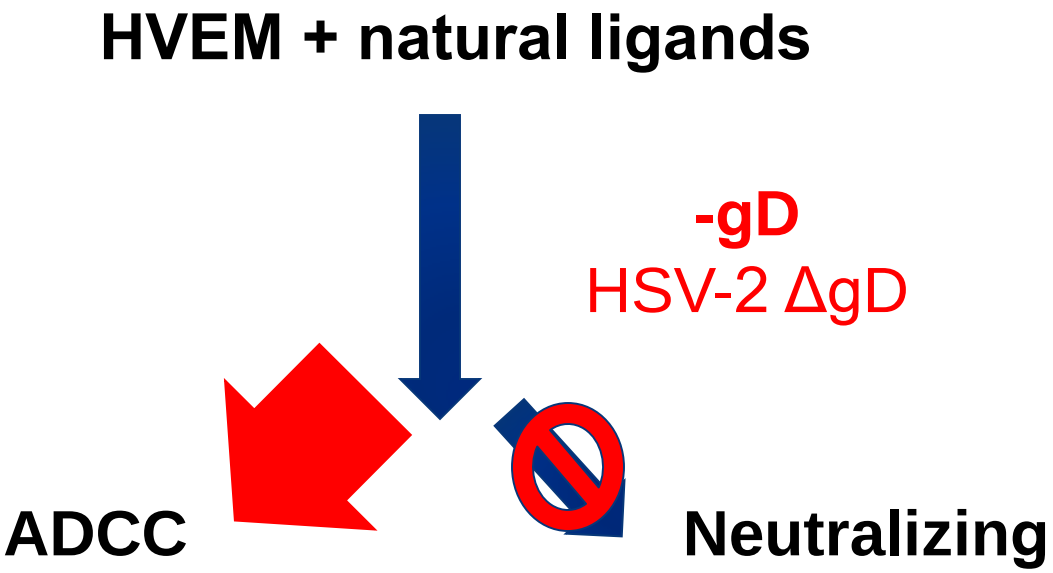

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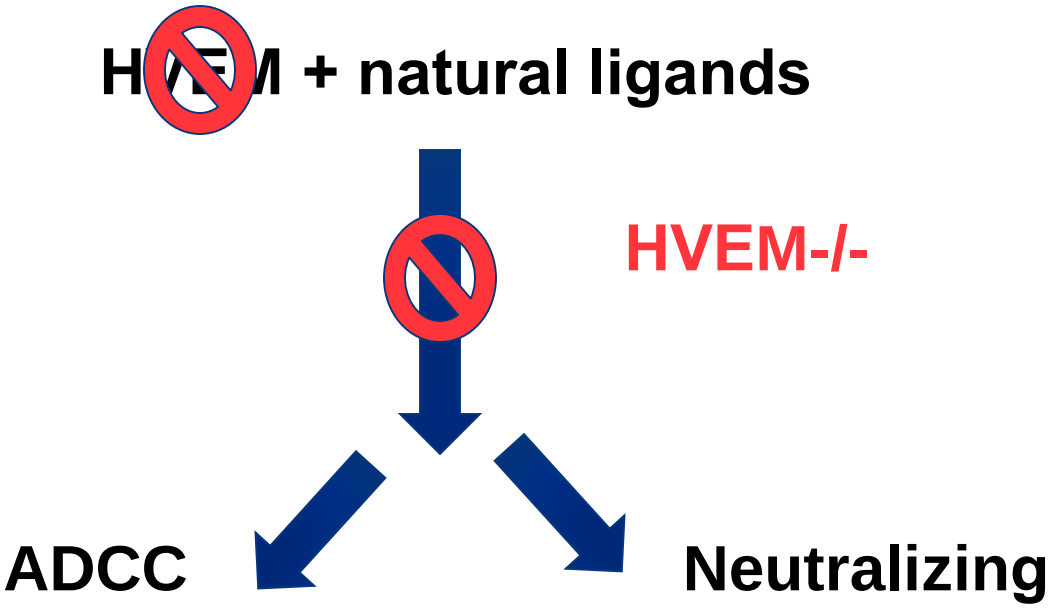

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