Transient T-cell costimulation blockade prevents immune responses and allows AAV readministration

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Immunological challenges in AAV-mediated gene transfer

Immune responses to AAV vector

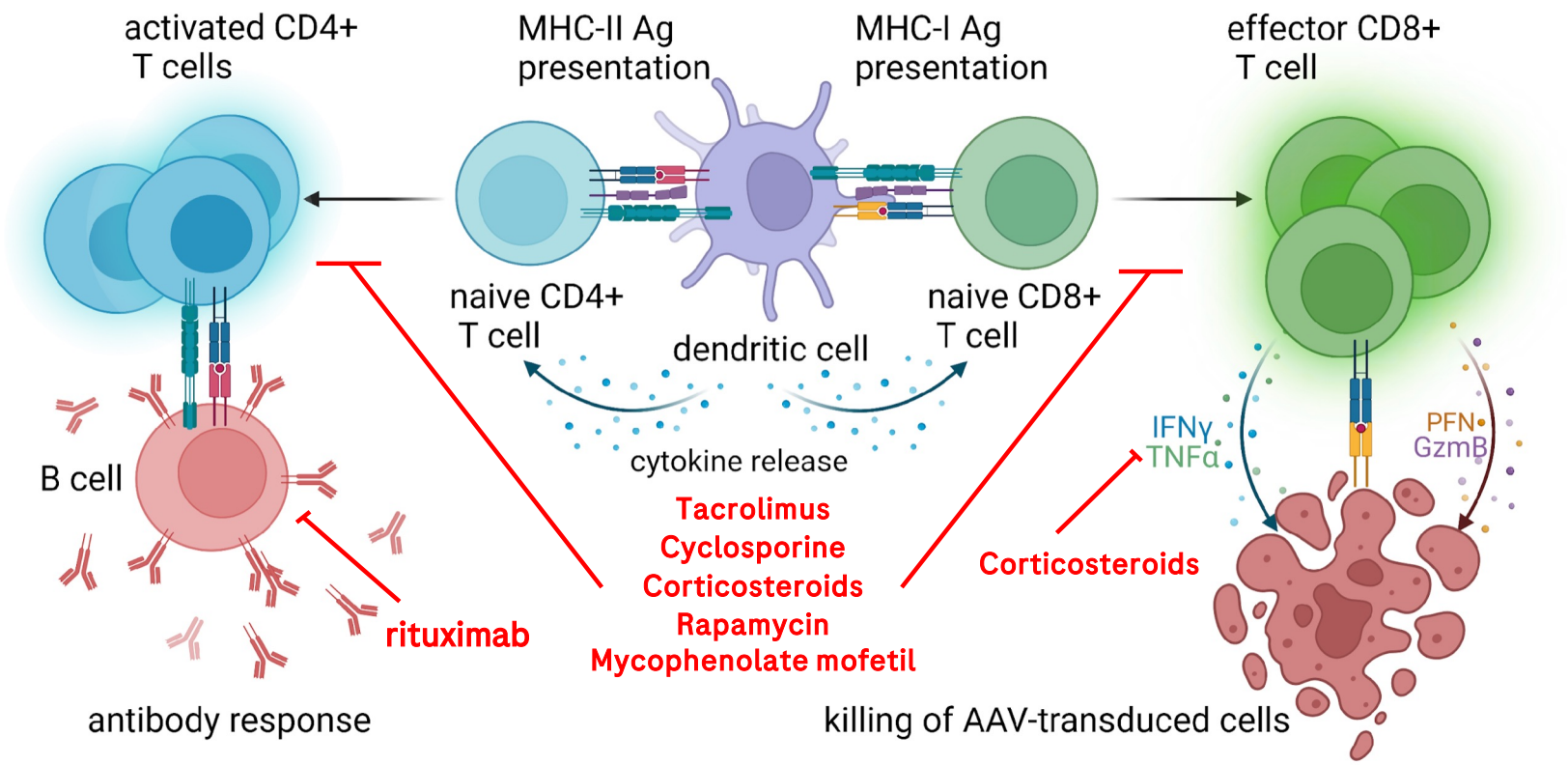
After treatment, development of anti-AAV innate and adaptive immune responses, that may induce

- ✓ **Anti-capsid antibodies**
  - Prevent re-dosing (NAbs)
  - Activate complement and mediate TMA (Thrombotic Microangiopathy)
- ✓ **Cytotoxic CD8+ T cell responses to AAV capsid**
  - Decrease the persistence of AAV-transduced cells and transgene expression, resulting in non-therapeutic PK/PD
  - Mediate liver toxicities

Immune responses to the transgene product - Patient's immune system may recognize the transgene product as "foreign"

- ✓ **Anti-transgene antibodies**
  - Lead to non-therapeutic PK/PD (i.e. Factor IX inhibitors)
- ✓ **Cytotoxic CD8+ T cell responses to transgene product**
  - Decrease transgene expression
  - Mediate tissue toxicities (i.e. T cell response to micro-dystrophin leading to immune-Mediated Myositis)

Current clinical strategies to modulate immune responses to rAAV



⇒ Need for better targeted treatments

Modified from Prasad *et al*, Human Gene Therapy 2022

Targeted immunomodulation strategies for AAV-based gene therapy

T-cell costimulation blockade with:

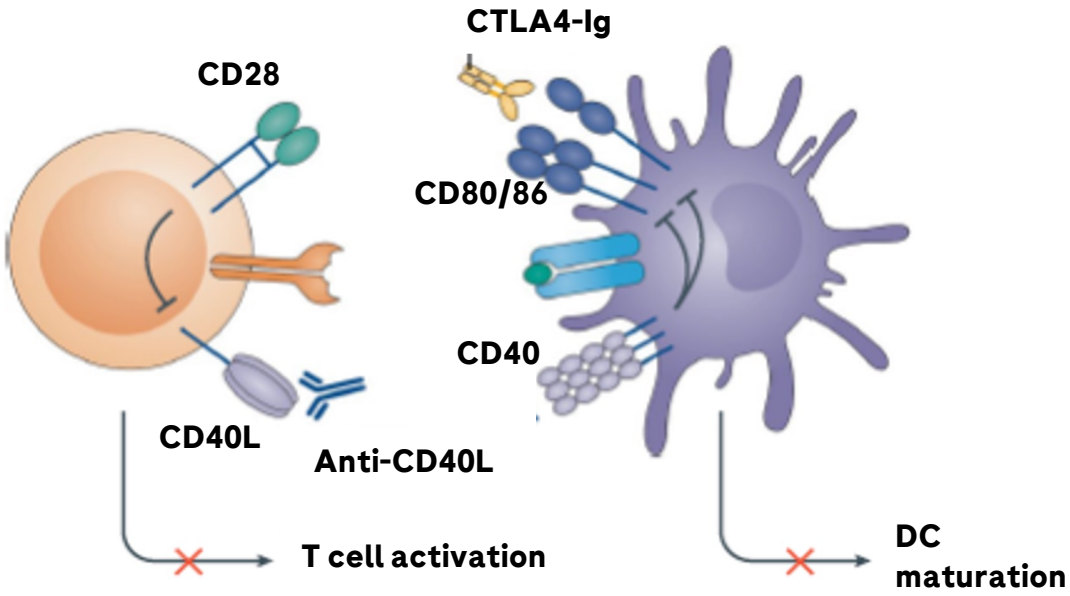
Abatacept / CTLA4-Ig

- Fc-modified to prevent effector mechanisms (ADCC, CDC, FcR binding)
- Binds to the CD80 and CD86 costimulatory molecules
- Long-lasting T cell unresponsiveness + prevention of B-cell help
- Clinically approved for arthritis indications and GVHD prophylaxis

Anti-CD40L (MR-1):

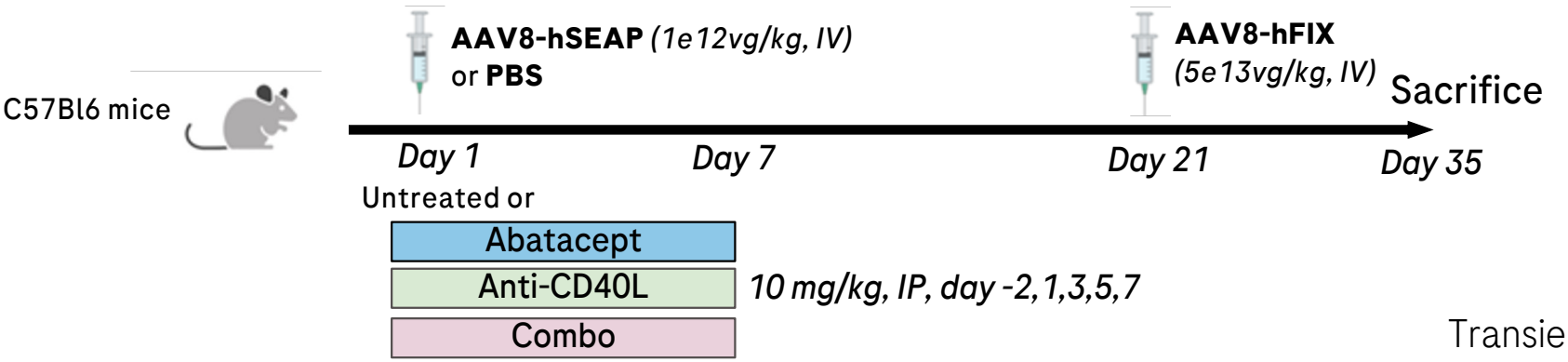
- Reacts with mouse CD40L (CD154)
- Inhibits in vitro activation of B cells by blocking the binding of CD154 cells with CD40 on T helper

CTLA4-Ig + CD40-CD40L blockade

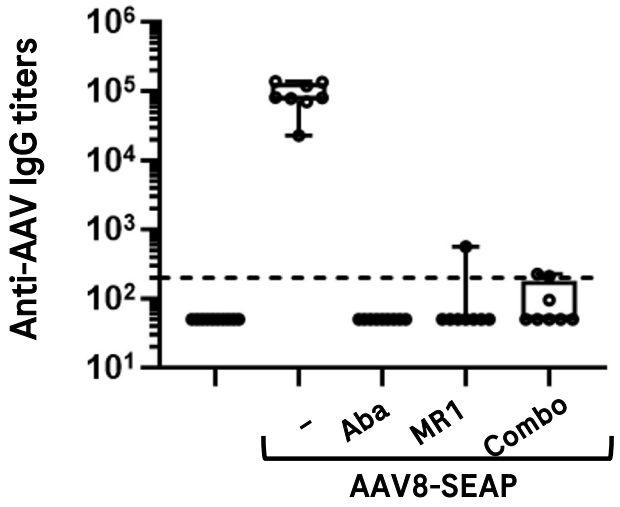


Edner NM, Carlesso G, Rush JS, Walker LSK. Targeting co-stimulatory molecules in autoimmune disease. Nat Rev Drug Discov. 2020 Dec;19(12):860-883. doi: 10.1038/s41573-020-0081-9.

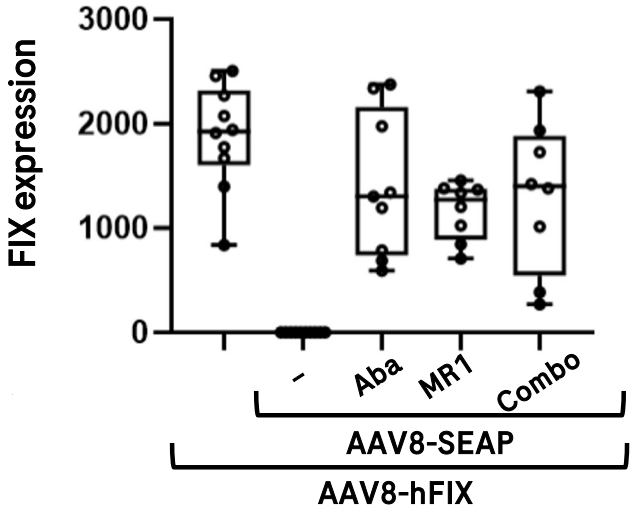
Costimulation blockade inhibits anti-AAV Ab formation and enables redosing



Day 21
2 weeks after immunosuppression



Day 35
2 weeks after AAV8 redosing

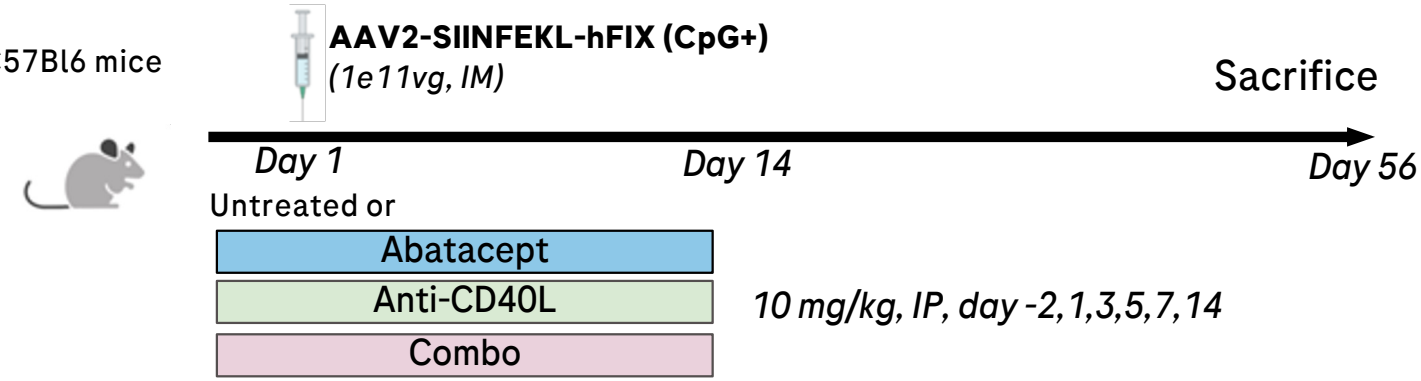


Transient treatment with abatacept inhibited anti-AAV8 antibody formation in 10/10 mice

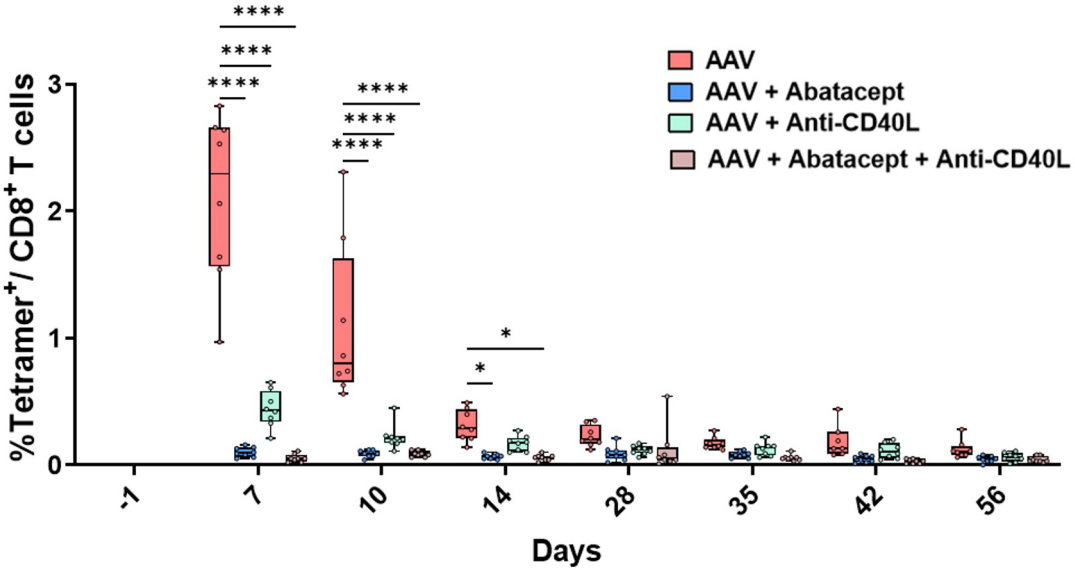
Anti-CD40L MR1 was less effective

AAV8 redosing was effective in all abatacept or/and MR1 treated mice

Transient T-cell costimulation blockade inhibits T cell response to AAV

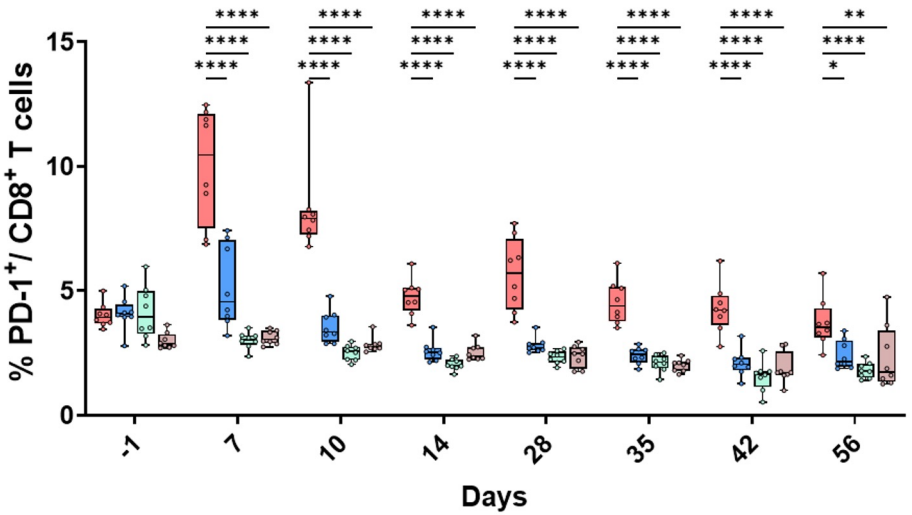


Frequency of Tet+ among CD8+ T cells in PBMCs



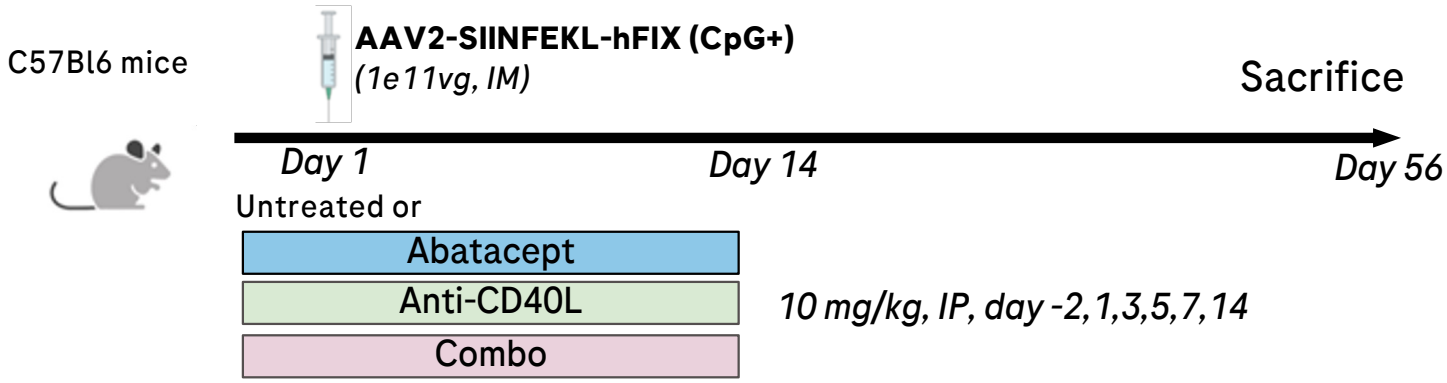
Inhibition of AAV-specific T cell proliferation

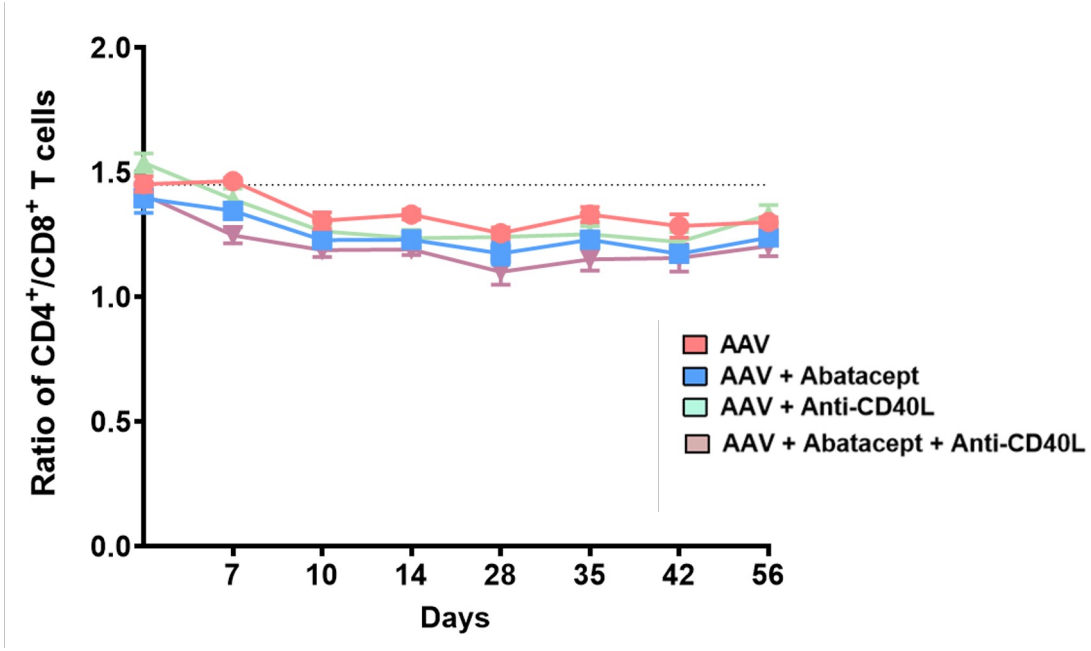
Frequency of PD1+ among CD8+ T cells in PBMCs



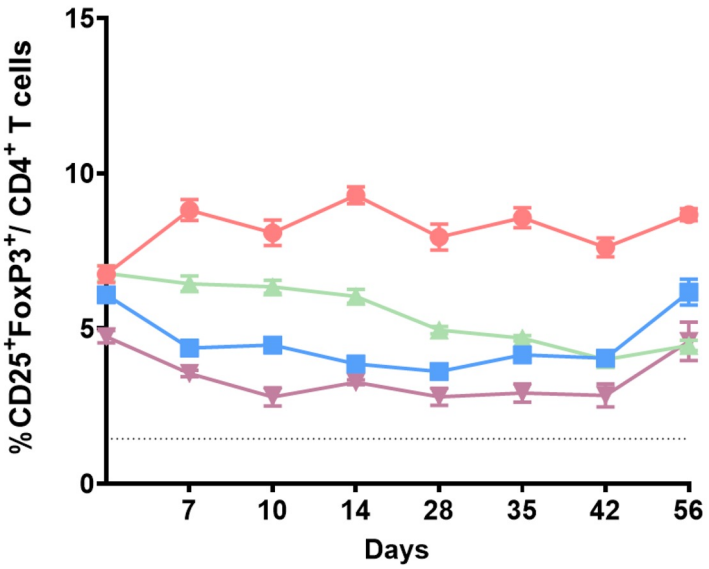
Inhibition of T cell activation

Transient T-cell costimulation blockade: effects on T cell populations



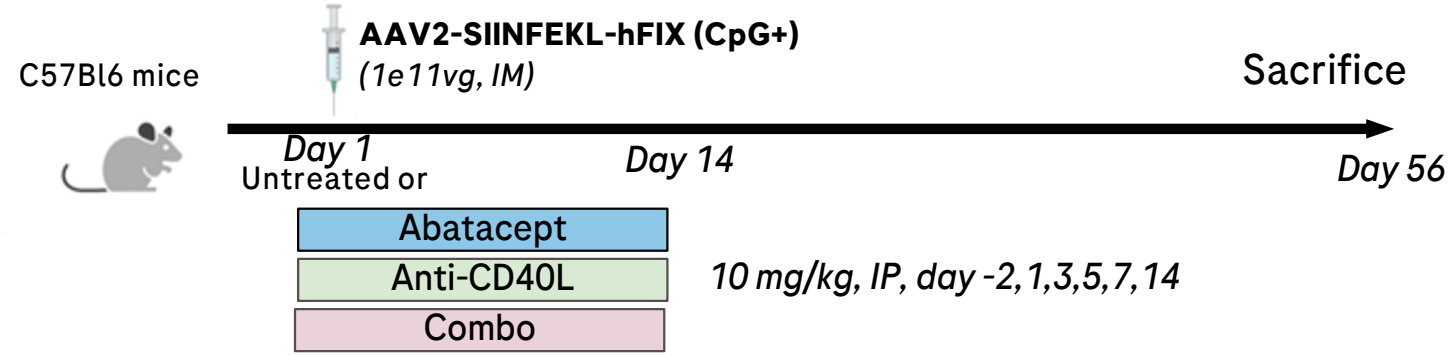


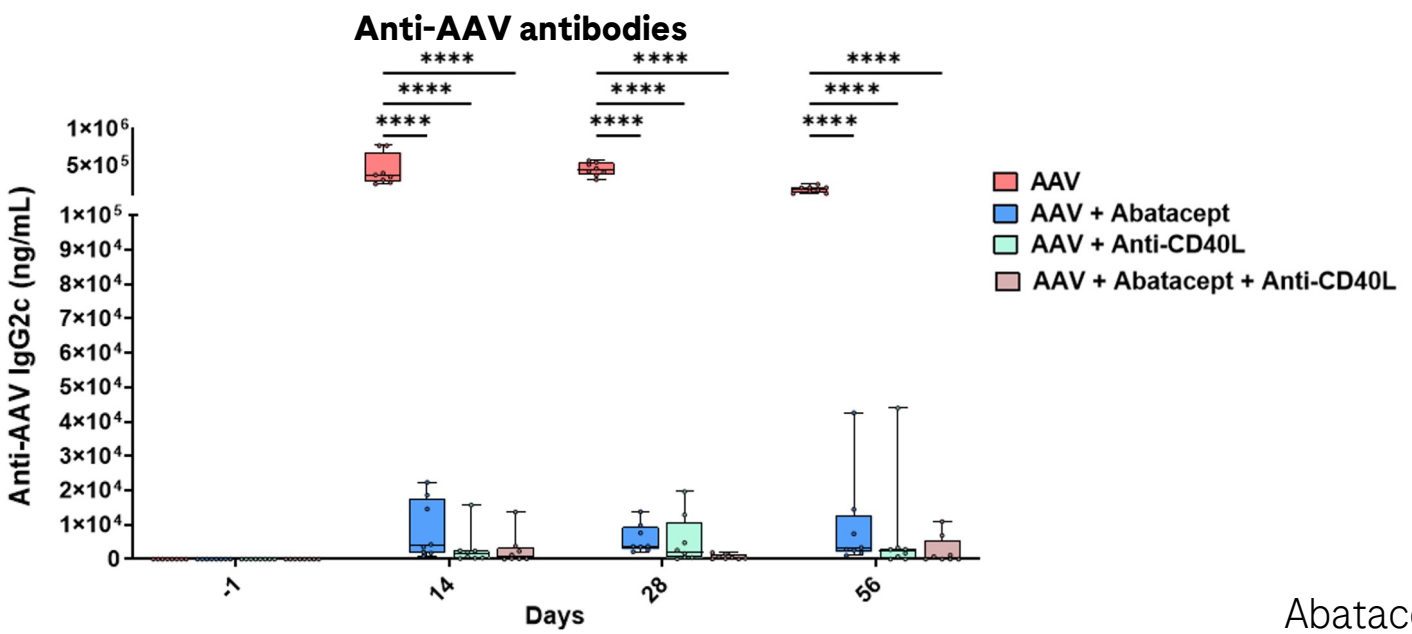
No impact on CD4/CD8 ratio



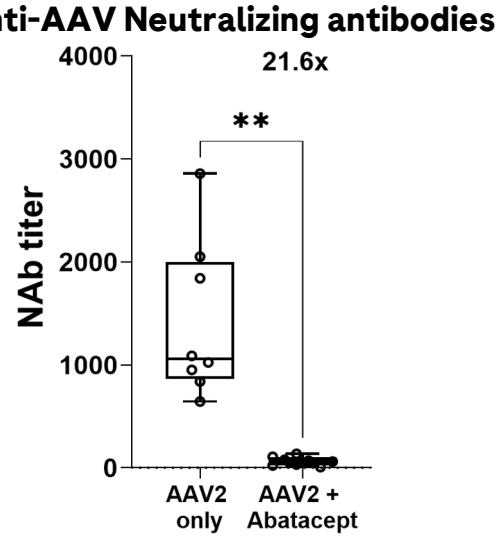
Reduction in percentage of Treg

Transient T-cell costimulation blockade inhibits anti-AAV2 antibody response



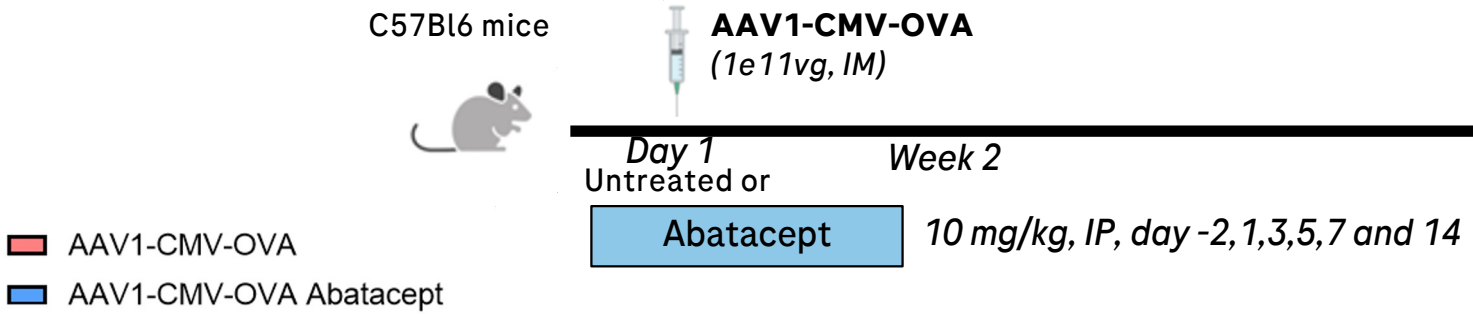


Inhibition of anti-AAV IgG2c (and IgG1) formation

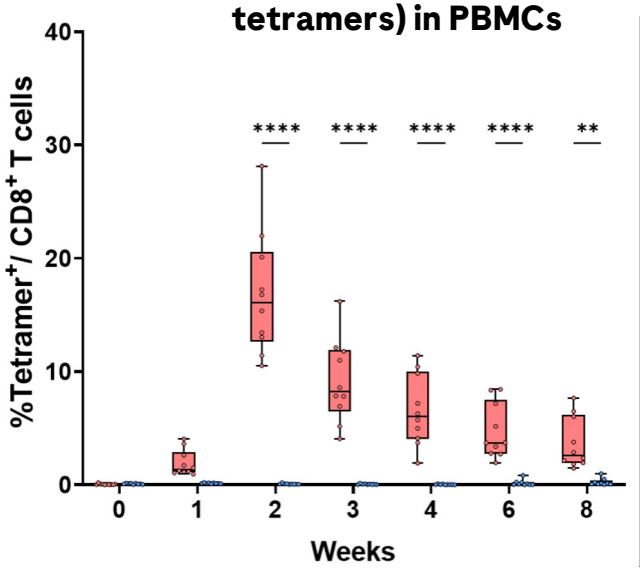


Abatacept treatment inhibits the formation of anti-AAV2 NAbs

Transient treatment with abatacept inhibits anti-transgene immune response

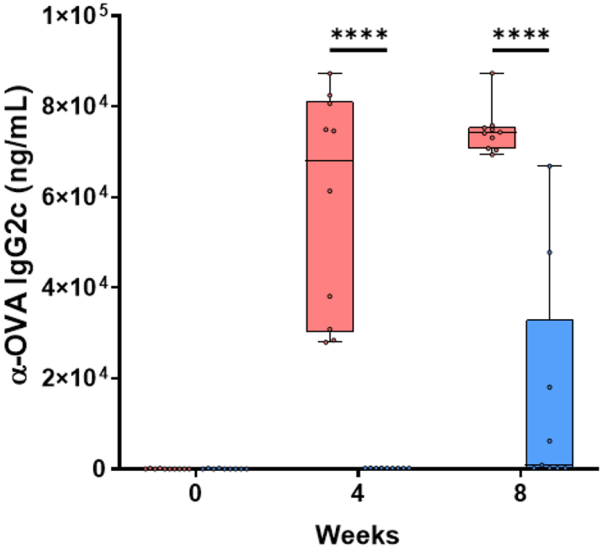


Frequency of Tet+ among CD8+ T cells (OVA tetramers) in PBMCs



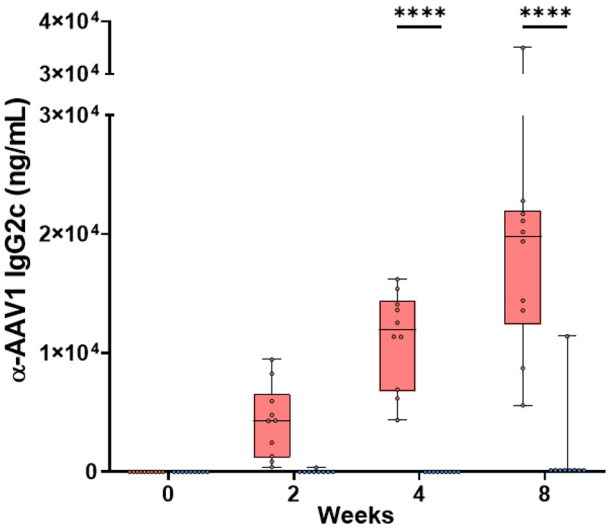
Abatacept suppresses OVA-specific CD8+ T cells

Anti-OVA antibodies



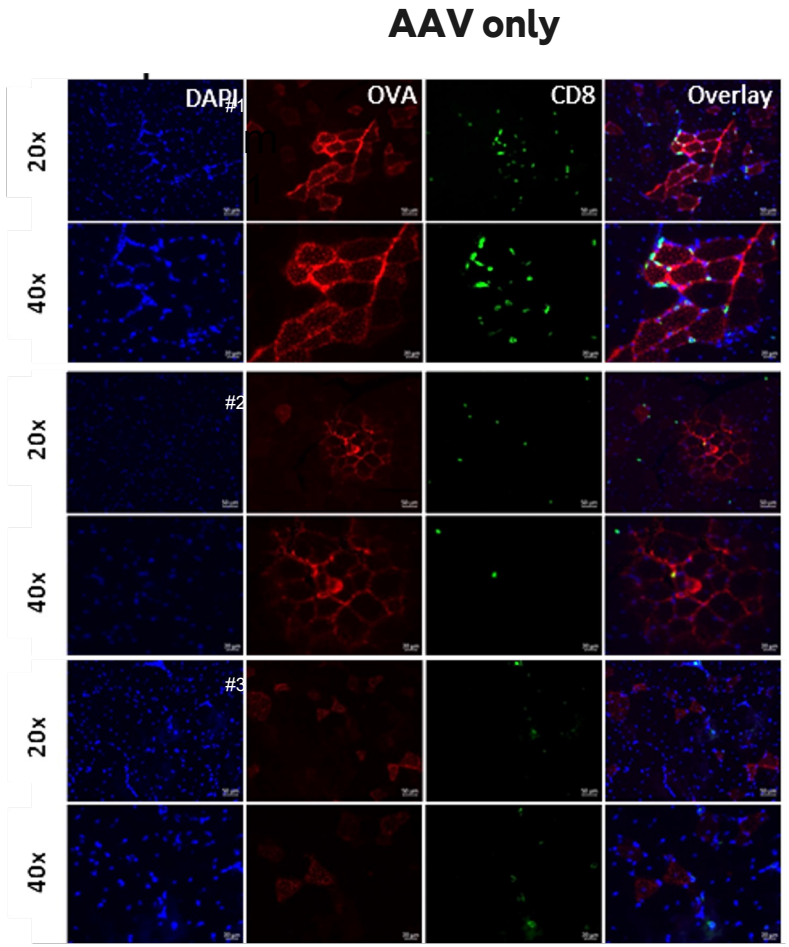
Abatacept reduces the Ab response to OVA transgene

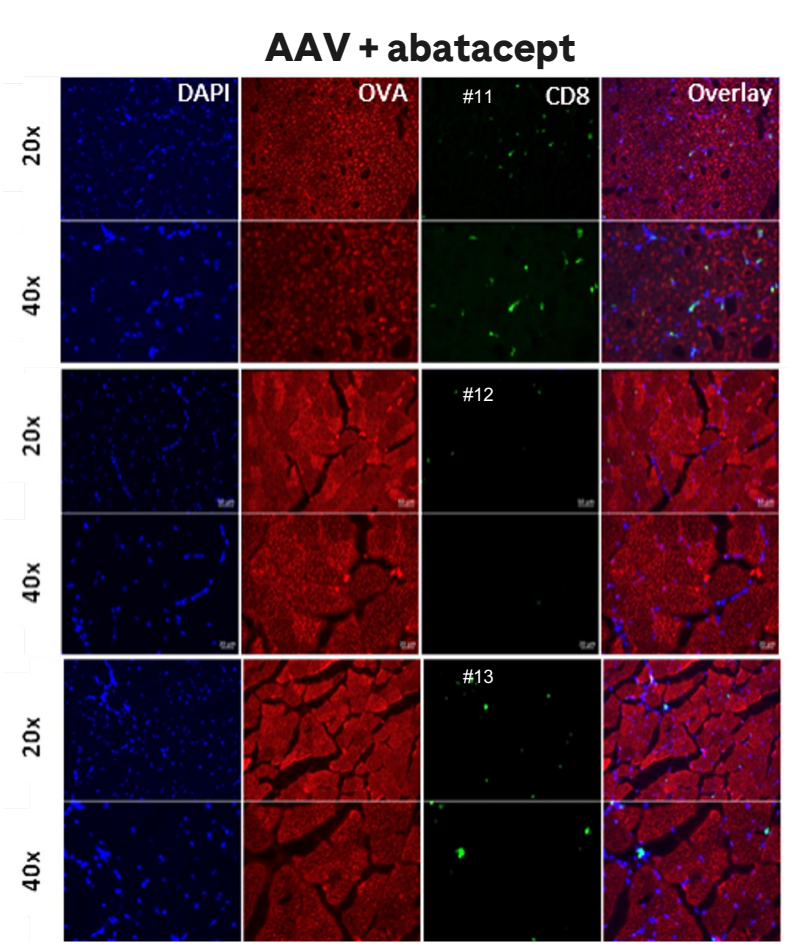
Anti-AAV antibodies

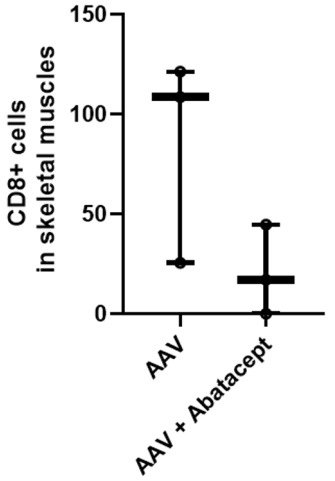


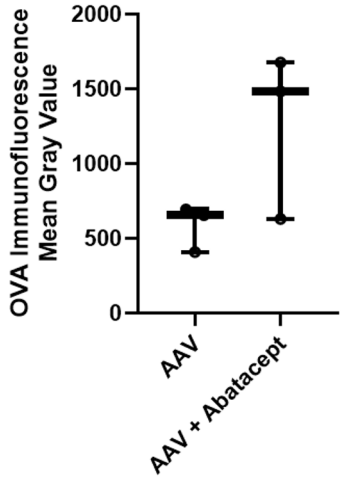
Abatacept inhibits the Ab response to AAV1 capsid

Transient treatment with abatacept inhibits anti-transgene immune response









Abatacept reduces CD8+ T cell infiltrates in muscle

Abatacept improves OVA expression in muscle cells

Transient costimulation blockade at the time of AAV dosing to enable safe and efficient gene transfer

- ✓ **Costimulation blockade with abatacept or anti-CD40L suppressed antibody responses** to three different AAV serotypes (AAV8, AAV1 or AAV2), resulting in almost full inhibition of NAb formation after AAV1 or AAV2 dosing through the IM route, opening the possibility to
  - –> mitigate complement activation and TMA
  - –> redose AAV

- ✓ **CD8+ T cell responses to AAV capsid were most efficiently suppressed by abatacept**, which may
  - –> prevent immune-mediated liver toxicities
  - –> improve transgene expression

- ✓ **Transient prophylactic treatment with abatacept can mitigate both humoral and cellular immune responses to the AAV-encoded transgene product**, which may
  - –> prevent immune-mediated tissue toxicities
  - –> prevent inhibitor formation to the transgene product

Abatacept shows promising activity in preclinical settings and can be repurposed for gene therapy indications

Acknowledgements

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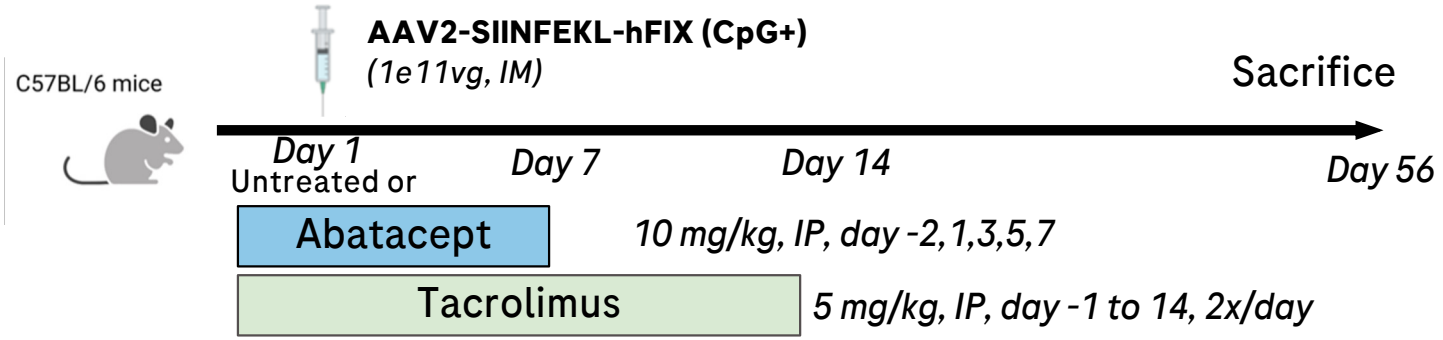
Doing now what patients need next

Abatacept is more efficient than Tacrolimus



Both transient IS treatment inhibited proliferation of AAV-specific T cells

Only abatacept treatment inhibited anti-AAV IgG2c (and IgG1) formation