**Introduction**

- CD8+ T cells in chronic hepatitis B virus (HBV) infection are limited by progressive impairments of their functions.
- Herpes Simplex Virus gD protein (gD[50]), when expressed as a fusion protein with target antigens, acts as an immunodominant HIV-1 gp120 antigen.
- Enhances early CD8+ T cell activation resulting highly potent and durable antigen-specific CD8+ T cell responses.
- Broadens T cell responses to sub-dominant epitopes, which are more resistant to impairments by chronic HBV virus exposure.

**Vaccine Constructs**

- Frequencies and phenotypes of CD8+ T cells in C57Bl/6 mice (n=8) were challenged intravenously via their tail vein with 1x10^9 viral genomes (vg) of AAV8-1.3HBV. They were subsequently vaccinated with 5x10^9 viral particles (vp) of AdC6-gDPolN. 9 weeks after vaccination in HLA-A2-tg mice, functional CD8+ T cells to one immunodominant epitope within PolN were tested for by flow cytometry.

**Methods**

**Vacine Constructs**

- The N-terminal of Pol (of Pol[50]) was genetically fused into gD and inserted into either AdC6 or AdC7, two serologically distinct adenoviral vectors (Ex: AdC6-gD plus PolN[488-503]).
- The two vectors are not cross-neutralized by antibodies, thereby allowing for their use in effective prime and boost regimens.

**ImmunoGnostics**

- C57Bl/6, BALB/c, and AA2-tg mice (n=3-5/group) were injected with graded concentrations of AAV8-1.3HBV and 4 weeks later received a single IM injection of 5x10^10 vp of AdC6-gDPolN. Liver lymphocytes were harvested 8 weeks later and tested by ICS for PolN-specific CD8+ T cell responses.

**Discussion**

Here we describe the impact of chronic HBV infection in an AAV8-1.3HBV vector mouse model on the magnitude, breadth, functions, and phenotypes of vaccine-induced CD8+ T cell responses. Despite months of AAV-induced HBV infection, functional CD8+ T cells to one immunodominant epitope within PolN were tested for by flow cytometry.

**Conclusions**

- Chronic HBV infection causes a reduction in CD8+ T cell responses and a shift in epitope recognition.
- If these results translate to humans, therapeutic HBV vaccines containing gD in a chronic HBV-infected human may produce de novo CD8+ T cell responses to the virus and potentially enhance immune responses needed for functional cure strategies.

**Abstract #0826**

**Glycoprotein D, a Checkpoint Inhibitor of Early T cell Activation, Broadens HBV-specific CD8+ cell Responses and Produces HBV Viral Load Declines in Preclinical Studies**

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**Results**

- **Vaccine-Induced Immunogenicity**
  - Vaccination induces robust CD8+ T cell responses, however, these responses are lower by ~35% in AdC6-gDPolN-treated mice (No AAV/AAV (median values) - Week 2: 2 x 10^7 IFN+ T cells/cell; Week 4: 2 x 10^7 IFN+ T cells/cell; P<0.0001).

- **Vaccine-Induced Changes in Serum HBV DNA Viral Loads**
  - Despite months of AAV-induced HBV infection, functional CD8+ T cells to one immunodominant epitope within PolN were tested for by flow cytometry.

- **Immunogenicity**
  - AdC6-gDPolN prime/AdC6-gDPolN boost increases frequencies of hepatic CD8+ T cells in C57Bl/6 mice as compared to unvaccinated animals (Fig 5A).

- **Discussion**
  - Here we describe the impact of chronic HBV infection using an AAV8-1.3HBV vector mouse model on the magnitude, breadth, functions, and phenotypes of vaccine-induced CD8+ T cell responses.

**Methods**

**Vaccine Constructs**

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