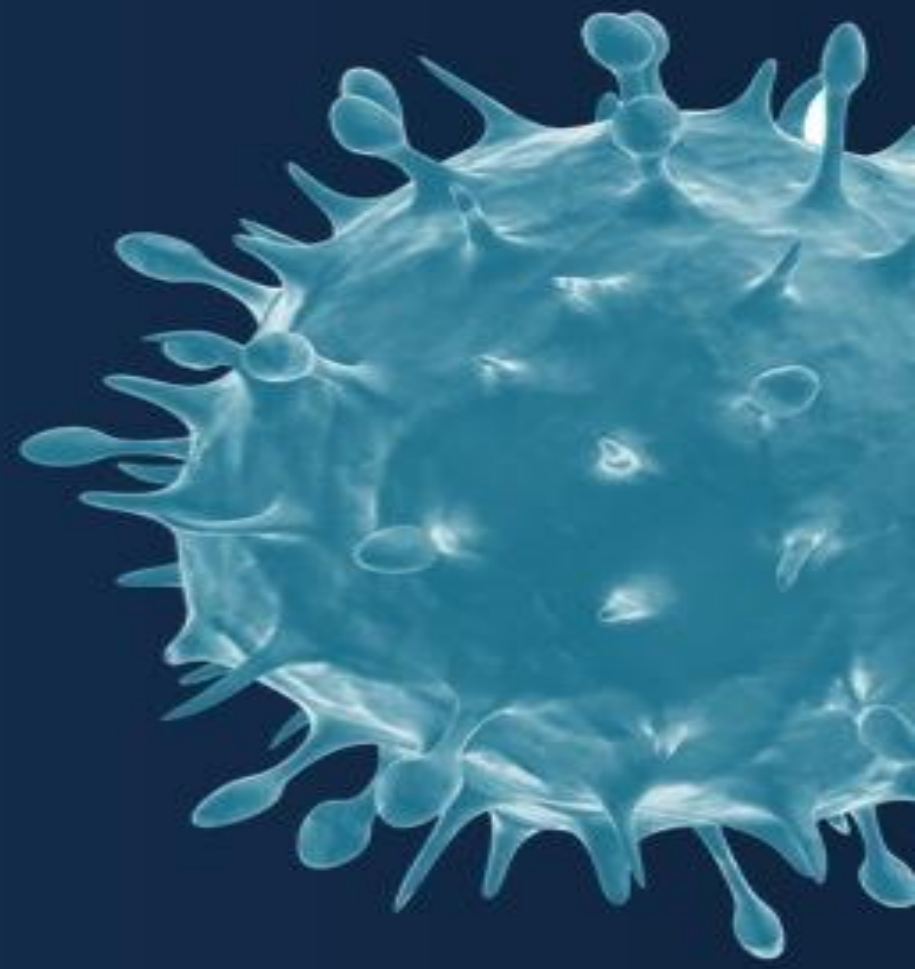
GEN-003, a Herpes Simplex Virus Immunotherapy, Elicits Significant Neutralizing Antibody and Cellular Responses in HSV-2 Seropositive Subjects



Tyler Fenske

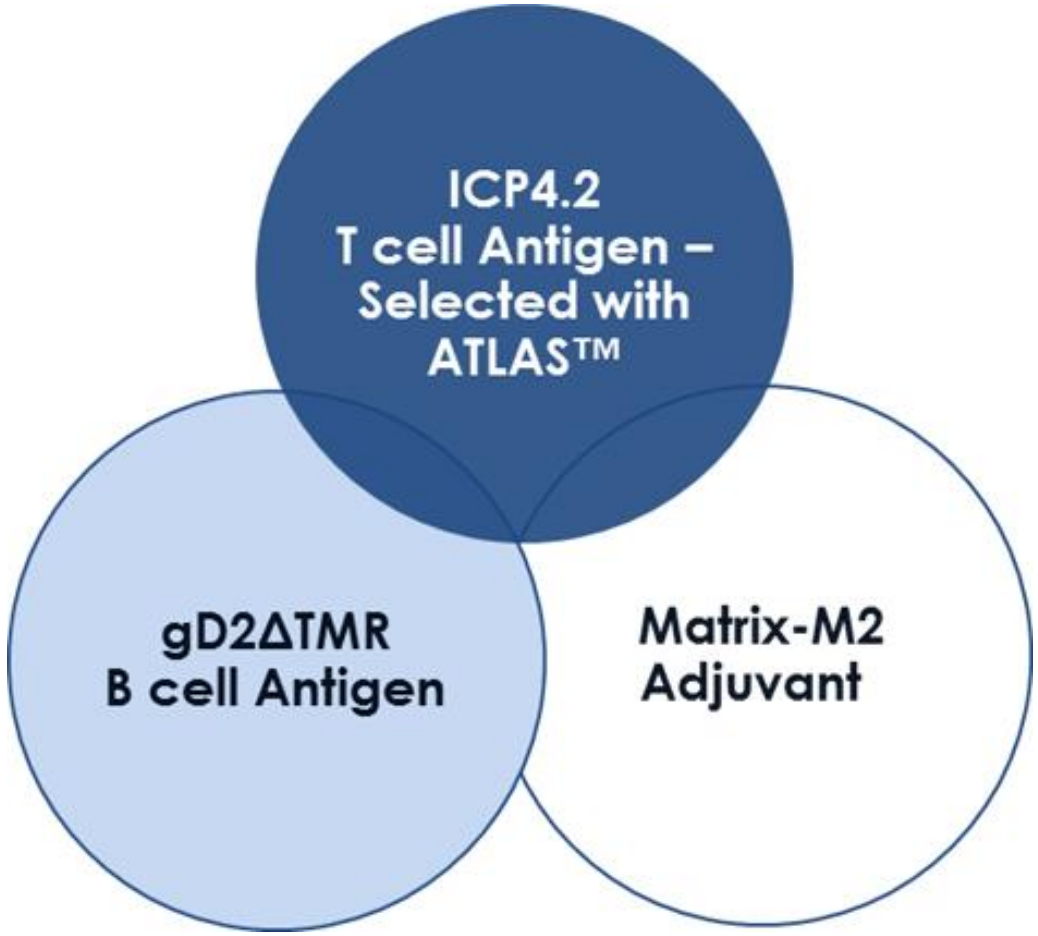
Wednesday, July 19, 2017

Prevention and Vaccines, IHW, 2017

genocea BIOSCIENCES

GEN-003: An immunotherapy for HSV-infected individuals

- An adjuvanted, protein subunit vaccine preparing to enter Phase 3
  - **ICP4.2**: fragment of infected cell protein 4 selected by ATLAS™ (antigen-screening platform)
    - An activator of both $CD4^+$ and $CD8^+$ T cells
  - **gD2ΔTMR**: transmembrane deletion mutant of glycoprotein D
    - Target of both neutralizing antibodies and T cells
  - **Matrix-M2™** (Novavax Inc.): saponin-derived adjuvant
    - Stimulates both B and T cell responses



GEN-003-003 Phase 2b Clinical Trial Study Design

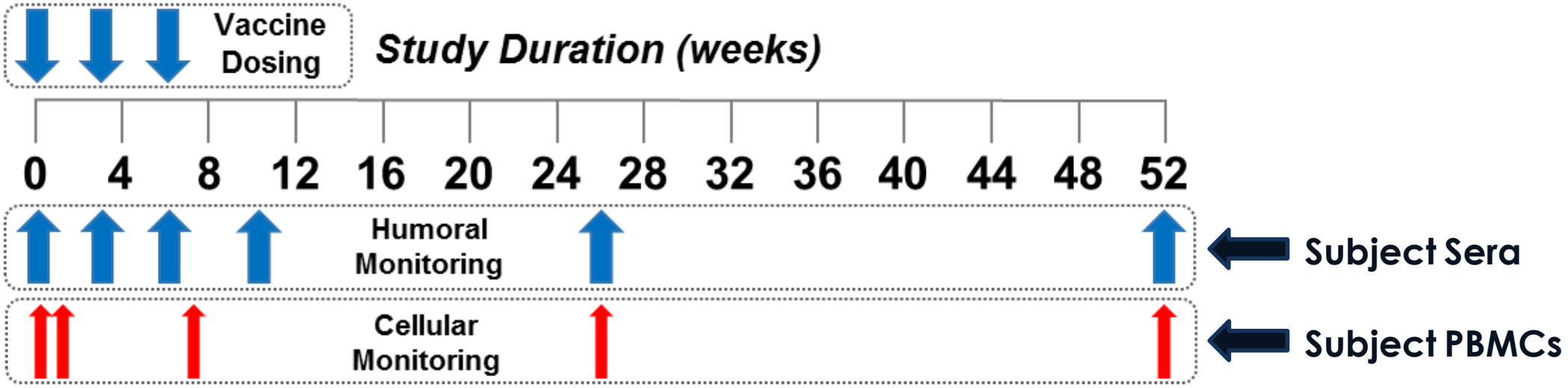
Design

- A randomized, double-blind, placebo-controlled trial evaluating a new formulation of GEN-003
  - Subjects aged 18-50 years with diagnosis of genital HSV-2 for >1 year

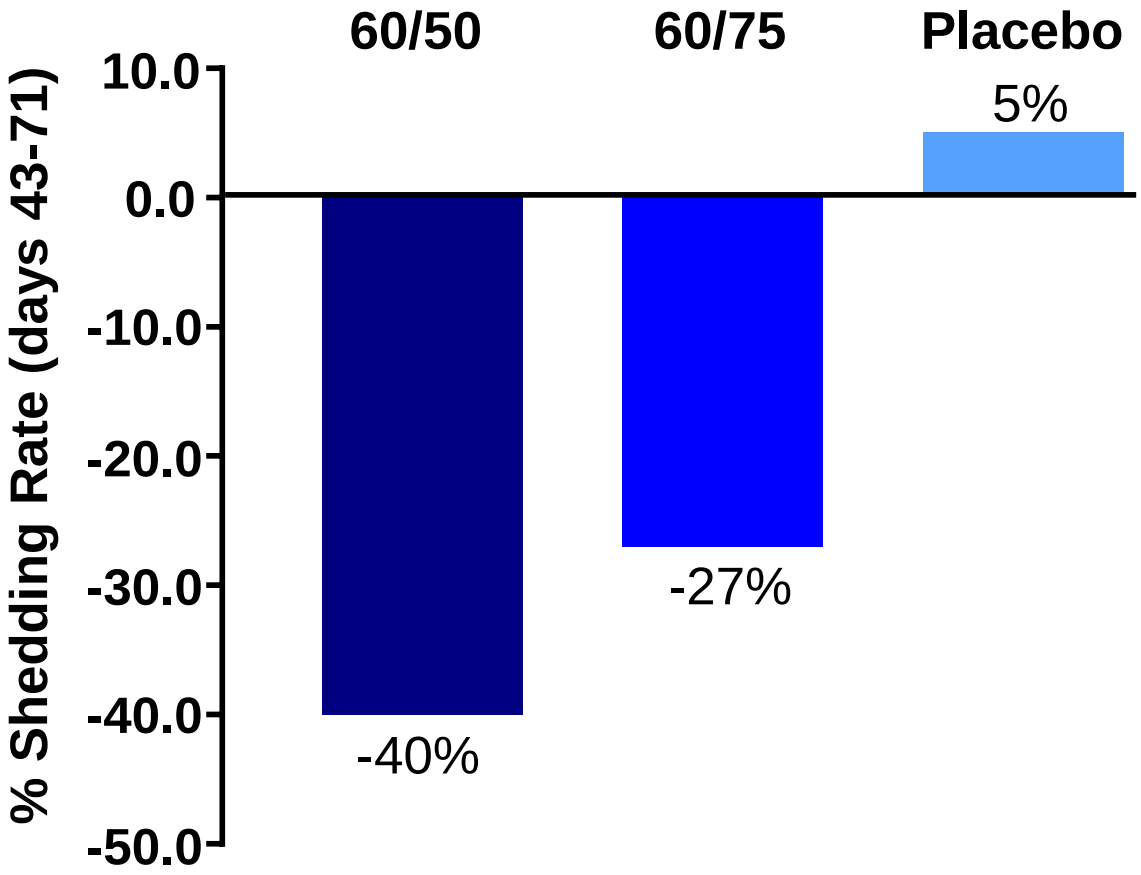
Objectives

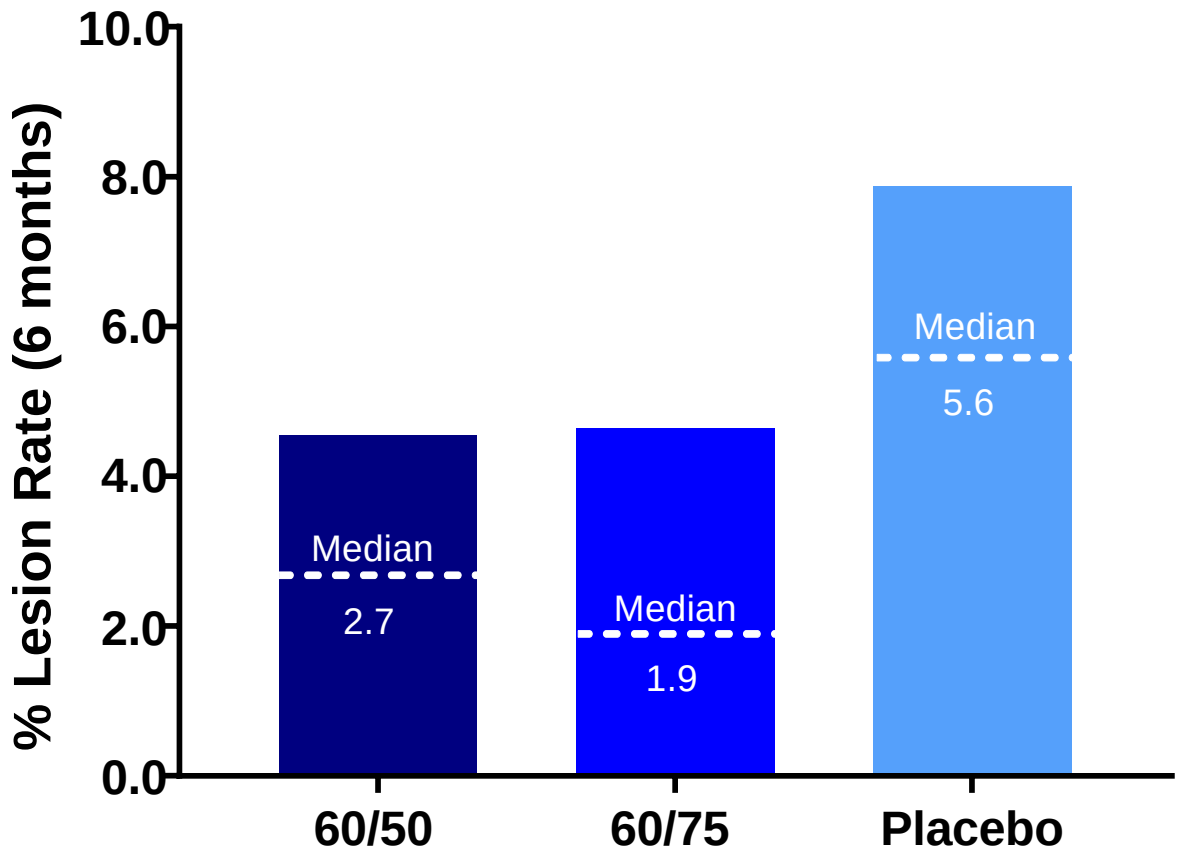
- Quantify the reduction in HSV-2 viral shedding rate post immunization
- Evaluate clinical outcomes post immunization (lesion rate and safety)
- **Analyze humoral and cellular immune responses to ICP4.2 and gD2ΔTMR**

Treatment/Control Group
Placebo
GEN-003: 60 µg antigens / 50 µg adjuvant
GEN-003: 60 µg antigens / 75 µg adjuvant



GEN-003 significantly reduced viral shedding and lesion rates



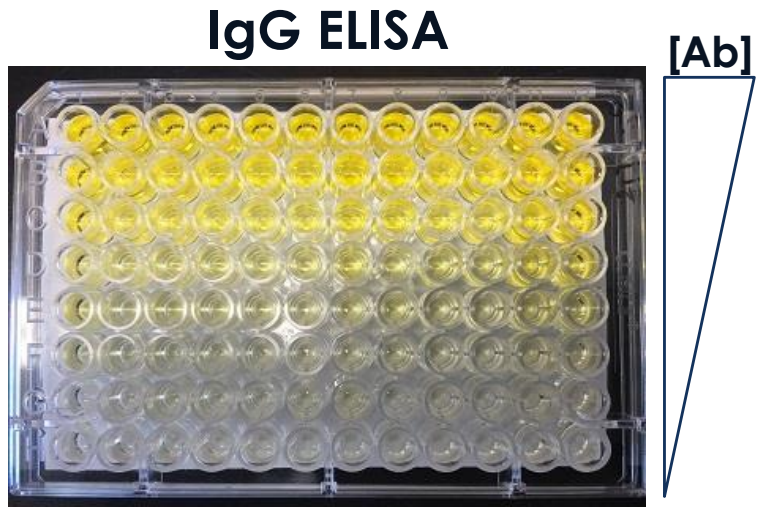


*See poster #8.31 (M. Croshier) and poster #8.25 (T. Heineman)

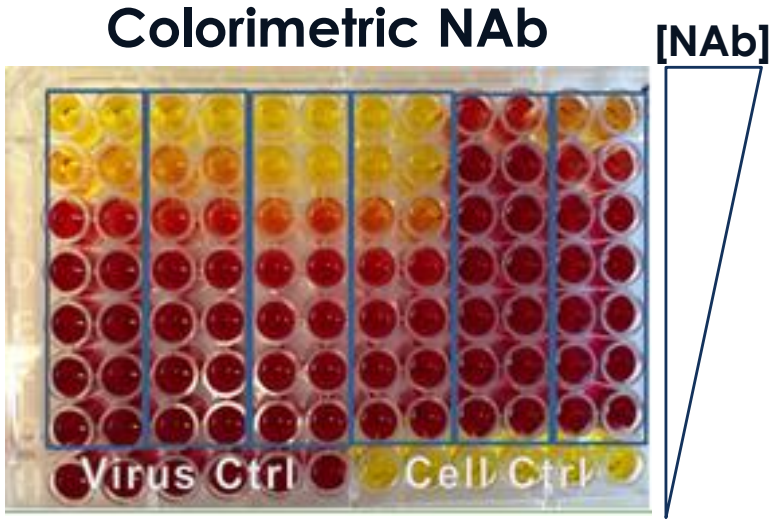
An ELISA and NAb assay are used to measure humoral immune responses

Humoral Responses

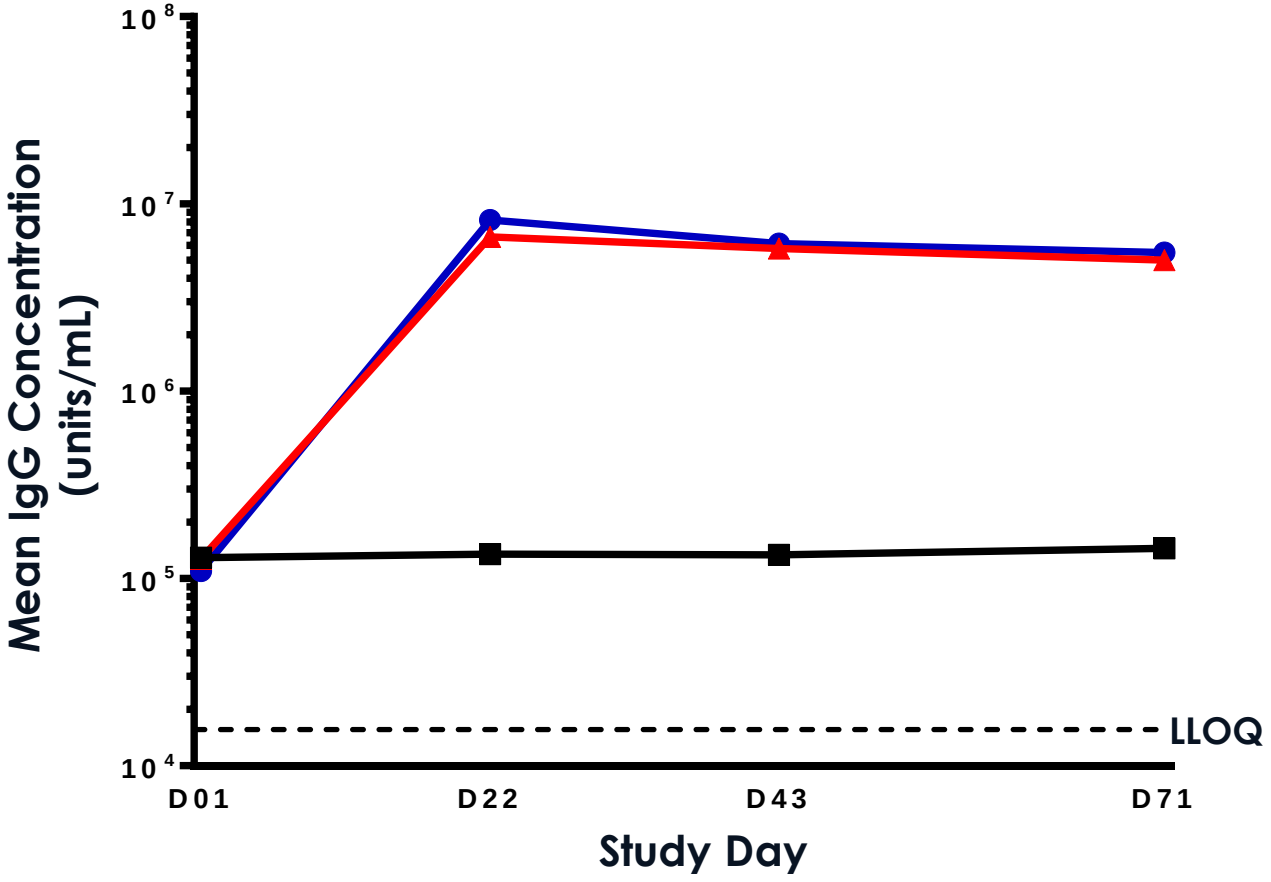
- Indirect IgG ELISA
  - Determines antigen-specific IgG titers

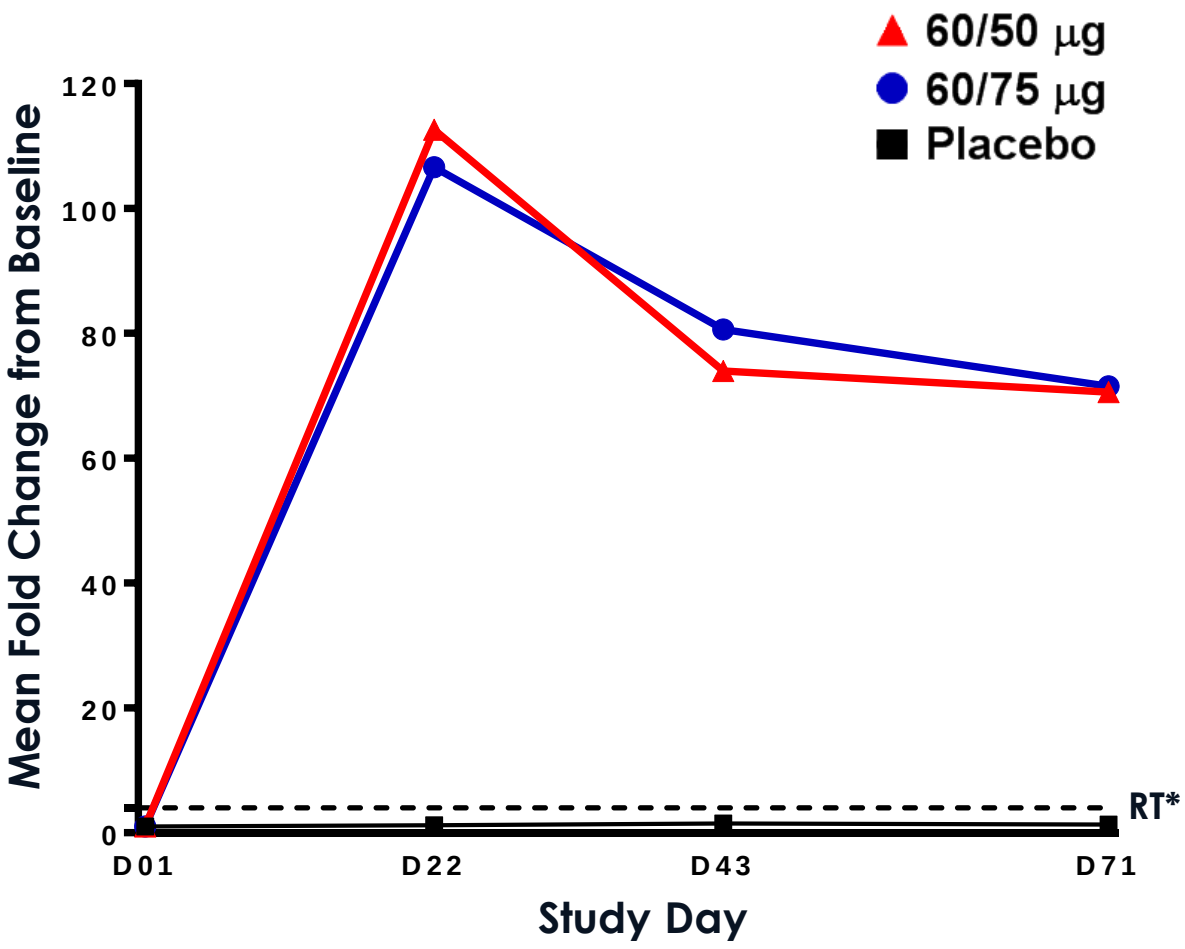


- Colorimetric Neutralizing Antibody Assay
  - Measures 50% HSV-2 neutralizing titers from human sera



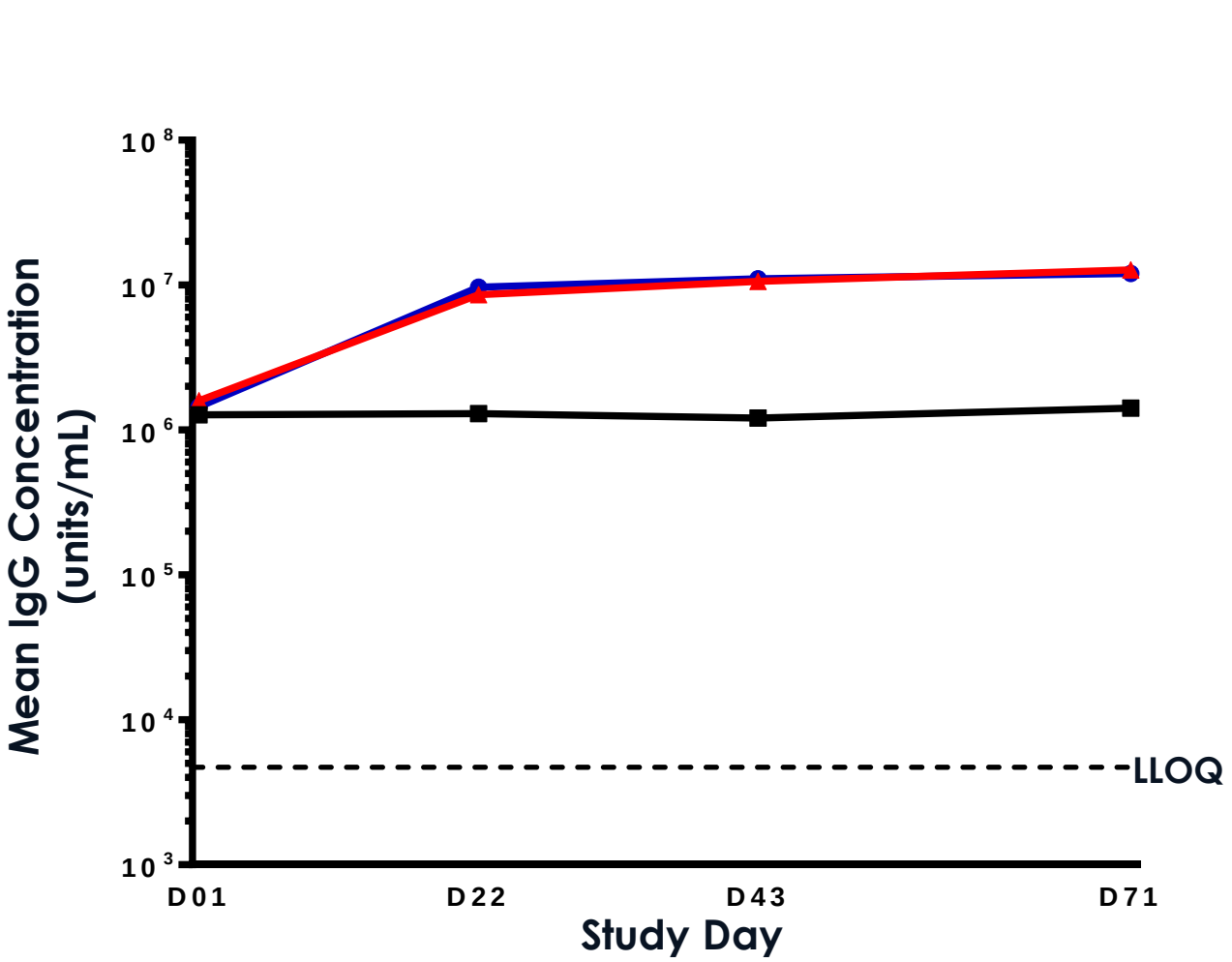
GEN-003 stimulated an increase in antibodies specific for ICP4.2

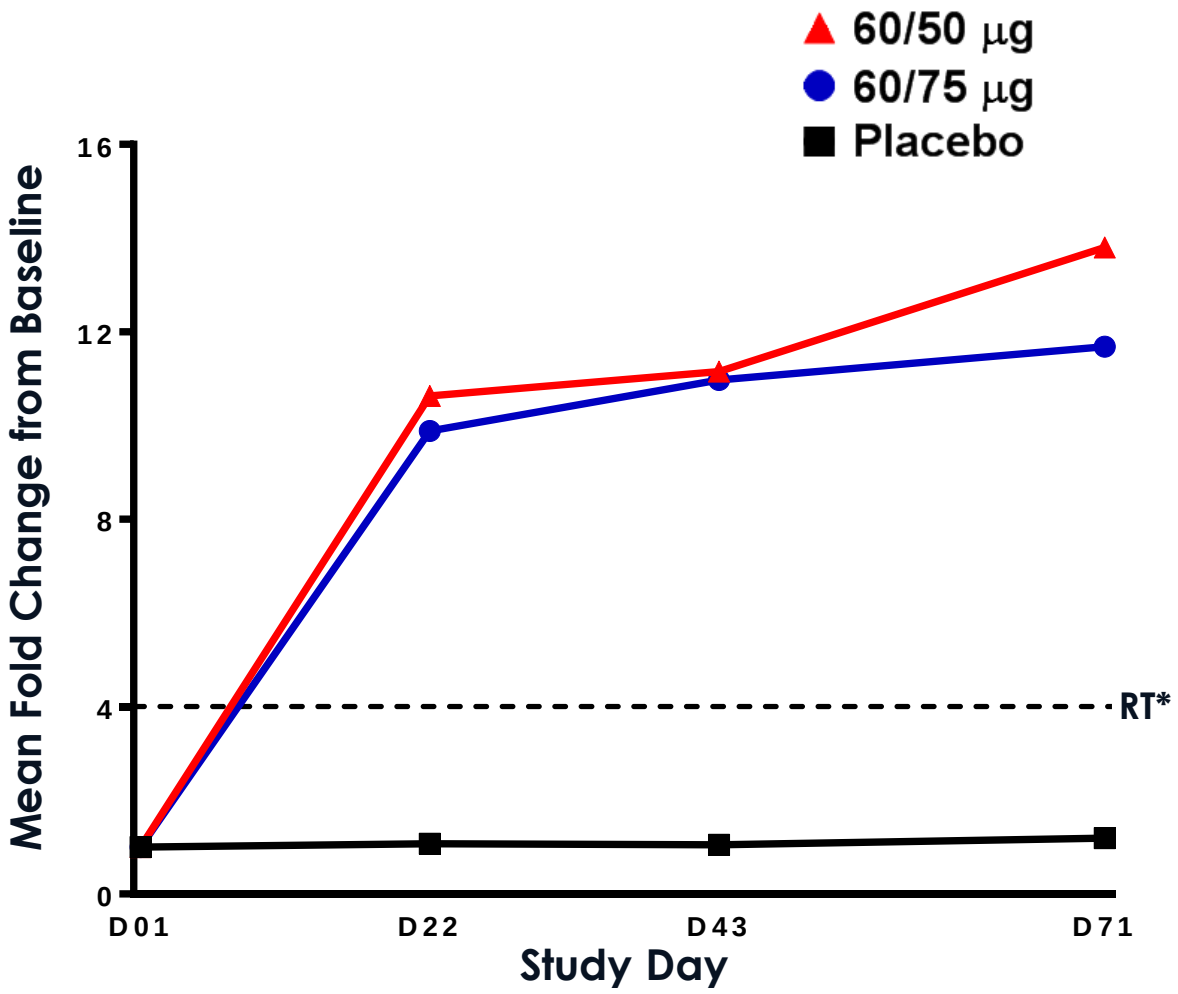




*Response Threshold

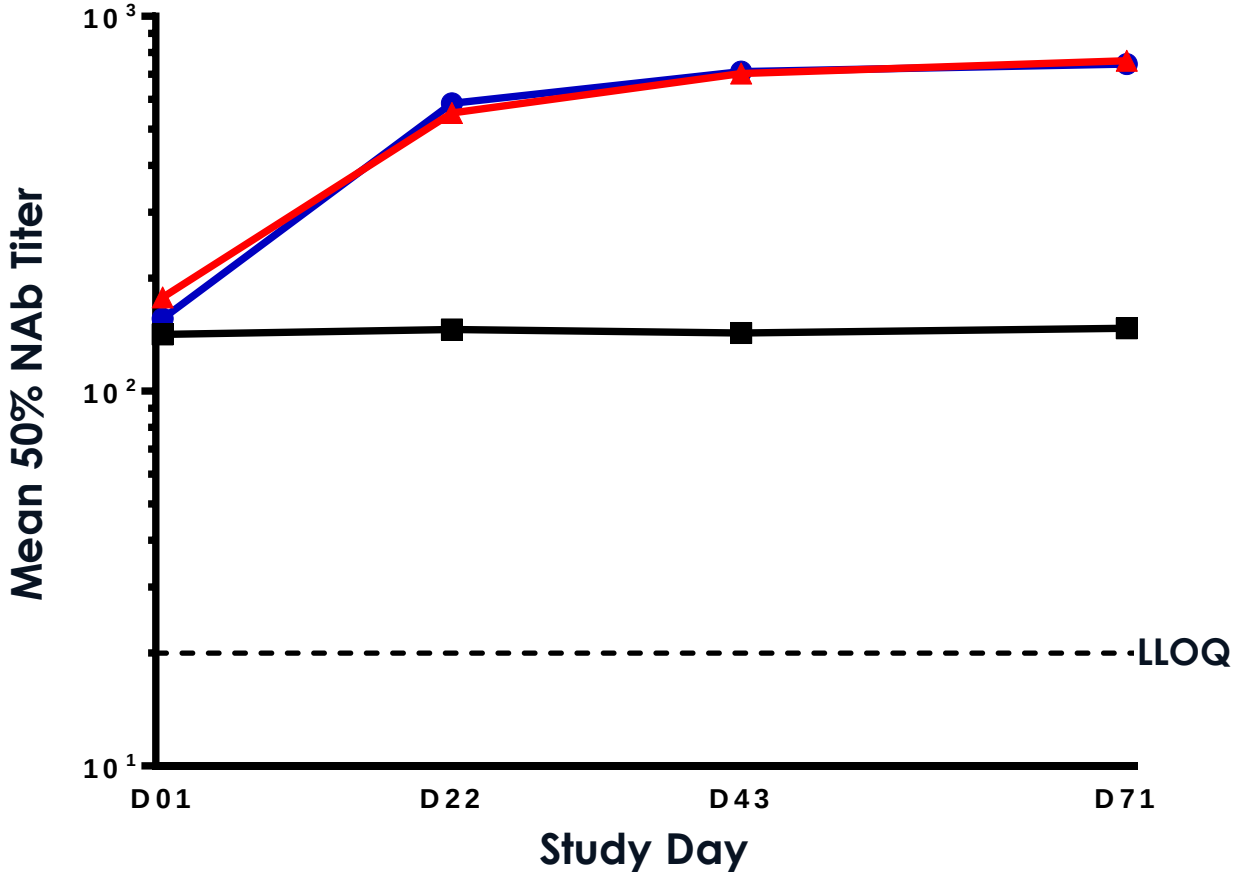
GEN-003 stimulated an increase in antibodies specific for gD2ΔTMR

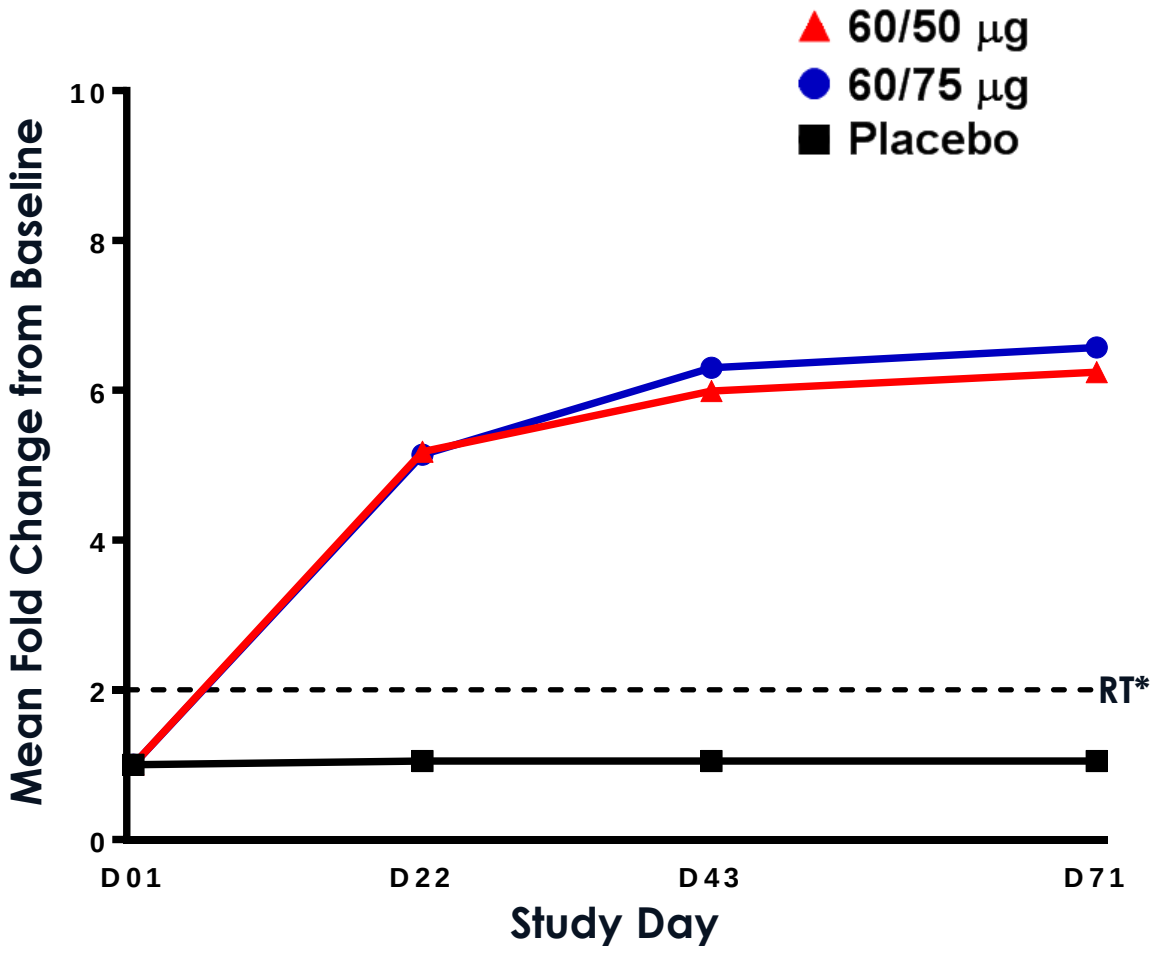




*Response Threshold

GEN-003 stimulated an increase in 50% neutralizing antibody titers

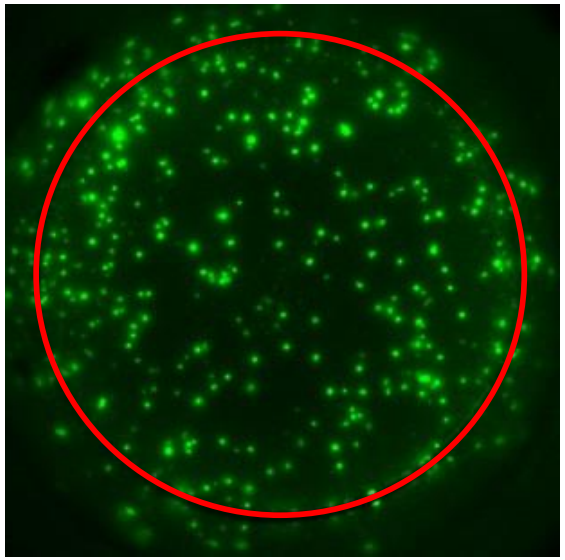




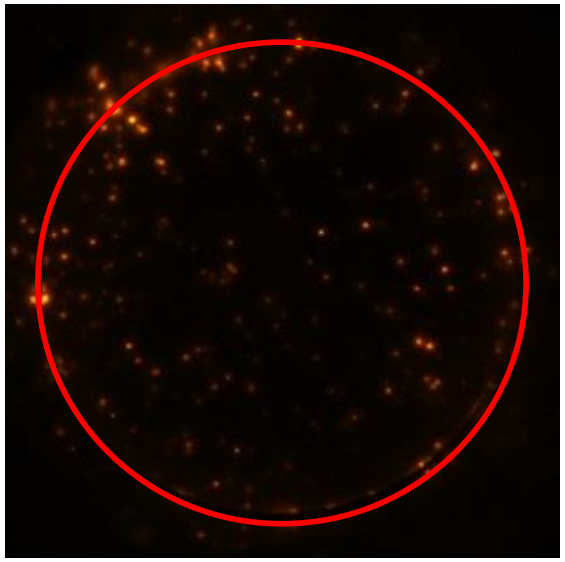
*Response Threshold

The IFN-γ/GrB Fluorospot assay was used to measure T cell responses

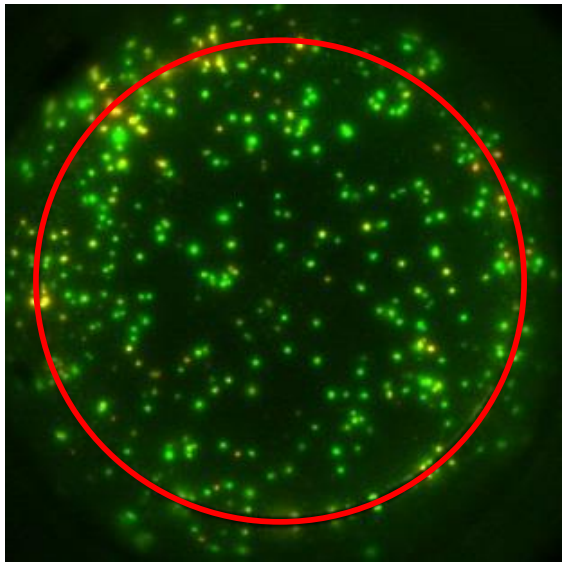
- Measures T cells that secrete IFN-γ or GrB when stimulated by ICP4.2 or gD2ΔTMR overlapping peptides
  - IFN-γ: cytokine mediating antiviral immunity
  - GrB: serine protease with cytolytic activity



IFN-γ

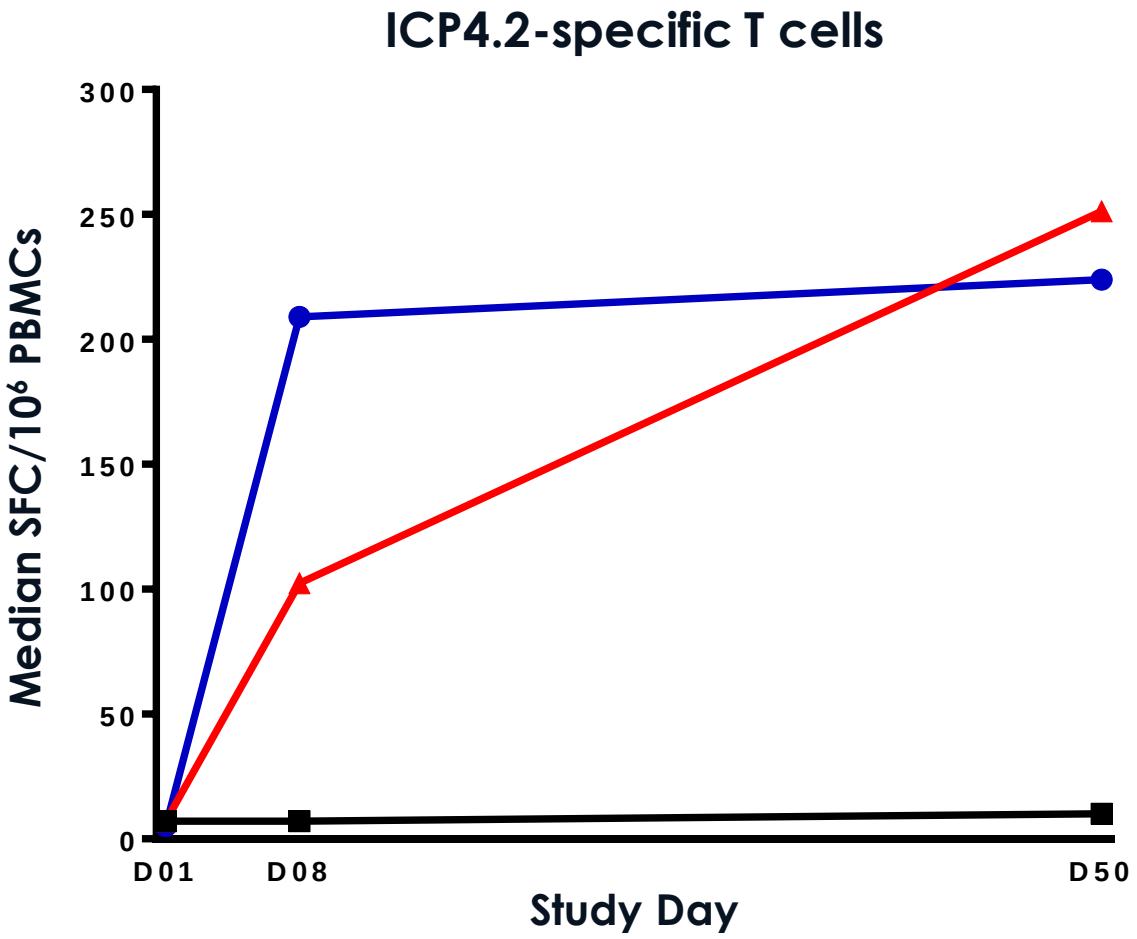


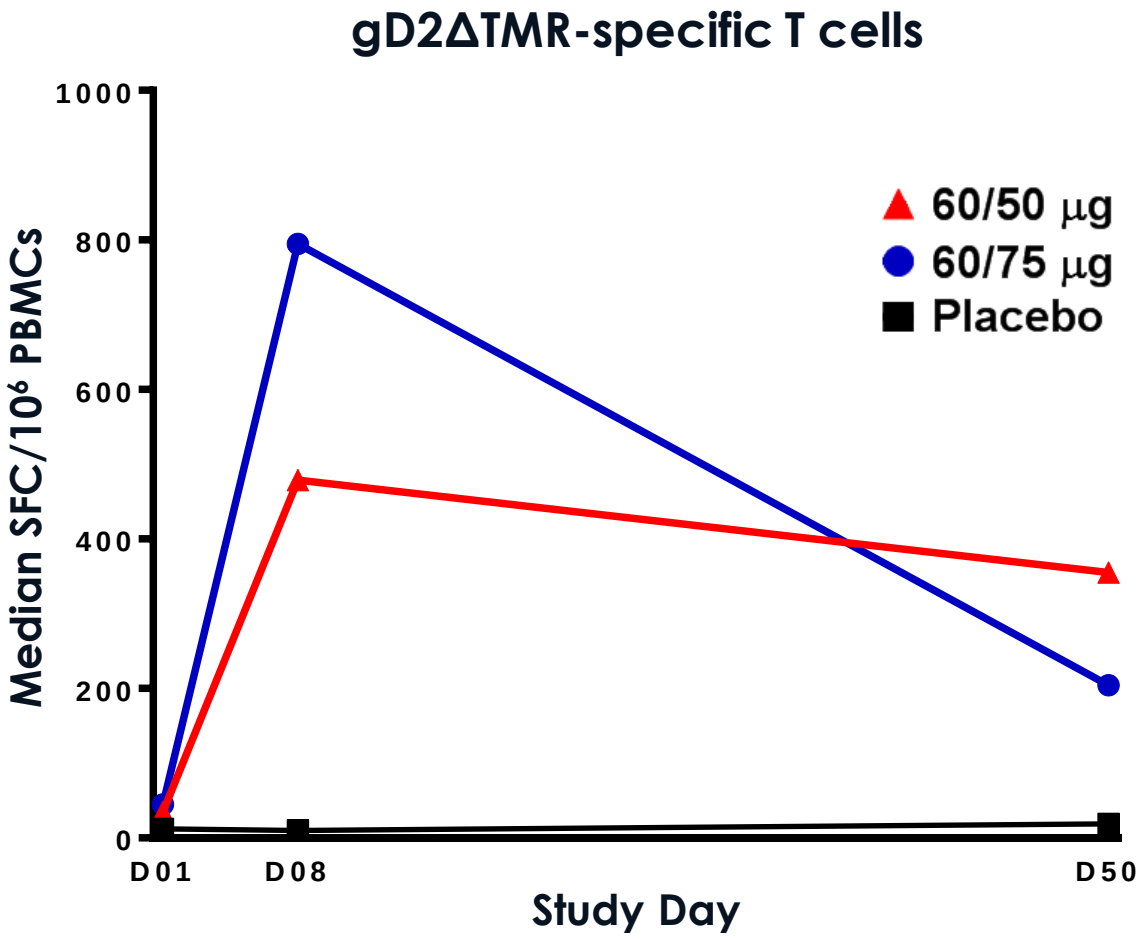
Granzyme B



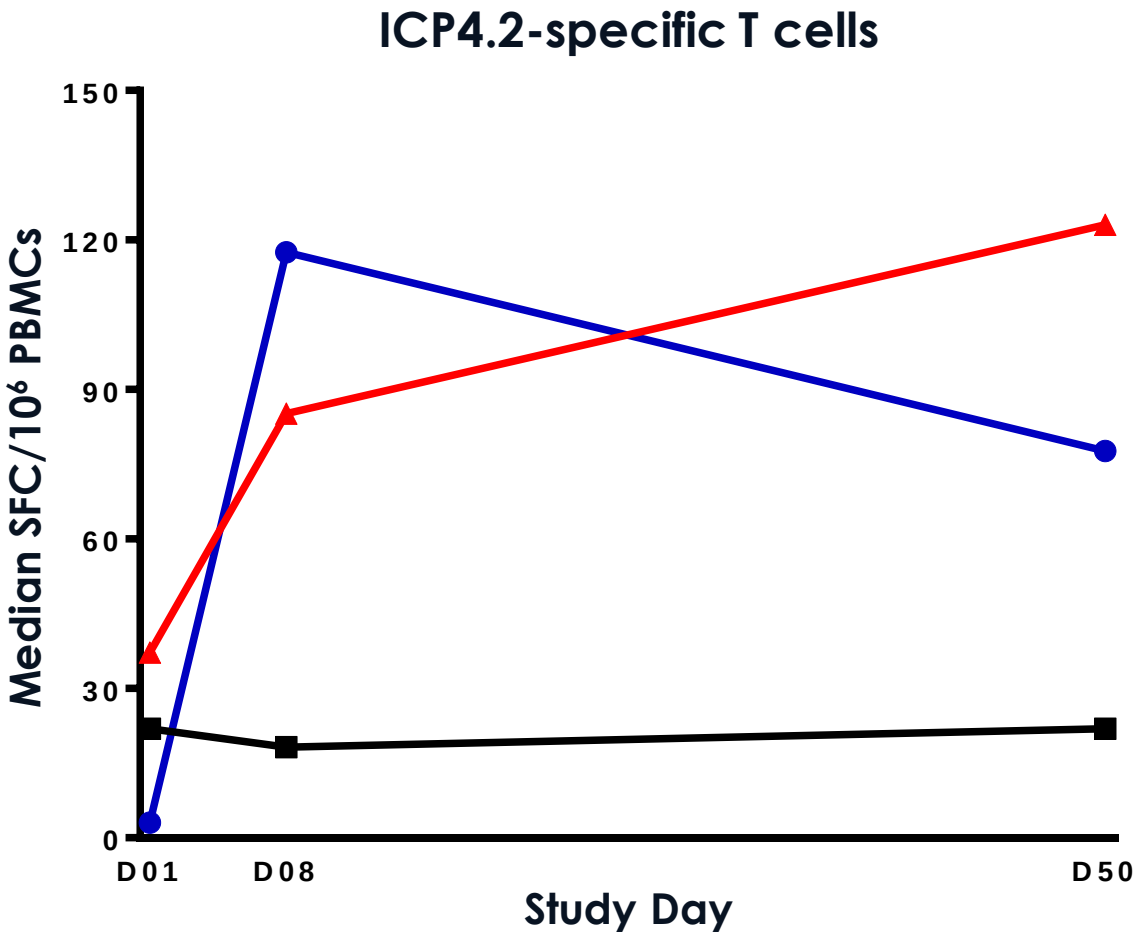
Double positive (Image overlay)

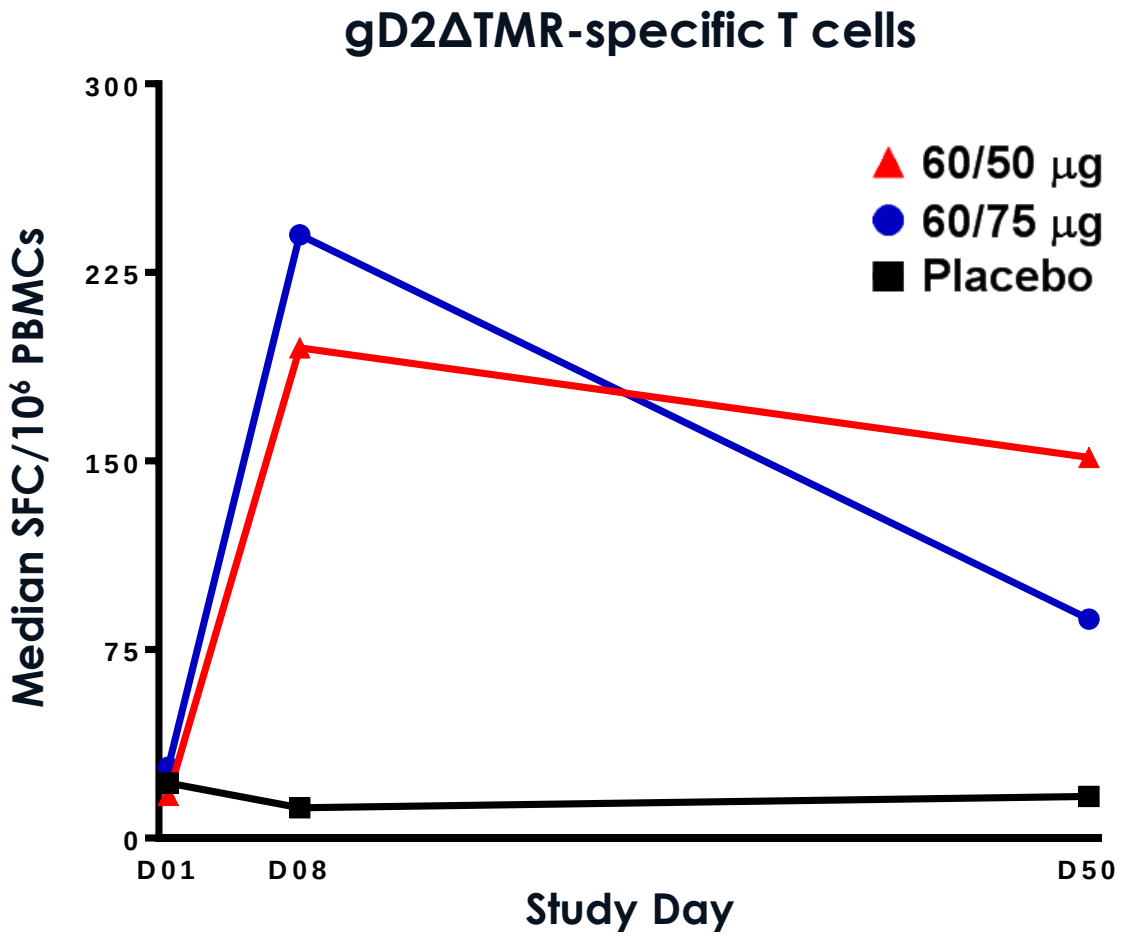
GEN-003 induced antigen-specific T cells secreting IFN-γ



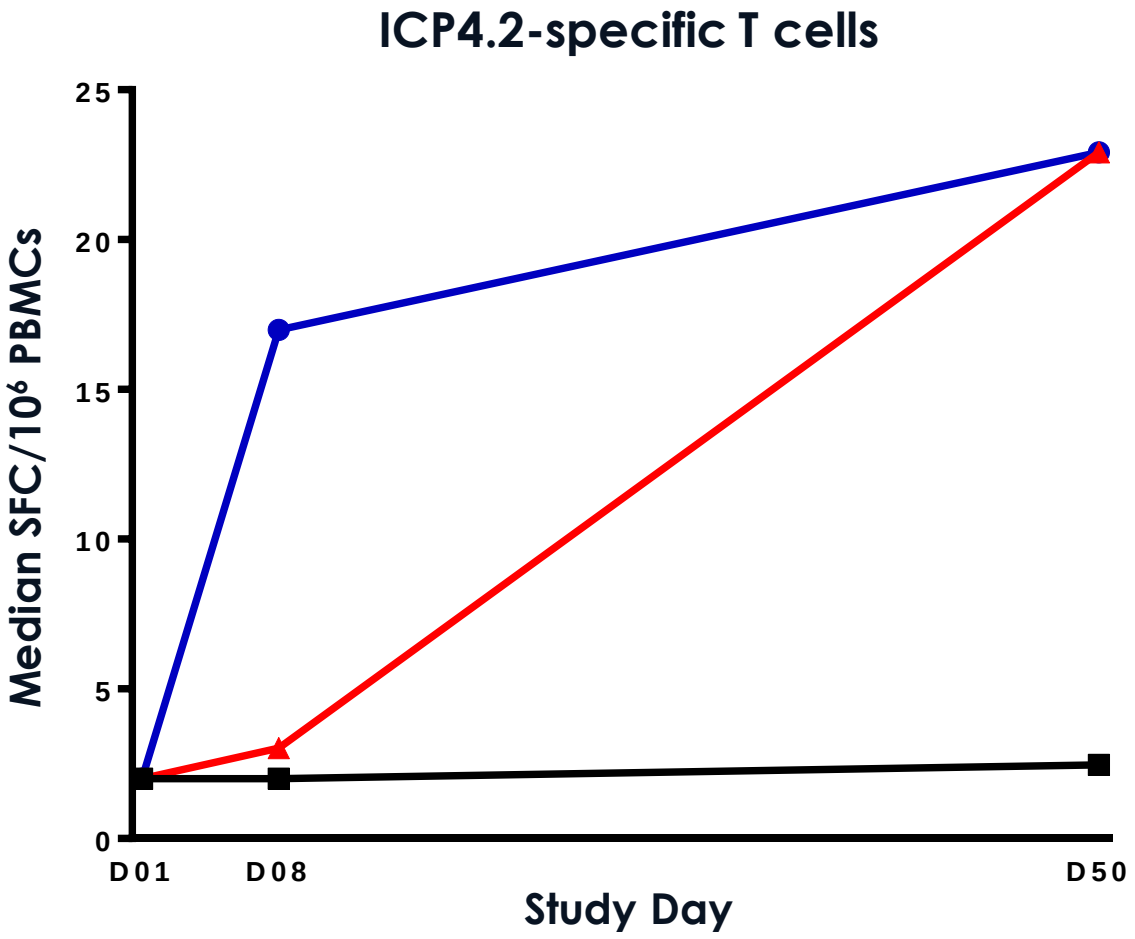


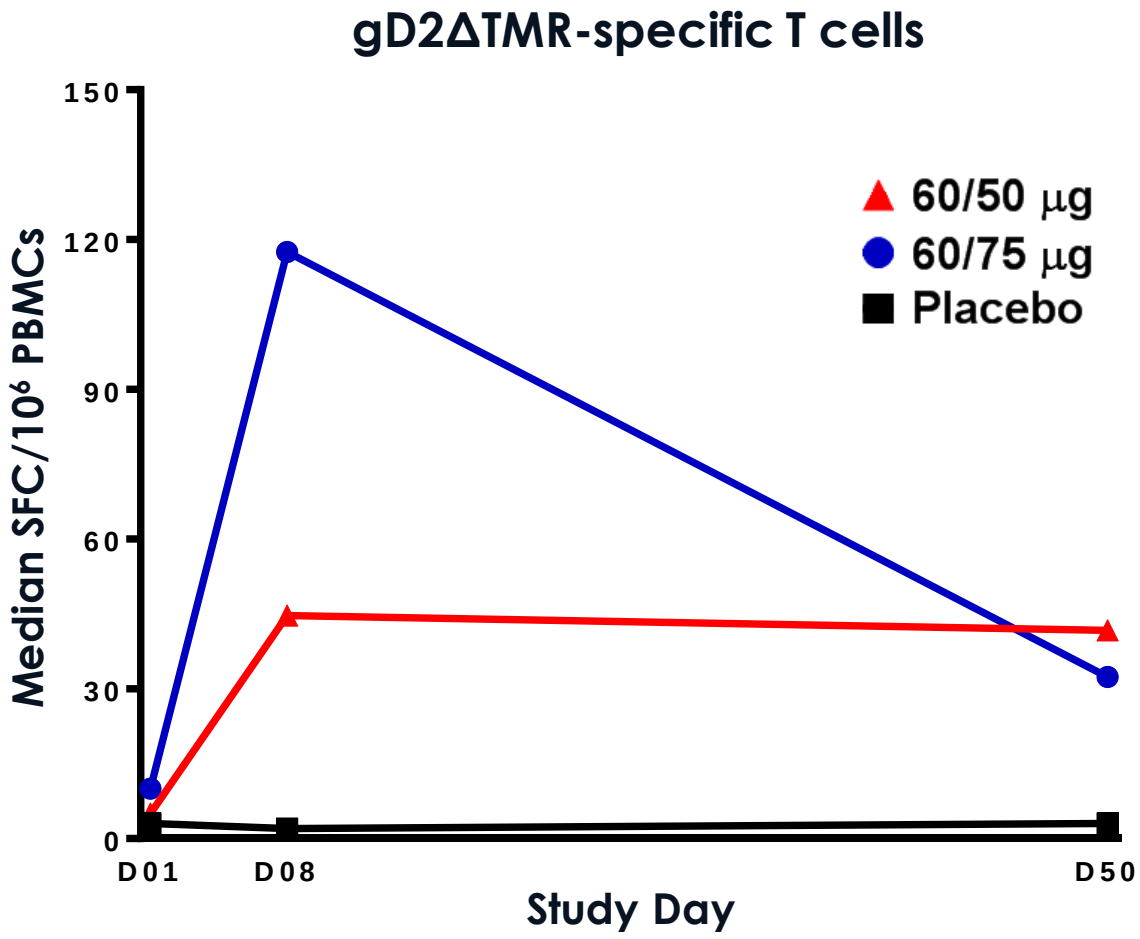
GEN-003 induced antigen-specific cytolytic T cells secreting GrB



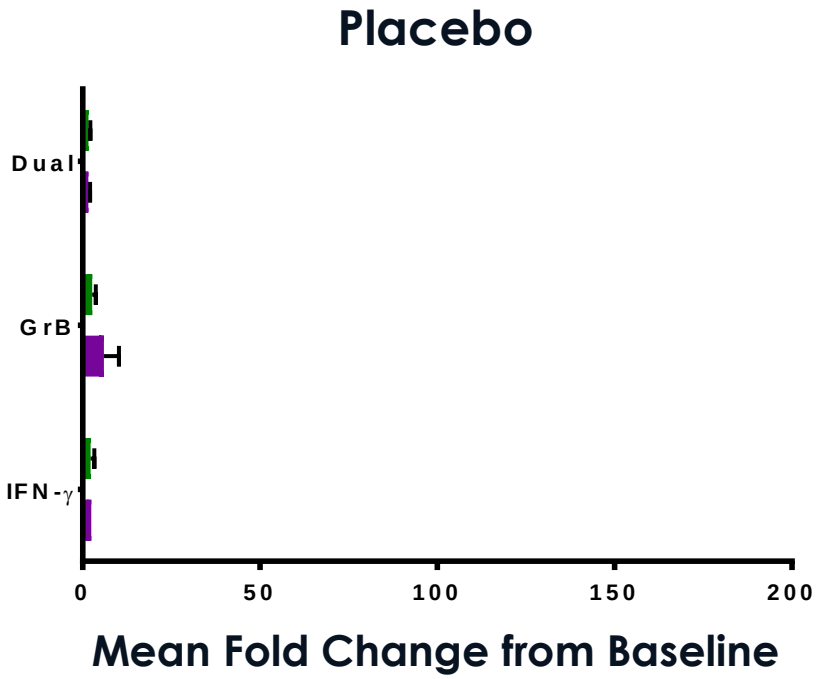


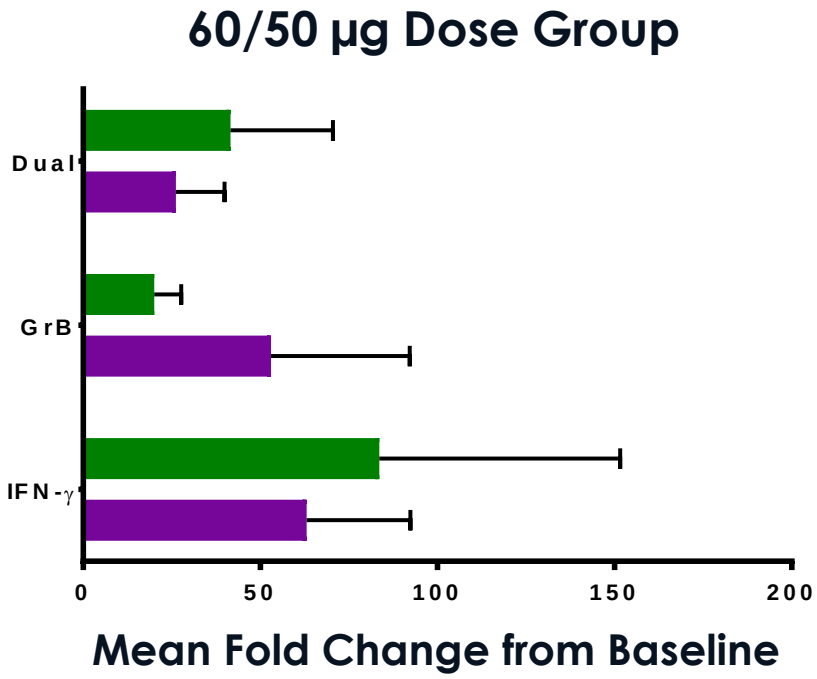
GEN-003 induced polyfunctional T cells secreting both IFN-γ and GrB

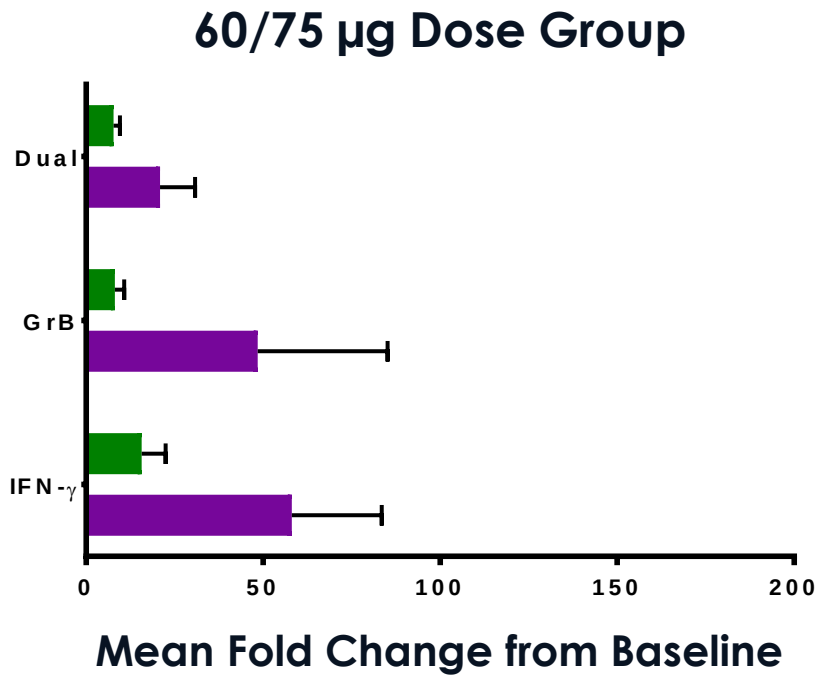




GEN-003 stimulated increases in cytolytic T cells at day 50







ICP4.2
gD2ΔTMR

GEN-003 is a promising immunotherapy for HSV infected individuals

- **GEN-003 augmented pre-existing humoral immunity in subjects**
  - Mean IgG titers increased greater than 60-fold and 8-fold specific for ICP4.2 and gD2ΔTMR, respectively; neutralizing antibody titers increased greater than 4-fold
  - Humoral response rates were >80% at day 71, while placebo remained <3%, indicating a highly immunogenic vaccine

- **Cytolytic T cells, believed to be essential for control of HSV-2 infection, were increased in subjects immunized with GEN-003**
  - IFN-γ, GrB, and dual secreting T cells increased greater than 20-fold to ICP4.2 and 7-fold to gD2ΔTMR
  - A decrease in T cell response between days 8 and 50 was observed in the 60/75 µg dose group, suggesting increased adjuvant composition may lead to T cell exhaustion

- **Though increases in immunogenicity were observed in subjects immunized with GEN-003, the protective threshold for antiviral effect will need to be investigated further**

- **The immunogenicity data generated supports the selection of the 60/50 µg dose of GEN-003 for upcoming Phase 3 clinical trials**

Acknowledgements

- **Clinical Trial Subjects**
- Clinical sites
- Genocea colleagues
- Innovative Analytics
- IND 2 Results

IND 2
R·E·S·U·L·T·S