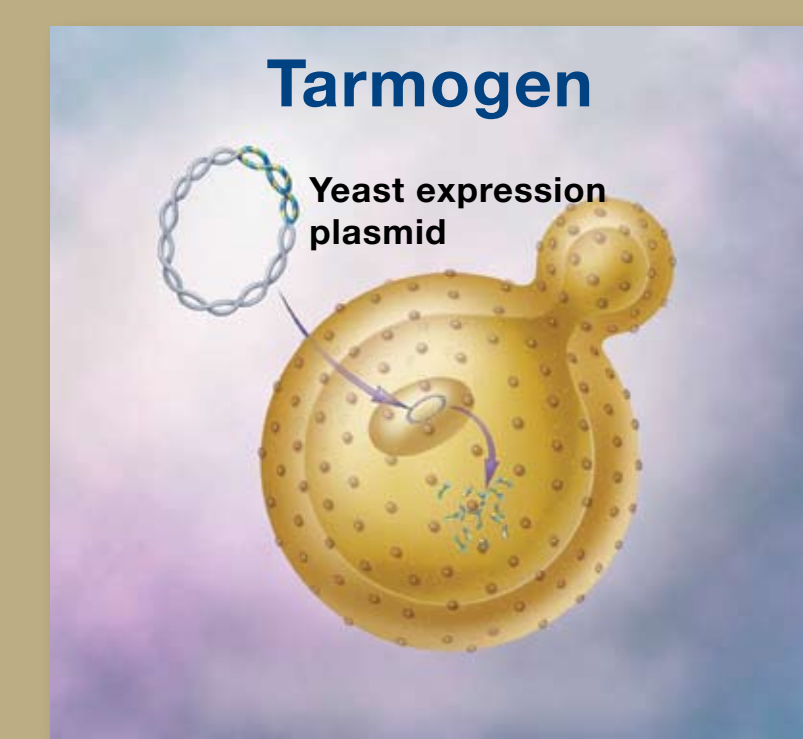
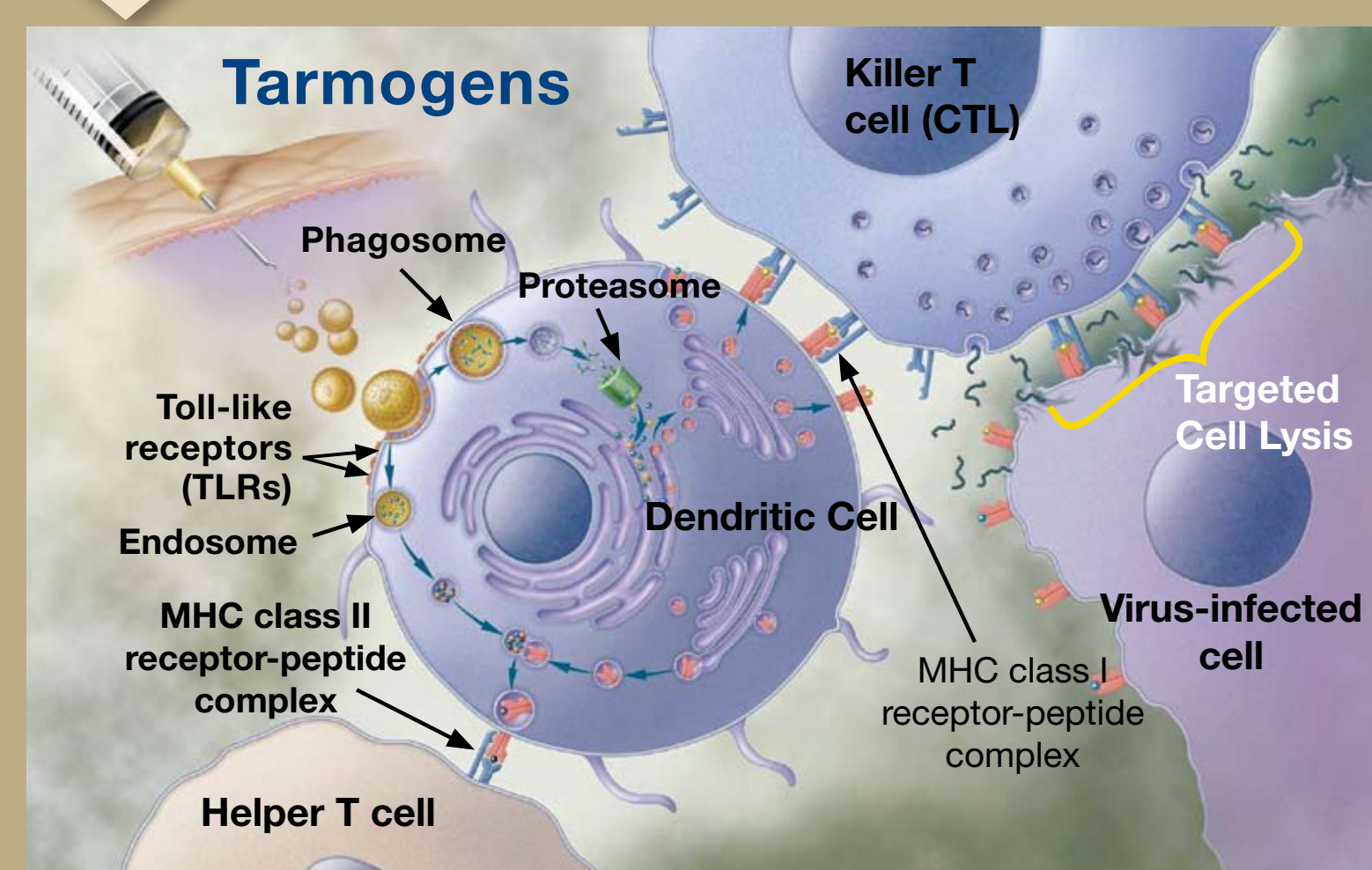


## Introduction



GI-5005 – HCV NS3-Core  
GI-8004 – Influenza M1-NP-M2e

Uptake of Tarmogens by dendritic cells results in the activation of antigen-specific helper and cytotoxic T cells.

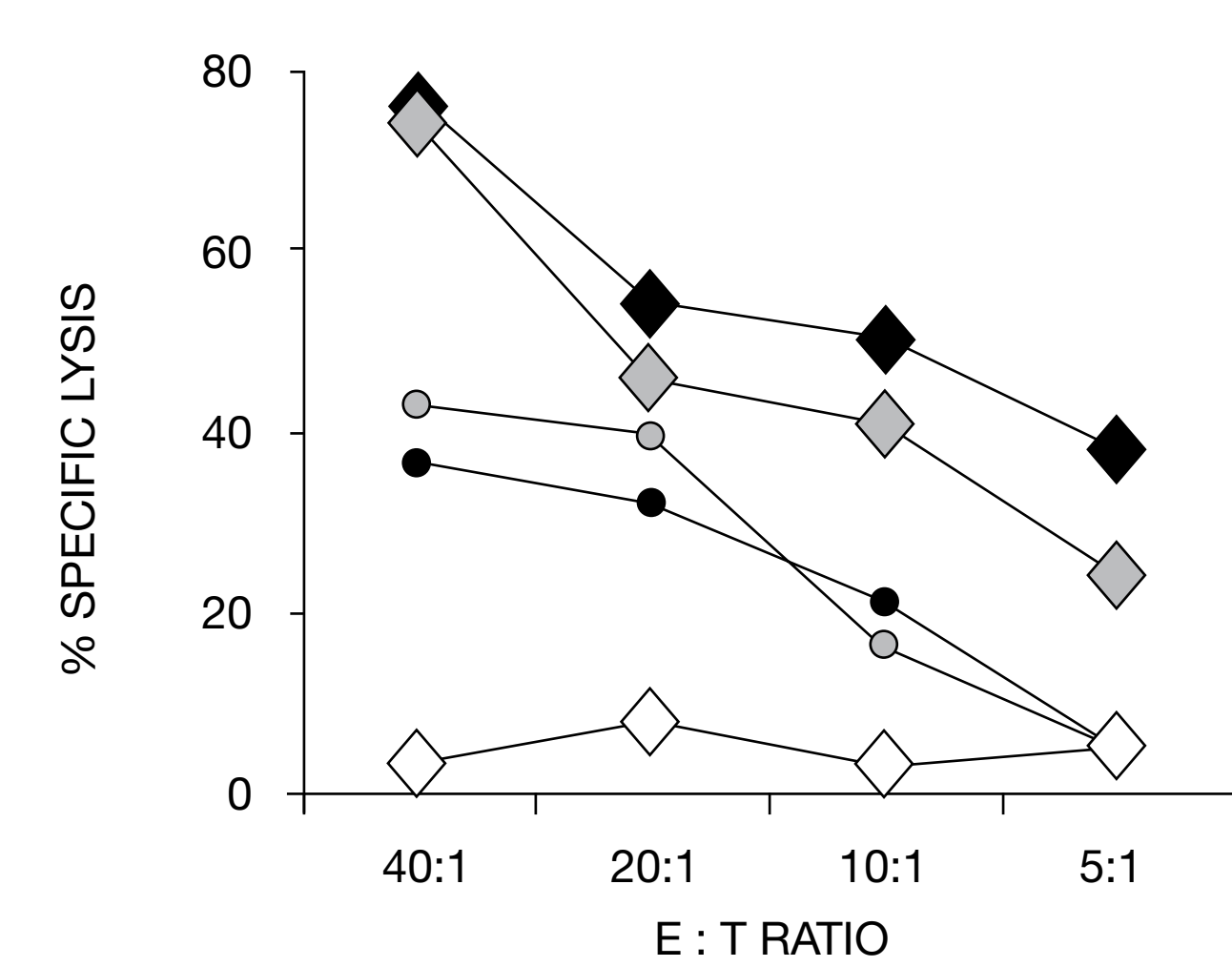


Tarmogens (targeted molecular immunogens) are whole, heat-killed recombinant *Saccharomyces cerevisiae* yeast engineered to express one or more target protein antigens, and activate both an innate immune response via Toll-like receptors (TLRs), as well as an adaptive, antigen-specific immune response. This technology can be employed for therapeutic as well as prophylactic treatment therapies. GI-5005, the therapeutic product for treatment of chronic Hepatitis C, expresses a hepatitis C virus (HCV) fusion protein comprised of large segments of NS3 protease and Core protein sequences. GI-8004, a prophylactic influenza vaccine, expresses a tripartite fusion protein consisting of the matrix protein (M1), the nucleoprotein (NP), and the M2e peptide derived from the A/PR/8/34 strain. The HCV and influenza proteins were chosen because they are essential for virus replication, contain multiple epitopes recognized by both CD4<sup>+</sup> and CD8<sup>+</sup> T cells in acute and chronic infections, and are highly conserved among the different virus clades. The expression of multiple antigens in yeast is designed to induce a broad cellular immune response for efficient virus control in patients.

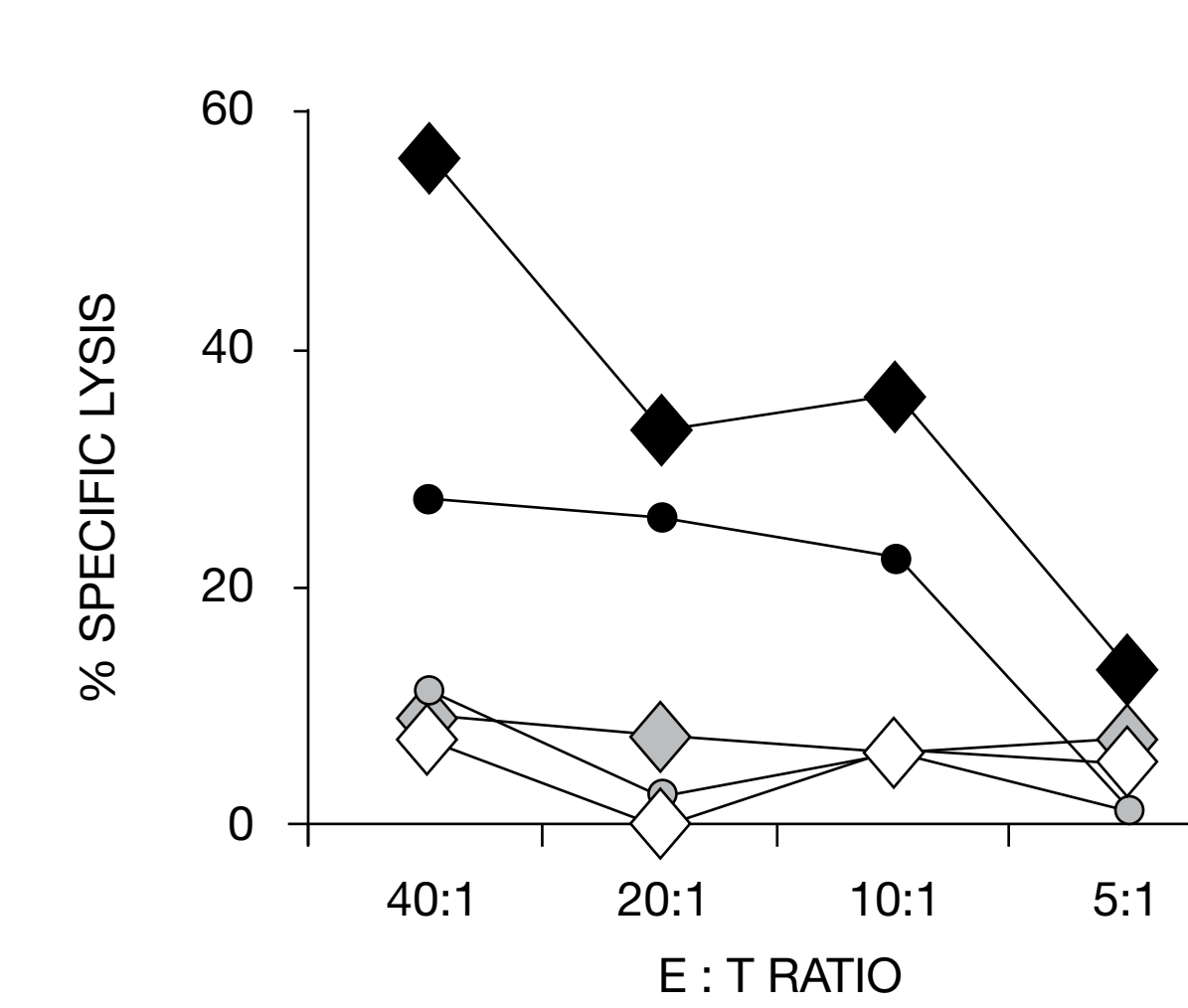
## GI-5005 for the treatment of chronic hepatitis C infection

**Figure 1. Dose-dependant, antigen-specific T cell killing of cells expressing HCV NS3 or Core antigens**

### 1a. Killing of P815-rVV-NS3



### 1b. Killing of P815-rVV-Core



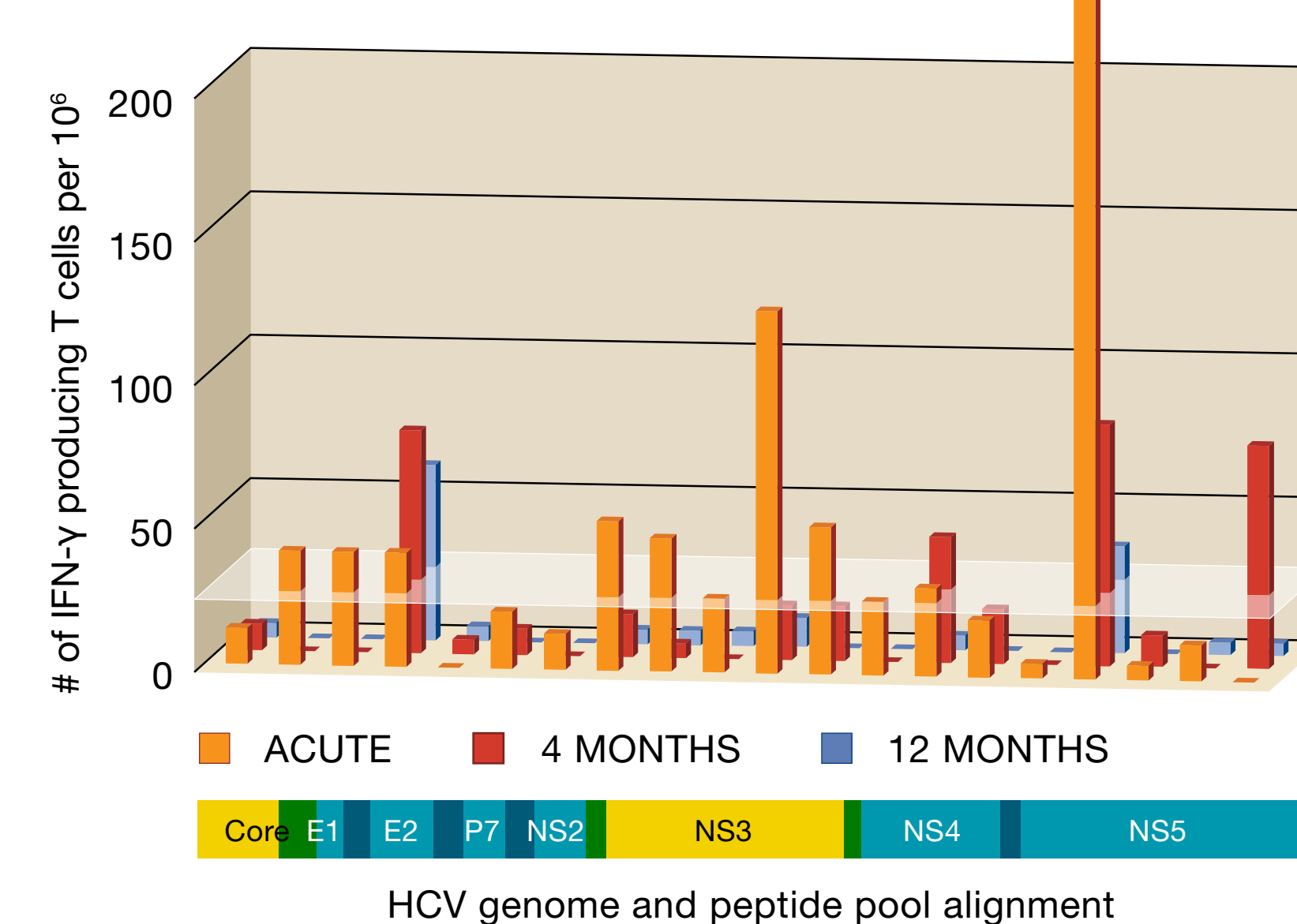
Dosing with Tarmogens expressing:		
NS3-Core	NS3	RAS
◆ GI-5005 (5 YU)	◇ GI-5003 (5 YU)	◇ GI-4014 (5 YU)
● GI-5005 (0.1 YU)	○ GI-5003 (0.1 YU)	

<sup>51</sup>Cr release assay of antigen-specific CTL killing of P815 tumor cells infected with vaccinia virus expressing NS3 (panel A) or Core (panel B) protein.

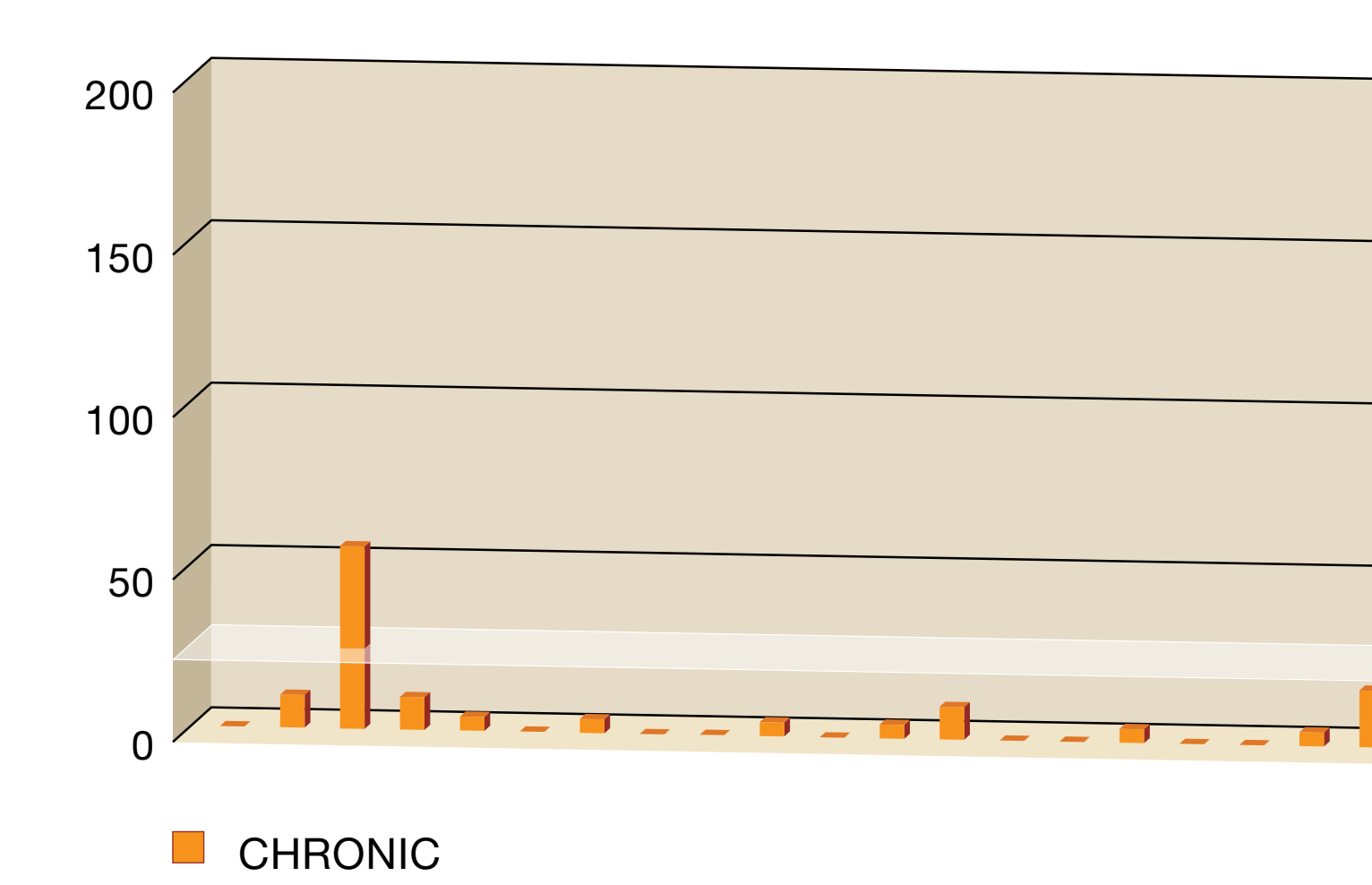
## Figure 2: HCV Natural History

For individuals that are acutely infected with hepatitis C virus, approximately 20% clear the virus without medical intervention; the remaining 80% become chronically infected. An example ELISpot profile from a patient (non-study) that acutely cleared the hepatitis virus is shown in Figure 2a. An ELISpot assay measures the number of T cells activated in response to HCV antigens *ex vivo*. The lack of immune response by the 80% of individuals that are chronically infected is characterized by weak cellular immune responses and narrow (i.e. single dominant) immune responses to HCV epitopes, as shown in the representative profile in Figure 2b.

**Figure 2a: T Cell Responses in Acute Infections**



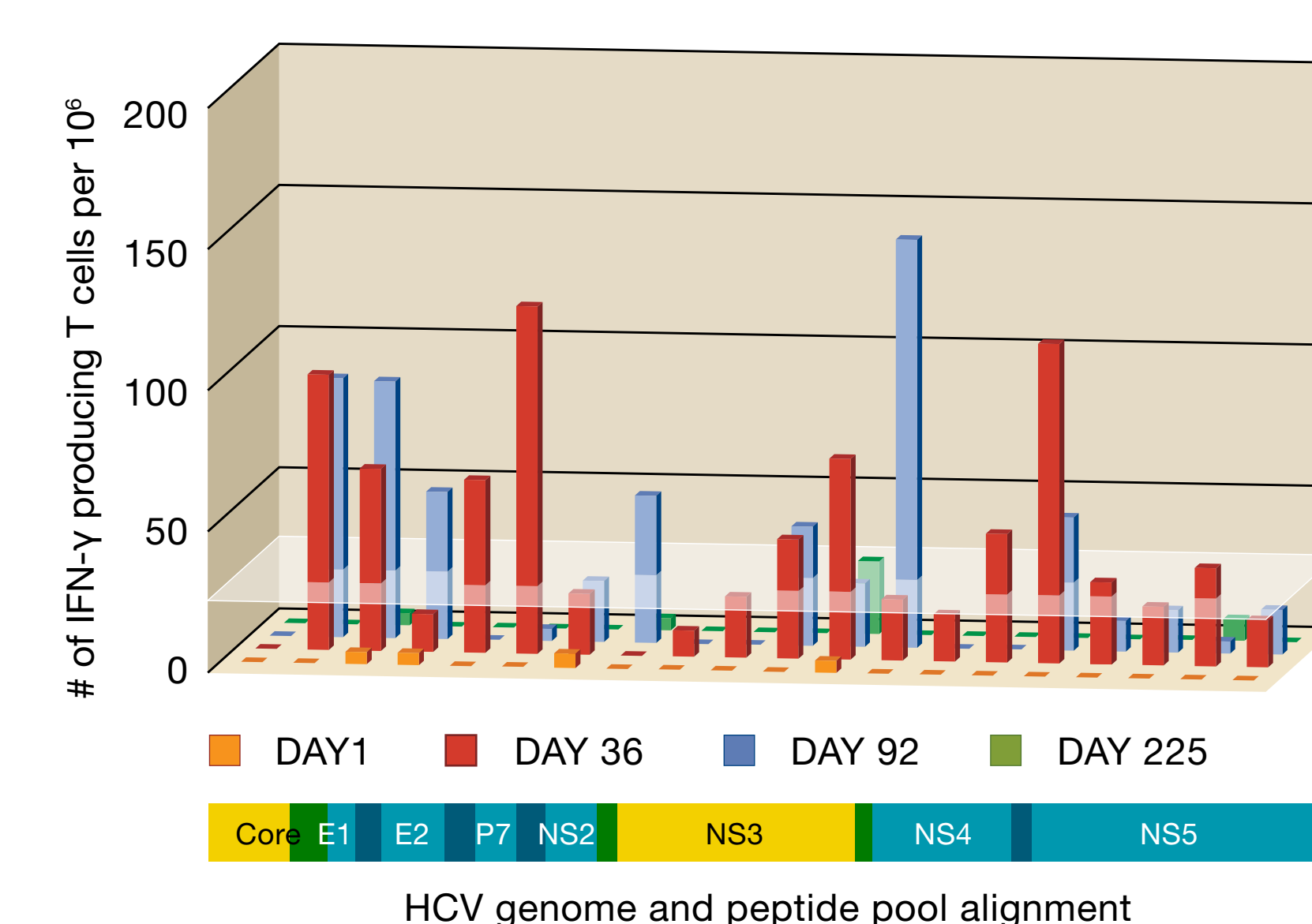
**Figure 2b: T Cell Responses in Chronic HCV Patients**



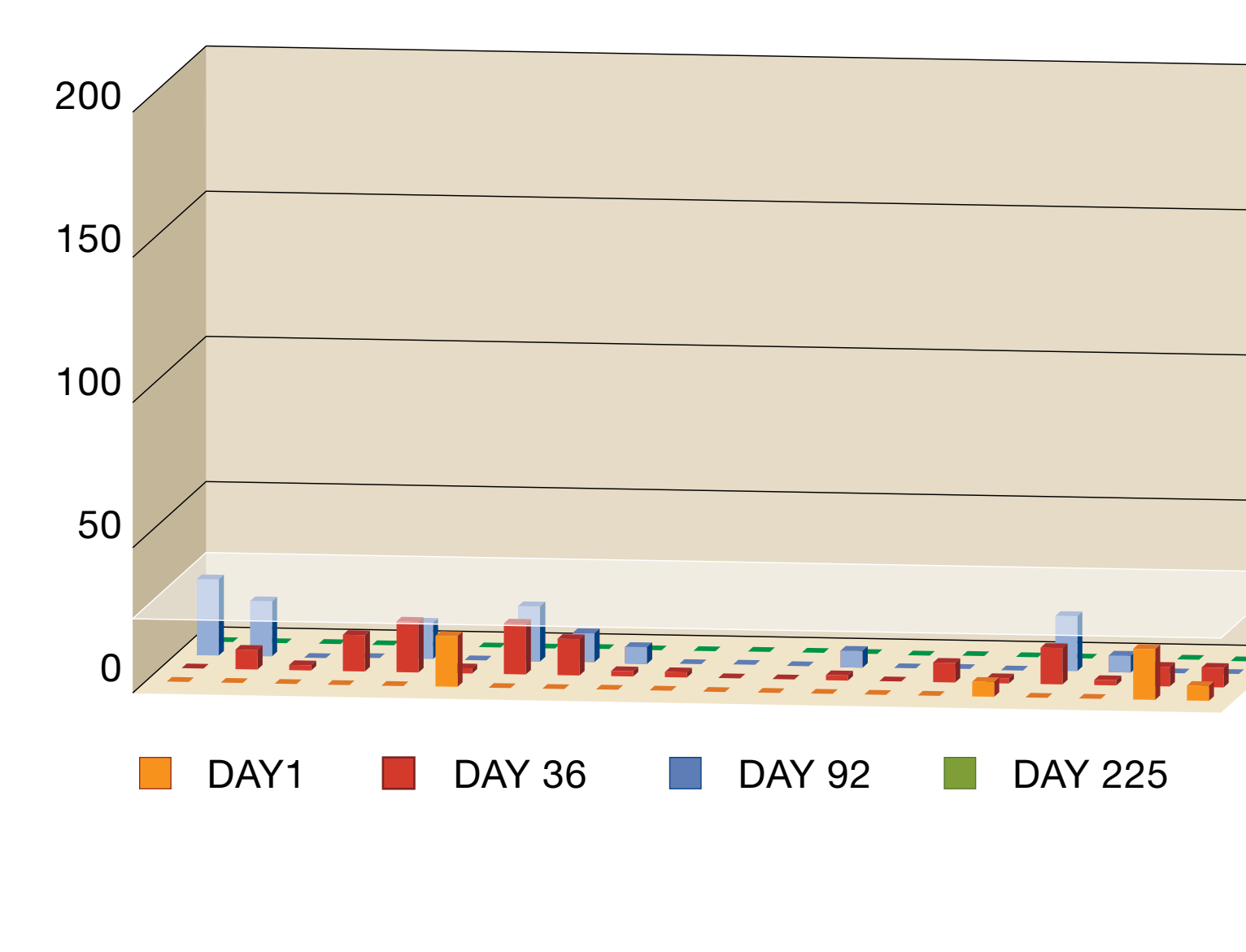
**Figure 3: GI-5005 induces potent T cell responses in chronic HCV patients**

ELISpot results from subject 037 (Fig. 3b) is representative of responses from the placebo group, and typifies the profile seen in untreated chronic HCV-infected individuals, as in Fig. 2b. ELISpot results from subject 014 (Fig. 3a) were representative of T cell responses in GI-5005-treated subjects (7/29 from the first 4 cohorts), and were not observed in any placebo-treated subjects. The conversion of baseline T cell profiles to broad and strong ELISpot responses occurred in GI-5005-treated subjects irrespective of HLA types.

**Figure 3a: Subject 014 (treated)**



**Figure 3b: Subject 037 (placebo)**



## Design for GI-5005 Phase 1b Clinical Trial

GI-5005-01 is a double-blind, placebo-controlled, multi-center, dose cohort-escalation, therapeutic trial evaluating the subcutaneous administration of GI-5005 in subjects with chronic Hepatitis C infection who were either partial responders or relapsers to an interferon based regimen (with or without ribavirin), or treatment naïve. The dosing regimen was weekly x5 doses followed by two additional monthly doses (Table 1). Administration of 0.05, 0.5, 2.5, and 10YU at a single injection site was given to the first four cohorts, then 10 YU at two sites (20YU) or four sites (40YU) per dosing visit was given to the final two cohorts.

**Table 1.**

Treatment Period										Monitoring / Follow up					
1	8	15	22	29	36	43	57	64	71	85	92	99	169	225	336
• Viral load and ALT testing on all visits										• Immunology (ELISPOT and LPA) at baseline and days 36, 99, 225					
• 71 subjects were enrolled in 6 dose cohorts at 9 U.S. centers															
■ Dosing Days										■ Monitoring					

## GI-8004 influenza prophylaxis

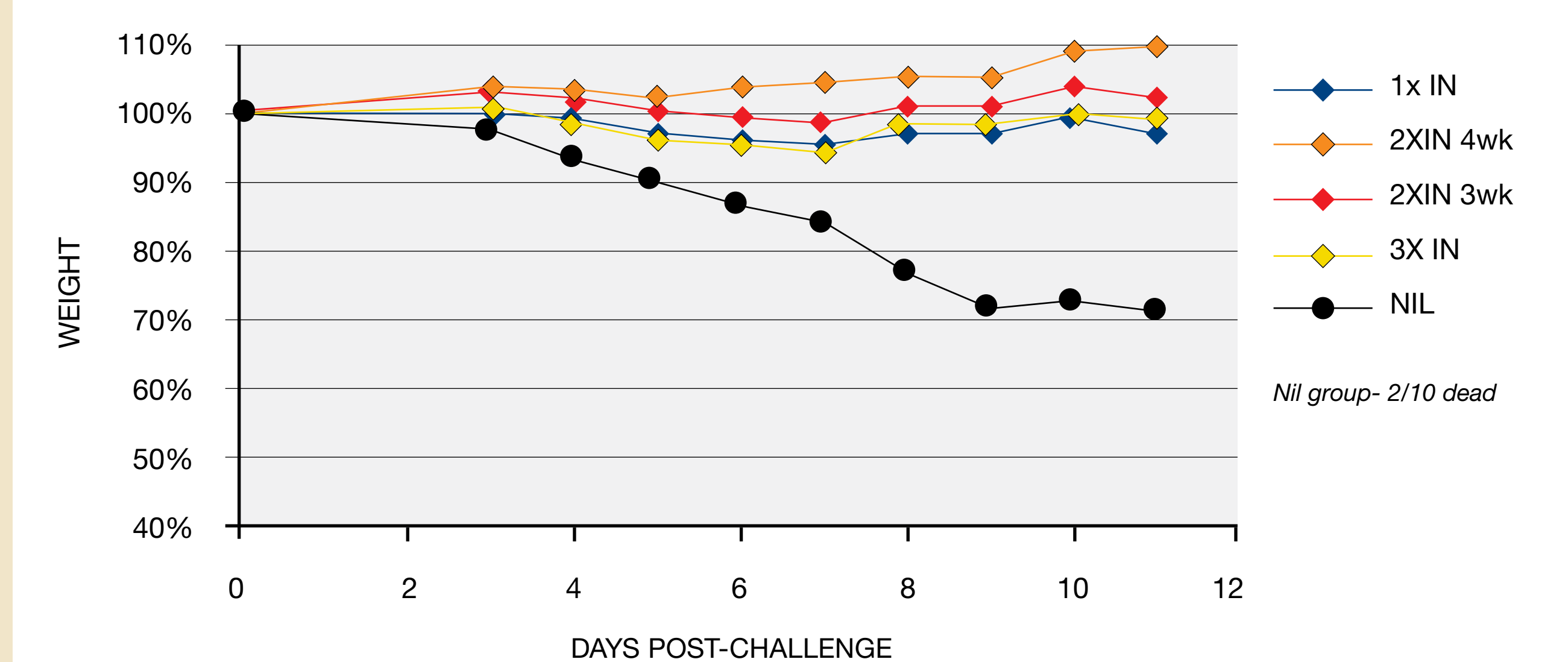
**Table 2: GI-8004 delivers an Influenza fusion protein for universal T cell immunity**

GI-8004	M1	NP	M2e	M2e	M2e	M2e
vs. H1N1	> 90%	> 90%	> 90%	> 90%	> 90%	> 90%
vs. H3N2	> 90%	> 90%	> 90%	> 90%	> 90%	> 90%
vs. H5N1	> 90%	> 90%	> 90%	> 90%	> 90%	> 88%

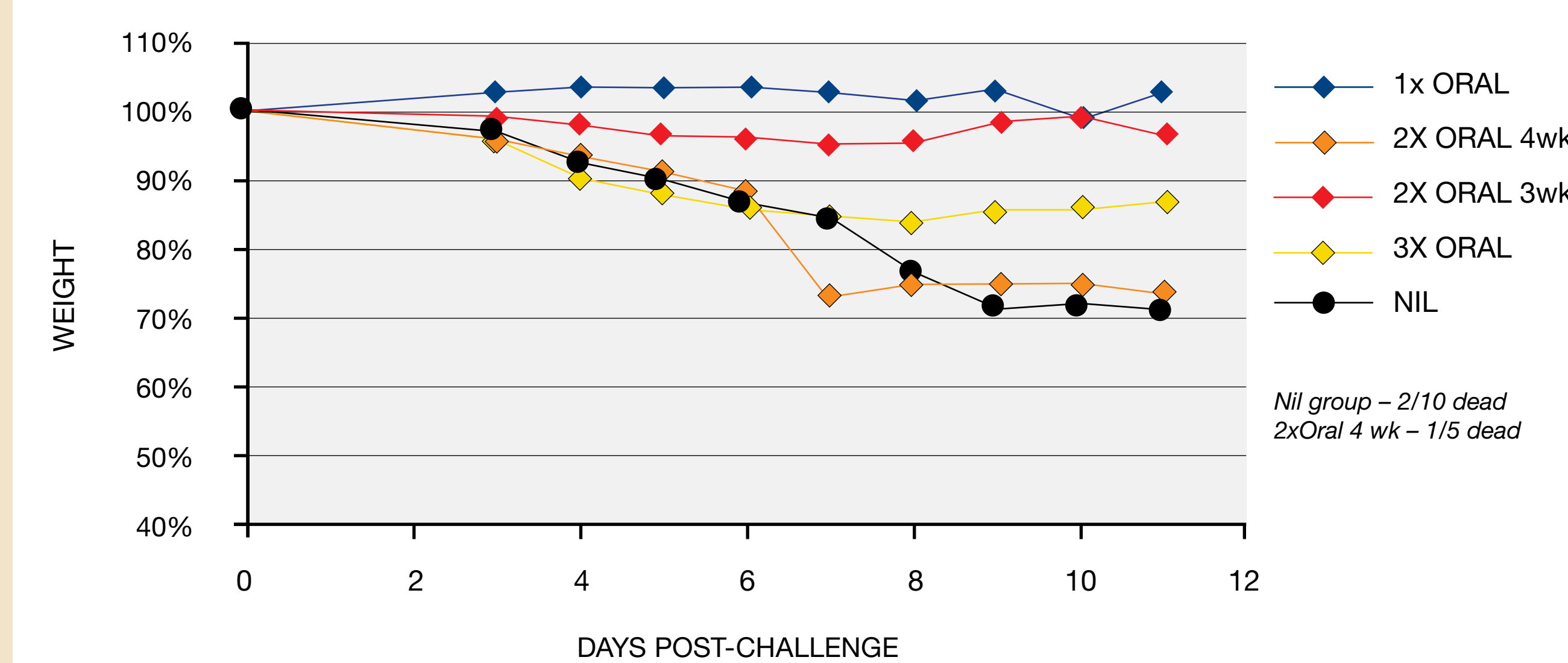
Table 2 shows the % identity in amino acid sequence between matrix (M1, 252aa), nucleoprotein (NP, 500aa), or M2e ion channel proteins (4x25aa) encoded in the GI-8004 fusion protein with any member of H1N1, H3N2 or H5N1 serotypes that were evaluated.

**Figure 4: GI-8004 protects mice from respiratory challenge with wild type influenza virus**

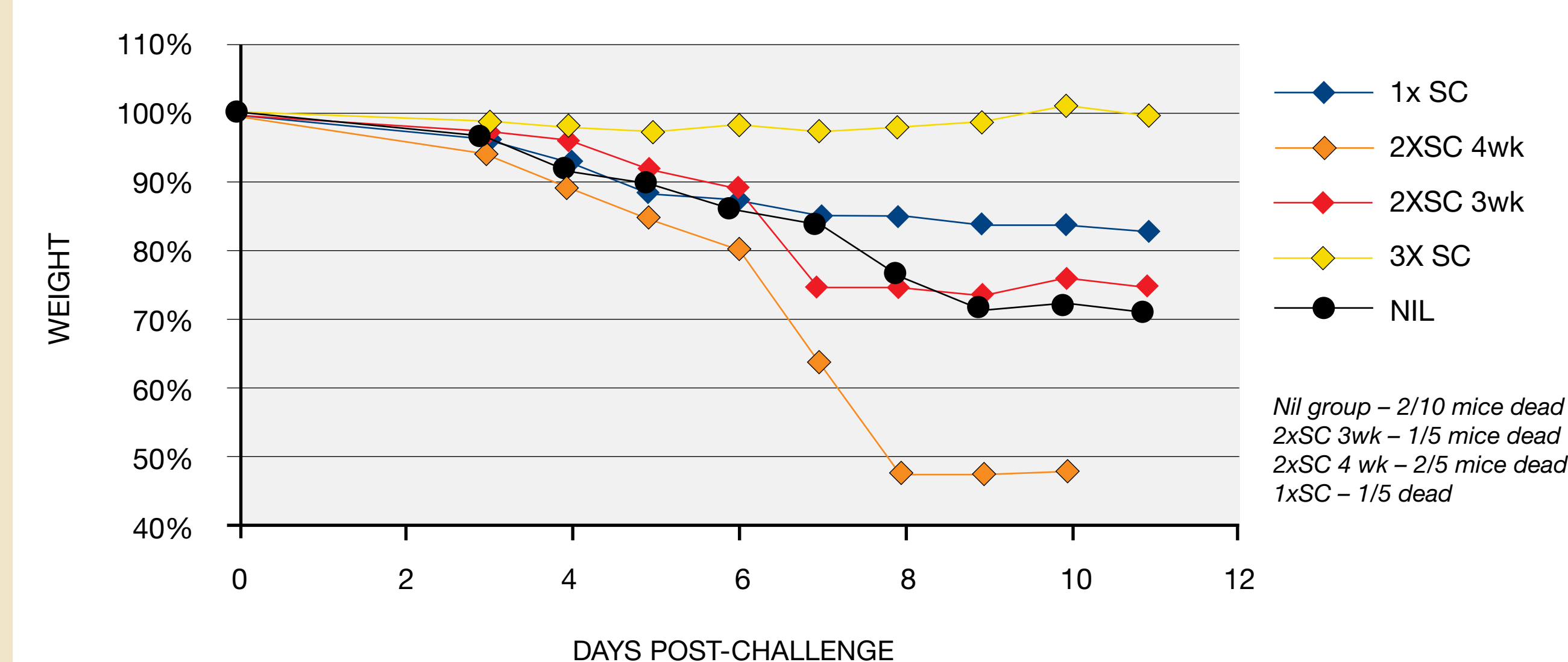
### Intranasal (IN) route



### Oral route



### Subcutaneous (SC) route



Female BALB/c mice were dosed once, twice (3 or 4 weeks apart) or 3 times (once weekly) with GI-8004, yeast expressing a fusion protein comprised of M1, M2e and NP influenza proteins. Two weeks after the last vaccination, a respiratory challenge with wild type A/PR/8/34 (1x10<sup>4</sup> PFU/mouse) was performed. Weight, measured daily, is shown.

## Conclusions

- Tarmogens directly couple innate and antigen-specific immunity
- GI-5005 demonstrates antigen-specific, dose-dependent killing of infected cells in preclinical models.
- GI-5005 demonstrates robust antigen-specific T cell responses, normalization of ALT and viral load decreases in a proportion of GI-5005 treated patients.
- A single dose of GI-8004 (either IN or Oral) demonstrates complete protection from live virus challenge in mice. Three subcutaneous doses of GI-8004 are required to demonstrate the same, emphasizing the impact of the route of administration.
- Ferret studies of H5N1 and seasonal influenza are underway; human clinical trials are being designed.