Initiation of clinical studies with SL-701, a synthetic multi-peptide vaccine with enhanced immunostimulatory properties targeting multiple glioma-associated antigens, in adults with first recurrence of glioblastoma

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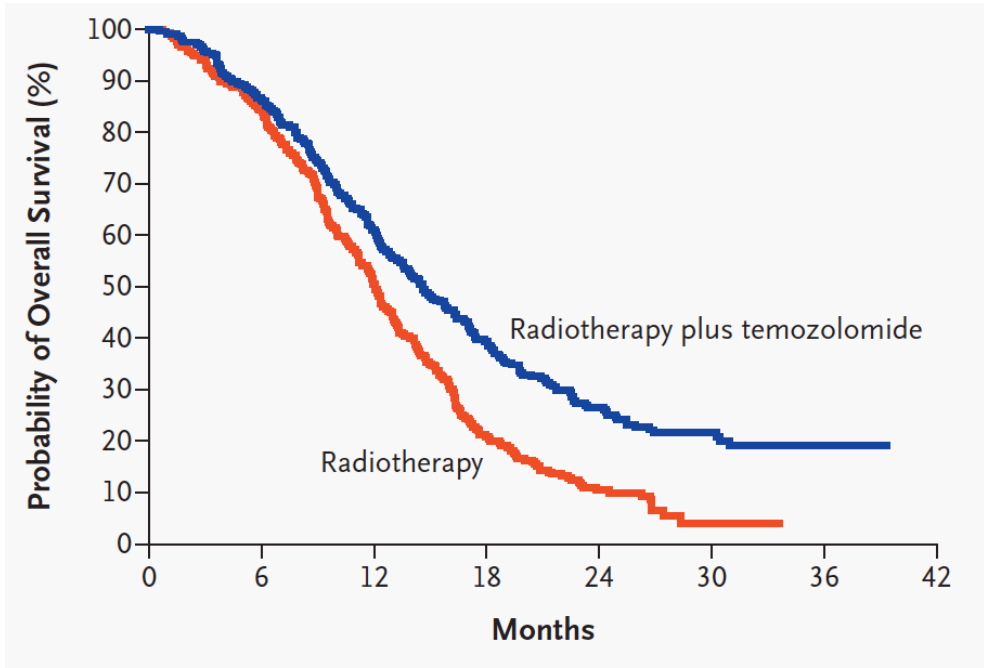
Glioblastoma multiforme: a significant unmet medical need

- Glioblastoma multiforme (GBM) is the most frequent malignant primary brain tumor in adults.
- Resection, radiation, and temozolomide confer survival benefit; however median overall survival (OS) remains limited: ~ 15 months.[1]
- Glioma stem cells are resistant to radiation and chemotherapy and thought to be key contributors to tumor recurrence.
- Therefore, a multi-pronged approach targeting both tumor bulk and cancer stem cells is a necessary therapeutic strategy for GBM.
- Immunotherapies have shown promise in many solid tumors, and emerging evidence suggests that the central nervous system is immunocompetent and accessible to immune cells. [2]



Patients with newly diagnosed, histologically confirmed GBM were randomly assigned to receive radiotherapy alone or radiotherapy + continuous daily temozolomide, followed by 6 cycles of adjuvant temozolomide.[1]

[1] *Stupp, R. et al. N Engl J Med. 2005; 352 (10);* [2] *Reardon, D. A. et al. Neuro Oncol. 2014 Nov; 16 (11)*

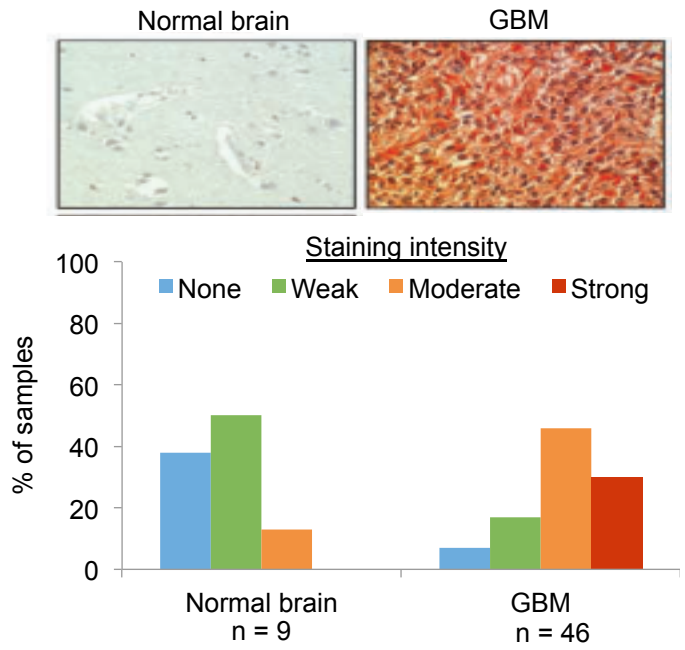
SL-701 background

- SL-701 is a synthetic multi-peptide immunotherapy.
  - Consists of three shortened peptides corresponding to targets overexpressed by GBM.
  - Includes peptides of IL-13Rα2 and survivin that have been engineered with amino acid substitutions to increase immunostimulatory activity.
- Most gliomas studied to date express two or three of these targets.[3]
- An earlier version of this therapy was associated with major responses, including durable complete responses (CRs), in advanced brain cancer patients.
- SL-701 has been optimized over this earlier version for enhanced immunostimulation and ease of administration.
- SL-701 peptides are emulsified and administered via s.c. injection; immunostimulants are co-administered to induce maximal activation of the immune system.
- SL-701-0114 clinical trial is currently open and recruiting adult patients with second-line GBM.

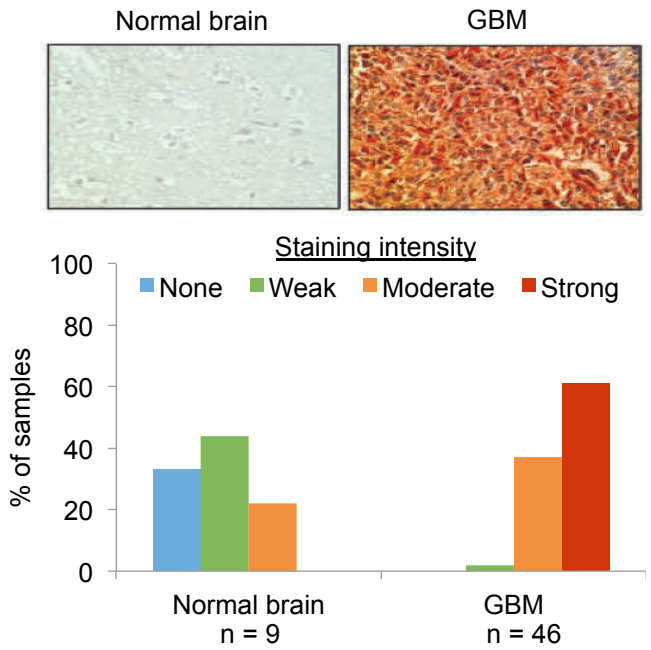
[3] *Okada, H. et al. J Neurooncol. 2008; 88 (3)*

Overexpression of SL-701 targets on GBM

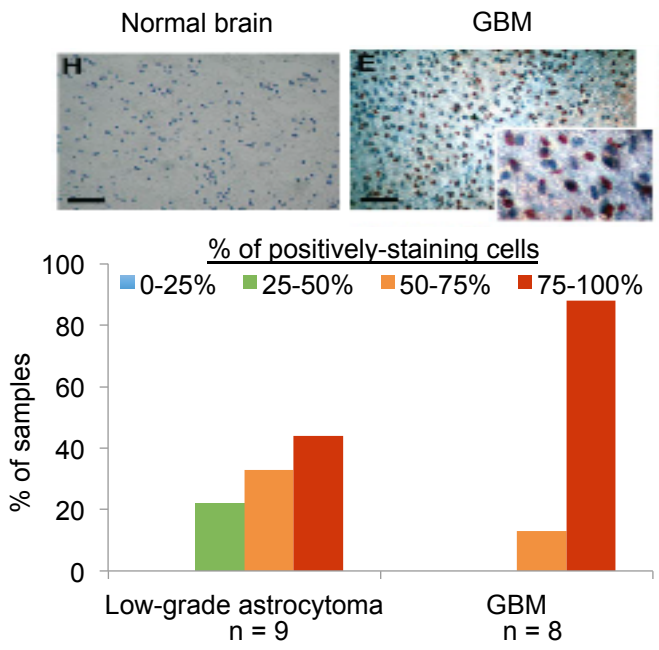
A **IL-13Rα2**



B **EphA2**



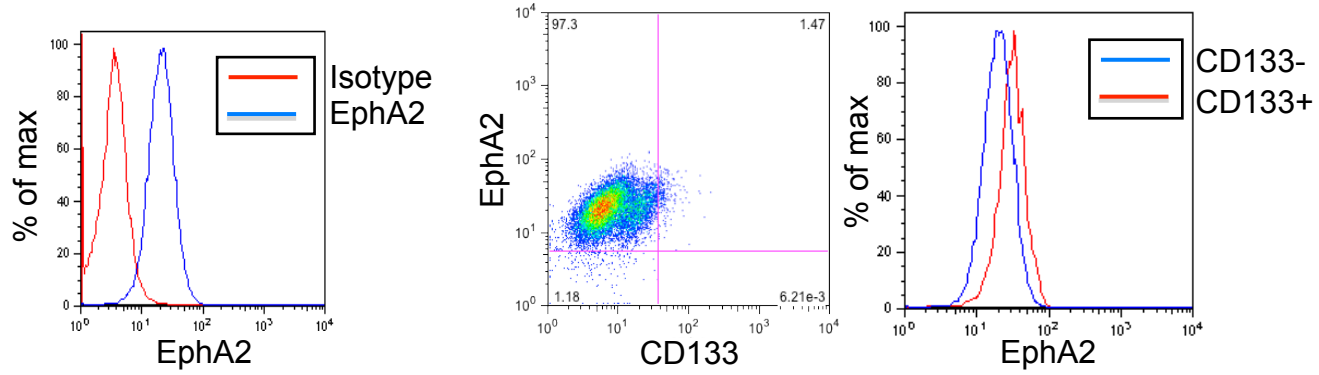
C **Survivin**



(**A-C**): Expression of IL-13Rα2, EphA2, and survivin was examined on normal brain and GBM specimen by immunohistochemistry. Adapted from Uematsu, M. et al. and Wykosky, J. et al.[4,5]
(**D**) EphA2 is expressed on GBM stem-like cells. A-172 GBM cells were stained with antibodies to EphA2 and CD133 and analyzed by flow cytometry.

D

A-172



[4] *Uematsu, M. et al. J Neurooncol. 2005; 72 (3);*
[5] *Wykosky, J. et al. Clin Cancer Res. 2008; 14 (1)*

Previous clinical experience

Earlier version of SL-701, comprised of similar peptides, demonstrated tumor regressions, including durable CRs and partial responses (PRs), in adults with GBM and children with malignant glioma in investigator-sponsored Phase 1/2 trials.

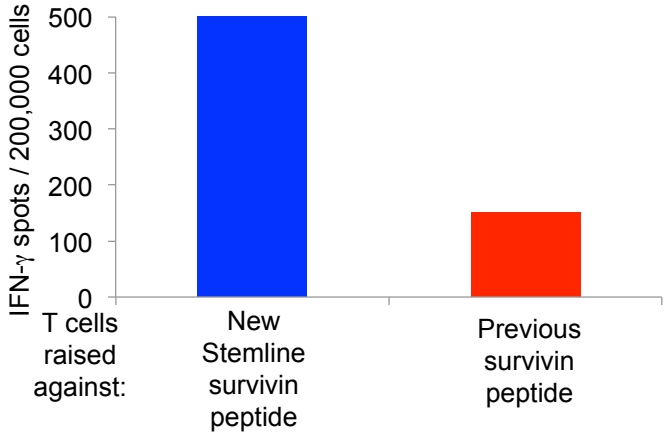
Study population	Peptides	Administration	Ref.
Adult patients with recurrent high-grade glioma	IL-13Rα2$_{345\text{-}353:1A9V}$ EphA2$_{883\text{-}891}$ YKL-40$_{202\text{-}211}$ gp100$_{209\text{-}217}$ PADRE	i.n. injection of peptide-loaded DCs; i.m. injection of poly-ICLC	6
Adult patients with recurrent low-grade glioma	IL-13Rα2$_{345\text{-}353:1A9V}$ EphA2$_{883\text{-}891}$ Survivin$_{96\text{-}104:M2}$ WT1$_{126\text{-}134:Y1}$ Tet$_{A830}$	s.c. injection of emulsified peptides; i.m. injection of poly-ICLC	7
Children with malignant glioma	IL-13Rα2$_{345\text{-}353:1A9V}$ EphA2$_{883\text{-}891}$ Survivin$_{96\text{-}104:M2}$ Tet$_{A830}$	s.c. injection of emulsified peptides; i.m. injection of poly-ICLC	8

[6] Okada, H. et al. 2011. J Clinical Onc. 29 (3); [7] Okada, H. et al. AACR 2012 abstract nr LB-135; [8] Pollack, I. F. et al. J Clin Oncol. 2014; 32 (19)

SL-701, an enhanced immunotherapy for GBM

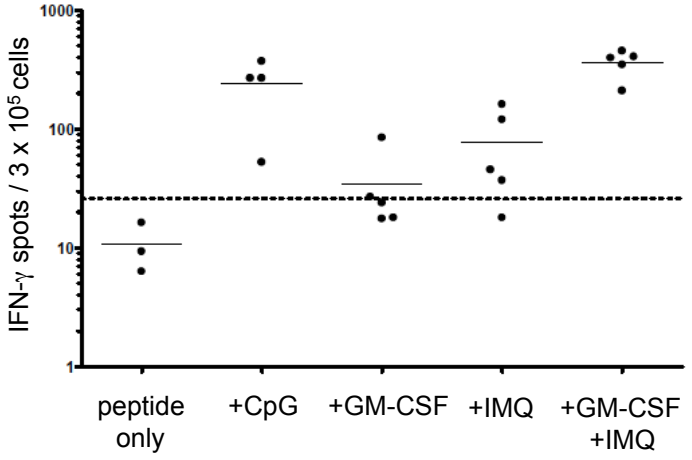
SL-701, comprised of IL-13Rα2 variant, EphA2, and survivin variant peptides, has been optimized over earlier version for enhanced immunostimulation and ease of administration.

- Replaced previous survivin peptide with a novel, highly immunogenic mutant survivin peptide.
- T→M substitution in wildtype survivin$_{95\text{-}104}$ peptide increases binding affinity to HLA and enhances anti-survivin cytotoxic T cell responses.[9]



T cells from a normal donor were raised against the new Stemline survivin peptide or the survivin peptide used in previous glioma trials.[7,8,9] IFN-γ–secreting cells in response to the corresponding wildtype peptides were enumerated by ELISPOT. Adapted from Bernatchez, C. et al.[9]

- Co-administration of imiquimod and GM-CSF immunostimulants employed to synergistically enhance cytotoxic T cell responses.[9]



Mice were immunized s.c. with OVA peptide on days 0 and +7. GM-CSF was applied s.c. with peptide vaccine and 24 h before. A 5% imiquimod (IMQ) cream was applied to the skin at the vaccination site 30 min before and 24 h after vaccination. Splenocytes were isolated on day 14 to test for the presence OVA-specific CD8+ T cells. Adapted from Hilf, N. et al.[10]

[7] Okada, H. et al. AACR 2012 abstract nr LB-135; [8] Pollack, I. F. et al. J Clin Oncol. 2014; 32 (19); [9] Bernatchez, C. et al. Vaccine. 2011; 29 (16); [10] Hilf, N. et al. AACR 2010, abstract nr 5623

Phase 1/2 study of SL-701 in adults with recurrent GBM

Multi-center clinical trial for adults with recurrent GBM is now **open and accruing** (NCT02078648).

Eligibility

- GBM or WHO Grade IV variants
- First tumor recurrence or progression on initial multi-modality treatment regimen
- HLA-A2+
- Measurable disease, tumors at least 1 cm in 2 planes (required for 80 of 100 planned subjects)
- No multi-focal tumors or tumors measuring ≥ 4 cm in any dimension
- No prior locoregional or systemic therapy (other than second resection) for recurrent/progressive GBM

Study Population

- Approx. 100 adults

Study Centers

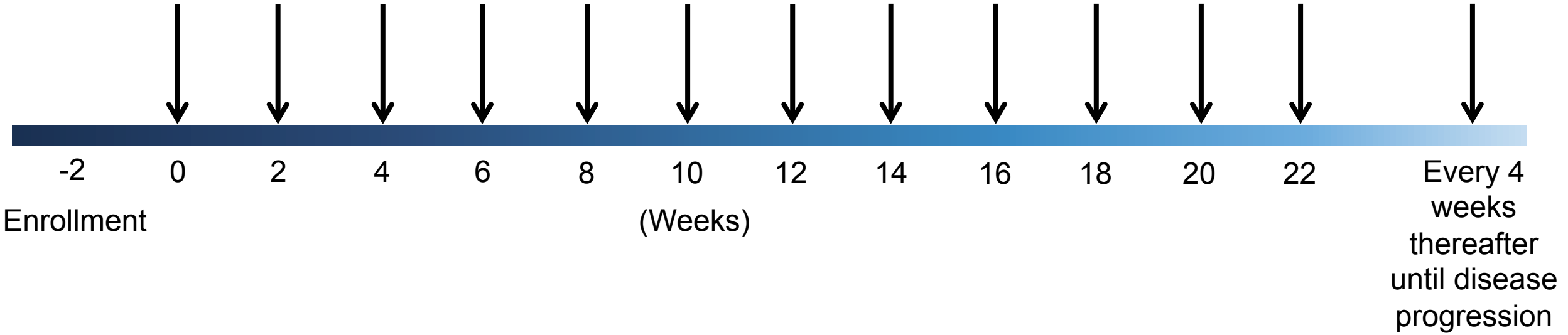
- Approx. 30 sites in North America

Objectives

Primary	• Characterize safety and tolerability of SL-701 • Estimate percent of patients alive 12 months after initiation of SL-701 • Estimate objective response rate (RANO & other)
Secondary	• Estimate duration of response • Estimate percent of patients alive and progression-free survival at 6 months after initiation of SL-701 • Estimate distributions of progression-free survival and overall survival
Exploratory	• Estimate relationships between measures of immunologic response and anti-tumor efficacy • Evaluate available post-SL-701 tissue for expression status of SL-701 target antigens and infiltration of antigen-specific T cells

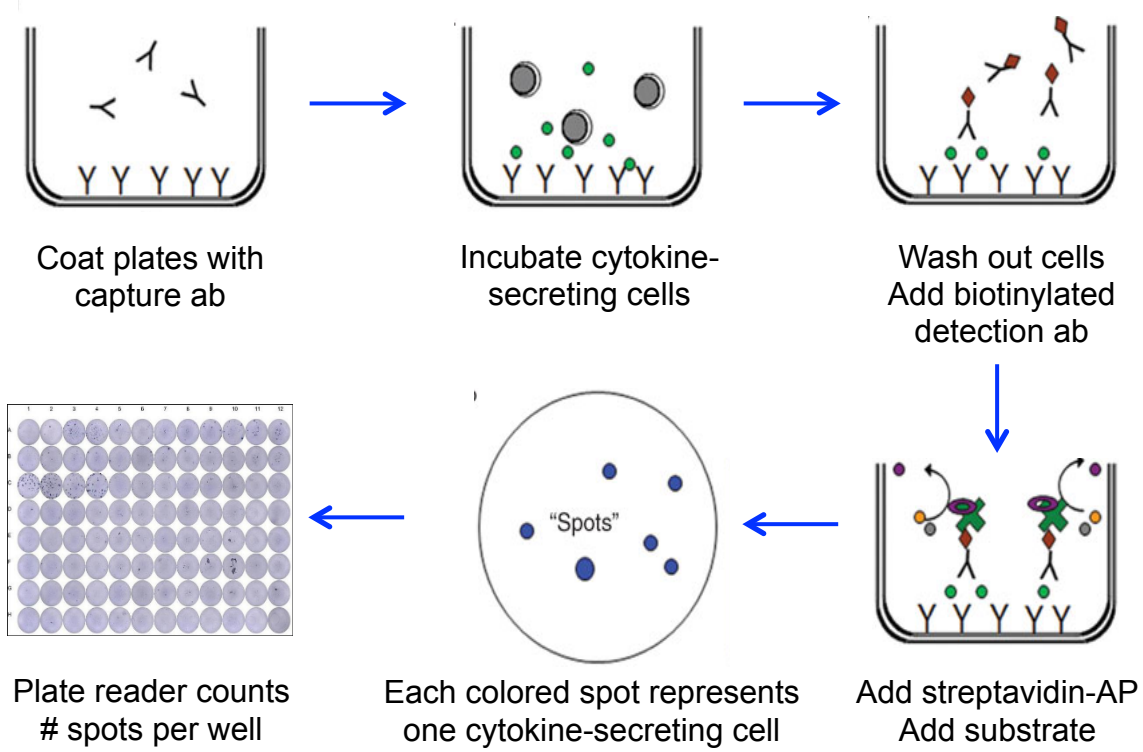
SL-701 regimen

- SL-701 subcutaneous injection in the right or left upper arms with intact draining axillary nodes, alternating locations between administration dates
- 150 μg GM-CSF subcutaneous injection immediately after SL-701 administration and within 1 cm from the center of the SL-701 administration site
- 125 mg 5% imiquimod cream applied topically to the SL-701 administration site immediately and 24 hours post-SL-701 administration

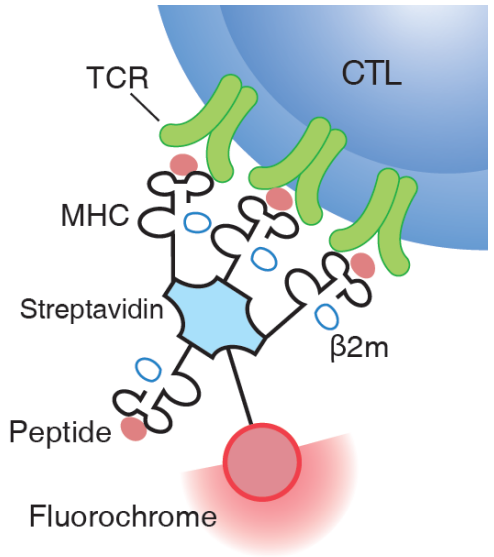


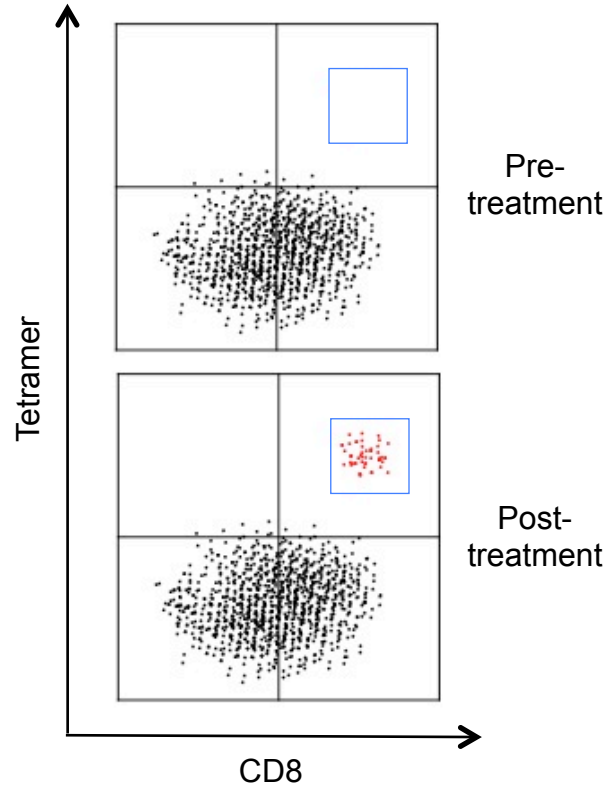
Measuring immunologic responses to SL-701

Frequency of IFN-γ-secreting T cells that develop in response to SL-701 treatment to be measured by ELISPOT[11]



Presence of antigen-specific CD8+ T cells that develop in response to SL-701 treatment to be assessed by tetramer analysis[12]





[11] *Adapted from Streek, H. et al. Nat Protoc. 2009; 4 (4) ;* [12] *Image from www.mobitec.com*

Summary

- SL-701 is a synthetic multi-peptide immunotherapy.
- SL-701 consists of three peptides corresponding to targets overexpressed on glioma – including peptides of IL-13Rα2 and survivin engineered with amino acid substitutions to increase immunostimulatory activity.
- SL-701 has been enhanced from an earlier clinically active version by the addition of an immunogenic mutant peptide of survivin, as well as immunostimulants that may synergistically enhance cytotoxic T cell responses.
- A multi-center clinical trial with SL-701 in adults with recurrent GBM is now open and actively accruing patients (NCT02078648).