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T_{reg} and T_{mem} in Immunotherapy Platform: A Twilight of Life-Long Immunity Against Cancer and Infection for Future Decade

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Abstract

T-regulatory cells (Tregs) are found infiltrating tumors in a vast array of tumor types, and tumor-infiltrating Tregs are often associated with a poor clinical outcome. Memory T-cells are derived from a normal T-cells that have learned how to overcome an invader by 're-membering' the strategy used to defeat previous infections. Here the impact of Tregs in the tumor microenvironment and its effect on CD8+T Cell as well as in antitumor activity was amplified so that a future antigen specific T-Cell stimulation (Protein/ DNA vaccine) can be patented. Moreover, recent innovation of central memory T-Cell have been considered to evaluate its role in future, having a lifelong immunity from Protein/DNA vaccine.
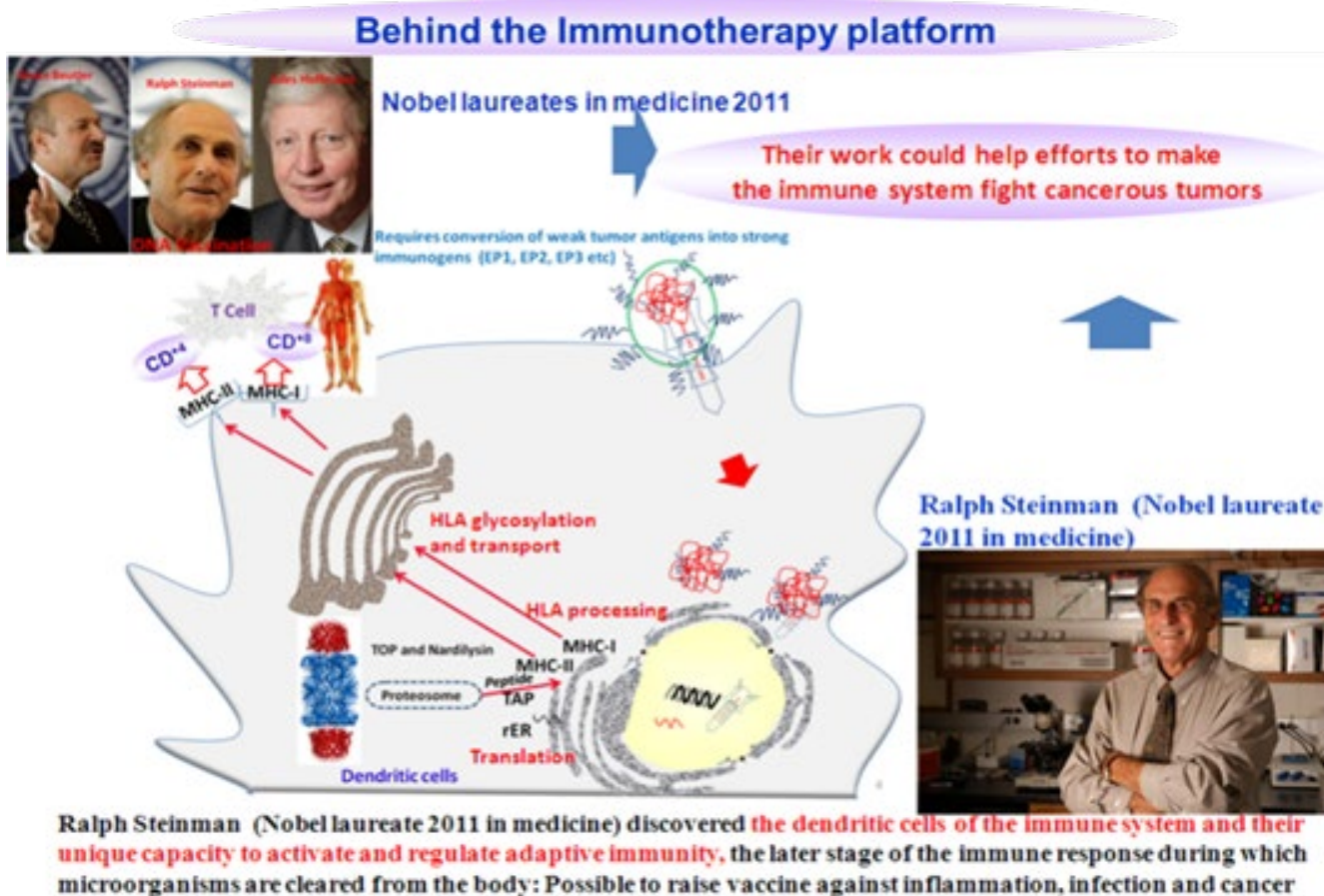
## Behind the Immunotherapy platform

Nobel Laureates of medicine in 2011 showed that the immune system fight against cancerous tumor and Ralph Steinman one of the Nobel Laureates of medicine in 2011 discovered dendritic cells and their unique capacity to activate and regulate adaptive immunity and the later stage of the immune system to clear microorganism from the body. Dendritic cells are the potential immune cells to represent the antigen to T-Cells against foreign bodies in the biological system. There are various types of T-Cells like Th1, Th2, Th3, Th17, ThFM, Treg, Cytotoxic CD8 T-Cell, and memory T-cells (Tmem).

Immunotherapy, also called biologic therapy, is a type of cancer/fatal disease treatment designed to boost the body's natural defenses to fight the cancer/fatal disease. It uses materials either made by the body or in a laboratory to improve, target, or restore immune system function. It is not entirely clear how immunotherapy treats cancer/fatal disease

Figure 1. Immunotherapy platform and antigen delivery to dendritic cell for vaccine
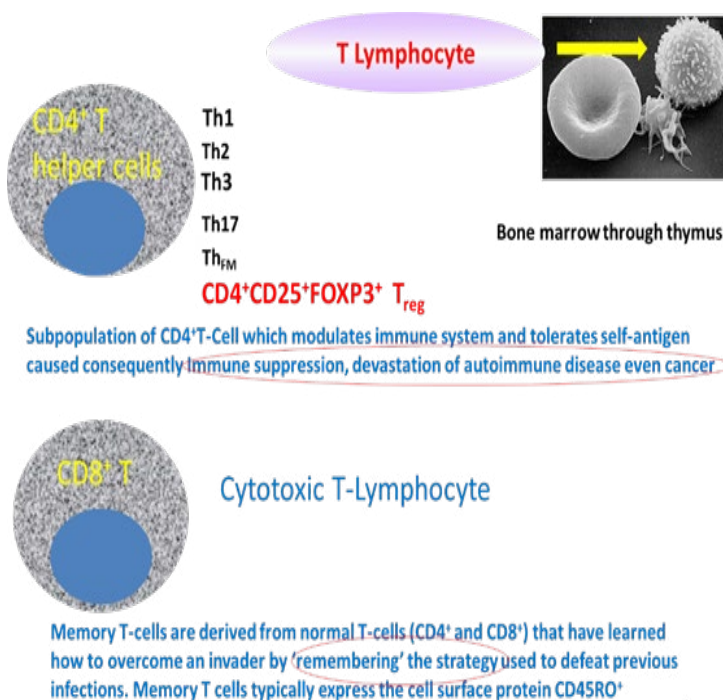
Figure 2. Treg and Tmem lymphocyte in nature

There are several types of immunotherapy, including: a) Monoclonal antibodies, b) Non-specific immunotherapies, c) Cancer vaccines and d) Oncolytic virus therapy,

Monoclonal antibodies

When the body's immune system detects something harmful, it produces antibodies. Antibodies are proteins that fight infection. Monoclonal antibodies are a specific type of therapy made in a laboratory. They are designed to attach to specific proteins in a cancer cell. These therapies are highly specific, so they do not affect cells that do not have that protein.

Monoclonal antibodies are used as cancer treatments in various ways:

To allow the immune system itself to destroy the cancer cell. The immune system doesn't always recognize cancer cells as being harmful. This is one of the ways that cancer can grow and spread. Researchers have identified the PD-1 pathway as being critical to the immune system's ability to control cancer growth. Blocking this pathway with PD-1 and PD-L1 antibodies can stop or slow cancer growth. These immunotherapy drugs may be referred to as checkpoint inhibitors because they interrupt an important part of the immune system process. Examples of checkpoint inhibitors include ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda). Additional drugs are being studied.

Non-specific immunotherapies

Like monoclonal antibodies, non-specific immunotherapies also help the immune system destroy cancer cells. Most non-specific immunotherapies are given after or at the same time as another cancer treatment, such as chemotherapy or radiation therapy. However, some non-specific immunotherapies are given as the main cancer treatment.

Two common non-specific immunotherapies are:

Interferons.Interferons help the immune system fight cancer and may slow the growth of cancer cells. An interferon made in a laboratory, called interferon alpha (Roferon-A [2a], Intron A [2b], Alferon [2a]), is the most common type of interferon used in cancer treatment. Side effects of interferon treatment may include flu-like symptoms, an increased risk of infection, rashes, and thinning hair.

Interleukins. Interleukins help the immune system produce cells that destroy cancer. An interleukin made in a laboratory, called interleukin-2, IL-2, or aldesleukin (Proleukin), is used to treat kidney cancer and skin cancer, including melanoma. Common side effects of IL-2 treatment include weight gain and low blood pressure, which can be treated with other medications. Some people may also experience flu-like symptoms.

Cancer vaccines

A vaccine is another method used to help the body fight disease. A vaccine exposes the immune system to an antigen. This triggers the immune system to recognize and destroy that protein or related materials. There are two types of cancer vaccines: prevention vaccines and treatment vaccines.

Prevention vaccine. A prevention vaccine is given to a person with no symptoms of cancer. It is used to keep a person from developing a specific type of cancer or other cancer-related disease. For example, Gardasil and Cervarix are vaccines that prevent a person from being infected with the human papillomavirus (HPV). HPV is a virus known to cause cervical cancer and some other types of cancer. In addition, the U.S. Centers for Disease Control and Prevention recommends that all children should receive a vaccine that prevents infection with the hepatitis B virus. A hepatitis B infection may cause liver cancer.

Treatment vaccine. A treatment vaccine helps the body's immune system fight cancer by training it to recognize and destroy cancer cells. It may prevent cancer from coming back, eliminate any remaining cancer cells after other types of treatment, or stop cancer cell growth. A treatment vaccine is designed to be specific, which means it should target the cancerous cells without affecting healthy cells. At this time, sipuleucel-T (Provenge) is the only treatment vaccine approved in the United States. It is designed for treating metastatic prostate cancer. Additional cancer treatment vaccines are still in development and only available through clinical trials. Recent findings provided a preclinical rationale to apply CD27 agonist antibodies, either alone or combined with PD-1 blockade, to improve the therapeutic efficacy of cancer vaccines and immunotherapy generally .

Oncolytic virus therapy

Oncolytic virus therapy is a new type of immunotherapy that uses genetically modified viruses to kill cancer cells. First, the doctor injects a virus into the tumor. The virus enters the cancer cells and makes copies of itself. As a result, the cells burst and die. As the cells die, they release cancer antigens. This triggers the patient's immune system to launch an attack on all cancer cells in the body that have those same antigens. The virus does not enter healthy cells.

In October 2015, the U.S. Food and Drug Administration approved the first oncolytic virus therapy to treat melanoma. The virus used in the treatment is called talimogenelaherparepvec (Imlygic), or T-VEC. The virus is a genetically modified version of the herpes simplex virus that causes cold sores. The doctor can inject T-VEC directly into melanoma lesions that a surgeon cannot remove. Patients receive a series of injections until there are no lesions left. A potential issue limiting the immune response to vaccination is the presence of regulatory T cells (Tregs) that suppress T cell activation[3,4]
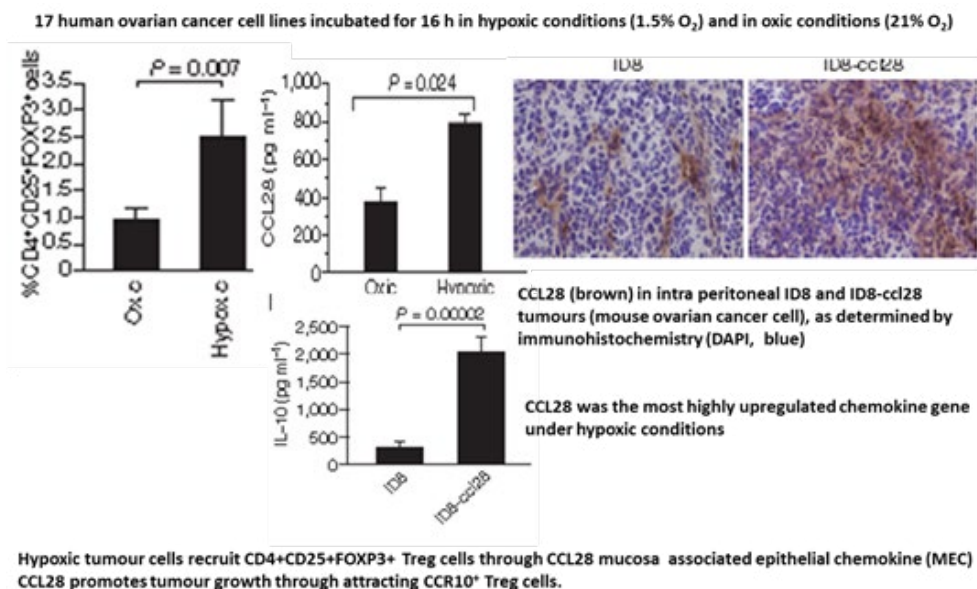
Treg, Regulatory T-Cells

Treg is functionally known as CD4+CD25+FOXP3+.A selective increase of the chemokines CXCL9 and CXCL10 inTreg-cell-depleted tumors, which was accompanied by accumulation of CXCR3+T cells, and increased IFN-γ mRNA expression. Treg-cell depletion increases the accumulation of conventional T cell .

Treg in Tumor Hypoxia environment

Tumor hypoxia promotes tolerance and angiogenesis via CCL28 and Treg cell[6]

Figure 3. Treg cells in Hypoxia and CCL28 MEC, mucosa associated epithelial chemokine4

Tregand Tumor-Specific CD8+ T Cells in tumor microenvironment Suppression of Tumor-Specific CD8+ T Cells by Regulatory T Cells Treg and Treg cells secrete interleukin-10 as well as transforming growth factor-beta1, mediates immune suppression in the tumor microenvironment . The following figures (Figure 4 and Figure 5) illustrated that suppression of Treg increased the population of CD8+ T cells and interferon gamma secretion. These events outcome of a promising antitumor activity. Epitope antigen successively can control such kind of suppression of Treg, which can potentiate functionally future Protein/DNA vaccine. Treg depletion improves the efficacy of vaccines against pathogens in mice . Therefore, vaccine strategies that target both the innate and adaptive immune systems for the generation/upregulation of potent anti-pathogenic immune responses and simultaneously overcome Treg-mediated immune inhibition are more likely to succeed.
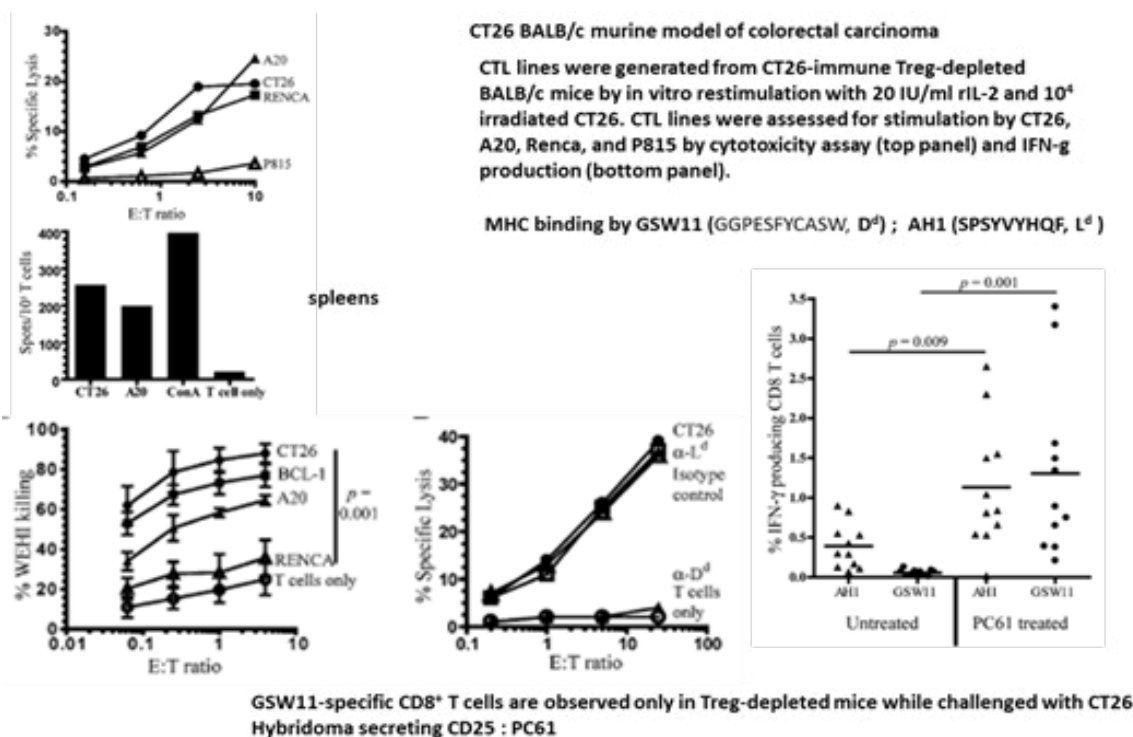
**Figure. 4** CD8+T cells in colorectal carcinoma and Treg depletion
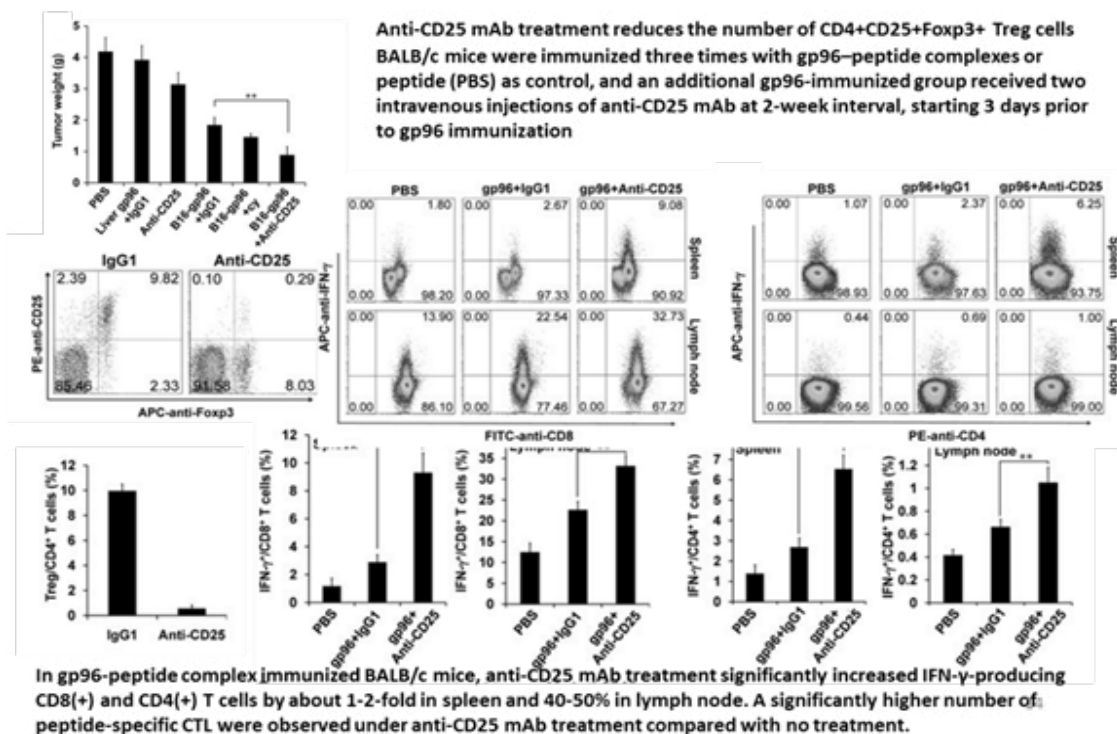
Figure 5. GP96 immunization as well as Anti-CD25mAb treatment and IFN-gamma producing CD8+ cells. Regulatory T-cell depletion synergize with gp96-mediated cellular responses and antitumor activity .

Memory T-Cell

Adaptive immunity is said to have memory because the immune system learns. In this way we gain life-long immunity to infections such as against mumps, small pox, tuberculosis and so on. Memory T cells comprise two subtypes: central memory T cells (TCmCells) and effector memory T cells (TEmem Cells).
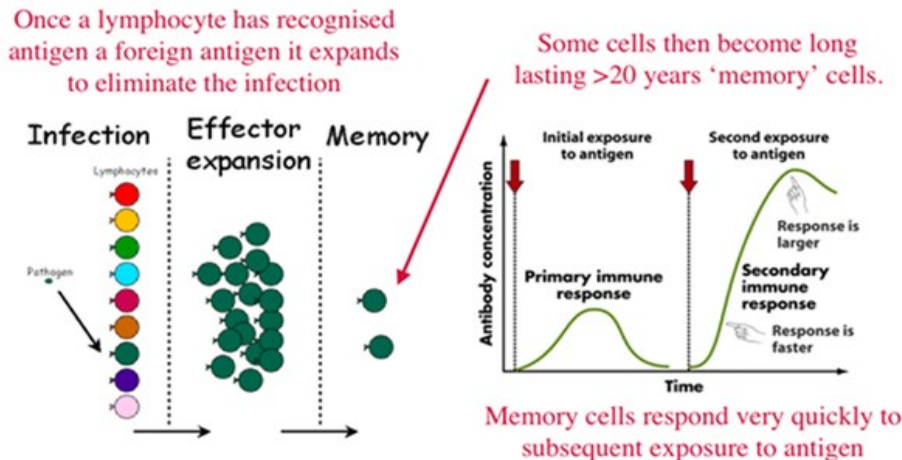
Figure 6. A schematic diagram of long term Immunity by T-Cell group, University of Cardiff, UK.

A novel self-assembled nanoparticle vaccine with HIV-1 Tat49-57/HPV16 E749-57fusion peptide and GM-CSF DNA elicits potent and prolonged CD8+ T cell-dependent anti-tumor immunity in mice. Very recently one research group discovered that central memory CD4+ T-cells (TCm) of SMs (Sooty Mangabeys) are exquisitely resistant to (mucosal CD4+ T-cells expressing the SIV co-receptor) CCR5 up-regulated upon in vivo and in vitro activation, and that this pattern of reduced CCR5 expression is associated with lower in vivo and in vitro susceptibility of CD4+TCmto direct SIV infection.

Mice vaccinated with Tat-E7/pGM-CSF generated a significantly higher amount of CD3+CD8+CD45RO+ T memory cells, as compared to those mice vaccinated with the control agents (P < 0.01). Low levels of SIV infection in sooty mangabey central-memory CD4+ T-cells is associated with a limited CCR5 expression that caused the host uninfected
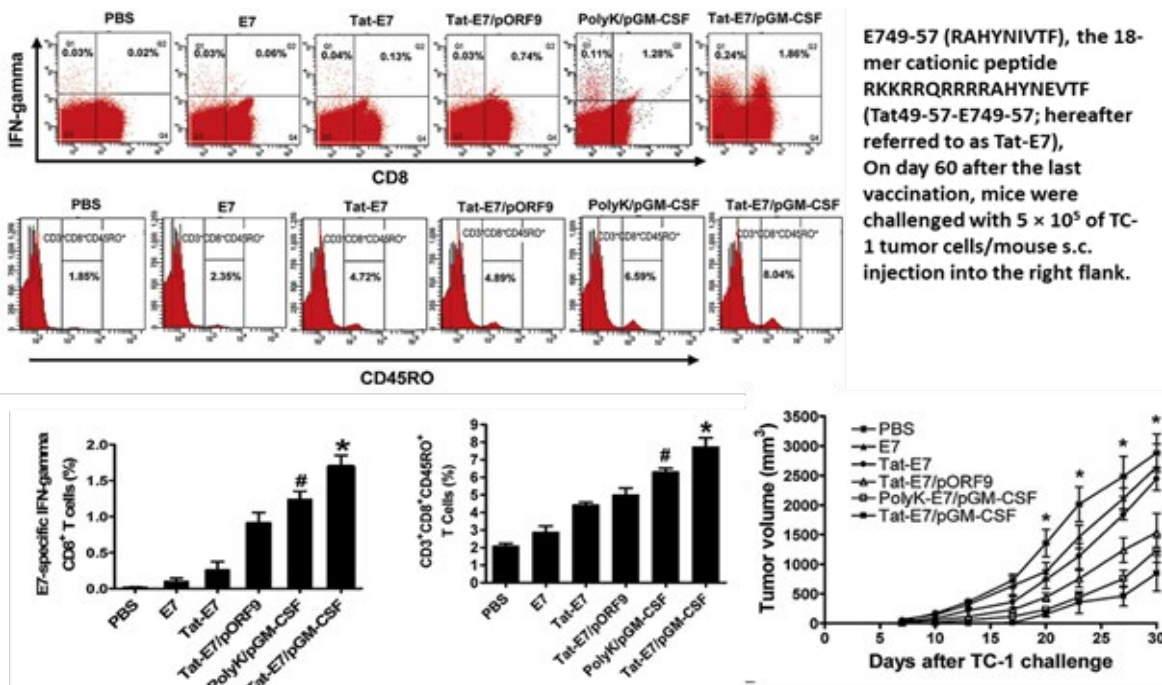
Figure 7. HIV-1 Tat49-57/HPV16 E749-57 fusion peptide and GM-CSF DNA: A prolonged CD8+ T cell-dependent anti-tumor immunity in mice . Mice vaccinated with Tat-E7/pGM-CSF generated a significantly higher amount of CD3+CD8+CD45RO+ T memory cells, as compared to those mice vaccinated with the control agents (P < 0.01)
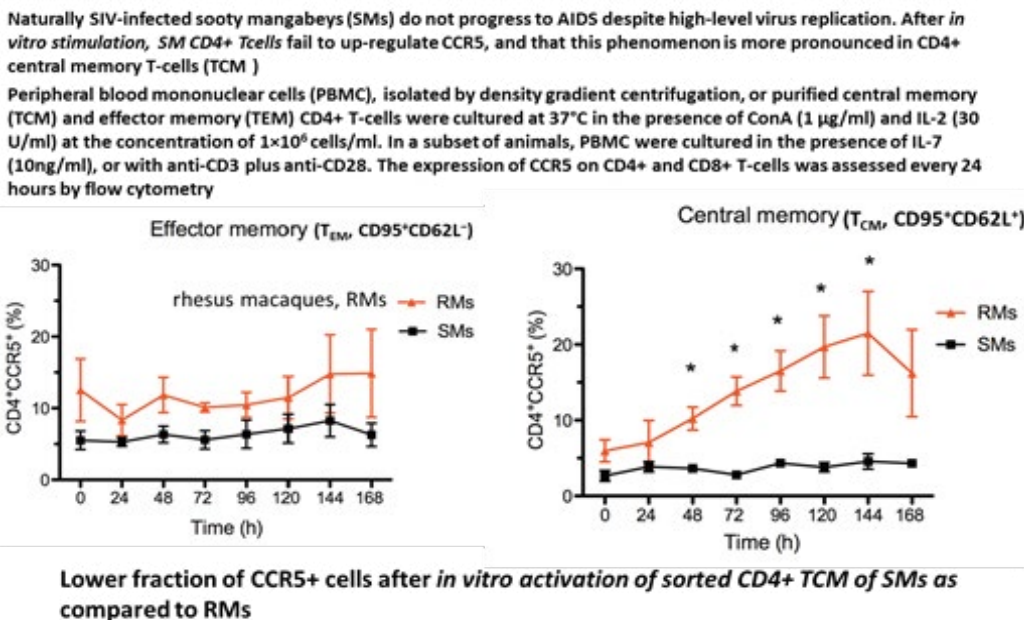
Figure 8. Central-memory CD4+ T-cells and CCR5 expression in SIV infected sooty mangabey. Low levels of SIV infection in sooty mangabey central-memory CD4+ T-cells is associated with a limited CCR5 expression that caused the host uninfected
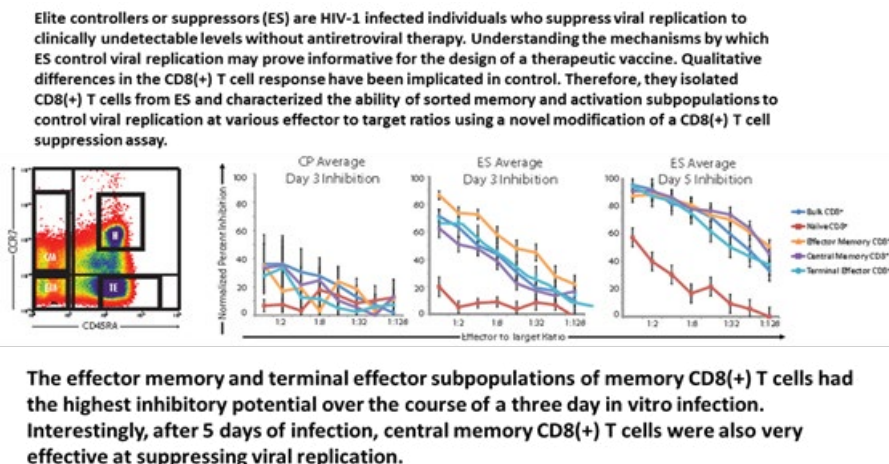
Elite controllers or suppressors (ES) are HIV-1 infected individuals who suppress viral replication to clinically undetectable levels without antiretroviral therapy. Understanding the mechanisms by which ES control viral replication may prove informative for the design of a therapeutic vaccine. Qualitative differences in the CD8(+) T cell response have been implicated in control. Therefore, they isolated CD8(+) T cells from ES and characterized the ability of sorted memory and activation subpopulations to control viral replication at various effector to target ratios using a novel modification of a CD8(+) T cell suppression assay.

The effector memory and terminal effector subpopulations of memory CD8(+) T cells had the highest inhibitory potential over the course of a three day in vitro infection. Interestingly, after 5 days of infection, central memory CD8(+) T cells were also very effective at suppressing viral replication.

Figure 9. Inhibitory Potential of Subpopulations of CD8+ T Cells in HIV-1 Infected Elite Suppressors

T memory/effector cells (Tmem/off) isolated from psoriasis patients are chronically activated and poorly suppressed by regulatory T cells (Treg). The proinflammatory cytokine IL-6, which signals through Stat3, allows escape ofTmem/effcellsfromTreg-mediated suppression in a marine system. One research group showed that IL-6 protein was markedly elevated and most highly expressed by CD31 (+) endothelialcellsand CD11c (+) dermal dendritic cells (DCs) in lesional psoriatic skin. They hypothesized that exposure to high IL-6 in lesional tissue may lead to the dampenedTreg function observed in psoriasis patients[15] .

Activation of Th17 cells in experimental autoimmune encephalitis is associated with the escape of Teff from Treg control[16] . Given that IL-6 signaling leads to a loss of Treg function (Fig. 5↑, IL-6-producing cells in the lesion likely contribute to the reactivity of tissue Teff by dampening normal Treg control mechanisms. As a critical factor in the homeostatic balance between Th17 cells and Treg , the high levels of IL-6 generated by DCs and endothelial cells in lesional skin likely tips the balance in favor of pathogenic Th1 and Th[17] cells over Treg, further allowing for unrestrained T cell activation. Thus, targeting IL-6 and its downstream signaling pathways within the lesional psoriatic skin holds promise in the restoration of functional Treg control over Tmem/off activation.

One research group presented the evidence for intranasal delivery of the model antigen ovalbumin (OVA) along with alpha-galactosylceramide adjuvant as a protein vaccine to induce significantly higher levels of antigen-specific effector and memory CD8+T cells in the FRT (Female Reproductive Tract), relative to other systemic and mucosal tissues. Antibody blocking of the CXCR3 receptor significantly reduced antigen-specific CD8+ T cells subsequent to intranasal delivery of the protein vaccine, suggesting an important role for the CXCR3 chemokine-receptor signaling for T cell trafficking. Further, intranasal vaccination with an adenoviral vector expressing OVA or HIV-1 envelope was as effective as intramuscular vaccination for generating OVA- or ENV-specific immunity in the FRT. These results supported the application of the needle-free intranasal route as a practical approach to delivering protein as well as DNA/virus vector-based vaccines for efficient induction of effector and memory T cell immunity in the FRT[18].

Conclusion

Central memory CD4+ RO+ and CD8+T RO+cells were very effective at suppressing viral replication. Evaluating and developing the Central memory CD4+ RO+ and CD8+T RO+cells in immunization by both DNA and protein vaccine, life-long antigen specific immunity might be possible against cancer and many other fatal diseases ahead.

http://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines/understanding-immunotherapy

2. Ahrends T, Bąbała N, Xiao Y, Yagita H, van Eenennaam H, Borst J. CD27 agonism plus PD-1 blockade recapitulates CD4+ T cell help in therapeutic anti-cancer vaccination.Cancer Res. 2016 Mar 28. pii: canres.3130.2015. [Epub ahead of print]

3. Aloysius MM, Mc Kechnie AJ, Robins RA, Verma C, Eremin JM, et al. (2009) Generation in vivo of peptide-specific cytotoxic T cells and presence of regulatory T cells during vaccination with hTERT (class I and II) peptide-pulsed DCs. J Transl Med 7: 18.

4. Toka FN, Suvas S, Rouse BT (2004) CD4+ CD25+ T cells regulate vaccine-generated primary and memory CD8+ T-cell responses against herpes simplex virus type 1. J Virol 78: 13082–13089.

5. Akeus P,Langenes V, Kristensen J, von Mentzer A, Sparwasser T, Raghavan S, Quiding-Järbrink M., Treg-cell depletion promotes chemokine production and accumulation of CXCR3+ conventional T cells in intestinal tumors.Eur J Immunol. 2015

6. Facciabene A et al. Nature. 2011;475(7355):226-30.

7. James E,Yeh A,King C,Korangy F,Bailey I,Boulanger DS,Van den Eynde BJ,Murray N,Elliott TJ. Differential suppression of tumor-specific CD8+ T cells by regulatory T cells. J Immunol.2010;185(9):5048-55.

8. Cabrera G, Mundinano J, Camicia G, Costa H, Nepomnaschy I, et al. (2011) [Regulatory T cell depletion increases the number of CD8 cells during mouse mammary tumor virus infection]. Medicina (B Aires) 71: 243–246.

9. Dietze KK, Zelinskyy G, Gibbert K, Schimmer S, Francois S,

et al. (2011) Transient depletion of regulatory T cells in transgenic mice reactivates virus-specific CD8+ T cells and reduces chronic retroviral set points. Proc Natl AcadSci U S A 108: 2420–2425

10. Yan X et al. Cancer ImmunolImmunother. 2011 Dec;60(12):1763-74

11. http://www.tcells.org/scientific/memory/

12. J. Tang et al. / Vaccine 30 (2012) 1071– 1082

13. Paiardini et al. Nat Med. 2012 ; 17(7): 830–836

14. Buckheit RW 3rd,Salgado M,Silciano RF,Blankson JN., InhibitorypotentialofsubpopulationsofCD8+TcellsinHIV-1-infectedelitesuppressors.J Virol. 2012 Oct 10J Virol.2012 Dec;86(24):13679-88.

15. Goodman WA,Levine AD,Massari JV,Sugiyama H,McCormick TS,Cooper KD. IL-6 signaling in psoriasis prevents immune suppression by regulatory Tcells. J Immunol.2009 ;183(5):3170-6.

16. Serada, S., M. Fujimoto, M. Mihara, N. Koike, Y. Ohsugi, S. Nomura, H. Yoshida, T. Nishikawa, F. Terabe, T. Ohkawara, et al 2008. IL-6 blockade inhibits the induction of myelin antigen-specific Th17 cells and Th1 cells in experimental autoimmune encephalomyelitis.Proc. Natl. Acad. Sci. USA 105:9041-9046.

17. Lochner, M., L. Peduto, M. Cherrier, S. Sawa, F. Langa, R. Varona, D. Riethmacher, M. Si-Tahar, J. P. Di Santo, G. Eberl.2008. In vivo equilibrium of proinflammatory IL-17+and regulatory IL-10+Foxp3+RORγ+T cells.J. Exp. Med.205:1381-1393.

18. Singh S, Schluns KS, Yang G, Anthony SM, Barry MA, Sastry KJ, Intranasal Vaccination Affords Localization and Persistence of Antigen-Specific CD8+T Lymphocytes in the Female Reproductive Tract. Vaccines (Basel).2016 Mar 17;4(1). pii: E7. doi: 0.3390/vaccines4010007.