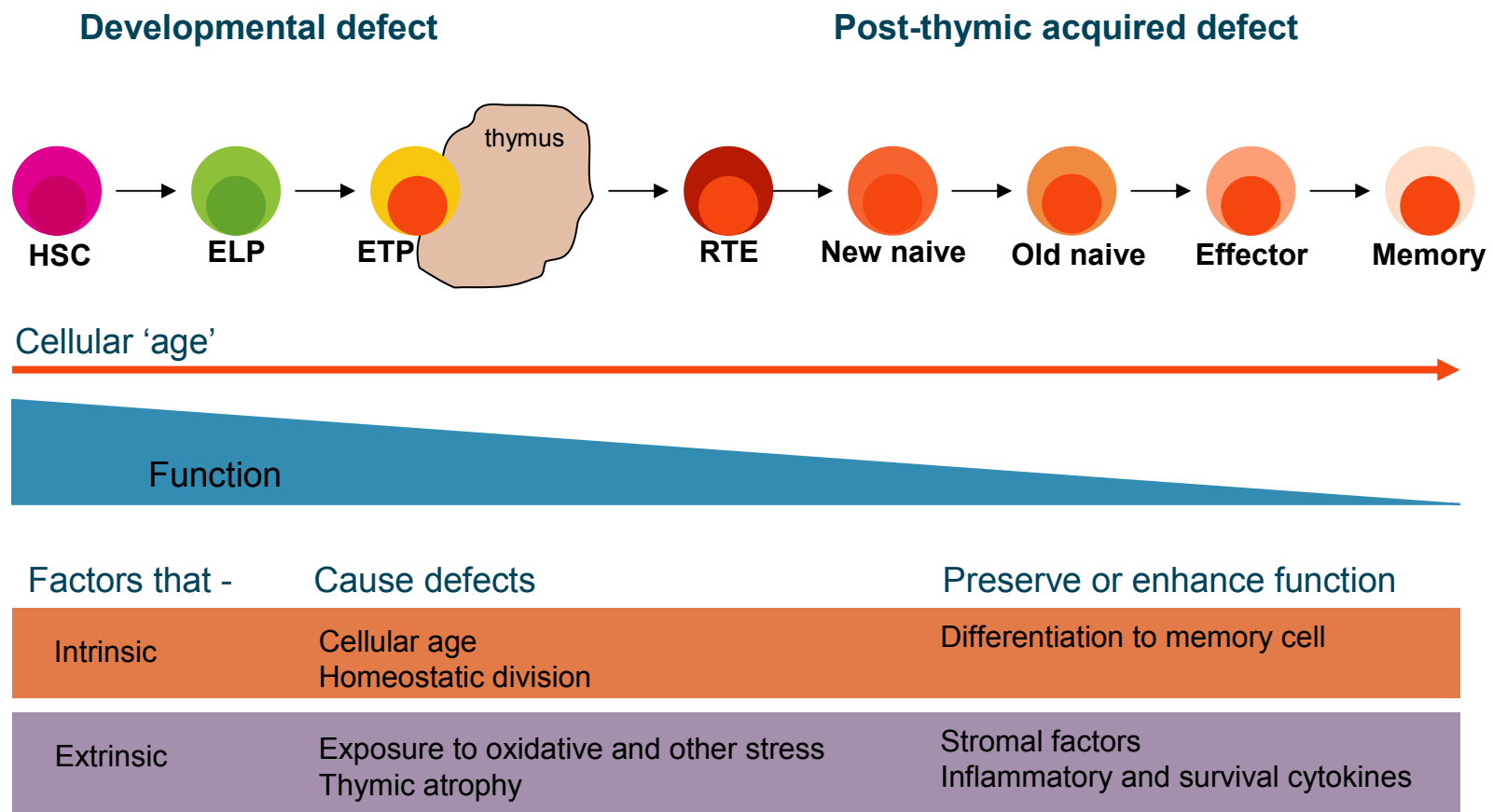


Therapeutic strategies to boost the ageing immune system

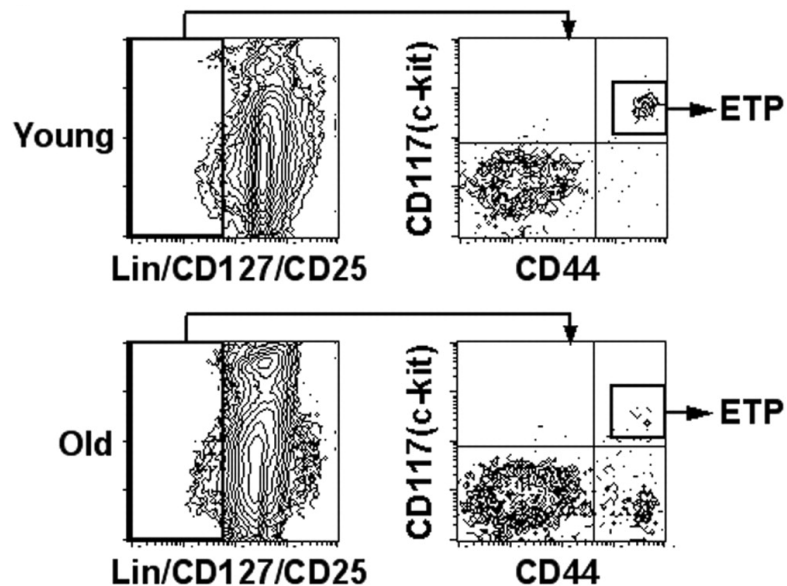
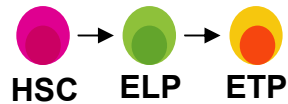
Dr Sian Henson

Challenges of the ageing immune system



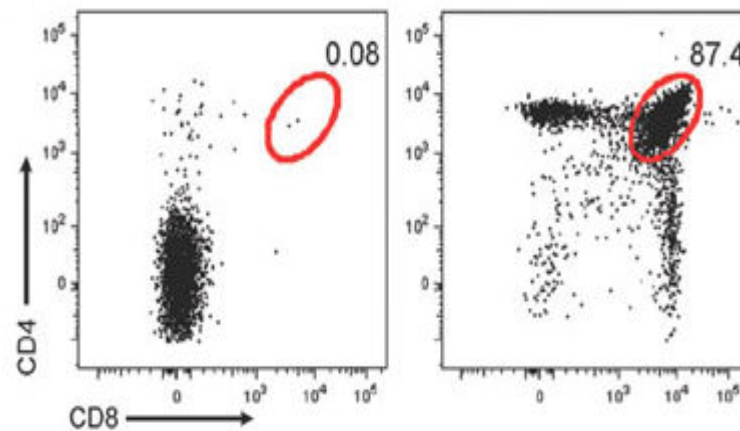
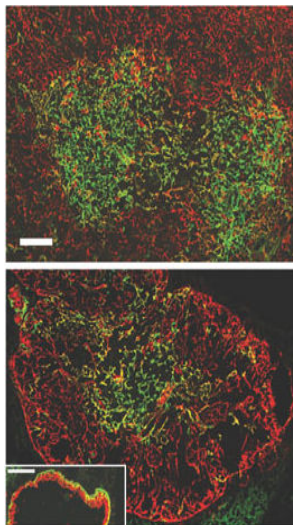
Challenges of the ageing immune system

Developmental defect



- Gene therapy?
- Stem cell therapy?

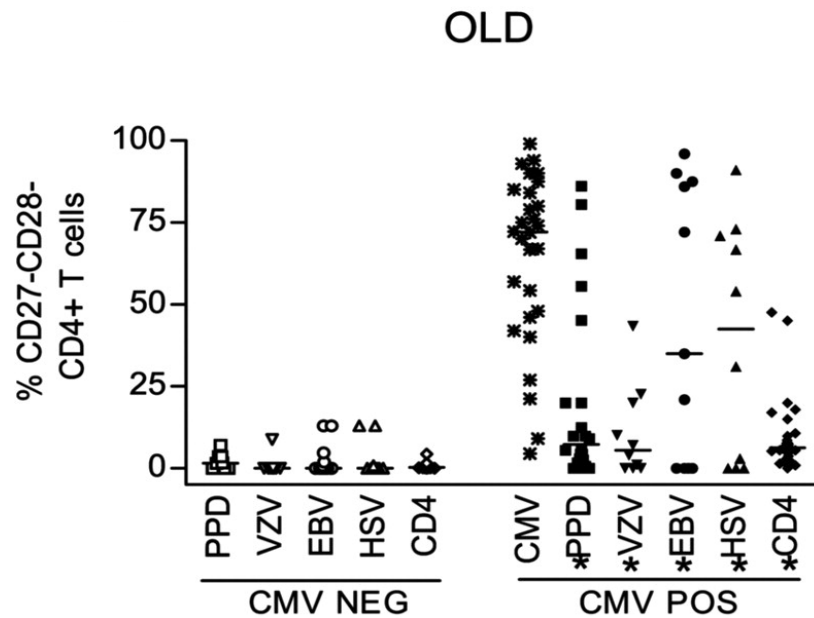
Formation of a functional thymus by a epithelial progenitor cells



- Addition of FoxN1⁺ ETPs
- Formation of thymic lobules containing both cortical and medullary areas
- Can support normal T cell development

Challenges of the ageing immune system

Post-thymic acquired defect



Fletcher et al. 2006 J. Immunol

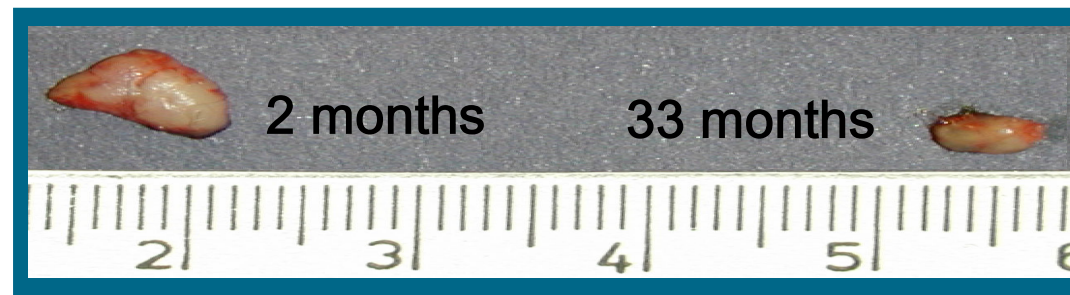
- Treat the CMV infection?
- Vaccination against CMV?

Currently no licensed vaccine against CMV

- Many CMV vaccines have been tested in human trials
- Recipients who were originally CMV +ve do not benefit from vaccination
- Vaccination of CMV -ve renal transplant recipients results in a reduction of disease severity but not a prevention in infection

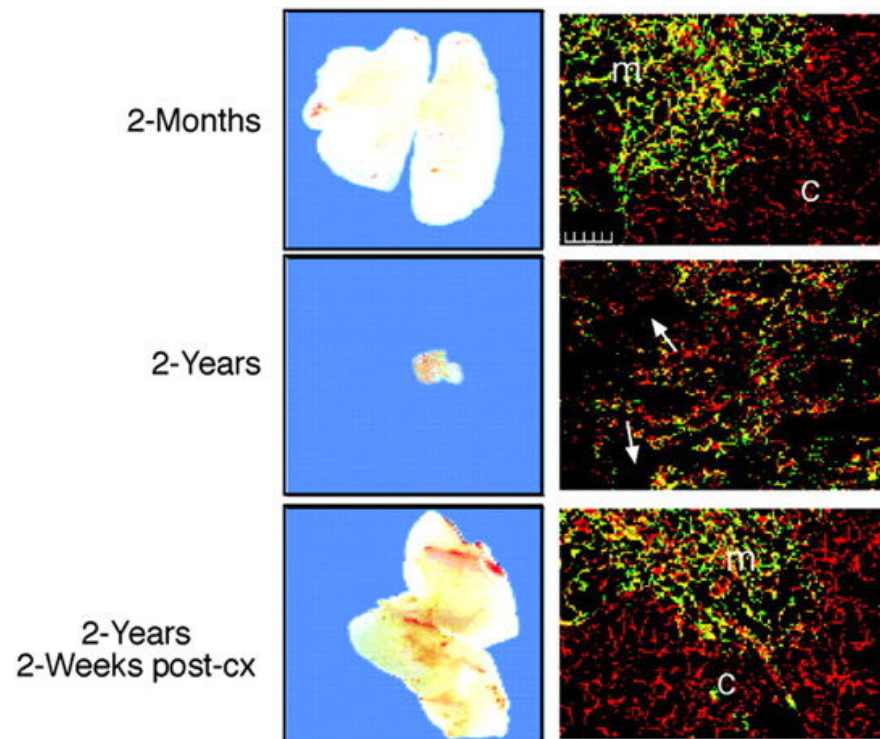
Challenges of the ageing immune system

Thymus



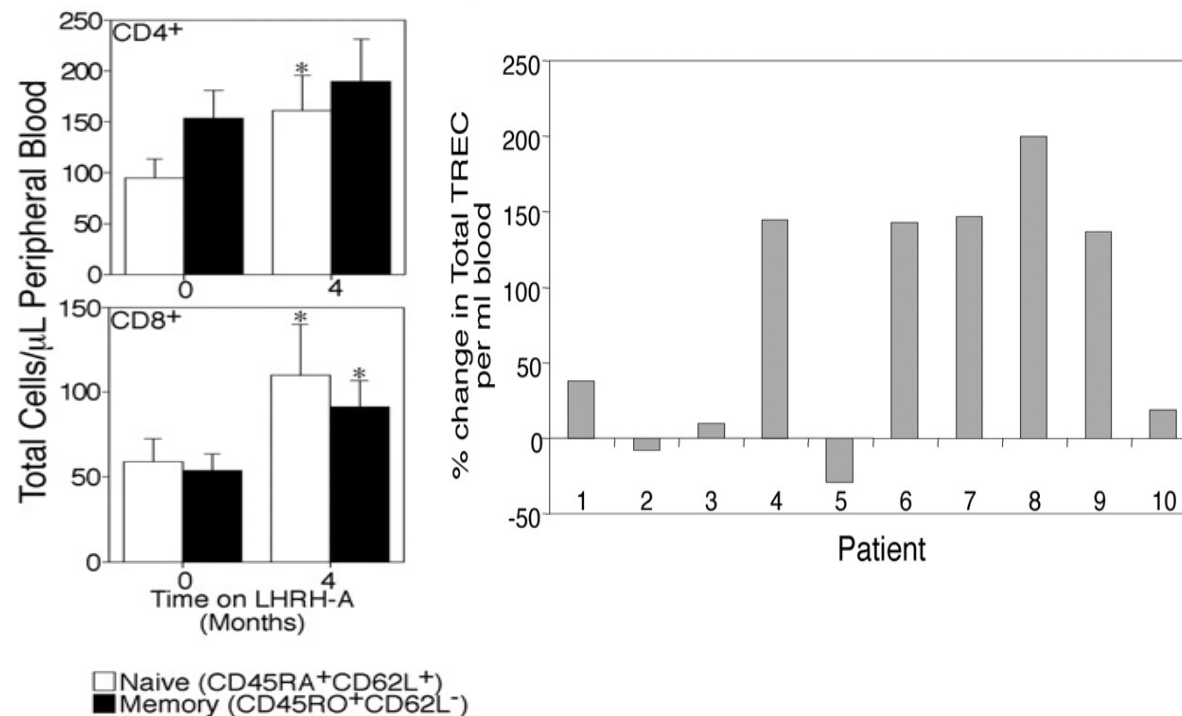
- Castration
- Sex steroid ablation
- Survival cytokines

Thymic regeneration in mice following castration



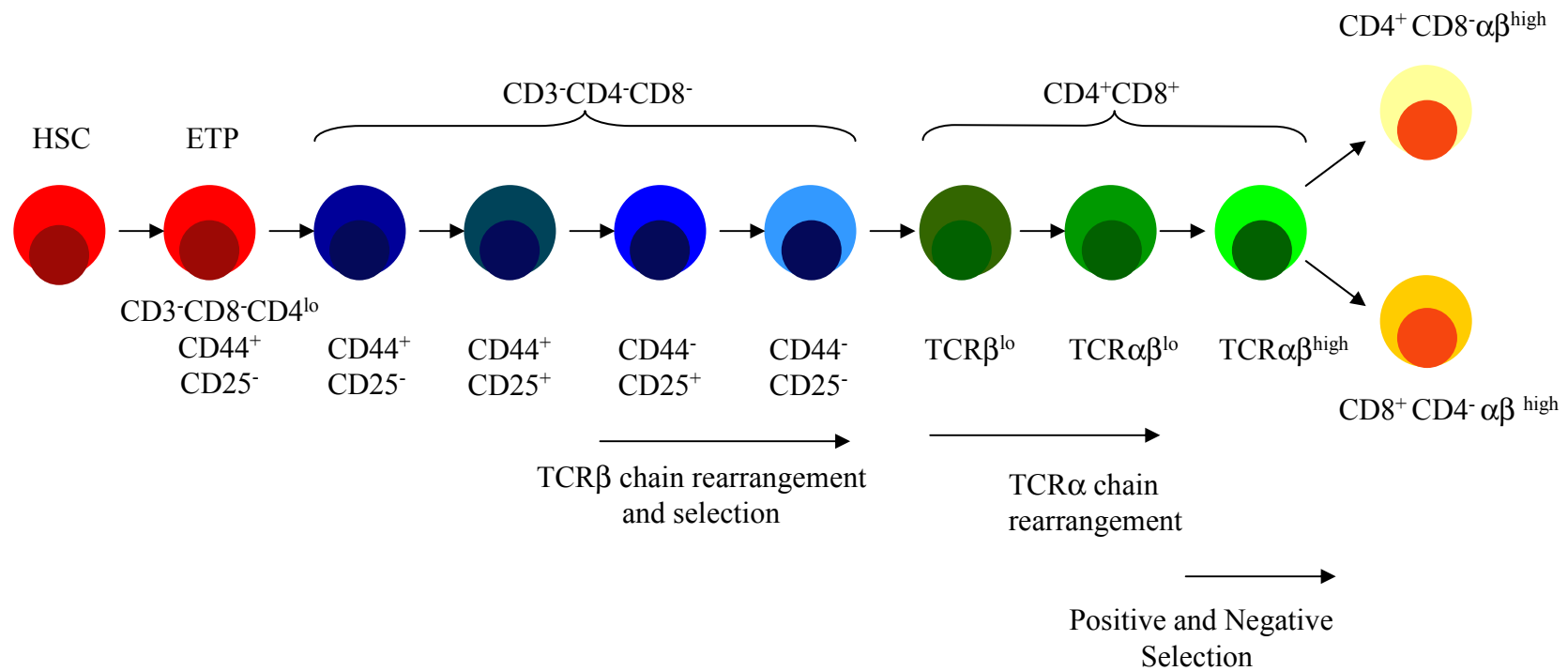
- Restoration of thymic architecture following castration

Thymic regeneration in humans following androgen blockade

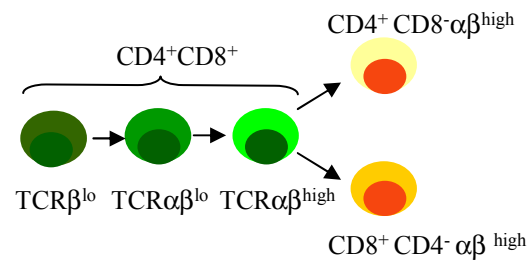


- Prostate cancer patients given LHRH
- After 4 months showed increased T cell numbers
- These cells are coming from the thymus

T cell development in the thymus

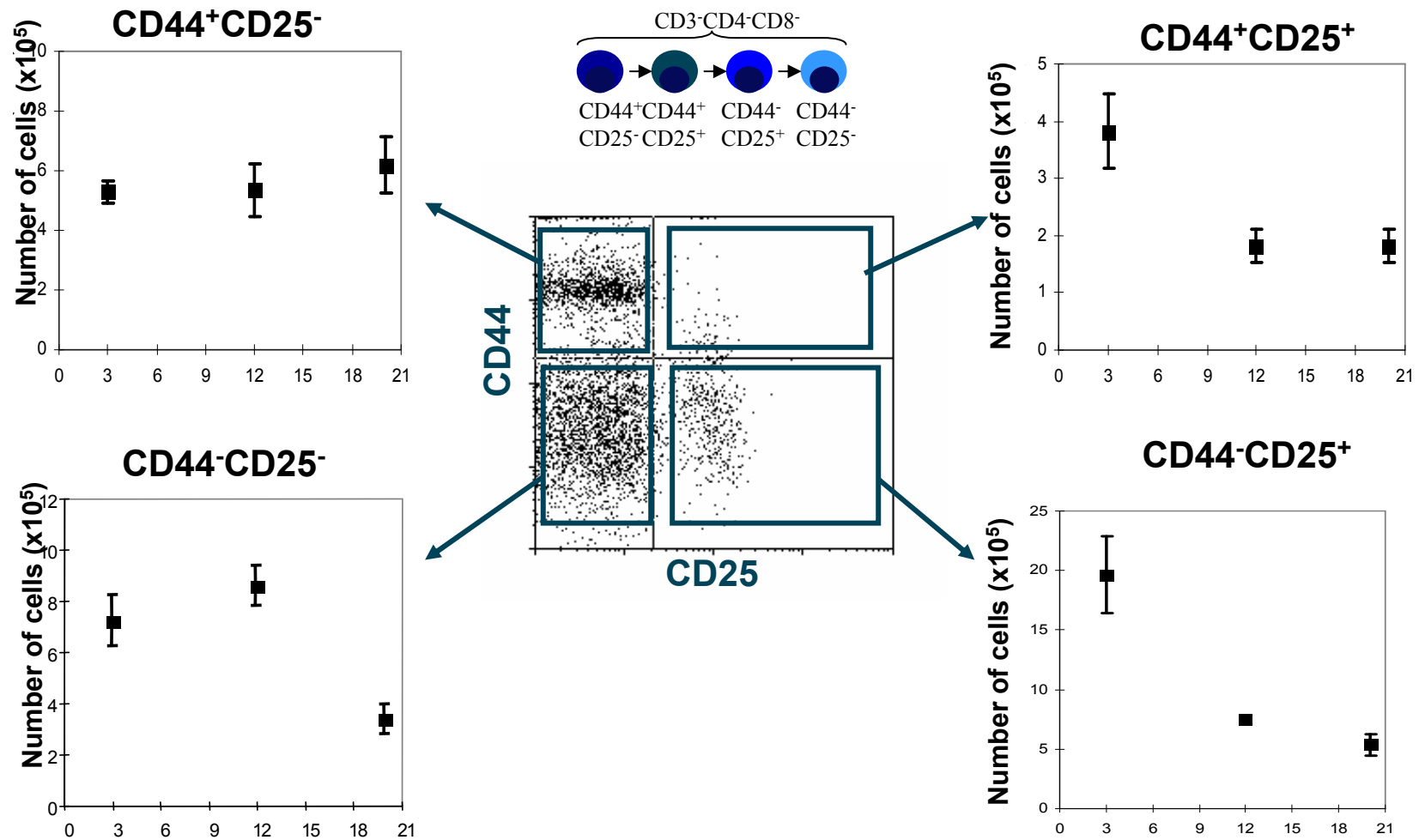


Effect of age on the T cell numbers

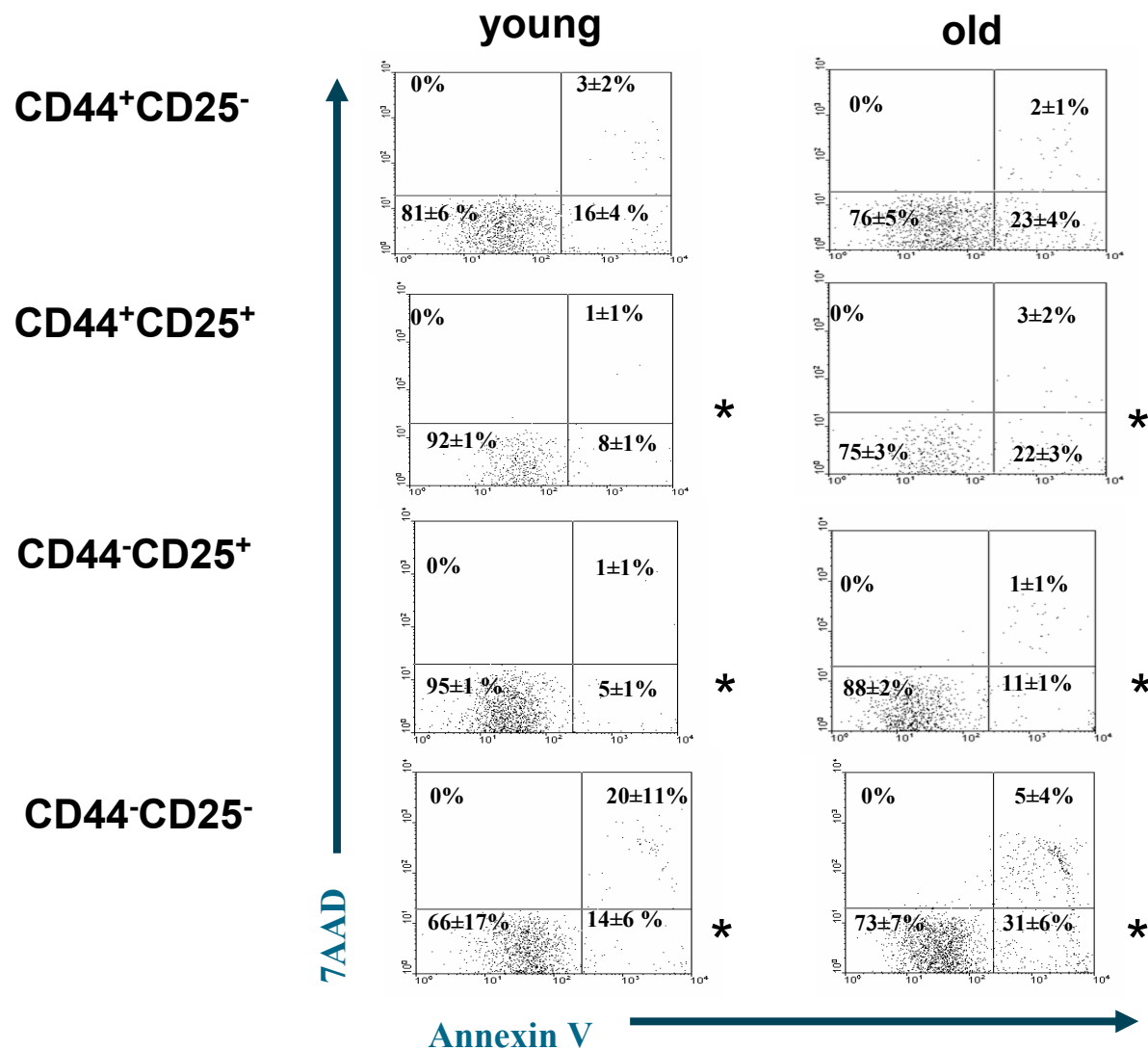


Age	n	Total	CD4 ⁺ CD8 ⁺	CD4 ⁺ CD8 ⁻	CD4 ⁻ CD8 ⁺
3 mo	9	1.64±0.3x10 ⁸ (100%)	1.4±0.3x10 ⁸ (86±3%)	1.2±0.4x10 ⁷ (7±2%)	8.5±4.7x10 ⁶ (5±2%)
20 mo	8	2.75±0.6x10 ⁷ (100%)	2.2±0.5x10 ⁷ (83±19%)	2.6±0.89x10 ⁶ (10±3%)	1.1±0.4x10 ⁶ (4±1%)
difference		1.36x10⁸	1.17x10⁸	9.32x10⁶	7.38x10⁶

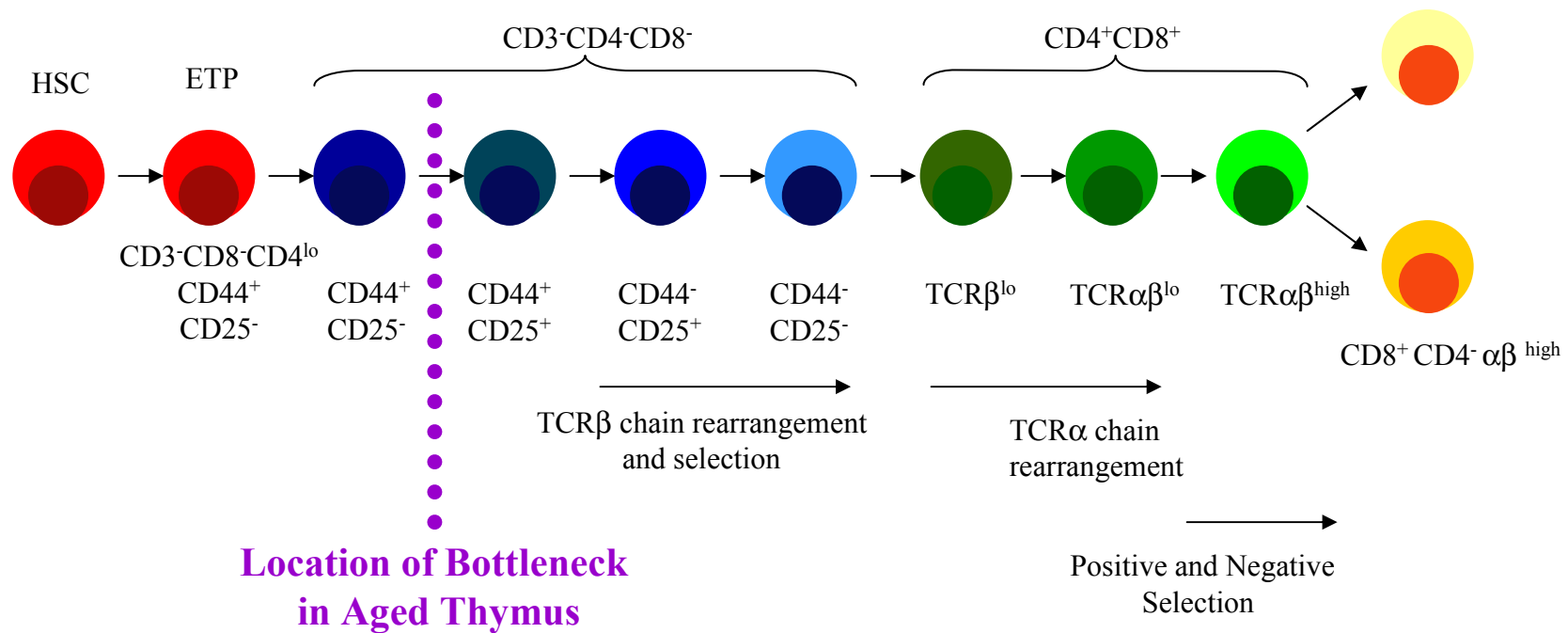
Ageing and intrathymic differentiation



Analysis of triple negative thymocytes



T cell development in the thymus

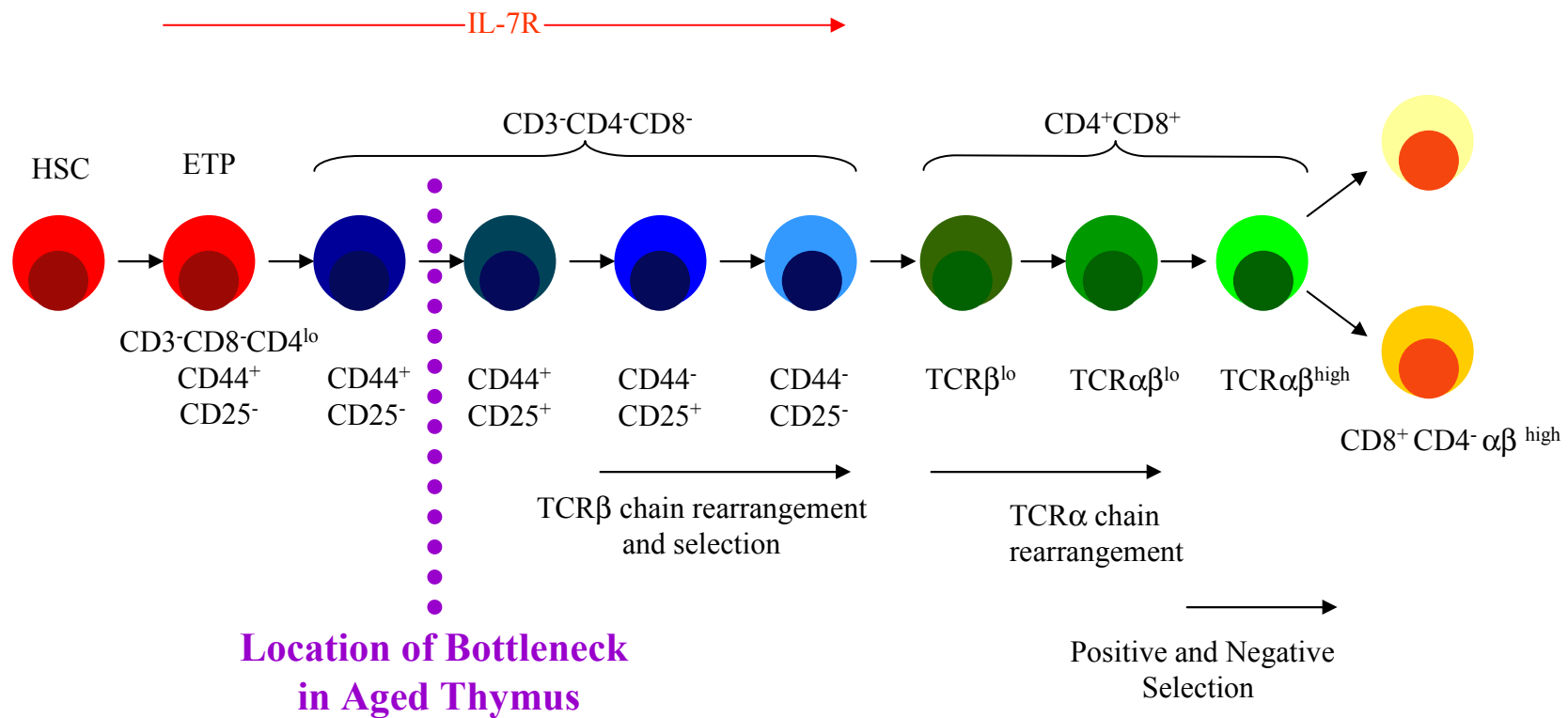


Possibly causes for this atrophy

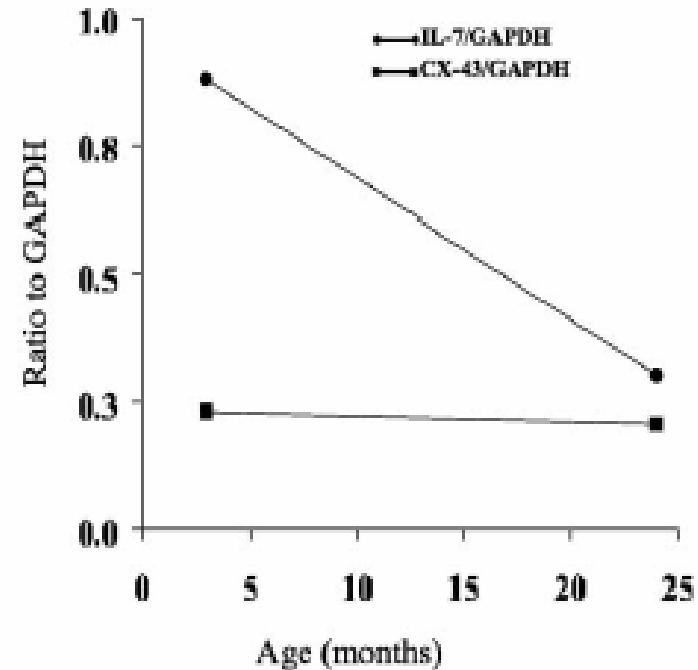
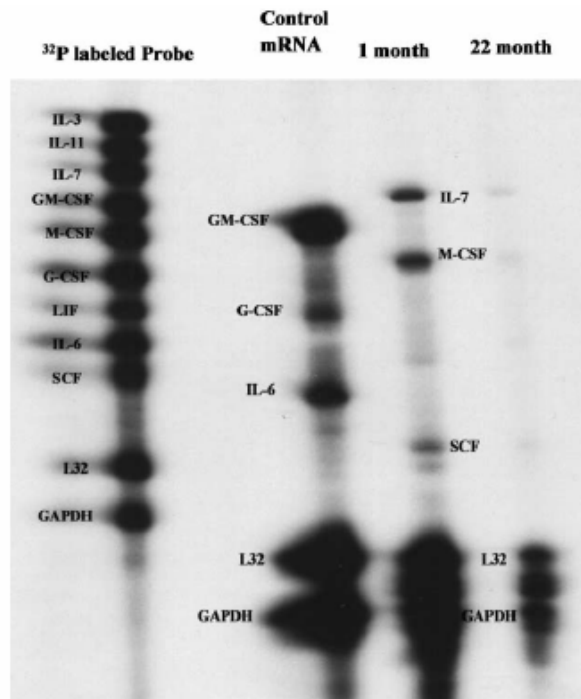
- Hypothesis

cells seeding from the bone marrow fail to differentiate and survive because of the environment.

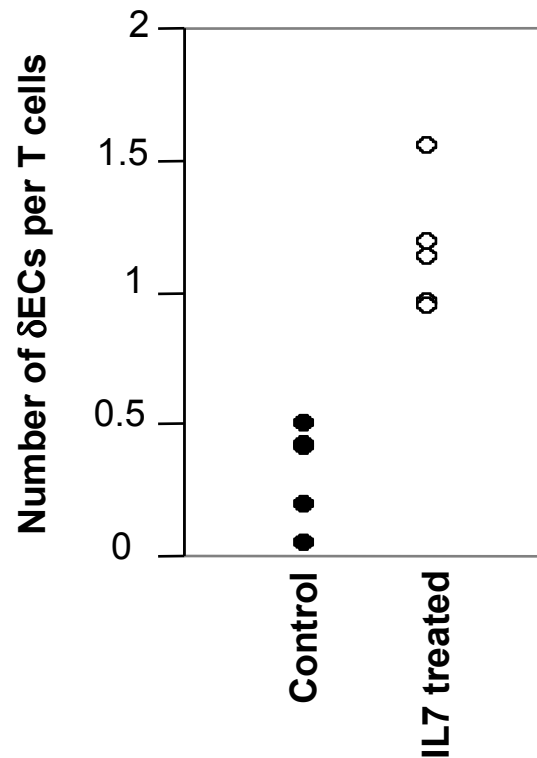
T cell development in the thymus



IL-7 production in the thymus declines with age

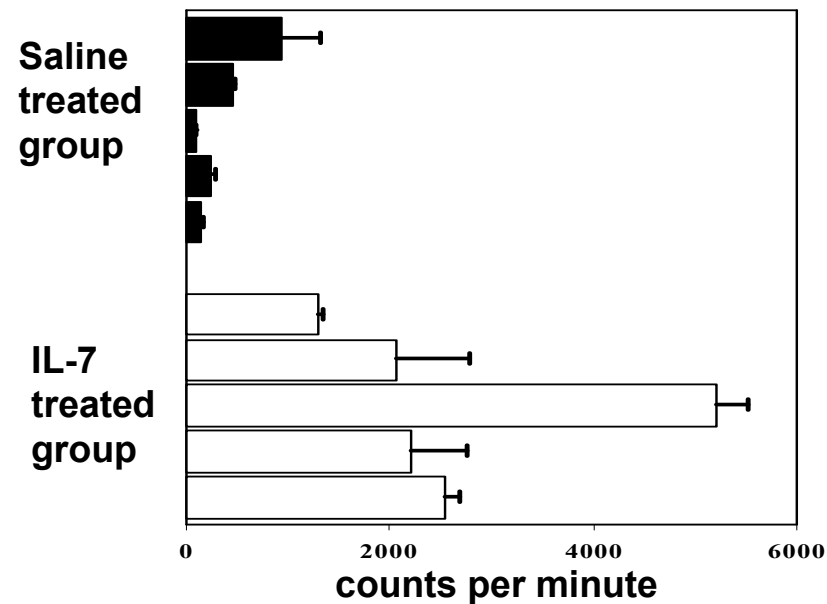


Benefits of IL-7 therapy - mouse



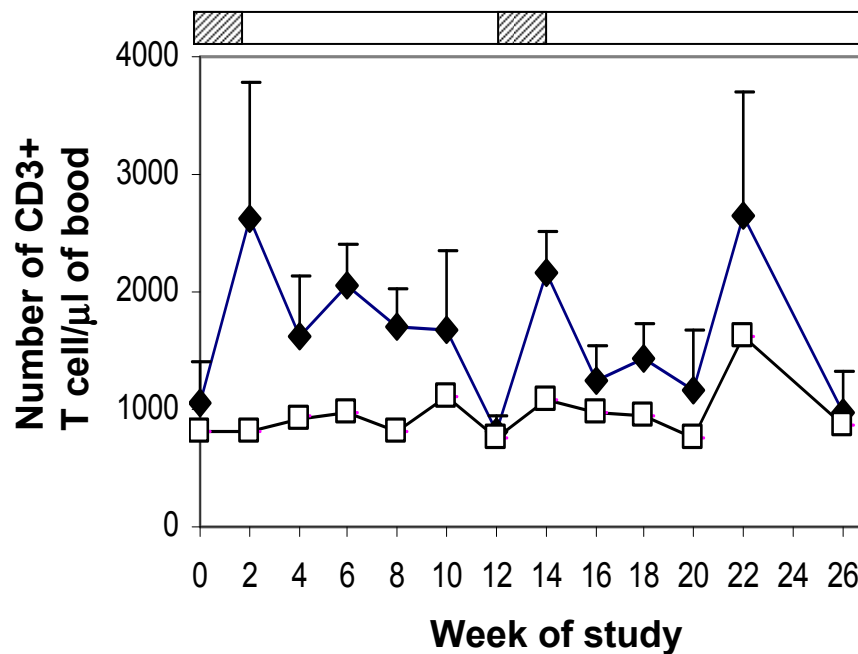
- Increased thymic output
- 24 month old mice, treated with IL-7 rested for 3 weeks, then 0.5×10^6 spleen cells used to measure δ EC levels

Benefits of IL-7 therapy - mouse



- Increased function
- 24 month old mice, treated with IL-7 rested for 3 weeks, then spleen cells tested for ability to proliferate to anti-CD3

Benefits of IL-7 therapy - rhesus macaque



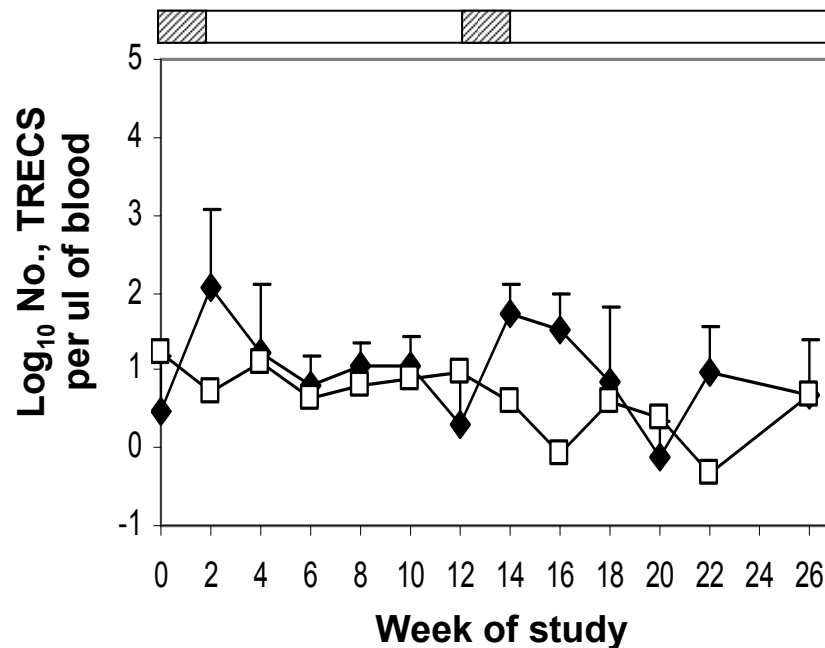
- Increased T cell numbers
- 20 year old rhesus macaques, treated with IL-7, blood taken and T cell numbers assessed

▨ IL-7 treatment period, 60 μ /Kg alternate days

Open symbols = saline controls

Closed symbols = IL-7 treated

Benefits of IL-7 therapy - rhesus macaque



▨ IL-7 treatment period, 60 μ /Kg alternate days

Open symbols = saline controls

Closed symbols = IL-7 treated

- Increased thymic output
- 20 year old rhesus macaques, treated with IL-7, blood taken and thymic output determined

Benefits of IL-7 therapy - rhesus macaque

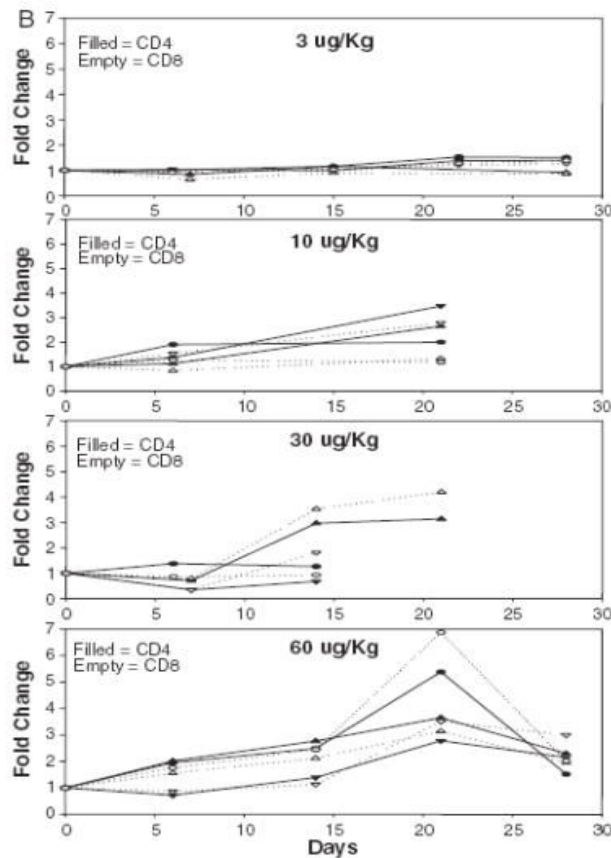
T=IL-7 S=saline	Animal	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 26
T	1FV	<10	10	10	10	10	20	20	20
T	1VQ	<10	<10	<10	<10	<10	20	10	<10
T	1JW	<10	<10	<10	80	80	160	80	30
T	YJ	<10	<10	<10	80	10	40	20	10
S	1JV	<10	<10	15	10	20	20	20	10
S	1WJ	<10	<10	<10	10	10	40	20	20

- A protective serum anti-HI titre of ≥ 40 can be found in about 80% of individuals after a natural bout of influenza and for vaccines
- European Agency for the Evaluation of Medical Products states that for HI tests seroconversion corresponds to a pre vaccination/post vaccination titre ratio of ≥ 40
- After the first vaccination shot, 50% of the treated animals show a titre ratio of ≥ 40

Human trials involving IL-7

- **Recruiting:** IL-7 in treating patients with metastatic melanoma or locally advanced or metastatic kidney cancer
- **Recruiting:** Safety study of IL-7 in HIV-infected patients
- **Recruitment ended:** Safety of IL-7 in HIV infected people currently taking anti-HIV
- **Recruitment ended:** IL-7 in treating patients with refractory solid tumors
- **Completed:** IL-7 and vaccine therapy in treating patients with metastatic melanoma
- **Completed:** IL-7 to treat HIV-infected people receiving antiretroviral therapy

Benefits of IL-7 therapy - human



- Increased numbers of CD4 and CD8 T cells over the 21 day treatment period

- These increases were seen in the naïve T cell compartment

Problems with IL-7 therapy

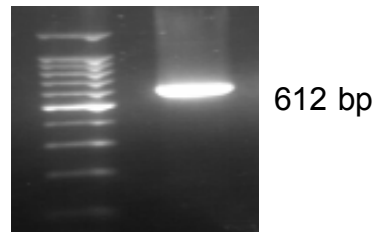
- Half life of IL-7 is short, 115 minutes in vivo
- Frequent injection at a dose high enough to reach the thymus in sufficient quantity to have an effect

Modification of IL-7 to improve effectiveness

- Targeting

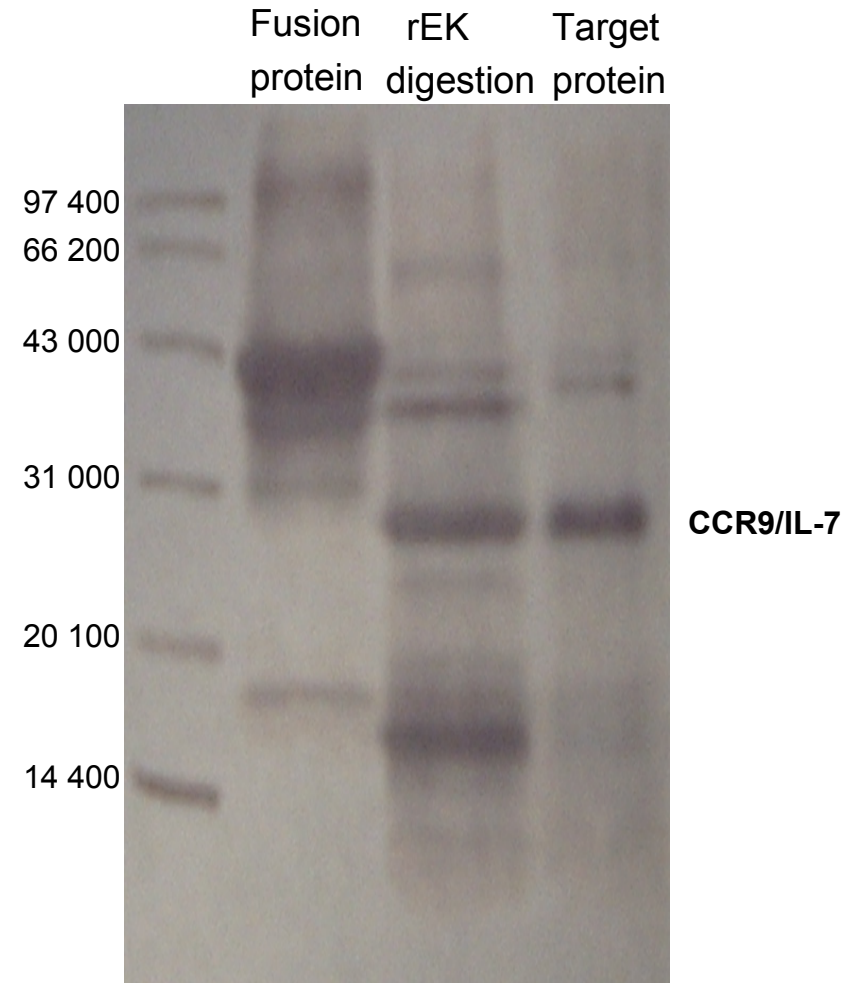
create a fusion protein between IL-7 and a chemokine receptor whose ligand is organ specific

CCR9/IL-7 fusion clone

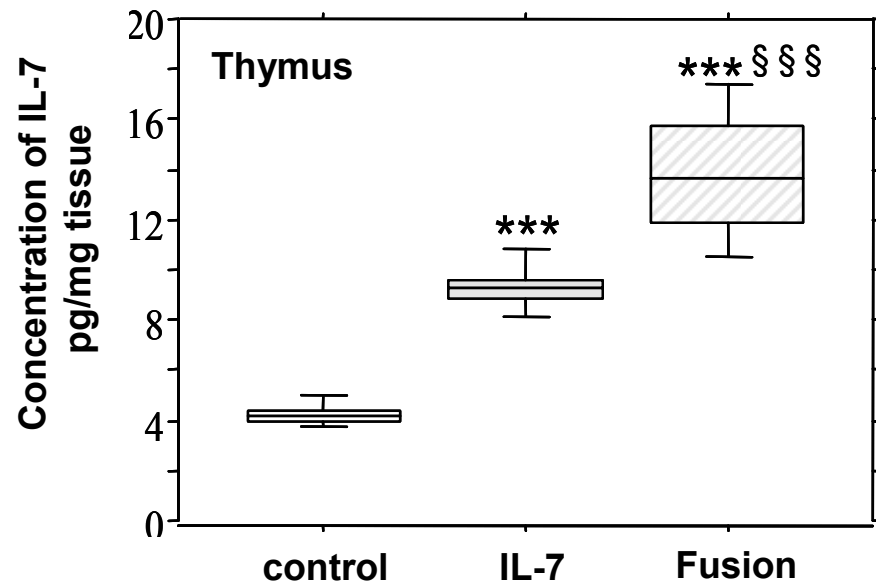


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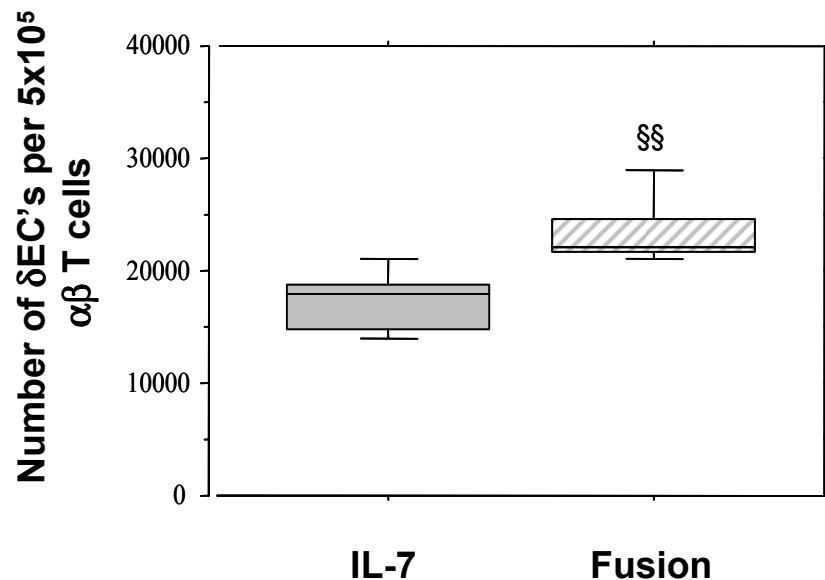


Improved benefits of giving the CCR9/IL-7 Fusion Protein



- Increased amounts of IL-7 in the thymus
- 24 month old mice, treated with CCR9/IL-7 rested for 3 weeks, then thymus removed and IL-7 content measured

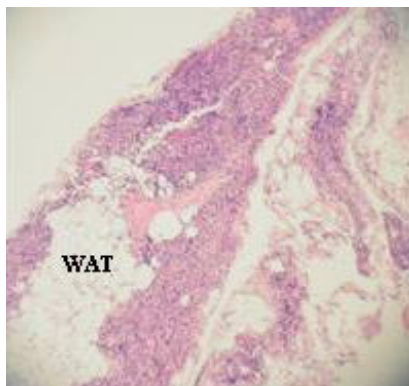
Improved benefits of giving the CCR9/IL-7 Fusion Protein



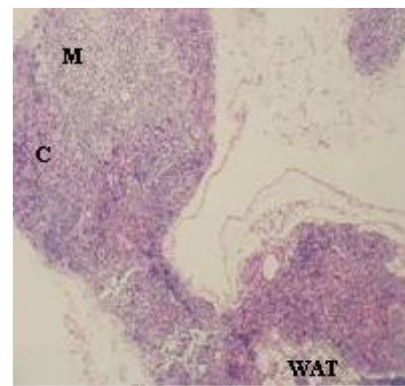
- Increased thymic output
- 24 month old mice, treated with IL-7 rested for 3 weeks, then 5×10^5 spleen cells used to measure δ EC levels

Restoration of thymic architecture after treatment with the fusion protein

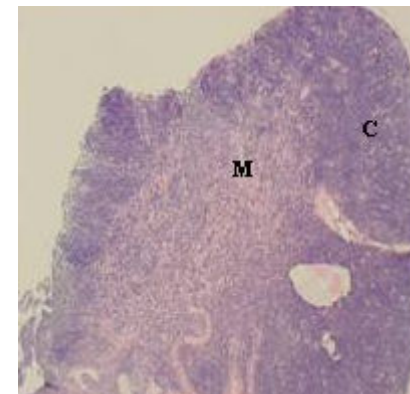
Control



IL-7

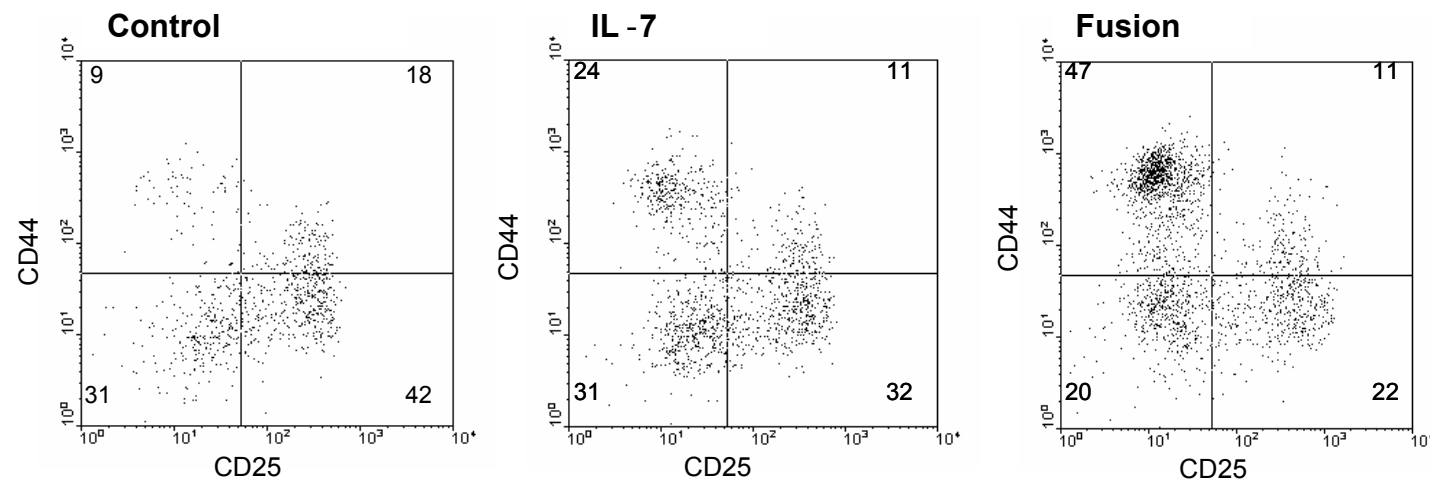


Fusion



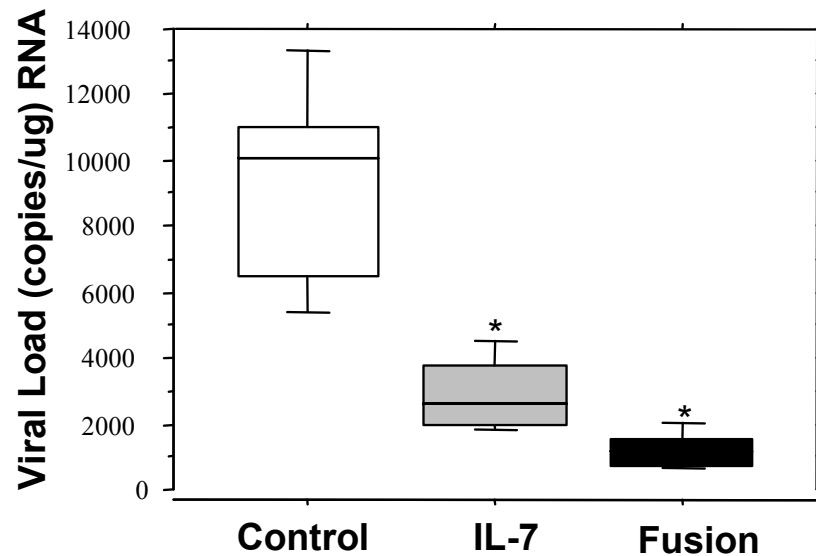
- Rejuvenation of thymic medulla and cortex
- 24 month old mice, treated with fusion protein or IL-7 rested for 3 weeks, then the thymus removed sectioned and stained

Increased thymocyte numbers after treatment with the fusion protein



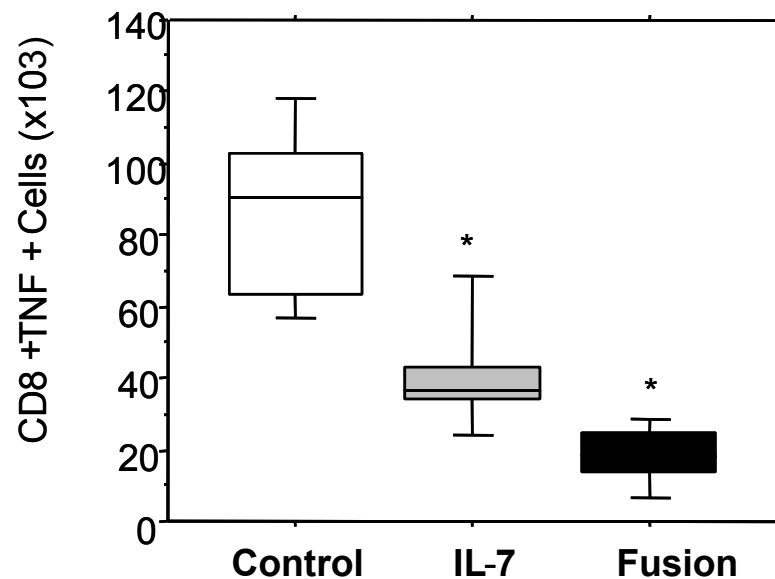
- Increased numbers of CD44⁺CD25⁻ thymocytes
- 24 month old mice, treated with fusion protein or IL-7 rested for 7 days, the thymus removed and thymocyte numbers determined

Fusion treatment causes reduced influenza disease progression



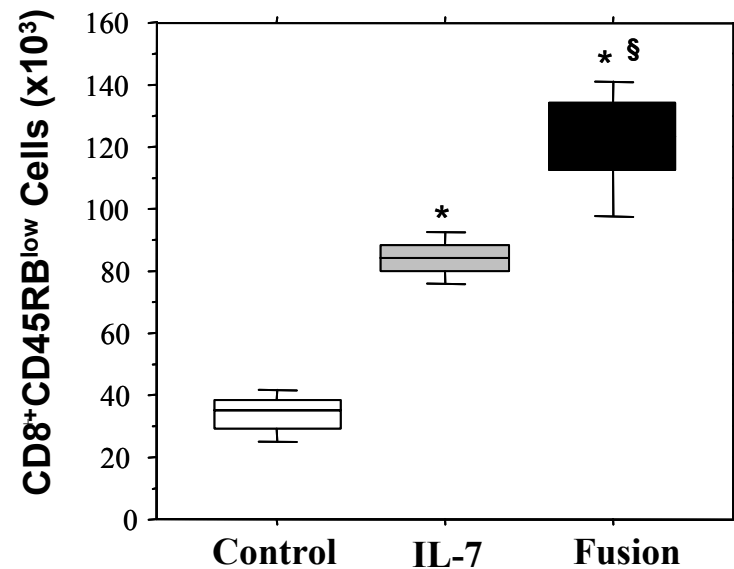
- Reduced viral load
- 24 month old mice infected with influenza, treated with fusion protein or IL-7 rested for 3 weeks, then spleen cells used to measure viral load

Fusion treatment causes reduced influenza disease progression



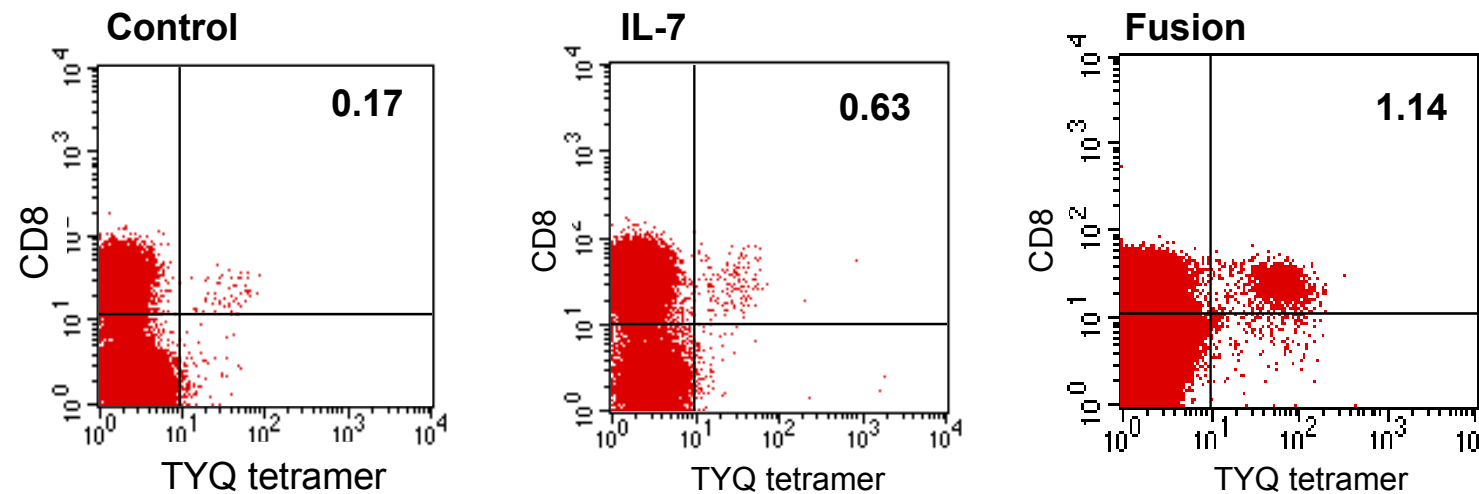
- Reduced amounts of $\text{TNF}\alpha$
- 24 month old mice infected with influenza, treated with fusion protein or IL-7 rested for 3 weeks, then the $\text{TNF}\alpha$ concentration measured

Fusion treatment increases the amount of cells fighting the influenza infection



- Increased CD45RB^{low} expression in CD8 T cells
- 24 month old mice infected with influenza, treated with fusion protein or IL-7 rested for 3 weeks, then the amount of CD45RB cells measured

Fusion treatment increases the amount of cells fighting the influenza infection



- Increased expression of influenza specific CD8 T cells
- 24 month old mice infected with influenza, treated with fusion protein or IL-7 rested for 3 weeks, then the amount of influenza specific cells measured

Conclusions

- There are therapies in development to boost the ageing immune system
- IL-7 therapy is yielding the most promising results

Acknowledgments



IL-7 Work
Imperial College

Richard Aspinall

Influenza Work
Kennedy Institute

Tracy Hussell
Robert Snelgrove

Support

