

# Induction of Therapeutic Breast Cancer Immunity with an IL-2 Immunotoxin

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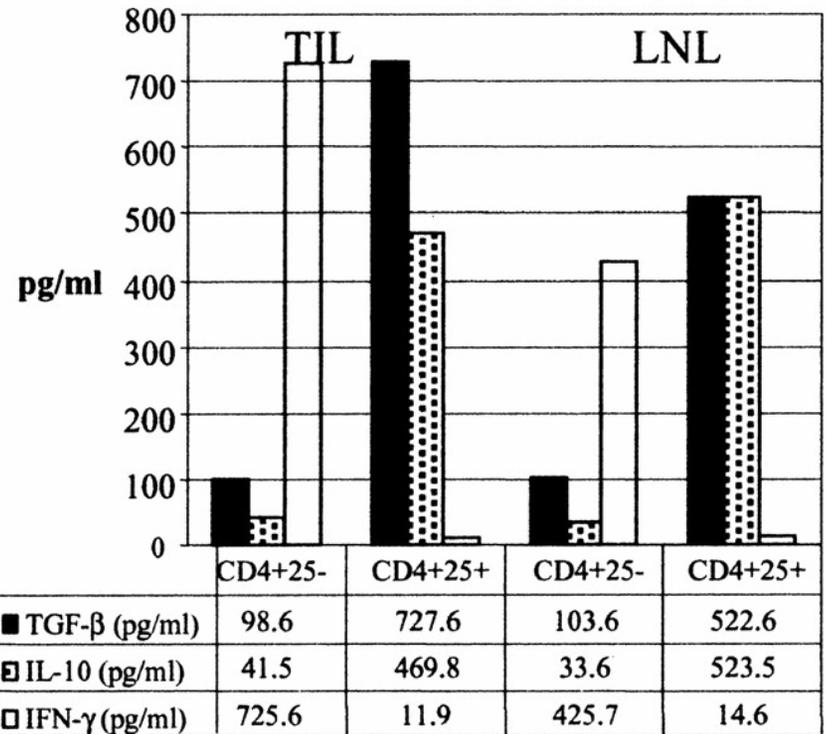
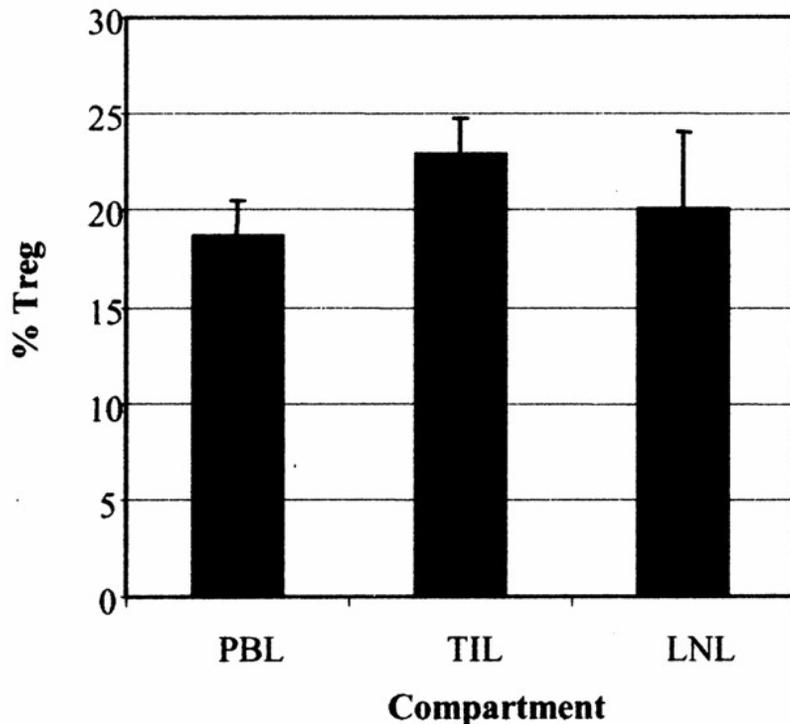
# Breast Cancer is Naturally Immunogenic

- T cells are associated with tumors and correlate with improved survival.
- Several tumor antigens have been identified by virtue of a pre-existent immune response.

# Natural immune defense against breast cancer is blocked

- Recruitment of regulatory T cells
- Induction of peripheral tolerance
- Recruitment of immature dendritic cells
- Loss of MHC molecules

# Human breast cancer recruits regulatory T cells



# Immunotherapy strategies

## Augmenting Immune Effectors

- Cancer vaccines
- Adoptive T cell therapy
- Cytokine therapy
- Monoclonal antibody therapy

## Blocking Immunosuppression

- Anti-CTLA-4
- IL-2 Immunotoxin
- Small molecules

## Restoring immune recognition

- MHC upregulation

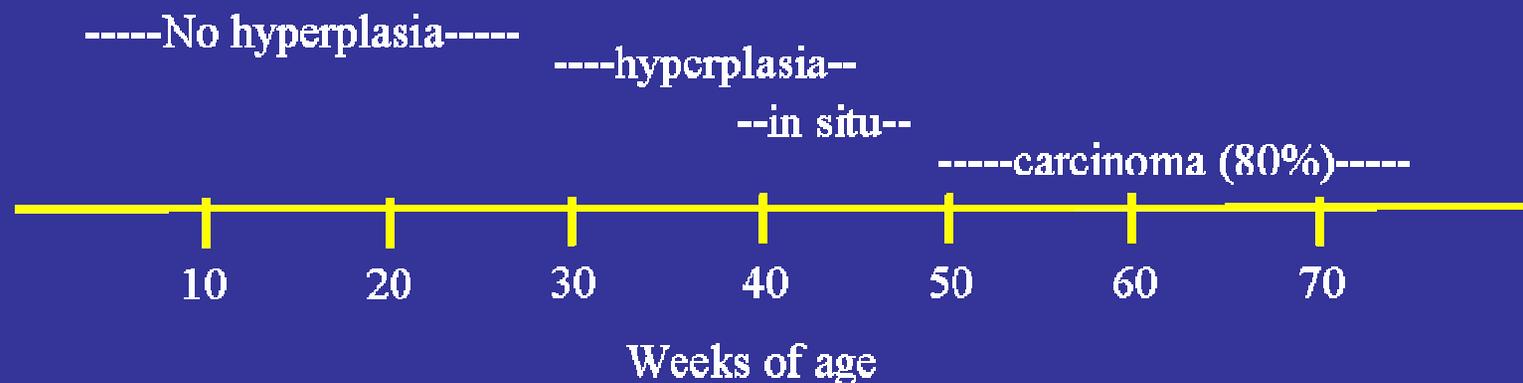
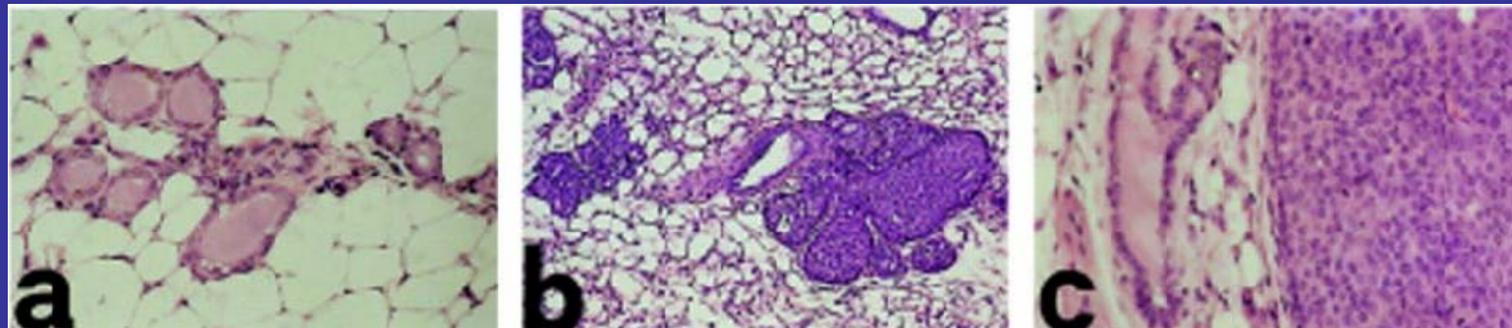
Understanding of tolerance and editing *critical* to rational design

# Tumor development: neu-transgenic mouse

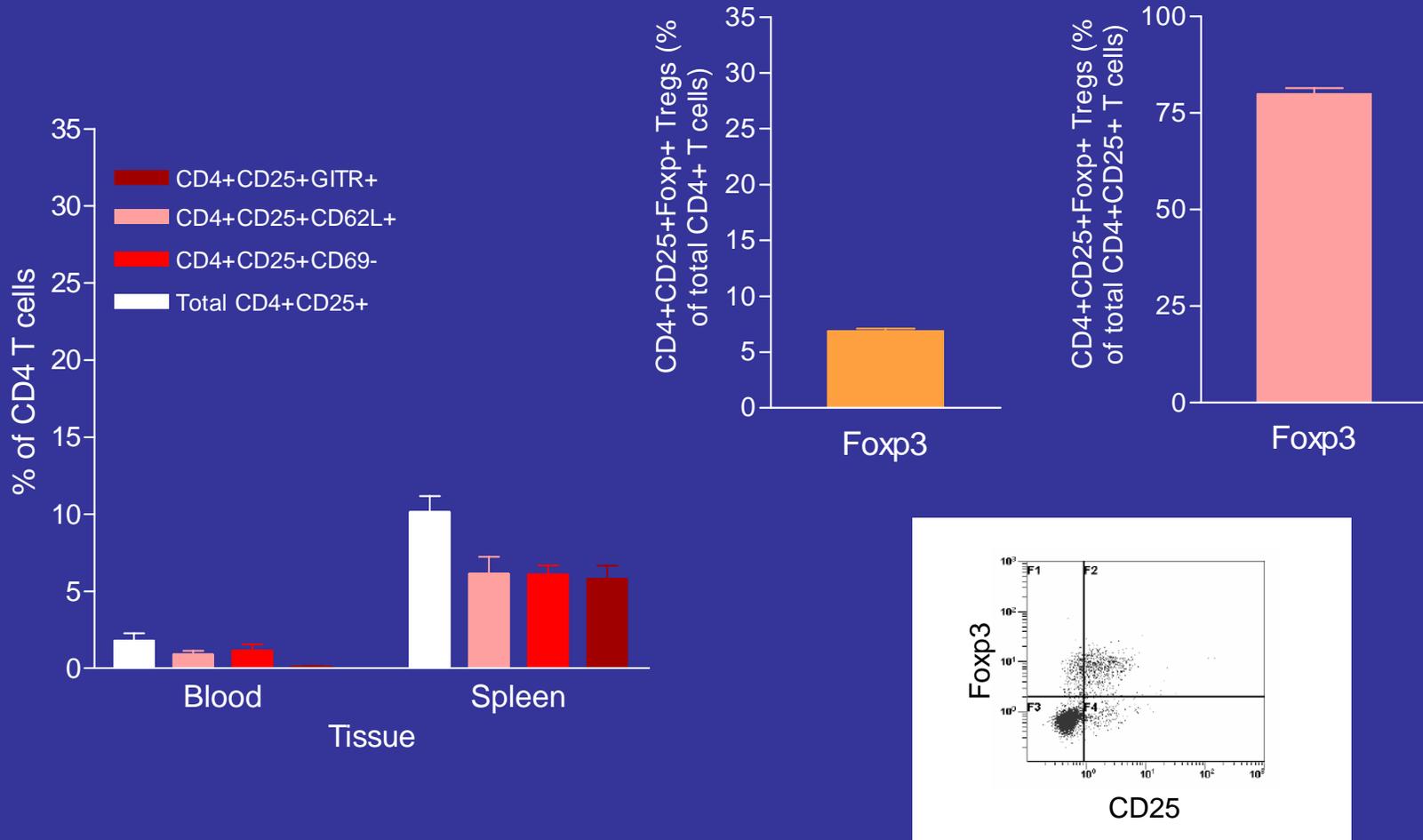
Normal epithelium

In situ

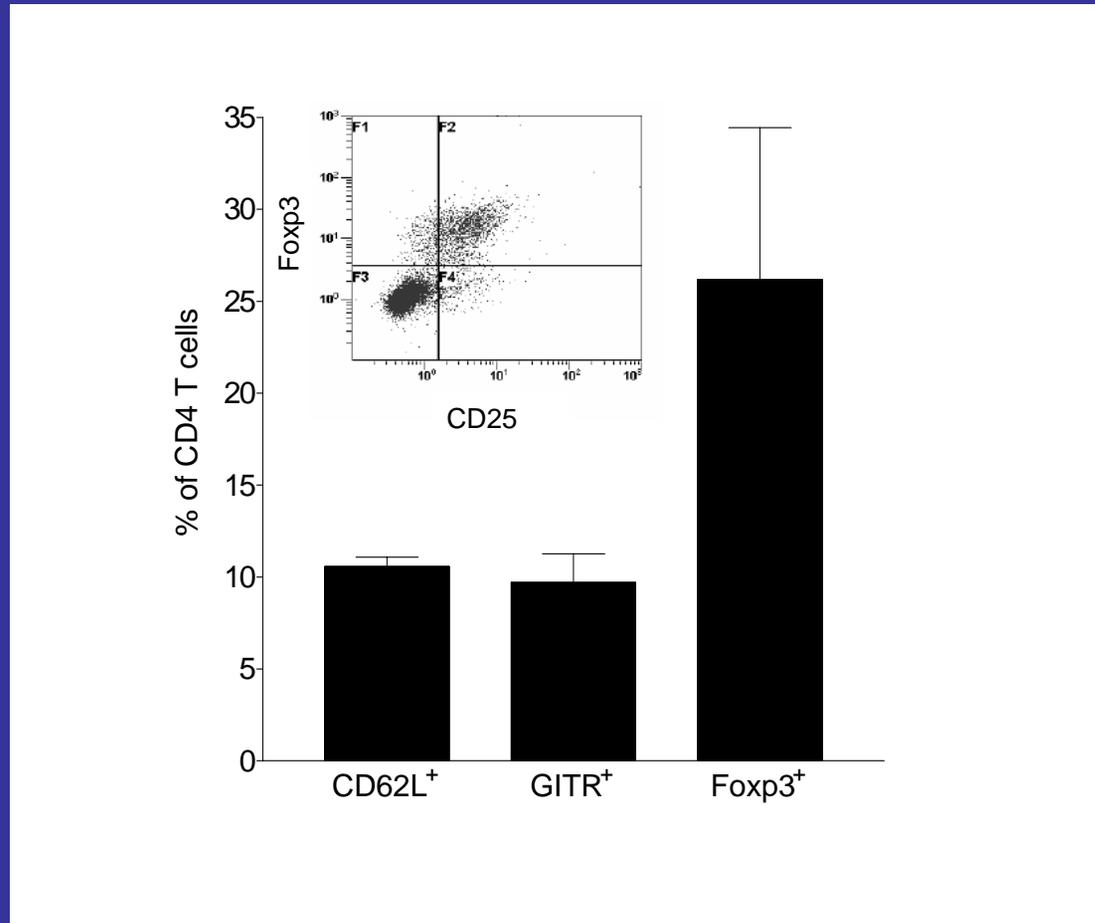
carcinoma



# Regulatory T cells in the neu-tg mouse



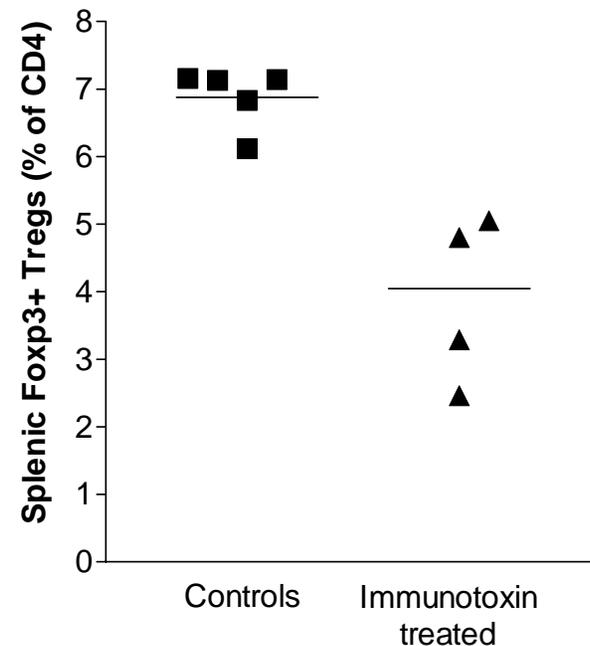
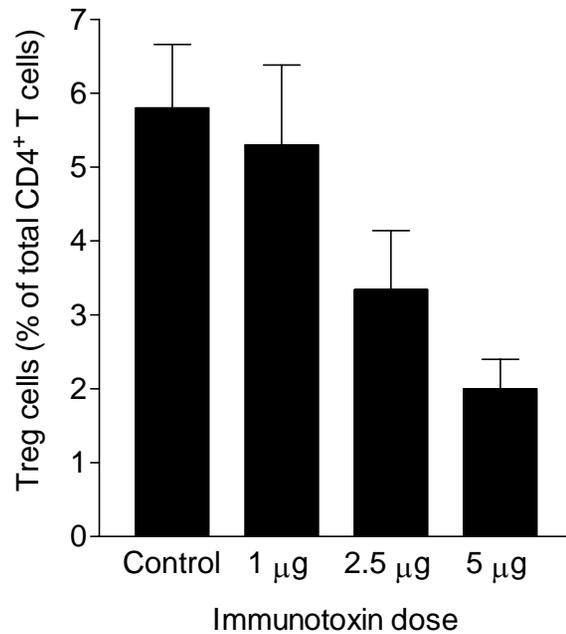
# Regulatory T cells associate with breast tumors in the neu-tg mouse



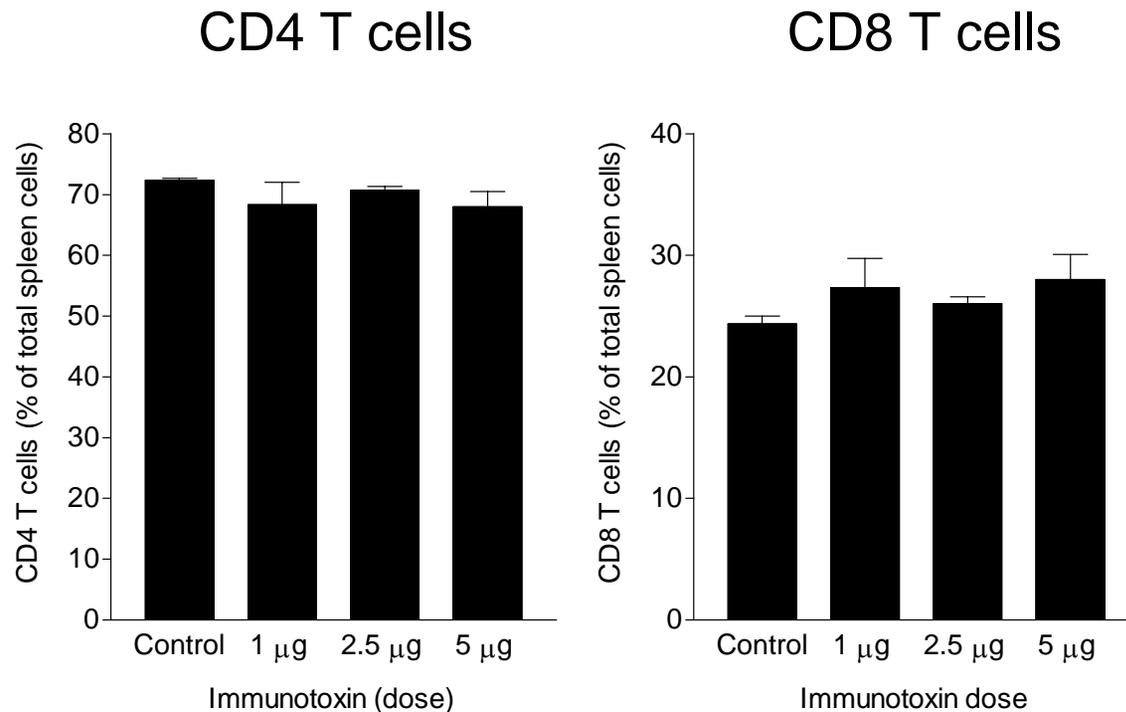
# Denileukin Diftitox

Diphtheria toxin fragments A and B (Met1-Thr387)

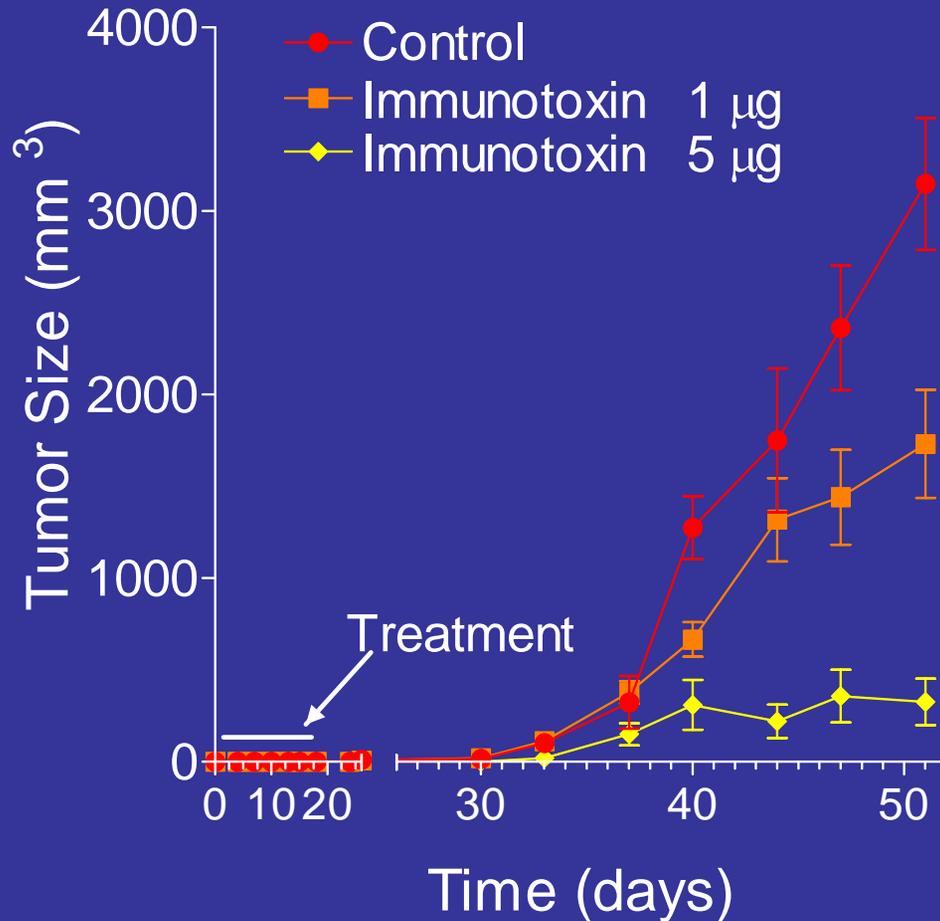
IL-2 (Ala1-Thr133)



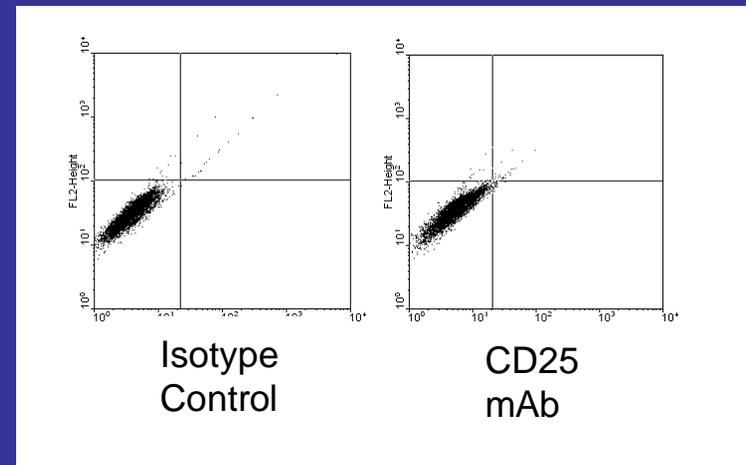
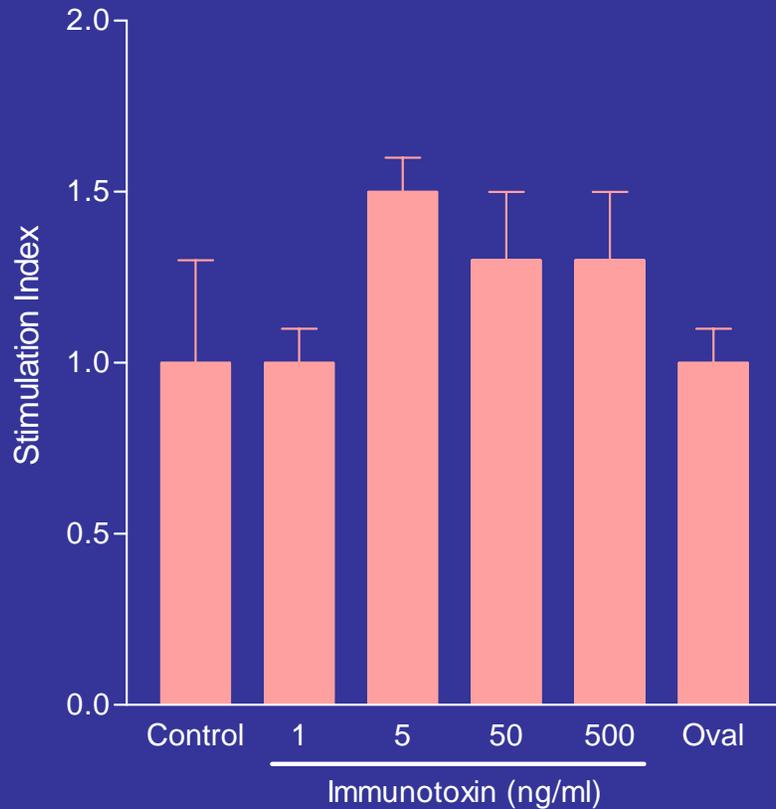
# IL-2 immunotoxin therapy does not result in lymphopenia



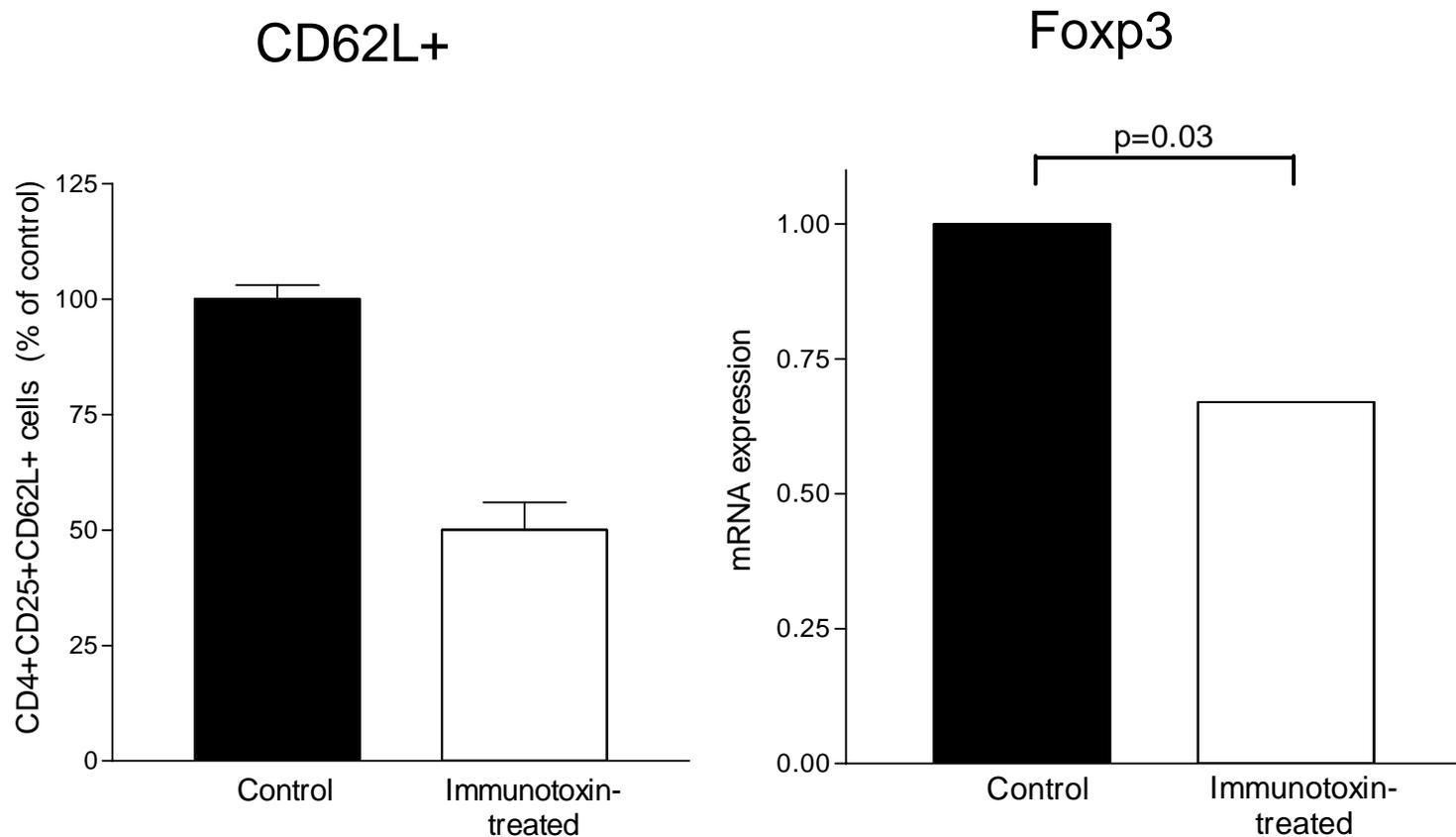
# Depletion of regulatory T cells leads to persistent tumor rejection



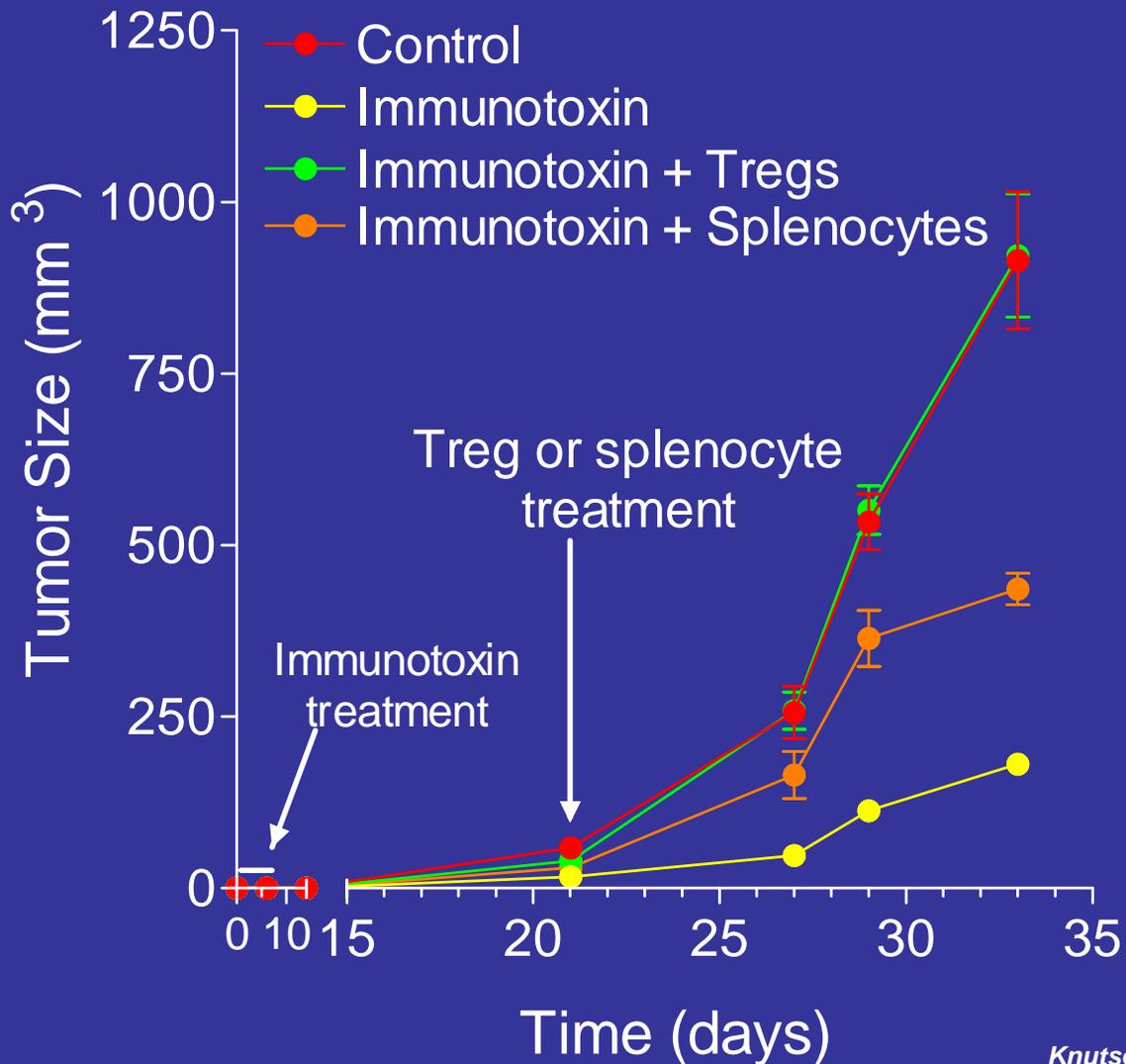
# Denileukin diftitox fails to directly kill CD25-negative tumor cells



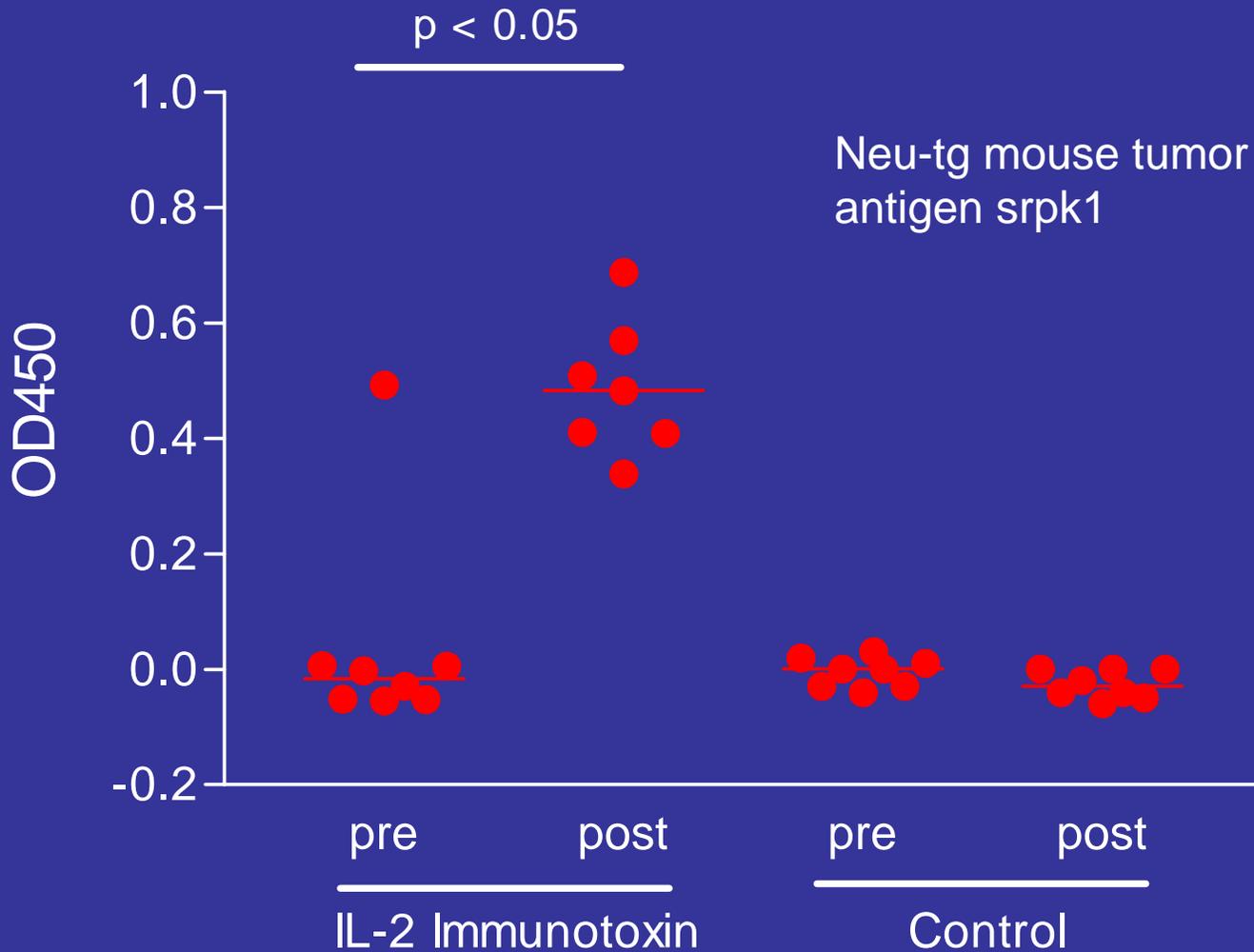
# Sustained downmodulation of intratumoral regulatory T cells



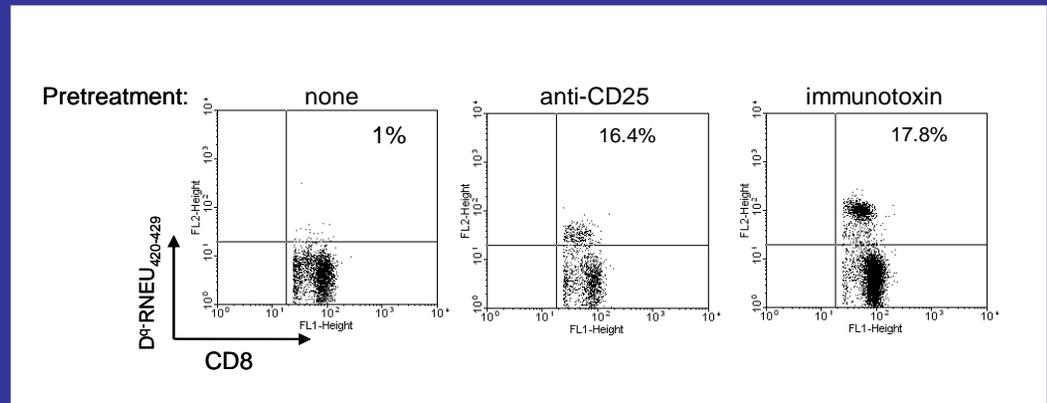
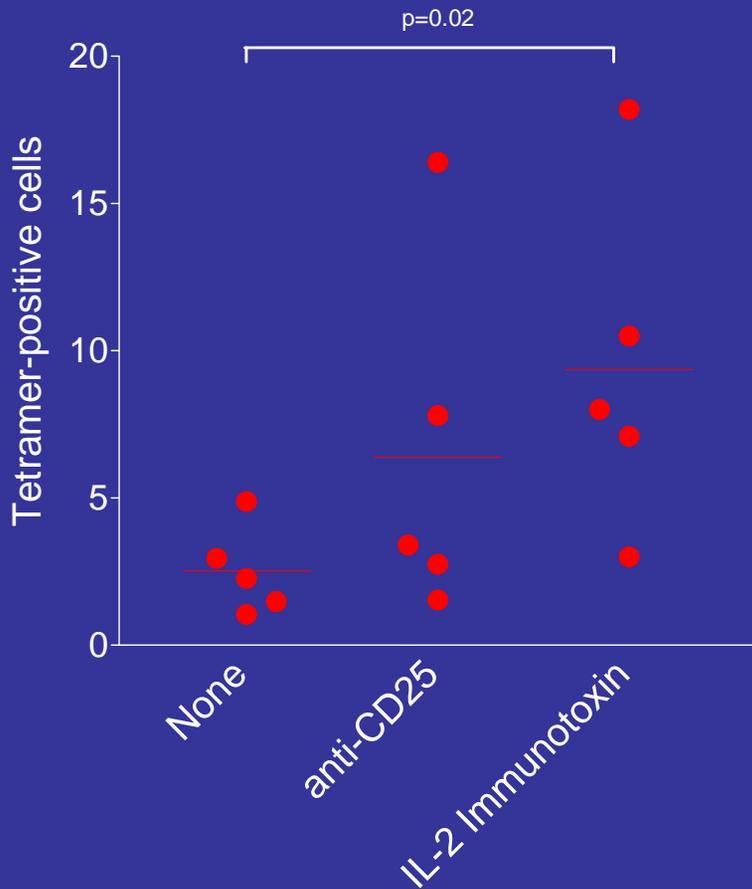
# Reconstitution of regulatory T cells restores normal tumor growth



# Induction of tumor antigen-specific humoral immunity



# Breaking tolerance to neu



# Conclusions

- Natural breast cancer immune defense may be blocked by regulatory T cells.
- Regulatory T cells can be specifically deleted without significant hematopoietic disturbance using targeted immunotoxin.
- Blockade of regulatory T cells can to long-lasting immune rejection of breast cancer without further therapy (e.g. vaccines).
- The window of opportunity following depletion of regulatory T cells may be an opportunity to boost immunity with vaccines or T cell therapy.

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