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

Liyanage, et al., 2002
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 ---

--- No hyperplasia ---

--- In situ ---

--- Hyperplasia ---

--- Carcinoma (80%) ---

Weeks of age

10 20 30 40 50 60 70

Adapted from Boggio et al., J.E. M., 1998, 188:589
Regulatory T cells in the neu-tg mouse

Knutson et al., 2005, submitted
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)

Knutson et al., 2005, submitted
IL-2 immunotoxin therapy does not result in lymphopenia.

Knutson et al., 2005, submitted
Depletion of regulatory T cells leads to persistent tumor rejection

Knutson et al, 2005 (submitted)
Denileukin diftitox fails to directly kill CD25-negative tumor cells

Knutson et al., 2005, submitted
Sustained downmodulation of intratumoral regulatory T cells

Knutson et al., 2005, submitted
Reconstitution of regulatory T cells restores normal tumor growth

Knutson et al, 2005 (submitted)
Induction of tumor antigen-specific humoral immunity

Knutson et al, 2005 (submitted)
Breaking tolerance to neu

Knutson et al, 2005 (submitted)
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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