Conditioning Treatment with A CD27 Antibody Enhances in vivo Expansion and Antitumor Activity of Adoptively Transferred T Cells

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Study Rationale

- T cell depletion is critical in adoptive cell therapy (ACT).
- Lymphodepletion enhances expansion of the transferred T cells through:
  - Removing a potential cytokine sink
  - Removing regulatory cells (Tregs)
  - Activating the innate immune system
- Cyclophosphamide (Cy) and fludarabine (Flu) are current conditioning agents.

Varli can neither deplete nor block modified T cells. CAR-T or TCR-T cells with engineered specificity and CD70 binding but not CD27 binding.

Hypothesis

Does more selective Treg depletion plus agonistic activity make Varli a better conditioning regimen?

Adaptive T Cell Transfer Schema

Working Model of Varliumab Conditioning Treatment

- Hypothesis
- CD27 is a member of the TNFR family, constitutively expressed on most T cells, with the highest level on Treg (CD4+ CD45R0+ CD27+).
- CD27(-/-) mice exhibit decreased important T cell activation.
- CD27 agonists activate T cells 
  - CD70 signals through CD27 providing an important mechanism for T cell activation.
  - mCD27+ T cells are injected i.v.
  - CD27(-/-) mice exhibit decreased T cell activation.
  - Varli can neither deplete nor block 
    - mCD27-/-
    - mCD27+/+ w.t.

Tumor expansion by varli in PB

CD27 Signal in Donor or Recipient Cells Plays Distinct Role on Transferred T Cell Expansion upon Varliumab Pretreatment

- Hypothesis
- CD27 signal in the presence or absence of CD70 signal after Varli injection influences T cell Transfer
- Transferred T cell expansion is enhanced by CD70 costimulation.

Translation of Varliumab Conditioning Treatment into ACT Clinical Practice

- Hypothesis
- Varli blocks recipient cells from accessing CD70, thus increasing GMT availability to transferred cells.
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