Novel RORγ Agonists Enhance Anti-Tumor Activity of Adoptive T Cell Therapy

Adoptive cell transfer (ACT) therapy using tumor infiltrating lymphocytes or engineered, redirected T cells is a promising anti-cancer approach. Evidence suggests Th17 or Tc17 cells display superior anti-tumor activity over unpolarized T cells and are associated with good prognosis in some cancers.

RORγ is the master transcription factor for Th17/Tc17 differentiation and modulates expression of genes in a program enhancing immunity and decreasing immune suppression. Lycera has developed RORγ agonist compounds and is exploring their utility to enhance anti-tumor responses both as an addition to ex vivo expansion cultures for ACT and as a systemically administered oral therapeutic.

SUMMARY OF KEY FINDINGS

- RORγ agonists increase production of pro-inflammatory cytokines and chemokines
- RORγ agonists increase co-stimulatory and decrease co-inhibitory receptor expression
- RORγ agonists desensitize cells to PD-L1 inhibition
- Addition of RORγ agonists to ex vivo T cell expansion cultures significantly enhances anti-tumor responses
  - Effective in CD4 and CD8 model systems
  - Effective +/- Type 17 polarization
  - Induction of long-lasting effects consistent with RORγ biology
- RORγ agonists also effective as monotherapy in syngeneic tumor models

RESULTS

RORγ Agonists Enhance Cytokine Production

CD4 T Cells-Th17 Conditions

CD8 T Cells-Tc17 Conditions

Th0 Condition (IL-2)

RORγ Agonists Shift the Balance of Co-stimulation over Co-inhibition

RORγ Agonists Desensitize Cells to PD-1 Checkpoint Inhibition

Ex vivo RORγ Agonist Treatment Generates Potent, Persistent anti-Tumor Effectors

- OT-1 Tc17 + EG7 Tumors
- Trp-1 CD4 T Cells
- PMEL-1 CD8 T Cells
- Trp-1 CD4 Th0 cells
- PMEL-1 CD8 Th17 cells
- Trp-1 CD4/pMEL-1 CD8 + B16F10 Tumors
- Tumor-specific TIL Day 71
- Cytokine Profile of Splenocytes