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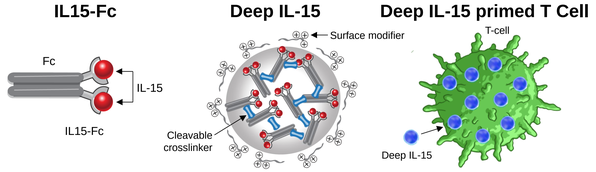
Deep™ IL-15 primed T cells synergize with PD-L1 blockade to overcome resistance to checkpoint immunotherapy

Elena Geretti, Xiaoyan Liang, Jesse Lyons, Philip Bardwell, Santina Caruso, Sanela Bilic, Becker Hewes, Jonathan Fitzgerald, Karsten Sauer, Thomas Andresen. Torque Therapeutics, Cambridge, MA

Introduction

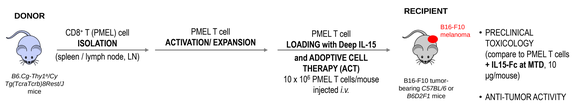
Interleukin-15 (IL-15) activates and expands both CD8⁺ T cells and NK cells but not immunosuppressive T_{reg} cells. While IL-15 is an attractive asset for cancer immunotherapy, its systemic administration is limited by toxicities[1]. To limit IL-15 systemic exposure, we have developed Deep™ IL-15, a multimer of chemically crosslinked IL-15/IL-15 Rα/Fc heterodimers (IL15-Fc). Deep IL-15 is surface anchored to tumor reactive T cells prior to adoptive cell transfer (ACT). This novel therapeutic approach enables Deep IL-15 loading onto cells at exposures unachievable with systemic IL15-Fc, causes autocrine T cell activation and expansion, yet limits systemic exposure and associated toxicities. The anti-tumor activity of T cell therapies has been limited by insufficient T cell expansion, and by checkpoint mediated immunosuppression. Here, we combined Deep IL-15 Primed T cells with PD-L1 blockade to overcome these limitations.

Deep IL-15 Provides Autocrine Cytokine Stimulation



The PMEL T cell model: a surrogate for human Deep IL-15 primed multi-targeted T cells

- Donor CD8⁺ PMEL T cells express a transgenic T cell receptor (TCR) directed against PMEL-17, an epitope of gp100, expressed on B16-F10 melanoma cells.
- Model enables evaluation of antigen-specific T cell activity in fully immunocompetent mice
- Deep IL-15 loading on mouse PMEL T cells and human multi-targeted T cells is comparable
- PMEL T cell *in vitro* expansion is comparable to that of human multi-targeted T cells



Results

Deep IL-15 primed T cell ACT causes lower systemic exposure to IL15-Fc, and lower IFN-γ release than co-injection of T cells with soluble IL15-Fc, and does not expand endogenous circulating CD8⁺ and NK cells

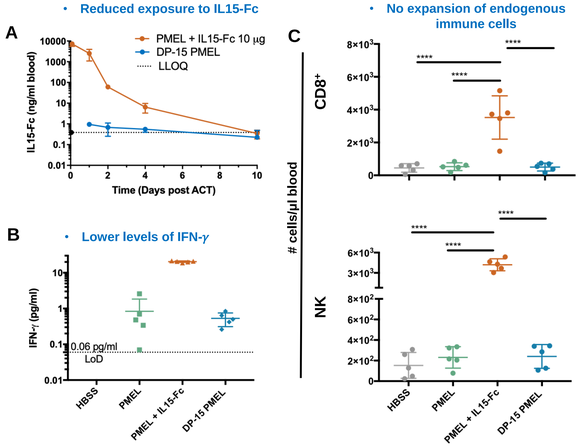


Figure 1. PMEL T cells were activated *ex vivo* on αCD3/αCD28 coated plates, loaded with HBSS (PMEL, 10 x 10⁶) or Deep IL-15 (DP-15 PMEL, 10 x 10⁶), and injected into B16-F10 tumor-bearing C57BL/6 mice. HBSS and PMEL T cells (10 x 10⁶) co-administered with IL15-Fc (10 µg/mouse) were injected as controls. Blood was drawn at 2, 24, 48, 96 and 240 h for quantification of IL15-Fc (**A**), IFN-γ (24 h post-dose) (**B**), and endogenous (CD90.1⁻) CD8⁺ and NK cells (96 h post-dose) (**C**).

Deep IL-15 priming improves PMEL T cell expansion and anti-tumor activity

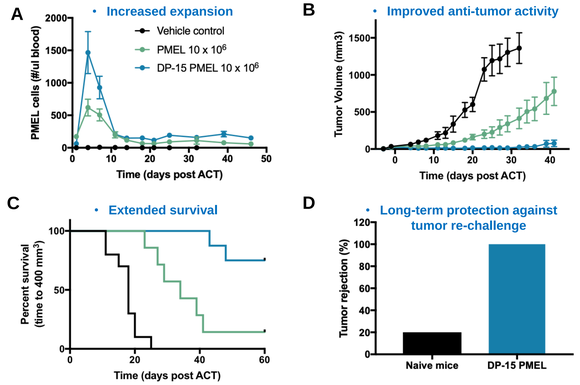


Figure 2. C57BL/6 mice were inoculated with B16-F10 melanoma cells (0.2 x 10⁶, intradermal). When tumors reached an average volume of 29 mm³, mice were treated with cyclophosphamide (4 mg/mouse, Day -1), followed by administration of vehicle control (HBSS), PMEL T cells (10 x 10⁶) or Deep IL-15 primed PMEL T cells (DP-15 PMEL, 10 x 10⁶, Day 0). Blood was drawn at the indicated time points for enumeration of transferred and endogenous T cells (**A**). Tumor volumes (**B**) and % survival (time to 400 mm³ tumor volume, **C**) were monitored over time. 60 days post dose, the remaining mice on study were re-challenged with a second injection of B16-F10 melanoma cells (**D**).

Combination of Deep IL-15 primed T cells with PD-L1 blockade results in complete tumor regression and prolonged survival

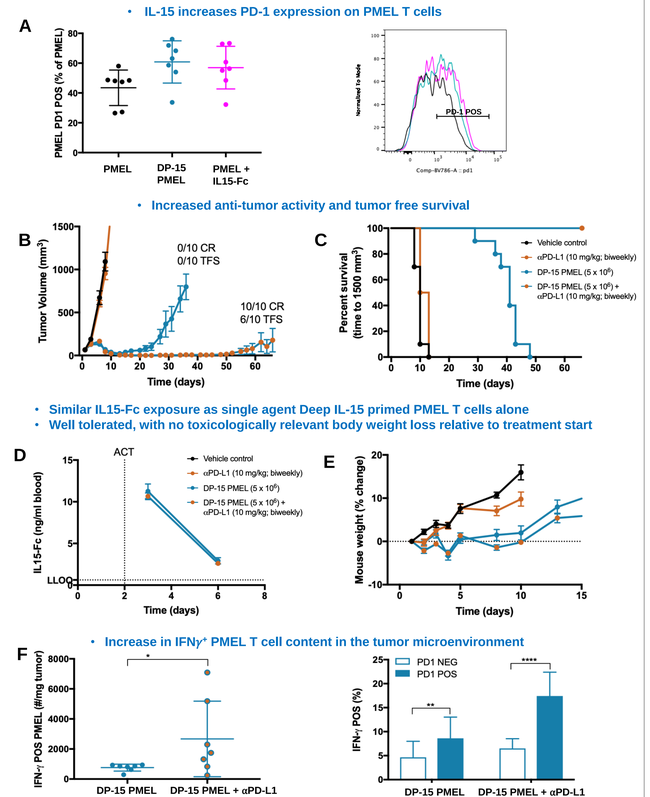


Figure 3. B6D2F1 mice were inoculated with B16-F10 melanoma cells (1 x 10⁶, *s.c.*). When tumors reached an average volume of 200 mm³ (**A**, **F**) or 60 mm³ (**B**-**E**), respectively, mice planned to receive ACT were treated with cyclophosphamide (4 mg/mouse, Day 1), followed by administration of vehicle control (HBSS), αPD-L1 (10 mg/kg biweekly for the entire study), Deep IL-15 primed PMEL T cells (DP-15 PMEL, 10 x 10⁶) alone or combined with αPD-L1 (Day 2). (**A**, **F**) Mice were euthanized 7 days post ACT for intratumoral PMEL T cell profiling by Flow Cytometry. (**A**) PD-1 expression on PMEL T cells. (**F**) Tumor content of IFN-γ⁺ PMEL T cells. (**B**, **C**, **E**) Tumor volumes, survival and body weights over time. (**D**) Blood was drawn at the indicated time points to measure systemic IL15-Fc levels. CR, mice with complete regressions. TFS, mice with tumor-free survival at the end of study.

Conclusions

- Deep IL-15 primed PMEL T cells:
  - Result in dramatically lower systemic exposure to IL15-Fc than injected soluble IL15-Fc.
  - Do not induce significant systemic IFN-γ release
  - Do not increase circulating bystander endogenous immune cells, including NK cells, which are associated with the immunotoxicity of systemic IL-15[1]
  - Do not result in significant body weight loss
  - Result in histopathology findings of lower severity compared to IL15-Fc across multiple organs
- Deep IL-15 primed PMEL T cells show improved *in vivo* expansion and anti-tumor activity compared to PMEL T cells.
- A regimen of Deep IL-15 primed PMEL T cells in combination with PD-L1 blockade:
  - Results in increased anti-tumor activity and improved survival compared to single agents
  - Is well tolerated and does not cause body weight loss or increased systemic IL15-Fc exposure
  - Results in more pronounced PMEL T cell activation in the tumor microenvironment
- A Phase I clinical trial of Deep IL-15 primed multi-targeted T cells (TRQ15-01) in solid cancers and lymphoma is currently enrolling (NCT03815682). A Phase I/II trial in combination with Keytruda® is planned to initiate in late 2019.

KEYTRUDA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA.

References

1. Guo Y et al., *J Immunol* (2015), **IL-15 Superagonist-Mediated Immunotoxicity: Role of NK Cells and IFN-γ.**
2. Tang L et al *Nat Biotechnol* (2018) **Enhancing T cell therapy through TCR-signaling-responsive nanoparticle drug delivery.**

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