Washington University in St. Louis
Office of Technology Management

PROTEIN TO ENHANCE T CELL EXPANSION FOR CAR-T CELL THERAPY AND OTHER ADOPTIVE CELLULAR IMMUNOTHERAPY

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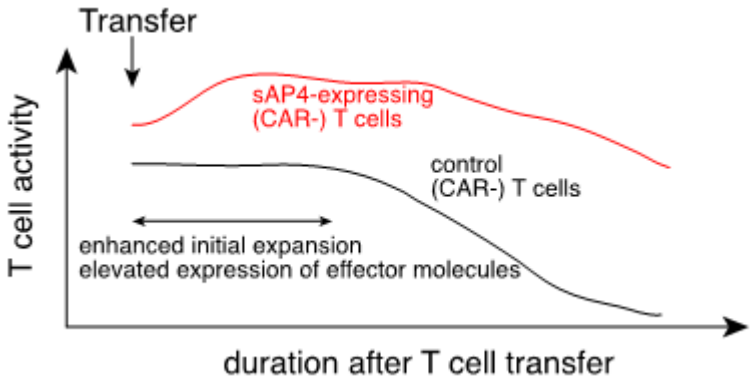
T-016284

Technology Description

Researchers in Prof. Takeshi Egawa's laboratory have developed a mutant AP4 protein that is designed to reduce the time and expense of *ex vivo* T cell expansion for adoptive cellular immunotherapy, including CAR-T cell cancer immunotherapy. AP4 is a transcription factor that amplifies and prolongs CD8+ T cell-mediated immune response following induction and maintenance by the cytokine IL-2 and the transcription factor c-Myc. Therefore, this protein could potentially counteract T cell exhaustion in cancer immunotherapy. However, wild type AP4 is an unstable protein with a short half-life (2-3 hours) and requires constitutive IL-2 receptor signals.

This technology increases the half-life of AP4 to 48 hours by introducing at single mutation that enhances stability without affecting function, thus making its expression independent of the natural activator IL-2. The resulting mutant AP4 could be introduced to cytotoxic T cells *ex vivo* to boost their activity and functionality. These effects are compatible and synergistic with both autologous T cell therapy and checkpoint inhibitors. By maintaining the cellular programs of T cells, mutant AP4 could maximize T cell expansion and effector differentiation to improve immunotherapy.



Stage of Research

The inventors have confirmed that the mutant AP4 is functional and that it resists degradation when expressed ectopically in CD8+ T cells. They have also demonstrated that the half-life of mutant AP4 is ~48 hours (compared to wild type AP4 which has a half-life of 2-3 hours).

Applications

- **Cancer immunotherapy –** improve CD8+ T cell proliferation for downstream use in CAR-T cell therapy and other adoptive cellular immunotherapy therapies

Key Advantages

- **Prolonged T cell proliferation, activation and differentiation** independent of the natural activators IL-2 and c-Myc
- **Reduced cost and time:**
  - with enhanced proliferation, the cost and time of in vitro expansion could potentially be reduced by generating therapeutic effects with a smaller number of cells
  - no tumor antigen screen needed because AP4 enhancement is independent of tumor specific antigen
- **Synergistic effects –** compatible and synergistic with autologous T cell therapy and checkpoint inhibitors

Publications

- **Chou** C, Verbaro DJ, Tonc E, Holmgren M, Cella M, Colonna M, Bhattacharya D, **Egawa** T. (2016). The Transcription Factor AP4 Mediates Resolution of Chronic Viral Infection through Amplification of Germinal Center B Cell Responses. Immunity. 2016 Sep 20;45(3):570-582. doi: 10.1016/j.immuni.2016.07.023. Epub 2016 Aug 23. PMID: 27566940
- **Chou** C, Pinto AK, Curtis JD, Persaud SP, Cella M, Lin CC, Edelson BT, Allen PM, Colonna M, Pearce EL, Diamond MS, **Egawa** T. (2014). c-Myc-induced transcription factor AP4 is required for host protection mediated by CD8+ T cells. Nat Immunol. 2014 Sep;15(9):884-93. doi: 10.1038/ni.2943. Epub 2014 Jul 13. PMID: 25029552

Patents

- Ap4 and methods of promoting t cell activation (PCT Application, Publication No. WO2018075941A1)