Docket #: S21-181

A Method to Enhance CAR T Efficacy through Adenosine Deaminase Overexpression

Stanford Scientists have developed an innovative approach that enhances the antitumor efficacy of CAR T cells by overexpressing Adenosine Deaminase 1 (ADA), an enzyme responsible for metabolizing adenosine into inosine, to attenuate the immunosuppressive tumor microenvironment.

Although promising, CAR T cell therapy efficacy in solid tumors is limited by hostile tumor microenvironments, limited CAR T persistence, and lack of tumor killing. Extracellular adenosine contributes to the hostile tumor microenvironment by binding the adenosine A2a receptor on immune cells. Blocking A2aR or enhancing ADA-mediated adenosine metabolism to inosine protects T cells from adenosine-mediated immunosuppression. Stanford scientists showed that human CAR T cells are also susceptible to adenosine-mediated immunosuppression. They developed an approach where they overexpressed ADA in exhausted and non-exhausted CAR T cells leading to a higher frequency of stem cell-like memory T cell effectors, and a simultaneous decrease of exhausted subpopulations. Both antigen-driven proliferation and effector function of CAR T cells also significantly improved after ADA overexpression. Therefore, overexpression of adenosine deaminase in CAR T cells is a novel and efficient way to evade immunosuppression.

Stage of Development

Research – in vitro

Applications

- CAR T immunotherapy, especially for solid tumors

Advantages

- Brand new approach
- Can increase resistance to immunosuppression and improve potency of existing cancer immunotherapies against solid tumors

Publications

- **Dorota D. Klysz**, Carley Fowler, Meena Malipatlolla, Lucille Stuani, Katherine A. Freitas, Yiyun Chen, Stefanie Meier, Bence Daniel, Katalin Sandor, Peng Xu, Jing Huang, Louai Labanieh, Vimal Keerthi, Amaury Leruste, Malek Bashti, Janette Mata-Alcazar, Nikolaos Gkitsas, Justin A. Guerrero, Chris Fisher, Sunny Patel, Kyle Asano, Shabnum Patel, Kara L. Davis, Ansuman T. Satpathy, Steven A. Feldman, Elena Sotillo, **Crystal L. Mackall** (2024). Inosine induces stemness features in CAR-T cells and enhances potency. *Cancer Cell*, Volume 42, Issue 2, Pages 266-282.e8, ISSN 1535-6108.

Patents

- Published Application: WO2023034742
- Published Application: 20250134998

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