

Enhancing the anti-tumor immunity of TILs or CAR-T cells by inhibiting Sirt2.



Sirt2 deficiency was found to metabolically reprogram T cells to amplify aerobic glycolysis during activation, leading to hyper-reactive T-cell effector functions against tumors. This could increase the effectiveness of TIL therapy where presently there is a 24% complete response rate in metastatic melanoma patients. It could also potentially increase the effectiveness of CAR-T therapies for solid tumors that have a poor response compared to TILs and checkpoint inhibitors. Even the high response rates of CAR-T therapies for blood borne cancers might benefit from inhibiting Sirt2 by increasing the durability of responses where about a third of patients with complete responses in ALL with Kymriah relapsed within 18 months.

COMMERCIAL OPPORTUNITY

- TIL therapy has been shown to be clinically effective as demonstrated by a 24% Complete Response rate in 101 metastatic melanoma patients by Dr. Steven Rosenberg at the NCI. With a median potential follow-up of 40.9 months, only one of 24 patients who achieved a CR recurred. TIL company valuations can be represented by Iovance Biotherapeutics that has a market cap of \$3B. Iovance's most advanced product is a TIL therapy in a registration trial for melanoma.
- Chimeric antigen receptor (CAR) T-cell therapy has worked well in the treatment of some hematologic malignancies, but CAR-T therapies are not showing as strong results in solid tumors. For example, a CAR-T therapy for pediatric B-cell ALL had a response rate of 82.5% while a review of 22 solid tumor CAR-T studies up to June 1, 2018 gave an overall pooled response rate of 9% (95% CI 4-16%). Given that about 90% of cancer related deaths have been due to solid tumors, there is a strong unmet need for technologies that would make CAR-T cells more effective at killing solid tumors.
- Two-thirds of children and young adults with acute lymphoblastic leukemia (ALL) who attained complete responses with tisagenlecleucel (Kymriah) remained in remission at 18 months. Overall, 70% of 79 patients followed for at least 3 months were alive at 18 months as reported at the 2018 American Society of Hematology (ASH) annual meeting.

TECHNOLOGY

Sirt2 Deficiency protects mice from B16F10 cell challenge. Lungs from WT and Sirt2KO mice challenged i.v. with B16F10 cells, collected 18 days post-injection contained subcutaneous tumors that were dissected from 10 WT and Sirt2KO mice challenged s.c. with B16F10 cells 21 days post-injection that showed at least about a 50% reduction in tumor size. Blocking Sirt2 with AGK2 increases glycolysis and effector functions of human TILs from NSCLC patients. Human TILs samples isolated from tumor biopsies of NSCLC patients were stimulated with anti-CD3 in combination with Sirt2 inhibitor AGK2 vs. vehicle for 48 hours. IFN- γ ELISPOT assay was performed on CD3-stimulated TILs with increasing concentrations of AGK2 versus vehicle for an additional 48 hours showed a statistically significant increase in IFN- γ as the concentration of AGK2 was increased.

PUBLICATION/PATENT

- Provisional Patent filed on February 8, 2019 for Dr. Sungjune Kim.

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LICENSING OPPORTUNITY



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