High-throughput discovery of constitutive promoters to drive strong expression of next-generation gene circuits in CAR-NK and -T cells

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Promoters play an important role in cell therapies

Promoters are important components of gene circuit design for cell therapies. They are responsible for regulating the expression of transgene payloads, which ultimately impact the overall functionality of engineered cell therapies such as CAR-NK and CAR-T cells. To improve cell therapy performance in solid tumors, next generation designs often involve the need to express multiple payloads under the control of a single promoter, which substantially increases the demand for having a strong promoter.

Complex multi-payload circuits have high promoter demand

Challenges and solutions in today’s complex multi-payload circuit designs are illustrated in the figure. Promoters with high demand and payload architectures are crucial for next generation promoters.

Next generation promoter discovery using automation at Senti

We leveraged our high-throughput discovery platform, which integrates a custom-built automated liquid handler that can screen hundreds of promoters in an end-to-end process, to accelerate our "Design, Build, Test, Learn" style of engineering stronger next generation promoters for cell therapies.

Our promoters can also drive high payload expression in CAR-T cells

Our next generation promoters can also be engineered to drive high surface expression of multiple transgenes and transmembrane cytokines. Majority of these promoters perform similarly well in both primary NK and T cells.

Take-aways

1. High-throughput promoter discovery platform. Senti developed a high-throughput promoter discovery platform that integrates pooled library screening approaches with automated clonal screening systems. This accelerates our ability to engineer and optimize strong promoters for cell therapies.
2. Strong promoters improve payload expression and enhance CAR-NK functionality. We engineered promoters that can drive high expression of every component from our Senti-401 circuit in CAR-NK cells, and these "smart" cells have enhanced abilities to recognize and kill cancer cells while protecting healthy cells.
3. Strong next generation promoters in NK and T cells. We engineered a collection of next generation promoters functional in both NK and T cells for different cell therapy modalities.