

Composition and Method for Autonomous RNA Switches for Translational Control

Stanford scientists have discovered that the untranslated region (UTR) of RNA can be engineered into autonomous switches capable of both sensing native biological conditions (e.g. T cell activation) and promptly responding by initiating the translation of a therapeutic sequence (e.g. a chimeric antigen receptor). Autonomous mRNA switches can provide dynamic regulation within cellular immunotherapies and offer broad utility in next-generation mRNA therapeutics, such as engineering chimeric antigen receptor (CAR) T cells *in vivo*.

Ex vivo CAR T cell therapy has shown significant success in treating oncology patients and combating malignant tumors. However, this approach is limited by the expensive and time-consuming *ex vivo* production process, which can take several weeks, and the challenge of administering only a single effective dose to patients, leading to potential tumor relapse. In contrast, *in vivo* CAR T cell therapy offers a promising solution by directly engineering T cells within patients using mRNA therapeutics. This innovative approach enables rapid and customizable production, with the transient nature of mRNA therapies allowing for precise temporal control of therapeutic doses. Nevertheless, advancements are needed to develop technologies capable of sensing relevant biological conditions and tightly regulating the translation of therapeutic payloads. Novel strategies for controlling mRNA expression in T cells will enable the development of *in vivo* T cell therapies that can alleviate T cell dysfunction while preserving the protective immune responses required for human health.

Novel engineered UTR sequences resulted in RNA elements that can sense T cell signals and modulate therapeutic mRNA expression as ON/OFF switches. These mRNA switches have been shown to induce the translation of genetic payloads upon

T-cell activation. The use of these mRNA switches to control the translation of a CAR in engineered T cells resulted in the expression of the CAR and the killing of antigen-positive tumor cells. Importantly, when co-cultured with antigen-negative cells, there was no difference in CAR expression or killing when compared to baseline. Consequently, autonomous mRNA switches have the potential to enhance cellular immunotherapies and enable the development of *in vivo* CAR T cell therapies.

Stage of Development:

Preclinical – *in vitro* data

Continued research – *in vivo* demonstration of efficacy and further description of switches that capture other immune cell states (e.g. T cell exhaustion, NK cell activation, etc.). The inventors have demonstrated that the switch works efficiently with viral delivery methods, and future work will demonstrate its utility with non-viral delivery methods in various molecular forms.

Applications

- Production of mRNA switches that can sense and respond to native biological conditions (e.g. T cell activation)
- Synthetic regulation of therapeutic payloads *in situ*
- Engineering of cellular immunotherapies *in vivo*

Advantages

- Precise control of the translation of genetic payloads
- Rapid and customizable production of mRNA switches
- Flexible temporal control of therapeutic dosing due to the transient nature of mRNA

Patents

- Published Application: [WO2025160191](https://www.wipo.int/patents/search/en/PCT/2025/160191)

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