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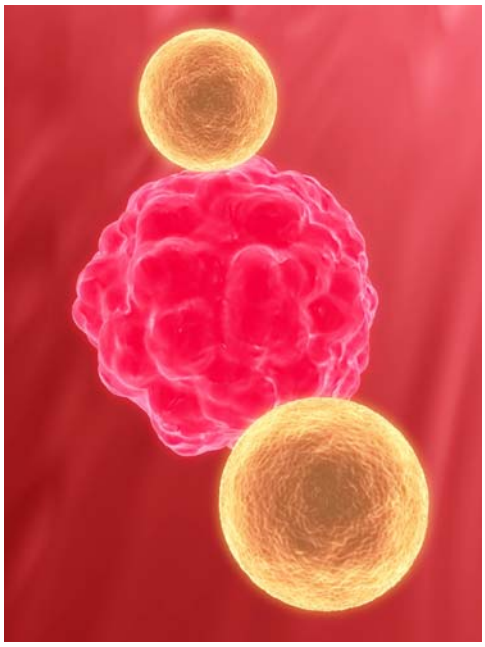
City of Hope
NATIONAL MEDICAL CENTER AND
BECKMAN RESEARCH INSTITUTE

Regulating Cells through Synthetic RNA Switch Control Systems



DESCRIPTION

This joint City of Hope and Caltech technology inserts a nucleic acid construct into cells to create a synthetic, controllable switch to affect a cell fate, such as activation, proliferation, differentiation, or apoptosis. The construct encodes two components: a gene product, such as a protein, cytokine, or siRNA sequence, and a RNA switch, which is further composed of sensor and actuator domains. The sensor domain can be designed to either bind to large proteins already within the cell or to a small, cell permeable molecule. The structural change caused by the binding-event activates or inhibits the actuator domain, typically a ribozyme, to regulate expression of the gene product.

This technology can be leveraged to improve cell based immunotherapies. Early attempts at engineering tumor-reactive T-cells have provided proof of concept; however effects diminish as the T-cells ultimately die. Effective treatment requires cells to proliferate to create persistent T-cell memory. This technology can create drug-regulated proliferation by triggering T-cells to produce autocrine growth cytokines. Alternative cell fates can also be utilized, such as a kill switch that triggers expression of PUMA, an apoptosis-inducing protein, to be deployed in gene therapy products after therapeutic endpoints are met. For example, engineered anti-CD19 T-cells have been effective in attacking B-lymphocytes to treat Chronic Lymphocytic Leukemia but cause permanent hypogammaglobulinemia when engineered cells remain in circulation. Programming a kill switch into engineered T-cells would allow physicians to administer a drug, after leukemia symptoms resolve, to trigger apoptosis in those T-cells and allow B-lymphocyte levels to return to normal levels.

KEY ASPECTS

- Small molecule-triggered "switch" modulates gene expression to induce cell fates such as activation, proliferation, differentiation, and apoptosis
- Applications in gene therapy and cell based immunotherapeutics

INTELLECTUAL PROPERTY

Title	US Patent Application	Filed
Genetic Control of Mammalian Cells with Synthetic RNA Regulatory Systems	12/708,506	2/18/2010

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