Abstract
B52

Triggering immune response from **within cancer cells**

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EDITY THERAPEUTICS

INTRODUCTION

The perforin-granzyme pathway delivers lytic payloads into target cells anywhere in the body with supreme efficiency and specificity. Edity therapeutics has designed a platform technology that uses this machinery to deliver therapeutic proteins using immune cells, without direct cytotoxicity.

This technology opens the possibility to modulate all intracellular targets, and has tremendous potential for conquering the thus-far unmet need of treating a vast host of diseases.

To leverage this platform technology for cancer treatment, we launched an investigational stage clinical program; ED007, in which we deliver immune-sensor proteins into cancer cells.

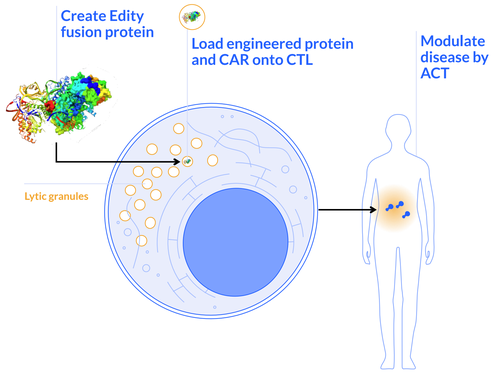
We use CAR technology to target the therapeutic cells to tumors. Once there, the engineered immune cells transfer immune sensor proteins to tumor cells. Each affected cancer cell is thus transformed into an inflammation mediator, that recruits the natural immune response to the tumour site, thereby complementing killing with inflammation.

Testing this method in vitro, we were able to demonstrate significant and specific type 1 interferon upregulation in cancer cells upon co-culture with immune cells loaded with immune sensors.

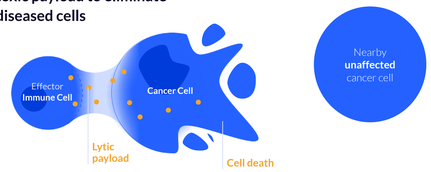
Our solution holds promise as a therapeutic approach to enable enhanced efficacy and persistence of cell therapy in solid cancer indications by mimicking natural inflammation, thus leading to activation of the comprehensive transcriptional program necessary for cellular immune response.

Edity's technology integrates therapeutic proteins into the perforin-granzyme pathway, delivering directly to the cytosol of target cells.

Sophisticated protein design and highly efficient transformation protocols ensure superior protein expression and transferability

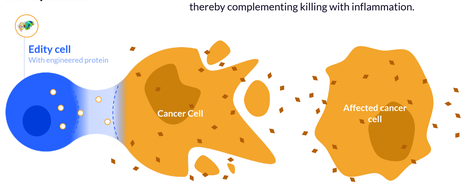


In nature, immune cells deliver a toxic payload to eliminate diseased cells



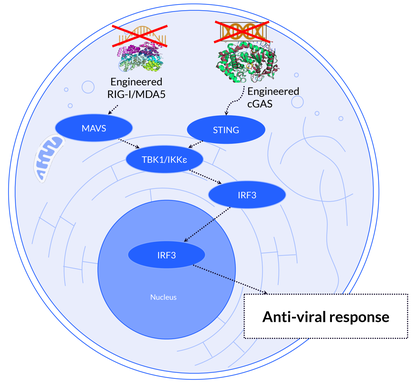
We redesign the immune cells to deliver protein therapeutics

The protein transferred by the engineered immune cell transforms each affected cancer cell into a factory of inflammatory mediators, that recruits the immune response to the tumor site, thereby complementing killing with inflammation.



Constitutively active **Immune Sensors**

The therapeutic protein is an immune sensor, that was engineered to constitutively activate its downstream pathway, independently of the presence of activating nucleic acids (AIS)

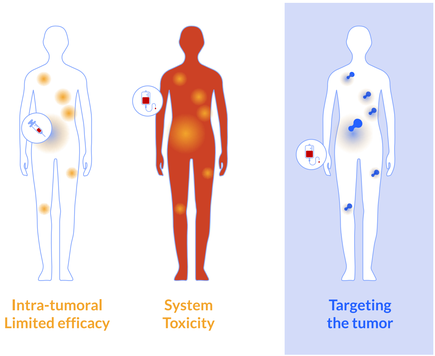


Adapted from Zhubing Shi and Zhaocai Zhou (2017). MST kinases in innate immune signaling. Cell Stress 2(1): 4-13. doi: 10.15698/cst2018.01.119

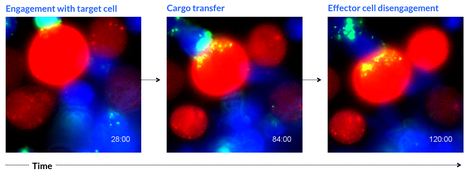
Edity's technology targets lesions throughout the body without causing systemic toxicity

By encapsulating the therapeutic agent inside the lytic granules of effector cells, we shield healthy cells from its toxic effect

Unlike small molecule treatment that requires high, often toxic, dosage and whose effect is measured in hours, CAR T-mediated treatment reaches lesions with high efficiency and endures for weeks



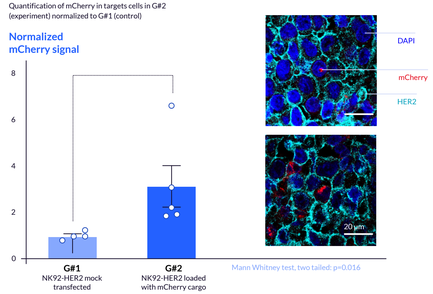
An Edity engineered HER2 CAR-NK92 cell (blue) transfers GFP protein cargo to RFP-expressing HER2+ MDA-MB-453 target cells



Snapshots captured from live imaging microscopy.

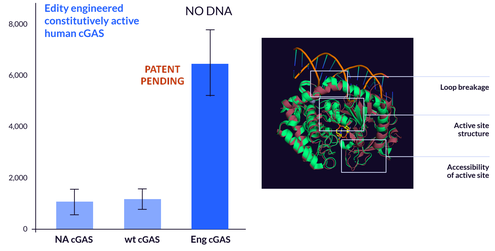
Live imaging of Edity Tech!

Demonstration of successful in vivo cherry delivery using NK-HER2 to MDA453 tumor (G#2) versus control (G#1)



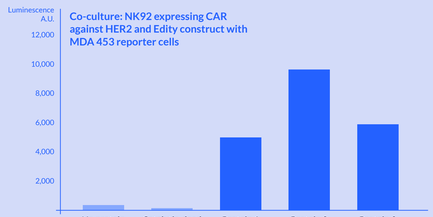
Protein Design of Constitutively Active Immune Sensor

We use both rational design and in silico modeling to generate activation-independent candidate mutants, and screen them experimentally. In the case of the DNA-activated cGas, constitutive activity is achieved by breaking a protein loop, to mimic the conformational change that results from interaction with DNA



Preliminary Transfer results

We saw significant interferon induction in target cells after co-culture using several protein candidates including enzymes, adaptor proteins and transcription factors



Using this method, we were able to demonstrate significant and specific type 1 interferon upregulation in vitro. Our solution mimics natural inflammation, thus leading to the comprehensive transcriptional program necessary for cellular immune response.

SUMMARY

- Edity is developing a novel platform technology which uses the immune system to deliver therapeutic proteins directly to the cytoplasm of target cells, to modulate disease
- We have thus far substantiated the core technology by demonstrating robust in vitro transfer of fluorescent proteins and preliminary evidence for fluorescent protein cargo transfer in an intra-tumor in vivo setting
- Robust functional transfer of enzymes, mediators and transcription factors provided in vitro proof of concept for the ED007 project
- Current efforts are focused on demonstrating in vivo functional transfer of immune sensors upon systemic adoptive cell transfer of ED007-CAR T cells
- In the long term, we envisage this technology as a platform for delivering a vast range of therapeutic proteins, from intracellular antibodies to genome editing and modifying enzymes