1217 TRIGGERING IMMUNE RESPONSE FROM WITHIN CANCER CELLS

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Background Even as adoptive cell immunotherapy exhibits great success against liquid cancers, solid tumors continue to present a challenge. A straightforward way of triggering an immune response in solid tumors would be to have immune-provoking proteins act in tumor cells. However, the field of cell therapy has yet to provide a way of introducing functional proteins to the interior of cells.

Methods We developed a method of harnessing the adaptive immune response to do just that. The perforin-granzyme pathway delivers lytic payloads into target cells anywhere in the body with supreme efficiency and specificity. Our technology allows incorporation of therapeutic proteins directly into this pathway hence they are delivered directly to the cytosol of target cells. This is achieved by fusing an immune sensor protein that has been engineered to be constitutively active to a lytic granule navigator moiety, and express the resulting chimera in immune cells. Sophisticated fusion protein design and highly efficient transformation protocols ensure superior expression and transferability. Using available CAR technologies, we target the therapeutic cells to tumors. Once there, the engineered immune cell does not kill all malignant cells due to suppressive effects of the tumor microenvironment. Rather, the transferred immune sensor protein transforms each cancer cell into an inflammatory mediator factory that recruits the immune response to the tumor site, thereby complementing killing with inflammation.

Results Using this method, we were able to demonstrate significant and specific type 1 interferon upregulation in vitro, as well as a measurable paracrine effect. Our solution mimics natural inflammation, thus leading to the comprehensive transcriptional program necessary for cellular immune response. 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. We have thus far demonstrated effective transfer of fluorescent proteins, as well as functional enzymes, mediators and transcription factors, and observed preliminary evidence for protein cargo transfer in an *in vivo* setting.

Conclusions 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. The ability to deliver an active protein to the inner compartment of a cell affords an immense, unprecedented power that promises to open a whole new universe of therapeutic targets.

Ethics Approval Animal studies were performed at Vivox Ltd Israel. Ethics Committee approval number IL-2109–138-5

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