

# Modulating Hexokinase 2 (HK2) as a Novel Approach for Simultaneous Targeting of the Tumor and Its Immunosuppressive Microenvironment

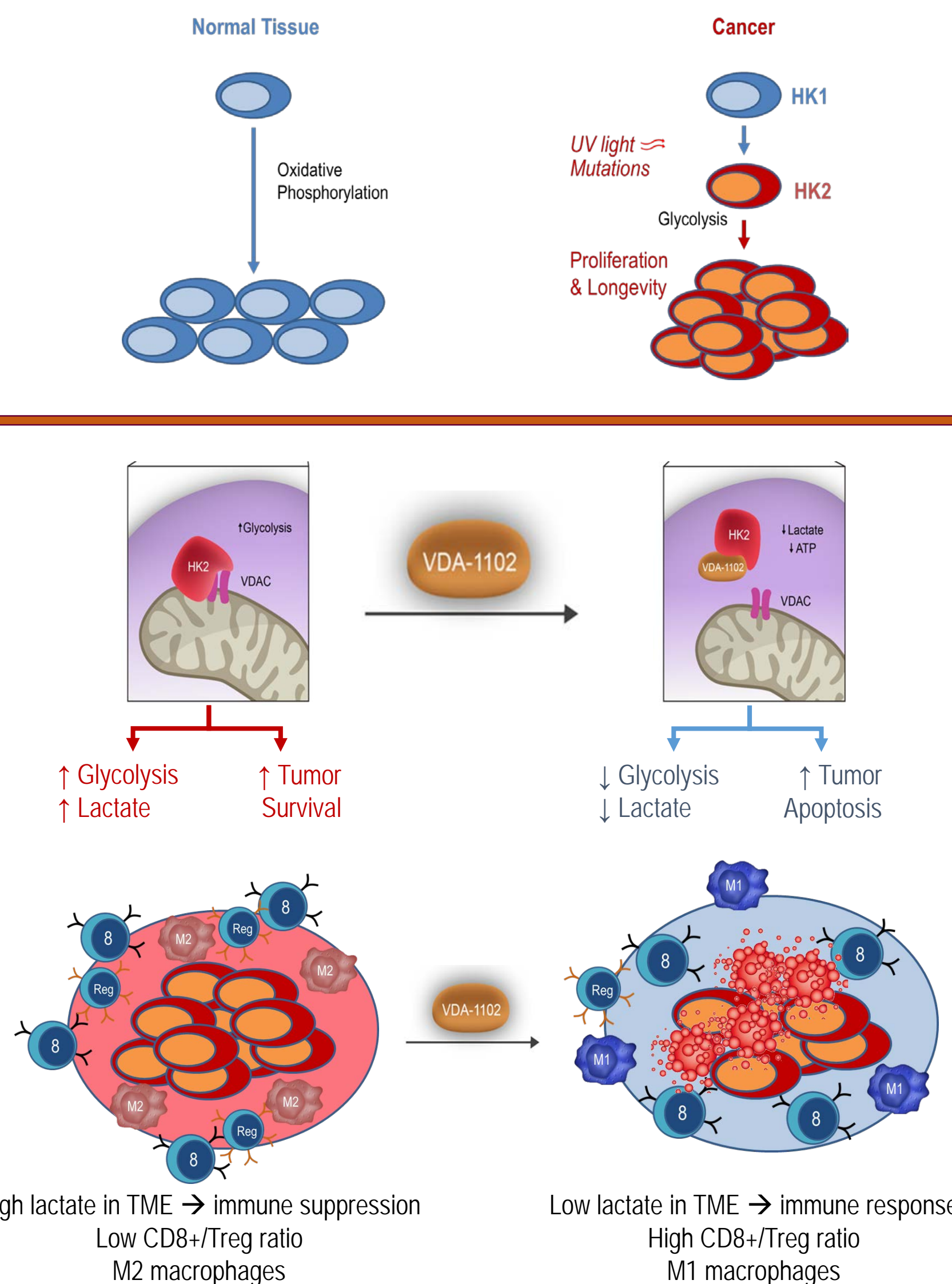
SITC 2018

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## BACKGROUND

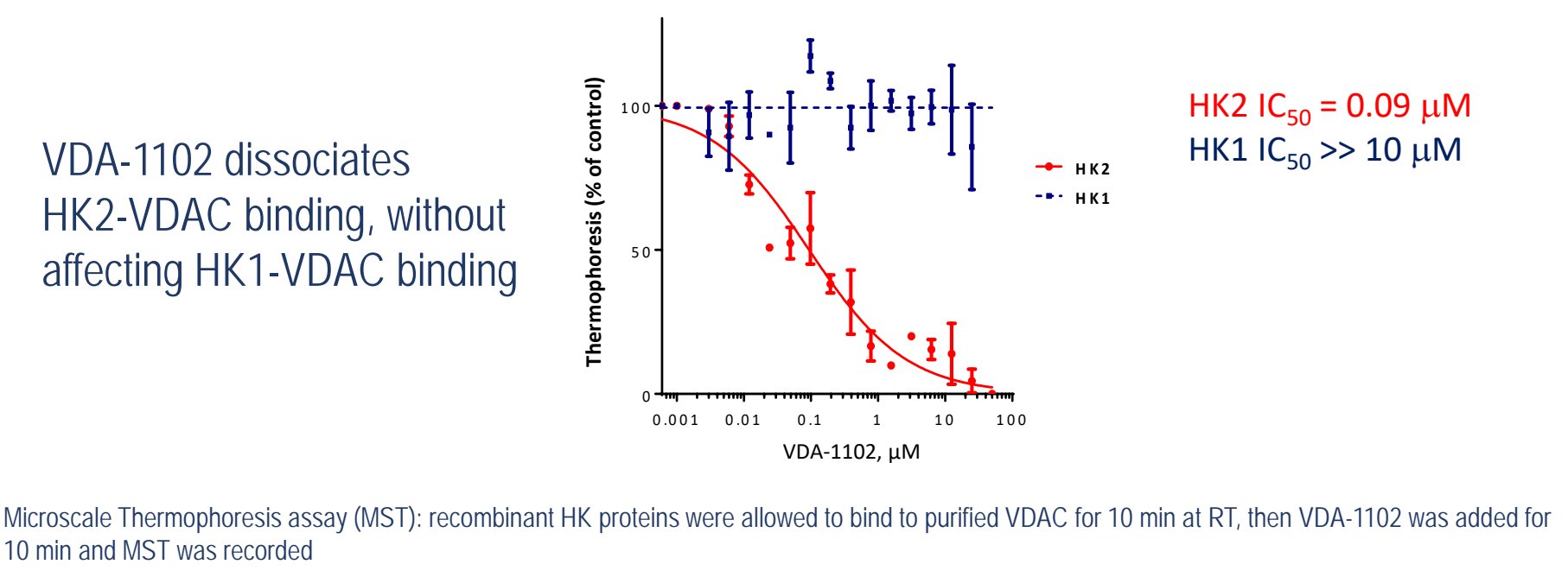
- Metabolic re-programming to aerobic glycolysis, known as the Warburg effect, allows cancer cells an efficient conversion of glucose to biomass and energy required for rapid cell growth and proliferation. It is associated with expression of the hexokinase 2 (HK2) isotype, instead of the ubiquitous HK1, as the first enzyme in glycolysis.
- HK2 attaches to the outer mitochondrial membrane via the VDAC1 channel. VDAC1/HK2 association results in apoptosis prevention and a high rate of glycolysis.
- The high utilization of glucose by cancer cells results in the accumulation of extracellular lactate and concomitant acidification, which was shown to suppress immunity in the tumor microenvironment (TME). Increased lactate levels in the TME also attenuates recruitment and activity of cytotoxic CD8+ T cell, and stimulates polarization of macrophages to an immune-suppressive M2 state.
- VDA-1102 is a novel small-molecule HK2 modulator that selectively detaches HK2 from VDAC1, triggering apoptosis in cancer cells and promoting anti-tumor immune response (Behar V et al., J. Invest. Dermatol 2018).

## VDA-1102 Mechanism of Action

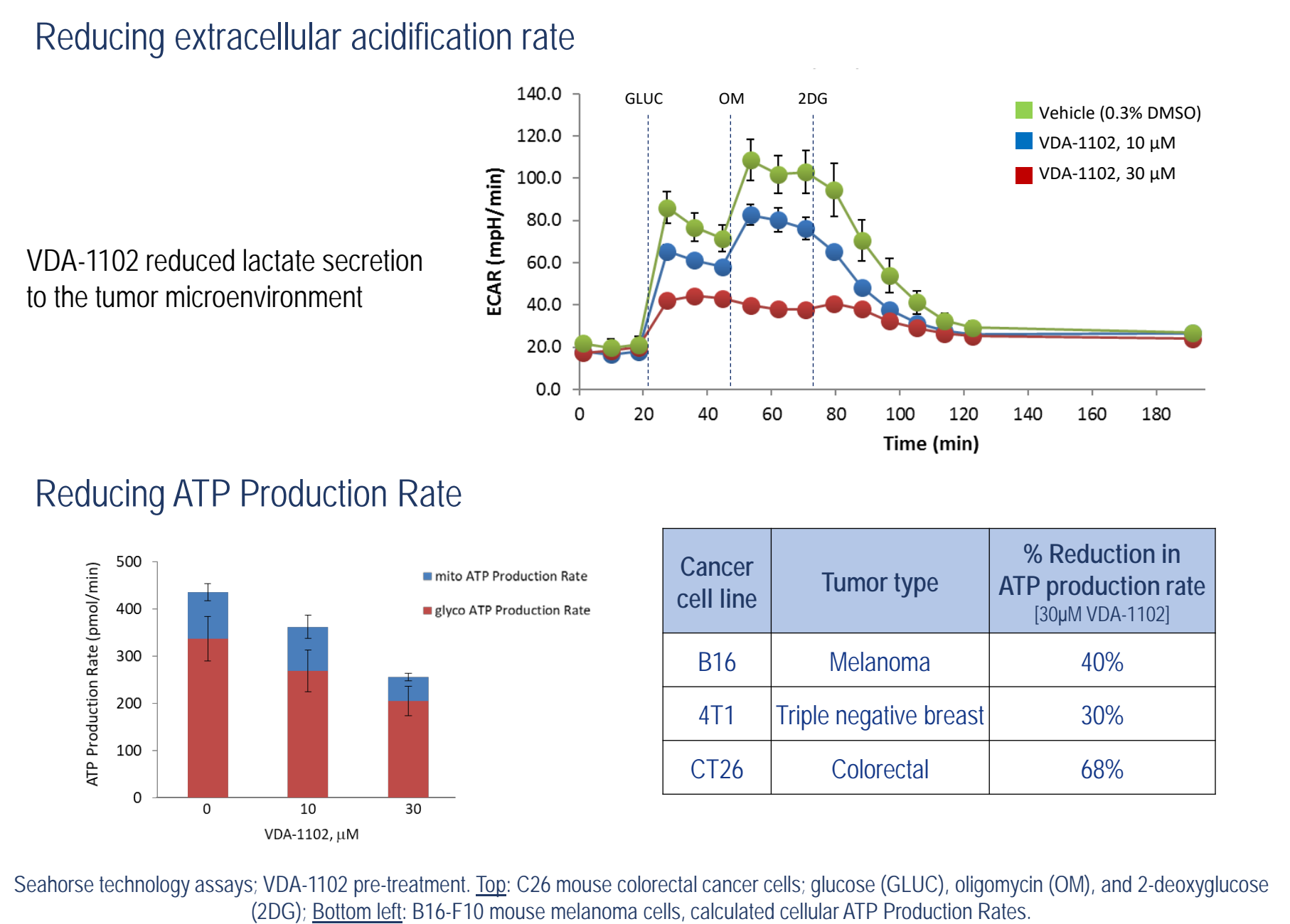


## EFFECTS on CANCER CELLS

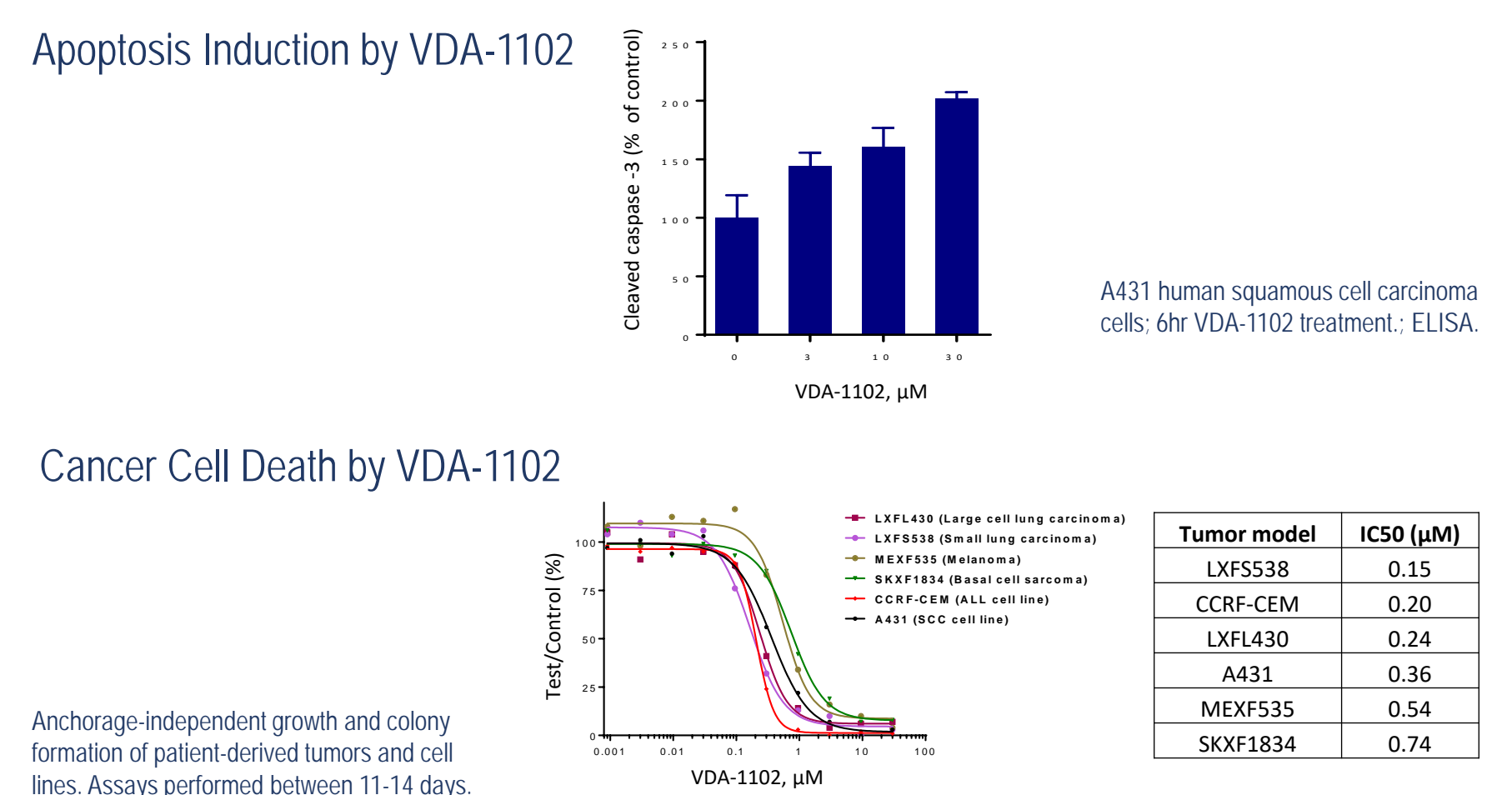
### Selective HK2-VDAC Dissociation



### Reduction of Lactate Secretion, ATP Production Rate

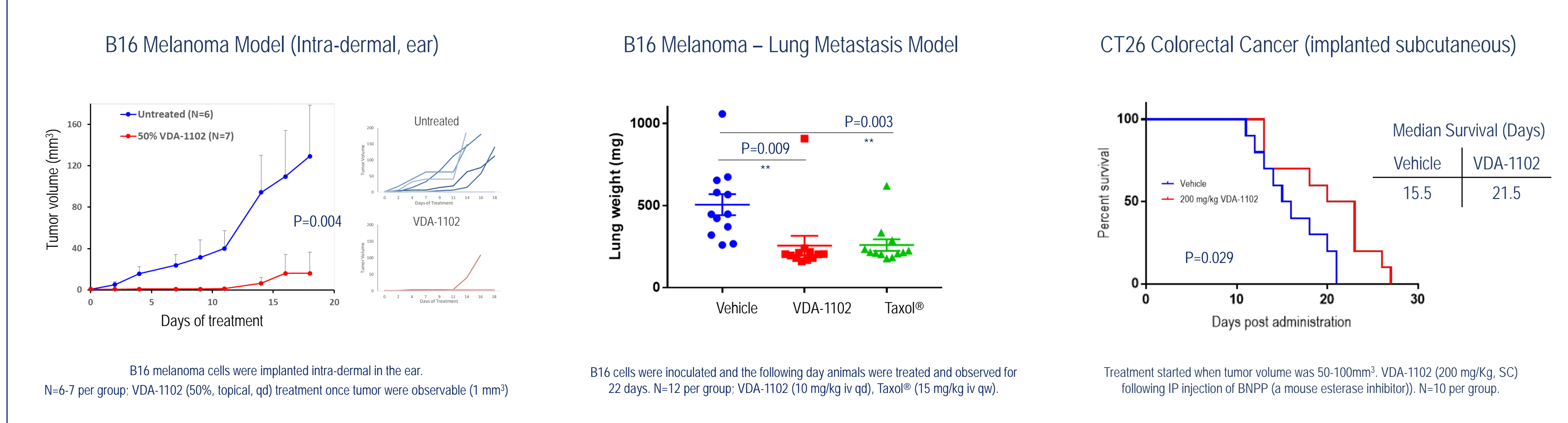


### VDA-1102 Induces Apoptosis and Cancer Cell Death

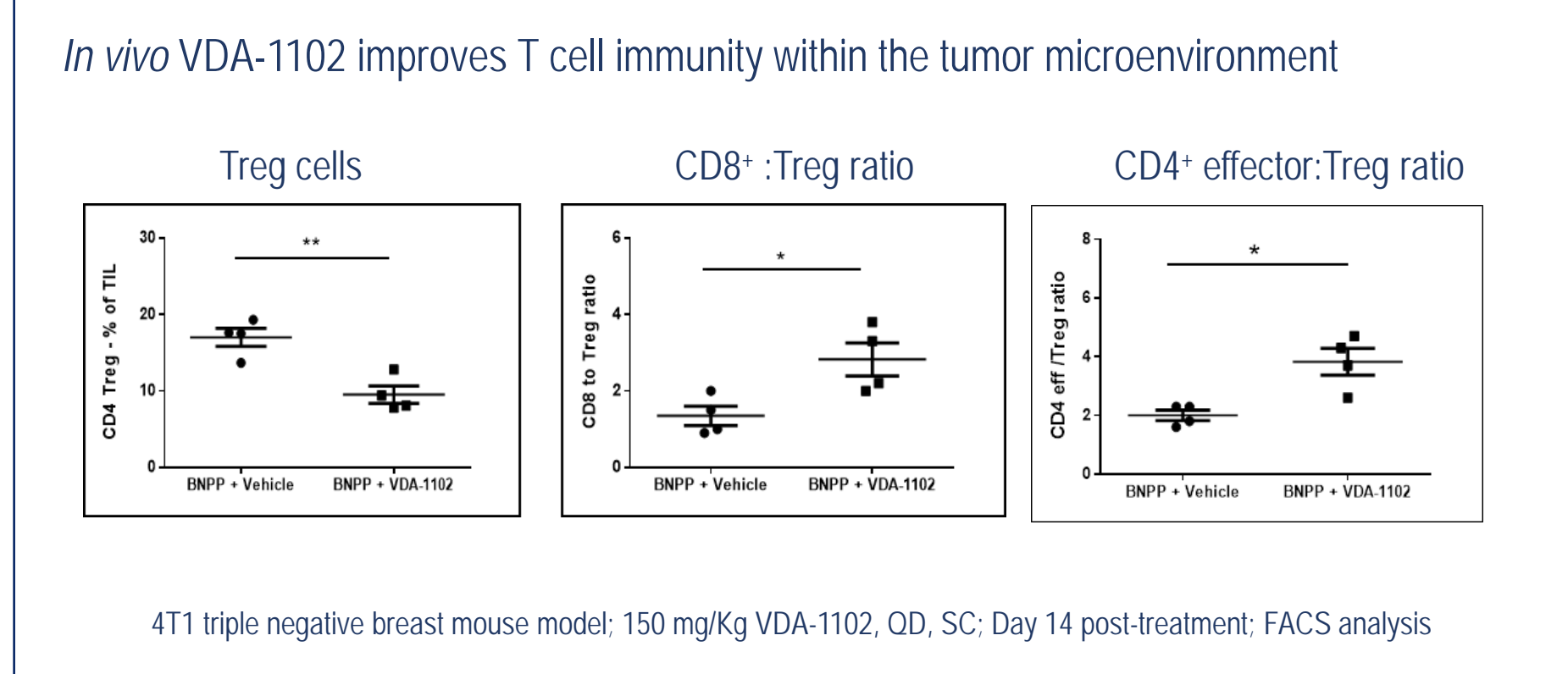
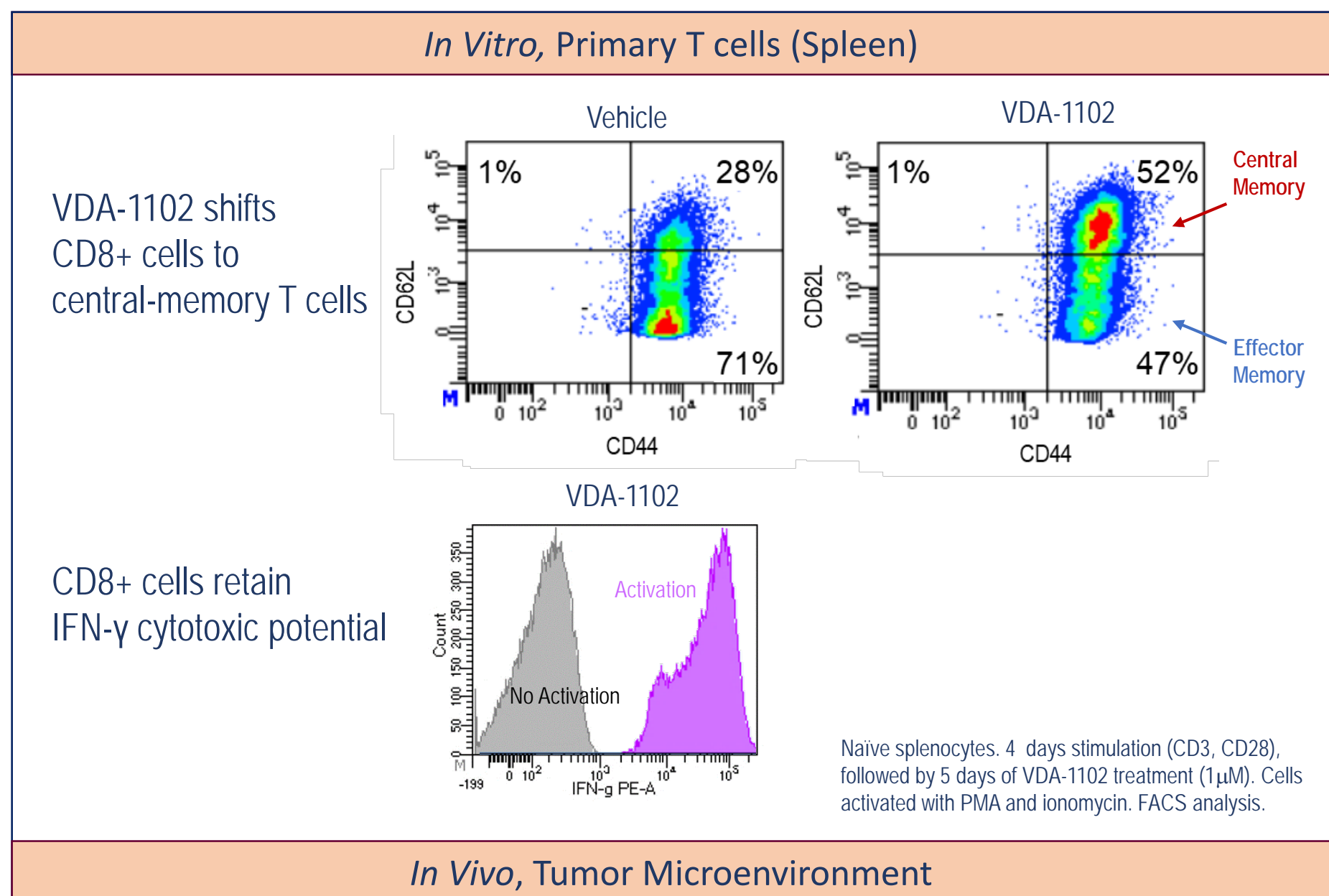


## NON-CLINICAL EFFICACY

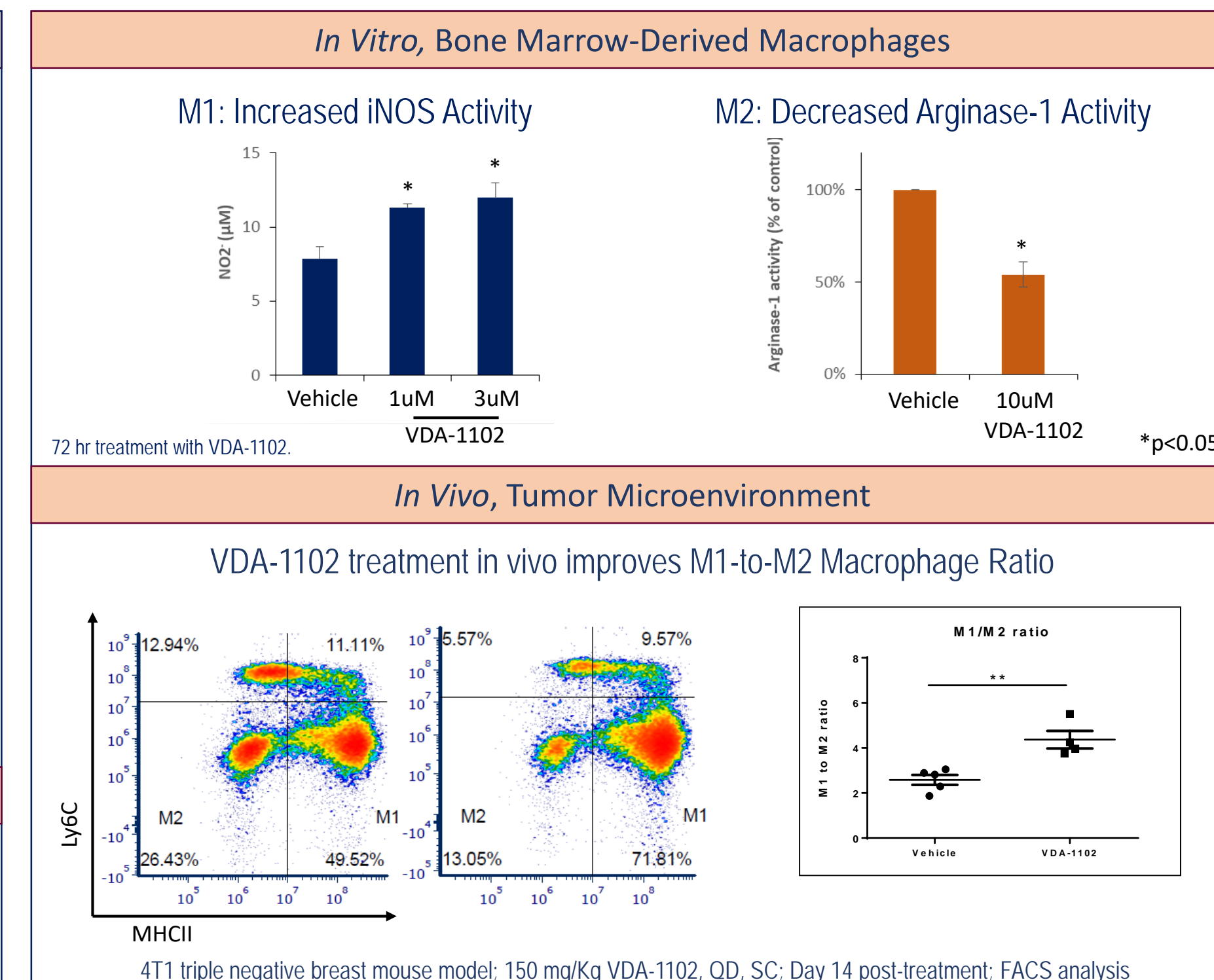
### Anti-Cancer Effects of VDA-1102 in Syngeneic Mouse Tumor Models



## EFFECTS of VDA-1102 on T CELLS



## EFFECTS of VDA-1102 on MACROPHAGES



## SUMMARY

- VDA-1102 is a novel, selective, small-molecule HK2 modulator that reduces tumor glycolysis and inducing cancer cell apoptosis.
- VDA-1102's glycolysis inhibition results in reduced lactate secretion to the tumor microenvironment (TME), leading to stimulation of an anti-cancer immune response (CD8+ T cells and M1 macrophages).