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KINETA

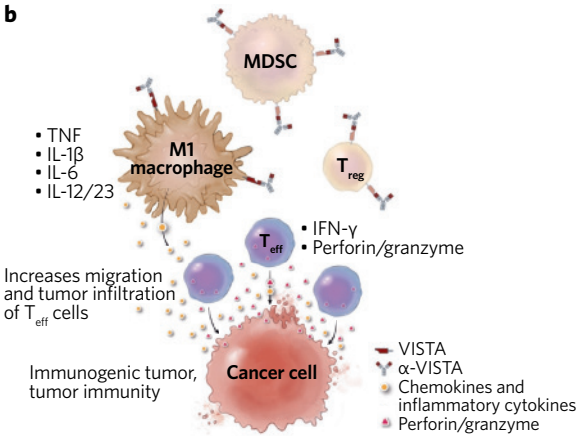
Targeting VISTA to halt tumor growth

By reprogramming the tumor microenvironment Kineta is developing an anti-VISTA immuno-oncology therapy for the treatment of a variety of cancers, including gastric, ovarian, lung and pancreatic cancers.

a

Treatment group	Median tumor volume (mm^3)	Tumor growth inhibition (%)
Isotype control	1,717	–
Anti-mouse PD-1	1,497	13
Anti-mouse VISTA	841	51

b



c

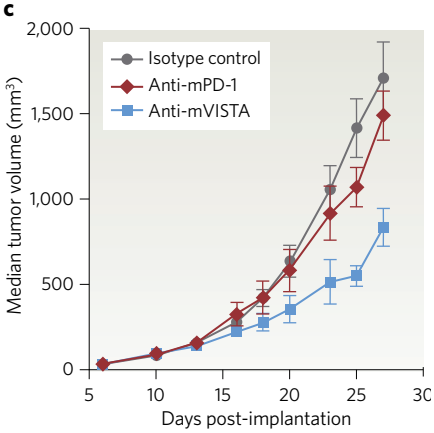


Fig. 1 | Blocking VISTA. a, In preclinical models, blocking VISTA substantially inhibited tumor cell growth. **b**, Antibody treatment inhibits tumor growth by blocking VISTA-mediated suppression of T cells and remodeling the TME. **c**, A mouse syngeneic colon carcinoma model was treated with antibodies to the mouse VISTA protein that resulted in tumor growth inhibition by 51% at day 27, compared with 13% inhibition in mice treated with the checkpoint inhibitor (CPI) anti-PD-1. IFN, interferon; IL, interleukin; MDSC, myeloid-derived suppressor cell; T_{eff} cell, T effector cell; TNF, tumor necrosis factor.

Kineta is leveraging its deep expertise in innate immunity, and particularly myeloid cells, to develop innovative, first-in-class therapies with a primary focus on cancer. To date, immune-based oncology (IO) treatments have focused on the adaptive immune system, mainly acting on T cells. Yet myeloid cells (monocytes and macrophages) initiate and orchestrate both innate and adaptive immune responses, sending proinflammatory or immunosuppressive signals, in response to pathogens, tumors or cell damage.

Kineta is preparing to enter the clinic with a unique IO therapy that reprograms the tumor microenvironment (TME) by inhibiting VISTA, a protein mainly expressed on macrophages. In preclinical models, blocking VISTA substantially inhibited tumor cell growth (Fig. 1a), surpassing the effects of a checkpoint inhibitor (CPI). Kineta is seeking investors to complete investigational new drug (IND)-enabling studies and move the VISTA program into the clinic, while continuing to pursue other innate immune targets in oncology and a partnered program in chronic pain.

Targeting tumors unresponsive to CPIs

Although CPI therapies represented a breakthrough in treatment for some cancers, notably melanoma, many tumor types, and 70–80% of patients, fail to benefit. These CPI-unresponsive tumors often lack T lymphocytes and other mediators of immune responses in the TME. Kineta has selected a novel IO target, VISTA, a protein highly expressed on myeloid-derived suppressor cells (MDSCs), as well as on T regulatory (T_{reg}) cells, both negative regulators of immune responses. In pancreatic cancer, high VISTA expression in the TME is prognostic for poor outcomes, both generally and in response to CPI treatment[1]. Blocking the suppressive effects of VISTA with an antibody has been shown to subvert the immunosuppressive activity of MDSCs, shift macrophages to a proinflammatory M1 phenotype, enhance dendritic cell (DC) activity and promote tumor cell killing by T effector (T_{eff}) cells (Fig. 1b). In a syngeneic mouse model of colon carcinoma, CT26, treatment with an antibody to the mouse VISTA protein inhibited tumor growth by 51% at day 27, versus 13% inhibition in mice treated with the CPI anti-PD-1 (Fig. 1c).

Anti-VISTA IO therapy has broad potential to generate anti-tumor responses in a variety of cancers, including pancreatic, gastric, ovarian and lung cancers. Kineta is seeking to raise institutional investment capital to support clinical development of VISTA, with a phase 1 trial slated to begin in 2021. Kineta is exploring an initial indication in CPI treatment failures, as recurrent tumors evidence high levels of resident VISTA-positive myeloid cells. No mechanism-associated safety issues have been identified for VISTA-blocking antibodies.

Pipeline at Kineta

In addition to its in-house VISTA program, Kineta is focusing discovery stage research efforts on undisclosed innate immune targets that have the potential to turn cold tumors hot and complement CPI therapy.

Kineta's pipeline also includes KCP506, a first-in-class nonopioid drug for chronic pain. Kineta is partnering with Genentech–Roche in an on-going research, option and licensing agreement to develop an antagonist of the α9/α10 nicotinic acetylcholine receptor (nAChR) for treatment of neuropathic chronic pain and inflammation. The deal includes an undisclosed upfront payment and up to $359 million in potential milestone payments. The approach is highly differentiated from opioid drugs, as the nAChR target is expressed in the peripheral nervous system instead of the central nervous system, making tolerance or addiction unlikely.

In preclinical studies, KCP506, a pegylated peptide inhibitor of α9/α10 nAChR, reduced pain behaviors in animals and also showed anti-inflammatory and neuroprotective properties, suggesting that it has the potential to slow or halt the progression of chronic pain. In November 2019, Roche made an additional payment to expand preclinical research collaboration on KCP506.

As Kineta moves aggressively to rapidly advance the VISTA IO program into the clinic, the company also sees myriad opportunities to develop further innovative treatments for cancer that harness the power of innate immunity to improve clinical outcomes.

1. Blando, J. et al. *Proc. Natl Acad. Sci. USA* **116**, 1692–1697 (2019).

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