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(71) Applicants: **BETH ISRAEL DEACONESS MEDICAL CENTER, INC.** [US/US]; 330 Brookline Avenue, Boston, MA 02215 (US). **ANTAGEN INSTITUTE FOR BIOMEDICAL RESEARCH** [US/US]; 650 Albany Street, Unit 112, Boston, MA 02118 (US).

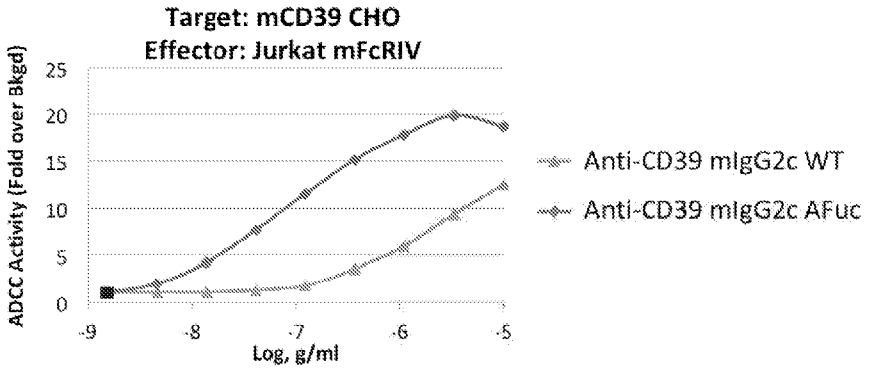
(72) Inventors: **ROBSON, Simon, C.**; 6 Candleberry Lane, Weston, MA 02493 (US). **SHANG, Yan, Wu**; 435 Park Street, North Reading, MA 01864 (US). **GAO, Wenda**; 15 Concord Rd, Sharon, MA 02067 (US). **ZHANG, Haohai**; 10 Larch Street, Brighton, MA 02135 (US). **DE ANDRADE MELLO, Paola**; 160 Cambridgepark Drive, Unit 343, Cambridge, MA 02140 (US).

(74) Agent: **ARMSTRONG, Richard, Todd**; Clark & Elbing LLP, 101 Federal Street, 15th Floor, Boston, MA 02110 (US).

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(54) Title: COMPOSITIONS AND METHODS FOR PREVENTING OR REVERSING T-CELL EXHAUSTION THROUGH ECTONUCLEOTIDASE INHIBITION AND ANTIBODY-MEDIATED TARGET CYTOSIS

Fig. 1A



(57) Abstract: In combination with conventional therapies (e.g., targeted therapy, chemotherapy, and angiogenesis inhibitors etc.), immunotherapies targeting checkpoint molecules have shown promise in the treatment of solid or liquid tumors. However, apoptotic regulatory T cells (Treg) induced by such therapies often become more suppressive in the tumor microenvironment (TME), through increased generation of adenosine tightly controlled by ectonucleotidases, viz. CD39 and CD73. CD39/ENTPD1, a novel checkpoint molecule, is highly expressed and activated on the tumor vasculature and infiltrating immune cells, promoting tumor growth. Deletion or blockade of CD39 enhances anti-tumor activity by augmenting anti-tumor immune responses and inhibiting tumor angiogenesis. The present invention is based at least in part on the development of anti-CD39 antibodies which mediate CD39 downregulation on immune cells, such as T-cells with markers of T-cell exhaustion, and the demonstrated utility of these antibodies in blocking tumor growth with minimal side effects in pre-clinical models.

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