851 HARNESSING INNATE IMMUNITY IN CANCER THERAPIES: THE EXAMPLE OF NATURAL KILLER CELL ENGAGERS

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Background Most immunomodulatory approaches have focused on enhancing T-cell responses, with immune checkpoint inhibitors, chimeric antigen receptor T cells or bispecific antibodies. Although these therapies have led to exceptional successes, only a minority of cancer patients benefit from these treatments, highlighting the need to identify new cells and molecules that could be exploited in the next generation of immunotherapy. Given the crucial role of innate immune responses in immunity, harnessing these responses opens up new possibilities for tumor control. Antibody engineering provides us with great opportunities to induce synthetic immunity and to optimize the biological functions of innate immune cells, in particular by boosting the capacity of Natural Killer (NK) cells to kill tumor cells directly and to stimulate T-cell responses indirectly.

Methods In order to leverage the advantages of harnessing NK cell effector functions, we used our Antibody-based NK cell Engager Therapeutics (ANKET) molecular platform[1] and designed a new generation of molecules that can engage activating receptors NKp46 and CD16, the IL-2Rβ chain and a tumor antigen in a single tetra-specific molecule (ANKET4). The variant of interleukin-2 (IL-2v) integrated in the ANKET4 molecule is unable to bind the α-subunit of its receptor to limit regulatory T cell activation and IL-2Rα-mediated toxicity.

Results In vitro, ANKET4 provides proliferation and activation signals targeted to NK cells and induces primary human NK cell cytolytic activity and the secretion of cytokines and chemokines only after binding to the tumor target. In mouse models of both invasive and solid tumors, ANKET4 induced NK cell proliferation and accumulation at the tumor bed, and had a higher anti-tumor efficacy than approved therapeutic antibodies targeting the same tumor antigen. Mechanistically, transcriptomic analysis and in-vivo studies revealed that the geometry of the ANKET4 molecule including NKp46, CD16 and IL-2 receptor binding moieties on the same molecule was essential for its strong activity which results from a synthetic cooperativity between immunoreceptor tyrosine-based activation motif (ITAM) and cytokine signaling pathways. In non-human primates, CD20-directed ANKET4 resulted in sustained CD20+ B-cell depletion with minimal systemic cytokine release and no clinical sign of toxicity.

Conclusions Tetra-specific ANKET4 thus constitutes a technological platform combining the induction of NK cell proliferation and effector functions with a manageable safety profile, supporting its clinical development for next-generation cancer immunotherapies.

REFERENCE

1. Gauthier L, Morel A, Anceriz N, Rossi B, Blanchard-Alvarez A, Grondin G, *et al*. Multifunctional natural killer cell engagers targeting NKp46 trigger protective tumor immunity. *Cell* 2019;**177**(7):1701–13 e16.

Ethics Approval Primary immune cells were purified from buffy coats from healthy donors obtained from Etablissement Francais du Sang (EFS, Marseille) with written consent from each volunteer.All mouse experiments were performed in accordance with the rules of the Innate Pharma ethics committee and were approved by the Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation – France (APAFIS# 19272).All non human-primate procedures were conducted according to European guidelines for animal care and use for scientific purposes (Directive 63-2010, "Journal Officiel des Communautés Européennes", L276, September 22, 2010) and according to CEA institutional guidelines. The study was approved by the local ethical committee under the number A18_080 and by the French Administration (APAFIS#20525-2019050616506478 v1)

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