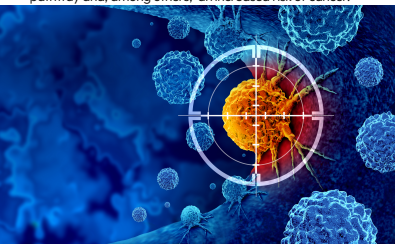
Antidromic strategies to target RASopathies

Immunotherapies have revolutionized cancer treatment but relapses frequently happen due to resistance development and there is a high medical need for effective and new targeted therapies. A key obstacle is the lack of unique extracellular tumor antigens. Interestingly, oncogenes RAS (KRAS, HRAS, and NRAS) are often expressed in resistant malignant cells. These genes are the most common oncogenes in human cancer. RASopathies are a heterogeneous group of rare diseases in which mutations in the Ras genes lead to overactivation of the RAS-MAPK signaling pathway and, among others, an increased risk of cancer.



Direct RAS targeting with bispecific PCC antibodies

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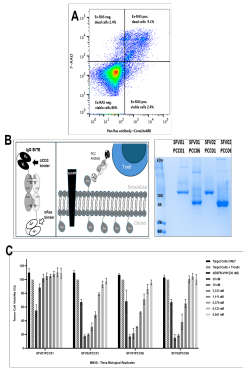
2025

Competing antibody or CAR T-cell strategies against RAS exist and all are using HLA restricted binders against specific RAS mutant peptides with major drawbacks. Our data shows expression of RAS on the cell surface of viable tumors cells not in complex with the HLA system avoiding all major disadvantages of the competitors.

01 First report of RAS detected at low levels on cell surface independent of the HLA complex
02 Succesful generation of novel PCC antibodies against extracellular RAS
03 Effective targeting of low extracellularly expressed RAS on cancer cells via bispecific T cell engager
04 Relevant for novel immunotherapies for RAS-driven malignancies



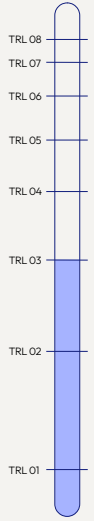
A. Expression of RAS protein on the surface of acute monocytic leukemia cells (NOMO1). B. Design and recombinant production of different RAS binding PCC antibodies. C. Human Multiple Myeloma cancer cells (MM1.S) incubated with human T-cells and 4 different PCC antibodies. Viability of tumor cells was analyzed after 48 hours.

CHALLENGE

Ras proteins are hubs of various signaling pathways activated by external stimuli and control gene expression and regulate cell proliferation, differentiation and survival. Strategies to target RAS directly in malignant cells include small-molecule inhibitors, intrabodies crossing the plasma membrane and binding RAS in the cytosol or targeting RAS mutant peptide in the HLA complex present on the cell surface via HLA-restricted antibodies. However, current RAS targeting antibodies have major drawbacks.

INNOVATION

It was discovered that on certain malignant cancer cells RAS proteins are expressed in very small quantities on the outer side of the cell membrane. Aberrant RAS expression was found on CD138+ cells from multiple myeloma (MM) patients using mass spectrometry and low expression of RAS was found on viable leukeimc cells. Different antibodies, targeting all three RAS proteins (KRAS, NRAS and HRAS), were recombinantly produced to target bispecific T cell engagers . These PCC (protein catalyzed capture) antibodies effectively target lowly expressed extracelullar RAS antigens on MM cells constructs were shown to redirect cytotoxic T cells against a human pancreatic tumor cell line in vitro.



01 Basic principles observed · **02** Technology concept formulated · **03** Experimental proof of concept · **04** Technology validated in lab · **05** Technology validated in relevant environment · **06** Technology demonstrated in relevant environment · **07** System prototype demonstrated in operational environment · **08** System complete and qualified

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