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Combination immunotherapy with tumor-targeting monoclonal antibodies and anti-CD137

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Tumor-targeting monoclonal antibody (mAb) therapy has changed the natural history of patients with B cell lymphomas, breast cancer, and colorectal and head and neck cancers, respectively. Despite their promise, response rates are suboptimal at less than 25%, highlighting the need to enhance mAb activity. Natural killer (NK) cells are important effector cells mediating antibody dependent cell-mediated cytotoxicity (ADCC), a primary antitumor mechanism of action of mAbs. Approaches that specifically augment NK cell function can thus complement and enhance mAb therapy.The costimulatory molecule CD137 (4-1BB), a member of the tumor necrosis factor receptor superfamily, is expressed following NK and memory T cell activation. We found that isolated human NK cells substantially increased expression of CD137 when exposed to tumor cells bound by their tumor-targeting mAb, including rituximab-coated-CD20-expressing lymphoma, trastuzumab-coated, HER2-expressing breast cancer, and cetuximab-coated, EGFR-expressing head and neck and colorectal cancercell lines. Furthermore, activation of CD137 with an agonistic mAb(anti-CD137) enhanced NK cell degranulation and cytotoxicity. In multiple murine syngeneic and xenograft models, combined tumor-targeting mAband anti-CD137 mAb administration was synergistic and led to complete tumor resolution and prolonged survival, which was dependent on the presence of NK cells. In patients receiving mAb therapy, the level of CD137 on circulating NK cells increased post mAb infusions. This sequential antibody strategy, combining a tumor-targeting mAb with anti-CD137 to activate the host innate immune system, may improve the therapeutic effects of tumor-targeting mAbs and is now being investigated in clinical trials.

Biography:

Dr. Amani Makkouk is a postdoctoral fellow in Dr. Holbrook Kohrt's lab at Stanford University. She studies novel strategies to potentiate the immune responses of tumor-targeting monoclonal antibodies through immunomodulation of natural killer cells. Dr. Makkouk was trained as a pharmacist and has a Masters degree in microbiology and immunology and a Masters degree in health physics. She obtained her PhD in immunology from the University of Iowa under the mentorship of Dr. George Weiner. Her doctoral thesis focused on devising a framework for combining agents for in situ immunization using biodegradable microparticles and immunomodulatory antibodies.