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**BDC-3042: A DECTIN-2 AGONISTIC ANTIBODY FOR TUMOR-ASSOCIATED MACROPHAGE-DIRECTED IMMUNOTHERAPY**

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**Background** Tumor-associated macrophages (TAMs) generally support tumor progression through their immunosuppressive effects on the tumor microenvironment (TME) and are the predominant immune cell population in most cancers. TAMs express the pattern recognition receptor Dectin-2 (*CLEC6A*), an activating C-type lectin receptor (CLR) that binds to high-mannose glycans on fungi and other microbes and induces protective immune responses against infectious disease. Dectin-2 ligation mediates enhanced phagocytosis, antigen processing and presentation, and proinflammatory cytokine production. Agonism of Dectin-2 on TAMs using naturally derived ligands drives potent anti-tumor immunity in syngeneic mouse tumor models. Given these findings, we developed a human Dectin-2-targeted agonistic antibody, BDC-3042, which is capable of robustly activating TAMs as a novel approach to myeloid-directed immunotherapy.

**Methods** Dectin-2 expression was assessed by flow cytometry, immunohistochemistry, and using public databases. Human whole blood, monocyte-derived macrophages, and single-cell suspensions from dissociated human tumors were stimulated overnight with BDC-3042. Activation was assessed through cytokine analysis. Immune profiling and anti-tumor efficacy were assessed in vivo utilizing MDA-MB-231 tumor-bearing CD34+ HSC engrafted mice (huNOG-EXL, Taconic Biosciences).

**Results** Dectin-2 is expressed by TAMs across many tumor types, including breast, colon, and lung cancers, but exhibits minimal expression in most normal tissues. BDC-3042 binds to recombinant Dectin-2 and Dectin-2-expressing cells with low-nanomolar affinity. BDC-3042 elicits robust activation of primary TAMs and in vitro-generated macrophages, leading to secretion of proinflammatory mediators characteristic of tumor-destructive “M1” macrophages, such as TNF $\alpha$ , IL-1 $\beta$ , and CCL3/4. Low levels of BDC-3042 binding are detected on blood monocytes, with minimal binding to other peripheral immune cells. Importantly, BDC-3042 elicits little to no activation of peripheral monocytes or cells in whole blood. BDC-3042 activity is dependent on both Dectin-2 and Fc $\gamma$ R $\alpha$ s, as indicated by the increased activation of macrophages elicited with an Fc-enhanced IgG1 backbone. Systemically administered BDC-3042 activates TAMs and mediates anti-tumor efficacy in mice with humanized immune systems.

**Conclusions** The data presented demonstrate the therapeutic potential of targeting Dectin-2 expressed by TAMs with the agonistic antibody BDC-3042 as a novel pan-cancer approach for myeloid cell-directed tumor immunotherapy.

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