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In vitro-based nonclinical development pathway for a DNA-encoded bispecific T cell activator (dBTA) targeting HER2

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We have recently described the clinical proof of concept for in vivo expression of biological relevant levels of functional monoclonal antibodies after local delivery of synthetic pDNA constructs to the muscle. Here we describe employing this gene delivery technology to a synthetic DNA plasmid (pGX93237) encoding a bispecific T cell activator (DBTA) engaging epidermal growth factor receptor 2 (ERBB2; HER2) tumor antigen on cancer cells and CD3 on T cells (DBTA-HER2CD3). Preclinical in vivo proof of concept studies demonstrated a single intramuscular (IM) administration of a synthetic plasmid DNA drug, pGX93237 with CELLECTRA® in vivo electroporation (EP) technology resulted in durable DBTA-HER2CD3 expression with measurable levels of the functional therapeutic in mice. pGX93237 treatment demonstrated dose-dependent control of tumor growth and improved animal survival in a humanized mouse model. To advance pGX93237 towards clinical testing we have designed a nonclinical development strategy to guide first in human doses of this highly active therapeutic. Due to the lack of cross-reactivity of theDBTA-HER2CD3 anti-human CD3 binding moiety with its non-human counterparts, no pharmacologically relevant animal species for safety and toxicology studies exist. In response, we have designed an in vitro strategy using the minimum anticipated biological level (MABEL) approach to assess nonclinical safety. This approach has been recommended by both the EMA and FDA for therapeutics such as bispecific antibodies to determine maximum recommended starting dose (MRSD) in clinical trials. Guidance published by regulatory agencies suggests the utilization of data collected from relevant in vivo PK data models, target binding and receptor occupancy studies using relevant cell lines, and response curves against target cells measuring functional cytotoxicity and cytokine release. Specifically, we detail our approach demonstrating dose dependent DBTA-HER2CD3 activation of T cells, induction cytokine production, and mediation of cytotoxicity against HER2-expressing cancer cells. We observed differential activity in T cell co-cultures with HER2-expressing cancer cells expressing a range of HER2 levels suggesting a wide therapeutic window. The data collected from these studies was utilized to identify the MABEL of DBTA-HER2CD3, which can be combined with pharmacokinetic (PK) modelling to determine the MRSD clinical dosing parameters for pGX93237.