Abzyme Therapeutics
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Tech ID: Abz005

pH-dependent antibodies binding to human CD3

Enhancing *in vivo* solid tumor delivery and tumor-specific functional activities of T-cell engaging antibodies by reducing CD3-binding affinity at neutral pH to avoid on-target off-tumor toxicities in T-cell mediated immunotherapy.

T lymphocytes play a central role in the adaptive immune response to antigen and also can be activated by antibody T cell engagers. Bispecific T cell engager antibodies or BiTE have at least two arms, one arm binds to a T cell, a second arm binds to a cancer cell. Thus, the cell-linking antibodies direct a host's immune system, more specifically the T cells' cytotoxic activity, against cancer cells. T cell engaging antibodies bound to target cells are known to trigger the cytotoxic activity of T-lymphocytes by crosslinking to CD3, irrespective of T-cell receptor specificity, major histocompatibility (MHC) restriction, or MHC down regulation on tumor cells. This action mimics physiological processes observed during T cell attacks against tumor cells. Therapeutic bispecific T-cell engaging antibodies have been used to successfully treat a variety of leukemias. While Blinatumomab and other T cell engagers have been successful in clinical trials for hematological cancers, no clinical successes using BiTE in solid tumors have been reported to date due to BiTE dose-limiting toxicity and short half-life. Sufficient dosing to reach poorly perfused tumors without causing serious adverse events (AEs) is challenging. Another problem with non-lymphoid tumors is that tumor-associated antigens (TAA) are often not exclusively expressed on cancer cells, raising the issue of on-target but off-tumor toxicities which can be dose and efficacy limiting.

One way to circumvent the on-target off-tumor antibody activity is to create antibodies that are only active in the tumor microenvironment. Such conditionally-active antibodies will potentially have low off-tumor toxicity allowing dose-escalation and improved cancer immunotherapeutic efficacy.

How it Works

The present technology reduces on-target off-tumor toxicity via reduction of T-cell engager's binding affinity when in the neutral pH environments that prevail outside of the tumor. Due to poor vascular perfusion, regional hypoxia, and fermentative glycolysis, the extracellular pH in most solid tumors is in the 6.0–6.8 range. However, non-cancerous cells maintain their extracellular pH at physiological levels (7.3–7.4). Thus, a TAA-specific antibody with high binding affinity at acidic pH (pH 6.0 – pH6.8), but with no or reduced binding affinity at normal pH will significantly reduce on-target off-tumor toxicity. Modulation of anti-CD3 binding activity in a pH-dependent manner is achieved thanks to a number of amino acid substitution mutations engineered into anti-CD3 antibodies. The present invention provides humanized antibodies against human CD3 with high affinity to CD3 in acidic pHs, while have no or insignificant binding at neutral pHs.

Applications

Therapeutic bispecific T-cell engaging antibodies for solid tumors.

Intellectual Property

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Why it is Better

T-cell mediated immunotherapy is rapidly becoming a mainstream option in cancer treatment. Activation of T cells by normal non-cancerous cells followed by T-cell attack on the normal tissues would cause devastating life-threatening side-effects. Avoiding unwanted T-cell activation outside the tumors would reduce potential T-cell mediated side effects, allowing dose-escalation in the course of treatment. The ability of the technology to reduce off-tumor T cell activation without compromising the on-tumor T cell activity will a) reduce on-target off-tumor toxicity b) improve tumor antibody accumulation thanks to reduced off-tumor binding; and c) allow dose-escalation to achieve therapeutic efficacy end-points.

Benefits

Immunotherapy is a mainstream option for leukemia treatment in which antibody activated T-cells have been shown to effectively eliminate cancer cells. However, since in the solid tumor setting antigens are also expressed in normal tissues, on-target off-tumor binding of antibodies potentially activates T-cells outside of tumors. Unwanted T-cell cross-linking to normal cells can cause life-threatening side effects that limit dose-escalation required to achieve therapeutic efficacy in the solid tumor setting. The pH-dependent anti-T cell receptor CD3 of the present technology alleviates this burden by providing a means to generate therapeutic BiTE with reduced off-tumor binding, less T-cell mediated on-target off-tumor toxicity, and with improved tumor accumulation.

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