Mutant-Selective HER2 Antibodies for Treatment of Major Cancer Types

Selective, differentiated, and efficacious antibody-based treatment for mutant HER2-mediated cancers without HER2 overexpression.

Technology

The Koide research group has generated anti-HER2 mutant-specific fully human antibodies that selectively kill cancer cells expressing oncogenic HER2 mutations. Using their proprietary antibody library and engineering workflow, the innovators have created exquisitely specific human antibodies against HER2 isoforms harboring the most common single-point oncogenic mutations in its extracellular domain (S310F and S310Y). As described in the published patent application and soon-to-be-published manuscript, in vitro binding experiments have determined these antibodies to selectively bind to HER2 S310F and S310Y mutant isoforms with low nanomolar affinity and without any detectable binding to wild-type HER2. Cryo-EM structures revealed these antibodies to engage domain II of the HER2 and form molecular interactions with S310F/Y residues. This binding mode is hypothesized to inhibit mutant HER2 dimerization and block downstream oncogenic signaling cascades. In a variety of in vitro cellular experiments, the anti-HER2 S310F/Y antibodies (in drug-conjugated or T-cell bispecific formats) selectively and potently killed HEK293T cells exogenously expressing HER2 S310F/Y with low picomolar EC50 values while sparing wild-type HER2 cells. More importantly, when in a T-cell bispecific framework and tested in a mouse xenograft model of a bladder cancer cell line, the most promising anti-HER2 S310F/Y antibody clone entirely suppressed tumor growth. In all, these mutant-specific HER2 antibodies are promising early-stage antibody candidates for preclinical development and their preliminary efficacy serves to establish HER2 ECD mutations as tractable targets for the development of precision cancer therapeutics.

Background

Selective targeting of tumors remains an important challenge in cancer drug discovery and development. The tumor-selectivity of current FDA-approved HER2 antibodies, such as trastuzumab, pertuzumab, and their derivatives, exploits the overexpression of HER2 in tumors relative to healthy tissues. Such anti-HER2 antibodies carry the risk of on-target, off-tissue cardiotoxicity since HER2 is expressed in normal epithelial cells throughout the body at a low level. Consequently, cardiac toxicity is a known side effect of current anti-HER2 antibodies. The discovery of oncogenic mutations located in the extracellular region of HER2 present attractive targets for the development of more selective antibody-based therapeutics. These oncogenic mutations promote tumorigenesis through hyperactive signaling, and they are, by definition, tumor-specific antigens. In particular, the S310F and S310Y mutations have a particularly high cancer incidence and are estimated to be present in more than 57,000 new cancer cases every year worldwide. Therefore, these HER2 oncogenic mutations are highly attractive targets for more precise treatment of multiple major cancer types and would address the current unmet need in HER2-targeted cancer immunotherapy.

Technology ID

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Category

Life Sciences/Biologics

Life

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Development Stage

This innovation has a considerable pre-clinical data package, validating multiple antibody formats and showing in vivo efficacy. NYU is currently seeking a commercial partner to facilitate further development and commercialization of the most promising mutant-selective HER2 antibody candidates.

Applications

This innovation is a promising therapeutic candidate for the treatment of:

- **Major Cancer Types:** Including lung, colon, breast, ovarian, and urinary bladder cancer, of which 1-9% of total cases have HER2 mutations.
- **"HER2 Negative" Cancers:** Effication against HER2 oncogenic mutation-mediated tumorigenesis in the absence of HER2 overexpression, accounting for an estimated 58,000 new cases annually across lung, breast, colorectal, and bladder cancers.

Advantages

- **Precision medicine approach:** Mutant-specific HER2 antibodies can selectively target and kill HER2 mutant cancer cells limiting off-target toxicity.
- **Applicable to currently underserved cancer patient market:** Mutant-specific HER2 antibodies can treat "HER2 negative" cancers.
- **Validated target:** HER2 is a well-established drug target of many cancer types.
- **Proven approach:** Antibody candidates targeting HER2 can kill HER2 mutant-driven cancers.
- **Established modality:** Antibodies are already used to therapeutically target HER2, albeit with major limitations due to their lack of oncogenic mutation specificity.

Intellectual Property

NYU has filed as U.S. non-provisional patent application covering the sequences of the mutant-selective HER2 antibodies in a variety of formats and their method of use in cancer treatment.