

Abstract

In Vitro Characterization of an Anti-HER2 Affibody-Monomethyl Auristatin E Conjugate in HER2-Positive Breast Cancer Cells †

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† Presented at the 1st International Electronic Conference on Biomedicine, 1–26 June 2021; Available online: <https://ecb2021.sciforum.net/>.

Published: 31 May 2021

Abstract: Antibody-drug conjugates (ADCs) are used in anticancer therapy with some limitations due to their molecular properties. An alternative to monoclonal antibodies is the affibody, composed of 58 aminoacids, with lower binding affinities, small size, and rapid blood clearance and tissue distribution. We investigated the in vitro efficacy of a novel anti-HER2 ZHER2:2891 affibody conjugated to a cytotoxic drug auristatin E (MMAE) in HER2-positive human cancer cells. Adenocarcinoma cell line SK-BR-3, expressing high levels of HER2, and mammary gland adenocarcinoma MDA-MB-231, expressing basal levels of HER2, were treated with ZHER2:2891DCS-MMAE and trastuzumab (as reference compound).

ZHER2:2891DCS-MMAE induced a significant time-dependent toxic effect in SK-BR-3 cells. A 30% reduction in cell viability was found after 10 min exposure at 7 nM with an IC₅₀ of 80.2 nM. On the contrary, MDA-MB-231 cells were not affected by the affibody complex. The HER2-specific cytotoxic effect of the ZHER2:2891DCS-MMAE has been also confirmed by measuring apoptosis by flow cytometry. In SK-BR-3 cells, increasing concentrations of conjugated affibody, induced cell death after 10 min of treatment with the strongest effect observed after 48 hours. Also, treatment with ZHER2:2891DCS-MMAE reduced (up to 50%) HER2 expression at both mRNA and protein levels in SK-BR-3 cells after 24 hours of treatment.

In conclusion, the cytotoxic conjugate based on the anti-HER2 affibody and MMAE efficiently interacts with HER2 over-expressing cancer cells, allowing the selective and specific delivery of the cytotoxic payload. The basal HER2 expressing cells are not affected most probably due to a lower uptake of drug conjugate. This confirms that affibody may be used to target HER2 overexpressing cells while sparing normal cells.

Keywords: affibody; HER2; trastuzumab; breast cancer