Humanized monoclonal antibodies specific for CA IX protein are able to suppress hypoxia.

Monika Baráthová[1,2], Miriam Zaťovičová[1,2], Petra Belvončíková[1,2], Katarína Grossmannová[1,2], Kamila Bernátová[2], Barbora Puzderová[1,2], Martina Labudová[1,2], Richard Imrich[1], Adrian L. Harris[3], Jaromír Pastorek[1]

[1] MABPRO, a.s., Dubravska cesta 2, 841 04 Bratislava, Slovakia

[2] Department of Tumour Biology, Biomedical Research Center, Slovak Academy of Sciences, Dubravska cesta 9, 845 05 Bratislava, Slovakia

[3] Department of Oncology, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Oxford OX3 7DQ, UK

Carbonic anhydrase IX (CA IX), a highly active transmembrane metalloenzyme, represents one of the best markers of tumor hypoxia. The presence of CA IX in hypoxic tumors is associated with the aggressive tumor phenotype, metastatic tendency and poor response to conventional therapy. Expression of CA IX is principally driven by hypoxia through the HIF1 pathway, the extracellular part of CA IX can be cleaved and the soluble form of CA IX is detected in body fluids. Almost exclusive expression of CA IX in a wide spectrum of solid tumors, transmembrane localization with extracellularly exposed catalytic region suggests CA IX as a highly promising target for therapeutic management of cancer patients.

Mabpro developed unique new humanized antibodies specific to the CA IX protein, which could represent a new approach in the treatment of aggressive hypoxic tumors, where the CA IX is highly expressed. Both humanized antibodies are of IgG1 isotype. CA9hu-1 antibody recognizes the catalytic domain of CAIX, and has the ability to internalize. The second antibody CA9hu-2 binds to the proteoglycan domain of CA IX and can affect the metastatic potential of cancer cells. Both antibodies inhibit the enzymatic activity of CA IX and the acidification of the extracellular environment, disturb the pH balance in the tumor, as a result of which tumor cells are unable to adapt to hypoxic stress. A unique feature of CA9hu-1 is the ability to activate antibody dependent cellular cytotoxicity (ADCC). In vivo experiments on nude mice showed uptake of humanized CA IX-specific antibodies into xenografts. These antibodies were detected in the xenograft even after 7 days from i.v. applications. CA IX-specific humanized antibodies recognize CA IX protein in hypoxic regions of spheroids with a naturally occurring gradient of oxygen and pH. Preclinical research on organoids derived from tumor tissue showed activation of apoptotic and necrotic signalling after treatment of organoids with CA9hu-1 in the presence of autologous immune cells and activation of ADCC.

A characteristic manifestation of the action of our CA IX-specific humanized antibodies is also a decrease of oxygen consumption in CA IX-expressing cells treated with CA9hu-1. Furthermore, humanized antibodies are able to affect the hypoxic machinery and suppress hypoxia.

Our preclinical results show that CAIX-specific humanized antibodies have high therapeutic potential and could represent an effective therapeutic approach in monotherapy or in combination with other therapeutics in the treatment of hypoxic aggressive tumors.

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