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Novel anti-Trop-2 monoclonal antibodies with unique binding specificities show therapeutic synergy against most human cancers

Short Title:
Therapeutic anti-Trop-2 antibodies

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Abstract:
Trop-2 is an epithelial transmembrane glycoprotein that transduces a calcium signal and activates a growth-signaling network that converges on AKT. Trop-2 is overexpressed in the majority of carcinomas, where it drives tumor cell proliferation, and in its mature, glycosylated/functionally-competent form associates with worse prognosis. Trop-2 extracellular domain contains an N-terminal cysteine-rich globular region followed by a cysteine-less region as a connecting "stem" to the transmembrane domain. Trop-2 molecules engage in homophylic interactions between adjacent cells and establish multimeric complexes with tight junction proteins, which may hinder accessibility by therapeutic antibodies. Up to now, Trop-2-targeted approaches have employed anti-Trop-2 monoclonal antibodies (mAb) which essentially recognize a single immunodominant epitope poised between the globular and stem regions. Such mAb have limited or no therapeutic efficacy. In order to untap the potential of anti-Trop-2 immunotherapy we generated novel anti-Trop-2 mAb with tailored specificity towards the globular versus stem regions. Hybridoma diversity was maximized by immunization with soluble human Trop-2 extracellular region produced in different transformed mammalian cell lines (human 293 and murine L) and in insect cells/baculovirus expressing system. These were expected to provide native folding of Trop-2 together with a broad spectrum of differential glycosylation. Trop-2-binding hybridomas were further selected by multiple rounds of flow cytometry analysis using live 293 cells expressing different Trop-2 extracellular portions. Two classes of mAb were identified, that bound the stem versus the globular region. These mAb efficiently bound Trop-2 expressing cancer cells and were able to inhibit cell growth *in vitro*. *In vivo* the naked anti-globular OX-G64 and anti-stem OX-S55 mAb were most effective in inhibiting the growth of distinct tumors, including colon, ovary and prostate cancers. Notably, they showed differential efficacy for established tumors versus isolated-cell models of metastatic dissemination, consistent with our strategy of maximizing differential accessibility of Trop-2 according to growth mode. Most remarkably, we demonstrated *in vivo* synergy of these anti-Trop-2 mAb, paving the way for game-changing anti-cancer mAb therapy. The differential efficacy of the OX-G64 and OX-S55 anti-Trop2 mAb against different tumor histotypes and growth stages further allows to exploit their cancer-killing potential in pathological stage-tailored therapeutic approaches.
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Author Disclosure Information:

E. Guerra: ; ONCOXX Biotech srl. **M. Trerotola:** None. **V. Relli:** ; ONCOXX Biotech srl. **C. Pedicone:** ; ONCOXX Biotech srl. **A. D' Amore:** ; ONCOXX Biotech srl. **F. Dini:** None. **S. Fratarcangeli:** None. **S. Alberti:** ; ONCOXX Biotech srl.
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