The oncolytic peptide LTX-315 enhances T cell clonality and induces synergy with chemotherapy

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Background

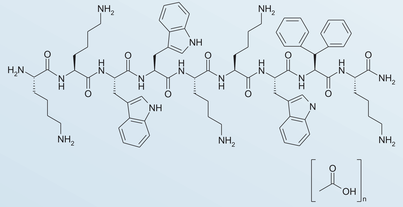
LTX-315 is a novel **oncolytic peptide** derived from the naturally occurring host defense peptide, bovine lactoferricin [1]. LTX-315 interacts electrostatically with anionic components of negatively charged cancer cell membranes as well as intracellular targets such as mitochondria. This causes cellular lysis and a subsequent release of endogenous cellular content including danger signals and tumor antigens, leading to long lasting tumor-specific immune responses [2-9].

Low-dose chemotherapy often exerts a dual mode of action. In addition to direct tumor cell killing several chemotherapeutic drugs, e.g. cyclophosphamide and doxorubicin, have been shown to display immune modulating properties. Low-dose cyclophosphamide has been shown to selectively downregulate immunosuppressive regulatory T cells and doxorubicin immunosuppressive myeloid-derived suppressor cells. Treatment with LTX-315 modulates the tumor microenvironment, changing "cold" or non-inflamed tumors into "hot" or inflamed tumors through the induction of a unique type of immunogenic cell death. Thus, we hypothesized that an enhanced antitumor effect and augmented tumor-specific immune responses could be achieved when LTX-315 was combined with low-dose chemotherapy.

Aim

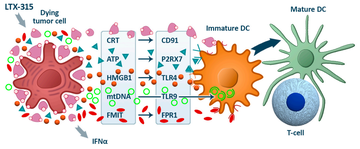
Investigate the antitumor efficacy and potential synergy of LTX-315 in combination with low-dose chemotherapy in experimental mouse models.

LTX-315

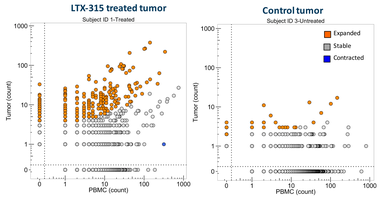


Mode of action

LTX-315 induces a unique type of immunogenic cell death



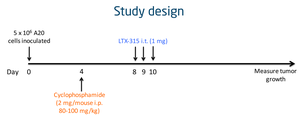
LTX-315 increases the number and diversity of T cell clones



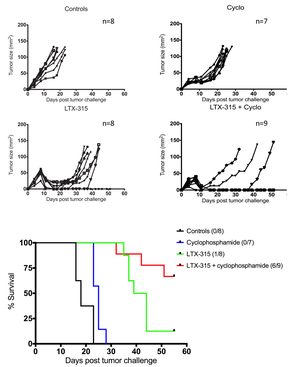
T cell clones in LTX-315-treated and control tumors were amplified and sequenced using the ImmunoSeq platform by Adaptive Biotech. Multiplex PCR was used to amplify the rearranged TCR3b sequences from sample DNA (VDJ region).

Results

LTX-315 in combination with cyclophosphamide

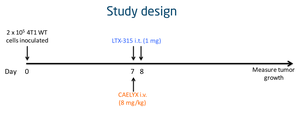


LTX-315 in combination with cyclophosphamide induced complete regression of A20 B-lymphomas (s.c.)

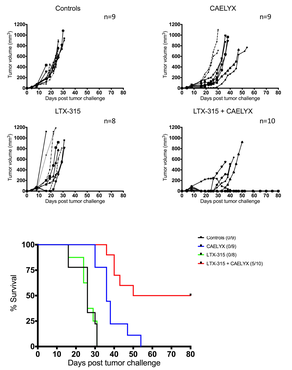


Tumor growth of subcutaneously established A20 tumors in animals injected intratumorally with LTX-315 alone (1 mg/50 µl), intraperitoneally with cyclophosphamide alone (2mg/mouse), or with LTX-315 in combination with cyclophosphamide.

LTX-315 in combination with doxorubicin

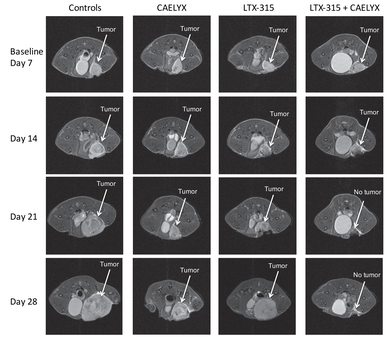


LTX-315 in combination with doxorubicin induced complete regression of orthotopic 4T1 mammary carcinomas



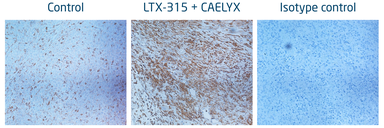
Tumor growth of orthotopically established 4T1 tumors in animals injected intratumorally with LTX-315 alone (1 mg/50 µl), intravenously with CAELYX alone (8mg/kg), or with LTX-315 in combination with CAELYX. CAELYX is liposomal doxorubicin.

MRI



Representative magnetic resonance images are shown using a BioSpec 7T animal MR scanner from Bruker Corporation.

Histology



Combination treatment with LTX-315 and CAELYX induces infiltration of CD3+ T cells into the tumor parenchyma.

Conclusion

- LTX-315 showed an enhanced anticancer efficacy against A20 lymphomas and 4T1 breast carcinomas when combined with cyclophosphamide and doxorubicin, respectively.
- The LTX-315 unique "release and reshape" properties make it a promising candidate for combination with several types of immunotherapies.
- LTX-315 is currently in clinical phase 1/2a studies.

References

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