LTX-315: A first-in-class oncolytic peptide that reshapes the tumor microenvironment

Background
The oncolytic peptide LTX-315, which has been de novo designed based on structure-activity relationship studies of host-defense peptides, has the ability to kill human cancer cells and induce long-lasting anticancer immune response when injected locally into tumors established in immunocompetent marine models (1-3). The oncolytic effect of LTX-315 involves perturbation of the plasma membrane and the mitochondria with subsequent release of danger-associated molecular pattern molecules (DAMPs) such as ATP, Cytochrome C and HMGB1 (4-9). Furthermore, LTX-315 effectively disintegrates the cellular compartments with subsequent release of tumor antigens as demonstrated by a greater T-cell infiltration (TILs), TILs clonality and the number of clones with greater abundance in the tumor microenvironment. In experimental tumor models, LTX-315 exerts abscopal effects and reshapes the tumor microenvironment by decreasing the local abundance of immunosuppressive cells and by increasing the frequency of effector T-cells (9,10). LTX-315’s ability to convert immunogenically “cold” tumors to “hot” makes it ideal combination partner with other immunotherapies as confirmed in experimental animals injected intratumorally with LTX-315 alone (1 mg/50 μl), intra peritoneally with cyclophosphamide alone (2mg/mouse), or with LTX-315 in combination with cyclophosphamide.

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.

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 cyclophosphamide induces complete regression of A20 B-cell lymphomas

Conclusion
- LTX-315 shows an enhanced anticancer efficacy against A20 lymphomas and 4T1 breast carcinomas when combined with cyclophosphamide and doxorubicin, respectively.
- LTX-315 acts in synergy with checkpoint inhibition.
- The LT3-315 unique “release and reshape” properties make it a promising candidate for combination with several types of immunotherapies.
- LT3-315 is currently in clinical phase 1/2a studies.

References
5. Elke et al. Oncotarget. 2015
11. Sveinbjørnsson et al. Future Medicinal Chemistry. 2017

Mode of action
LTX-315 induces a unique type of immunogenic cell death

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

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