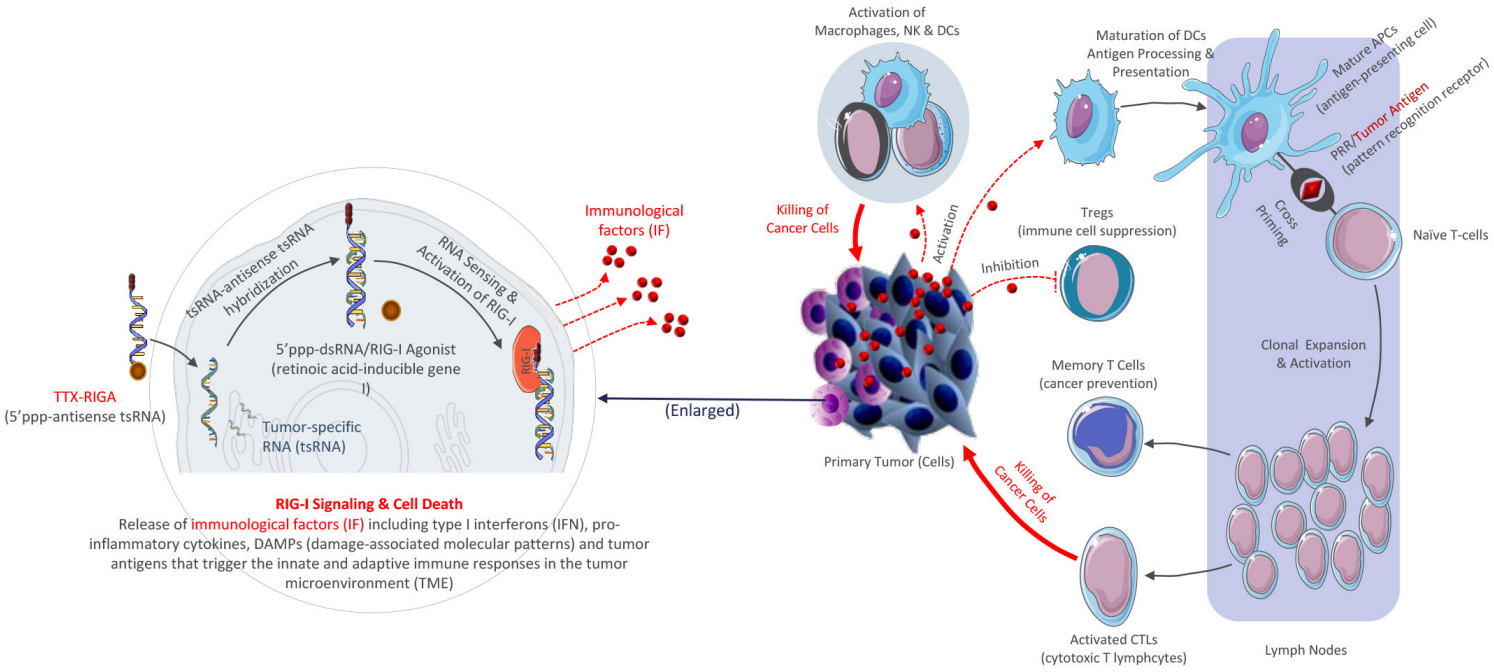
TTX-RIGA

Targeting endogenous RNA to activate the RIG-I signaling pathway in a variety of solid tumor indications

- Retinoic acid-inducible gene I, or RIG-I, is a cytosolic nucleic acid sensing Pattern Recognition Receptor, or PRR, of the innate immune system. Essential for recognizing certain RNA viruses, RIG-I is ubiquitously expressed in all cell types including tumor cells. RIG-I engagement leads to tumor cell death, and to activation of the innate and adaptive immune systems. These factors suggest it could be an attractive immuno-therapeutic approach in targeting a variety of solid tumor indications.
- Tumor cell death induced by RIG-I activation has been reported in multiple types of cancer, including pancreatic, prostate, head and neck, gastric, and breast cancer as well as glioblastoma. However, RIG-I-based therapeutic strategies face multiple challenges, such as designing highly specific and stable agonists, and developing efficient agonist delivery modes while avoiding uncontrolled release of pro-inflammatory cytokines.
- TTX-RIGA, a therapeutic candidate in pre-clinical development, utilizes the TransCode TTX delivery system. Study results to date support continuation of our research with this candidate.

TTX-RIGA is intended to activate the RIG-I signaling pathway in turn triggering an immune response that targets cancer.



Upon release from the nanoparticle after delivery of TTX-RIGA into a tumor cell, 5'ppp-antisense tsRNA combines with a tumor specific RNA (tsRNA) to produce a 5'ppp-dsRNA, a potent agonist of the RIG-I signaling pathway. Activation of RIG-I signaling leads to type I interferon (IFN)-driven immune response and immunogenic cell death (ICD), releasing cytokines, esp. type I IFNs, DAMPs (danger-associated molecular pattern) and tumor antigens. These immunogenic factors heat up the cold tumor, activate and recruit immune cells to amplify the innate responses and trigger the adaptive immune responses to kill cancer cells. *The ability of RIG-I signaling to make a tumor immunologically "hot" provides an excellent therapeutic opportunity in combination with immune-checkpoint inhibition (e. g., Anti-PD-1, Anti-PD-L1, and Anti-CTLA-4 antibodies).*

TTX-RIGA

Targeting miR-21 to activate the RIG-I signaling pathway

About miR-21

Our first TTX-RIGA candidate targets microRNA-21 as the tsRNA. miR-21 is one of the most frequently upregulated miRNAs in solid tumors, and its high levels were first described in B cell lymphomas.

- Overall, miR-21 is considered to be a typical 'onco-miR', which acts by inhibiting the expression of phosphatases, which limit the activity of signaling pathways such as AKT and MAPK
- As most of the targets of miR-21 are tumor suppressors, miR-21 is associated with a wide variety of cancers including breast, ovarian, cervical, colon, lung, liver, brain, esophagus, prostate, pancreatic, and thyroid

miR-21 is also relatively highly expressed in a number of well-established cell lines including MDA-MB-231. This makes it an ideal candidate for conducting the study using cell lines by simply delivering 5'ppp ssRNA, which binds the endogenous miR-21 to activate the RIG-I signaling pathway.

Petrović, N. miR-21 Might be Involved in Breast Cancer Promotion and Invasion Rather than in Initial Events of Breast Cancer Development. Mol Diagn Ther 20, 97–110 (2016). https://doi.org/10.1007/s40291-016-0186-3. Feng YH, Tsao CJ. Emerging role of microRNA-21 in cancer. Biomed Rep. 2016;5(4):395-402. doi:10.3892/br.2016.747.

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The FDA has not evaluated or approved TTX-RIGA and it is currently not available for patient use.