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Editorial

# Loading sd-rxRNAi into Tumors: Are We Getting Close with TGF-β1 Targeting?

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Adoptive cell therapies (ACT) that redirect T cells to specifically target cancer using genetically engineered T cell receptor or chimeric antigen receptor T cells are emerging forms of immunotherapy. Natural killer (NK) cells serve as a crucial first line of defense against tumors and can be activated rapidly to target and kill tumor cells without prior sensitization. NK cells are winning candidates for use in ACT because matching to a specific patient is not required. Thus, making an off-the-shelf NK therapy product could be possible. Inhibitory receptors are responsible for limiting the therapeutic use of NK cells against hematological malignancies thereby overexpression of such receptors, has been shown to reduce NK cell-mediated cytotoxicity. Overcoming this inhibition paves the way for a more potent antitumor response following ACT. Phio Pharmaceuticals (RXi Pharmaceuticals) investigated ACT using RXi's self-delivering RNAi (sd-rxRNAi) technology platform in tumor infiltrating lymphocytes for the potential treatment of cancer, including melanoma, ovarian cancer and solid tumors.

By March 2019, few related preclinical data were presented in 16th Annual Discovery on Target Conference and the 33rd Annual Meeting and Pre-Conference Programs of the Society for Immunotherapy of Cancer. Study results demonstrated potent silencing activity as well as phenotypic effect of NK cells treated with sd-rxRNA compounds targeting checkpoints such as CBL-B, T cell immunoglobulin and ITIM domain. By treating NK cells ex-vivo with sd-rxRNA compounds the anti-tumor response of these cells can be improved.

Interestingly, an immunosuppressive tumor micro-environment is one of the leading causes of non-responding tumors with existing immunotherapies. Immunoregulatory cells, in part, mediate the suppressive nature of the TME e.g. Myeloid derived suppressive cells, T regulatory cells, and immunosuppressive cytokines/chemokines produced by cancer cells. Transforming growth factor beta 1 (TGF-β1) has recently emerged to be a key suppressive factor responsible for facilitating "cold" or immune-excluded tumors. In these tumors, T cell activity is restricted, and a crucial approach was demonstrated to enhance anti-tumor T cell activity by reducing TGF-β1 levels. The study evaluated that the down regulation of TGF-β1 with a sd-rxRNA in TME reduces immunosuppressive activity and promotes T cell anti-tumor activity.

| Company | Region | Active Indications | Treatment area | Target-based Actions |
|---|---|---|---|---|
| Phio Pharmaceuticals Corp | US | Aging/Cancer; Wound healing | Dermatologic; Other/Miscellaneous; Cancer | Metalloprotease-1 inhibitor |

**Table**

In April 2019, preclinical data were presented at AACR Annual Meeting in Atlanta, Georgia, United States. A single dose of sd-rxRNA demonstrated good tumor distribution and target pathway down regulation in an orthotopic breast cancer mouse model. In the orthotopic breast cancer mouse model, three doses of sd-rxRNA mediated TGF-β1 downregulation was associated with a reduction in tumor growth and decreased lung metastasis. Results were presented from in vitro and in vivo studies performed to exhibit the feasibility and efficacy of sd-rxRNA, a self-delivering RNAi against TGF-β1, for the potential treatment of cancer. sd-rxRNA compound targeting TGF-β1 was utilized to regulate the tumor milieu in vitro and in vivo.

It was observed that sd-rxRNA targeting TGF-β1 appeared to be effectively taken up by cancer and immune cells and specifically down-regulated target gene expression. In an ex-vivo co-culture Real-Time Cell Analysis (RTCA), down-regulation of TGF-β1 in tumor milieu was associated with improved antitumor activity of T cells. A single dose of sd-rxRNA demonstrated good tumor distribution and target pathway down regulation in an orthotopic breast cancer mouse model. It was noted that immunohistochemistry analysis

of mice tumor micro-environment treated with sd-rxRNA TGF-β1, potentially decreased macrophages. In the orthotopic breast cancer mouse model, three doses of sd-rxRNA regulated TGF-β1 was linked to the reduction in tumor growth and decreased lung metastasis.

In conclusion, sd-rxRNA was efficiently taken up by cancer and immune cells in a mouse model of breast cancer. The sd-rxRNA targeting TGF-β1 demonstrated favorable distribution and pathway down regulation. Study results indicated that the intratumoral injection of sd-rxRNA mediated TGF-β1 signaling could decrease the immuno-suppressive tumor micro-environment and potentially boost immune effector cell activity, thus, paving the way for future clinical development activities in combination with adoptive cell therapy or other immuno-oncology efforts.