
Session PO.ET01.06 - Cancer Therapeutic Targets

# 5167 / 22 - Identification and validation of a novel immuno-oncology target and selection of a therapeutic antibody candidate with a pharmacologically beneficial activity profile

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**Presenter/Authors**

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**Disclosures**

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**Abstract**

Identification of novel targets in cancer immunotherapy is needed to address the significant number of patients that either do not respond to current therapies or encounter unacceptable toxicities. The first two generations of immuno-oncology drugs have been antagonist antibodies against immune checkpoint proteins, such as cytotoxic T lymphocyte protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Moving forward, there has been progress in targeting co-stimulatory receptors like inducible T cell co-stimulator (ICOS), OX40 and CD137 with agonist antibodies. At Oxford BioTherapeutics, in-depth expression profiling of membrane proteins from intact tumors collected in the proprietary OGAP database revealed novel IO targets in primary tumor-derived lymphocytes (TILs). Proteomic and flow cytometry analysis of TILs and PBMCs establish that OX003R is a novel co-stimulatory IO target. It is expressed on naïve T and B cells; however, higher expression is observed in TILs and activated or exhausted T cells. OX003R expression is observed by immunohistochemistry in infiltrating lymphocytes in a variety of solid tumor types. A Fab phage display library was screened by FACS for binding to target on the cell surface. All the Fabs were also profiled by an interferon gamma release assay for T cell activation. Five best binders demonstrating T cell activation were reformatted into full-length chimeric mAbs and expressed in mammalian Expi 293 cells. Recombinant antibodies were extensively screened for T cell activation in an *ex vivo* 3D tumor culture system developed in-house using fresh non-small cell lung and colorectal carcinomas. Interferon gamma release was assessed by ELISpot assay and expression of the target was confirmed by immunohistochemistry on the corresponding tumor samples. Chimeric antibody 1B3 robustly activated T cells in most of the tumor samples in a dose-dependent manner as compared to isotype control and was chosen as the lead therapeutic antibody for humanization. The lead therapeutic antibody was tested for the propensity to facilitate the undesirable cytokine storm in whole blood and did not induce the release of dangerous levels of cytokines.

**Conclusion:** OX003R is a validated immuno-oncology target and chimeric 1B3 is

being developed as a promising therapeutic antibody with agonistic TIL activity, specifically in the tumor microenvironment.