Identification of responders for Anti-CTLA4 in refractory colorectal cancers using CANScript™ platform

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Abstract

Predicting clinical response to anticancer drugs remains a major challenge in the treatment of cancer. Indeed, while biomarker-guided strategies for personalizing anticancer drugs have shown strong promise in certain cases, recent studies have shown that the tumor microenvironment and heterogeneity can limit the predictive power of biomarkers alone. Here we have engineered a personalized tumor ecosystems, termed CANScript™, that contextually conserve tumor heterogeneity and phenocopy the tumor ecosystem using thin tumor explants maintained in defined tumor grade-matched matrix support and autologous ligands from patients. We then demonstrated that the CANScript™ platform can be used to predict clinical response. Specifically, functional readouts obtained by exposing the CANScript™ ecosystems from more than 1100 patients to a panel of anticancer drugs, together with the corresponding clinical outcomes, were used to train a novel machine learning algorithm; the learned model was then applied to predict clinical response to anticancer drugs in a test group comprising of 905 new patients, where it achieved 100% sensitivity in its predictions while also keeping specificity in a desired high range. We have also observed that CANScript™ retains patient tumor immune environment which is important for clinical response of not only immunomodulators but other anti-cancer drugs. Here we report the effect of immunomodulators in refractory CRC tumors which remains difficult to treat. Data demonstrate that Anti-CTLA-4 molecule has profound antitumor effect in refractory CRC tumors by increasing cytotoxic T-Cells count. In this cohort of 16 patients tumors CANScript™ platform identifies 31% responders (5/16) where conventional tumor sections culture model shows only 6% responders.

Objective

• Development and clinical validation of a model system (CANScript) that recreates patient tumor micro-environment in laboratory

Results

Development of CANScript™ platform: Importance of matrix proteins and autologous ligands in preserving various active phenotypic properties of TME

Anti-CTLA4 activates CD8+ T cells in tumor in CANScript platform. Flow (top), IF and IHC (bottom)

Summary

• CANScript™ a novel platform technology mimics patient tumor heterogeneity in laboratory.

• Along with cancer signaling network native immune compartments and CSC cells are also preserved in this platform.

• Anti-CTLA4 mediated activation of CD8+ T cells is essential but not only the criterion for antitumor efficacy in tumor from refractory CRC patients.

Data supports the application of CANScript™ to evaluate novel anti-cancer immunomodulators in patient tumor-explant setting.