Application of a robust and novel ex vivo platform mimicking patient heterogeneous tumor microenvironment for personalized cancer treatment

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Abstract

Background: Predicting clinical response to anticancer drugs remains a major challenge in the management of cancer. Recent advances show that tumor microenvironment (TME) and heterogeneity impact therapy outcomes; indicating the limitations of biomarker-guided strategies for personalizing therapy. There is a need for platforms that can predict treatment outcome with high fidelity by contextually integrating tumor heterogeneity and phenocopying the TME.

Methods: Tumor grade-matched matrix support and autologous sera from individual patients were used to engineer personalized tumor ecosystems (CANScript™) in head and neck, breast and colorectal cancers. We evaluated functional outcomes as a measure of response to a panel of anticancer drugs in this platform. In the training data set obtained from a cohort of patients, CANScript™ read-outs were integrated with their corresponding clinical outcomes for generation of a machine learning (M-score) algorithm to predict clinical response to these drugs. This algorithm was further validated in a test cohort of new patients.

Results: Histopathological and molecular characterization of the tumor slices cultured in CANScript™ revealed a close approximation to the parental tumor at baseline as confirmed by Ki-67 and critical phosphoprotomic status, global transcriptomic profiles and balance in active components of tumor and stromal phenotypes. The M-score algorithm when applied to the test cohort of more than 100 patient tumors assessed in the functional CANScript™ achieved 100% sensitivity while keeping specificity in a desired high range for predicting short term clinical outcome.

Conclusions: The high specificity and sensitivity observed in predicting clinical outcomes using the CANScript™ supports the use of this novel platform for personalized cancer treatment. (Part of the data is published in Nature Communications).

Objectives

- Development of an ex vivo high throughput model system (CANScript™) that recreates patient tumor microenvironment in laboratory
- Clinical validation of CANScript™ in HNSCC and CRC

Results

Biomarker-based CRC patient selection CANScript™ based CRC patient selection

Regimen: Cetuximab +FOLFIRI (CRC)

CANScript™ prediction is a better tool than biomarker (KRAS) based prediction of response to Cetuximab in CRC

Summary

- Tumor heterogeneity is one of the causes that leads to varied response and recurrences in clinic
- Existing preclinical models are homogeneous and fail to mimic patient tumor heterogeneity in the laboratory
- CANScript™ cultures fresh patient tumor sections in a system where patient own tumor microenvironment is contextually preserved
- CANScript™ captures all major functional parameters after treatment with anti-cancer agents within 3-4 days of live culture of tumor
- A machine learning algorithm was built using clinical and CANScript™ data to predict the clinical outcome of a drug regimen
- CANScript™ outcome was further validated using prospective clinical studies using standard of care
- Results show that CANScript™ predicts tumor response of anti-cancer drugs with very high sensitivity and specificity

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