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.

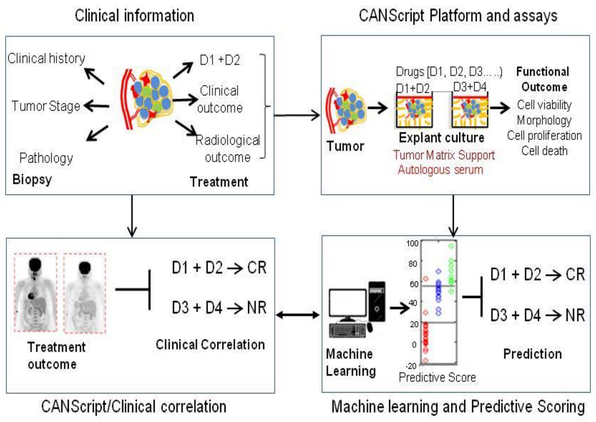
Methods: Tumor grade-matched matrix support and autologous sera from individual patients were used to engineer personalized Tumor Ecosystems (CANScript™) in head and neck, breast and colorectal cancers. We evaluated functional outcomes as a measure of response to a panel of anticancer drugs in this platform. 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 group 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 phosphoproteomic 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 Feb-2015).

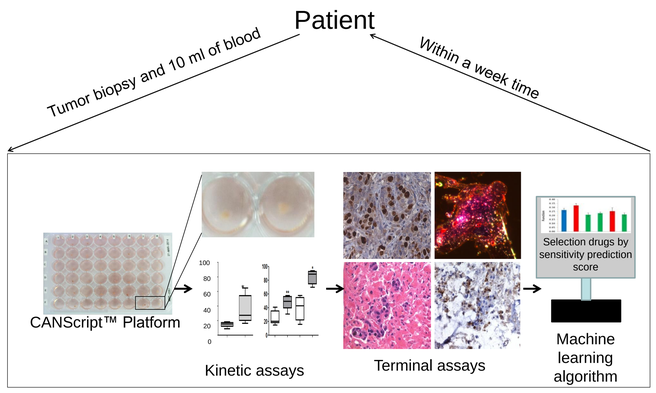
Objectives

- 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

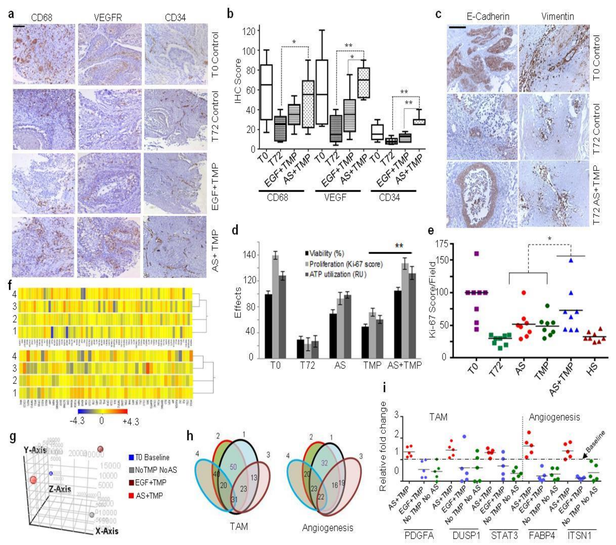


Schematic diagram of CANScript™ model development and clinical validation

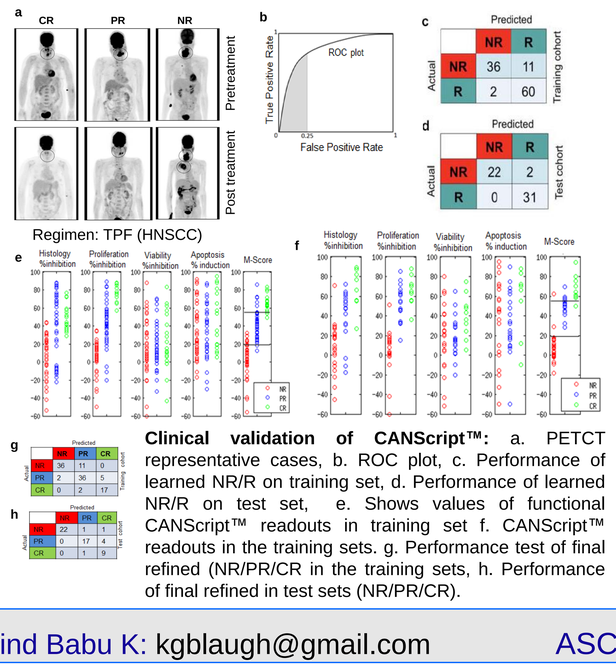
Real time data capture



Results

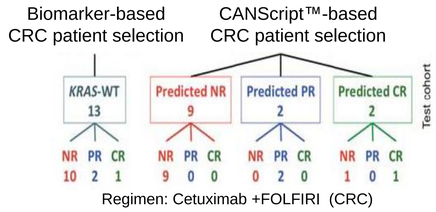


Development of CANScript™ platform: Importance of matrix proteins and autologous ligands in preserving various active phenotypic properties of TME



Clinical validation of CANScript™: a. PETCT representative cases, b. ROC plot, c. Performance of learned NR/R on training set, d. Performance of learned NR/R on test set, e. Shows values of functional CANScript™ readouts in training set f. CANScript™ readouts in the training sets. g. Performance test of final refined (NR/PR/CR in the training sets, h. Performance of final refined in test sets (NR/PR/CR).

Results



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

Ref:

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2. Goldman A, Majumder B, Dhawan A, Ravi S, Goldman D, Kohandel M, Majumder PK and Sengupta S. Temporally sequenced anticancer drugs overcome adaptive resistance by targeting a vulnerable chemotherapy-induced phenotypic transition. ***Nature Communications***, 2015 Feb 11;6:6139. doi: 10.1038/ncomms7139, page 1-13.

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