The right drug, the right patient, the right time

Background
- Circulating tumor DNA (ctDNA) was recently shown to be a predictor of poor response and recurrence in breast cancer.
- ctDNA shedding from breast tumors rapidly decreases during treatment, resulting in reduced sensitivity in measuring tumor response.
- We recently reported the discovery of orphan non-coding RNAs (oncRNAs), as a large class of cancer specific small RNAs that are not present in healthy cells, but emerge from cancer cells.
- We hypothesized that oncRNAs provide an opportunity for a sensitive, rapid, and inexpensive liquid biopsy platform that does not require individualized assay development.

Annotating circulating orphan non-coding RNAs (oncRNAs):
- oncRNAs were annotated using small RNA sequencing across breast cancer cell lines (HCC1395, T47D, MDA453, A231, HCC38, and MCF10A), and human normal-tissue samples (the Cancer Genome Atlas).
- We discovered thousands of oncRNAs that are uniquely expressed in breast cancer cell lines compared to normal-tissue.
- Analysis of extracellular compartment revealed that oncRNAs are shed from breast tumors rapidly decreases during treatment, suggesting a utility as an extracellular marker.

We have since annotated more than 250,000 oncRNAs across human breast cancer lines.

Patients and Methods
- Patients received standard NAC only (n=147) or with Pembro (n=63) or Pembro (n=53). Tumor tissue was collected from the ~200 individuals in this dataset. Gene expression values are derived from TCGA-BRCA.
- We hypothesized that oncRNAs provide an opportunity for a sensitive, rapid, and inexpensive liquid biopsy platform that does not require individualized assay development.

Figure 1. Discovery, annotation, and validation of cancer-specific orphan non-coding RNAs (oncRNAs) to forecast breast cancer prognosis. We investigated the abundance of oncRNAs in breast cancer tissue derived from TCGA-BRCA. We discovered thousands of oncRNAs that are uniquely expressed in breast cancer cell lines compared to normal-tissue.

Figure 2. OncRNAs as digital circulating biomarkers. (A) OncRNA profiles in conditioned media of breast cancer cell lines. The detection of oncRNAs in sera from breast cancer patients with stage III disease. (B) Healthy individuals from an independent study as reference. Figure adapted from (2).

Figure 3. OncRNAs as digital circulating biomarkers. (A) Heatmap representing the abundance of oncRNAs in breast cancer patients (T0) and healthy individuals (T0). (B) Heatmap representing the abundance of oncRNAs in breast cancer patients (T0) and healthy individuals (T0).

Figure 4. OncRNAs in breast cancer patients. A binary heatmap where rows indicate our annotated oncRNAs that were detected in one or more sera from breast cancer patients, and columns represent individual serum samples. (Right) results for TCGA-BRCA samples, and (Left) the same oncRNAs shown in non-cancer extracellular data. ctDNA dynamics and clinical outcomes.

Figure 5. Changes in oncRNA content (oncRNA) in response to therapies. (A) Summary of overall survival (OvS) and disease-free survival (DFS) outcomes from the 10 arms tested (HR=3.9, P=0.02) (B) Multivariate Cox model for oncRNA. (C) Forest plots for multivariate Cox models with oncRNA and pCR as covariates. oncRNA was significantly correlated even after controlling for these other clinical markers.

Conclusion:
- oncRNAs provide a rapid (~4 days of processing), inexpensive, and robust approach to measure disease burden from <1mL of serum.
- Our results highlight that oncRNA clearance in response to treatment is prognostic across multiple arms.
- Our preliminary results indicate that even after controlling for known markers such as pCR and RCB class, oncRNAs remained prognostic.

Advocate perspective: Liquid biopsies have emerged as effective, non-invasive, diagnostic tools in disease monitoring and minimal residual disease detection. While ctDNA has been shown to be a significant predictor of poor response and metastatic recurrence, small non-coding RNAs (oncRNAs), actively released into the blood by some tumors, may prove to be a more sensitive biomarker. Identifying oncRNA over time (before, during and after treatment) can enable providers to predict tumor response to therapy. This simple way to get at disease burden through serum, which does not require individualizing a test for each patient, could be rapidly generated, and may provide the complementary, more sensitive information to other circulating DNA tests.

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