First Look

The Next Wave of Cancer Breakthroughs

Monday, 25th | 8AM – 12PM

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Overcoming tumor heterogeneity associated with drug resistance

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Personalized cancer medicine approaches, inhibiting kinases in tumors driven by defined genomic alterations, have demonstrated striking efficacy in many cancer types. However, the development of drug resistance is a major limitation to the efficacy of targeted therapies in oncology. Identifying and understanding the molecular mechanisms driving resistance may foster opportunities to develop therapeutic strategies to overcome resistance. For example, in the ~10% of colorectal cancer patients whose tumors harbor BRAF V600 mutations, we have found that feedback reactivation of MAPK signaling, often mediated by EGFR, underlies the relative insensitivity of these cancers to RAF inhibitors. The development of targeted therapy combination strategies to block feedback reactivation of MAPK signaling has led to marked improvements in response rates for these patients from ~5% to >30% over the past few years. However, in patients who respond to these targeted combinations, the rapid development of acquired resistance still limits clinical benefit. Acquired resistance in BRAF mutant colorectal cancer and in other molecularly-defined tumor types can be marked by the development of extensive molecular heterogeneity due to the selection of sub-clonal tumor cell populations, capable of growing under drug pressures, which poses significant diagnostic and therapeutic challenges. We will present data demonstrating how a single-lesion biopsy at disease progression to diagnose the mechanism of acquired resistance can vastly underrepresent the molecular heterogeneity of resistant tumor clones in an individual patient, and may fail to detect the existence of distinct but important resistance mechanisms that can drive mixed or lesion-specific responses and treatment failure to subsequent targeted therapy. By contrast, new “liquid biopsy” approaches analyzing circulating tumor DNA have the potential to detect the presence of simultaneous resistance mechanisms residing in separate metastases in a single patient and to monitor the effects of subsequent therapies on specific sub-clonal tumor cell populations. These findings highlight the critical role of tumor heterogeneity in driving therapeutic resistance and how convergent targeted therapy strategies blocking common signaling nodes capable of overcoming multiple resistance mechanisms may be needed.

Title of Presentation

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Title

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Recent progresses in digital sensors and computational approaches create new opportunities for point-of-care (POC) cancer diagnostics and care delivery. By integrating ideas and techniques embodied in microelectronics, and nanotechnology, my research focuses on advancing sensitive, fast, and cost-effective diagnostic platforms.

Digital diffraction diagnostics (D3)
Smartphones and wearable electronics have advanced tremendously over the last several years but fall short of allowing their use for molecular diagnostics. We have developed a generic approach to enable molecular diagnostics on smartphones. Termed D3 for digital diffraction diagnostics, the method utilizes molecular-specific microbeads to generate unique diffraction patterns which can be recorded and deconvoluted by digital processing (Fig. 1). We applied the D3 to resolve individual pre-cancerous and cancerous cells as well as to detect cancer-associated DNA targets. Because the system is compact, easy to operate and readily integrated with the standard, portable smartphone, this approach could enable medical diagnostics in geographically and/or socioeconomically limited settings with pathology bottlenecks.

Point-of-care exosome screening.
Exosomes are an emerging new biomarker for cancer management. Exosomes are nanoscale vesicles (50 – 200 nm in diameter) actively secreted by cancer cells. These extracellular vesicles carry molecular constituents of their originating cells, and can thus serve as cellular surrogates that can be repeatedly and conveniently obtained with minimal complications. We have been developing new biosensors to streamline clinical exosome analyses. Developed systems include acoustic-wave based microfluidics for exosome isolation and nanotechnology-inspired sensors exosome molecular screening (Fig. 2). The ensuing clinical studies with patient samples (glioblastoma multiforme and ovarian cancer) have demonstrated the clinical utility of exosomes as a novel biomarker for cancer detection, treatment monitoring, and resistance prediction.

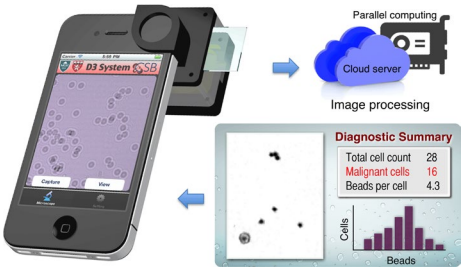

Fig. 1. Digital diffraction diagnostics (D3). A smartphone is used to record the diffraction images of the specimen. The recorded images are transferred to a server via the cloud service for real-time image reconstruction and analyses.

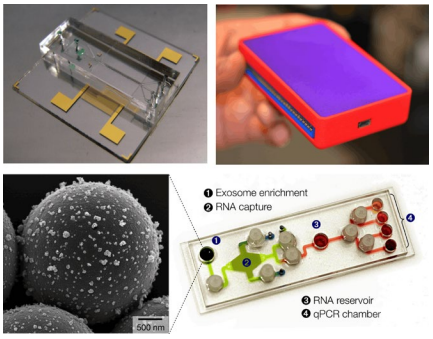

Fig. 2. Exosome diagnostic systems. New miniaturized system have been developed to facilitate exosome diagnostics. (Top left) a microfluidic chip for exosome separation in blood. (Top right) a portable sensor for exosome protein screening. (Bottom) a cartridge for on-chip exosome RNA profiling.