



Shriners Hospitals for Children®
Boston, Massachusetts

CIRCULATING TUMOR CELLS

One of the proposed mechanisms of cancer metastasis is the dissemination of tumor cells from the primary organ into the blood stream. A cellular link between the primary malignant tumor and the peripheral metastases has been established in the form of CTCs in peripheral blood. While extremely rare (1 in 10 billion cells), these cells provide a potentially accessible source for early detection, characterization and monitoring of cancers that would otherwise require invasive serial biopsies. The emerging fields of medical technology and microfluidics offer a radically different approach to rare cell detection, which is particularly relevant to the isolation of CTCs.

At Shriners Hospitals for Children — Boston we have designed a microfluidic device, the CTC-Chip, that allows for the isolation and characterization of CTCs from the peripheral blood of cancer patients. The chip design was centered on the concept of passive mixing of blood through the generation of microvortices, ultimately improving the capture of rare cells by dramatically increasing the number of interactions between the target CTCs and the antibody-coated substrate. Using blood from patients with metastatic and localized cancer, we have demonstrated the ability to isolate, enumerate and molecularly characterize putative CTCs with high sensitivity and specificity. Additionally, microclusters of CTCs have been captured in a rare number of patient samples. These clusters of CTCs present an intriguing phenomenon; however their significance has yet to be determined. Ongoing projects include translating the technology for early cancer detection, exploring these clusters of CTCs, increasing capture sensitivity through amplification of cell surface antigens, and the design of biomaterials for the release of the rare cells from the device surface.

Recent Publications

1. Stott S.L.*, Lee R.J.*, Nagrath S.*, Yu M., Miyamoto D.T., Ulkus L., Inserra E.J., Ulman M., Springer S., Nakamura Z., Moore A.L., Tsukrov D.I., Kempner M.E., Dahl D.M., Wu C.L., Iafrate A.J., Smith M.R., Tompkins R.G., Sequist L.V., Toner M., Haber D.A., Maheswaran S. Isolation and characterization of circulating tumor cells from patients with localized metastatic prostate cancer. *Science Translational Medicine* 2010; 2(25):25. *co-authors
2. Stott S.L.*, Hsu C.-H.*, Tsukrov D.I., Yu M., Miyamoto D.T., Waltman B.A., Rothenberg S.M., Shah A.M., Smas M.E., Korir G.K., Floyd Jr. F.P., Gilman A., Lord J.B., Winokur D., Springer S., Irimia D., Nagrath S.N., Sequist L.V., Lee R.J., Isselbacher K.J., Maheswaran S., Haber D.A., Toner M., "Isolation of circulating tumor cells using a microvortex-generating herringbone-chip," *Proc Natl Acad Sci.* 107 (43), 18392-19397, 2010.* co-authors.
3. Yu M., Stott S.L., Toner M., Maheswaran S., Haber D.A., "Circulating Tumor Cells: Approaches to Isolation and Characterization" *Journal Cell Biology* 192 (3), 373-382, 2011.

4. Shah A.M., Yu M., Nakamura Z., Ciciliano J., Ulman M., Kotz K.T., Stott S.L., Maheswaran S., Haber D.A., Toner M., "A Biopolymer System for Cell Recovery from Microfluidic Cell Capture Devices" *Analytical Chemistry* 84 (8), 3682–3688, 2012.
5. Yu M.*, Ting D.T.*, Stott S.L., Wittner B.S., Ozsolak F., Paul S., Ciciliano J.C., Smas M.E., Gilman A.J., Ulman M.J., Contino G., Alagesan B., Brannigan B.W., Milos P.M., Ryan D.P., Sequist L.V., Bardeesy N., Ramaswamy S., Toner M., Maheswaran S.*, Haber D.A.* "RNA sequencing of pancreatic circulating tumour cells implicates WNT signalling in metastasis" *Nature*, 487 (7408), 510-513, 2012 *co-authors
6. Miyamoto D.T.*, Lee R.J.*, Stott S.L.*, Ting D.T., Wittner B.S., Ulman M., Smas M.E., Lord J.B., Brannigan B.W., Tratuwein J., Bander N.H., Wu C.L., Sequist L.V., Smite M.R., Ramaswamy S., Toner M., Maheswaran S., Haber D.A., "Androgen receptor signaling in circulating tumor cells as a marker of hormonally responsive prostate cancer" *Cancer Discovery*, Oct23 epub, 2012 *co-authors
7. Yu M.*, Bardia A.*, Wittner B.S., Stott S.L., Smas M.E., Ting D.T., Isakoff S.J., Ciciliano J.C., Wells M.N., Shah A.M., Concannon K.F., Donaldson M.C., Sequist L.V., Brachtel E., Sgroi D., Baselga J., Ramaswamy S., Toner M., Haber D.A., Maheswaran S., "Circulating Breast Tumor Cells in Humans Exhibit Dynamic Changes in Epithelial and Mesenchymal Cell Composition" *Science*, 339 (6119), 2013 *co-K>>>>>