Microfluidic Device for Cancer Diagnosis & Monitoring of Metastasis

Shelby, Yogini and Furva

Cancer Intro

- 1,900,000 will get new cancer diagnosis in 2020
  - 630,000 will die of their cancer
- Patient specific treatment = better outcomes
  - Targeted treatment
  - Pharmacogenomics

Multiple Primary Cancers

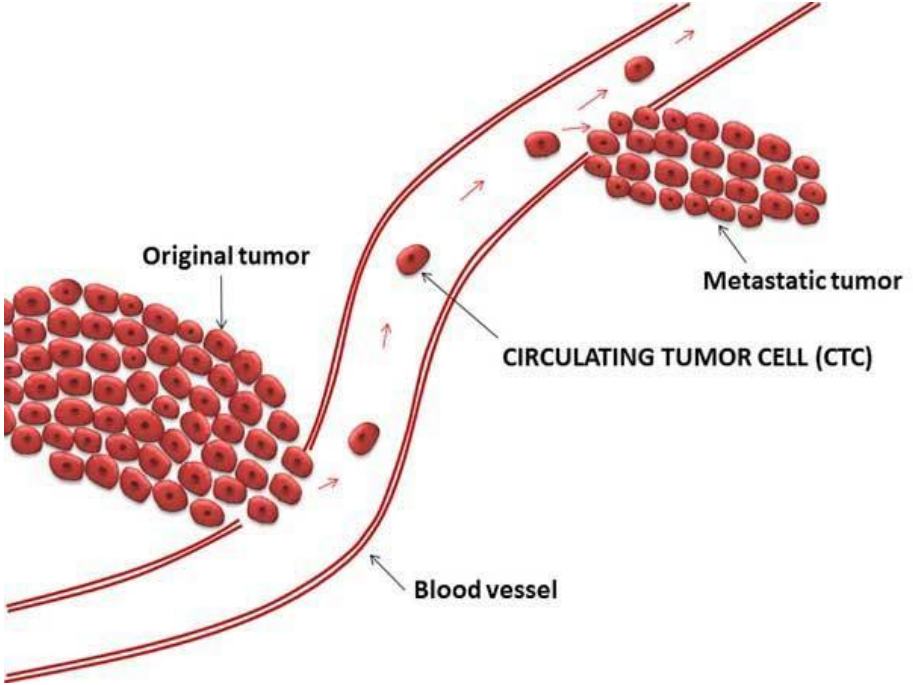
- 2.4 - 17% of cancer patients diagnosed
  - Multiple diagnoses on the rise
  - Some cancers associated with increased risk for others
    - breast cancer, ovarian, uterine, colorectal, pancreatic, thyroid, gallbladder
  - Some cancer treatments increase risk
    - radiation therapy in breast cancer patients: lung cancer
- Which cancer is metastasizing?

Circulating Tumor Cells (CTCs)

A cell that has shed into the vasculature or lymphatics from a primary tumor and is carried around the body in the blood

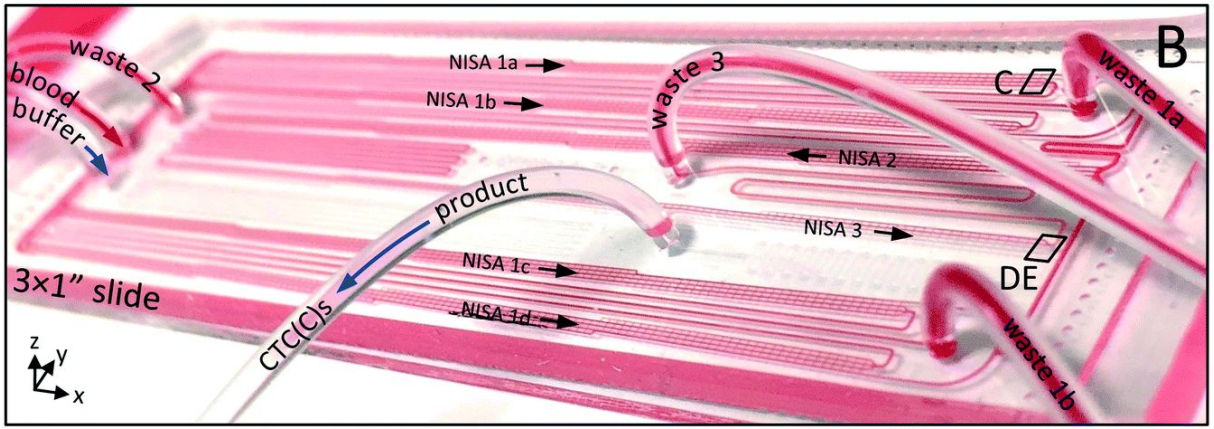
CTCs & CTC Clusters

- Account for metastasis
  - Biomarkers
- In 7.5 mL of blood:
  - 150 billion erythrocytes
  - 9 billion platelets
  - 180 million leukocytes
  - **1-50 CTC clusters**
- Some locations difficult to biopsy
- Multiple primary cancer metastasis



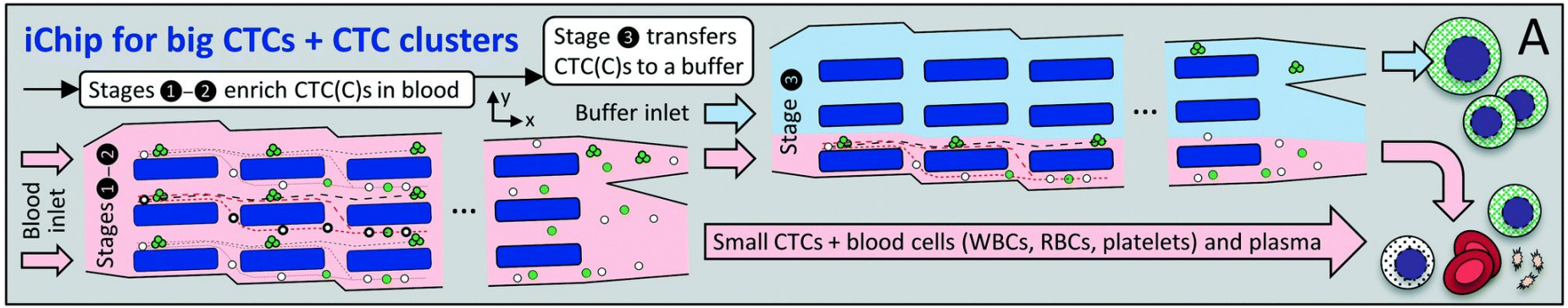
Predicate Devices: NISA-XL CTC-iChip

- Non-equilibrium Inertial Separation Array
- Isolates CTC clusters from minimally or undiluted whole blood
- 100 µm channels concentrate clusters in the blood
- Similar array transfers into a small volume of buffer
- 15 mL whole blood in 30 min



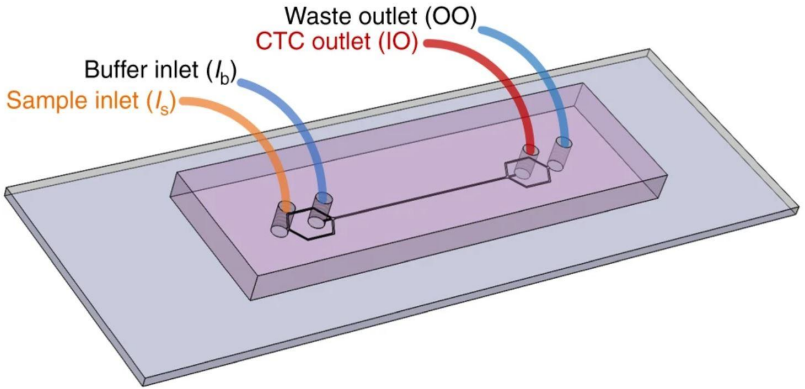
CTC-iChip Process

1. CTC(C)s concentrated by 10x in the blood
2. CTC(C)s separated into clean buffer by a final stage of NISA
    a. 25% injection of sample alongside buffer



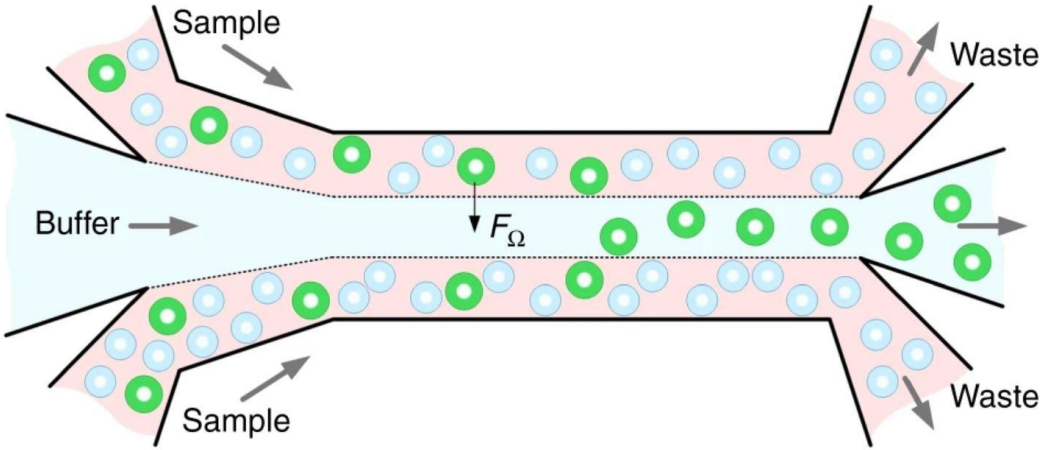
Predicate Devices: Zhou, et al

- Isolates CTCs using multi-flow microfluidic channel
  - Size based separation
- High purity of separation (>87%) without labeling
- Channel cross section = 150 µm x 50 µm
- Channel length = 20 mm
- 2 sample inlets → 2 waste outlets
- 1 PBS buffer inlet → CTC outlet



Zhou Device: Process

1. Cells migrate toward sidewalls
2. Cells migrate to equilibrium positions centered on each sidewall under F_{Ω}
    a. Size based separation



Proposed Device Design

In series:

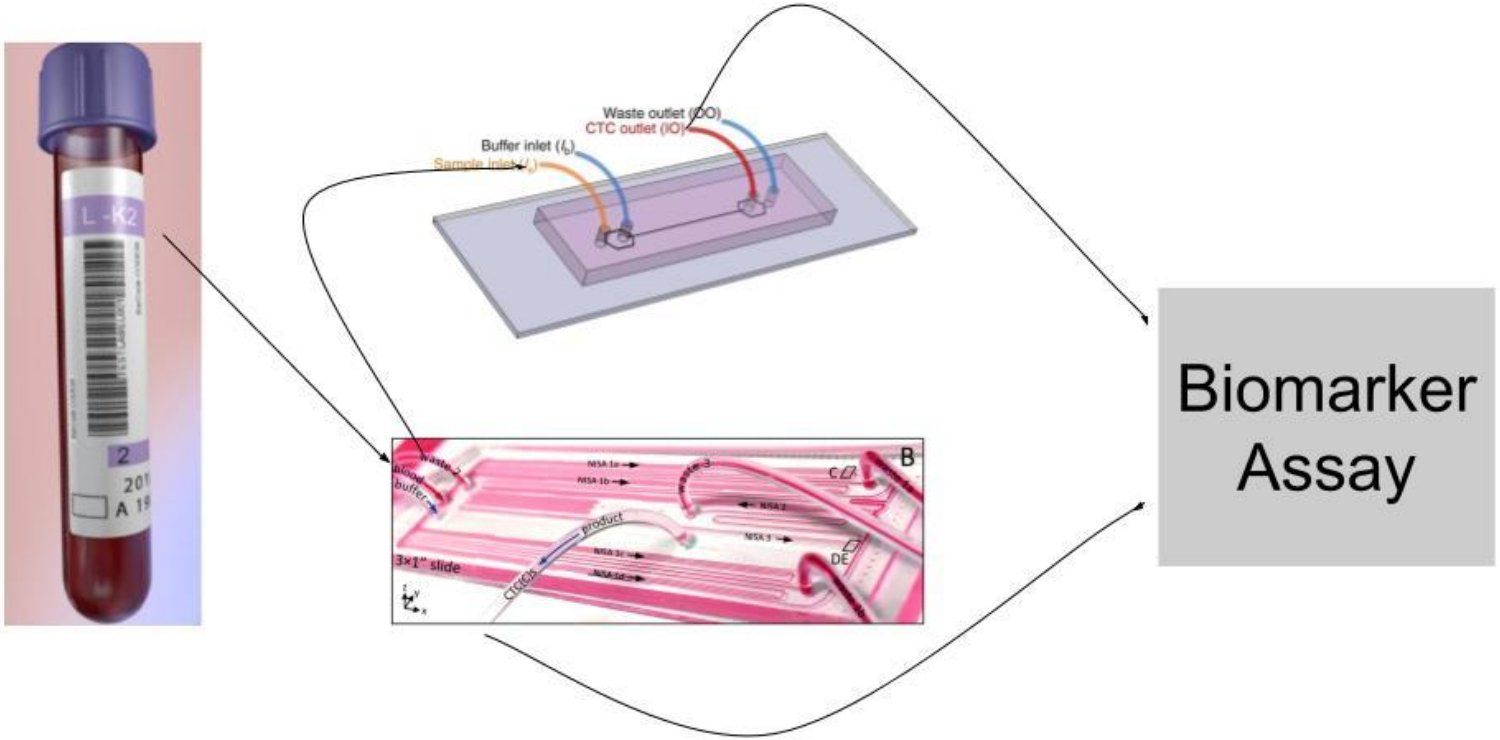
1. Isolate CTCCs and large CTCs in NISA-XL CTC-iChip

    a. Waste from CTC-iChip goes into Zhou device to isolate CTCs

2. Run CTCs + CTCCs through biomarker assay

- Test multiple markers for different types of cancer
- Optical label-free biosensor (LSPR)

Circuit Schematic

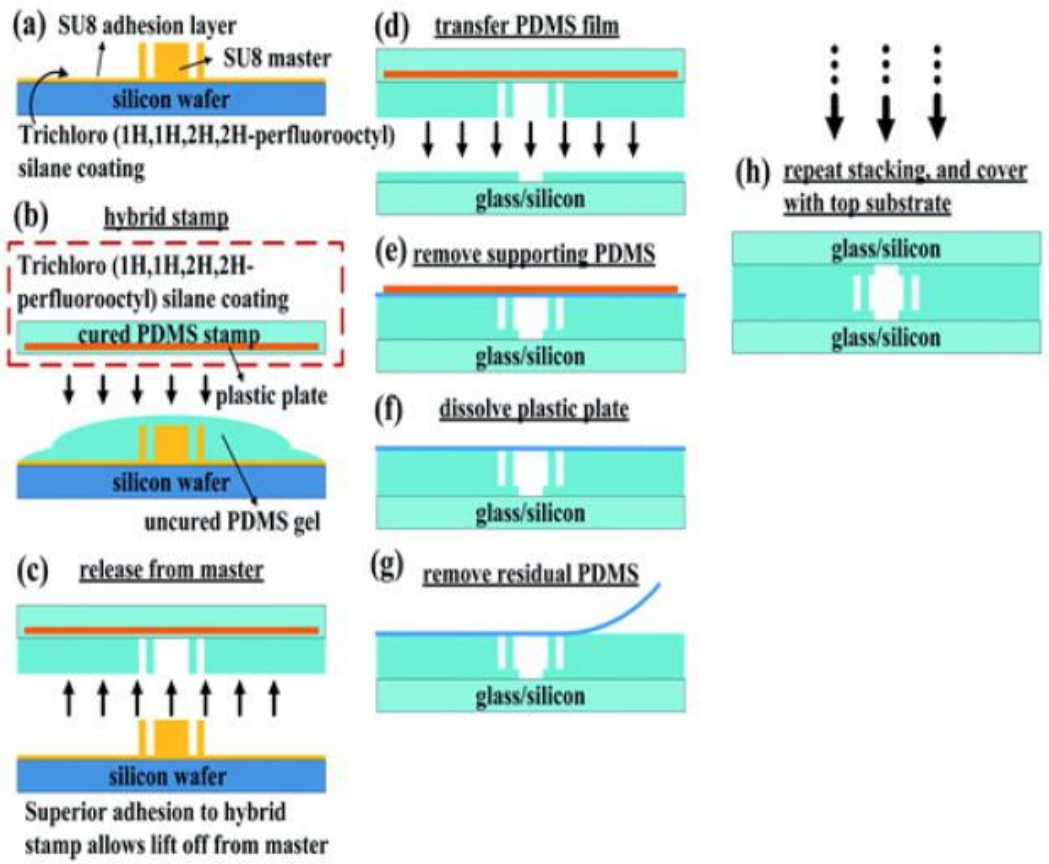


Innovation

- Personalized medicine
- Faster, easier, more affordable way to detect cancer
- CTCCs especially good for when cancer location is difficult to biopsy
- Multiple primary cancers
  - Which one is highly metastatic?
    - Tailor treatment to be aggressive where necessary
    - Limiting toxicity as much as possible
  - Multiplexed detection of many biomarkers in a single sample with high accuracy and excellent sensitivity.

Device Fabrication

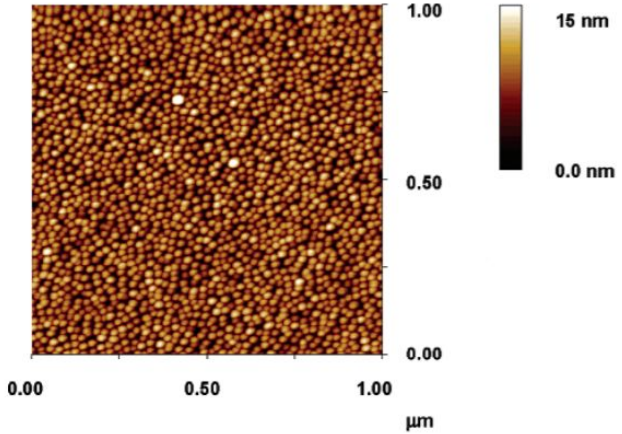
- Create PDMS interface
  - Soft Lithography
  - Multiple microfluidic channels
- Controlled by micromechanical valves
- PDMS chip aligned over the plasmonic glass substrate
- Sample delivery (inlet)

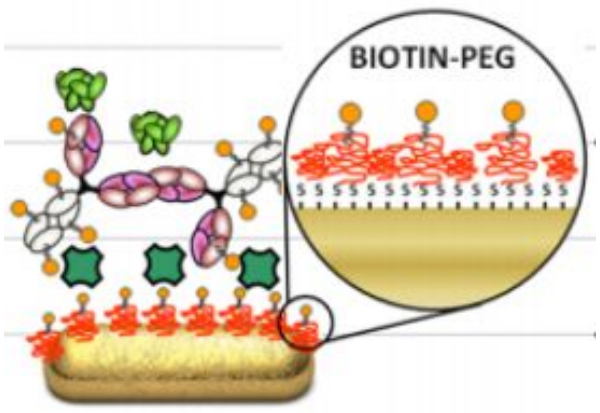


Fabrication

Parallel biosensor chip:

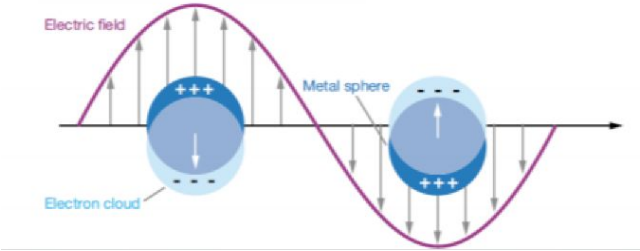
- Gold nanorods immobilized on a glass substrate
  - Citrate stabilized Au
  - Silane method (APTES)
  - Aligned with PDMS
- Biotin-avidin to anchor receptor to surface
  - Detect target molecule/antigen (cancer marker)
- Cancer markers
  - AFP
  - PSA
  - CEA
  - Ca-153

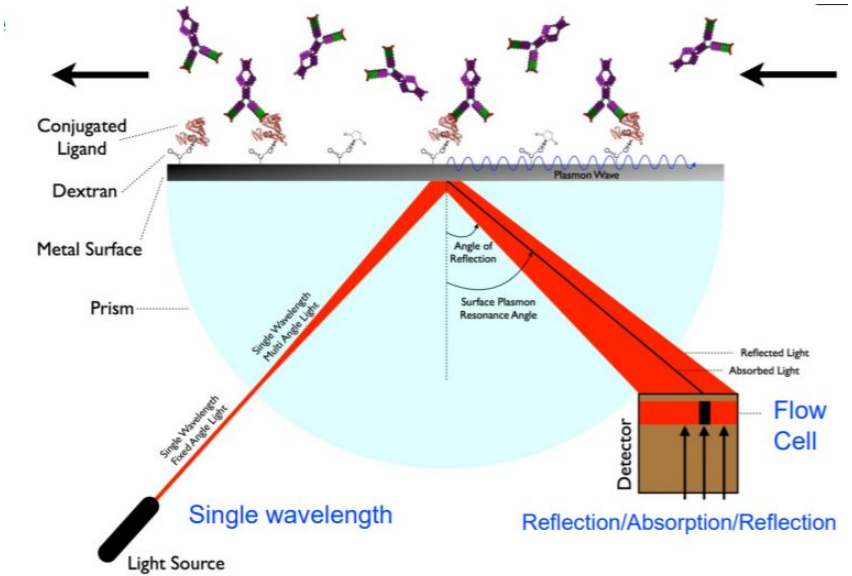




Device Testing

- Cancer markers at various concentrations are injected and monitored in 50% serum
- Detection completed by using secondary polyclonal antibodies
- 10–100 ng/mL sample
- Run for 30 min
- LSPR spectroscopy





Device Validation

- 15 multiple cancer patients with known metastatic cancer
- 15 patients with multiple cancers but unknown metastasis status
- 15 patients without cancer
- Run blood samples through devices
  - Compare with diagnoses
    - >80% of match

Limitations

- Some CTCs are smaller than blood cells
  - Not isolated by NISA-XL CTC-iChip or Zhou device
- Does not analyze circulating tumor microemboli
  - Too large for our device
  - More aggressive
- LSPR biosensor chip
  - Substrate nanostructuring cost
  - Complex

References

[1]https://www.cdc.gov/cancer/dcpc/research/articles/cancer_2020.htm
[2]https://www.nature.com/articles/s41378-019-0045-6.pdf
[3]https://pubs-rsc-org.ezp3.lib.umn.edu/en/content/articlelanding/2020/LC/C9LC01122F#!divAbstract
[4]https://www.cancer.net/navigating-cancer-care/how-cancer-treated/personalized-and-targeted-therapies/what-personalized-cancer-medicine
[5]https://www.cancer.gov/news-events/cancer-currents-blog/2018/liquid-biopsy-breast-cancer-late-recurrence
[6]https://www.managedhealthcareexecutive.com/health-management/cancer-rates-decline-young-people
[7]https://www.cancer.org/cancer/breast-cancer/living-as-a-breast-cancer-survivor/second-cancers-after-breast-cancer.html
[8]https://www.cancernetwork.com/article/multiple-primary-tumors-over-lifetime
[9]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604043/
[10]https://pubs-acs-org.ezp1.lib.umn.edu/doi/pdf/10.1021/ac049741z
[11]http://josegc.weebly.com/uploads/2/0/8/7/20878744/nl500574n.pdf