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3D TISSUE CULTURE DEVICE THAT MIMICS CANCER METASTASIS FOR IN VITRO DRUG DISCOVERY

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Technology Description

Engineers in Prof. Amit Pathak's laboratory have developed a 3D tissue culture device with chambers of variable, tunable stiffness to mimic the multiple microenvironments cancer cells experience in vivo as they metastasize. Traditional 3D extracellular matrix (ECM) models do not capture the range of biomechanical conditions that cancer cells experience in the human body throughout the invasion trajectory as they move from primary tumor to the surrounding tissue. Therefore, cellular measurements and analysis of a drug's effects on those cells are not representative of in vivo situations where cells adapt in unpredictable ways in response to their environment. This invention solves that problem by recapitulating the journey of cancer cells along the invasion trajectory - first mimicking the stiffness of a primary tumor then the softer secondary metastatic sites. This enables in vitro drug tracking as the cancer cells' characteristics change, particularly with respect to de-clustering and outward migration. In addition, the device is easy to fabricate with tunable stiffness to tightly control biomechanical properties of the ECM. These features could enhance drug development of robust therapeutic agents, particularly for preventing and treating metastatic tumors.

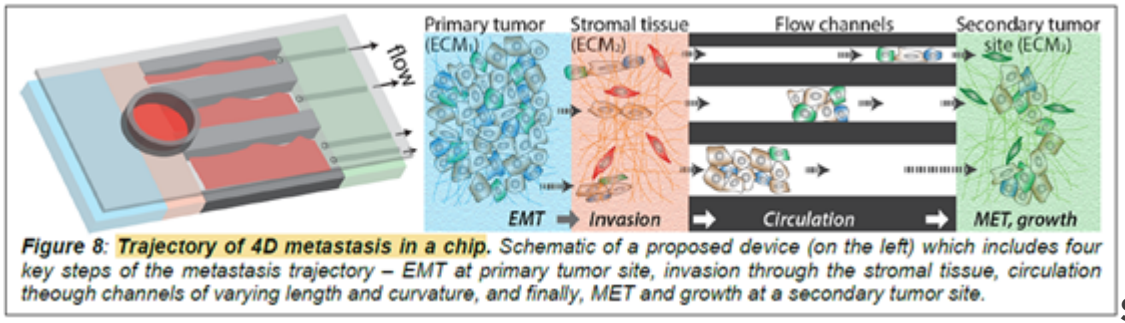

*Figure 8: **Trajectory of 4D metastasis in a chip.** Schematic of a proposed device (on the left) which includes four key steps of the metastasis trajectory – EMT at primary tumor site, invasion through the stromal tissue, circulation theough channels of varying length and curvature, and finally, MET and growth at a secondary tumor site.*

Stage of Research

The inventors fabricated the device and used it to demonstrate that the extracellular matrix of the primary tumor site creates a "mechanical memory" that greatly affects cellular motility and migration even after leaving that site. Specifically, they showed that epithelial cells that are primed on a stiff (primary tumor-like) matrix migrate faster, display higher actomyosin expression, form larger focal adhesions and retain nuclear YAP expression even after arriving onto a soft secondary matrix.

Applications

- **Drug discovery** – 3D cell culture device to test effects of drug candidates on cancer cells, particularly for metastatic cells as they move along the invasion trajectory
- **Research** – 3D cell culture device for basic studies of mechanisms involved in cancer metastasis as well as embryonic development, wound healing or other scenarios where microenvironment-

dependent cell motility plays a role

Key Advantages

- **Continuously track drug effects through microenvironments of cancer invasion:**
  - closely mimics biomechanics of in vivo invasion
  - regions on the device with varying stiffness recapitulate the microenvironments of metastatic cancer cells in vivo as they progress from primary tumor to secondary metastatic sites
  - cellular measurements to determine influence on tumor growth at every step
  - tunable stiffness to tightly control biomechanical properties of the extracellular matr**ix**
- **Simple device fabrication** with easy to use configurable geometry

Publications

- Nasrollahi, S., Walter, C., Loza, A. J., Schimizzi, G. V., Longmore, G. D., & Pathak, A. (2017). Past matrix stiffness primes epithelial cells and regulates their future collective migration through a mechanical memory. *Biomaterials*, 146, 146-155.
- Cells' mechanical memory could hold clues to cancer metastasis, *theSource*, Nov. 3, 2017.

Patents

- Device with multiple microenvironments and methods thereof (U.S. Patent Application, Publication No. US20180105793)

Website

- Cellular Mechanobiology Laboratory