Manufacturing low cost, high fidelity, portable medical devices for the monitoring of cardiovascular health and diabetes.

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Improved risk stratification and early detection of disease is a broad, unmet need in clinical medicine. Most efforts have focused on identifying biomarkers (e.g., biomolecules or cell extracts measured in a sample such as urine or blood, which can inform regarding presence or level of activity for diagnosis of a disease). Despite substantial biomarker research efforts, success to date has been extremely limited. It is our conviction that a fundamental reason for failure is that biomarkers are typically studied in a "static" paradigm, with one-time measurements (or if measured multiple times, they are measured at very low time resolution of weeks to months, rather than days). We envision that the ability to measure biomarkers daily, easily, and at low cost can enable the collection of information related to dynamic changes within an individual over time, would substantially increase the sensitivity, as well as, specificity of biomarkers for early detection and monitoring of a range of diseases, including cardiovascular diseases and diabetes mellitus.

Here, we propose the manufacturing of medical devices that serve as a versatile platform for providing real-time, quantitative information pertaining to the concentration of different biomarkers of interest for cardiovascular health and diabetes monitoring. Our approach leverages and integrates recent breakthroughs made by our team in the areas of surface science, microfluidics, functional thin films, chemical synthesis, and molecular biology. The envisioned platform will consist of selectively patterned, paper-based substrates that take microscopic amounts of blood, sort them into constituents, extract cell contents, and provide immediate quantitative output pertaining to the different bioanalytes of interest.

Our proposed device will consist of a central, paper based microfluidic chip that will split up blood into its water-soluble and oil-soluble components. These components will then either be extracted or lysed within the microfluidic device. We will attach different auxiliary paper based microfluidic chips to this central chip in a manner that they can accept the extracted / lysed bio-fluid components from the central chip and conduct different assays required to quantify the concentration of the different biomarkers. The system will require very low fluid volumes (typically < 1ml), allowing for blood collection in a less invasive, and less painful manner, as compared with the traditional venous puncture needle.

To enable this technology platform, the following scientific breakthroughs and questions will be addressed: a. Optimization of central microfluidic chip for the extraction of bioanalytes from blood b. Fabrication of paper based devices that quantify the concentration of glucose, insulin, cholesterol (HDL, LDL and Triglycerides) c. Integration into optoelectronic devices for multiplexed, real time quantification d. Large scale fabrication of the central and auxiliary paper based microfluidic devices using direct printing of omniphilic channels on top of omniphobic paper. e. Testing, analysis and quantification of biomarkers from diverse patient-derived samples, and integration of information from individual diagnostic devices, for precision health.

The proposed research covers broad scientific disciplines such as molecular design, chemical synthesis, surface chemistry, device design and fabrication, biomarkers and bioanalytes, modern material characterizations, signal detection and performance analysis, necessitating a

long-term interactive collaboration among multiple PIs having expertise in these research thrusts. We have assembled a world leading team with expertise in each of these thrust areas, as discussed below:

a. Paper-based microfluidic devices: Paper has recently emerged as a promising materials platform for microfluidic devices due to its low cost, easy disposal, high surface area, capillary-based wetting, flexibility, and compatibility with a wide range of patterning and printing techniques. Tuteja and Mehta have recently developed a method of generating omniphobic paper surfaces that are resistant to wetting by a broad range of liquids, including numerous low surface tension solvents. Further, we have also developed a methodology to induce selective wetting of liquids with different surface tensions and polarities on a paper surface. Such selective extreme wettabilities of fluidic channels, combined with improved fluidic control, make several new applications of paper-based microfluidic devices possible. As a result, we recently demonstrated the first-ever paper based devices capable of oil-water separation, as well as liquid-liquid extraction for the selective removal of miscible components (such as different bioanalytes) from a bulk fluid (such as blood; see Fig. 1). We have also recently developed the first-ever paper based microfluidic systems capable on cell and blood lysing directly on the chip.

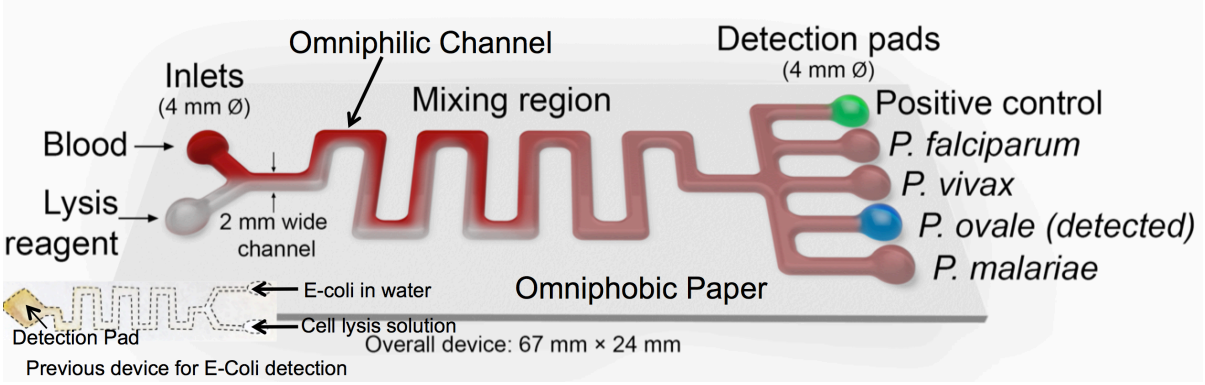

***Figure 1**: A schematic for a paper based microfluidic device for Malarial detection. The device is fabricated using easy to print omniphilic channels on top of an omniphobic piece of paper. The inset shows a similar device fabricated in our labs for E-Coli detection with extremely high sensitivity. Dashed lines are added to the image for easier observation of the actual omniphilic channels. The edges of the detection pad shown in the inset are dark brown due to the presence of E-Coli. Note that the edges of the detection pad are dark, yet the center is still white. This is due to the so-called Marangoni effect, and allows for the extremely high detection sensitivity of the fabricated device.*

b. Multiplexed molecular recognition, signal generation, and integration: Kim's lab designed novel conjugated organic molecules and polymers incorporating molecular receptors that generate optical and/or electronic sensory signals upon selective recognition of a target molecule or chemical. Antibodies, specific chemistries, DNA aptamers, supramolecular intermolecular interactions, lipids, and enzymes have been devised as a receptor having a specificity toward various target analytes, with demonstrated selective and sensitive detection of biological molecules and chemicals, such as, DNA, influenza virus A, prostate specific antigen, antibiotic, potassium, mercury, melamine, lead III, fluoride anion, oxygen, water, and warfare gases. Combined with signal amplification via intermolecular coupling, as well as, incorporation into transistor and optical cavity devices, molecular binding events can be detected at sub-nanomolar analyte concentration. Moreover, the ability of these molecules to form high quality thin films enables their integration in a pattern into optoelectronic devices for multiplexed, real time detection. These devices will be created using inkjet printing, spin / drop casting, contact

coating, and vapor jet printing. Shtein's lab recently demonstrated a breakthrough, solvent-free method for direct-printing of multiple active pharmaceutical ingredients on a variety of substrates, including low cost and biodegradable materials, while enhancing dissolution rate and bioavailability. In order to demonstrate these capabilities in an integrated, paper based sensor platform, we will research the material properties, optical and electronic processes, and process conditions required to achieve the desired structures and signals.

c. Quality assurance and personalized data management: Given that variability is a key parameter in the biological data points generated, Mehta lab will contribute towards standardization and data management, in order for the bioanalytes data captured to be meaningful for diagnostics and easily implementable into clinical workflow. Using established and novel biomarkers and clinical correlates, the patient data will be organized in integration matrices, and followed temporally, to accurately quantify disease status. Mehta lab has previously established precision health models for gynecologic cancers for rapid identification of optimal personalized treatment routes. Using similar skill sets in this project, Mehta lab will detect and quantify a variety of biomarkers from diverse patient-derived samples, collate information from individual clinical diagnostics devices, thereby expanding quantitative data collection to broader populations and improve clinical outcomes.