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A microfluidic platform for drug screening in a 3D cancer microenvironment

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ABSTRACT

Development of resistance to chemotherapy treatments is a major challenge in the battle against cancer. Although a vast repertoire of chemotherapeutics is currently available for treating cancer, a technique for rapidly identifying the right drug based on the chemo-resistivity of the cancer cells is not available and it currently takes weeks to months to evaluate the response of cancer patients to a drug. A sensitive, low-cost diagnostic assay capable of rapidly evaluating the effect of a series of drugs on cancer cells can significantly change the paradigm in cancer treatment management. Integration of microfluidics and electrical sensing modality in a 3D tumour microenvironment may provide a powerful platform to tackle this issue. Here, we report a 3D microfluidic platform that could be potentially used for a real-time deterministic analysis of the success rate of a chemotherapeutic drug in less than 12 h. The platform (66 mm×50 mm; L×W) is integrated with the microsensors (interdigitated gold electrodes with width and spacing 10 μm) that can measure the change in the electrical response of cancer cells seeded in a 3D extra cellular matrix when a chemotherapeutic drug is flown next to the matrix. B16-F10 mouse melanoma, 4T1 mouse breast cancer, and DU 145 human prostate cancer cells were used as clinical models. The change in impedance magnitude on flowing chemotherapeutics drugs measured at 12 h for drug-susceptible and drug tolerant breast cancer cells compared to control were 50,552 ± 144 Ω and 28,786 ± 233 Ω, respectively, while that of drug-susceptible melanoma cells were 40,197 ± 222 Ω and 4069 ± 79 Ω, respectively. In case of prostate cancer the impedance change between susceptible and resistant cells were 8971 ± 1515 Ω and 3281 ± 429 Ω, respectively, which demonstrated that the microfluidic platform was capable of delineating drug susceptible cells, drug tolerant, and drug resistant cells in less than 12 h.

1. Introduction

Cancer has become a universal health problem. It is presently the second major cause of death in the United States and is predicted to outpace heart diseases in the next few years. In 2016, 1,685,210 new cancer cases and 595,690 cancer deaths are projected to occur in the United States (Siegel et al., 2016). Selecting the correct chemotherapeutic agents for a particular patient is imperative in the effective treatment of cancer. First line therapy against cancer involves a standard set of treatments, such as surgery followed by chemotherapy and radiation. Imaging-based technologies using Computerized Tomography (CT) scan and Magnetic Resonance Imaging (MRI) to monitor tumour size are the current standard methods for evaluating treatment success. Sometimes, first line therapies take a long time to show progress followed by a stalling or continued growth of cancer (Hassan et al., 2010; Kuczynski et al., 2013). In addition, cancer cells may develop resistance to the chemotherapeutic agents. Currently, the therapy efficacy can be determined only after a few weeks to several months, which represents one of the major challenges in the timely management of cancer (Morabito et al., 2014; Gottesman, 2002). Therefore, there is a need to develop approaches for rapid screening techniques to evaluate the efficacy of anti-cancer drugs on tumours that would help in stratifying patient responders and non-responders early on.

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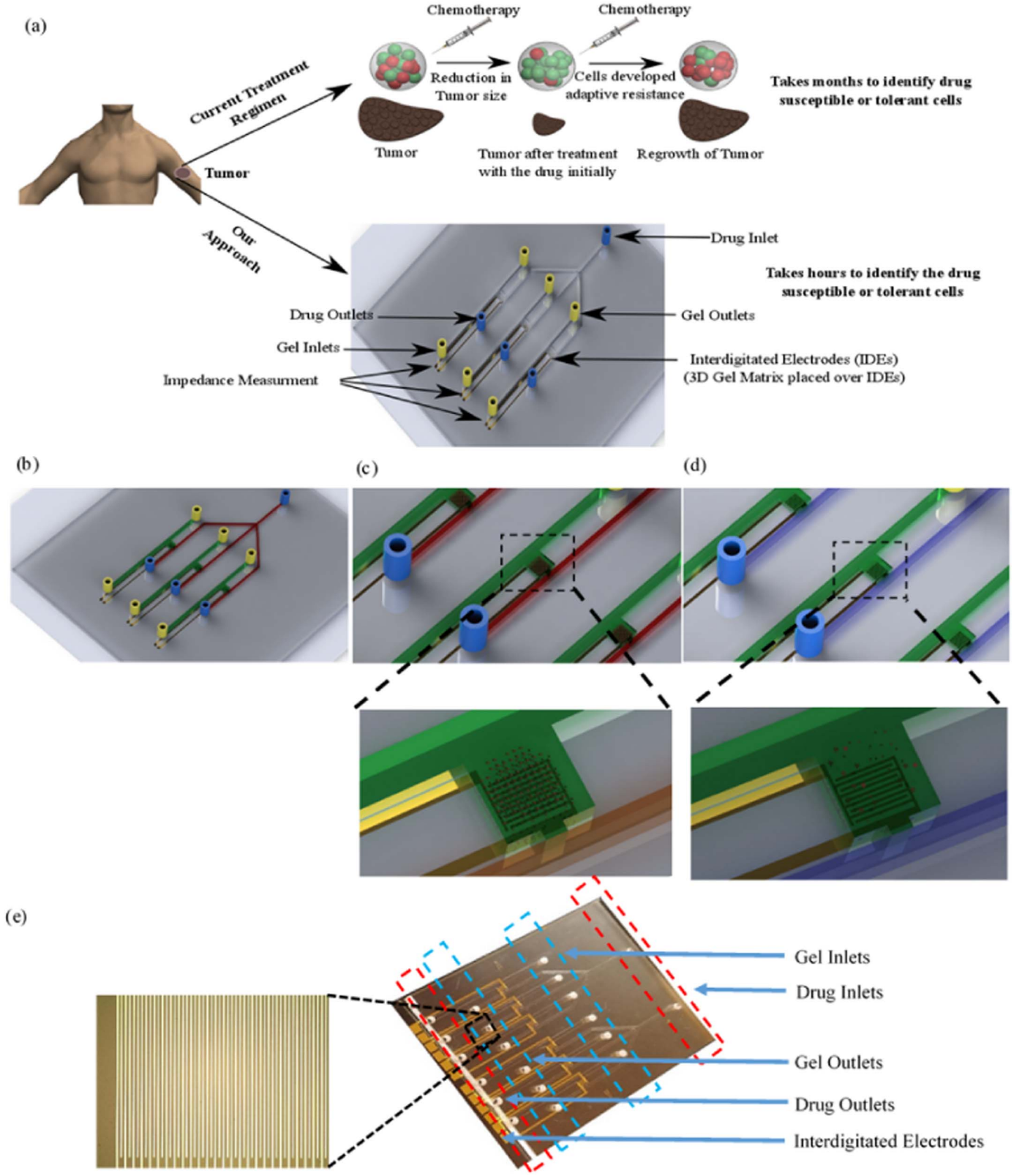

Fig. 1. Lab-on-a-Chip for chemotherapy drug response screening. (a) 3D schematic of the presented platform for multiplex drug susceptibility testing, (b) Cancer cells are placed in a 3D matrix in a separate microchannel (green) that is connected to a parallel microchannel for drug flow (red), (c) Cancer cells are intact and viable in the 3D gel structure and before the introduction of drugs. In the presence of effective drug flow, the cancer cells respond (lyse), (d) We observed that the number of intact cancer cells reduced after introducing effective drug flow in the chip, (e) Image of a fabricated device. The chip involves interdigitated electrodes with 10 μm width and spacing. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)