AEROSOL DRUG DELIVERY FOR LUNG ON A CHIP

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ABSTRACT

Animal models for drug toxicity and efficacy are expensive and often do not accurately reflect the human response, resulting in wasteful clinical trials and ineffective drug development. Expanding human cell culture systems to microenvironments that mimic *in vivo* organ-level function may increase human relevance and translation of products to patients. Here we present a method of delivering aerosolized drug to a previously described biomimetic microfluidic device or 'Lung-on-a-Chip" that reproduces the alveolar-capillary interface of the human lung under physiologically relevant cyclic mechanical strain and flow conditions (Huh et al., *Science* 2010; 328:1662-1668). We demonstrate the first reported deposition of aerosol into a microfluidic channel using a commercial nebulizer as a source of aerosol. This method should enable toxicity and efficacy testing of pulmonary drugs in a human-relevant *in vitro* system.

KEYWORDS: Aerosol, Drug Delivery, *In Vitro*, Air-Liquid Interface, Lung-on-a-Chip

INTRODUCTION

In vitro model systems that accurately predict drug efficacy, bioavailability and toxicity in humans are needed to replace costly and time-consuming animal studies to speed development and regulatory approval of new and safer medical products. Although advances have been made in cell culture models, these methods, in many cases, still fail to accurately predict toxicity and efficacy in humans mainly due to insufficient reconstitution of the key structural and mechanical features of the whole organ. Recently, we demonstrated a biomimetic microfluidic device that reproduces the alveolar-capillary interface of the human lung under physiologically relevant cyclic mechanical strain and flow conditions [1]. We and others also have demonstrated morphological and phenotypic differences of cells cultured at an air interface as opposed to in liquid media [1,2]. But delivering drugs to cells at an air interface in a physiologically relevant manner constitutes a challenge, especially on the microscale. This paper addresses this challenge and reports a method to deliver aerosolized microdroplets into a microfluidic device designed for the culture of human cells at an air interface. Coupling of this aerosol delivery system to the breathing lung-on-a-chip microdevice provides a new method to measure pulmonary absorption, efficacy and toxicity of aerosolized drugs, particles and toxins.

Figure 1: Photograph of PDMS-glass microfluidic device with 100 µm inner diameter glass capillary for aerosol delivery to a microchannel.

EXPERIMENTAL

Microscale liquid droplets are delivered to a polydimethylsiloxane (PDMS) microfluidic device (Fig. 1) with microchannel dimensions identical to the air culture channel of the previously reported lung-on-a-chip [1]. In this system, two 80 x 200 µm channels used to applying cyclic mechanical distortion using suction are placed on either side of the central 80 x 400 µm channel where human alveolar epithelial cells and capillary endothelial cells are placed on either side of a porous flexible PDMS membrane. We used a commercial prescription nebulizer (Pari) to generate aerosolized liquid droplets with a nominal median mass diameter of 3.8 µm by forcing air through an orifice. The liquid droplets in air are

sampled with fused silica tubing inserted into the flow from the nebulizer (Fig. 2). The droplets flow through the capillary into the 80 x 400 µm microfluidic channel of the device (Fig.1); cells were not included in the system in these initial studies designed to validate aerosol delivery. The suspended droplets passing through the microchannel were viewed on a microscope and images were captured with a camera set to 0.1 millisecond exposure time. The droplets' size and velocity distribution (Fig. 3) was processed using ImageJ software (rsbweb.nih.gov/ij/).

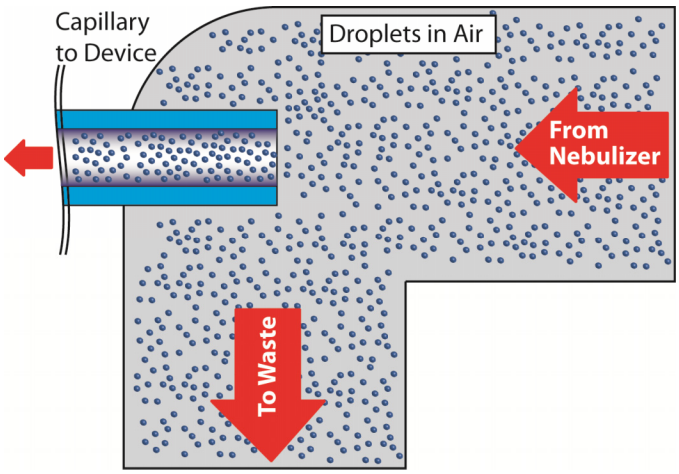

Figure 2: Schematic illustrating the sampling of microdroplets from a commercial prescription nebulizer for pulmonary drug delivery to a microdevice through fused-silica capillary.

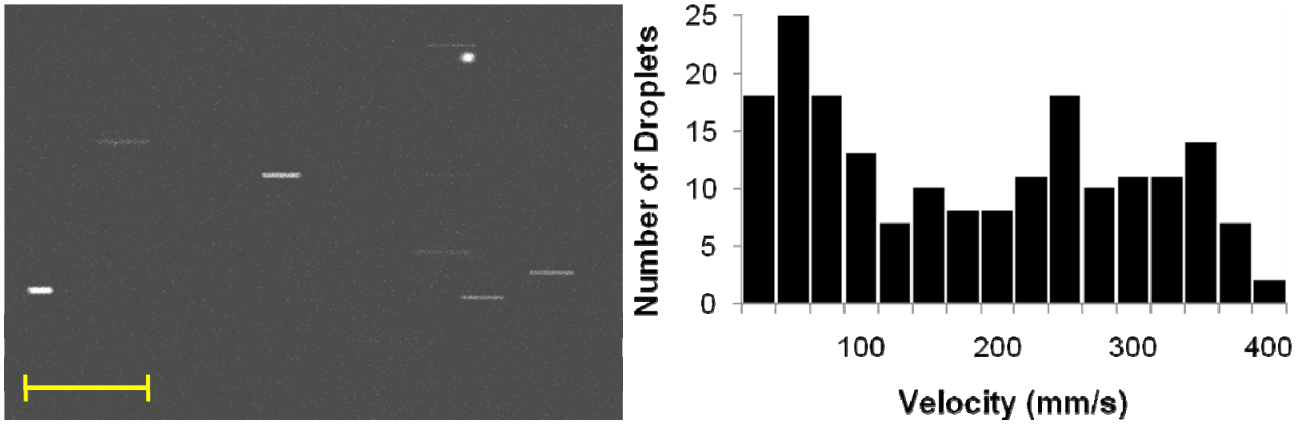

Figure 3: Micrograph of water droplets passing through an 80 µm deep microchannel with a 0.1 ms exposure (left, scale bar=100 µm) and a histogram of the velocities of the suspended droplets (right).

RESULTS AND DISCUSSION

The histogram in Fig. 3, which shows the distribution of velocities of individual droplets, indicates that the distribution is fairly broad with main peaks at approximately 25 and 250 mm/s. The air velocity must be selected not to disrupt the cells cultured at the air interface. The droplets transported through the channel have a broad size distribution with an average diameter of approximately 7 µm. As the droplets suspended in air travel through the microchannel, some of them are deposited on the channel walls. This is the key process necessary for delivering the aerosolized drug to the surface of the membrane where cells are cultured (Fig. 4). The bright field images of the channel before (top) and after (bottom) deposition of water droplets show an even distribution along the channel. We believe that this is the first demonstration of aerosol delivered to a microfluidic device. Using this method, drugs and toxins can be administered to human lung cells cultured at an air interface in the microfluidic channel, where the environment closely mimics the *in vivo* mechanical and structural environment of the human lung alveolar-capillary interface [1]. Ultimately, aerosol drug delivery to microfluidic cell culture devices should provide a more accurate model for drug and toxicity screening.

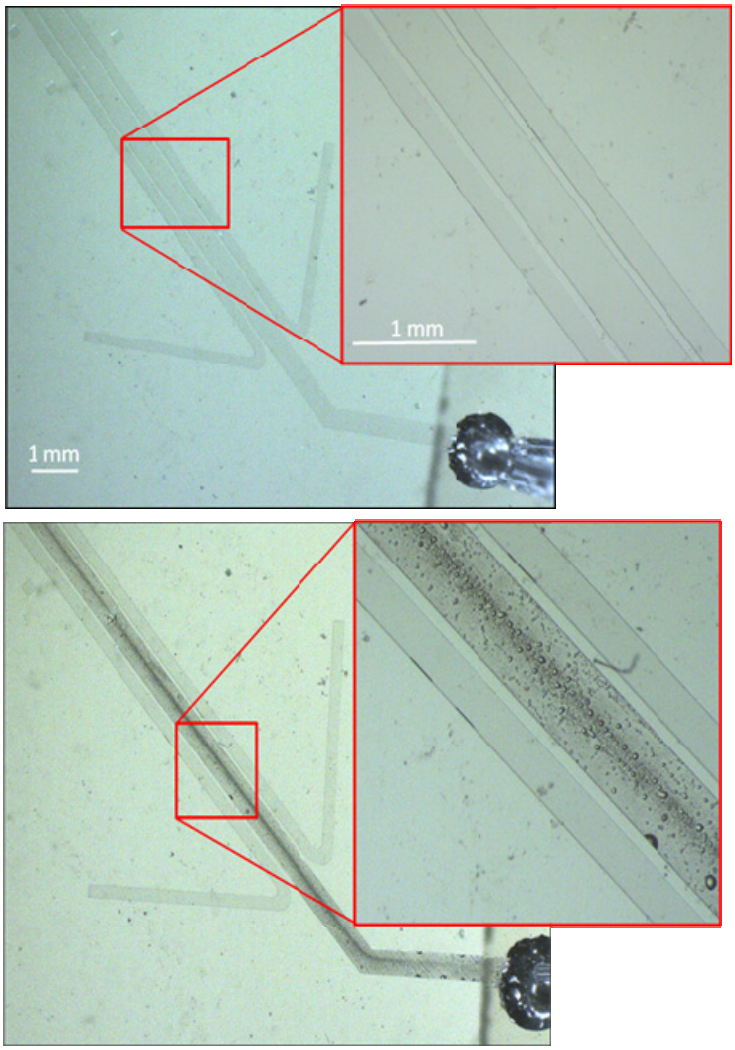

Figure 4: Micrograph of microchannel with fused-silica capillary before (top) and after (bottom) deposition of water microdroplets to the channel walls.

CONCLUSION

We demonstrated suspended liquid droplets flowing through and depositing onto a microfluidic channel. The droplets were sampled from the output of a commercially available, prescription nebulizer and delivered to a microfluidic channel. Once coupled to human microfluidic cell culture, this method will enable *in vitro* efficacy and toxicity testing of aerosolized drugs and particles in a microfluidic device.

ACKNOWLEDGEMENTS

This work was supported by a grant (U01 NS073474) from the NIH Common Fund, through the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), Office of the Director, NIH and by the Food and Drug Administration (FDA).

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