Polymer-Based Microfluidic Platforms for High Throughput Screening

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ABSTRACT

High throughput screening (HTS) of elements from combinatorial libraries represents the first step in the drug discovery pipeline. Microfluidics is a viable platform for performing HTS due to its ability to automate fluid handling and generate fluidic networks with high numbers of processors over small footprints appropriate for optical imaging. Unfortunately, few efforts have been invested into developing microfluidic platforms to generate high information content systems appropriate for HTS. While most HTS campaigns depend on fluorescence, readers typically use point detection and serially address the assay results, significantly lowering throughput. To address these challenges, we present here the fabrication of high density microfluidic vias packed into the imaging area of a large field-of-view (FoV) ultrasensitive fluorescence detection system. *Two* different fluidic architectures were evaluated for providing an optical system with single molecule sensitivity, *(1)* High density fluidic network using epi-illumination with beam shaping optics to provide a large FoV. The fluidic channels are 1 μm (width and depth) with a pitch of 1 μm. A 40X objective (numerical aperture = 0.75) creates a FoV of 200 μm providing the ability to interrogate ~100 vias. A charge couple device (CCD) operated in a frame transfer mode is used for tracking fluorescent molecules as they pass through the irradiating field. *(2)* Embedded waveguide situated orthogonal to the fluidic vias, which defines the excitation volume. Fluorescence sampling is accomplished using an evanescent field with extremely shallow channels to keep the sampling efficiency high (~60% for 500 nm deep channels) due to the small penetration depth (~300 nm) of the evanescent field. The fluidic structures were fabricated using UV-LiGA to produce Ni electroforms. Embossing of the structures was accomplished with a JenOptik HEX02 high-precision hot embossing system to create high fidelity in the features over large areas. The utility of these multichannel networks for HTS with an optical system for producing the prerequisite sensitivity was demonstrated by performing high throughput single molecule fluorescence detection with epi-illumination. Single fluorescent dyes (AlexaFluor 660) were identified using a test high density fluidic device (5 μm x 1 μm; pitch = 5 μm) fabricated in PMMA. The fluidic system for HTS will be evaluated by screening potential therapeutic agents for L1-Endonuclease (L1-EN), a target that induces DNA double-strand breaks and is associated with 45 different diseases including aging.