A VERSATILE HIGH-THROUGHPUT MICROFLUIDIC PLATFORM FOR ANTIBODY DISCOVERY FROM NATURAL IMMUNE REPERTOIRES

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The large majority of monoclonal antibody (mAb) therapeutics have been generated and isolated from natural immune systems, typically using murine hybridomas. As the "low-hanging" fruits of antibody discovery targets have become saturated, next-generation antibody discovery approaches hold high potential for finding improved mAbs with optimal properties, for addressing targets that have proven difficult or intractable by traditional methods, and for harnessing novel sources of antibody diversity.

We have developed an antibody discovery platform based on microfluidic selection of mAbs directly from single immune cells. Antibody-secreting cells (ASCs) from patients or immunized animals are loaded and compartmentalized into microfluidic devices containing arrays of nanoliter-volume chambers, enabling the detection of antibody secretion from single cells within minutes. Integrated microfluidics allow for the programmed exchange of reagents to implement a wide array of selection assays including bead-based binding measurements, as well as cell-based assays of binding or function. A fully automated instrument enables the identification and recovery of selected ASCs based on fluorescent imaging and analysis. Recovered cells are then analyzed for high-efficiency recovery (>75%) of paired heavy and light chain variable region sequences using a next-generation sequencing approach. This platform allows for the multi-parameter antibody selection from any species, with throughput of over 1,000,000 cells per run and recovery of over 100 paired sequences in approximately 7 days.

We will present preliminary data in the isolation of antibodies against ion channel (Nav1.7) and GPCR (CXCR4) targets in mice and rabbits. We will further demonstrate our platform in the isolation of fully human mAbs from blood samples, including antibodies cross-reacting with different influenza hemagglutinin types, and targeting virulence factors from a bacterial pathogen. In the later we will show that very deep screening (~1,000,000 ASCs) allows for the detection and isolation of ultra-rare antigen-specific mAbs from healthy human patients with no detectable titers.