# SMART MICROPARTICLES, PARTIPETTING, AND LIQUID MICROARRAYS : FROM BASIC TECHNOLOGIES TO APPLICATIONS

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### ABSTRACT

There are many multiplexed arrays for surface bound molecules such as DNA or proteins but multiplexing large number of liquid based assays are still in need. Highly heterogeneous liquid handling in pico-nano liter volume is the key to handle large number of chemical libraries. In this talk, I will introduce "partipetting", a method of simultaneously dispensing large number of different liquids into microwells with only one pipetting event. I will first review core basic technologies of partipetting such as fabrication of various encoded microparticles and various self-assembly technologies. Then I will present a few application examples of partipetting that have been developed in my lab.

#### **KEYWORDS**

Encoded microparticles, magnetically tunable structural color, fluidic self-assembly, liquid microarrays, screening

#### PARTIPETTING

Multiplex analysis using suspended encoded particles have received much attention in high throughput bio-molecule screening thanks to their outperforming scalability and fast reaction kinetics over conventional 2D biochips. However, current multiplexed assays based on encoded beads are limited to multiplexing of surface bound probe molecules such as DNA or proteins and are not able to handle chemical compound liquid libraries, which is essential for drug screening. Highly heterogeneous liquid chips for high throughput liquid cell based screening assay has not been developed yet due to challenges mainly in small volume liquid handling. In this talk, we present an ultraplex compound screening platform based on our new liquid handling method named 'partipetting'.

**Partipetting** is defined as a single pipetting operation of simultaneously self-assembling million different liquid drug-laden microparticles into million separate reaction wells in a microfabricated well plate, implying 'Pipetting encoded **Particles**'. First, a liquid chemical compound is either encapsulated by an encoded polymer shell or absorbed in a lithographically formed encoded hydrogel (Fig. 1A). Millions of different chemical library are then processed same way but with different code to form a library or a stock solution of millions of different encoded drug-laden microparticles (Fig. 1B). Using only one pipetting event, millions of the drug-laden microparticles are self-assembled to a microfabricated well plate with million separate wells to form a chemical chip with million variations (Fig. 1C). Then the code in the liquid particle is read by image based reader system to make spatial registration mapping between assembled liquid containing coded particles and reaction wells. Therefore, fabrication of various encoded functional particles and self-assembly of them into the microwell is core technologies required for partipetting.



Figure 1. Schematic of partipetting A. Different chemical laden encoded particle generation. Each particle has each different code. B. Different chemical laden particles library. C. Partipetting. Heterogeneous assembly platform is generated with a single pipetting of different encoded particles.

## SMART MICROPARTICLES AND THEIR APPLICATIONS

We fabricated various encoded particles with different function and application: liquid capped Teflon microshells for liquid array chip, drug-laden encoded microparticles for large scale cell based drug screening, encoded virus micropatch for multiplexed gene transfection, and multi-level color barcoded microparticles for DNA analysis. (the particle schemetics are shown in top of Fig. 2A-D). Basic fabrication technologies such as optofluidic maskless lithography and M-Ink will be reviewed as particle forming scheme and encoding schemes, respectively [1-4]. Via one partipetting event, these encoded microparticles with various contents are self-assembled into microfabricated well array and forms heterogeneous array of chemical library, viruses, and DNAs (bottom figures of Fig. 2A-D). Based on the partipetted self-assembled assay, ligand screening assay for G-protein coupled receptor (GPCR) has been successfully mimicked in highly multiplexed format (Fig. 3A). Also cell based screening assay is performed partipetting anti-cancer drug (sodium salicylate) absorbed encoded hydrogels into the cell containing microwells. (Fig. 3B).



Figure 2. Types of microparticles with various contents. A.Core-shell microparticle. Chemical liquid is encapsulated with polymerized Teflon. B. Drug-laden coded microparticle. Drug is absorbed into the hydrogel. C. Encoded virus micropatch. D. Color barcoded microparticle. Aligned magnetic chain forms color code.



Figure 3. Cell-based assay via partipetting A. Local gene delivery using encoded virus micropatch. Heterogeneous viral vector transduction and GPCR internalization assay B. Absorbed drugs diffused out to the target cells after the assembly of encoded particle assembled chip and cell chip. Heterogeneous cell staining and anti-cancer drug screening on cancer cells in microwells

## CONCLUSIONS

We have developed an ultraplex liquid chip with heterogeneous liquid capped encoded particles and demonstrated these arrays can replicate conventional well based screening with much higher throughput. We envision that this technique will enable users simply choose and order a type of chemical compound chips from a catalog instead of repeating million pipetting in-house.

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