Non-contact, label-free printing of single, living cells

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Summary

The presented single cell manipulator (SCM) technology features:

- Single cells confined in picoliter-droplets
- Non-contact drop-on-demand printing
- Label-free optical detection and sorting
- Integrates into typical laboratory workflow

It is intended to deliver single cells from suspension alive at certain target with high accuracy and precision. Typical printing yield is 70 - 92% depending on cell type and concentration.

Introduction

Separation and manipulation of individual living biological cells for single cell analysis remains a challenging task for many life science applications. Amongst others single cell PCR, stem cell research, isolation of circulating tumor cells, single cell microarrays and similar applications in basic research, drug discovery or medical diagnostics can benefit significantly from analytical approaches based on single cells.

Our platform is designed to be highly flexible and can serve a wide range of biological and medical applications.

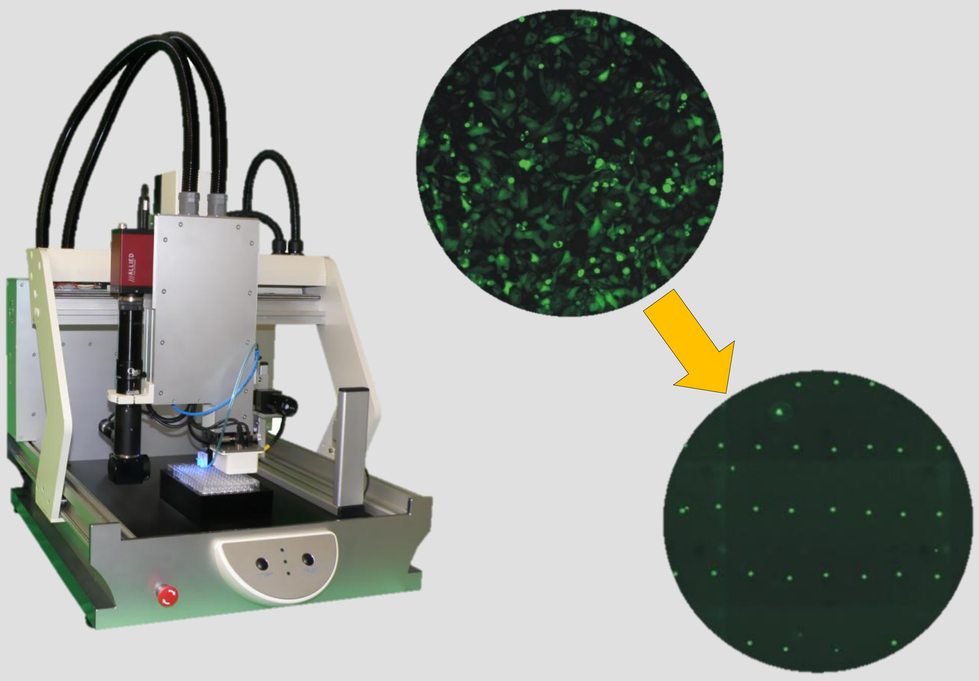

Figure 1: SCM Instrument developed within PASCA project (left), a typical cell culture (top) and individual separated cells in a microarray (right).

Design

Core of the system is a non-contact drop-on-demand micro-dispenser creating 150 picoliter droplets. The nozzle is observed by a high-magnifying vision system coupled with a fast object detection algorithm recognizing and classifying cells inside the chip [1]. Thus it can be predicted how many cells the next droplet will contain before it is actually created. A high-speed pneumatic shutter sucks off all droplets not containing exactly one single cell, such that only single cell droplets arrive on the substrate.

Experimental Results

Standard cell printing technologies yield single cell printing efficiencies of 50 % and less by random printing [2]. Figure 2 demonstrates the performance increase of controlled compared to random printing using 20 µm beads.

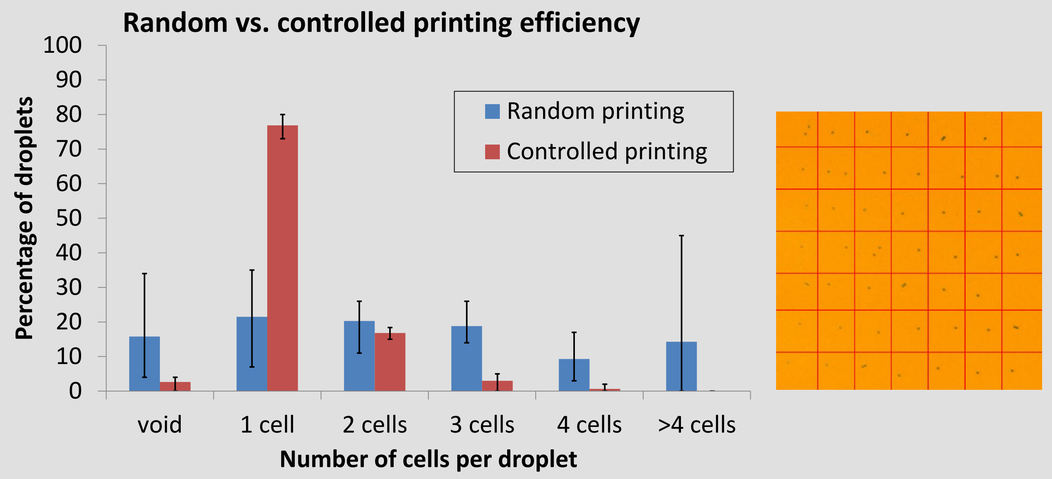

Figure 2: Average printing efficiencies for random and controlled cell printing using the SCM instrument. Right picture shows a section of a typical printed single bead array used for validation.

Beside printing cells in arrays and well plates, we also demonstrated more advanced applications like production of clonal cells lines, separation of rare cells, sorting of cells from multi-cell suspensions by size, sorting of primary cells as well as single cell PCR and single cell RNA sequencing.

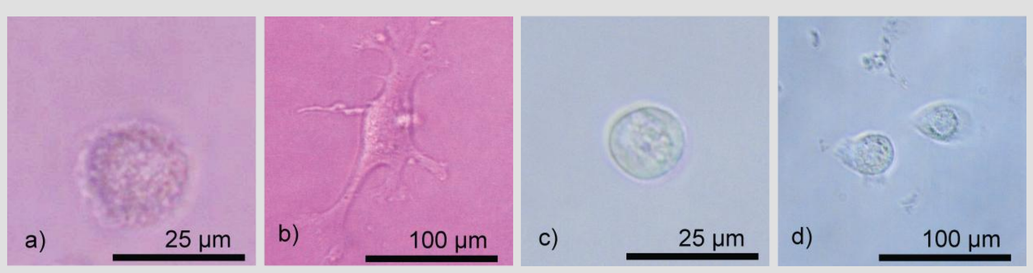

Figure 3: Single human fibroblast (a) and human keratinocyte (c) directly after printing and after 24 hours of incubation respectively (b, d).

Conclusions

The presented technology allows precise, label-free detection and separation of individual living cells from suspension by inkjet-like printing. High viability rates, high printing yield and proof-of-principle for multiple representative downstream applications could be shown in this work.

Acknowledgements

We gratefully acknowledge the intense work of all PASCA consortium members. Furthermore we want to thank all IMTEK members working hard on the project. Finally the European Commission for founding the project within the seventh framework program (FP7 GA257073).

References

[1] Yusof et. al., *Lab on a chip*, 11(14), 2447-54.
[2] Ringeisen et. al. *Biotechnology journal*, *1*(9), 930-48.