ETH zürich

NEXUS Personalized Health Technologies

Automation of organoid assays for drug screening

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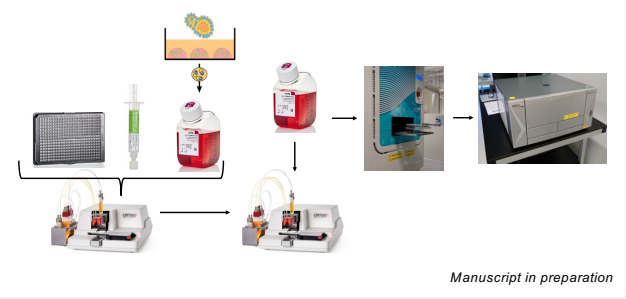
1 Introduction

The last years have shown an enormous increase in the popularity of using organoids for in vitro drug testing due to their improved physiological relevance which is anticipated to reduce the number and size of in vivo studies required to confirm the results. The setup of a high-throughput screen with organoids is a technical challenge due to the unavailability of sufficient organoids and due to the reagents, that are traditionally used. Therefore, most of the current organoid screens are performed in small scale[1,2]. As core facility of the ETH Zurich, NEXUS Personalized Health Technologies has performed several successful organoid screens for different disease models over the last years[3]. We developed an organoid high-throughput screening platform (HTS) for hepatocellular carcinoma (HCC) that is compatible with 1536 well plates where we have eliminated the usage of animal-derived basement membrane extracts as well as the usage of pipette tips.

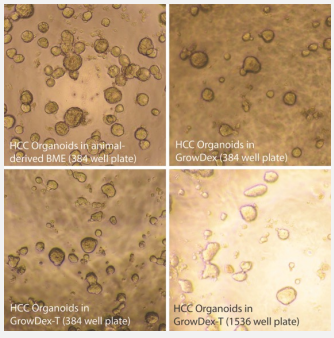
2 Methodology



Manuscript in preparation

To overcome technological challenges associated with animal-derived BME for 3D culture, we optimized a screening workflow to 1536 well plate format with GrowDex-T (UPM Biomedicals). No cooling is needed. Organoids are trypsinized and mixed with GrowDex-T and are subsequently dispensed into 384- or 1536 well plates using a Certus Flex (Gyger AG). Immediately after cell seeding, growth medium is added. Test compounds are dispensed using an acoustic dispenser (Echo 655) and a cell viability readout is performed using CellTiterGlo 3D (Promega).

3 Comparison of GrowDex with animal-derived BME



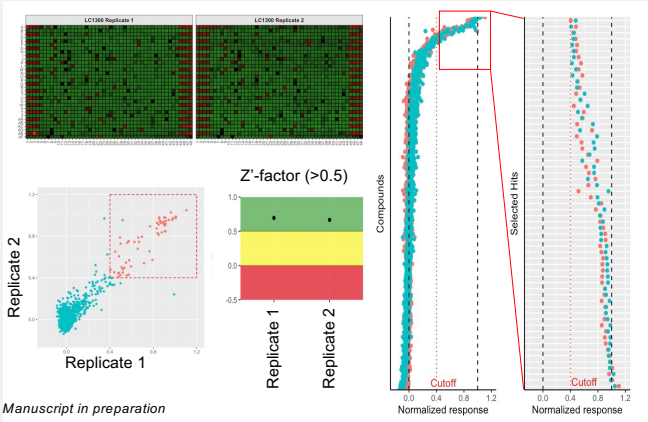
HCC organoids form in animal-derived basement membrane extract (BME), as well as in GrowDex and GrowDex-T.

There is a marginally reduced growth rate of the organoids in GrowDex(-T) compared to the animal-derived BME.

Organoids can be cultured both 'in-gel' and 'on-gel' with GrowDex(-T).

Organoid screens can be miniaturized to 1536 well plate format with GrowDex(-T) ('in-gel').

4 Screening FDA-approved drugs



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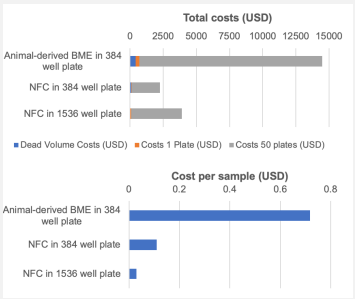
Screening FDA-approved drugs in technical duplicate with HCC organoids showed high assay quality (Z'>0.5) and good correlation of the replicates (most hits are known anti-cancer drugs). We also found a 77% overlap of the identified hits with a biological replicate performed a year earlier using animal-derived BME in 384 well plates (not shown).



Total screening costs and per sample costs are reduced 5-10 times [4].

5 Conclusion

- To enable screening more compounds on physiologically relevant cell models, we developed a screening platform for HCC organoids that uses nanofibrillar cellulose as matrix in 1536 well plates
- A screen of FDA-approved drugs showed high assay stability and a list of hits containing many anti-cancer drugs
- The elimination of animal-derived basement membranes and pipette tips caused a 5-10 times reduction in screening costs
- We expect that the developed methods can be extrapolated to other organoid types, specifically those growing in suspension

References

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3. Booij, Cattaneo and Hirt (2022) Cells 11(21), https://doi.org/10.3390/cells11213440
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