Advanced Development of Primary Pancreatic Organoid Tumor Models for High-Throughput Phenotypic Drug Screening

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Abstract

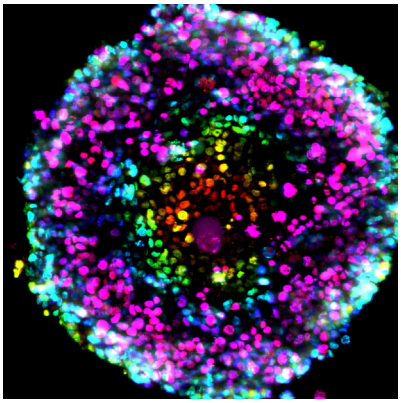
For the performed magnetic 3D assay, standard flat bottom 384 and 1536 well plates featuring a cell repellent surface were employed, combined with the magnetic 3D bioprinting technology. The homogeneous HTS organoid-based assay was standardised using well known anti-cancer agents against four patient-derived pancreatic cancer KRAS mutant associated primary cell lines, including cancer associated fibroblasts. This technology was further validated for its compatibility with HTS instrumentation and robotics by completing a cytotoxicity screen with a library of 3300 approved drugs. To determine the validity of 3D vs 2D HTS, a parallel screen was performed on the same cells in monolayer culture. These results indicate that an ex vivo clinically relevant 3D tumor model can be rapidly adapted and used for large scale drug screening, taking us one step closer to applying precision medicine to the treatment of cancer.

Key features

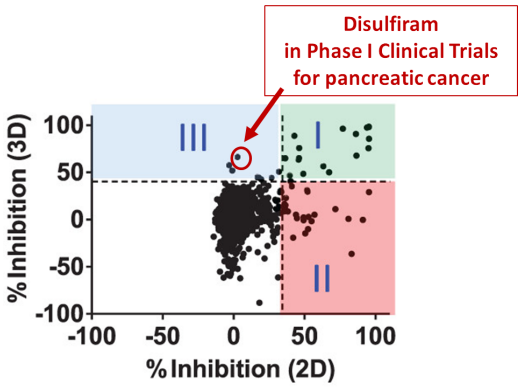
In this work, magnetic 3D bioprinting provided a key strategic advantages, since it is a rapid, relatively easy, and reproducible method to print 3D cultures in high throughput, including key points:

- validated 384 and 1536 well magnetic 3D bioprinting systems as a powerful tool for HTS
- homogeneous HTS organoid-based assay
- standardised using well known anti-cancer agents against four patient-derived pancreatic cancer KRAS mutant associated primary cell lines
- screen included cancer associated fibroblasts (CAF)
- this technology was further validated for its compatibility with HTS instrumentation and robotics
- cytotoxicity screen with a library of 3300 FDA approved drugs
- *ex vivo* clinically relevant 3D tumor model can be rapidly adapted and used for large scale drug screening,
- taking us one step closer to applying precision medicine to the treatment of cancer.
- compared 3D vs. 2D HTS of 3,300 compound FDA library (FDA approved compounds)
- shows value 3D over 2D:
  - 2D showed many more active compounds which should not, “false positives” result
  - 3D identified compound that is currently undergoing clinical trial for pancreatic cancer, 2D did not
- HTS done with flat bottom plates in 384 and 1536 well

Results



A Z-stack image was obtained after staining nuclei with Hoechst using confocal microscopy at 5 micron intervals and then assembled using ImageJ software.



Correlation plot of the percent inhibition values of the approved drug library tested at 2 µM in the 3D and 2D models of pancreatic cancer-associated cell. Disulfiram was identified as the “needle in a haystack” since it is only active in 3D cultures, not in 2D. Out of the 3,300 approved drugs, Disulfiram was the compound that is currently undergoing Phase I clinical trials for the treatment of pancreatic cancer.

Quote

“This work demonstrates a faster and more physiologically relevant cost-efficient drug discovery process, which ultimately will aid in avoiding possible false positives and improving the accuracy" said **Drs. Timothy Spicer and Louis Scampavia**, leaders of this project from The Scripps Research Institute.

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