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Scaling up with spheroids opens up new possibilities in cancer therapy

Researchers at Uppsala University in Sweden develop innovative quiescent spheroid cell models and a unique process of high throughput screening to conduct drug-repositioning anti-cancer research.

In the first high throughput drug-repositioning screening analysis of its scale—with 1,600 total existing compounds successfully screened—Wojciech Senkowski and colleagues from the Department of Medical Sciences at Uppsala University and from Karolinska Institute analyzed the effects of these compounds on three-dimensional colorectal cancer cell cultures (i.e., 'multicellular tumor spheroids'), ultimately discovering that when the cells were made quiescent, several anti-parasitic drugs demonstrated strong anti-cancer activity[1].

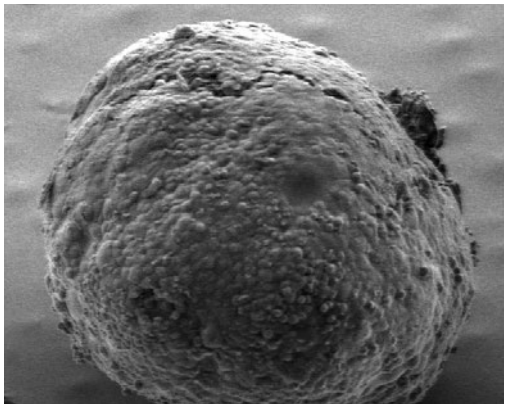
These findings are compelling—but it doesn't end there. In a follow-up gene-expression analysis study utilizing the same 3D cell culture method, Senkowski, et al., identified additional compounds to be toxic to quiescent cancer cells, further supporting the rationale for high throughput screening in 3D cell culture. In addition, they presented a novel platform to study the gene expression in 3D cell cultures in a large scale[2].

"In these two publications, we have shown that culture conditions are critical, both in terms of gene expression and drug responses," said team leader Mårten Fryknäs.

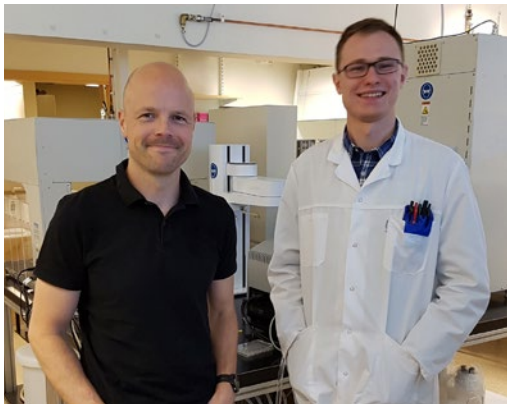
Why Quiescent Cells?

The majority of cancer cells within human tumors are well oxygenated and have easy access to nutrients, which allows them to proliferate easily and quickly. When exposed to traditional methods of cancer treatment, such as chemotherapy, these cells are easily attacked, and the desired effects are often achieved. Other cancer cells that are distant from the conducive environment, however, become quiescent, and it is difficult for standard treatments to eradicate these cells. Quiescent cancer cells, unaffected by chemotherapy, can remain dormant until the environment becomes favorable enough for them to resume proliferation. This often contributes to relapse of the disease once the therapy is withdrawn.

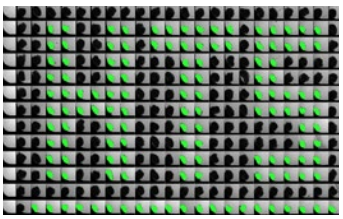
"Quiescent cells are far from blood vessels, so they can't get enough oxygen and nutrients to proliferate, but they can still survive. Most of standard chemotherapy agents have a hard time to even reach these cells, so they often are able to recover, which can lead to relapse of the disease. This is why we are testing compounds to specifically target these dormant, quiescent cells," said postdoctoral researcher Wojciech Senkowski.



An electron microscopy photograph of a HCT116 (colon cancer cell line) spheroid from a Corning 384-well spheroid microplate, featuring U-bottom shaped wells.



Mårten Fryknäs and Wojciech Senkowski in the high-throughput screening lab at the Department of Medical Sciences, Uppsala University.



Corning 384-well microplate Ultra-Low Attachment (ULA) microplate (flat-bottom) with untreated (showing GFP fluorescence) and treated (dead, non-fluorescent) spheroids.

A Background in 3D Cell Culture and High Throughput Screening

The Uppsala University research group specializes in creating relevant *in vitro* models designed to mimic quiescent cancer cells in the body by using spheroid models to test them against pharmaceutical compounds. By utilizing high throughput screening, the research team is able to test as many compounds as possible to increase the understanding of how cancer cells can be targeted and to identify known drugs that may be able to be repurposed as cancer therapy.

But how do they do this?

Looking to Corning for the Tools to Discovery

Early drug repositioning research for Fryknäs' team involved the use of Corning® Ultra-Low Attachment (ULA) microplates to culture spheroid models of cancer. Through trial and error, the research team discovered a reproducible method of culturing cancer cells as 3D models, but this process was not without complications.

"There was a portion of serendipity involved with the initial testing," Fryknäs said, "...the plates were slightly slanted, so cells slid to the corners of the wells and aggregated. We learned we could use a rocker inside the incubator to form spheroids, but this was laborious and complicated. We needed a more standardized format."

Before being released on the market, Fryknäs' team was offered the opportunity to try Corning's new spheroid microplates. Coated with the ULA surface and designed with a uniquely shaped well-bottom, spheroid microplates enable highly reproducible growth of 3D cell cultures. Spheroids may be generated, cultured, and assayed for fluorescent or luminescent signals in the same plate without the need for transferring the spheroids, which can decrease variability, increase throughput, benefit automation, and improve high throughput screening platforms.

Once the team switched to the spheroid microplates, the compound testing system became even more reproducible and easier to use. Using the spheroid microplates was, "the obvious choice," said Senkowski.

Benefits of Drug-repositioning Research in Cancer Treatment

When testing compounds already on the market, the clinical information for those compounds already exists. The safety data from clinical trials can be referred to when testing new indications for an existing treatment. In the case of high throughput research like that being conducted by Fryknäs and his research team, thousands of potential therapies can be tested to identify potential treatment opportunities, as well as further increase the understanding of tumor cell response to both existing and potential new therapies.

For More Information:

Read the first study http://mct.aacrjournals.org/content/14/6/1504.long

Read the second study http://www.cell.com/cell-chemical-biology/pdf/S2451-9456(16)30353-1.pdf

Learn more about Corning spheroid microplates and other solutions for 3D cell culture at **www.corning.com/3D**

References

1. Senkowski W, Zhang X, Oloffson MH, et al. Three-dimensional cell culture-based screening identifies the anthelmintic drug nitazoxanide as a candidate for cancer treatment. Mol Cancer Ther. 2015;(6):1504-1516.
2. Senkowski W, Jarvius M, Rubin J, et al. Large-scale gene expression profiling platform for indentification of content-dependent drug responses in multicellular tumor spheroids. Cell Chem Biol. 2016;(23):1428-1438.

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