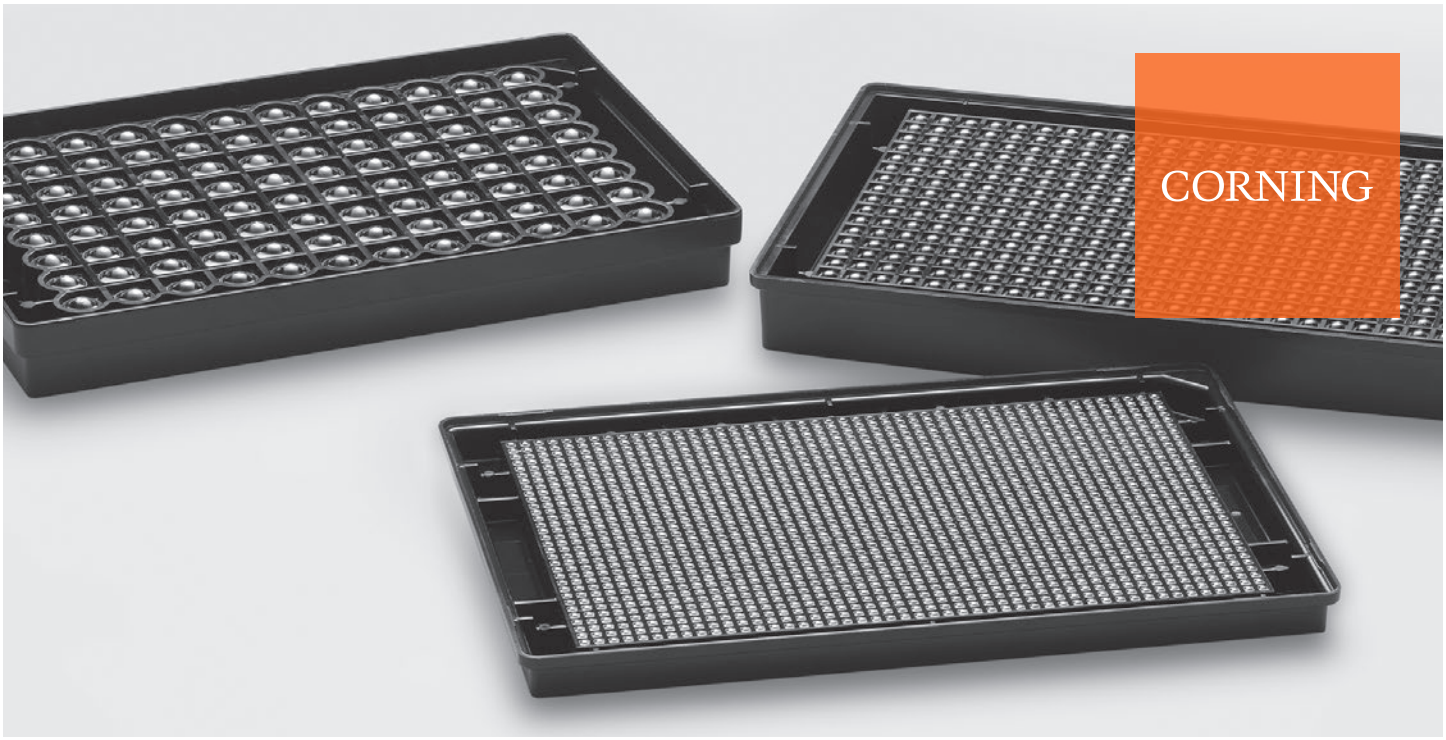

Citations on Corning® Spheroid Microplates with Ultra-Low Attachment Surface

Spheroids are organized and functional 3-Dimensional cell aggregates that better mimic the structure of cells in tissues compared to 2D cell culture. This characteristic makes spheroids a powerful tool to study more physiologically relevant cell behavior, resulting in more biologically relevant results.

2D versus 3D

The *in vivo*-like 3D structure of spheroids, in comparison with 2D cell culture, closely resembles the natural environment of cells.

1. **Mathews Griner LA, et al. Large-scale Pharmacological Profiling of 3D Tumor Models of Cancer Cells**

   Cell Death & Disease 7/12:e2492, 2016.

   In this study, the compound-induced pharmacologic responses of cells cultured in either in 2D or 3D were analyzed and the authors show the responses are crucially different between the culture methods, notably in the magnitude of their synergistic cytotoxic effects.

2. **Stock K, et al. Capturing Tumor Complexity *In Vitro*: Comparative Analysis of 2D and 3D Tumor Models for Drug Discovery**

   Scientific Reports, 6:28951, 2016.

   Choosing a proper model to conduct drug discovery can be challenging. The authors present a guide to select the most suitable *in vitro* model for specific assay types. Includes a review of three different cell carcinoma cell lines and methods for 3D cell culture.

3. **Senkowski W, et al. Large-Scale Gene Expression Profiling Platform for Identification of Context-dependent Drug Responses in Multicellular Tumor Spheroids**

   Cell Chemical Biology, 23:1428-1438, 2016.

   The combination of high throughput gene expression profiling with tumor spheroid-based drug-screening is a potent tool for identifying promising drug candidates. The authors highlight the necessity to implement gene expression profiling as a measure for cellular response profiles to evaluate and understand the effect of compounds. Using this approach, the authors identified a synergistic effect of two compounds on quiescent spheroids not detected in 2D monolayers. This illustrates the importance of using 3D cell culture and spheroids over 2D cultures.

4. **de Hoogt R, et al. Protocols and Characterization Data for 2D, 3D, and Slice-based Tumor Models from the PREDECT Project**

   Sci Data 4:170170, 2017.

   The PREDECT consortium presents a characterization of *in vitro* models of three different solid tumor types (2D, 3D and tumor slice models). Detailed protocols and procedures were developed for the three tumors and are presented in this work.

Drug Discovery

Spheroids enable to determine the efficacy and toxicity of a drug on human cells in a more *in vivo*-like context compared to traditional 2D cell cultures. This alignment of cellular models with pre-clinical animal models and patient tumors can accelerate the screening and evaluation of new drug candidate.

1. **Baek N, et al. Monitoring the Effects of Doxorubicin on 3D-Spheroid Tumour Cells in Real-Time**

   Onco Targets Ther. 9:7207-7218, 2016.

   In this work, 12 tumor cells lines were tested in a 3D-spheroid real-time culture assay model for the effects of doxorubicin, a known cytostatic drug. It was demonstrated that the degree of sensitivity against this drug in traditional 2D cultures was not observed in 3D cell cultures: IC_{50} values usually were higher compared to conventional culture. As drugs often exhibit variation in their effects on patients or animals compared to the 2D tissue culture results, the 3D models may help to better understand sensitivities and tolerances.

2. **Fryknas M, et al. Iron Chelators Target Both Proliferating and Quiescent Cancer Cells**

   Scientific Reports, 6:38343, 2016.

   The most common cancer drugs target the cell-cycle pathway. Quiescent cells, due to their nature, are thus more resistant to cancer drugs. In this study the authors have identified VLX600, an iron chelator, as potential compound for chemotherapy. The efficacy of the compound was evaluated by the survival rate of quiescent cells in a spheroid.

3. **Sirenko O, et al. Phenotypic Characterization of Toxic Compound Effects on Liver Spheroids Derived from iPSC Using Confocal Imaging and Three-Dimensional Image Analysis**

   Assay and Drug Development Technologies, 14:381-394, 2016.

   The authors developed a phenotypic assay read out for analyzing 3D model systems formed with human iPSC-derived hepatocytes. The effect of compounds was evaluated with the use of a confocal microscope scoring multi-parametric cellular information. This setup is suitable for high throughput screening to evaluate hepatotoxicity *in vitro*.

4. **Martinez NJ, et al. A High-Throughput Screen Identifies 2,9-Diazaspiro[5.5]Undecanes as Inducers of the Endoplasmic Reticulum Stress Response with Cytotoxic Activity in 3D Glioma Cell Models**

   PloS One, 11, e0166506, 2016.

   Cancer cells were shown to be more susceptible to stress of the endoplasmic reticulum, which results in apoptosis. The efficacy of small molecules to induce stress of the endoplasmic reticulum, which was, amongst others, analyzed by the survival rate of treated cells in spheroids.

5. **Hagemann J, et al. Spheroid-based 3D Cell Cultures Enable Personalized Therapy Testing and Drug Discovery in Head and Neck Cancer**

   Anticancer Research 37:2201-2210, 2017.

   Standardized chemotherapy shows varying response rates with unpredictable efficacy due to tumor heterogeneity and the different, individual mutations. Personalized tumor therapy can increase the efficacy of the treatment by addressing the specific characteristics of the patient's tumors. Therefore, the authors developed a model using spheroids subjected to standardized, high throughput *in vitro* assays in which spheroids were grown and analyzed for therapy susceptibility. The ultimate goal is to grow spheroids from patient cells and analyze the individual therapy susceptibility.

Fundamental Research

The microenvironment in spheroids mimics the *in vivo* physiology. Therefore, spheroids represent a valuable tool for research on the development and homeostasis of organs and tissues and provide crucial insights into the formation and structural composition of tumors.

1. **Sirenko O, et al. High-Content Assays for Characterizing the Viability and Morphology of 3D Cancer Spheroid Cultures**

   Assay Drug Dev Technol 13/7:402-414, 2015.

   Researchers use 96- or 384-well Ultra-Low Attachment surface-coated spheroid microplates for the generation of 3D spheroids from three different human tumor cell lines. They were able to demonstrate that these spheroids could be analyzed with high content imaging using low and high magnifications. The relevance of the model was confirmed by testing 119 known approved anticancer drugs on one of the cell lines.

2. **Comley J. Spheroids Rapidly Becoming a Preferred 3D Culture Format**

   Drug Discovery World Spring 2017, 31-49, 2017.

   In this article, several current approaches for 3D spheroid cultures, including Corning spheroid microplates, are reviewed and discussed.

3. **Molla A, et al. Unsuccessful Mitosis in Multicellular Tumor Spheroids**

   Oncotarget 25/8:28769-28784, 2017.

   Binucleated cells, originating from unsuccessful mitosis, are frequently observed in human tumors. The authors of this article demonstrate that certain human tumor cells, cultured as spheroids in 3D, also exhibit unsuccessful mitosis. However, these multicellular tumor spheroids remain sensitive to certain mitotic drugs. In conclusion, multicellular tumor spheroids can be used as a relevant model for drug testing.

4. **Senkowski W. High-throughput Screening Using Multicellular Tumor Spheroids to Reveal and Exploit Tumor-specific Vulnerabilities**

   Doctoral Thesis, Uppsala: Acta Universitatis Upsaliensis, p.50, 2017.

   Senkowski describes in his online-published Ph.D. thesis the use of multicellular tumor spheroids, containing both proliferating and quiescent cells, for more consistent drug testing and screening when compared to conventional two-dimensional tissue culture models. In particular, this work demonstrates that previously unknown tumor-specific vulnerabilities can be detected using the more *in vivo*-like 3D model.

5. **Kota S, et al. A Novel Three-Dimensional High-throughput Screening Approach Identifies Inducers of a Mutant KRAS Selective Lethal Phenotype**

   Oncogene, 2018.

   The authors demonstrate the necessity of evaluating potential drugs in the 3D cell environment. Spheroids were generated of isogenic cell lines in which genes of the RAS proteins were mutated. RAS proteins play an important role in the extra-cellular-intracellular signaling pathways and are found to be commonly mutated in cancer. Spheroids were subjected to Proscillaridin A, which was identified as selective inhibitor of cells in which the RAS protein KRAS was mutated. The discovery of Proscillaridin A would have been missed out if the efficacy would have been tested in standard 2D culturing methods.

6. **Madoux F, et al. A 1536-well 3D Viability Assay to Assess the Cytotoxic Effect of Drugs on Spheroids**

   SLAS Discovery: Advancing Life Sciences R & D, 22:516-524, 2017.

   In this work the authors from the SCRIPPS Institute investigate the cytotoxic effects of about 3,300 drug compounds in a 3D assay using spheroids which were generated in a 1536-well microplate custom designed by Corning. The plate features an Ultra-Low Attachment surface which allowed for the parallel formation, measurement of size as well as viability testing of the spheroids in a robust and reproducible manner.

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- 1536-well spheroid microplate with Ultra-Low Attachment surface (Corning Cat. No. 4527)

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