Citations on Corning® Matrigel® Matrix and Organoid Culture

In recent years, organoid cultures in Corning Matrigel Matrix have developed into a powerful new tool for basic research and drug discovery. In particular, 3D organoids cultured from tumor-patient-derived cells potentially will drive drug discovery towards more *in-vivo* like models and personalized medicine. The selection below highlights some of the recent publications in which Matrigel matrix was used.

1. **Intestinal Epithelial Tuft Cells Initiate Type 2 Muosal Immunity to Helminth Parasites**

   Gerbe F, et al. Nature 529(7585):226-230, 2016.

   This work aims to understand host defense mechanisms against parasite helminths. By employing organoid cultures from mouse intestinal crypts using Matrigel matrix, the data indicates that in the absence of tuft cells, IL-25 and IL-13 expressions remain low. Type 2 mucosal responses and worm expulsion are also delayed. This indicates a critical function of tuft cells in initiating mucosal type 2 responses following infection with helminths through IL-25 secretion.

2. **Organoid Cultures for the Analysis of Cancer Phenotypes**

   Sachs, N and Clevers H. Curr Opin Genet Dev. 24:68-73, 2014.

   This paper outlines a comprehensive overview on the benefits and drawbacks of cancer models utilizing cancer cell lines and primary patient-derived tumor xenografts, and proposes primary patient derived organoids as the preclinical cancer model suitable for high-throughput screens.

3. **Organoid Models of Human and Mouse Ductal Pancreatic Cancer**

   Boj SF, et al. Cell 160(1-2):324-338, 2015.

   Organoid models from normal and neoplastic murine and human pancreas tissues were used to investigate pancreatic ductal adenocarcinoma pathogenesis using Corning Growth Factor Reduced Matrigel matrix. To overcome the challenges associated with the isolation of ductal fragments, digested material was directly embedded into Matrigel matrix and cultured using conditioned media. This approach resulted in isolation efficiency of 75% to 80% for human normal organoids. Organoids derived from these tissues survived cryopreservation and exhibited ductal- and disease stage-specific characteristics. This work established pancreatic organoids as a tractable and transplantable system to identify molecular pathways that correlate with disease progression in mice and humans, and that represent therapeutic and diagnostic opportunities.

4. **Long-Term Culture of Genome-Stable Bipotent Stem Cells from Adult Human Liver**

   Huch M, et al. Cell 160(1-2):299-312, 2015.

   This work describes culture conditions for long-term expansion of adult bile duct-derived progenitor cells from human liver. Researchers demonstrate that primary human bile duct cells can readily be expanded *in vitro* as bipotent stem cells into 3D organoids using Corning Matrigel matrix. These cells were able to differentiate into functional hepatocyte cells *in vitro* and generate bona fide hepatocytes upon transplantation. Organoids cultured *in vitro* demonstrated genetic stability. The expanded cells preserve their genetic integrity over months in culture. Overall, the results open up experimental avenues for toxicology studies, gene therapy, regenerative medicine, and liver disease modeling.

5. **Prospective Derivation of a Living Organoid Biobank of Colorectal Cancer Patients**

   van de Wetering M, et al. Cell 161(4):933-945, 2015.

   3D organoid cultures derived from healthy and tumor tissue from colorectal cancer patients were successfully generated using Basement Membrane Extract (BME). Organoids generated were expanded and frozen to create a master cell bank. Upon thawing, cell survival was typically >80%. Using high throughput drug screening these organoids were assessed to identify clinically relevant biomarkers. This study has opened up avenues for further investigation of drug sensitivity in colorectal carcinoma.

6. **Creation of Engineered Cardiac Tissue *In vitro* From Mouse Embryonic Stem Cells**

   Guo XM, et al. Circulation, 113(18):2229-2237, 2006.

   In this study, researchers produced engineered spontaneously contracting cardiac tissue constructs *in vitro* from the mouse embryonic stem (ES) cell-derived cardiomyocytes in the presence of type I collagen supplemented with Matrigel matrix. Data indicate that engineered cardiac tissue resemble both structurally and functionally to neonatal native cardiac muscle. Results suggest that ES cells can be used as a source for cardiac muscle tissue engineering for potential cardiovascular disease therapy.

7. **Direct Transfection of Clonal Organoids in Matrigel Microbeads: A Promising Approach toward Organoid-Based Genetic Screens**

   Laperrousaz B, et al. Nucleic Acids Res, gky030, 2018. [Epub ahead of print].

   To overcome the challenges associated with direct 3D transfection on already formed organoids, a novel approach for transgene expression in 3D organoids was used in this study. Researchers combined automatic generation of microencapsulated organoids in Corning Matrigel matrix microbeads with electroporation. Results demonstrate improved siRNA transfection efficiency in 3D organoids by modulating microbead size and Matrigel matrix concentration. Reduced amounts of Matrigel matrix and direct electroporation of encapsulated organoids showed up to 80% transfection efficiency in RWPE-1 organoids. This setup is more cost effective than traditional 3D culture as it requires two to three times less Matrigel matrix to obtain the same amounts of organoids. This approach opens up new perspectives to study tissue development and tumorigenesis as well as applications in fundamental research and organoid/spheroid-based drug assays.

8. **Oncogenic b-Catenin and PIK3CA instruct Network States and Cancer Phenotypes in Intestinal Organoids**

   Riemer P, et al. J Cell Biol 216(6):1567-1577, 2017.

   In this study organoids from mouse small intestine were cultured in Corning Matrigel matrix and used to study cooperation of oncogenic Wnt–β-catenin and PI3K activities. By using a panel of pharmaceutical inhibitors in combination with phenotypic assays and phosphoprotein profiling, this work demonstrates that survival and motility of organoid cells are associated with 4EBP1 and AKT phosphorylation. Data supports transgenic intestinal organoid as a tool towards the understanding oncogene activities and opportunities for the development of targeted therapies.

9. **Biofabrication Enables Efficient Interrogation and Optimization of Sequential Culture of Endothelial cells, Fibroblasts and Cardiomyocytes for Formation of Vascular Cords in Cardiac Tissue Engineering**

   Iyer RK, et al., Biofabrication. 2012 September; 4(3):035002. doi:10.1088/1758-5082/4/3/035002.

   In this study, researchers tested the hypothesis that first seeding the endothelial cells (ECs) on Matrigel matrix and then fibroblasts (FBs) 24 hours later to stabilize the endothelial network would enhance vascular cord formation in engineered cardiac organoids. Data supports that sequential preculture of ECs prior to FBs and cardiomyocytes (CMs) promoted vascular cord formation on Matrigel matrix-coated poly(ethylene glycol) microchannels and enhanced architecture and contractile function of engineered heart tissues. The 8% EC group developed into functional cardiac organoids with excitation threshold comparable to organoids engineered using CMs and the whole heart cell isolates. This work suggests sequential preculture with 8% ECs may support engineering heart tissues that can enhance the vascularization potential of the tissue besides resembling characteristics of native myocardium.

10. **The Use of Murine-derived Fundic Organoids in Studies of Gastric Physiology**

    Schumacher MA, et al. J Physiol 593(8):1809-1827, 2015.

    Gastric fundic-derived organoid cultures were used to investigate the expansion of fundic stem cells and maintenance of mature cell lineages of the fundus. Organoids maintained in Matrigel matrix and gastric organoid growth medium were proliferative and expressed high levels of stem cell markers CD44 and Lgr5. Gastric organoids co-cultured with immortalized stomach mesenchymal cells express mature cell lineages that include surface mucous pit, mucous neck, chief, endocrine, parietal, and CD44/Lgr5+ cells. Results support the feasibility of using fundic gastric organoids for the study of gastric physiology and disease.

11. **Biphasic Electrical Field Stimulation Aids in Tissue Engineering of Multicell-type Cardiac Organoids**

    Chiu LL, et al. Tissue Eng Part A, 17(11-12):1465-1477, 2011.

    The effects of monophasic or biphasic electrical field stimulation on structure, function, and electrical excitability of engineered cardiac organoids (from enriched cardiomyocytes) was investigated. Organoids resembling cardiac myofibers were cultured on Matrigel matrix-coated microchannels fabricated of poly(ethylene glycol)-diacrylate. Data support that biphasic electrical field stimulation during cultivation resulted in the improved functional and structural properties of cardiac organoids. Furthermore, biphasic stimulation was also effective at improving electrical excitability of cardiac organoids based on mixed cell populations (fibroblasts, endothelial cells, and cardiomyocytes) by improving the three-dimensional organization of the cells, increasing cellular elongation and increased expression of Connexin-43.

12. **Epithelial Cell-Specific Raptor is Required for Initiation of Type 2 Mucosal Immunity in Small Intestine**

    Aladegbami B, et al. Sci Rep 7(1):5580-5589, 2017.

    Using Matrigel matrix for organoid culture of intestinal epithelium tuft cells, this study demonstrates enterocyte-specific Raptor is required for initiating a type 2 immune response to parasite infection which appears to function through the regulation of mTORC1 activity.

13. **Three-Dimensional Gastrointestinal Organoid Culture in Combination with Nerves or Fibroblasts: A Method to Characterize the Gastrointestinal Stem Cell Niche**

    Pastula A, et al. Stem Cells Int., Article ID 3710836, 16 pages, 2016.

    Researchers highlight the modification and establishment of three distinct 3D culture methods (organoid culture, multilayered systems such as organotypic cell culture and culture of intestinal tissue fragments *ex vivo*) that can be used to analyze the role and function of different stem cell niche components *in vitro*. Differentiated as well as proliferative zones could be distinguished in small intestinal organoids cultured in Matrigel matrix. Differentiated cells showed a monolayer of polarized columnar epithelial cells, presence of lumen, and secretion of mucus into the lumen. Cells with proliferative activity were accumulated in areas where buds grew. Moreover, small intestinal organoids expressed Lgr5, which is a marker of intestinal stem cells. Overall, studies indicate these 3D culture methods mimic the *in vivo* physiological state of intestinal crypts.

14. **Assay Establishment and Validation of a High-Throughput Screening Platform for Three-Dimensional Patient-Derived Colon Cancer Organoid Cultures**

    Boehnke K, et al. J Biomol Screen 21(9):931-941, 2016.

    This study shows the establishment of primary organoid cultures from patient-derived colon cancer cells using Corning Growth Factor Reduced Matrigel matrix, and validation as an automated drug sensitivity platform. Complex 3D structures were formed from single cells in 384-well microplates with regular organoid morphogenesis. The results demonstrate the feasibility of using patient-derived tumor samples as disease-specific human models for high-throughput technologies in the drug discovery pipeline.

15. **Six-Month Cultured Cerebral Organoids from Human ES Cells Contain Matured Neural Cells**

    Matsui TK, et al. Neurosci Lett. 670:75-82, 2018.

    In this study, cerebral organoids induced from H9 human embryonic stem cells were cultured in Corning Growth Factor Reduced Matrigel matrix. Established cerebral organoids were cultivated for up to six months to study the effects of extended culture on these organoids. Results indicate the presence of matured oligodendrocytes, as well as functionally differentiated neurons in long-term human cerebral organoid cultures. These findings highlight the possibility of human cerebral organoids for research of human brain development and various demyelinating diseases.

16. **Prostaglandin E2 Supports Growth of Chicken Embryo Intestinal Organoids in Matrigel Matrix**

    Pierzchalska M, et al. Biotechniques 52(5):307-315, 2012.

    Organoid formation from adult mouse intestinal epithelial cells require the use of serum-free medium supplemented with epithelial growth factor, Wnt agonist (R-spondin 1), and bone morphogenetic protein inhibitor (Noggin), which may limit use of the model in long-term or large-scale industrial and laboratory applications due to substantial increase in cost. This work demonstrates the feasibility to use chicken embryonic intestinal cells to create an organoid culture using Corning Matrigel matrix with a modified protocol. Prostaglandin E2 in the medium was as effective as R-spondin 1 in supporting the growth of organoids in Matrigel matrix thus providing a cost-effective alternative to R-spondin 1 and Noggin treatment. Organoids formed in Matrigel matrix show the appearance of empty spheres and comprise cells expressing intestinal cell markers cytokeratin, villin, and Sox-9. Long-term culture confirmed that epithelial spheroids remained viable and visible in Matrigel matrix after 5 weeks. This application opens up new perspectives for studies on avian gut physiology and new ways to investigate mechanisms of drugs and feed absorption.

17. **Modeling Pancreatic Cancer with Organoids**

    Baker LA, et al. Trends Cancer 2(4):176-190, 2016.

    This review outlines methods for modeling pancreatic ductal adenocarcinoma models using organoids cultured in Matrigel matrix. As each model system has unique benefits and drawbacks, in the end, organoids provide valuable insights for the development of personalized medicine.

18. **Organoid Culture of Human Prostate Cancer Cell Lines LNCaP and C4-2B**

    Ma L, et al. Am J Clin Exp Urol. 5(3):25-33, 2017.

    The present study demonstrates that LNCaP and C4-2B cells formed organoids in Corning Growth Factor Reduced, Phenol Red Free Matrigel matrix and defined culture conditions. Organoids contained luminal adenocarcinoma cells but not basal cells that express p63. The cells in the organoids responded to interleukin-17A treatment differently compared to cells in the monolayer culture.

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CORNING

Corning Incorporated
Life Sciences
836 North St.
Building 300, Suite 3401
Tewksbury, MA 01876
t 800.492.1110
t 978.442.2200
f 978.442.2476
www.corning.com/lifesciences

ASIA/PACIFIC

Australia/New Zealand
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Singapore
t 65 6572-9740
f 65 6861-2913

Taiwan
t 886 2-2716-0338
f 886 2-2516-7500

EUROPE
CSEurope@corning.com

France
t 0800 916 882
f 0800 918 636

Germany
t 0800 101 1153
f 0800 101 2427

The Netherlands
t 020 655 79 28
f 020 659 76 73

United Kingdom
t 0800 376 8660
f 0800 279 1117

All Other European Countries
t +31 (0) 206 59 60 51
f +31 (0) 206 59 76 73

LATIN AMERICA
grupoLA@corning.com

Brasil
t 55 (11) 3089-7400

Mexico
t (52-81) 8158-8400