Human-Derived Hydrogel in a PDX Model

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Abstract

Xenograft and allograft models using homologous cell lines have been used for several years in small animals for preclinical cancer research. However, these methods lead to high variability in tumor formation, engraftment, and growth. They lack some of the key structural requirements for eliciting a response that mimics the original tumor within the host, and they can be incredibly expensive. Orthotopic and heterotopic models have been deployed to overcome some of these challenges. Matrigel® from Corning, Cultrex® from Bio-Techne, and Geltrex™ from Life Technologies are hydrogels produced from Engelbreth-Holm-Swarm (EHS) mouse sarcoma basement membrane extract (BME). As mouse tumor-derived materials, they present several challenges to the development of a consistently performing and clinically relevant, human-based tumor growth model *in vivo*. Herein we describe ObaGel®, a human blood-derived hydrogel that has been successfully deployed for supporting 3D cell culture, organoid, and microphysiological system development for studying obesity, type II diabetes, and various forms of related cancers. ObaGel gels at 37°C within 15 minutes and performs similarly in supporting tumor volume when compared to Cultrex, Geltrex, and Matrigel in a PDX model of lung adenocarcinoma.

Problem Statement

There is a need for a replacement for animal-derived matrices for supporting innovative, human-relevant tumor models for therapeutic development.

Background

Xenograft and allograft models using homologous cell lines have been used for several years in small animals for preclinical cancer research. These methods lead to high variability in tumor formation, engraftment, and growth. They lack some of the key structural requirements for eliciting a biochemical and biophysical response that mimics the original tumor within the host, and they can be incredibly expensive, due to the need for large sample sizes of animals per treatment arm. Orthotopic and heterotopic models have been deployed to overcome some of these challenges. To this end, 3-dimensional hydrogels have been developed to support these robust tumor models that more accurately mimic tumorigenesis in small-animals. These models also have the advantage

of providing a platform for observing cell-cell and cell-matrix interactions of the native microenvironment (Sayde, et. al.).

Synthetic hydrogels, such as those using alginate and calcium (Grosskopf et. al.), have been used to study cancer in mouse models. Some of these synthetic hydrogels claim to possess easily tunable mechanical properties and low lot-to-lot variability. However, some are nonbiodegradable and have shown poor biocompatibility, with a disadvantage of inducing unwanted pro-inflammatory responses. Moreover, the complex tissue architecture of ECM-derived hydrogels promotes an environment that more closely recapitulates that of a living organism (Sayde et. al.).

Natural hydrogels can be derived from both animal and human sources. Popular animal-derived hydrogels are made from murine tissue and mainly consist of collagen. Matrigel® from Corning®, Cultrex® from Bio-Techne, and Geltrex™ from Life Technologies are hydrogels produced from Engelbreth-Holm-Swarm (EHS) mouse sarcoma basement membrane extract (BME). They contain many extracellular matrix proteins such as collagen IV, nidogen, entactin, laminin, and heparin. These products can mimic the stiffness of human tissues and can be degraded by cell mediated proteases such as matrix metalloproteinases for cell retrieval (Caliari et. al.). Yet Matrigel, the market leader, is known to suffer from lot-to-lot inconsistencies, gelation below room temperature, and the expression of tumor-derived xenoproteins. As a result, these products are not amenable to clinical applications. A study by Soofi, et. al., showed that the stiffness of Matrigel differed greatly between multiple lots with the elastic modulus ranging from 400-840 Pa. The literature suggests that these discrepancies are caused by the nature of Matrigel to gel inconsistently at temperatures below 37ºC. There is also a greater risk of contamination in cell cultures when using animal by-products.

Solution

Obatala Sciences™ manufactures a human blood-derived hydrogel called ObaGel®. This product has been successfully deployed for supporting 3D cell culture, organoid, perfusion bioreactor, and microphysiological system development for studying obesity, type II diabetes, and various forms of related cancers. ObaGel gels at 37°C within 15 minutes, has over 100mg/mL protein content, and performs similarly in supporting tumor volume when compared to Cultrex, Geltrex, and Matrigel in a PDX model of lung adenocarcinoma. The stiffness and protein concentration of ObaGel can be modified with the addition of the companion product and activation agent, ObaVate™. In 3D, the gel, in combination with the activation agent will provide a multi-protein matrix that is rich in cytokines and growth factors that promotes healthy proliferation and differentiation of stem cells, whether primary or immortalized as cell lines. ObaGel is easy to work with prior to gelation and has shown promising results with stromal/stem cell growth in 3D for more than 40 days. The platform can also be adapted for use as a xenograft for implantation in an animal model.

Conclusion

When compared to Cultrex, Geltrex, and Matrigel, ObaGel® performed similarly in terms of engraftment and tumor kinetics using a patient-derived xenograft culture of lung adenocarcinoma. These data show that human-derived ObaGel performs equivalently to BME derived hydrogel competitors in terms of tumor volume over time when used *in-vivo*.

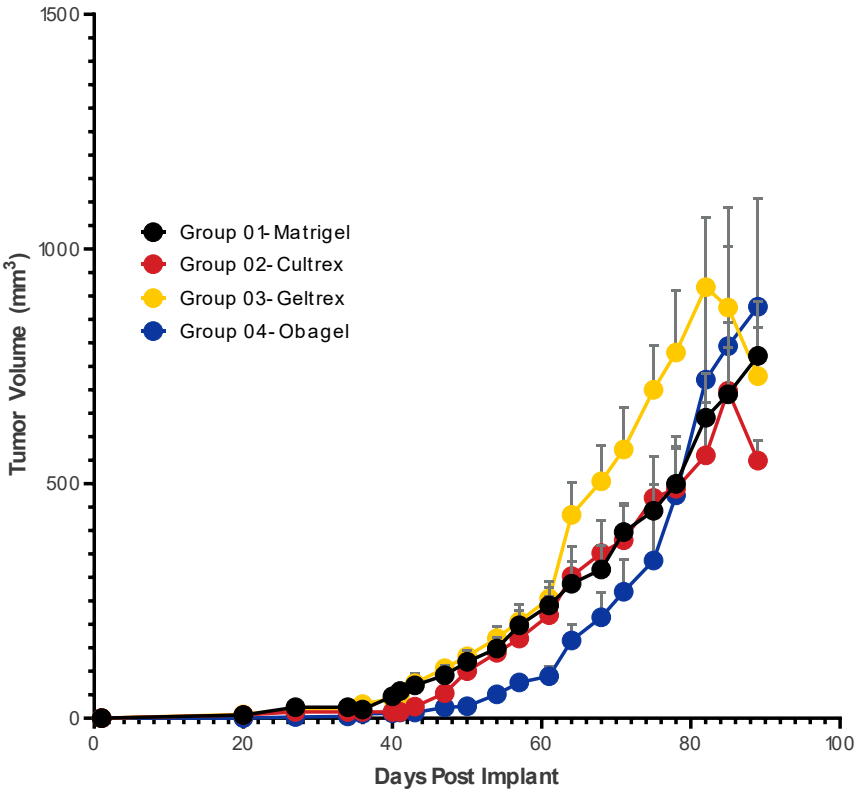

Figure 1: Comparison between Tumor volume growth of CRT_295 Lung Adenocarcinoma 3 x 10^6 cells per injection site, 100 ul of 50:50 Gel:PBS, n=10 between Matrigel, Cultrex, Geltrex, and ObaGel/ObaVate mixture (3:1)

References

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