Validated DMS273 Xenograft Model:

Subcutaneous, Metastatic, And Orthotopic Xenograft Tumor Model

By Altogen Labs, 11200 Menchaca Road, Suite 203, Austin, TX 78748
Phone: (512) 433-6177 | Email: info@altogenlabs.com

Advancing Lung Cancer Research Through Xenograft Models

Lung cancer is one of the leading causes of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) being the two main subtypes. Despite advances in early detection and treatment, the prognosis for lung cancer patients remains poor, particularly for those diagnosed at advanced stages or who develop resistance to chemotherapy. Xenograft models, where human cancer cells or tissues are implanted into immunocompromised mice, are used to mimic human tumor behavior more accurately than traditional cell culture systems, allowing researchers to study tumor progression, metastasis, and therapeutic responses *in vivo*. By using xenografts, scientists can evaluate the efficacy of novel drugs, test combination therapies, and explore mechanisms of drug resistance. Lung cancer xenografts, in particular, provide valuable insights into the biological complexity of the disease and are critical for the development of targeted treatments. These models continue to play a pivotal role in advancing our understanding of lung cancer and improving clinical outcomes for patients.

DMS273 Cell Line

The DMS273 cell line was established in 1978 from a pleural fluid specimen obtained from a 50-year-old female patient diagnosed with small cell carcinoma of the lung and had relapsed following chemotherapy and radiotherapy. DMS273 cells are characterized by their tumorigenic properties and are capable of forming tumors when implanted in immunocompromised nude mice, making them a useful model for preclinical studies of cancer biology and therapeutic responses. The cell line exhibits intercellular processes, which are often observed in aggressive cancer types. Additionally, DMS273 cells express both retinoblastoma mRNA and protein, which is significant in understanding cell cycle regulation and the role of the retinoblastoma protein in cancer progression. As a result, DMS273 is an important resource for studying small cell lung cancer, as well as for evaluating novel cancer treatments, including those targeting the cell cycle. Researchers also utilize this cell line to investigate the mechanisms behind chemotherapy resistance and relapse in lung cancer patients.

Altogen Labs Validated DMS273 Xenograft Model

DMS273 cells are maintained in the exponential growth phase under aseptic conditions, with cell viability assessed using flow cytometry, MTT, or trypan blue exclusion assays, ensuring a minimum of 98% viability. The cell suspension is adjusted to the appropriate density before each mouse is injected subcutaneously with 10^6 cells in 100-150 µL of a Matrigel-DMS273 cell mixture into the right flank. Tumor growth is monitored by palpation up to three times per week until tumors reach an average size of 50-100 mm³, measured using digital calipers. The animals are then randomized into treatment groups, and the test compound is administered according to the established schedule. Mouse weights are recorded three times weekly, and tumor size is monitored and documented daily. The study concludes when tumor size reaches 2,000 mm³ or the predetermined size limit, in accordance with the approved IACUC protocol. At study termination, necropsy and tissue collections are conducted for downstream analysis. Tumors are excised, weighed, and digitally imaged, with tissues preserved in

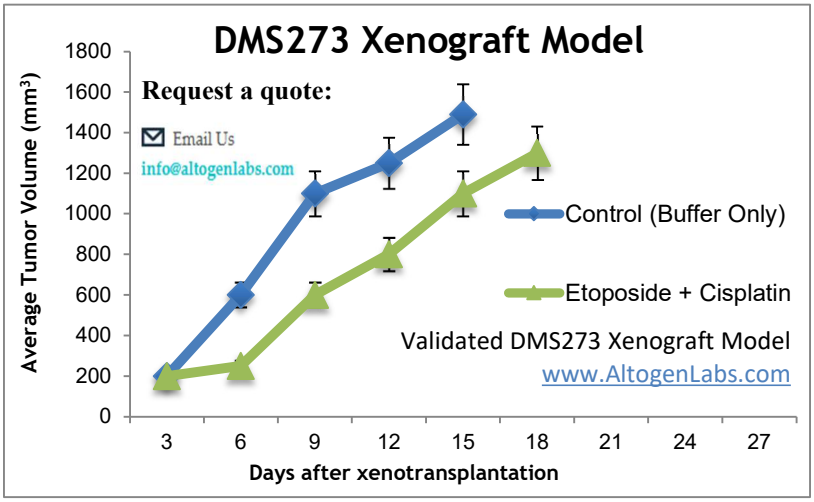

Figure 1. DMS273 small cell lung carcinoma xenografted in immunocompromised mice, mean values +/- SEM (Altogen Labs).

RNAlater, snap-frozen in liquid nitrogen, or prepared for histological examination.

Disrupting Nucleotide Metabolism in SCLC

The DMS273 cell line serves as a crucial model in understanding tumor progression and treatment responses in SCLC. Research shows that targeting ribonucleotide reductase subunit M1 (RRM1), a key enzyme in deoxyribonucleotide synthesis, significantly reduces the growth of DMS273 cells both *in vitro* and *in vivo*. Knockdown of RRM1 in these cells leads to DNA damage accumulation, S-phase cell cycle arrest, and impaired tumor growth in xenograft models. Furthermore, metabolic profiling of DMS273 cells revealed that disrupting nucleotide biosynthesis alters key metabolic pathways, potentially exposing new therapeutic vulnerabilities. These findings suggest that RRM1 and deoxyribonucleotide metabolism play a vital role in SCLC progression, making them promising targets for novel treatment strategies. Understanding the metabolic dependencies of SCLC, as demonstrated in DMS273, could pave the way for improved therapeutic interventions aimed at overcoming drug resistance and reducing tumor aggressiveness.

Exploring Tumor Progression and Treatment Responses with the DMS273 Subcutaneous Model

The DMS273 subcutaneous model involves the implantation of DMS273 cells, a human-derived cancer cell line, into the subcutaneous tissue of immunocompromised mice. The tumor growth in this model mimics the characteristics of human breast tumors, making it a valuable tool for evaluating therapeutic efficacy, including targeted therapies, chemotherapies, and immunotherapies. It provides insights into tumor progression, metastasis, and the impact of specific genetic mutations on cancer behavior. Additionally, the model allows researchers to assess the pharmacokinetics and pharmacodynamics of drug candidates *in vivo*. The subcutaneous location of the tumor makes it easy to monitor tumor size and evaluate responses to treatment through non-invasive imaging techniques, providing a reproducible and efficient system for preclinical cancer research. Overall, the DMS273 subcutaneous model is an essential tool for advancing our understanding of cancer biology and developing novel therapeutic strategies.

DMS273 Orthotopic Model Mimics Human SCLC

The DMS273 orthotopic model is a preclinical system designed to study small cell lung cancer (SCLC) progression and metastasis in a physiologically relevant setting. In this model, DMS273 cells are implanted directly into the lungs of immunocompromised mice, allowing for tumor growth within the native tumor microenvironment. The DMS273 orthotopic model serves as a valuable tool for evaluating novel therapies, studying tumor-microenvironment interactions, and understanding mechanisms of SCLC metastasis. This model is particularly useful for testing targeted treatments aimed at limiting tumor growth and overcoming therapy resistance.

DMS273 Metastatic Model: Studying SCLC Metastasis

The DMS273 metastatic model is a preclinical xenograft system used to study the metastatic progression of small cell lung cancer (SCLC). In this model, DMS273 cells, a human-derived SCLC cell line, are implanted into immunocompromised mice through orthotopic transplantation into the lungs. This setup allows the tumor to replicate the metastatic behavior observed in human SCLC, with secondary tumors forming in distant organs such as the bone, brain, lymph nodes, kidney, and adrenal gland. A GFP-labeled subline, G3H, derived from a bone metastasis, exhibits enhanced metastatic potential, highlighting the role of the HGF/MET signaling pathway in promoting invasion and survival. Pharmacological inhibition of the MET receptor has been shown to significantly reduce distant metastases, underscoring the therapeutic potential of targeting this pathway. The DMS273 metastatic model provides a valuable tool for evaluating therapies aimed at halting metastasis and exploring the underlying mechanisms of disease spread. It also offers an opportunity for drug testing that addresses both primary tumor growth and metastatic dissemination.

Case Study: Targeting HGF/MET in DMS273 Enhances Anti-Metastatic Therapy in SCLC

A study conducted by Nagel R, *et al.*, published by *Molecular Cancer Therapeutics* journal introduces a novel metastatic model of small-cell lung cancer (SCLC) using the human DMS273 cell line, which was orthotopically transplanted into nude mice. The GFP-labeled DMS273 cells displayed significant metastatic activity, forming lesions in distant organs such as bone, kidney, and brain, mirroring clinical SCLC metastasis. A highly metastatic subline, G3H, was derived from a bone metastasis, exhibiting increased hepatocyte growth factor (HGF) expression, which promoted cell motility and invasion via the HGF/MET signaling pathway. Pharmacological inhibition of MET using PHA665752 and ARQ-197 significantly reduced metastatic spread, validating the role of HGF/MET in SCLC progression. Importantly, DMS273-GFP and G3H cells retained sensitivity to cisplatin, but metastasis incidence was notably reduced upon treatment, suggesting the model's

utility in evaluating metastatic interventions. This model outperforms previous SCLC models in replicating distant metastasis, making it a valuable tool for investigating novel therapies targeting SCLC dissemination.

Additional Case Study: DMS273 Tumors and Therapeutic Approaches

DMS273 is a highly aggressive small-cell lung cancer (SCLC) subtype known for its rapid proliferation and metastatic potential. In a study by Szot C, *et al.*, published by *Journal of Clinical Investigation*, researchers explored the efficacy of a novel antibody-drug conjugate (ADC) targeting TEM8, a protein broadly expressed in tumor stroma, including fibroblasts, endothelium, and pericytes. DMS273 tumors responded significantly to TEM8-ADC therapy, leading to tumor regression and, in some cases, complete eradication. The ADC selectively delivered a potent cytotoxic payload to the tumor microenvironment, exploiting the unique stromal composition of SCLC. Notably, the TEM8-ADC demonstrated superior antitumor activity against DMS273 compared to other treatments, highlighting its potential as a targeted therapy for aggressive lung cancers. Additionally, genetic disruption of TEM8 in DMS273 cells reduced ADC effectiveness, confirming TEM8's role in mediating drug response. Importantly, TEM8-ADC therapy was well tolerated in preclinical models, with minimal systemic toxicity. These findings underscore TEM8 as a promising therapeutic target for treating metastatic SCLC, particularly in highly invasive subtypes like DMS273.

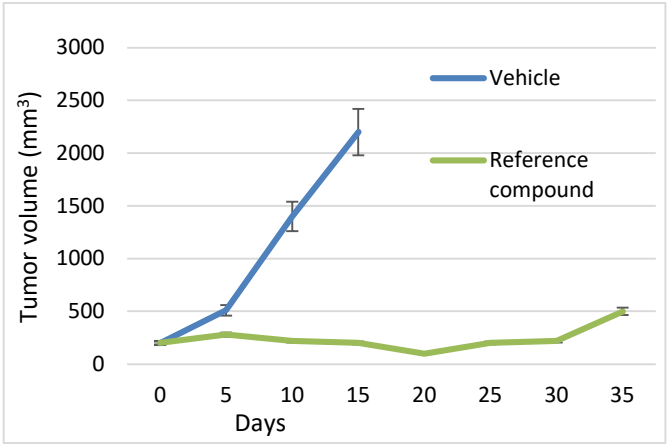

Figure 2. The reference compound (10 mg/kg) successfully induced regression of DMS273 tumors.

DMS273 SCLC Model: Uncovering Oncogenic Drivers and Metastatic Potential

DMS273 is a highly aggressive variant of small-cell lung cancer (SCLC) characterized by its rapid proliferation, high metastatic potential, and dependence on oncogenic signaling pathways such as c-MYC and HGF/MET. Unlike classic SCLC subtypes, DMS273 exhibits enhanced motility and invasion, leading to frequent metastases in vital organs, including the bone, brain, and kidney. The overexpression of c-MYC in DMS273 contributes to uncontrolled cell growth, metabolic reprogramming, and resistance to standard therapies. Additionally, its autocrine activation of the HGF/MET pathway further amplifies its invasive properties, making it a challenging target for treatment. Studies using orthotopic transplantation models have demonstrated that DMS273 faithfully recapitulates the metastatic behavior observed in SCLC patients, making it a valuable model for drug discovery. Notably, while DMS273 retains some sensitivity to cisplatin, its metastatic dissemination remains a major obstacle, necessitating novel therapeutic strategies. Targeted inhibitors of MET and c-MYC have shown promise in preclinical studies, highlighting the importance of disrupting these key oncogenic drivers. Understanding the molecular mechanisms governing DMS273's aggressive phenotype will be crucial in developing more effective treatment options for SCLC.

Patient-Derived Tumor Organoids in Advancing Cancer Drug Testing

Organoids are three-dimensional in vitro cultures derived from patient tumor samples that preserve key characteristics of the original tumor, including genetic and phenotypic diversity. Unlike conventional 2D cell cultures, organoids retain complex tissue architecture and can be efficiently expanded from primary patient material, making them valuable for personalized cancer research and drug testing. While xenograft and allograft models provide tumor-stroma and immune interactions, organoids offer a faster, more scalable platform for evaluating therapeutic responses. Recent advancements in organoid technology have led to the creation of patient-derived tumor organoid (PDTO) biobanks, which serve as living resources for studying cancer progression and drug resistance. These models have proven particularly useful for high-throughput drug screening, enabling researchers to identify potential treatments tailored to individual tumor profiles.

The DMS273 xenograft model provides a versatile platform for investigating the biology of small cell lung cancer (SCLC) and evaluating potential therapies. At Altogen Labs, this model can be examined for tumor growth delay (TGD) and tumor growth inhibition (TGI) studies, allowing researchers to investigate a range of dosing regimens, including intravenous, intraperitoneal, intratumoral, subcutaneous, oral gavage, and intranasal administration, allowing for flexibility in experimental design. Immunohistochemical analysis of tumors can be performed to examine molecular markers, and

alternative engraftment sites such as orthotopic implantation, tail vein injection, or mammary fat pad injections can be used to explore tumor behavior and metastasis. Additional studies include survival analysis, blood chemistry profiling, and toxicity assessments, with gross necropsies and histopathological evaluations providing detailed insights into tumor morphology and treatment responses. The model is also suitable for advanced imaging techniques, such as fluorescence-based whole-body imaging, to track tumor progression non-invasively. A positive control group using cyclophosphamide (50 mg/kg, intramuscular) may be incorporated to validate treatment efficacy. The DMS273 xenograft model is a powerful and comprehensive tool for preclinical research on SCLC and other therapeutic strategies.

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