

Gastric Carcinoma

Introduction

Gastric carcinoma remains a common disease with a dismal prognosis. It represents the fourth most frequent malignancy and second leading cause of cancer-related death worldwide. A significant geographic variation exists with high-risk areas including Japan, Central and South America and Eastern Asia. Despite the major improvements in diagnosis and treatment, less than 20% of patients survive to 5 years. Chemotherapy and radiochemotherapy may be applied, but do not cure the disease. Thus, improvement of gastric cancer therapy will depend on novel therapeutic approaches.

Membrane-bound human epidermal growth factor receptors (HER), c-MET, and insulin-like growth factor 1 receptor (IGF-1R) mediated mitogenic signals have been implicated in gastric tumor growth in response to the extracellular ligands, such as epidermal growth factor (EGF), hepatocyte growth factor (HGF) and insulin growth factors (IGF), respectively. Clinical observations have also suggested that the organ environment can influence the tumor response to chemotherapy. Therefore, orthotopic implantation of human gastric cancer cells or tissues in nude mice is a more ideal model for evaluation of different anti-tumor therapies for the gastric cancers.



PharmaLegacy Models and research Tools

Gastric Cancer (GC) Models:

- * Human GC s.c. xenograft models in nude mice (MKN-45, NCI-N87, and AGS)
- * Human GC orthotopic implantation model (3 lines to choose)
- * Luciferase-reporter GC orthotopic implantation model (MKN-45-Luc, orthotopic growth and metastasis)
- * Human primary gastric tumors models in nude mice (s.c. xenograft or orthotopic implantation)

Model Characteristics:

- * AGS tumor grows slower than NCI-N87 and MKN-45 tumors subcutaneously and usually with no metastasis
- * Different tumor lines may present different responses to specific drug treatment
- * Orthotopic tumor in the stomach mimics the tissue microenvironment of GC progression in the patients and provides additional windows to examine both local and remote metastasis of GC malignancy
- * With luciferase reporter expression, MKN-45-Luc tumor growth and metastasis can be dynamically monitored with imaging system following the orthotopic inoculation

Tumor biology, biomarkers, and molecular pharmacology:

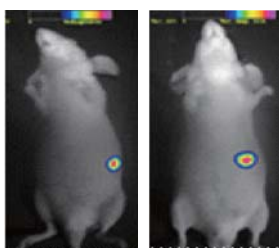
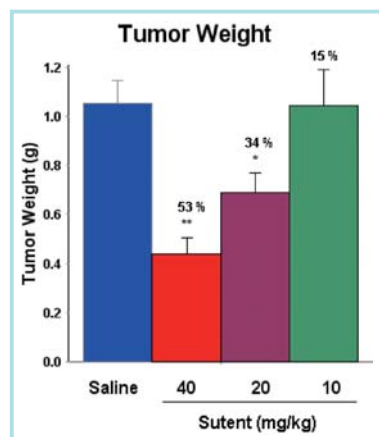
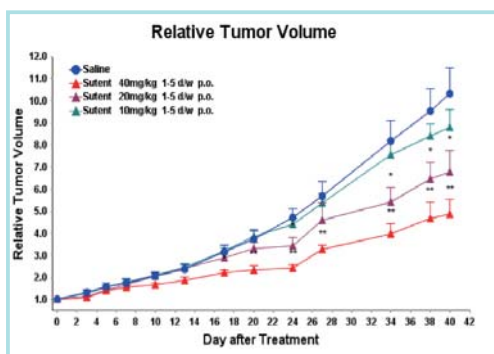
- * GF/cytokines/chemokines/biomarkers analysis (ELISA, RT-PCR)
- * Drug target levels (RT-PCR, ELISA, Western Blot)
- * Drug target activities (Kinase/phosphorylation)
- * Cell based assays (MTT, apoptosis and invasion in culture)

Tumor Histopathology:

- * Histology and immunohistochemistry (proliferation, apoptosis, angiogenesis)

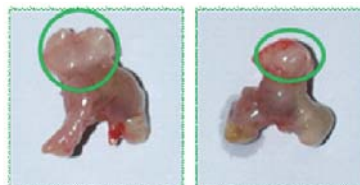
Case Study - Inhibition of Tumor Growth

Dose-dependent inhibition of NCI-N87 human GC growth by Sutent (s.c. xenograft)



MKN-45-Luc GC tumor growth at 1 week (left) and 3 weeks (right) following orthotopic inoculation in nude mice

5'-FU inhibition of MKN-45 GC tumor growth at 4 weeks following orthotopic inoculation in nude mice: Vehicle (left) and 5-FU (right), 20mg/kg, twice weekly).



In addition to the fully validated human GC subcutaneous xenograft mouse models, PharmaLegacy has established a number of orthotopic GC models in nude mice by continually improving the surgical skills for tumor implantation. With 100% success rate in surgical inoculation, these models provide clients with expert tools in the investigation of GC malignant behaviors, tumor interactions with local tissue and different strategies of intervention. Our special services can also be expanded to the evaluation of drug mechanism-of-action using in vitro tumor biology & ex vivo molecular pharmacology methods, providing an early proof-of-concept for early drug development candidates.

About PharmaLegacy Services

- World-class quality with increased speed and output at competitive cost.
- International GLP and QA-based operation.
- Electronic data management system (BioBook) for quality execution and maximum IP protection.
- AAALAC accredited large capacity to house over 10,000 animals under SPF and conventional conditions.
- Availability of 4,000 non-human primates for research use.