

Colorectal Carcinoma

Introduction

With 655,000 deaths worldwide per year, colorectal cancer (CRC) is the second leading cause of cancer-related death in Western society and the incidence and mortality are increasing dramatically in the rest of the world. Approximately 25% of patients have a family history of CRC, suggesting a genetic contribution, common exposures among family members or a combination of both. Other risk factors for CRC include diet, use of non-steroidal anti-inflammatory drugs (NSAIDs), postmenopausal hormone use, cigarette smoking, colonoscopy with removal of adenomatous polyps and physical activity. Two major molecular events are associated with the disease: chromosomal instability (CIN) is involved in about 85% of CRCs and microsatellite instability (MSI or MIN) in remaining 15%. For example, loss/mutations of APC gene, associated with CIN is one of the early events in the colorectal tumor progression and predisposition to colorectal tumors.

Great advances have been made in the treatment and prevention of advanced CRC in the past 20 years. Survival time has increased from 6 months to over 2 years. However, among patients diagnosed with metastatic colorectal cancer (mCRC), the 5-year survival rate is only 8% on average. Effective new drugs to arrest the progression or prevent the occurrence of CRC are very desirable. Great efforts have been paid to investigate the therapeutic effects of novel compounds using different CRCs and treatment strategies in animal models.



PharmaLegacy Models and Research Tools

CRC models:

- * Human CRC subcutaneous xenograft models in nude mice (HCT-116, HT-29, COLO205, HCT-15)
- * Human CRC orthotopic implantation models in nude mice
- * Human primary CRC models in nude mice (7 tumors, subcutaneous xenograft or orthotopic model)
- * Luciferase-reporter based CRC imaging model (orthotopic growth and metastasis, HT-29-Luc)

Model characteristics:

- * Metastasis is rare in subcutaneous xenograft tumor models
- * Different tumor lines may respond differently to specific drug treatment
- * Orthotopic tumor models recreate human CRC with a similar microenvironment of CRC growth with both local and remote metastasis
- * Collection of human primary CRC tumors features Asia CRC patients and facilitate the animal based Phase II like studies and translational studies
- * HT-29-Luc tumor model with Luciferase reporter allows real time imaging of the orthotopic tumor growth and metastasis

Tumor biology, biomarkers, and molecular pharmacology:

- * Tumor volume/weight, animal body weight and mortality
- * Cytokine/chemokine/biomarker analysis (ELISA, Q-PCR, Western blot)
- * Kinase activity assay and phosphorylation analysis
- * Hematology

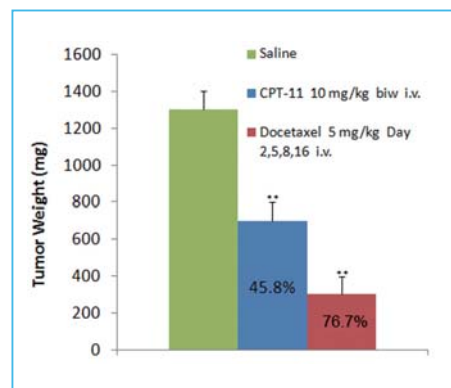
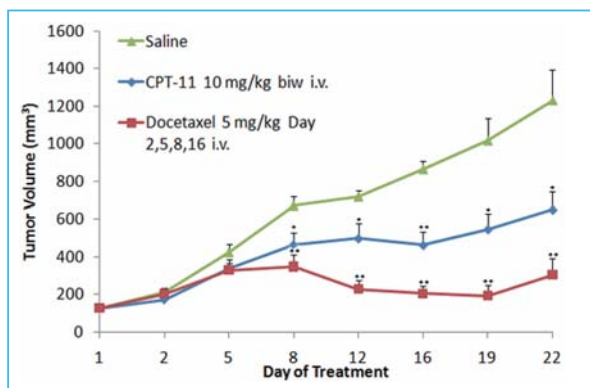
Tumor Histopathology:

- * Histology: morphology and differentiation
- * Immunohistochemistry: proliferation, apoptosis, angiogenesis, and tumor markers

In Vivo Imaging System

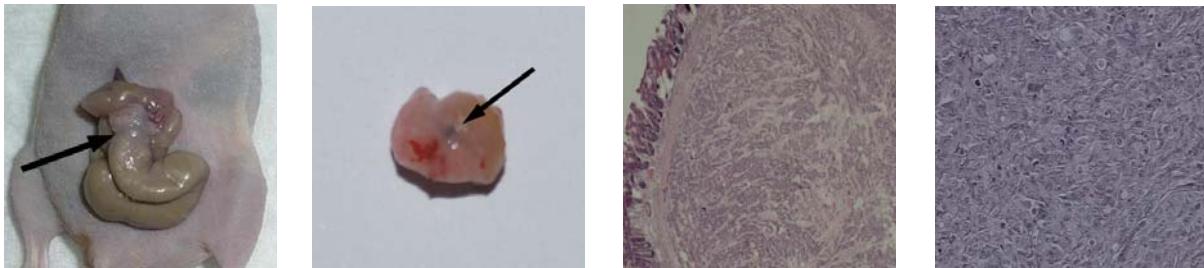
Case Study 1 - Inhibition of Tumor Growth

Growth Inhibition of COLO205 s.c. xenograft tumor by CPT-11 and Docetaxel in nude mice
(6 mice/group, *P<0.05, **P<0.01 vs Saline group by Dunnett's multi-comparison test)



Case Study 2 - Orthotopic Model

CRC orthotopic model in nude mice (HCT-116, 21 days after inoculation)



PharmaLegacy has the full capacity and skills to provide drug discovery research and preclinical pharmacology studies on CRCs; with thoroughly validated xenograft and orthotopic CRC models and the collection of human CRC cell lines and human primary CRC tumors. The endpoints from molecular pharmacology, tumor biology, tumor histopathology present an added value to our client's data package for characterization of effective agents in the treatment of CRC.

About PharmaLegacy Services

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- 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.