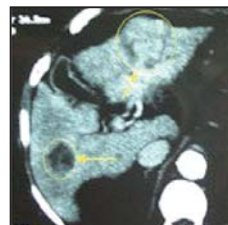


Hepatocellular Carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the primary malignancy of the liver. The disease is usually fatal within 3 to 6 months and only 10 - 20% of HCCs can be removed by surgery. While HCC is common in Southeast Asia and sub Saharan Africa, HCC incidence has continued to increase in the United States and Western Europe in the past 25 years and incidence and mortality rates are expected to double in the next 10 to 20 years.

pRB
Jak/STAT
Wnt/b-catenin
MAP kinase



P53
EGF/TGFb
Stress
Inflammation

HCC etiology: HBV, HCV, aflatoxin, alcohol

Aflatoxin or chronic infection with hepatitis B and C virus is the predominant risk factor for HCC in Southeast Asia and Africa, while chronic infection with hepatitis C virus and hepatic cirrhosis (mostly alcoholism) are the predominant risk factors for HCC in Western countries and Japan.

Hepatocarcinogenesis is a complex process associated with accumulation of genetic and epigenetic changes that occur during initiation, promotion and progression of the disease. Some important cellular signaling pathways such as Wnt, P53, Jak/STAT, pRB, Ras/Raf Akt/ mTOR and growth factor are involved in HCC progression.

Systemic cytotoxic therapies have demonstrated a very limited impact on advancing HCC. Recently, the strategy of using specific inhibitors targeting tyrosine kinase and associated pathways has been tested in HCC clinical trials, such as Sorafenib, Bevacizumab and Sunitinib.

PharmaLegacy Models and Research Tools

HCC tumor models:

- * Human HCC s.c. xenograft model in nude mice (> 10 tumor cells lines, > 5 Asian HCC lines)
- * Human HCC s.c. xenograft model in nude Rats (Combinational study of PK-PD and local drug delivery)
- * Human HCC orthotopic implantation models, both in mice and rats (Liver orthotopic modeling)
- * Human primary tumor derived HCC models in nude mice (representing human HCC)
- * Luciferase-reporter based HCC imaging model (growth and metastasis following orthotopic implantation)

Hepatocarcinogenesis, biomarkers and molecular pharmacology:

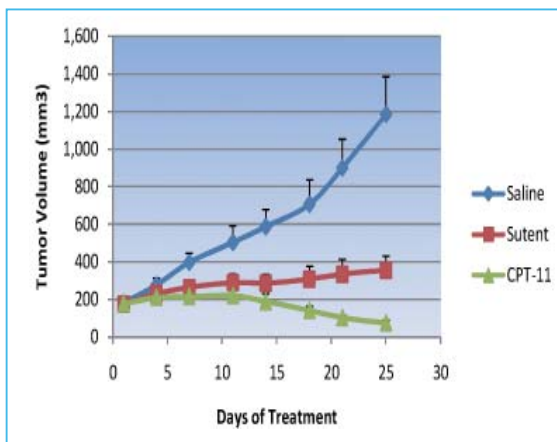
- * HCC cell culture based assays (MTT, invasion, etc.)
- * Hematology and liver chemistry
- * Cytokines / chemokine / biomarker analysis (ELISA)
- * Drug target levels in liver/tumor (Real Time PCR and Western Blot)
- * Drug target activities in liver/tumor (kinase assays and phosphorylation)

Histopathology:

- * Histology
- * Immunohistochemistry (proliferation, apoptosis, angiogenesis)

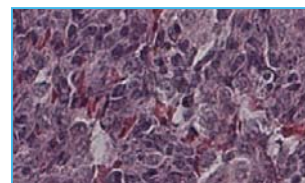
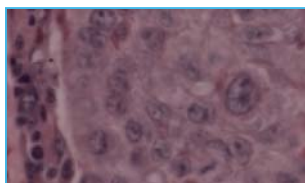
Case Study - Inhibition of Tumor Growth

Inhibition of HCC tumor growth by Sutent and CPT-11 in nude mice (Hep3B, s.c. xenograft model)



Asia HCCs
SMMC-7721
BEL7402
MHCC97L (primary HCC derived)
MHCC97H (primary HCC derived)
HCCLM3 (primary HCC derived)

HCC tumor growth and metastasis in nude ratst (HCCLM3, 9 weeks after orthotopic inoculation)



HCC in Liver

Lung Metastasis

PharmaLegacy's HCC specialty service is rooted in a sound knowledge of oncology, hepatology, hepatic surgery and hepatopathology. The Asia region collections of HCC research materials not only provide help in evaluation of drug efficacy, but also the drug mechanism and drug sensitivity in different HCC patient populations. The proprietary HCC xenograft rat model adds a significant expediency for the design of PK-PD-pharmacology combinatory studies and allows for the evaluation of different drug delivery strategies. Plus, the skillful liver inoculation and the full capacity of in vitro & ex vivo tumor analyses make orthotopic HCC models a powerful synergy to your new drug R&D for liver cancers.

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.