Mouse models of hepatocellular carcinoma: a comprehensive and functional preclinical platform for immunotherapy research

#1654

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1 CONTEXT & OBJECTIVES

• Background:

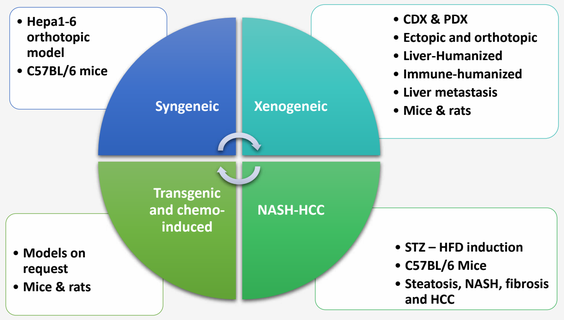
Hepatocellular carcinoma (HCC) is a multistep process comprising chronic liver injury, inflammation, fibrosis/cirrhosis and cancer formation. Therefore, providing palliative and curative options remains a high medical need. Of importance, Non-alcoholic steatohepatitis (NASH) has emerged as the most rapidly growing indication for liver transplantation in HCC patients. And with the recent success of immunotherapies in HCC, mouse models that better recapitulate the human disease and antitumor immune response are needed.

• Objectives:

In order to better evaluate new preventive and curative treatments of liver cancers we developed complementary and integrated strategies to mimic the liver cancer initiation and progression steps in mouse models. These models involve chemotoxic agents, diet-induced disorders and syngeneic or xenogeneic tumor implantation strategies.

3 CONCLUSION

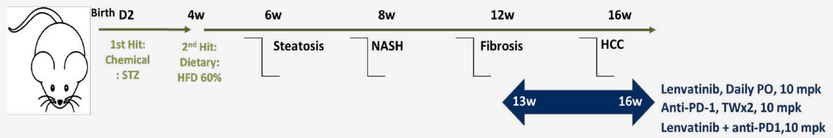
- Altogether, these results demonstrate the usefulness of this comprehensive platform of preclinical in vivo HCC models to discover and identify novel therapeutic strategies that could circumvent the progression of liver cancers
- **Hepa1-6** : a highly suitable syngeneic HCC model for drug screening; Many proof of strong efficacy with compounds targeting TLR or STING pathways
- **NASH-HCC**: a very useful model for the development of novel treatments, from therapies targeting the cause of the disease, i.e. dysregulated metabolism, to therapies targeting inflammation, fibrosis, and liver tumors at different stages



Perspectives:
- Hep3b tumor cells in NOG-IL15 mice humanized with hNK cells for NK specific therapies
- Developments of double humanized mice (liver and immune systems) engrafted with liver PDX tumors
- Optimization of radiotherapy treatment regimen in orthotopic liver PDX models in comparison to liver metastases from colon PDX tumors

2 RESULTS

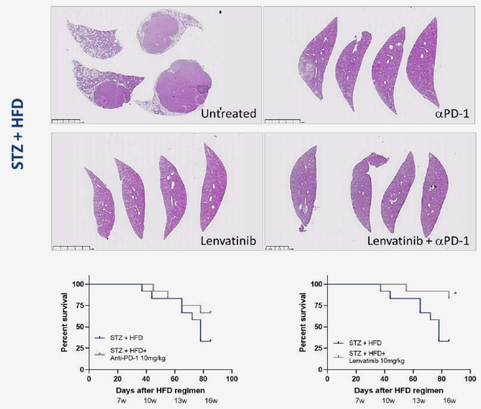
NASH-HCC MODEL: STZ + HFD

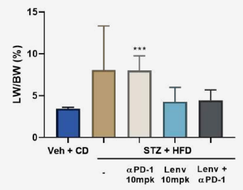


• Increased survival after treatment with Lenvatinib or/and anti PD-1

Neonate male mice were injected with STZ on day 2 and fed with a high fat diet from week 4. Mice were treated from week 13 to week 16.

Improvement of tumor burden and survival

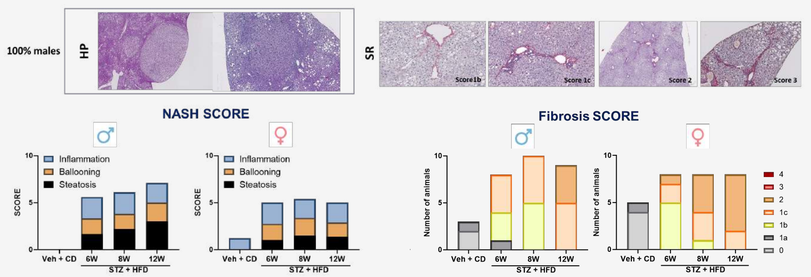




• 100% of males develop HCC; Females develop higher grade of fibrosis

Representative images of HCC stained by HE; and of scoring methods using Sirius Red staining.

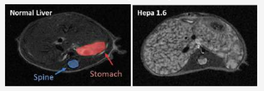
Sex differences in the course of the NASH-HCC model



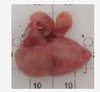
ORTHOTOPIC HEPA1.6 SYNEGENEIC LIVER TUMORS

HEPA1.6 TUMOR CELLS ENGRAFTMENT IN 80-90% OF TOTAL LIVER MASS

MRI on D10



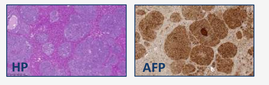
Untreated



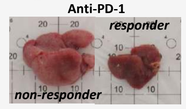
RESPONSE TO ANTI-PD-1

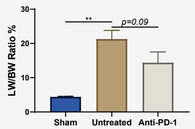
- 42% of mice responded to anti-PD-1

HISTOLOGY ANALYSIS



Anti-PD-1



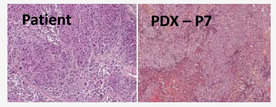


ELISA, IHC, qPCR, also used to assess tumor development and/or immune response

ECTOPIC OR ORTHOTOPIC PDX LIVER TUMORS

SA-LIV-0265 PDX liver model: Moderately differentiated hepatocellular carcinoma (grade III Edmonson) appeared in a non-cirrhotic liver of 80 years old man, and engrafted subcutaneously in SCID mice

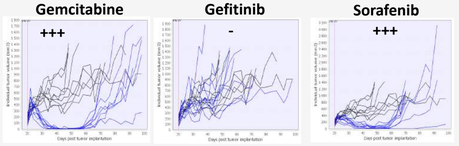
Highly conserved histology of the PDX



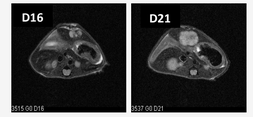
Highly conserved genomic profile of the PDX

Genes	polymorphism	Mutations	RNA expression
TP53	Unchanged	Mut	++
VEGFA	Unchanged	Wt	+
EGFR	Unchanged	Wt	++
MET	Unchanged	Wt	+
PTEN	Unchanged	Wt	-/+

Gemcitabine +++ | **Gefitinib** - | **Sorafenib** +++

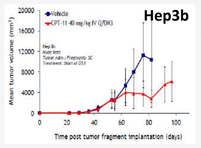


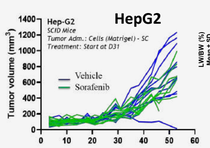
MRI monitoring of the PDX tumor growth



SA-LIV-0265 PDX model is highly sensitive to gemcitabine and sorafenib and is able to growth in an orthotopic environment in SCID mice

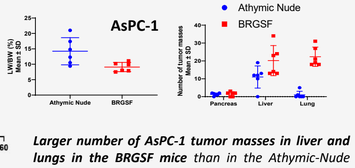
ECTOPIC CDX LIVER TUMORS





*In vivo sensitivity of **Hep3b** and **HepG2** tumor models respectively SC xenografted in Nude Rats or SCID mice and treated either with CPT-11 or sorafenib*

LIVER METASTASIS MODELS



Larger number of AsPC-1 tumor masses in liver and lungs in the BRGSF mice *than in the Athymic-Nude mice. AsPC-1 pancreatic cells were intrasplenically injected in either BRGSF or Athymic-Nude mice.*

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