

## Hepatocellular carcinoma: How could we imagine the future research?

Hepatocellular carcinoma (HCC) and advanced liver disease comprise a major public health burden for which we have only unsatisfactory treatment options. According to the European Association for the Study of the Liver (EASL), the prevalence of liver diseases is about 6% in the Europe (29 million individuals) and the associated mortality rate was estimated at 14.3 per 100,000 (70,000 deaths/year) (1). HCC is the third most common cause of cancer-related death and the leading cause of death among cirrhotic patients (2). According to the EASL, the HCC incidence and mortality rates were of 65,000 and 60,240 cases in Europe, respectively (1). Given the growing incidence of HCC, the economic burden will significantly increase in Western populations during the next decades (3). Treatment options for liver steatosis, fibrosis, cirrhosis and HCC are unsatisfactory. Furthermore, there are no efficient chemopreventive strategies to limit HCC development once cirrhosis is established. Although early-stage tumors can be curatively treated using surgical approaches, they are often undiagnosed and treatment options for advanced HCC are unsatisfactory. Although the multikinase inhibitor sorafenib improves a survival benefit for patients with locally advanced or metastatic HCC, adverse effects and moderate efficacy limit its use in patients with advanced liver disease (4). Thus, a therapy that is well tolerated, cost-effective, and poses an acceptable risk-to-benefit ratio is missing.

Virus-induced chronic hepatitis is a leading cause of HCC in France, Europe, and in Asia. In the developed Western world, only 10-15% of cases can be attributed to hepatitis B virus (HBV) infection, while chronic hepatitis C appears to be the major risk factor for HCC (up to 70% of cases) in Europe (1). Importantly, there are common alterations of pathways that likely account for viral and non-viral pathogenesis regardless of their etiology (5,6). Unsatisfactory therapeutic options are due to several hurdles:

- Mechanisms: pathogenesis only poorly understood
- Targets: limited number, clinical validation pending
- Models: limited small animal model only partially addressing pathogenesis
- Genetics: HCC is highly heterogenous
- Clinical: Advanced liver disease is a key determinant for management and survival

Given these hurdles there is a need for better understanding of pathogenesis of HCC, discovery of novel targets and better animal models for study of hepatocarcinogenesis and preclinical evaluation of therapeutic approaches. Further given the genetic heterogeneity of HCC and their origin in advanced liver disease and cirrhosis, it is of paramount interest to develop individualized treatment approaches and clinical care needs to integrate management of advanced liver disease using surgical and medical approaches

Addressing these unmet medical needs and limited knowledge, four main research axes should be developed in the future:

- Understand pathogenesis and discover targets using HCV-induced HCC as a model
- Develop relevant animal models for pathogenesis and preclinical therapeutic studies
- Develop strategies for individualized treatment using functionalized nanovectors
- Optimize clinical management of HCC using advanced imaging and modeling

In the future, we need to conduct interdisciplinary research projects with high synergistic expertise by using innovative and state-of-the art approaches in molecular and clinical hepatology, surgery, virology, cell biology, chemistry, immunology, functional genomics, genetics, biomaterials, nanovectors, and animal models, to obtain a strong medical relevance with a high likelihood to change the outcome of disease.

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