THREE-DIMENSIONAL MATRICES AND ENGINEERED NANOPARTICLES FOR LOCOREGIONAL TREATMENT OF HEPATOCELLULAR CARCINOMA (ManoHCC)

***This project was developed within the framework of the European Union–funding "NextGenerationEU" – PNRR Mission 4, Component 2, Investment 1.3, and implemented within the HEAL ITALIA PE program* (https://www.healitalia.eu/)**

SPOKE N. 6 HEALTY TOOLBOX (UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA)

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The project was implemented by a multidisciplinary consortium of academic partners, including the University of Milan (UNIMI), the University of Messina (UNIME), and the University of Bari "Aldo Moro" (UNIBA), bringing together complementary expertise in materials chemistry, nanotechnology, bio-organic chemistry, advanced drug delivery systems, liver disease biology, and in silico pharmacology.

Hepatocellular carcinoma (HCC) is one of the fastest-growing malignancies worldwide and remains largely refractory to effective pharmacological intervention. Within the framework of the HEAL ITALIA Foundation, and funded by the European Union–NextGenerationEU (PNRR), this BAC aimed at advancing next-generation locoregional therapeutic strategies for HCC. By integrating engineered nanocarriers, advanced biomaterial matrices, and targeted therapeutic approaches, the project established a platform potentially capable of overcoming key limitations of current treatments. Functionalized nanoparticles, including silica nanocages and liposomal systems, were designed to achieve selective tumour delivery, while injectable biocompatible hydrogel matrices enabled localized, sustained, and controlled drug release, minimizing systemic toxicity and enhancing therapeutic precision. Multiscale physico-chemical characterization was carried out to assess structure, surface charge and spectroscopical fingerprint.

A defining strength of the project was the development of advanced *in vitro* disease models, spanning 2D systems and 3D primary HCC organoids, challenged to recapitulate the tumour microenvironment and the metabolic landscape associated with metabolic disease associated steatotic liver disease (MASLD). The implementation of steatotic microenvironment models provided a physiologically relevant and predictive platform for evaluating therapeutic response in HCC patients with MASLD, bridging the gap between experimental systems and clinical reality. These models were employed for the functional evaluation of engineered nanocarriers, allowing the assessment of cellular uptake, controlled drug release, and supporting robust preclinical validation of the proposed therapeutic strategies for disease treatment.

Beyond its scientific impact, the project holds significant technological and translational potential, opening new avenues for precision oncology, for technology transfer and industrial exploitation in the fields of nanomedicine and liver disease. Given the growing burden of MASLD/MASH-associated HCC and its poor clinical outcomes, these advances contribute to addressing a critical unmet need in public health.

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