**Panel S2:** HISTOPATHOLOGY AND FLUORESCENCE ANALYSES

To analyse HLSC-EV uptake, snap frozen liver samples were collected at the end of each experiment, then serial slices were cut (3-5 μm) by a cryostat and fixed in acetone. After the re-hydration step in phosphate buffered saline (PBS) (Sigma-Aldrich), the nuclear staining Hoechst was used at 1:5000 dilution, then the slides were washed three times in PBS and mounted using the aqueous mountant Fluoromount (Sigma-Aldrich). Images were acquired by Cell Observer SD ApoTome laser scanning system (Carl Zeiss).

To evaluate liver histologic features and assess glycogen deposits, part of the biopsies was fixed and processed according to the Pathology Unit liver biopsies routine protocols. Five-μm sample slides were then cut and stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), and periodic acid-Schiff-diastase (PAS-D). Two pathologists (AG and ED) independently assessed and graded tissue injury signs using the Suzuki score system [35]. Accordingly, sinusoidal congestion, hepatocytes cytoplasmatic vacuolization, and parenchymal necrosis were first quantified and then graded from 0 (none) to 4 (severe). Glycogen deposits were evaluated throughout the liver parenchyma, and, according to their distribution, they were reported as located in hepatocytes, sinusoids or both. In case of dissimilar analyses, slides were discussed and reviewed to reach a concordant evaluation.

Cellular proliferation was detected with Proliferating Cell Nuclear Antigen (PCNA) analysis.[18] Negative and positive PCNA cells were blindly counted on 10 microscopic fields (400× magnification) and the PCNA index was calculated as the ratio between positive cells and total cells.