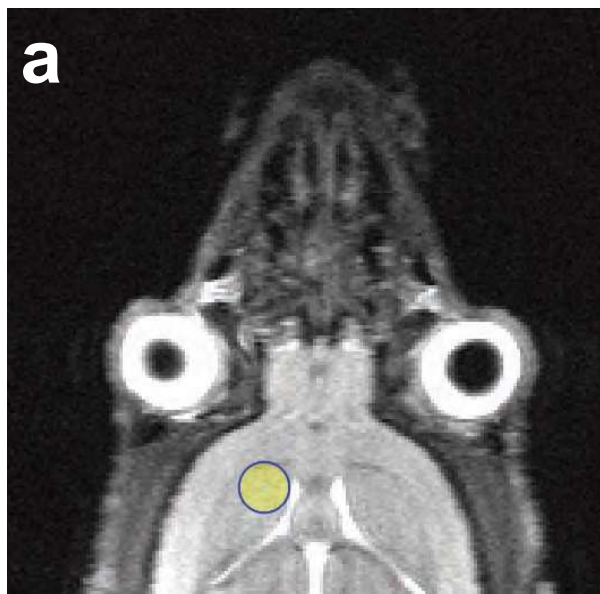
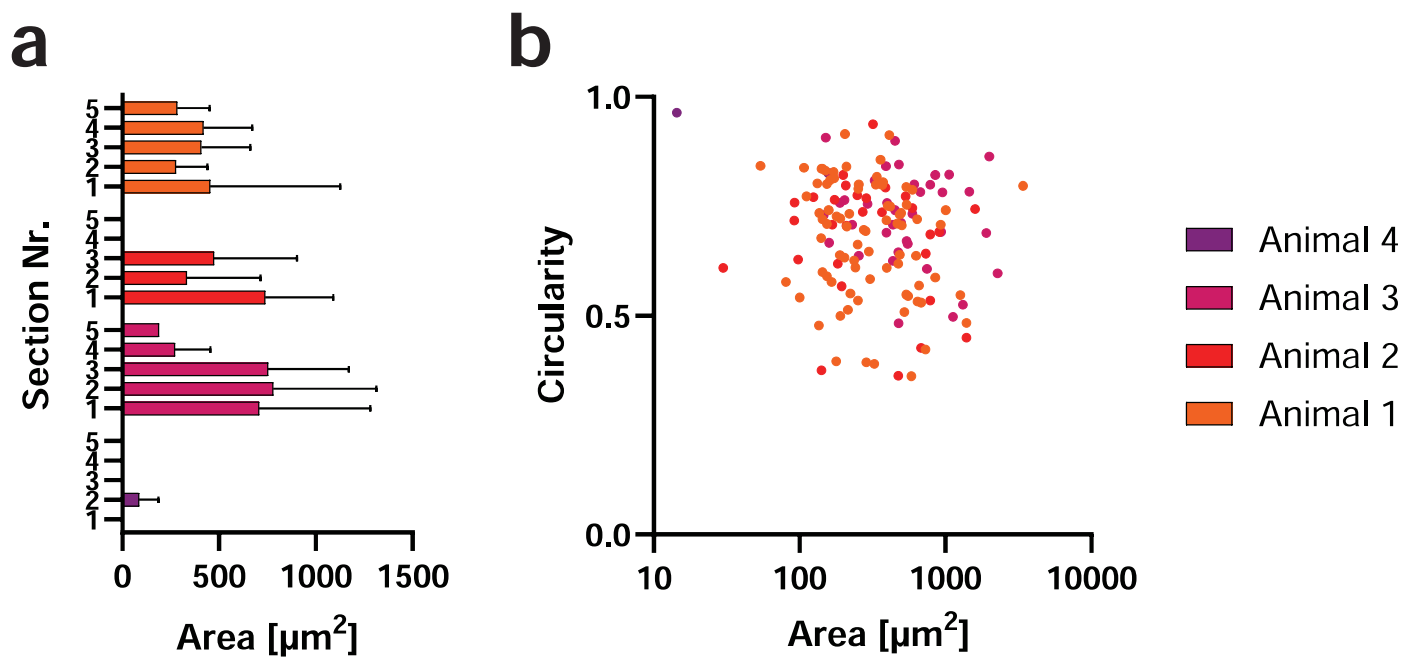




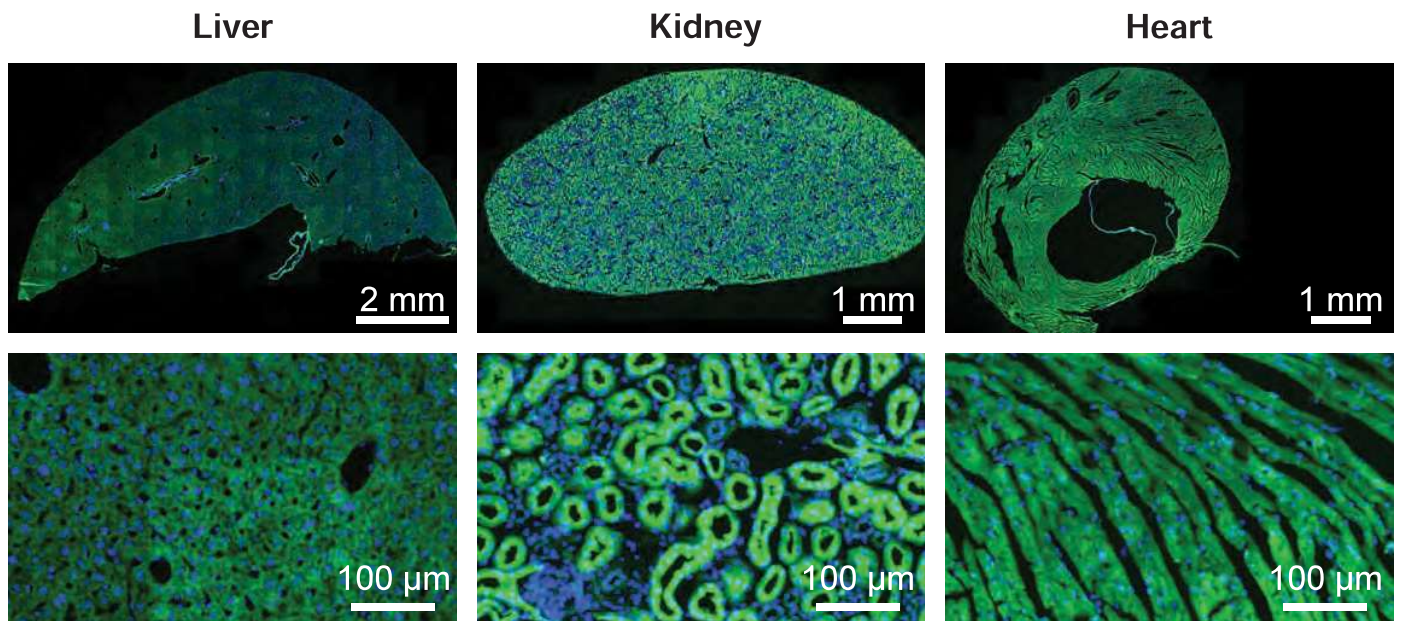
Supplementary Fig. 1: Representative spatial validation of the focused ultrasound targeting and tissue harvesting pipeline.

(a) Unedited, raw software interface export of the pre-acquired T2-weighted MRI used for anatomical targeting. The yellow cursor indicates the real-time target placed over the right striatum based on individual animal anatomy prior to sonication. Estimated focal dimensions of the 1.0 MHz transducer are 1.5 mm (lateral width) × 6.0 mm (axial length). (b) Macroscopic confirmation of successful targeting. A representative frozen brain specimen mounted in the cryostat demonstrates localized extravasation of the Evans Blue permeability marker (blue smear) strictly within the targeted right striatum. (c) Validation of spatial overlap for downstream analysis. Coronal sections of the freshly harvested brain demonstrate the sequential macroscopic Evans Blue extravasation, which served as a direct, physical fiducial marker to guide the precise microdissection of the localized sonicated tissue volume for accurate LC-MS quantification.



Supplementary Fig. 2: Morphological characterization of microhemorrhages following 0.6 MPa sonication.

Quantitative evaluation of erythrocyte extravasation in high-magnification H&E sections spanning the sonicated volume (n=5 sections/animal from a total of 4 animals). **(a)** Surface area of detected microhemorrhagic events across sequential brain sections (Sections 1–5). Data represent mean+SD per section. **(b)** Morphological scatter plot displaying the circularity versus surface area of individual identified microhemorrhages (n=150 events).



Supplementary Fig. 3: Systemic biodistribution of the MALAT1 ASO in peripheral organs. Representative fluorescence microscopy images of the liver, kidney, and heart harvested 30 minutes post-intravenous injection and FUS treatment. (Top) Macroscopic tissue section overviews demonstrating the widespread systemic distribution and accumulation of the ASO (green) in primary clearance organs. (Bottom) High-magnification images detailing the cellular-level localization of the ASO within the respective tissues. Cell nuclei are counterstained with DAPI (blue).

Supplementary Table 1: Individual physiological metrics and LC-MS biodistribution profiles.

Metric	Animal 1	Animal 2	Animal 3
Animal Weight (g)	15	20	25
Tissue weights (mg)			
Brain - sonicated area	47	56	46
Brain - non-sonicated area	38	33	47
Liver	44	53	55
LC-MS Results			
Brain - sonicated area (pmol/g)	286	713	381
Brain - non-sonicated area (pmol/g)	77.3	80.2	58.7
Liver (pmol/g)	2460	2350	1440
Plasma (pmol/mL)	8540	9660	3920