Focused sound waves and immunotherapy combination shows promise in treating pancreatic cancers

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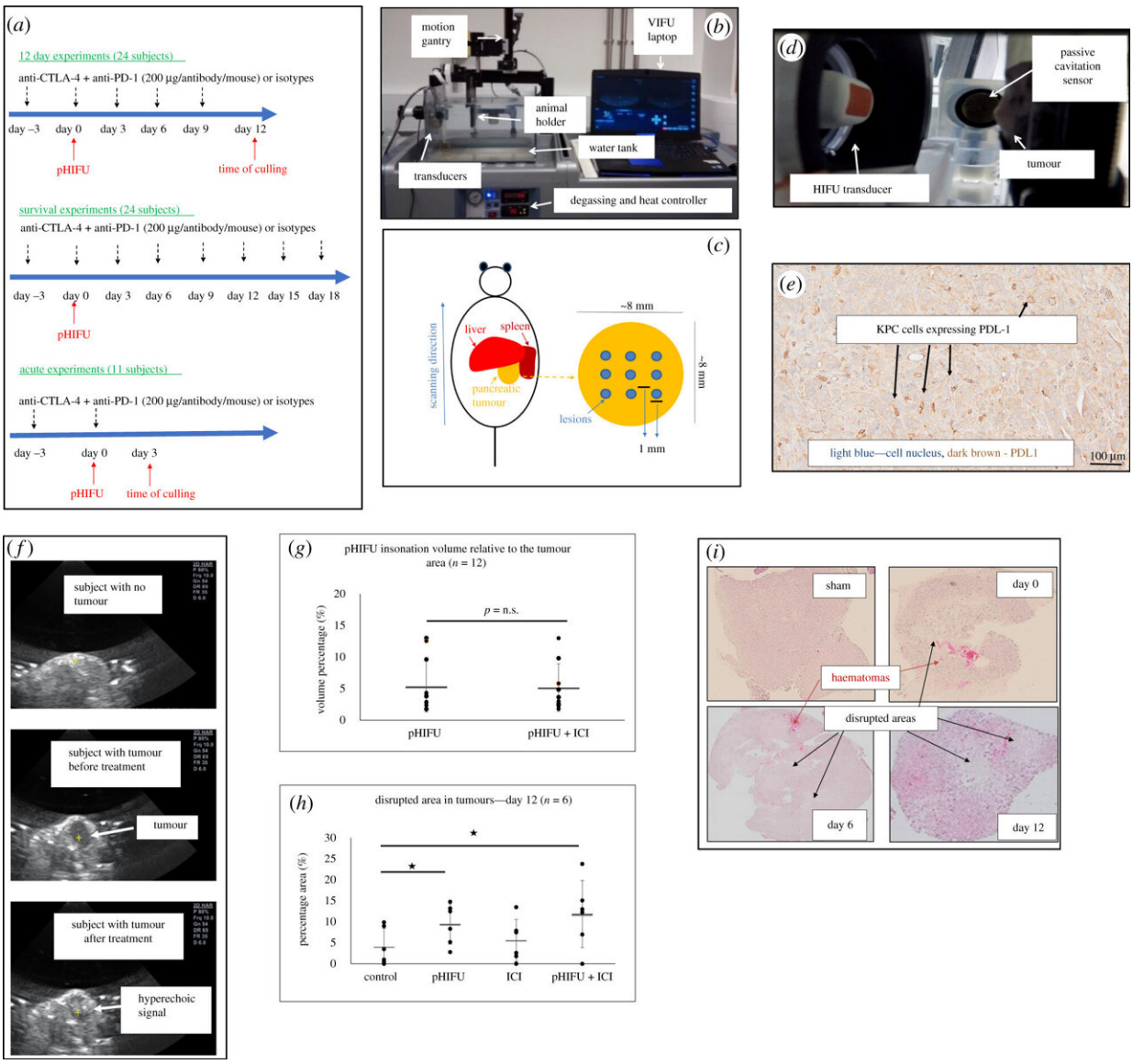

Figure 1. Characterization of baseline effects of pHIFU treatments on KPC tumors. (a) Treatment sequencing regime used in this study. Subjects were injected IP with a combination of anti-CTLA-4 and anti-PD-1 3 days before pHIFU exposures, on exposure day (immediately after pHIFU) and every 3 days thereafter until the time of culling (or up to 21 days for survival experiments). Subjects not treated with pHIFU were sham-exposed and subjects not treated with ICI were injected with isotype antibodies at the same dose and frequency as the ICI. (b) Alpinion small animal VIFU 2000 therapeutic ultrasound system comprising a 1.5 MHz HIFU transducer with a centrally mounted, co-aligned 7 MHz imaging probe for treatment guidance and monitoring facilitated by software control of the chosen target position within the mouse to the position of the focal peak using the automated gantry. (c) Schematic example representing targeting of the tumor with pHIFU. Lesions were placed every 1 mm in the horizontal and vertical direction. (d) Side-mounted broadband sensor used to detect cavitation (passive cavitation detector) in the HIFU focal volume. (e) PD-L1 expression in KPC tumors. (f) Typical examples of an image of a tumor-free animal, and a tumor imaged before and immediately after pHIFU with B-mode ultrasound are shown. (g) Comparison of the insonation volume of tumors in pHIFU and pHIFU + ICI subjects. (h) Percentage of tumor disrupted showing irregular or zero cell densities 12 days after treatment. (i) Staining of the tumors exposed to pHIFU + ICI and imaged immediately after and 6 and 12 days after treatment. Numerical results (g) and (h) are presented as means ± s.d. (n = 6) and statistical significance (denoted with an asterisk) is assumed at p

Combining targeted, focused ultrasound and immunotherapy drugs could work as a new treatment for pancreatic cancers, a new study has shown.

A team led by scientists at The Institute of Cancer Research, London, targeted pancreatic tumors in mice with high intensity focused pulses of ultrasound.

The technique, developed at the ICR, uses a beam of focused sound waves to vibrate cells and tissues and has shown potential in the clinic as a cancer treatment.

In this study, published in the *Journal of the Royal Society Interface* and largely funded by the Focused Ultrasound Foundation, the scientists used pulsed focused

ultrasound, "pHIFU," alongside injections of antibodies that mimic the effects of immune checkpoint inhibiting drugs.

Combining pHIFU and immunotherapy

Sometimes cancer cells evade attack from the immune system by using an immune cell brake, a 'checkpoint'—preventing the immune system from doing its job. Using immune checkpoint inhibitors releases this brake, allowing immune cells to attack cancer.

These immunotherapy drugs, such as pembrolizumab and nivolumab, are routinely used in the treatment of some cancers, but many patients—including most with pancreatic cancer—do not respond well to them.

However, combining immune checkpoint inhibitors with other treatments such as other drug types, radiotherapy or ultrasound could boost their effectiveness. HIFU can break up dense tissue structures that can exclude these drugs from tumors.

The researchers found that mice receiving the HIFU-antibody combination lived longer than mice treated with neither or just one of the treatments, and performed better in several other measures of treatment effectiveness.

The pulsed HIFU exposure leads to the formation of numerous cavities—'acoustic cavitation'—in the tumors. These can break up the tissue and allow immune cells to enter tumors more easily.

Treating pancreatic tumors

Some other recent studies have shown exciting potential for HIFU but in tumors grown just under the skin, where sound waves can penetrate more easily than deeper within tissue. Importantly, the mice in this study had 'orthotopic' pancreatic tumors, meaning that they grow in the pancreas itself, initiated by cancer cell injection.

This study proves the potential of the combination more convincingly than

previous studies in deep-lying tumors in organs such as the pancreas—as well as being the first ever study to show the anti-cancer benefit of HIFU and immune checkpoint inhibition in pancreatic cancer.

One point of particular interest to other HIFU researchers is the evidence for significant acoustic cavitation within tumors.

Acoustic cavitation is the term used to describe the rapid vibration of tiny 'microbubbles' of gas by the sound waves, and it is this which is thought to be enhancing the uptake of immune cells into the tumors by breaking them up—the shaking breaks up the tumor cells, causing them to spill their contents.

The spill then also alerts the immune system, attracting immune cells to the site to fight the cancer.

Targeting the tumors with rapid 'on-off' pulses of ultrasound lasting milliseconds enhances the treatment effectiveness, the researchers believe—and could be better than using a continuous HIFU beam.

The mice had tumors of a type called pancreatic ductal adenocarcinoma (PDAC), which accounts for the majority of human pancreatic cancer. Pancreatic cancer represents a cancer of significant unmet need in terms of its treatment, with life expectancy improving little over the past 40 years.

Paving the way for clinical trials

Study lead Professor Gail ter Haar, Professor of Therapeutic Ultrasound at The Institute of Cancer Research, London, and founding President of the International Society for Therapy Ultrasound, said:

"Our study shows that mice with pancreatic cancers lived longer when treated with a combination of pulsed HIFU and antibodies to mimic the effects of immune checkpoint inhibitors. Their tumors also showed evidence of cavitation activity, due to HIFU's ability to rapidly expand and collapse tiny microbubbles within the tumor—thus reducing tumor integrity and creating more space for the infiltration of drugs and cancer-killing immune cells.

"This is the first ever study to show the anti-cancer benefit of these two treatments, HIFU in combination with immunotherapy, in pancreatic cancer. This study paves the way for clinical trials of treating pancreatic cancer patients with HIFU, and we will be developing HIFU-delivery platforms to achieve that."

Study author Dr. Petros Mouratidis, Higher Scientific Officer in Therapeutic Ultrasound at The Institute of Cancer Research, London, said:

"High intensity focused ultrasound has shown potential in a range of cancer types and is of particular interest in pancreatic cancer—because tumors can be hard to access for surgery, and sound waves can physically weaken tumors and could allow other treatments, including immunotherapies, to have greater effect. We hope our study ultimately leads to a new type of treatment for patients with pancreatic cancer."

More information: Petros X. E. Mouratidis et al, Pulsed focused ultrasound can improve the anti-cancer effects of immune checkpoint inhibitors in murine pancreatic cancer, *Journal of The Royal Society Interface* (2021). DOI: 10.1098/rsif.2021.0266

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