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Perspective

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The synergistic potential of mechanotherapy and sonopermeation to enhance cancer treatment effectiveness

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Inefficient drug delivery in tumors, especially in desmoplastic cancers, arises from blood vessel collapse due to tumor stiffening and mechanical compression. Vessel collapse also leads to hypoxia, immune evasion, and metastasis, reducing treatment efficacy. Mechanotherapeutics and ultrasound sonopermeation, which address tumor stiffness and enhance vessel permeability, respectively, show promise in restoring tumor microenvironment abnormalities and improving drug delivery. This perspective highlights their independent and combined potential to optimize cancer therapy.

Cancer is responsible for approximately one in every six deaths globally, highlighting its significant impact on public health. Cancer development is a lengthy process, characterized by the gradual accumulation of various symptoms and a significant failure in the mechanisms that typically inhibit abnormal cell growth[1]. For many years, patients diagnosed with cancer had limited treatment options, which primarily include surgery, radiation therapy, and chemotherapy. These treatments could be used individually or in combination, but they often come with considerable side effects and varying degrees of effectiveness, leaving many patients seeking alternative approaches or additional support in their battle against this complex disease. While traditional treatments can effectively reduce tumor size or achieve temporary remission, they frequently fall short of providing a long-term cure, particularly in aggressive or advanced cancers. The failure of standard therapies to cure different types of cancer is rooted in a variety of complex biological and physiological challenges. In fibrotic tumors, this is attributed in large part to insufficient and heterogeneous drug delivery to the tumor site owing to physical abnormalities in the tumor microenvironment (TME) that induce hypo-perfusion, which in turn creates harsh hypoxic conditions[2–5].

Hypo-perfusion hinders the delivery of medicines and induces immunosuppression

Although standard-of-care treatments can be highly potent and capable of eradicating cancer cells in controlled in vitro settings, their therapeutic outcomes are largely compromised in real-world applications due to inefficient drug delivery. Inadequate delivery prevents therapeutics from reaching the tumor mass in sufficient amounts thus, diminishing their effectiveness and limiting their ability to significantly improve treatment outcomes[6]. In cancers with a highly fibrotic nature, complex interactions between cancer cells, stromal cells, and the dense extracellular matrix (ECM)-characterized by the excessive deposition of components like collagen and hyaluronan- lead to significant tumor stiffening. This stiffening is accompanied by the buildup of mechanical forces within the tumor, which are exerted on intratumoral blood vessels. As a result, tumor blood vessels are compressed (Fig. 1), disrupting normal blood flow and contributing to the challenging treatment environment typical of these tumors[7–16]. In cancer types, such as pancreatic and breast tumors and sarcomas, it has been observed that a significant portion of intratumoral blood vessels—up to 95% —may become compressed, with as much as 80% collapsed entirely[8,9,17–20]. This widespread vessel collapse leads to severely reduced blood flow within the tumor, a condition known as hypo-perfusion. Hypo-perfusion, in turn, poses a major barrier to effective drug delivery, preventing therapeutic agents from reaching the tumor in adequate amounts. Additionally, this lack of proper blood flow creates a hypoxic environment within the tumor, further hindering the effectiveness of various cancer therapies by inducing the expression of genes associated with drug resistance. The lack of oxygen reduces the effectiveness of radiation therapy, which relies on oxygen to generate reactive oxygen species that damage DNA in cancer cells[21,22]. Furthermore, hypoxia enables cancer cells to evade the immune system and enhances their invasive and metastatic potential through processes such as epithelial–mesenchymal transition (EMT) and upregulation of genes involved in extracellular matrix modulation in a hypoxia-inducible factor 1-alpha (HIF1α)- dependent manner[18,23–27]. Hypo-perfusion can also limit immune cell infiltration into the tumor, while hypoxia creates an immunosuppressive TME, shifting tumor-associated macrophages (TAMs) from the immunosupportive M1 type to the immunosuppressive M2 type, and diminishing the cytotoxic capacity of effector immune cells[13,28–32]. Moreover, hypoxia fosters pro-tumor immune responses by increasing PD-L1 expression in myeloid-derived suppressor cells (MDSCs), TAMs, dendritic cells (DCs), and cancer cells[33,34]. It also attracts immunosuppressive T-regulator cells (Tregs) by triggering the expression of the chemokine CCL28[35] and along with acidity[36], affects differentiation and function of T-lymphocytes and myeloid cells[37] and induces TAMs to promote angiogenesis[38]. In response to hypoxia, tumors often upregulate HIFs, which

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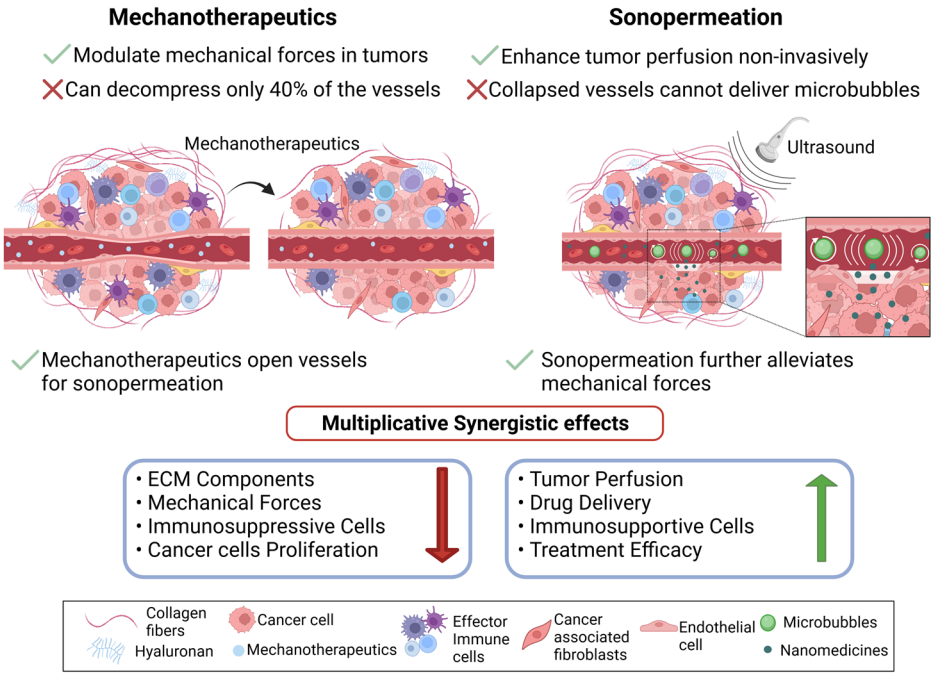

Fig. 1 | The synergistic potential of mechanotherapeutics and sonopermeation to mechano-modulate the tumor microenvironment and enhance cancer treatment effectiveness. The abnormal growth of cancer cells in normal host tissue, combined with interactions among stromal cells and the fibrotic ECM, creates mechanical forces that compress tumor blood vessels and stiffen the ECM, reducing tumor perfusion. This impaired blood supply limits immune cell infiltration, while hypoperfusion makes the TME immunosuppressive and supports pro-tumor immune responses. The use of mechanotherapeutics can normalize tissue stiffness, enhance perfusion, and boost immunostimulation, improving cytotoxic therapy effectiveness. However, mechanotherapeutics cannot decompress the majority of the vessels but only a percent. Ultrasound sonopermeation with microbubbles can enhance cell membrane permeability and decrease solid forces, increasing tumor perfusion and the uptake of therapies. However, sonopermeation cannot be effective in tumors with compressed vessels. Combining mechanotherapeutics with sonopermeation overcomes their limitations, effectively addressing tumor microenvironment abnormalities, enhancing drug delivery, and improving therapeutic outcomes. This approach increases tumor perfusion and oxygenation, activating effector immune cells while reducing immune regulator cells, resulting in greater drug delivery efficiency and more effective cancer cell elimination. Created with BioRender.com.

promote the expression of pro-angiogenic factors like vascular endothelial growth factor (VEGF) which leads to the formation of new blood vessels to supply the tumor with necessary nutrients and oxygen[39]. However, these newly formed vessels are frequently abnormal -leaky and poorly organized- resulting in uneven oxygen distribution and perpetuating hypoxic regions within the tumor[40,41]. This abnormal vasculature not only supports tumor growth but also contributes to increased tumor malignancy[39]. Indeed, higher perfusion levels, which indicate normoxia, serve as a predictive biomarker for therapy efficacy[13,20,42–44].

Strategies to modulate the tumor physical microenvironment

Mechanotherapeutics can improve perfusion, but not optimally

As we mentioned previously, vessel compression results from tumor stiffening and the buildup of mechanical forces within solid tumor components, which are modulated by cancer cells, cancer-associated fibroblasts (CAFs), collagen, and hyaluronan[8,27,45]. A therapeutic strategy to decompress vessels and improve perfusion is the use of mechanotherapeutics to alleviate stiffness and mechanical forces (Fig. 1)[46]. Mechanotherapeutics are often approved drugs (e.g., antihypertensive, anti-fibrotic, antihistamine) that are repurposed to modulate the TME by targeting ECM components or reprogramming CAFs, such as Transforming growth factor beta (TGFβ) inhibitors[18,20,47] (Table 1). Modulation of the TME by selective targeting any or all of these components can re-open compressed vessels and improve perfusion and thus, delivery of drugs and oxygenation[18,48,49]. While short-term improvements in perfusion and drug delivery might increase treatment efficacy, the longer-term effects of modulation can create a more favorable environment for cancer cells to spread and metastasize[50,51]. However, treatment with mechanotherapeutics is short-lived as two weeks post-treatment the tumor elasticity returns to the untreated tumors level[52]. Additionally, treatment with mechanotherapeutics did not favor metastasis in preclinical tumor models[20,53,54].

One mechanotherapeutic agent is the anti-hypertensive and angiotensin receptor blocker, losartan, which was successfully repurposed to improve the delivery of therapeutics in vivo by inducing blood vessel decompression and improving perfusion in various types of breast and pancreatic tumors in mice[47,55,56]. Importantly, losartan was the first mechanotherapeutic to successfully progress to clinical trials. It was found that the addition of losartan to the treatment regimen of FOLFIRINOX and radiation made 60% of previously unresectable, locally advanced pancreatic ductal adenocarcinoma tumors resectable[57]. Currently, losartan is under investigation in combination with chemoradiation and the immune checkpoint inhibitor (ICI) nivolumab for the treatment of pancreatic cancer (Clinical-Trials.gov identifier: NCT03563248). Losartan is a remarkable step forward and has established the term "mechanotherapeutics" as a new therapeutic strategy owing to first successes in clinical trials[46,57]. For this reason, it is considered a "gold standard" for mechanotherapeutics. However, in a clinical trial, the losartan dose could not be raised to decompress more vessels because of losartan's strong anti-hypertensive effects, and normotensive and hypotensive patients could not tolerate losartan and were excluded from the study.

Another such agent is ketotifen, an anti-histamine drug that inhibits mast cell activation, suppresses CAF proliferation and ECM components, whereas none of the doses of ketotifen induced any toxicity in preclinical model[58]. Notably, a phase II clinical trial is underway to evaluate ketotifen's potential in enhancing chemotherapy for sarcoma patients (EudraCT Number: 2022-002311-39). In this trial, the maximum tolerated dose (MTD) was administered to the patients, and many of them received ketotifen for a period longer than 100 days without any safety issues to have been reported. Additionally, in our previous studies, we successfully

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Table 1 | Mechanotherapeutics employed in pre-clinical and clinical trials

Drug name	Drug purpose	Mechanism	Tumor type	Pre-clinical studies	Clinical trials
Ketotifen	Anti-histamine	Inhibits mast cell activation, suppress CAF proliferation.	-Soft tissue sarcoma	-Fibrosarcoma MCA205 and osteosarcomas K7M2 cells in Balb/c and C57Bl/6 mice[52,93].	-Sarcoma: EudraCT No:2022-002311-39
Tranilast	Anti-fibrotic and antihistamine drug	Interfere with transforming growth factor-beta (TGF-β) signaling to inhibit cell proliferation.	-Prostate; -Colon cancer; -Breast Cancer; -Head and Neck Cancer	-LNCaP-SF cells in severe combined immunodeficient mice for prostate cancer[94]. -CT26 cells in Balb/c mice for colon cancer[95]. -4T1 and E0771 cells in Balb/c and C57Bl/6 mice for breast cancer[11,13,20,53].	-Head and Neck Cancer: NCT05626829
Pirfenidone	Anti-fibrotic and anti-inflammatory drugs extensively tested for lung fibrosis	Inhibition of TGFβ signaling and downregulation of ECM components including collagen and hyaluronan.	-Breast cancer; - Non-small cell lung cancer (NSCLC); -Colon cancer	-4T1 and E0771 cells in Balb/c and Black-6 mice for breast cancer[12,54]. - A549 cells in nude mice for Non-small cell lung cancer[96].	-Non-small cell lung cancer: NCT04467723, NCT03177291 - Colon cancer: NCT06484153
Dexamethasone	Synthetic glucocorticoid	Binds to the glucocorticoid receptor and regulates gene expression e.g., inhibits the production of inflammatory cytokines, suppresses activity of immune cells, promotes gluconeogenesis and induces apoptosis.	-Pancreatic cancer; -Prostate cancer; -Breast cancer	-Patient derived xenograft model (human pancreatic tumor tissues in NOD/SCID mice)[97]. -4T1 in Balb/c mice for breast cancer[98].	-Prostate cancer: NCT00176293
Metformin	Antihyperglycemic agent	-Suppress mTOR activity by activating LKB1 tumor suppressor and AMP-activated protein kinase (AMPK). -Inhibits of protein synthesis, halts the cell cycle, induce apoptosis and autophagy through p53 and p21, lowers blood insulin levels, inhibits the unfolded protein response (UPR) and stimulates the immune system. -Targets and eliminates cancer stem cells. -Prevents angiogenesis. -Decreases elevated lipid levels.	-Non-small cell lung cancer; - Pancreatic; -Breast cancer; -Prostate cancer; -Colon cancer; -Melanoma	-A549, HCC827-pSB388 and PC-9 cells in Balb/c mice for NSCLC[99]. -KPC cell in C57Bl/6 mice for pancreatic cancer[100]. -JIMT-1 human cancer cells in nude mice for breast cancer[101]. -LNCap cells in nude mice for prostate cancer[102]. -HCT116 cells in nude mice for colon cancer[103]. -A375 cells in nude mice for melanoma[104].	-Non-small cell lung cancer: NCT01864681, NCT03874000, NCT03071705, NCT04170959, NCT02285855, NCT02186847, NCT01997775, NCT05445791, NCT03048500, NCT01717482, NCT02115464 - Pancreatic: NCT02336087, NCT01210911, NCT02005419 NCT01666730 - Breast: NCT01310231, NCT01101438, NCT01302379 NCT02488564, NCT00930579 NCT01650506 - Colon cancer: NCT05921942, NCT03800602, NCT01941953, NCT03053544 - Prostate: NCT03137186, NCT01620593 - Melanoma: NCT03311308 NCT04114136, NCT01638676
Bosentan	Endothelin receptor antagonist used to treat pulmonary arterial hypertension	Inhibits the activity of endothelin-1, a peptide that promotes tumor growth, angiogenesis and metastasis.	-Pancreatic cancer; -Breast cancer; -Melanoma	-COLO357 cells in nude mice for pancreatic cancer[105]. -4T1 and E0771 cells in Balb/c and C57Bl/6 mice for breast cancer[60].	-Pancreatic cancer: NCT04158635 -Melanoma: NCT01009177
Paricalcitol	Synthetic vitamin D analog primarily used to treat secondary hyperparathyroidism in patients with chronic kidney disease	Agonist targeting the vitamin D receptor on CAFs. Decrease the production of collagen, decrease myeloid derived suppressor cells, decrease Tregs.	-Pancreatic cancer; -Breast cancer	-AsPC-1 cancer cells in nude mice for pancreatic cancer[106]. -MDA-MB-231 cancer cells in Balb/c mice for breast cancer[107].	-Pancreatic cancer: NCT02930902, NCT03331562 -Breast cancer: NCT00637897
Cilengitide	Cyclin peptide integrin antagonist	Inhibits Avβ3 and avβ5 integrins which are cell surface receptors involved in tumor cell adhesion to the extracellular matrix, angiogenesis and tumor cell migration and invasion.	-Non-small cell lung cancer; -Melanoma; -Breast cancer; -Pancreatic cancer	-M21 human cancer cells in Balb/c mice for melanoma[108]. -HBT 3477 cells in nude mice for breast cancer[109].	-Non-small cell lung cancer: NCT01118676, NCT00842712 -Melanoma: NCT00082875 -Pancreatic cancer: NCT00121238, NCT00103337

Table 1 (continued) | Mechanotherapeutics employed in pre-clinical and clinical trials

Drug name	Drug purpose	Mechanism	Tumor type	Pre-clinical studies	Clinical trials
Losartan	Angiotensin receptor blocker	Inhibits the activity of TGF-β and other profibrotic cytokines—reduces the levels of collagen and hyaluronan.	-Pancreatic cancer; -Breast cancer; -Glioblastoma; -Osteosarcoma; -Colon cancer	-SKOV3ip1 and Hey-A8 ovarian cancer cells in nude mice[110,111]. -AK4.4 chunks for pancreatic tumors in FVB mice[47]. -4T1 and EMT6 in Balb/c mice for breast cancer[112,113]. -GL261 cell line in C57Bl/6 mice for glioblastoma[114]. -CT26 cells in Balb/c mice for colon cancer[115].	-Pancreatic cancer: NCT01821729, NCT05077800, NCT03563248, NCT05861336 -Glioblastoma: NCT03951142, NCT01805453 -Osteosarcoma: NCT03900793

repurposed tranilast, an anti-fibrotic and antihistamine drug approved in Japan and South Korea, and pirfenidone, a globally approved anti-fibrotic drug for the treatment of idiopathic pulmonary fibrosis[20,54]. These therapeutic agents have demonstrated the ability to decrease the elastic modulus of tumors without affecting the elasticity of host organs and reduce both solid and fluid pressures within tumors, leading to improved tumor perfusion and a marked increase in the effectiveness of various cancer treatments. Specifically, they significantly enhanced the efficacy of chemotherapy, nanotherapy, and immunotherapy, not only in primary tumors but also in metastatic sites. The mechanism behind these improvements involved the suppression of TGFβ signaling, which plays a key role in tumor progression, as well as the downregulation of ECM components, including collagen and hyaluronan. By targeting these factors, the agents helped to remodel the TME, making it more receptive to therapeutic interventions and allowing for better drug delivery and immune response activation. Additional mechanotherapeutics include the anti-hyperglycemic agent metformin[59], the corticosteroid dexamethasone[47], and the endothelin receptor antagonist bosentan[60]. Notably, bosentan is being tested in a Phase I clinical trial in patients with unresectable pancreatic cancer (Clinical-Trials.gov identifier: NCT04158635). Another agent is paricalcitol—an agonist targeting the vitamin D receptor on CAFs[61].

These successes demonstrate the clinical potential of mechanotherapeutics, but several challenges remain as mechanotherapeutics cannot decompress the majority of the vessels but only a percentage of them[18,20,47,52].

Sonopermeation for instant mechano-modulation of the TME

Ultrasound is a widely utilized imaging modality in medical diagnostics, known for its safety and ability to provide real-time imaging. Over the past several decades, its use has expanded beyond diagnostics, gaining considerable attention in the field of therapeutic applications. Researchers have increasingly explored its potential in treating various medical conditions, recognizing the versatility and non-invasive nature of ultrasound technology in both imaging and therapy[62–65]. Because ultrasound can be focused, it is used to deliver energy to small volumes deep inside the body without affecting intermediate tissues. The use of ultrasound in the presence of exogenous gas bubbles (i.e., microbubbles) can lead to the development of local forces strong enough to cause membrane permeabilization of cells (Fig. 1). Specifically, sonopermeation works both through the formation of transient pores in endothelial cell membranes (traditional sonoporation), as well as via the opening of intercellular (tight) junctions[66,67], stimulated endocytosis, transcytosis and/or exocytosis[68,69] and causing macroscopic changes in perfusion[70] and/or changes in the perivascular and extracellular space of tumors[71]. As pressure waves move through tissues, microbubbles expand during the low-pressure (rarefaction) phases and contract during the high-pressure (compression) phases, producing volume oscillations that align with the applied ultrasound frequency. This oscillation creates a circulating fluid flow called microstreaming. When microbubbles are close to the endothelium, they can deform the cell membrane and may induce pore formation. At higher acoustic pressures, the oscillations become larger, leading to bubble collapse. The oscillation and collapse of microbubbles can also generate free radicals, which may increase cytotoxicity and lead to potential cell death[72]. Sonopermeation effects last between 4 and 24 h, with no significant effect beyond 24 h[73,74].

The promise of sonopermeation to improve perfusion and enhance the delivery of chemotherapeutics or nano-scale drugs to cancer has been extensively investigated in several preclinical studies. It has been demonstrated that combining sonopermeation with gemcitabine in a pancreatic adenocarcinoma mouse model resulted in more effective cancer treatment than gemcitabine alone, significantly inhibiting primary tumor growth, delaying metastasis formation, and extending the survival of the mice[75]. Recently, a study on pancreatic tumors found that combining sonopermeation with FOLFIRINOX (fluorouracil, irinotecan, oxaliplatin, and calcium folinate) significantly enhanced platinum uptake compared to untreated tumors or single-agent therapy[76]. Furthermore, when exposed to

ultrasound and microbubbles, increased tumor uptake of nanoparticle liposomal doxorubicin (Doxil) has been demonstrated in murine subcutaneous colorectal[77] and prostate adenocarcinoma[78] models and enhanced encapsulation of cabazitaxel in prostate cancer[79]. In a recent study[80], employment of sonopermeation in neuroblastoma xenografts increased Doxil uptake by increasing vascular lumen, disrupting tight junctions, inducing greater apoptosis, and resulting in increased survival. Assessment for side effects and toxicity in other organs, such as lung, liver, and kidney proved that treatment was safe. There was no evidence for injury in these organs, the red blood cell deposition within the lung capillaries was normal, as well as, the vasculature in the liver tissues. Also, there was no change in circulating tumor cells.

While sonopermeation primarily enhances drug delivery and therapeutic efficacy by facilitating the penetration of therapeutic agents into cells, it can also indirectly affect the TME through its influence on tumor cells and surrounding tissues. Besides forming transient pores, sonopermeation alters tumor perfusion and the TME. It has been reported that sonopermeation reduces intratumoral solid stress, improving perfusion in murine models of prostate adenocarcinoma and osteosarcoma[81]. Specifically, sonopermeation significantly enhanced perfusion, as shown by contrast-enhanced ultrasound (CEUS) imaging, and reduced tumor microvascular density, indicating vascular normalization of the TME in colon cancer[82]. These findings suggest that combining ultrasound with microbubbles can normalize TME and restore tumor perfusion. The enhanced perfusion may alter immune-suppressive factors, potentially increasing immune cell infiltration into hypo-vascular tumors. Effective immunotherapy relies heavily on sufficient $CD8^+$ T-cell infiltration, and sonopermeation not only can improve immunotherapy delivery but also it can significantly increase the percentage of infiltrating cytotoxic $CD8^+$ T-cells in murine models of colon cancer[83] and melanoma[84,85].

Sonopermeation efficacy has been studied in clinical trials, showing that ultrasound and microbubbles enhance the effects of conventional chemotherapy in patients with pancreatic cancer, liver metastases from colon cancer, and hepatic metastases from digestive system tumors[86–89]. A combination of gemcitabine and sonopermeation in ten inoperable pancreatic cancer patients has shown that can extend survival without causing additional toxicities[86]. Notably, the use of sonopermeation also allowed patients to undergo more treatment cycles, which corresponded to a longer period of well-being. However, recent findings indicated that sonopermeation did not enhance chemotherapy efficacy in patients with liver metastases[88,89], but still, several studies are currently underway involving patients with breast cancer, glioblastoma, pancreatic cancer, liver metastases from breast and colorectal cancer, and brain metastases from melanoma[90,91] (NCT03322813, NCT03477019, NCT04146441, NCT04021420, NCT03458975, and NCT03385200). These studies aim to further investigate the efficacy, safety, and clinical feasibility of this therapeutic strategy.

Despite these promising advancements, hypo-perfusion caused by vessel compression significantly undermines the effectiveness of sonopermeation, as microbubbles cannot be delivered effectively and uniformly in hypo-perfused tumors. This results in localized effects rather than a comprehensive therapeutic impact, ultimately compromising the overall efficacy of this treatment strategy[75,92].

Mechanotherapeutics and sonopermeation uniquely complement each other and optimize treatment efficacy in sarcomas

From the above analysis, it is reasonable to argue that mechanotherapeutics, by opening up some tumor vessels and improving tumor perfusion can significantly increase the distribution of microbubbles within the tumor, thereby enhancing the efficacy of sonopermeation. Furthermore, it has been recently reported that sonopermeation can reduce intratumoral solid stress and thus, improve perfusion[81]. Consequently, sonopermeation could support the use of mechanotherapeutics to further alleviate mechanical forces in tumors and potentially open up more tumor vessels, allowing more microbubbles and anti-cancer drugs to enter the tumor and thus, creating a positive feedback loop. Therefore, it makes good sense to argue that the mechano-modulation of the TME by combining mechanotherapeutics and sonopermeation will not only have additive effects but, due to the synergistic mechanisms and complementarity of the two methods, may yield multiplicative improvements in perfusion and therapeutic outcomes (Fig. 1).

To test this hypothesis, we conducted in vivo studies on sarcoma models[93] (Fig. 2). Our results showed that combining the mechanotherapeutic ketotifen with sonopermeation demonstrated optimal improvements in several key physiological parameters. Specifically, there was a statistically significant reduction in the tumor's elastic properties, as measured by Shear Wave Elastography (SWE), indicating a decrease in tissue stiffness, presumably due to a reduction in hyaluronan levels. This dual approach not only improved tumor perfusion but also facilitated more efficient drug delivery resulting in enhanced anti-tumor effectiveness of nano-immunotherapy. Consequently, blood vessel functionality was enhanced, leading to improved infiltration of immune cells -including $CD8^+$ T-cells- and a decrease of immunosuppressive Tregs, thereby strengthening the immune response against the tumor. To summarize, our study presented evidence that mechano-modulation of the TME through the combined use of mechanotherapeutics and sonopermeation can yield multiple, synergistic effects[93]. The combination of these strategies appears to amplify treatment efficacy beyond the benefits observed when each therapeutic method is applied separately.

Conclusions

Tumor stiffening and elevation of mechanical forces within its solid components compress tumor blood vessels, reducing blood flow and hindering uniform and efficient drug delivery, ultimately weakening treatment effectiveness[8,27,45]. As a result, standard therapies struggle to treat highly desmoplastic tumors effectively[2–5]. One therapeutic approach to alleviate blood vessel compression and enhance perfusion involves the use of mechanotherapeutics, which work to reduce stiffness and relieve mechanical forces within tumors[46]. Ultrasound-mediated drug delivery with microbubbles is another strategy that could noninvasively enhance perfusion and thus, the transport of therapeutic agents to targeted tumors via sonopermeation. Although both strategies have shown promising results, each has encountered certain limitations.

The innovative concept of combining mechanotherapeutics with sonopermeation into a unified approach offers a potential solution to these challenges. This combined strategy could establish a new foundation for treating highly desmoplastic cancer types, ultimately enhancing therapeutic outcomes and overcoming barriers that individual methods alone cannot fully address. In our previous study[93], we have shown for the first time, that mechano-modulation of the TME by combining mechanotherapeutics and sonopermeation can have multiplicative synergistic effects on improving perfusion and therapeutic outcomes. Importantly, mechanotherapeutics and sonopermeation synergistically modulated TME in sarcomas without causing any toxicity effects to the mice as the mouse weight, which was monitored throughout the treatment period for each group remained almost the same with no significant differences. While more research is needed, the current evidence suggests that mechanotherapeutics and sonopermeation have the potential to significantly improve drug delivery, enhance therapeutic response, and extend patient survival, offering a promising alternative for challenging cancers with poor prognosis.

Translating mechanotherapeutics and sonopermeation from preclinical models to humans involves challenges related to biological differences, safety, and feasibility. Variations in tissue structure and vascular properties between mice and humans can impact treatment efficiency and drug distribution. Scaling ultrasound parameters like frequency, intensity, and duration is crucial to maximize efficacy while avoiding off-target effects. Immune response differences and inadequate replication of the human tumor microenvironment in animal models further complicate translation. Regulatory hurdles and the need for standardized protocols add to the complexity. Glioblastomas may benefit most from this approach due to improved blood-brain barrier disruption, enhancing drug delivery. Other solid tumors, like pancreatic cancer,

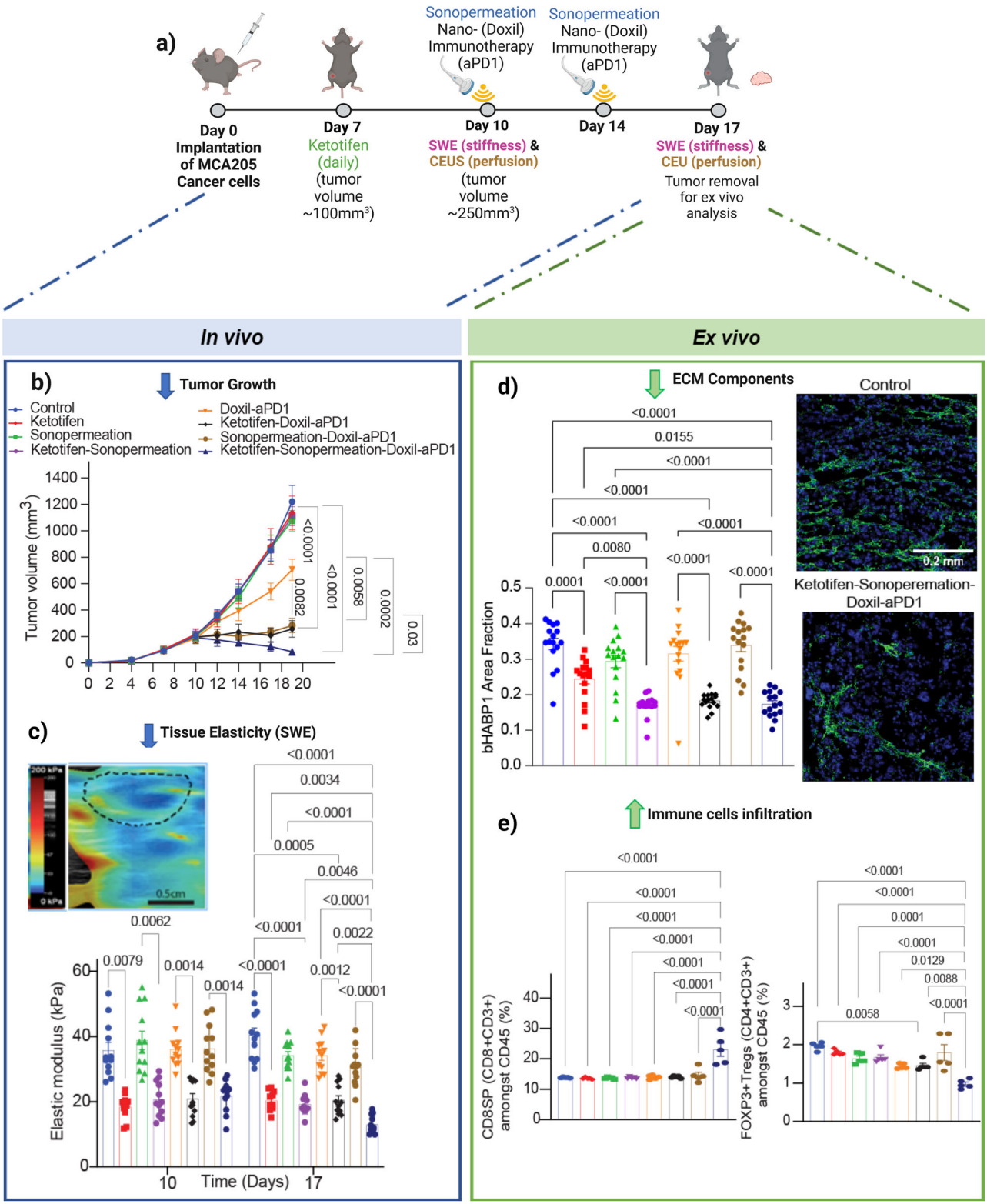

Fig. 2 | Mechanotherapy and sonopermeation synergistically overcome abnormalities in the tumor microenvironment and improve the effectiveness of nano-immunotherapy in sarcomas. a Experimental treatment protocol in MCA205 fibrosarcoma tumors. Created with BioRender.com. Combined treatment decreases **b** tumor growth, **c** tissue elasticity, **d** hyaluronan binding protein (bHABP1, green), and **e** boosts immune cell infiltration. Data adapted with permission from ref.[93].

triple-negative breast cancer, and desmoplastic sarcomas, could also benefit by increasing drug penetration and immune cell infiltration. Effective translation to humans will require tailored ultrasound protocols and thorough safety evaluations of drugs to ensure a successful application.

Data availability

No datasets were generated or analyzed during the current study.

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Author contributions

All authors contributed to the conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—review editing, and visualization of the article. C.N. and F.M. were responsible for writing the original draft. T.S. and F.M. were responsible for supervision and project administration and funding acquisition.

Competing interests

The authors declare no competing interests.

Additional information

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