No entanto, as *stablecoins* ainda têm algumas limitações. Por exemplo, não há a garantia de que uma *stablecoin* consiga manter o seu valor, apesar de estar associado a um índice ou reserva.

Sucede também que muitas *stablecoins* podem não ser completamente transparentes. Moedas como o *Tether* (USDT) e o *USD Coin* (USDC) ainda não lançaram auditorias públicas completas.

Cabe referir que a *stablecoin* mais popular atualmente é a *Tether* (USDT), sendo a terceira criptomoeda mais transacionada no mercado, tendo esta sido criada em 2018, a qual é indexada ao dólar.

As fiat-*backed stablecoins* são geralmente "mais centralizadas" do que outras criptomoedas. Uma entidade central é responsável pela criptomoeda e detém o valor de garantia, o que permite a sua sujeição à regulação financeira externa, o que confere um controlo significativo sobre a *stablecoin*.

ULTRASOUND REVOLUTION: BREAKING BARRIERS IN BRAIN CANCER THERAPY[470]

Mariana Varela Pereira[471]

Abstract: Focused ultrasound enables targeted drug delivery through temporary blood-brain barrier openings. This non-invasive technology enhances the effectiveness of treatments such as chemotherapy and immunotherapy while minimising damage to healthy tissue. Recent studies suggest using focused ultrasound for adult and paediatric brain tumours results in improved intratumoural drug concentration and penetration, alongside reducing tumour progression. While still ongoing clinical trials, this innovative approach offers new promise for more precise and effective brain cancer treatments.

Keywords: Focused Ultrasound; Brain tumours; Technology; Novel therapies.

[470] In this text, we have exceptionally preserved the author's original quotation style.

[471] PhD Researcher in Virotherapies for Paediatric Brain Tumours, Cardiff University; ORCA ID: A29982730.

In recent years, the use of Focused Ultrasound for the treatment of visceral diseases has exponentially increased, correlating with its associated research in the cancer therapy domain. Focused ultrasound is akin to channelling the sun's energy through a magnifying glass to start a small flame on a leaf. Practical application of this analogy involves the utilisation of an acoustic lens to precisely direct multiple converging ultrasound beams towards a deep target within the body, ensuring elevated levels of accuracy and precision. This mechanism of action involves generating both mechanical and thermal energy, which is transmitted through either high-pressure or low-pressure waves[472]. Focused Ultrasound produces reversible transient effects within tissue that are advantageous for therapeutic strategies such as the opening of the blood-brain barrier and neuromodulation. Conversely, the therapy may elicit irreversible effects including the destruction of tissue and clot lyses[473].

This novel technology has opened numerous doors pertaining to challenging medical conditions such as brain cancer. Brain cancer presents with numerous distinct subtypes, even when comparing adult to paediatric cases due to their tumours, growth patterns, genetic modifications and responses to treatment varying significantly between age groups. A significant obstacle in treatment of all known brain cancers is the inhibition of effective treatment delivery to tumour sites by the blood-brain barrier. The blood-brain barrier is a semi-permeable membrane consisting of several key components working dynamically to protect the brain. These include an endothelial lining with tight junctions to prevent the passage of harmful substances, pericytes that assist in blood flow regulation and structural support, microglia as the brain's resident immune cells, and astrocytic end-feet interacting with surroun-

[472] Haar G ter. Physical Principles of Focused Ultrasound Therapy. CRC Press eBooks. 2024 Jun 19;11–8.

[473] Arulpragasam AR, van 't Wout-Frank M, Barredo J, Faucher CR, Greenberg BD, Philip NS. Low Intensity Focused Ultrasound for Non-invasive and Reversible Deep Brain Neuromodulation-A Paradigm Shift in Psychiatric Research. Frontiers in Psychiatry. 2022;13:825802.

ding blood vessels to maintain the blood-brain barrier integrity. Lastly, the basement membrane, which is enriched with extracellular matrix proteins to provide structural support and further contribute to the barrier's selective permeability[474]. Together these elements regulate the movement of substances between the bloodstream and the brain, ensuring a protected environment for neural tissue. The blood-brain barrier is an efficient protective shield boasting numerous localised ancillary benefits, but its efficacy simultaneously poses a significant challenge for brain-targeted therapies. This issue extends beyond treatments for brain cancer, limiting the success of therapies for numerous neurological disorders, including Alzheimer's and Parkinson's diseases.

Focused Ultrasound's focal development principle revolves around providing a non-invasive approach which can potentially improve a patient's quality of life while simultaneously reducing overall treatment costs. The treatment provides a safe, targeted, and reversible method to increase transient permeability of the blood-brain barrier[475]. This permeability may significantly enhance the effective delivery of therapeutic solutions, such as pharmacological agents, stem cells, immunotherapeutics, and provide additional support for future delivery-vehicles including nanoparticles. Furthermore, the immense versatility of this technology for the field of oncology applies to not only treatment options, but to the initial diagnosis and further procedures involved in patient aid. Current research is investigating the use of focused ultrasound as a pre-surgical tool to precisely map and define tumour boundaries[476].

[474] Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood–brain barrier: structure, regulation, and drug delivery. Signal Transduction and Targeted Therapy. 2023 May 25;8(1):1–27.

[475] Gorick CM, Breza VR, Nowak KM, Cheng VWT, Fisher DG, Debski AC, et al. Applications of focused ultrasound-mediated blood-brain barrier opening. Advanced Drug Delivery Reviews. 2022 Dec 1;191:114583.

[476] Dixon L, Lim A, Grech-Sollars M, Nandi D, Camp S. Intraoperative Ultrasound in Brain Tumor surgery: a Review and Implementation Guide. Neurosurgical Review. 2022 Mar 30;45(4):2503–15.

In brain tumour research, ultrasound therapy has progressed through pilot trials for astrocytomas, pontine gliomas, and neuroblastomas; However, in glioblastomas, the therapy has advanced to pivotal trials[477]. The Microbubble-enhanced Focused Ultrasound (MB-FUS) approach enables temporary blood-brain barrier opening at the tumour site via low-pressure waves which facilitate combined treatments with drugs, genetic therapies, or immunotherapy while minimising damage to healthy tissue[478]. This approach utilises 1–2 μm microbubbles alongside low acoustic emissions to induce chemical rectified diffusion, which causes the bubbles to expand. This expansion generates physical pressure on the endothelial lining of the blood-brain barrier, leading to tissue disruption at the tight-junctions and barrier opening. The physical stimuli from this process results in ion channel response activation, causing them to open and thus, further increasing the overall permeability across the barrier.

Numerous *in vitro* and *in vivo* studies have examined the safe parameters for administering this therapy, with findings suggesting that an optimal pressure range of 75 to 150 kPa is necessary to achieve effective and safe blood-brain barrier opening[479]. This pressure range ensures sufficient permeability while minimising the risk of tissue damage, defining it as a critical factor for the successful application of the therapy in clinical settings. The literature defines the pressure level at which the stability of the environment becomes compromised as "the Blake threshold", and exceeding this threshold in-

[477] Schoen S, Kilinc MS, Lee H, Guo Y, Degertekin FL, Woodworth GF, et al. Towards Controlled Drug Delivery in Brain Tumors with microbubble-enhanced Focused Ultrasound. Advanced Drug Delivery Reviews. 2022 Jan;180:114043.

[478] Seas AA, Malla AP, Sharifai N, Winkles JA, Woodworth GF, Anastasiadis P. Microbubble-Enhanced Focused Ultrasound for Infiltrating Gliomas. Biomedicines. 2024 Jun 1;12(6):1230–0.

[479] Aleksandra Ćwiklińska, Dominika Przewodowska, Dariusz Koziorowski, Stanisław Szlufik. Innovative Approaches to Brain Cancer: the Use of Magnetic Resonance-Guided Focused Ultrasound in Glioma Therapy. Cancers. 2024 Dec 19;16(24):4235–5.

creases the risk of inertial cavitation. Inertial cavitation occurs when bubbles rapidly expand and collapse due to intense pressure changes which release significant amounts of energy[480]. This process can lead to a range of harmful effects, including tissue damage, localised heating, and the generation of shockwaves. The mechanical forces generated during cavitation can disrupt cell membranes, blood vessels, and the surrounding tissue, potentially causing injury or aggravating preexisting inflammation. When controlled, inertial cavitation can enhance therapeutical outcomes, but uncontrolled occurrence may conversely pose elevated risks to the surrounding healthy tissue[481].

For most brain cancers, temozolomide is the primary pharmacological treatment option due to it being the only currently available treatment agent capable of crossing the blood-brain barrier. While the compound can penetrate the barrier, the effective concentration found within the brain is significantly diminished compared to the initial dosage administered[482]. Several studies conducted since 2017 have evaluated various properties of temozolomide alongside other drugs such as etoposide, doxorubicin, paclitaxel, carboplatin, cisplatin, and irinotecan with regards towards their cerebral drug concentration, inhibition of tumour growth, and the survival rates of patients when administered with assistance from focused ultrasound against traditional administration. Notably, compounds administered alongside focused ultrasound resulted in further

[480] López-Aguirre M, Castillo-Ortiz M, Viña-González A, Blesa J, Pineda-Pardo JA. The Road Ahead to Successful BBB Opening and drug-delivery with Focused Ultrasound. Journal of Controlled Release. 2024 Aug;372:901–13.

[481] George B, Savšek U, Fischer D, Ermert H, Rupitsch SJ. Investigation of Inertial Cavitation Induced by Modulated Focused Ultrasound Stimuli. Current Directions in Biomedical Engineering. 2022 Aug 1;8(2):459–62.

[482] Lam M, Aw J, Tan D, Vijayakumar R, Yi H, Yada S, et al. Unveiling the Influence of Tumor Microenvironment and Spatial Heterogeneity on Temozolomide Resistance in Glioblastoma Using an Advanced Human in Vitro Model of the Blood- Brain Barrier and Glioblastoma. Small. 2023 Aug 30.

decreased tumour growth and heightened cerebral drug concentration at tumour sites compared to those applied under traditional methods[483]/[484].

In addition to enhancing permeability of the blood-brain barrier in conjunction with focused ultrasound, microbubbles provide additional therapeutic support by acting as a pharmacological delivery system capable of specifically targeting malignant cell with further minimised impact on surrounding healthy tissue. One such treatment is Boron Neutron Capture Therapy (BNCT), which uses boron-containing compounds that are preferentially absorbed by tumour cells. When these cells are exposed to a neutron beam, a nuclear reaction occurs, releasing toxic alpha particles that destroy the tumour while sparing surrounding healthy tissue[485]. Recent studies have explored combining focused ultrasound with microbubble technology to improve BNCT. Experiments performed in an animal glioblastoma multiforme (GBM) model, utilised VEGF-targeted microbubbles loaded with BCNU (a chemotherapy drug used in BNCT) to significantly increase the drug's concentration at the targeted site, leading to a marked reduction in tumour progression[486]. This approach, combining targeted drug delivery with focused ultrasound, could potentially improve the effectiveness of BNCT for treating malignant brain tumours.

[483] Park J, Aryal M, Vykhodtseva N, Zhang YZ, McDannold N. Evaluation of permeability, Doxorubicin delivery, and Drug Retention in a Rat Brain Tumor Model after ultrasound-induced blood-tumor Barrier Disruption. Journal of Controlled Release. 2017 Mar;250:77–85.

[484] Wei HJ, Upadhyayula PS, Pouliopoulos AN, Englander ZK, Zhang X, Jan CI, et al. Focused Ultrasound-Mediated Blood-Brain Barrier Opening Increases Delivery and Efficacy of Etoposide for Glioblastoma Treatment. International Journal of Radiation Oncology*Biology*Physics. 2021 Jun;110(2):539–50.

[485] Yura Y, Fujita Y, Hamada M. Ultrasound Combination to Improve the Efficacy of Current Boron Neutron Capture Therapy for Head and Neck Cancer. Cancers. 2024 Aug 5;16(15):2770–0.

[486] Fan CH, Wang TW, Hsieh YK, Wang CF, Gao Z, Kim A, et al. Enhancing Boron Uptake in Brain Glioma by a Boron-Polymer/Microbubble Complex with Focused Ultrasound. ACS Applied Materials & Interfaces. 2019 Mar 18;11(12):11144–56.

Low-intensity focused ultrasound used in combination with microbubbles is primarily recognised as a drug delivery method, however, recent studies have highlighted that the technique is also capable of producing inflammatory responses in healthy mice brains[487]. This is particularly relevant as new insights into the brain's immune surveillance, including the discovery of lymphatic vessels in the meninges, have sparked renewed interest in immunotherapy for brain tumours[488]. While treatments like anti-PD1 immunotherapy have proven effective against brain metastases, they have displayed limited success in primary brain tumours such as glioblastoma (GBM). This is largely due to the challenges of targeting immune cells within the tumour microenvironment and the restrictive nature of the blood-brain barrier in addition to the blood-tumour barrier. PD-1, a receptor on T-cells, suppresses immune activity when bound to PD-L1, a protein overexpressed by GBM cells to evade immune detection; anti-PD1 therapies block this interaction, thereby reactivating T-cells to attack GBM. By temporarily increasing blood-brain barrier permeability and modulating the tumour microenvironment, MB-FUS offers a promising approach to enhance the efficacy of immunotherapies[489].

In conclusion, focused ultrasound (FUS) represents a groundbreaking advancement in the treatment of brain tumours, offering a versatile, non-invasive approach to overcome the challenges posed by the blood-brain barrier. Its ability to enhance drug delivery, modulate the tumour microenvironment, and complement existing therapies, such as immunotherapy, underscores its transformative potential in oncology. Clinical trials and preclinical studies have demonstrated promising results in brain tumour therapies, where effective drug delivery remains a critical hurdle. As research progresses, the integration of FUS with emerging treatments could redefine the standard of care, providing safer, more precise, and effective solutions for patients with malignant brain tumours.

[487] Choi HJ, Han M, Seo H, Park CY, Lee EH, Park J. The New Insight into the Inflammatory Response following Focused ultrasound-mediated Blood–brain Barrier Disruption. Fluids and Barriers of the CNS. 2022 Dec 23;19(1).

[488] Zhou C, Xu H, Luo J. Meningeal Lymphatic vasculature, a General Target for Glioblastoma therapy? Fundamental Research. 2023 May 3;4(2):267–9.

[489] Lee H, Guo Y, Ross JL, Schoen S, Degertekin FL, Arvanitis C. Spatially Targeted Brain Cancer Immunotherapy with closed-loop Controlled Focused Ultrasound and Immune Checkpoint Blockade. Science Advances. 2022 Nov 16;8(46).