Human and mouse breast and lung cancer cells express protocadherin 7 (PCDH7), which promotes the assembly of carcinoma-astrocyte gap junctions composed of connexin 43 (Cx43). Once engaged with the astrocyte gap-junctional network, brain metastatic cancer cells use these channels to transfer the second messenger cGAMP to astrocytes, activating the STING pathway and production of inflammatory cytokines such as interferon-α (IFNα) and tumor necrosis factor (TNF). As paracrine signals, these factors activate the STAT1 and NF-κB pathways in brain metastatic cells, thereby supporting tumour growth and chemoresistance. The orally bioavailable modulators of gap junctions meclofenamate and tonabersat break this paracrine loop, and we provide proof-of-principle that these drugs could be used to treat established brain metastasis [1].

1)
Chen Q, Boire A, Jin X, Valiente M, Er EE, Lopez-Soto A, Jacob LS, Patwa R, Shah H, Xu K, Cross JR, Massagué J. Carcinoma-astrocyte gap junctions promote brain metastasis by cGAMP transfer. Nature. 2016 May 18;533(7604):493-8. doi: 10.1038/nature18268. PubMed PMID: 27225120; PubMed Central PMCID: PMC5021195.