

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 (IFN α) and [tumor necrosis factor](#) (TNF). As paracrine signals, these factors activate the STAT1 and NF- κ B 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.

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