SUSTAINED PAIN

CHANGING OUTCOME MEASURES FOR TARGETED PAIN THERAPY

TAKHLIQ AMIR

Chronic pain affects almost one-fifth of Canadians, representing around 6 million people.[1] Normally, the reaction to painful stimuli involves two distinct responses. The first-line response is a reflexive withdrawal to prevent or limit injury, while the second-line response involves coping behavioural reactions, such as pressing on an injury to alleviate sustained pain.[2,3] Despite being considered important evolutionary responses, the mechanism by which these signals travel between the body and the brain remains unknown.

A recent study published by Huang et al. presents an answer to this, demonstrating that separate neural pathways govern the reflexive and coping responses following an injury.[4] The researchers suggest that TAC1 neurons, located in the dorsal horn of the spinal cord, mediate the sustained pain nerve-signalling pathway. By assessing pain response in TAC1-intact mice in comparison to mice with chemically-inactivated TAC1 neurons, the researchers showed that TAC1-disabled mice exhibited loss of pain-coping behaviours (e.g. paw licking), with no effect on normal withdrawal reflexes.[4] In contrast, TAC1-intact mice exhibited normal prolonged paw licking following injury. It was further concluded that TRPV1 neurons, which are known to mediate the sensation of prolonged pain, connect to TAC1 neurons in the dorsal horn to relay pain signals to the brain.[4]

These findings are of great significance because of their clinical "bench-to-bedside" implications. Current methodologies to assess the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the sustained pain response due to tissue damage.[5,6] The researchers suggest that measuring the wrong outcome could have discounted some drug therapies as ineffective when they may have successfully ameliorated sustained pain. With the costly societal impacts of chronic pain and the ongoing opioid epidemic, the research by Huang et al. presents a new opportunity to develop treatments prioritizing the deep, sustained pain response over reflexive withdrawal behaviours.

1. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. *Pain Res Manag.* 2011;16(6):445-50. Available from: doi:10.1155/2011/876306.
2. Pesheva E. *Nerve-signaling pathway that drives sustained pain found* [Internet]. 2018 Dec 13. Available from: https://news.harvard.edu/gazette/story/2018/12/researchers-identify-pathway-that-drives-sustained-pain-following-injury/ [cited 2019 Feb 15].
3. Price DD, Dubner R. Mechanisms of first and second pain in the peripheral and central nervous systems. *J Invest Dermatol.* 1977;69(1):167-71. Available from: doi:10.1111/1523-1747.ep12497942.
4. Huang T, Lin SH, Malewicz NM, Zhang Y, Zhang Y, Goulding M, et al. Identifying the pathways required for coping behaviours associated with sustained pain. *Nature.* 2019;565(7737):86. Available from: doi:10.1038/s41586-018-0793-8.
5. J Cobos E, Portillo-Salido E. "Bedside-to-bench" behavioral outcomes in animal models of pain: Beyond the evaluation of reflexes. *Curr Neuropharmacol.* 2013;11(6):560-91. Available from: doi:10.2174/1570159X113119990041.
6. Smith ES. Advances in understanding nociception and neuropathic pain. *J Neurol.* 2018;265(2):231-8. Available from: doi:10.1007/s00415-017-8641-6.

OSTEOPOROSIS

A NEW MOLECULAR RECEPTOR LINKING EXERCISE AND BONE DEVELOPMENT

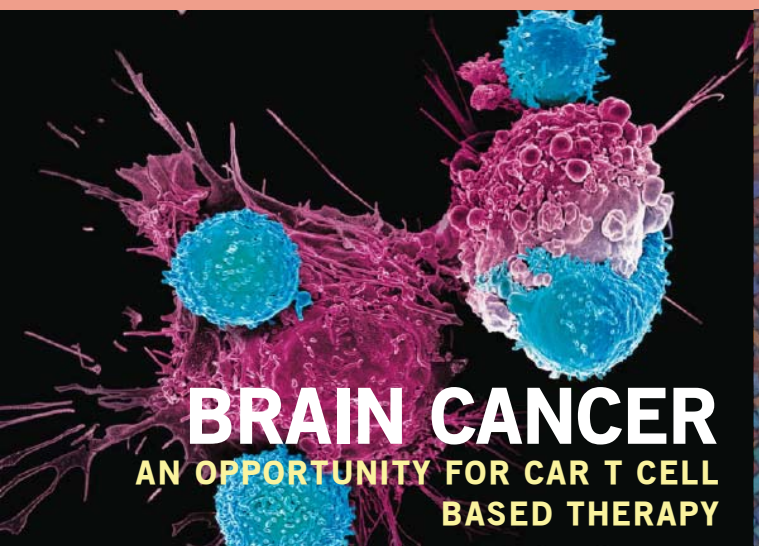
TAKHLIQ AMIR

Osteoporosis is a disorder characterized by the age-related weakening of bone, and is commonly associated with the decrease in estrogen production in women over time.[1] It is estimated that over 2 million Canadians suffer from osteoporosis.[2] The decrease in bone mineral density occurs when the rate of bone resorption exceeds formation, a process largely mediated by osteocytes, the most abundant regulatory cells found in bones.[3] Since osteocytes decrease in number over time, they play a key role in the pathogenesis of age-related osteoporosis.

Irisin is a hormone released by muscles during exercise that was discovered in 2012.[4] Despite its demonstrated beneficial effects in exercise, the underlying role of irisin in the molecular mechanisms of exercise and bone development has been unclear. A team of researchers from the Dana-Farber Cancer Institute recently discovered new irisin receptors, which may represent the link between exercise and bone development.[5] The newly discovered irisin receptors belong to the αV class of integrins, and enable irisin to bind to and activate osteocytes.[6] Using a mouse model, the group demonstrated that injection of irisin elevated sclerostin levels, which is characteristic of bone resorption.[6] Additionally, in mice that had undergone ovariectomies to simulate osteoporosis, the genetic ablation of irisin hindered osteocytic osteolysis, thereby protecting against bone loss.[6]

The discovery of irisin receptors has the potential to influence future therapies for osteoporosis. Despite its role in bone resorption, some patients have shown improvements in bone density following intermittent irisin treatment.[7] Future steps include investigating isoforms of irisin and its receptors as well as irisin inhibitors. Researchers are also interested in further exploring irisin's potentially differential effects in other areas where it is highly expressed, including skeletal muscle, the heart, and the brain.[6]

1. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: Now and the future. *Lancet.* 2011;377(9773):1276-87. Available from: doi:10.1016/S0140-6736(10)62349-5.
2. Osteoporosis Canada. *Impact Report 2018.* Canada: Osteoporosis Canada; 2018. 6 p.
3. Rochefort GY. The osteocyte as a therapeutic target in the treatment of osteoporosis. *Ther Adv Musculoskelet Dis.* 2014;6(3):79-91. Available from: doi:10.1177/1759720X14523500.
4. Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature.* 2012;481(7382):463. Available from: doi:10.1038/nature10777.
5. Saltus R. 'Exercise hormone' found to target key bone cells [Internet]. *The Harvard Gazette.* 2018 Dec 14. Available from: https://news.harvard.edu/gazette/story/2018/12/exercise-related-hormone-irisin-found-to-target-key-bone-cells/ [cited 2019 Feb 14].
6. Kim H, Wrann CD, Jedrychowski M, Vidoni S, Kitase Y, Nagano K, et al. Irisin mediates effects on bone and fat via αV integrin receptors. *Cell.* 2018;175(7):1756-68. Available from: doi:10.1016/j.cell.2018.10.025.
7. Colaianni G, Mongelli T, Cuscito C, Pignataro P, Lippo L, Spiro G, et al. Irisin prevents and restores bone loss and muscle atrophy in hind-limb suspended mice. *Sci Rep.* 2017;7(1):2811. Available from: doi:10.1038/s41598-017-02557-8.



BRAIN CANCER

AN OPPORTUNITY FOR CAR T CELL BASED THERAPY

JAMES YU

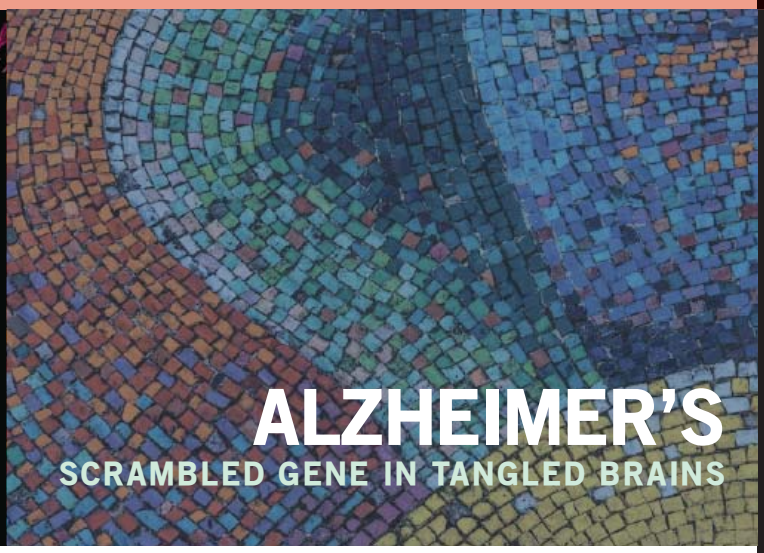
Chimeric antigen receptor (CAR) T cells are genetically-engineered T cells that bind to specific tumour markers via their CAR receptors. This leads to CAR T cell proliferation and elimination of their target cancer cells.[1] However, creating CAR T cells that target solid tumours is difficult because tumour tissues frequently downregulate ligands recognized by T cells.[1] Furthermore, brain cancers, including glioblastoma, are protected by the blood-brain barrier, which prevents CAR T cells from accessing these targets.

However, a recent study conducted by Samaha et al. could circumvent this challenge. Samaha et al. noted that cancer endothelial cells overexpress a protein called activated leukocyte cell adhesion molecule (ALCAM).[2,3] Binding of the T cell CD6 ligand to ALCAM allows T cells to migrate out of the blood vessel and infiltrate the brain.[3,4] With this in mind, the researchers generated a highly-specific synthetic CD6 analogue with multiple binding domains for ALCAM, named homing-system CD6 (HS-CD6).[3,4] This new ligand was inserted into a CAR T cell that recognizes tumour-associated antigens commonly found in glioblastoma cells.[2] The CAR T cells were then tested in a mice model with surgically-implanted glioblastomas.

The researchers found that mice injected with the HS-CD6 CAR T cells experienced complete remission of cancer.[3] While this finding is promising, further research is required to see if this CAR T cell therapy can also persist in an immunosuppressive microenvironment and cause minimal toxicity.[1,4] Ultimately, the findings by Samaha et al. will likely contribute to a novel strategy to target solid brain tumours using CAR T cells.

Editor's note: "A homing system targets therapeutic T cells to brain cancer" by Samaha et al.[3] has been retracted in *Nature* as of 20 February, 2019 due to issues with figure presentation and underlying data.

1. D'Aloia MM, Zizzari IG, Sacchetti B, Pierelli L, Alimandi M. CAR-T cells: The long and winding road to solid tumors. *Cell Death Dis.* 2018;9(3):282. Available from: doi:10.1038/s41419-018-0278-6.
2. Platten M. T cells engineered to home in on brain cancer. *Nature.* 2018;561(7723):319–20. Available from: doi:10.1038/d41586-018-05883-7.
3. Samaha H, Pignata A, Fousek K, Ren J, Lam FW, Stossi F, et al. A homing system targets therapeutic T cells to brain cancer. *Nature.* 2018;561(7723):331–7. Available from: doi:10.1038/s41586-018-0499-y.
4. Brown MH, Dustin ML. Steering CAR T cells into solid tumors. *N Engl J Med.* 2019;380(3):289–91. Available from: doi:10.1056/NEJMcibr1811991.



ALZHEIMER'S

SCRAMBLED GENE IN TANGLED BRAINS

JAMES YU

Emerging evidence indicates that neurons in the brain can display somatic mosaicism, which means that they are genomically different from one another.[1] These genomic differences between neurons are the result of mutations during aging, and may contribute to the development of neurodegenerative diseases including Alzheimer's disease (AD).[1,2] Patients who develop AD have more copies of the *amyloid precursor protein (APP)* gene in their neurons than healthy individuals.[1]

In a groundbreaking study, Lee et al. suggest a mechanism by which abnormal forms of the *APP* gene can be incorporated into the neurons of patients with AD.[3] Normally, neurons transcribe mRNA copies of the *APP* gene, which can be translated into proteins for common brain functions such as learning and memory. However, in some cases, the reverse transcriptase enzyme can turn the RNA back into DNA, creating copies of the *APP* gene that can be added back into the neuron's genome in the form of genomic cDNAs (gencDNA).[3] Because reverse transcriptase is prone to making errors when converting RNA into DNA, the copies of the *APP* gene integrated back into the genome are often mutated variants. The cleavage of these mutated *APP* variants can result in the creation of toxic beta-amyloid plaques that interfere with brain function and cause sporadic AD.[1,3]

In accordance with age being one of the strongest risk factors for AD, Lee et al. found that *APP* gencDNA increased with age in murine models.[3,4] Furthermore, when reverse transcriptase inhibitors were introduced, the formation of *APP* gencDNA greatly decreased. Consequently, the researchers suggested that drugs blocking reverse transcriptase may affect AD onset. These findings may prompt novel investigations in AD pathophysiology, a field that has long been stagnant.

1. Bushman DM, Kaeser GE, Siddoway B, Westra JW, Rivera RR, Rehen SK, et al. Genomic mosaicism with increased amyloid precursor protein (APP) gene copy number in single neurons from sporadic Alzheimer's disease brains. *Elife.* 2015;4:e05116. Available from: doi:10.7554/eLife.05116.
2. Lodato MA, Rodin RE, Bohrson CL, Coulter ME, Barton AR, Kwon M, et al. Aging and neurodegeneration are associated with increased mutations in single human neurons. *Science.* 2018;359(6375):555–9. Available from: doi:10.1126/science.aao4426.
3. Lee MH, Siddoway B, Kaeser GE, Segota I, Rivera R, Romanow WJ, et al. Somatic APP gene recombination in Alzheimer's disease and normal neurons. *Nature.* 2018;563(7733):639–45. Available from: doi:10.1038/s41586-018-0718-6.
4. Verheijen BM, Vermulst M, van Leeuwen FW. Somatic mutations in neurons during aging and neurodegeneration. *Acta Neuropathol.* 2018;135(6):811–26. Available from: doi:10.1007/s00401-018-1850-y.