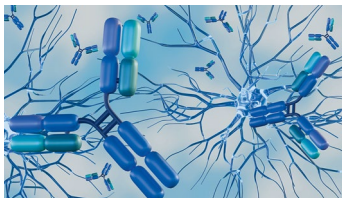
Neurodegenerative diseases

Transport vehicle delivers antibodies to the brain



The blood–brain barrier represents a considerable hurdle for drug delivery to the brain. A new study in *Science* describes a platform that uses the transferrin receptor (TfR) expressed on brain endothelial cells to transport a therapeutic antibody targeting amyloid-beta (Aβ) into the mouse brain. This approach showed improved brain distribution and safety compared with unshuttled Aβ-targeting antibodies.

Anti-Aβ antibodies are approved to treat Alzheimer disease (AD), but low brain penetrance necessitates high doses and could limit efficacy. Moreover, these antibodies are associated with amyloid-related imaging abnormalities (ARIA), which are caused by vascular inflammation in the brain and can be fatal.

In the current study, researchers at Denali Therapeutics used their Transport Vehicle platform, which is based on an antibody Fc domain engineered to bind TfR, leading to uptake by brain endothelial cells and transport into the brain parenchyma. In this case, the Fc domain was fused to an anti-Aβ antibody to form an antibody transport vehicle (ATV).

The researchers first sought to optimize the level of effector function of ATV. Some effector function is needed for therapeutic effect by enabling recruitment of microglia for amyloid clearance. However, reticulocytes express TfR, which could lead to depletion of these blood cells as a peripheral off-target effect if the antibody effector function were left unchecked.

By testing mutations in different locations in the Fc portion, the investigators found that asymmetric mutations in one Fc fragment (L234A/L235A) resulted in conditional antibody effector function only when bound to Aβ but not when bound to TfR, thus avoiding haematological liabilities in mice.

In an ex vivo flow cytometry assay in mouse brain cells incubated with amyloid, and in transgenic AD mice, the asymmetrically modified ATV was still able to recruit microglia and lead to amyloid clearance.

Confocal imaging of mouse brains 1 day post-dose showed broad distribution of the ATV throughout the brain parenchyma, reflecting uptake through brain capillaries expressing TfR. Standard anti-Aβ antibodies were present at lower overall brain concentration and were mainly localized to choroid plexus, perivascular regions, and brain tissue around arteries and arterioles.

Treatment with the ATV was associated with substantial reductions in ARIA-like lesions compared with a standard anti-Aβ antibody, as well as reduced vascular inflammation and disruption, possibly due to the pattern of distribution.

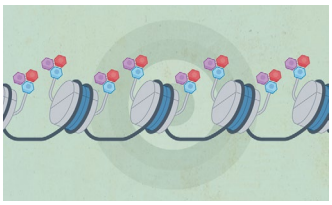
This platform could further unlock the potential of therapeutic antibodies in the brain and is being applied to deliver other drug modalities such as enzymes.

Katie Kingwell

Original article: Pizzo, M. E. et al. Transferrin receptor-targeted anti-amyloid antibody enhances brain delivery and mitigates ARIA. *Science* **389**, eads3204 (2025)

Anticancer drugs

Epigenetic inhibitor silences KRAS-driven oncogenes



The methyltransferase NSD2 (MMSET) catalyses the histone modification H3K36me2 — a mark associated with active gene transcription — and is deregulated in various cancers, including those with KRAS mutations. A paper in *Nature* describes small-molecule NSD2 inhibitors that restore silent chromatin at oncogenes and show efficacy in aggressive KRAS-driven tumour models.

NSD2 is overexpressed or overactive in many cancers and considered a promising drug target. For example, a prevalent chromosomal translocation t(4;14) causes NSD2 overexpression in multiple myeloma, and mutations in the catalytic SET domain enhance NSD2 activity in several malignancies. In mouse models, overactive NSD2 accelerates the growth of KRAS-driven tumours.

To identify NSD2 inhibitors, Jeong et al. synthesized a series of compounds based on a patent describing an NSD2 inhibitor, KTX-1001. Two of these compounds inhibited NSD2-mediated methylation of nucleosomes in vitro with IC_{50} values of about 8.8 nM and 19 nM, respectively, and were highly selective for NSD2 over related methyltransferases. The compounds also inhibited hyperactive NSD2 mutants and reduced the viability of KRAS-mutant cell lines.

High-resolution multidimensional NMR spectroscopy with the NSD2 SET domain indicated that the compounds inhibit the enzyme through multiple mechanisms, explaining their potency and selectivity. They interact with the binding pocket for the methyl donor S-adenosylmethionine, preventing its binding. In addition, interactions with residues in the catalytic tunnel would prevent H3K36 binding and promote an inactive state of the autoinhibitory loop.

Proteomic, epigenomic and transcriptomic analyses were performed on KRAS-driven cancer cell lines treated with an NSD2 inhibitor. Oncogenic gene expression programmes became suppressed, driven by depletion of H3K36me2 and gain of H3K27me3, a repressive histone modification. H3K27me3 invaded the genomic regions previously marked by H3K36me2 and restored them to their silenced state found in normal cell differentiation.

In KRAS-G12C-driven mouse models of pancreatic ductal adenocarcinoma and lung adenocarcinoma, intraperitoneal injection of the NSD2 inhibitors reduced tumour growth, extended survival and was well tolerated. Combining an NSD2 inhibitor with the approved KRAS-G12C inhibitor sotorasib had a synergistic effect.

The authors propose that the inhibitory mechanism of these compounds is relevant for developing selective inhibitors of other lysine methyltransferase targets. KTX-1001 and a related compound have entered phase I clinical trials for patients with multiple myeloma and metastatic prostate cancer, respectively.

Alex Eccleston

Original article: Jeong, J. et al. NSD2 inhibitors rewire chromatin to treat lung and pancreatic cancers. *Nature* https://doi.org/10.1038/s41586-025-09299-y (2025)