CXCR4 for CNS infections

By Brian Moy, Staff Writer

The purpose of the blood-brain barrier is to limit trafficking of leukocytes into the immune-privileged CNS. However, this becomes an undesirable trait when trying to clear acute CNS infections.¹ Indeed, one component of the body's response to viral encephalitis is the development of high titers of virus-specific T cells with only limited ability to invade the CNS parenchyma.²

Now, researchers at **Washington University School of Medicine** have enlisted chemokine (C-X-C motif) receptor 4 (CXCR4) antagonists to promote T cell trafficking across the barrier and thus treat acute viral infections of the CNS.³

The approach is not virus specific and thus could have broad applicability across multiple types of CNS infections, but some researchers worry that excessive entry of virus-specific T cells into the brain could have deleterious effects, such as autoimmune disease.

In the paper published in the *Proceedings of the National Academy of Sciences*, a team led by Robyn Klein, assistant professor of internal medicine in the Division of Infectious Diseases at the university's School of Medicine, showed that antagonizing CXCR4 promoted migration of virus-specific CD8⁺ T cells across the blood-brain barrier (BBB), which enhanced viral clearance and lowered immunopathology in mice with West Nile virus encephalitis.³

CXCR4 is the receptor for stromal cell-derived factor-1 (SDF-1), a cytokine that is strongly chemotactic for lymphocytes.

Infected mice treated with AMD3100, a CXCR4 antagonist from **Genzyme Corp.**, had significantly better survival than control mice treated with phosphate-buffered saline (PBS; $p=0.02$).

"Our findings suggest that promoting antiviral immune responses in the brain could be a new way to look at treating viral infections of the CNS," said Klein. "Rather than developing pathogen-specific therapies, CXCR4 antagonists or other agents that promote immune cell entry into the brain could be useful for treating any viral encephalitis that requires virus-specific CD8⁺ T cells to clear the infection."

—Robyn Klein,
Washington University
School of Medicine

Moreover, the authors of the *PNAS* paper wrote that "manipulation of the immune response by the use of chemokine receptor antagonists can promote an early increase in immune cell trafficking that controls viral infection, ultimately leading to a rapid dampening of inflammation that can have pathologic consequences."

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Table 1. CXCR4 pipeline. Selected compounds targeting chemokine (C-X-C motif) receptor 4 (CXCR4) in development.

Company	Product	Description	Indication	Status
Genzyme Corp. (NASDAQ: GENZ)	Mozobil plerixafor (AMD3100)	CXCR4 antagonist	Stem cell mobilization; tumor sensitization	FDA and EMEA review (stem cell mobilization); Phase II (tumor sensitization)
Chemokine Therapeutics Corp. (TSX:CTI; OTCBB: CHKT)	CTCE-9908	Stromal cell-derived factor-1 (SDF-1) analog ^A	Cancer	Phase I/II
Chemokine Therapeutics	CTCE-0214	SDF-1 analog ^A	Neutropenia; stem cell mobilization	Phase I
Polyphor Ltd.	POL6326	CXCR4 antagonist	Hematopoietic stem cell transplantation	Phase I
TaiGen Biotechnology Co. Ltd.	TG-0054	CXCR4 antagonist	Stem cell mobilization	Phase I
Metastatix Inc.	MSX-122	CXCR4 antagonist	Cancer	Phase I suspended
Biokine Therapeutics Ltd.	BKT140	CXCR4 antagonist	Cancer	Preclinical
Northwest Biotherapeutics Inc. (OTCBB:NWBO; LSE: NWBS)	mAb against CXCR4	mAb against CXCR4	Cancer	Preclinical
Metastatix	CXCR4 antagonists	Multiple CXCR4 antagonists	HIV; stem cell mobilization; cancer	Preclinical

^ASDF-1 is a ligand of CXCR4.

Traffic jam

Sofia Ribeiro, director of cell biology at **Metastatix Inc.**, said the *PNAS* paper “opens up an interesting possibility for treating CNS infections using CXCR4 antagonists. A drug that can promote rapid viral clearance and then restore normal T cell trafficking in the CNS would have a huge therapeutic advantage.”

Metastatix has a series of CXCR4 antagonists in preclinical development for HIV, stem cell mobilization and cancer. The company has suspended development of lead compound MSX-122, a CXCR4 inhibitor activated by SDF-1, for reasons that are undisclosed. The compound was in Phase I testing to treat solid tumors.

There are at least eight CXCR4 antagonists in preclinical and clinical development, the vast majority for cancer indications (see **Table 1, “CXCR4 pipeline”**). Mozobil plerixafor (AMD3100) is the most advanced, and is under FDA and EMEA review to mobilize stem cells for collection and transplantation in cancer patients. Genzyme acquired Mozobil through its acquisition of AnorMed Inc.

Genzyme said it has worldwide rights to Mozobil and would be exploring its full therapeutic potential.

Despite the new therapeutic real estate suggested by the *PNAS* article, companies with CXCR4 antagonists, including Genzyme, are not yet pursuing CNS infections. One reason is the concern that increased trafficking of virus-specific T cells across the BBB could cause potential problems.

Indeed, Klein noted that excessive entry of CD8⁺ T cells into the brain might lead to CNS-related autoimmune diseases, such as multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM).

However, she noted that “because MS is believed to be induced by autoreactive CD4 T cells, it is unclear whether increased entry of virus-specific CD8 T cells would induce this disease.”

Moreover, Ribeiro said that she is unaware of any CNS-related

adverse effects reported for Mozobil or any of the other CXCR4 antagonists in development.

In a pair of Phase III trials, Genzyme said the most common adverse events associated with Mozobil were GI-related and injection site reactions.

In the *PNAS* study, CXCR4 antagonists had no effect on CD4⁺ T cells and only promoted trafficking of CD8⁺ T cells. Thus, Klein said, “the lack of effect of CXCR4 antagonists on CD4⁺ T cell entry suggests that this treatment might not induce autoimmunity in the CNS.”

To address this issue, Klein and colleagues are studying whether increased penetration of virus-targeting immune cells into the brain parenchyma could stimulate autoimmune disease in mice predisposed to CNS autoimmunity.

Ribeiro suggested that acute use of CXCR4 antagonists would provide the optimal therapeutic regimen for treating CNS infections because there would be less of a chance that side effects could occur. “The goal is to temporarily increase T cell trafficking in the CNS without stimulating a situation with potentially significant side effects, such as autoimmune disease,” she said.

Ribeiro said additional research is needed to determine the side effects and safety profile associated with long-term use of CXCR4 antagonists when treating CNS infections.

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Contact: Robyn Klein, Washington University School of Medicine, St. Louis, Mo.
e-mail: rklein@id.wustl.edu

COMPANIES AND INSTITUTIONS MENTIONED

Genzyme Corp. (NASDAQ:GENZ), Cambridge, Mass.
Metastatix Inc., Tucker, Ga.
Washington University School of Medicine, St. Louis, Mo.