EAAT2 to mop up excess glutamate from extracellular space. Accumulation of the neurotransmitter can be toxic to myelin-making oligodendrocytes.

After spelling out the pathway in astrocyte in vitro assays, the team examined human tissue. Sure enough, NMO lesions along cadaver spines lacked both aquaporin–4 and EAAT2. Lesions from MS patients show no such deficiencies, highlighting another way in which the demyelinating disorders differ.

If the groups’ results are confirmed in vivo, drug development could be straightforward. Therapeutic trials for glutamate antagonists, created to treat other neurodegenerative diseases like Lou Gehrig’s disease (or ALS), are already underway.

Friend to the brain, foe to the spine
Shouting during a World Cup match and shouting during a funeral will be met with different reactions. Context is equally important in a cytokine outburst, find Lees et al. on page 2633. Regional responses to interferon-γ (IFNγ) dictated whether the spinal cord or cerebellum came under fire in mice with EAE, a mouse model of human multiple sclerosis (MS). In other words, both outburst and audience matter.

IFNγ, the signature T helper (Th)-1 cytokine, contributes to CNS inflammation during EAE. But not all forms of EAE are alike. In classical EAE, the T cell attack is focused on the spinal cord. But in atypical disease, the cerebellum and brain stem are the primary victims. A prior study suggested that the ratio of interleukin (IL)-17 to IFNγ determines whether disease pathology occurs in the spine or brain, with increasing levels of IL-17 associated with disease in the brain. But the data from Lees et al. instead show that lesion location is mainly controlled by the brain’s response to IFNγ.

When transferred into wild-type mice, the authors show, myelin-specific Th1 cells attacked the spinal cord. But when transferred into mice lacking the IFNγ receptor, the cells instead attacked the cerebellum and brain stem, sparing the spinal cord. The production of IL-17 by the transferred T cells was comparable in both settings. However, the production of IL-17 by non-T cells predominated in the cerebellum, suggesting that IL-17-producing cells contribute to atypical disease but do not determine its location.

In agreement with past reports, however, transferring mixed populations of IFNγ- and IL-17–producing cells resulted in a mixed disease phenotype, with increasing numbers of IFNγ producers causing progressively more spinal cord disease.

Why IFNγ induces inflammation in one tissue and not another remains unknown—particularly because no obvious regional differences in the expression of the receptor were detected. The authors suspect that IFNγ triggers a localized production of T cell–attracting chemokines in the spine.

Giving imatinib a hand
Researchers have discovered a new a way to make the anticancer drug imatinib more effective. By suppressing the oncogene AHI-1, Zhou and colleagues were able to hold chronic myeloid leukemia (CML) in check (page 2657).

Imatinib is currently the most popular targeted therapy for CML. The leukemia is associated with the abnormal fusion of BCR with a kinase gene, ABL, which results in a perpetually active kinase known as BCR-ABL. Imatinib, a tyrosine kinase inhibitor, slows down the spread of cancer by blocking BCR-ABL activity. But the drug doesn’t work in everyone and patients often relapse, most likely because the drug only targets mature cells, leaving CML stem cells behind. Scientists have therefore been hunting for complementary therapies that act on pathways left undeterred by kinase inhibitors.

Mutated versions of the recently identified protein AHI-1, whose function is unknown, have been shown to be highly expressed in leukemic stem cells—the same cells that express BCR-ABL in patients with CML. Here, Zhou et al. show that expressing AHI-1 in stem cells turns the cells cancerous in vitro, and these cells caused lethal leukemia when transferred into mice. When expressed in BCR-ABL–positive cells, AHI-1 exacerbated the growth-promoting effects of the fusion protein.

AHI-1’s growth-promoting activity was attributed to the ability of AHI-1 to bind to BCR-ABL, along with an activated version of the downstream signaling protein JAK2. Cells expressing this complex were resistant to the kinase–blocking action of imatinib. Indeed, blocking AHI-1 in cells from imatinib-resistant CML patients restored the cells’ sensitivity to the drug.

With this finding, the race is on to find a drug to block AHI-1. As other studies have recently suggested, the cure for CML and other leukemias may not lie in a miracle drug, but rather in a carefully concocted cocktail of targeted therapies.