

and will depend for its success on the next generation of submillimetre instruments.

Despite their limitations, these methods devised by Chapman *et al.*<sup>1</sup> and by Wiklind<sup>2</sup> take us towards a better understanding of star-forming systems, while the next generation of telescopes is awaited. But for the moment, many of the star-forming monsters of deep space will keep their secrets. ■

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## Medicine

# Collateral damage repaired

Lawrence Steinman

Multiple sclerosis is characterized by immunological attacks across a wide front in the brain and spinal cord. In mice, the damage can be partly repaired by neural precursor cells, delivered into the blood or spinal fluid.

Multiple sclerosis affects nearly one million people worldwide, subjecting people from young adulthood onwards to repeated immunological attacks on the brain and spinal cord. Twice as many women as men are afflicted with the disease. The effects vary depending on where exactly in the nervous system the attacks occur, but paralysis, blindness, loss of sensation and a lack of coordination are among the types of devastation wrought by an immune system gone awry. Until now, treatment strategies have generally been aimed at blocking the autoimmune attacks and reducing the amount of collateral damage caused. On page 688 of this issue, Pluchino and colleagues<sup>1</sup> describe a complementary approach — repairing some of the harm already done.

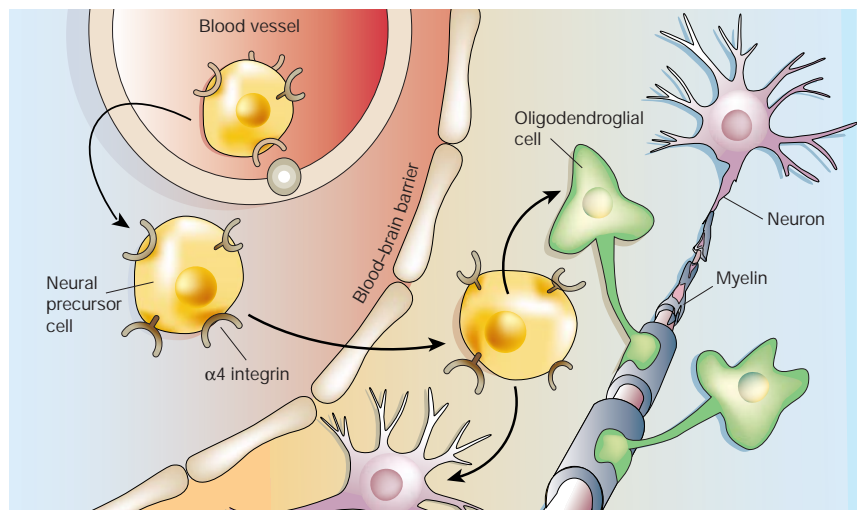
The immunological attacks that underlie multiple sclerosis damage the brain and spinal cord in several ways. First and foremost, the immune system mistakes myelin — the fatty sheath that insulates nerve cells — for foe instead of friend, and releases rounds of friendly fire. The myelin thereby becomes damaged and inflamed. That is also the fate of oligodendroglial cells, specialized types of non-neuronal (glial) cells in the brain, which both produce myelin and act as insulation in their own right. The inflammatory damage interferes with the flow of electrical impulses along underlying nerve fibres. The nerves themselves may also be harmed, ultimately leading to their demise. Finally, astrocytes — another type of glial cell — enlarge and proliferate in a manner analogous to the way in which scar tissue forms around injuries elsewhere in the body. This astrocytic scarring adds to the difficulty of propagating electrical activity down nerve fibres, by dispersing electrical impulses.

Most existing treatments for multiple sclerosis aim to block the immunological attacks on a wide front<sup>2,3</sup>. One method involves interfering with the adhesive, Velcro-like molecules that immune cells use to attach themselves to blood vessels as they prepare to move from the circulation to the brain. A decade ago, experiments<sup>4</sup> in an animal model of multiple sclerosis, called experimental autoimmune encephalomyelitis (EAE), showed that blocking a key adhesion molecule —  $\alpha 4$  integrin, found on the surface of attacking immune cells — could reverse paralysis. The results of clinical trials of patients with multiple sclerosis<sup>5</sup>

suggest that the same approach can block clinical attacks. Other strategies involve weakening rogue immune cells by reducing their production of inflammatory chemicals (including molecules such as tumour-necrosis factor- $\alpha$ , a type of cytokine protein), and by inhibiting destructive enzymes known as metalloproteases<sup>2</sup>.

These approaches are still being tested, but all hold the promise of impeding future immune attacks on myelin and nerve fibres. Equally important, however, is the repair of existing damage, and this is where Pluchino *et al.*<sup>1</sup> come in. The authors started by isolating neural precursor cells from the lining of the brains of mice, and then, remarkably, they used them to attenuate paralysis and neurological dysfunction in EAE. Although the exact nature of these cells is debatable, they fulfil many of the definitions of adult neural stem cells. They were isolated from a region called the periventricular zone, located next to the internal canals of the brain — the ventricles — where spinal fluid nourishes the nervous system. They are also multipotent, which means that they can develop into various specialized cell types when provided with appropriate signals.

Surprisingly, Pluchino *et al.* found that — like the attacking immune cells — the neural precursor cells express  $\alpha 4$  integrin. So, once injected into the blood or spinal fluid, they can move to points of inflammation within the brain and spinal cord of mice with EAE. There they somehow become involved in processes that decrease the levels of inflammatory chemicals (such as tumour-necrosis factor- $\alpha$ ) and metalloproteases. The neural precursors also reduce the astrocytic scarring associated with brain inflammation. In



**Figure 1 Rescuing the nervous system.** In people with multiple sclerosis, the immune system attacks both nerves and myelin, the fatty sheath that encompasses nerve fibres. Pluchino *et al.*<sup>1</sup> have isolated neural precursor cells from the brains of mice, and injected them into the blood or spinal fluid of mice with experimental autoimmune encephalomyelitis — an experimental model of multiple sclerosis. The cells express the  $\alpha 4$  integrin protein, and may use this to move from the blood into the brain. There the cells differentiate into both oligodendroglial cells, which generate myelin, and new neurons. The mice show a marked improvement in their symptoms.

damaged areas, they give rise to a pool of new myelin-producing cells (the oligodendroglial cells), and to new neurons (Fig. 1). They also produce growth factors, including ciliary neurotrophic factor, that may provide a restorative milieu<sup>6</sup>. Most importantly, the symptoms of mice improve even when the precursor cells are delivered to animals already suffering an attack of paralysis. Disability wanes, and electrical conductivity along nerve fibres increases.

The potential of strategies such as this to treat neurological damage on a wide front is impressive. Although some neurological disorders, such as Parkinson's and Huntington's diseases, are confined to specific brain regions, others, like multiple sclerosis and Alzheimer's disease, affect much broader areas. When the damage is confined, a local injection of neural precursors might be beneficial. Similarly, in previous studies<sup>7,8</sup>, precursors of myelin-generating cells have been transplanted directly into demyelinated brain regions. But this would be an impractical means of coping with the widespread damage seen in multiple sclerosis, which must be tackled differently. Until now, this requirement seemed daunting, but the results of Pluchino *et al.* put matters in a new light, by showing that neural precursors can be injected into the blood or spinal fluid and still find their way to the many areas where they are needed. One point of particular interest here is that these cells hitch a ride into damaged sites by using  $\alpha 4$  integrin — the very molecule that mobilizes the immunological attack<sup>2,4,5</sup>.

To give such cell-based strategies the best possible chance, it will be imperative to reduce the risk that newly formed myelin-

producing cells will be targeted in another round of friendly fire<sup>2,9</sup>. But on both fronts — in silencing the autoimmune attacks and in repairing the brain damage — there is, I believe, good reason to be optimistic. Many attractive methods for dampening the autoimmunity that is characteristic of multiple sclerosis are under development. These include broad-scale tolerization with myelin-derived peptides<sup>9</sup> and with genes encoding myelin proteins<sup>2,3,9</sup>. They can perhaps be combined with well-known drugs such as statins, which have recently been shown<sup>10</sup> to be extremely effective in suppressing autoimmunity. It should be feasible to stop collateral damage. And once the immune system has been made to surrender, the molecules at fault can perhaps be turned to help promote rehabilitation. If sufficient numbers of human neural precursor cells can be collected, and if we can work out how to make these cells proliferate and differentiate, then the results of Pluchino *et al.* might be translated into a treatment that eliminates collateral damage in multiple sclerosis. ■

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bacteria (known collectively as rhizobia). Through analysis of these nodules, they could then separate and dissect the processes of nitrogen reduction, assimilation of ammonium into amino compounds, and transport between the two partners. To the authors' surprise, the host plant cells could not assimilate ammonium when they were nodulated by bacterial mutants in which amino-acid transport was blocked.

There were two aspects to this observation. First, mutants that could fix nitrogen at rates comparable to the wild-type bacteria could not pass the products on to the host cell unless they were supplied with an amino acid, probably glutamate, by the host cell. Second, the host cell could not assimilate ammonium from bacteria unless it was also supplied with another amino acid, aspartate. Ludwig *et al.* propose that these two transport systems may have distinct functions in symbiosis (see Fig. 4 on page 725). One serves to import glutamate from plant to bacteria, and the other to export aspartate from bacteria to plant. So each side can impose a sanction on the other, by withholding a vital amino acid. If this circuit is in place, bacteria can export ammonium and ensure both their own amino-acid supply and that of their host. Thus, both sides have a strong interest in maintaining the marriage.

Before a host plant accepts bacteria into this intimate association, an intricate dialogue occurs between the two partners, which tests their mutual compatibility. Events begin in the soil, when plants and rhizobia exchange signals. They proceed via 'infection pathways' and nodule development (Fig. 1 shows a variety of nodule types). And they culminate in the formation of symbiotic units such as those studied by Ludwig *et al.*<sup>1</sup>. But does this courtship always end in harmony? Unfortunately not.

Problems may occur at any stage, and two are illustrated by the work of Ludwig *et al.* First, with bacterial mutants that can induce nodulation but cannot allow ammonium assimilation, numerous small, 'ineffective' nodules result, typical of those sometimes found in nature. In this case, host control over the number of nodules produced<sup>3</sup> is depressed. Second, mutants that cannot effectively use the host products of photosynthesis to fuel nitrogen fixation may store those products in the form of the polymer polyhydroxybutyrate (PHB). This polymer accumulates naturally in bacteria of certain nodules, most notably those of soybean, but much less so in their close relatives, such as *Phaseolus vulgaris* (French bean, navy bean) or species of *Vigna* (cowpea, green gram). Does this mean that soybean nodules and their bacteria are less well matched? Or does PHB have another function<sup>4</sup>? These are just two of the questions raised by the new results<sup>1</sup>.

More broadly, other issues arise when we

## Plant biology

# Mutual sanctions

Janet Sprent

The bacterium-filled nodules found on legumes represent a mutually beneficial arrangement. But it is evidently one with sophisticated checks and balances to ensure a fair deal for both partners in the marriage.

Some soil bacteria live in apparent harmony with plant cells in a mutually beneficial arrangement. The bacteria can reduce nitrogen gas, 'fixing' it into forms that the plants can use; in return, the plant cells provide the bacteria with products of photosynthesis. On page 722 of this issue<sup>1</sup>, Ludwig and co-workers describe an exchange-control system that enables the two partners to share their resources without either one becoming dominant.

The enzyme complex involved in nitrogen fixation is nitrogenase, which is ancient and widespread among bacteria. Nitrogenase can use a variety of substrates, but its main role in today's world is the production of

ammonia (NH<sub>3</sub>) from nitrogen gas (N<sub>2</sub>).

Whereas free-living nitrogen-fixing bacteria use ammonia for their own growth, those living in symbiosis with other organisms, such as in the nodules on roots of pea and bean plants, normally hand it over to their host in the form of ammonium ions, in exchange for products of photosynthesis that are used to provide the energy for nitrogen reduction<sup>2</sup>. Why should these bacteria behave so altruistically, when by so doing they lose their own source of amino acids?

Ludwig *et al.* propose an answer. Using plants of the garden pea, they induced the formation of root nodules containing either wild-type or mutant nitrogen-fixing