tance, that transmitted resistance is currently low and likely to only gradually increase and that transmitted resistance is unlikely to increase the overall number of new infections. Despite the overall positive message, Blower *et al.* point out that these predictions depend heavily on—among other parameters—the relative fitness of drug-resistant strains compared with drug-sensitive ones in the absence of therapy.

The relative fitness depends on the intrinsic transmissibility of the resistant strain but also on the degree to which therapies can decrease viral load in people with resistance, and hence reduce transmissibility. Thus, if resistant strains exist that are able to replicate to high levels in the presence of any available drug combination (which they probably do), and these strains are almost as or as transmissible as sensitive virus, then this value could approach 100%. In the simulations of Blower *et al.*, the range of possible values for this relative fitness spanned from 1% to almost 100%. As the authors point out, if the relative fitness is close to 100% then substantial transmission rates of drug-resistant HIV may well occur—up to 73% of new transmissions by 2005 for one combination of parameter values.

Such high rates of transmission of drug-resistant virus seem very unlikely by 2005, but the longer-term prospects depend largely on the intrinsic transmissibility of multi-drug resistant strains that replicate to high levels despite continued therapy. Relatively little is known about this key parameter. In studying treated populations, some investigators have tried to infer from the rates of unsuppressed viral replication (with a certain proportion assumed resistant) what the proportion of new resistant infections should be, and then compared this with the observed proportion. Most recent estimates using this crude approach indicate that a resistant virus might have little disadvantage in transmission compared with sensitive strains[6].

Another clue comes from studies of people that interrupt antiretroviral therapy and have high levels of replicating multi-drug resistant virus. In some patients observed over the course of several months, resistant virus was not out-competed by drug-sensitive virus—which must still be present in such individuals—indicating that replicative capacity of resistant viruses might be quite high in some circumstances[7].

During this period of uncertainty, what should we be doing to ensure that treatment options will still exist in the future if the relative fitness of resistant strains turns out to be as high as some fear? Blower *et al.* suggest we make efforts to improve treatment programs worldwide in order to reduce development of resistance in individuals on treatment; reduce the time before patients failing therapy are switched; initiate therapy relatively late in HIV infection; and prioritize development of new-drugs active against strains resistant to current therapies. To that list, I would emphasize the evaluation of new treatment strategies that are less susceptible to resistance development, such as interleukin-2 (refs. 8,9).

Blower *et al.* have shed light on an important and troublesome issue, and strategies must be developed and applied now if we are to preserve AIDS therapies for the future.

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Excitotoxic destruction facilitates brain tumor growth

Although it acts as a principal neurotransmitter in the brain, glutamate can be highly destructive if released in excess. Glutamate neurotoxicity has been implicated in stroke, head trauma, multiple sclerosis and neurodegenerative diseases. New research suggests that this abundant amino acid might also be involved the growth of brain tumors. (pages 1010–1015)

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Tumors often grow by displacing or invading surrounding tissues, moving organs and tissue aside as the tumor advances. But the brain is a closed system and little leeway exists to allow tissue to be pushed aside. Some brain tumors—often the most malignant—grow by invading like a destructive enemy, rapidly expanding and destroying brain tissue, a process that is often associated with a concomitant local inflammatory response. Reversing or preventing damage to the brain from the invasion and growth of brain tumors remains an elusive goal. Advances in therapy will depend on first developing a better understanding of the growth, invasion and destructive mechanisms of tumors. In this issue, Nedergaard and colleagues[1] describe a new property of experimental tumors that might provide insight into why they grow so quickly within brain tissue, and more importantly provide new ideas about how to slow their growth.

Gliomas are the most common tumors of the central nervous system (CNS), and have a wide range of properties. Glioblastoma multiforme is a highly malignant, almost uniformly fatal brain tumor. It is based on the cancerous transformation of astrocytes—spindly cells that are abundant in the brain that send out fine process encircling all neurons. Astrocytes act as a conduit for nutrients from blood to the brain, they buffer extracellular ions and can also regulate neurotransmitter metabolism. Neurons communicate with one another through areas of close cellular contact known as synapses, which are often also completely enveloped by the fine membranous processes of astrocytes.

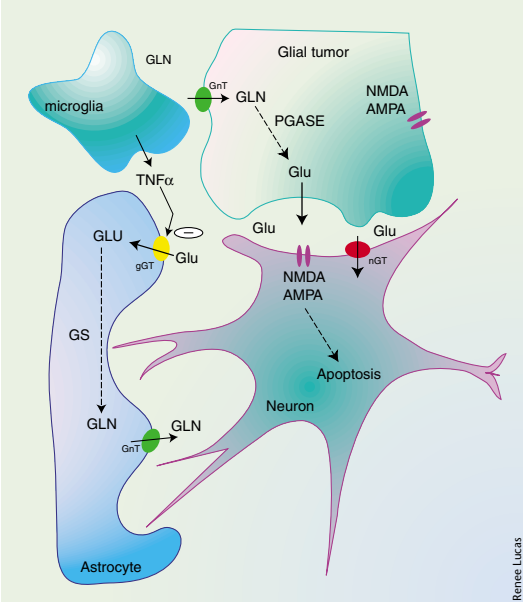

Fig. 1 Gliomas release glutamate, inducing a cytotoxic/apoptotic cascade in surrounding neurons, thereby clearing a path for growth in the brain. The mechanism of glutamate release is not known. Tumor activation—direct or indirect—of supporting microglia can lead to release of chemokines and tumor necrosis factor-α, which are both capable of altering glutamate release from astroglial cells (and perhaps gliomas). Multiple protective therapies might exist, including blockade of glutamate receptors (NMDA and AMPA), stimulation of neuronal (nGT) or astroglial glutamate transporters (gGT), inhibition of glutamate re-synthesis by disruption of precursor glutamine (GLN) supply via glutamine transporters (GnT), or inhibition of glutamine synthetase (GS) or phosphate activated glutaminase (PGASE).

Nedergaard and colleagues studied two different glioma cell lines, C6 and RG2, and found that both release glutamate, a ubiquitous amino-acid neurotransmitter, which when present in excess can cause an acute degeneration of neurons, a process known as excitotoxicity. Previous studies in culture have also documented glutamate release by gliomas and hypothesized that the excess glutamate could be linked to tumor-associated seizures, and possibly cell death[2]. However, in the new studies the authors demonstrate that release of glutamate is directly related to tumor growth: the more glutamate tumors release, the larger the tumor mass. The findings make it tempting to speculate that glutamate carves an excitotoxic path of destruction through brain tissue, thus explaining the particularly invasive and destructive nature of gliomas.

It follows that if glutamate release by tumors is directly responsible for their growth, then blocking 'downstream' glutamate receptors should slow growth. Nedergaard and colleagues observed precisely this effect *in vivo*. Blockade of the NMDA (*N*-methyl-D-aspartate) glutamate receptor subtype clearly abrogated the *in situ* growth of tumors in a rat model. Interestingly, the blockade of NMDA and AMPA (±-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) glutamate receptors has recently been reported to decrease the proliferation of various tumors such as colon, adenocarcinoma, breast, astrocytoma and lung carcinoma, suggesting a direct cytostatic effect, at least *in vitro*, of glutamate blockade[3].

How tumors exude glutamate is not clear. Glial cells do not typically release neurotransmitters by the vesicular mechanisms that are characteristic of neurons, yet laboratories have documented the *in vitro* ability of normal astrocytes to release glutamate by a prostaglandin E_2/chemokine-activated process[4,5]. Other mechanisms of release might exist as well. For example, glutamate transporter proteins that clear the extracellular space of glutamate can, under certain metabolic conditions, reverse and thereby 'dump' huge quantities of glutamate into the extracellular milieu. Tumors appear to down-regulate expression of glutamate transporters—a mechanism that, at a minimum, could act to enhance extracellular glutamate near the tumor cells by default.

Tempting though it is to extrapolate the findings of Nedergaard's group to the clinical setting, there are some caveats to drawing overarching conclusions from this work. First, the C6 cell line has not often provided relevant human tumor data. Will the present observations also be limited to the C6 and RG2 lines or will they turn out to have wider brain tumor applicability, that is, is the release of glutamate characteristic of other glial tumors, or other CNS tumors for that matter? Second, the C6 line is known to express neuronal, but not glial, glutamate transporters, so how is glutamate being released if not via the transporter route? Is the glutamate being released by astrocytes instead? Notably, this release pathway can be inhibited by cyclooxygenase inhibitors, indicating that these drugs might also be useful for the pharmacological manipulation of gliomas. This leads to the question of whether inflammation really does play a role in brain tumor development, and if so, would the concomitant inhibition of glutamate pathways and inflammation provide a better clinical outcome?

These studies, along with the recent work of Rzeski *et al.*[3], open up an entirely new treatment approach to fatal CNS tumors—glutamate therapy (Fig. 1). Novel therapies might be based on each aspect of normal CNS glutamate processing: synthetic enzymes, release and re-uptake, and receptor targeting. Other therapeutic investigations could include agents that stimulate the direct activation or synthesis of glutamate transporters as a more rapid clearance of extracellular glutamate might also minimize excitotoxicity. Additionally, disruption of the re-synthesis of glutamate release or uptake of the critical precursor, glutamine, could limit cytotoxicity. A potentially fruitful and immediate approach might be to focus on glutamate receptor antagonists that could block both the cell proliferation and excitotoxic degeneration associated with tumor glutamate release.

Riluzole, a voltage-activated sodium channel inhibitor that blocks the release of glutamate, is already in clinical use for the treatment of amyotrophic lateral sclerosis, a fatal neurological disease. In addition, several pharmaceutical companies developed glutamate receptor antagonists during the 1990s, although many of these compounds failed in large clinical trials for stroke, and were dropped from further product development. Nevertheless, these 'on-the-shelf' agents are at hand, and might provide an ideal starting point for preclinical and possibly clinical tests of the role of glutamate in brain tumor development if momentum gathers around the present findings.

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