cell morphology and cell death induced by Aβ toxicity. Finally, the generation of a series of bifunctional molecules with the aim of improving potency led to the discovery of an inhibitor that had an IC_{50} of ~50 nM — lower than that of CR by a factor of ~40, and of SLF-CR by a factor of ~6.

The development of further small molecules on the basis of this strategy might therefore lead to promising therapeutics for targeting an early, pre-symptomatic, pathological process in Alzheimer's disease. Moreover, this methodology might be generally applicable in other diseases in which it is desirable to target protein–protein interactions.

Alison Rowan

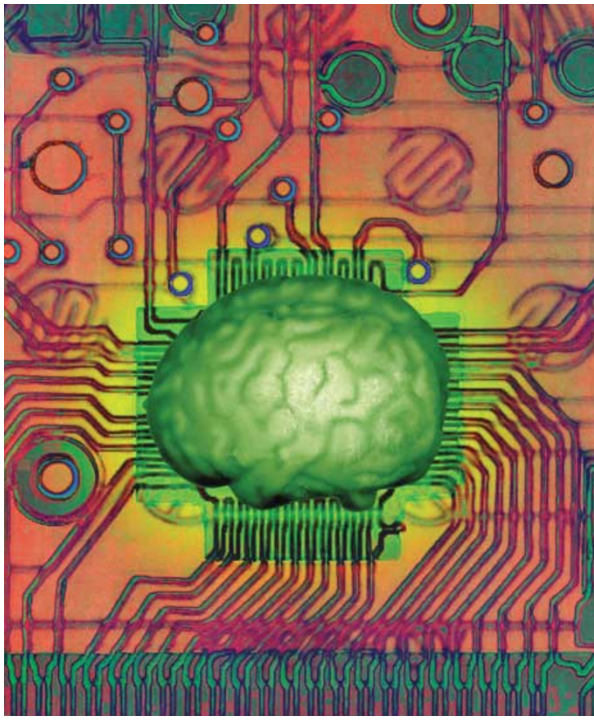
References and links

ORIGINAL RESEARCH PAPER Gestwicki, J. E., Crabtree, G. R. & Graef, I. A. Harnessing chaperones to generate small-molecule inhibitors of amyloid β aggregation. *Science* **306**, 865–869 (2004)

FURTHER READING Wolfe, M. S. Therapeutic strategies for Alzheimer's disease. *Nature Rev. Drug Discov.* **1**, 859–866 (2002) | Citron, M. Strategies for disease modification in Alzheimer's disease. *Nature Rev. Neurosci.* **5**, 677–685 (2004)

KINASES

Making gains on glioma



A small-molecule inhibitor of transforming growth factor-β (TGF-β) receptor I kinase could prove to be an effective treatment for human gliomas, according to a recent paper in *Cancer Research*. The investigational drug, SD-208, was shown to antagonize the immunosuppressive and pro-migratory properties that TGF-β exerts in cancer, and significantly prolonged the median survival of glioma-bearing mice.

Human glioblastoma is an aggressive form of brain cancer for which treatment options are limited and median patient survival is poor. TGF-β has become a key target in the search for more effective drugs because it is one of several immunosuppressive molecules commonly expressed by glioma cells. Although several approaches to inhibit TGF-β are being investigated, such as antisense and gene transfer, the identification of a small molecule that is more amenable to development as an oral drug would be desirable. Martin Uhl and colleagues report such a candidate molecule and describe its antagonistic effect on the biological activity of TGF-β *in vitro* and *in vivo*.

TGF-β exerts different biological effects depending on its cellular context and has roles in growth inhibition, immunosuppression and cell migration. The authors first determined whether SD-208 was an effective antagonist of TGF-β *in vitro* by demonstrating that SD-208 was able to reverse TGF-β-mediated growth inhibition of lung epithelial cells in a concentration-dependent manner. Moreover, SD-208 was able to neutralize the pro-invasive effect of TGF-β observed in assays of cell migratory activity, indicating that SD-208 could possibly prevent the further invasion of gliomas *in vivo*.

Perhaps most remarkable, however, was the ability of SD-208 to restore an immune response against glioma cells in culture. The lytic activity of peripheral blood lymphocytes or purified T cells was enhanced by co-incubation with SD-208 in a similar way to that observed with TGF-β-neutralizing antibodies, which confirms that the effect occurs through the inhibition of TGF-β. Furthermore, the inhibition of pro-inflammatory cytokine release and natural killer cell activation caused by glioma cells was reversed in the presence of SD-208, whereas release of the immunosuppressive cytokine interleukin-10 was inhibited.

Having established the efficacy of SD-208 *in vitro*, Uhl and colleagues then went on to study its potential anticancer effect in glioma-bearing mice. Measurement of TGF-β-dependent SMAD2 phosphorylation in mouse brain and spleen confirmed that SD-208 could inhibit TGF-β activity *in vivo*. Moreover, this inhibition correlated with a delayed onset of neurological symptoms in SD-208-treated glioma-bearing mice compared with untreated controls, and also a significantly improved survival rate after 30 days. These results were reflected by histological analysis, which showed a marked increase in immune infiltration in SD-208-treated mice that had smaller tumours compared with those that had larger tumours, indicating that SD-208 could attenuate the immunosuppression caused by TGF-β *in vivo*.

The authors conclude that treatment with TGF-β receptor-kinase inhibitors could prove useful to treat gliomas either alone or in combination with existing antisense therapies. Furthermore, SD-208 represents a potential new treatment paradigm in which neutralizing the effect of immunosuppressive cytokines secreted from tumours could be successful as an anticancer strategy.

Joanna Owens

References and links

ORIGINAL RESEARCH PAPER Uhl, M. *et al.* SD-208, a novel transforming growth factor β receptor I kinase inhibitor, inhibits growth and invasiveness and enhances immunogenicity of murine and human glioma cells *in vitro* and *in vivo*. *Cancer Res.* **64**, 7954–7961 (2004)

WEB SITES

The Hertie Institute for Clinical Brain Research: http://www.neurologie.uni-tuebingen.de

Scios, Inc.: http://www.sciosinc.com/home