than 100%.[4] The calculations are based on important assumptions. And even removal of all the reported risk factors will not prevent all cases of stroke. However, huge potential still exists for prevention of this serious disorder.[9] Many neurological disorders often coexist with other serious chronic diseases such as atherosclerosis, diabetes, kidney disease, and cancer.

The prevalence of neurological disorders will increase in the coming decades, because of the growth and ageing of the world population. Because few neurological diseases can be cured, preventive efforts need to be improved.

The GBD project is an important resource for health-care planning and resource allocation. It also provides key information on worldwide variation in occurrence of neurological disorders. The huge global variation in these disorders reflects the methodological challenges, as well as variations in occurrence of underlying environmental, lifestyle, social, and genetic risk factors. In addition to prevalence studies on the burden of neurological disorders, more analytical studies of potential risk factors are urgently needed to create opportunities for preventing these devastating diseases.

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Recovery from brain injury: a surprising new drug target

Although treatment for patients with acute stroke has been greatly advanced by interventions that restore blood flow through blocked arteries, no treatments exist to enhance the brain's recovery of lost function due to the injury. The same is true for individuals who survive traumatic brain injury. Now, however, surprising findings of a study published in February, 2019,[1] suggest that a therapy originally developed to treat HIV infection might also enhance recovery after brain injury.

Because the brain is the most plastic organ in a human being, it seems intuitive that molecular and cellular mechanisms involved in synaptic plasticity might be important for its repair. Indeed, spontaneous behavioural recovery occurs in parallel with reorganisation of neuronal circuits (or remapping), which can then support functions lost after brain injury. At the foundation of the investigators' approach was recognition that common molecular mechanisms are shared between brain repair and the processes of learning and memory. Driven by the observation that inhibition of C-C chemokine receptor type 5 (CCR5) signalling enhances learning, memory, and plasticity in hippocampal and cortical circuits,[2] the investigators tested the hypothesis that CCR5 signalling might have a role in the recovery of brain function following stroke or traumatic brain injury.

Under physiological conditions in humans, CCR5 is expressed in microglia but following stroke CCR5 expression is substantially upregulated in neurons. The investigators show that selectively reducing (or knocking down) gene expression of CCR5 in mouse neurons of the premotor cortex several days after an induced focal stroke in the motor cortex accelerated and enhanced behavioural recovery. These behavioural changes occurred in parallel with structural and physiological changes associated with synaptic plasticity, including the preservation of peri-infarct dendritic spines and the upregulation of a cascade of molecular messengers that are important in synaptogenesis.

Although these investigators used knockdown experiments to elucidate the role of CCR5 in mouse models of stroke, Joy and colleagues have turned to genetics to replicate these experiments in humans. Genetic variation,

whether a change in a single base pair, an insertion, a deletion, or a duplication of a stretch of DNA, occurs naturally and could substantially alter gene expression and result in measurable differences in phenotypes. Such genetic variation exists for human CCR5. *CCR5Δ32* (rs333) is a 32-base-pair deletion that leads to loss of function of the CCR5 receptor. In 446 survivors of stroke, the 68 survivors who carried *CCR5Δ32* appeared to recover slightly more motor and cognitive function than the 378 individuals without the mutation. Although these results are encouraging, it is very difficult to assign them clinical meaning given the small number of participants, their heterogeneity, their differences in stroke severity at admission, and the relatively mild degree of impairment in the cohort.

CCR5 has long been recognised to play a vital role in HIV infection, serving as the surface receptor through which HIV invades host cells. Carriers of *CCR5Δ32* are highly resistant to infection by HIV, which is why Chinese scientist He Jiankui controversially tried to do a human knockdown experiment[3] by genetically engineering the genomes of twin baby girls to mutate CCR5. The international research community has proposed a global moratorium on such editing of human germline DNA, since there are no data on its safety and efficacy, and there is no broad societal consensus on its appropriateness for preclinical research, as well as clinical use.[4]

Joy and colleagues tested the drug maraviroc that targets CCR5 and has been approved by the US Food and Drug Association (FDA) since 2007 for the treatment of HIV infection. Mice recovering from induced stroke or traumatic brain injury had improved motor and cognitive recovery when treated with concentrations of maraviroc comparable with those used in people who receive the drug for treatment of HIV infection. Notably, maraviroc appeared to be effective even when initiated as late as 3 weeks following experimentally induced stroke.

Although only well designed randomised clinical trials of maraviroc in patients with stroke and traumatic brain injury can confirm its efficacy, the research on CCR5 provides a blueprint for future efforts at discovering novel drug targets. The coincidence that CCR5 was already a well known therapeutic target for an FDA-approved drug is fortunate. Most cases of pleiotropy are likely to help researchers hone in on drug targets and candidate therapies that have not yet been fully developed. Nonetheless, biomedical science and human genetics have advanced sufficiently for an approach like that of Joy and colleagues to become the new standard in the discovery of drug targets. By combining forward translation (biological discovery originating in cellular and animal models) with reverse translation (biological discovery originating in human genomic and other genetic analyses) and taking advantage of pleiotropy (shared biological mechanisms across distinct diseases), modern approaches to drug discovery are positioned to yield even more novel results.

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