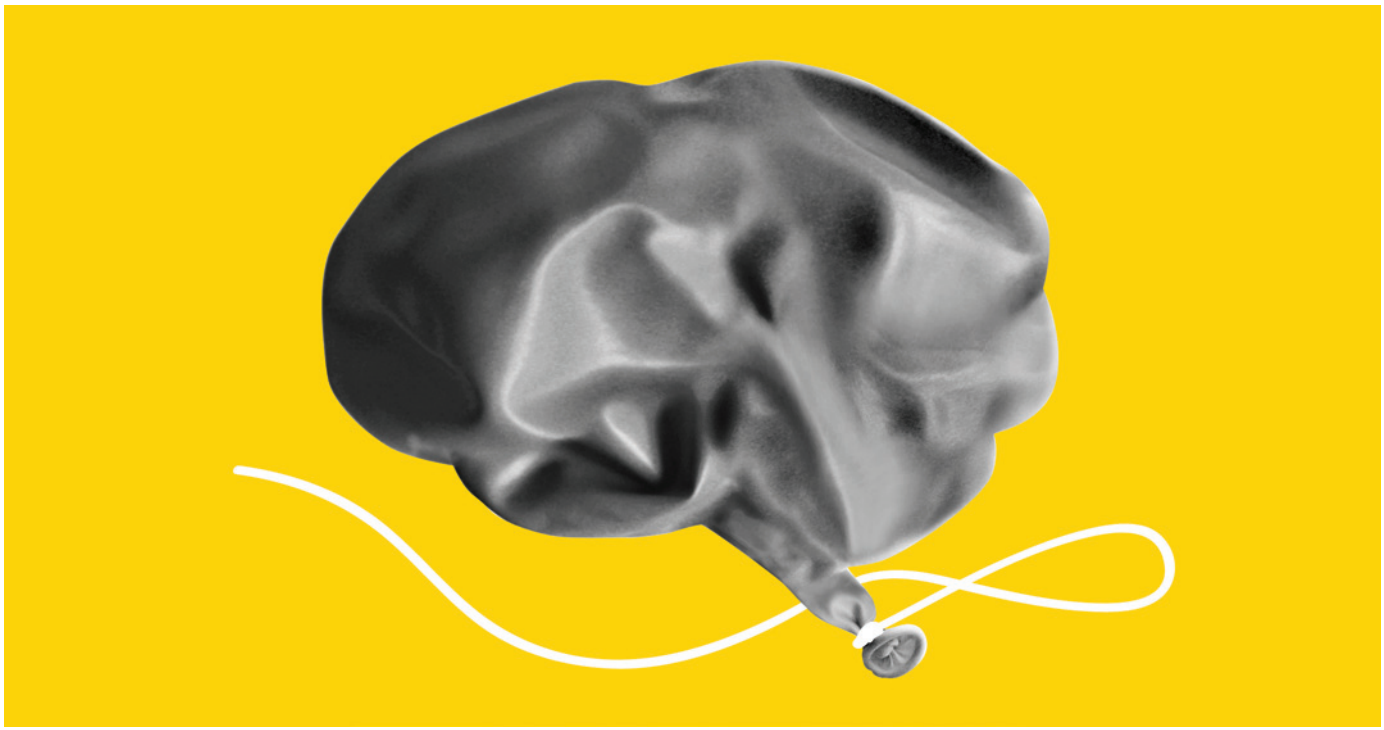
COMMENT

ILLUSTRATION BY O.O.P.S. FOR *NATURE*



Plug the real brain drain

Martin Schwab and **Anita Buchli** suggest ways to jump-start the stalled development of therapies for neurological diseases.

Recently, at the annual retreat of the Zurich Neuroscience Center, we ran into a former colleague who had often helped us to prepare for courses we were teaching. But he was not there to teach — he was participating in a demonstration as a patient. A stroke had left him paralysed on one side, wheelchair-bound and unable to speak. He had been looking forward to interacting with the students, but when he could not communicate with them, he broke into tears.

After a difficult rehabilitation, he was able to resume some of his work, but he still cannot speak. His arm and leg will probably remain paralysed for the rest of his life.

Our colleague was one of the 8.2 million Europeans who experience stroke every year[1]. The brain is a source of many devastating disorders — such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis — and injuries to the spinal cord or brain can lead to lifelong impairments. At present, disabling spinal-cord injuries affect roughly 350,000 people in Europe and 250,000 in the United States. Traumatic brain injuries are about ten times more common.

Treatments that could restore lost functions to people with such injuries would radically change their lives and decrease the burden to their families and social environment. The economic interest to drug companies and health insurers seems obvious. Yet drug companies have withdrawn from neuroscience, more so than from any other disease area. Last year, Novartis closed its preclinical neuroscience research facility in Basel, Switzerland. Pfizer, GlaxoSmithKline and AstraZeneca had already made similar moves. Merck and Sanofi are also cutting research on brain diseases.

Until recently, industry funded nearly half the budget for research and drug development for brain disorders[2]. Its retreat has left an abyssal hole.

The reason for companies' reluctance to pursue drugs for neurological disorders is fairly straightforward: their investments haven't paid off. In the past 10–15 years, dozens of clinical trials for stroke ▶

NATURE.COM
Read more about the crisis in brain-drug development:
go.nature.com/5goxwg

neuroprotection — involving thousands of patients — have failed.

To get drug development going again, we must tackle the problems that have stalled it in the past by building a culture of interdisciplinary exchange to generate promising compounds and setting aside public funds to conduct small, well-designed clinical studies of those compounds. We realize that in such a tight funding situation, every field is asking for more. But given the extraordinary burdens neurological diseases cause, they must become more of a priority.

A NEW HOPE

Drug companies have pulled out of neuroscience just as our understanding of brain plasticity has exploded. The antiquated view of the central nervous system as a hard-wired supercomputer has been overturned; the brain and spinal cord now appear as dynamic and adaptable biological systems.

Large injuries to the brain and spinal cord are not repaired spontaneously, causing lifelong impairment. But scientists have recently developed experimental interventions that enhance nerve-fibre growth and regeneration in animals with massive brain injury. In experiments with rats, mice and monkeys, researchers (in our laboratory and others) have induced regrowth of injured nerve fibres in the brain and spinal cord by suppressing growth inhibitors — enough for the treated animals to regain lost functions[3,4].

We and our colleagues at Novartis are now conducting a clinical trial in which people with spinal-cord injuries receive an antibody that counteracts the neural growth inhibitor Nogo-A (also known as reticulon-4A). Other clinical trials to enhance repair of the spinal cord and brain are or will soon be under way. But progress is slow — the biotechnology company Geron, for example, recently abandoned a promising phase I trial of stem cells in spinal-cord injury to concentrate instead on cancer[5].

"If researchers collaborate from the outset, they are more likely to produce a drug that works."

Why have so many trials failed, and what should be done better? A drug may be effective and still fail in a trial. One reason is that companies often look for the most broadly applicable drug — for example, 'for all stroke patients' — but disease conditions often differ among patients, resulting in huge variations in treatment responses. Another problem with past trials was that the often crude clinical endpoints missed small but meaningful treatment effects, such as improvements in hand, leg or bladder function. With novel approaches, we can do better.

To reinvigorate the field and avoid repeating past problems, more exchange should be fostered between basic and clinical scientists. When spinal-cord researchers began organizing retreats and workshops to bring together basic researchers and clinicians, they saw first-hand how little each side knows about how the other works. The mutual lack of knowledge was huge; each side had completely different language to describe the same scenario.

COSTS AND RESEARCH FUNDING IN EUROPE

Brain disorders are costlier and more prevalent than cancer but got similar research funding in 2005.

	Brain disorders	Cancer
Total costs for 2010 (ref. 1)	€798 billion (US$1 trillion)	€150 billion–250 billion
Direct costs†	60%	41%
Indirect costs‡	40%	59%
Proportion of all health-care expenditures	24%	6.3%
Percentage of 2004 disease burden[7]	35%	16.7%
Total 2005 research funding[2]	€4.1 billion	€3.9 billion
Industry contribution	€3.3 billion	€2.5 billion

†Expenses such as medication or doctor's visits. ‡Productivity lost to time off work or early retirement.

A WISER APPROACH

If researchers collaborate from the outset, they are more likely to produce a drug that works[6]. For instance, they could establish a set of criteria to evaluate a particular therapy in both animals and humans, so that what seems to work in one is more likely to seem to work in the other. Newer diagnostic tools will enable scientists to identify which subgroups might benefit most from a specific therapy. In addition, clinicians are now standardizing observations of functional improvement so that they can spot subtle changes that would have gone unnoticed in the past.

Neuroscience faculties and medical centres must work together to establish research consortia and networks that unite basic and clinical scientists. On a smaller scale, retreats with select groups of experts from both sides are inexpensive and can jump-start a field. Already, studies of spinal-cord injury are more focused now that the two sides are communicating — some basic researchers have begun using clinical criteria for functional improvement.

We can't just throw money and resources at the problem — we must use them wisely. Instead of investing billions in one drug, let's spread funding among smaller, proof-of-concept trials for compounds with good preclinical evidence. By focusing on well-selected populations (with tens of patients, not hundreds) and concentrating on a few centres, such trials would cost a few million euros rather than the €50 million (US$67 million) or more needed for one large trial. If smaller trials can bring a promising compound to an advanced stage, industry may then be willing to take it to market.

And, because the pharmaceutical industry isn't ready to invest in early-stage research in neurological diseases, we must turn to other sources. Insurance companies spend up to €2 million for each patient with a spinal-cord injury — a drug that could lower a patient's disability would save insurers huge amounts. In 2009, the top five US health insurers earned more than US$12 billion; investment of even a small percentage of these profits in research could result in a true win–win situation.

It is in countries' best interests to dedicate more public money to small trials of therapies for brain diseases. People with such disorders may spend decades of their lives disabled, which can have enormous effects on their lives and on those of the people around them.

In 2011, a report commissioned by the European Brain Council found that, in terms of health-care costs and lost productivity, brain disorders are a greater socio-economic burden than cancer, cardiovascular diseases and diabetes combined[1]. Yet in 2005, research funding for cancer and neurological diseases was roughly equal (see 'Costs and research funding in Europe'). More than half of that total comprised private funding; now that drug companies have shifted focus, cancer funding is likely to eclipse that of neuroscience. Funding agencies must revise their budgets to reflect the immediate and future needs of our society. ■ SEE COMMENT P. 269

Martin E. Schwab *and* **Anita D. Buchli**
are at the Brain Research Institute of the University of Zurich and the Department of Health Sciences and Technology at the Federal Institute of Technology, CH-8057 Zurich, Switzerland.
e-mail: schwab@hifo.uzh.ch

1. Gustavsson, *et al. Eur. Neuropsychopharmacol.* **21,** 718–779 (2011).
2. Sobocki, P., Lekander, I., Berwick, S., Olesen, J. & Jönsson, B. *Eur. J. Neurosci.* **24,** 2691–2693 (2006).
3. Zoerner, B. & Schwab, M. E. *Ann. NY Acad. Sci.* **1198,** E22–E34 (2010).
4. Liu, K., Tedeschi, A., Park, K. K. & He, Z. *Annu. Rev. Neurosci.* **34,** 131–152 (2011).
5. Baker, M. *Nature* **479,** 459 (2011).
6. Kwon, B. K., Hillyer, J. & Tetzlaff, W. *J. Neurotrauma* **27,** 21–33 (2010).
7. Andlin-Sobocki, P., Jönsson, B., Wittchen, H. U. & Olesen, J. *Eur. J. Neurol.* **12,** 1–27 (2005).