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No consensus on stem cells

Problems with reproducibility bedevil research on adult stem cells, yet treatments using the cells are moving rapidly into human clinical trials. Those working in the field need to adopt more robust experimental approaches.

It was hailed as the dawn of a new era in the treatment of heart attacks. Three years ago, when researchers led by Piero Anversa of New York Medical College in Valhalla reported that heart damage in mice could be treated by injecting the damaged tissue with stem cells sucked from the animals' own bone marrow, hopes surged of repairing human hearts in the same way.

Several clinical trials are now under way, triggered by the results in Anversa's original paper (D. Orlic *et al. Nature* **410,** 701–705; 2001). But this week's issue of *Nature* contains two reports of failures to replicate the findings that should give those who are running these trials pause for thought (see pages 664 and 668). Unfortunately, this is not an isolated incident. Over the past few years, several teams have claimed that adult stem cells can develop into a wide variety of tissues — only for other researchers to fail to obtain the same results.

Being able to repair damaged tissues using a patient's own cells is an attractive therapeutic prospect, and has been promoted vigorously by lobbyists opposed to the use of human embryonic stem cells. As long as a patient's stem cells are not genetically modified, there are currently relatively few regulatory hurdles to be overcome before testing their therapeutic potential in the clinic, at least in the United States. As a result, promising findings from animal experiments can move into the clinic before contrary results come to light.

Why are studies using adult stem cells so problematic? Are there systematic, technical problems inherent in the studies? Or are discrepancies between the results obtained by different groups merely more noticeable than in other fields because of the high profile of stem-cell research?

It's probably a bit of both. And this means that those working in the field must put their technical house in order. Many of the problems with reproducibility are thought to arise from the technique of immunofluorescent microscopy, in which specific antibodies bearing tags that fluoresce under laser light are used to track the migration and growth of injected stem cells. Unfortunately, this technique is prone to artefact. Antibodies may react with cells other than their intended targets, and microscopy is a notoriously subjective business. What's more, some cells fluoresce of their own accord under laser light.

Stem-cell researchers should adopt more robust techniques that incorporate marker genes that render stem cells visible using fluorescence and conventional microscopy. Ideally, the results should be confirmed using different marker genes. This will take time and work to achieve, but should be pursued as a high priority.

Other possible sources of variability in animal experiments include the techniques used to isolate, culture and characterize adult stem cells, and the precise type of tissue damage that the experimental treatment is designed to fix. Here, there are no clear answers, other than meticulous documentation of the methods used.

Researchers working on adult stem cells are under pressure both from severely ill patients and from companies looking for a profit. But a balance needs to be struck. Scientists embarking on studies likely to evoke clinical interest should work together, wherever possible, to resolve contradictions. Sadly, Anversa's team and the researchers who have failed to replicate his work have yet to exchange samples to try to understand why their results are at odds.

Perhaps it's time that institutional review boards and regulatory agencies, which in many cases have seemed happy to let therapies involving adult stem cells move towards the clinic with little intervention, started demanding a more robust consensus from animal studies before allowing human trials to go ahead. ■

Some sobering thoughts

We pay too much attention to the health benefits of alcohol and neglect the devastating effects of excessive consumption.

Compared with the tobacco industry, the companies that provide us with wine, beer and spirits have a glowing reputation. They have promoted campaigns to discourage drink driving and to educate the public in 'sensible' patterns of drinking.

Indeed, such is the drinks industry's status as a valued stakeholder that when the world's biggest research agency dealing with alcohol-related health problems, the US National Institute on Alcohol Abuse and Alcoholism (NIAAA), was looking for a new director in 2002, a representative of the San Francisco-based Wine Institute served on the search committee.

One popular refrain for the drinks industry is that, in moderation, alcohol can improve health. When the US Department of Agriculture revised its Dietary Guidelines for Americans in 1995, for example, the wine industry lobbied successfully for mention of the beneficial effects of moderate alcohol consumption on cardiovascular disease.

But you're unlikely to have heard industry representatives explaining that the beneficial effects of moderate drinking are limited to a relatively small proportion of the population. Many of the rest of us, lulled into thinking that our 'social' consumption of alcohol is good for us, are literally drinking ourselves to death (see page 598).

The industry's preferred message has found subtle echoes in the research agenda. From the mid-1990s, language in the reports accompanying spending bills passed by the US Congress urged the National Institutes of Health to support research into the effects of moderate alcohol consumption. This coincided with the first moves by the NIAAA to fund substantial research in this area. In 1996, grants given to study the risks and benefits of moderate drinking totalled $2.2 million. Although that was just 1.5% of the agency's budget, enthusiastic media coverage has since ensured that the findings from these projects have captured disproportionate attention.

Given the enormity of the world's drink problem, there is an urgent need to refocus public scrutiny on the harm caused by alcohol. If this harm is to be reduced, policy-makers will need to continue working in partnership with drinks manufacturers. But they should also put the alcohol industry's message of 'a little is good for you' in its proper context. ■