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Gene therapy deserves a fresh chance

Initial interest in gene therapy waned after the technology failed to live up to expectation. Progress made since has received little attention, but suggests that the pervading sense of disillusionment is misplaced.

In the early 1990s, when the first human trials got under way, it seemed to many that the era of gene therapy was at hand: the techniques of modern molecular biotechnology would make it possible to repair genetic defects by inserting healthy DNA directly into a patient's cells. The excitement was short-lived. Lasting effects proved difficult to obtain in early trials, and the community quickly grew sceptical. Then, in 2003, when it was announced that several gene-therapy patients in a Paris-based clinical trial had developed leukaemia, and that one of them had died, the mood became bleak. Subsequent reports of successful and effective gene-therapy trials have done little to lift the prevailing sense of doom. For most researchers, gene therapy now seems like a dead end.

But it doesn't have to be a dead end — not if scientists shift their perspective on the risks of gene therapy to be more in line with that of clinicians.

Scientists are trained to focus on understanding the systems that they study in great detail. And when they devise therapeutic interventions — for example, harnessing a viral shell to insert a therapeutic gene into a patient's DNA — they naturally want those systems to be engineered with equally great care, and for them to be as near to risk-free perfection as possible.

Clinicians, by contrast, care for real patients in real time, which makes treatment decisions a matter of pragmatism. How do the risks stack up against the benefits for each available alternative — given that the risks are never zero? Clinicians are certainly not cavalier about their patients' well-being, but they may well end up prescribing a therapy that has a poorly understood mechanism and potentially large side effects because it gives the patient the best odds of recovery or survival. If they — and patients — had shied away from such dangers in the past, life-saving interventions such as organ grafts and bone-marrow transplants might never have been developed.

From that perspective, the fact that, collectively, the Paris trial and others carried out since have produced positive results in some 20 patients out of a total of two dozen looms at least as large as the handful of leukaemia cases. To clinicians, such results suggest a treatment that is risky, but potentially life-saving — a new option for people for whom there are no alternatives.

However, this was not the view that prevailed. When the viral delivery vehicle itself turned out to be responsible for the leukaemia cases in the Paris trial, scientists deemed the trial a failure. Bad press ensued, proposals for gene-therapy clinical trials came under increased regulatory scrutiny and standards for demonstrating safety were set higher than for other approaches. Unsurprisingly in such a climate, the biotechnology and pharmaceutical industries gradually dropped out of the gene-therapy pursuit. This corporate disinterest slowed clinical progress: academic centres are ill-equipped to make gene-therapy vectors of clinical grade and scale, and research funding is typically insufficient to support clinical trials. More insidiously, it has become harder to recruit young talent to a field that is perceived as falling short of its promises.

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To reverse this trend, it is time for researchers and industry to refresh their perspective on gene therapy and to consider its successes with as much intensity as its setbacks. The focus on adverse events has had positive consequences: researchers dissected the exact molecular mechanisms that led to cancer, designed better vectors, devised animal models to test these vectors and developed sophisticated assays for monitoring patients. As a result, both scientists and clinicians now have a battery of extraordinarily refined tools for preclinical and clinical studies of gene therapy. The field is ripe for further successes. ■

Darwin and culture

A new series of essays traces the astounding variety of reactions to the theory of evolution.

The public reception of scientific ideas depends largely on two factors: people's ability to grasp factual information and the cultural lens through which that information is filtered. The former is what scientists tend to focus on when they give popular accounts of issues such as climate change. The assumption is that if they explain things very, very clearly, everyone will understand. Unfortunately, this is an uphill battle. The general public's average capacity to weigh facts and numbers is notoriously poor — although there is encouraging evidence that probabilistic reasoning can be improved by targeted education early in life (see page 1189).

Even more crucial, however, are the effects of the cultural lens. Over the coming month, *Nature*'s Opinion pages will explore particularly vivid examples of these effects in the world's widely divergent reactions to Charles Darwin's ideas about evolution in the late nineteenth and early twentieth centuries (see page 1200).

In England, for example, the Church reacted badly to Darwin's theory, going so far as to say that to believe it was to imperil your soul. But the notion that Darwin's ideas 'killed' God and were a threat to religion was by no means the universal response in the nineteenth century.

Darwin's theory reached the world at a time when many people were looking for explanations for social, political and racial inequalities,

and in many parts of the world were wondering how to improve their lot in the face of Europe's global imperialism. So from Egypt to India, China and Japan, many religious scholars embraced Darwin's ideas, often showing how their own schools of thought had anticipated the notion of evolution. Against the threat of Western imperialism and Western charges of 'backwardness', it was to their advantage to highlight the rationality of their creed.

In China, Darwin's ideas were seen as supporting Confucians' belief in the perfectibility of the cosmic order. Evolutionary theory also became fodder for political movements of revolution and reform, and eventually laid the groundwork for communism. Latin American politicians initially reacted to Darwin's ideas by attempting to entice white Europeans to emigrate and intermarry with local populations, believing that this would 'improve the stock'. But after two world wars had made European culture look less impressive, Latin America began to see its racial diversity as an advantage, and moved towards a social view that favoured a homogeneous blend of cultures.

In nineteenth-century Russia, meanwhile, a tendency to distrust rabid, dog-eat-dog capitalism helped incline naturalists away from a view of evolution that emphasized competition between species. Instead they embraced a 'theory of mutual aid', an account that focused on the role of cooperation in ensuring survival in a harsh environment.

The lesson for today's scientists and policy-makers is simple: they cannot assume that a public presented with 'the facts' will come to the same conclusion as themselves. They must take value systems, cultural backdrops and local knowledge gaps into account and frame their arguments accordingly. Such approaches will be crucial in facing current global challenges, from recessions to pandemics and climate change. These issues will be perceived and dealt with differently by different nations — not because they misunderstand, but because their understanding is in part locally dependent.

Darwin once said: "But then with me the horrid doubt always arises whether the convictions of man's mind, which has been developed from the mind of the lower animals, are of any value or at all trustworthy." Researchers and policy-makers would do well to mimic his humility when presenting science, and remember how people's minds truly work. ■

Mind the spin

Scientists — and their institutions — should resist the ever-present temptation to hype their results.

The circumstances surrounding the recent announcement of results from an HIV vaccine trial in Thailand are troubling. The sponsors of the US$119-million phase III clinical trial, a consortium led by the US Army, the National Institutes of Health and the Thai government, announced on 24 September that the trial had been a success: an analysis of the data showed that the vaccine had a statistically significant effect on preventing infection.

Other scientists could not immediately assess that claim, however: the full data from the trial were not made available until 20 October, when they were presented at an AIDS vaccine conference in Paris and in an article published online the same day (S. Rerks-Ngarm *et al. N. Engl. J. Med.* doi:10.1056/nejmoa0908492; 2009). The article contained two other data analyses, not mentioned in the initial announcement, showing smaller effects that were not statistically significant (see page 1187).

The trial's sponsors defend the premature announcement on the grounds that they had promised to inform the Thai people of the results first; 24 September is also Mahidol Day, the anniversary of the death of the king's father and a day of national observance in Thailand. The sponsors also argue that announcing the less-upbeat analyses along with the positive result would have been too complicated for the public to understand; they wanted to quickly deliver a clear-cut message on the trial's findings. Making the full data immediately available to scientists on 24 September would also have been impossible, they add, because of the conference and journal embargoes.

To their credit, the scientists involved did emphasize in their public statements that any vaccine effect was "modest", and that the vaccine itself was of no immediate public-health utility. At the same time, however, they hammered home the message that this was "the first time an HIV vaccine has successfully prevented HIV infection in humans", and implied that the event was somehow historic. Such statements, together with the selective initial presentation of the data, are well outside the scientific norms for presenting the results of clinical trials. They inevitably create suspicion that the trial sponsors may have put an excessively positive spin on results that are far from clear-cut, in a trial that has long been controversial (T. V. Padma *Nature Med.* **10,** 1267; 2004). The trial has also been six years in the works, and so there seems no particular public-health urgency to justify publication by press conference.

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Fortunately, such stories are still rare in science. Witness the way scientists have behaved since the beginning of the current H1N1 flu pandemic, in which the urgent threat to health creates legitimate tensions between getting results out fast and respecting peer review. Most researchers have negotiated this tension well, through a combination of fast-track publication by journals and online pre-publication sharing of preliminary data — but not through hyping their results.

Yet the temptation for scientists and their institutions to spin their research to the media, or to go publicity-mongering, is always there. And — as illustrated by the excessive public-relations campaign surrounding Ida, a fossil presented as a missing link in human evolution (see *Nature* **459,** 484; 2009 and **461,** 1040; 2009) — too many in the media will buy into the initial hype.

Such behaviour is corrosive to the process of scholarly scientific communication. Research institutions must not allow it to become the norm. ■