Bags of blood and not a donor in sight

Linda Geddes

RED blood cells generated in a lab have been successfully injected into a human volunteer for the first time. This is a vital step towards a future in which all the blood we need for transfusions can be made in the lab, so that blood donors are no longer essential.

Luc Douay at Pierre and Marie Curie University, Paris, and his colleagues extracted what are called hematopoetic stem cells from a volunteer's bone marrow. These cells were encouraged to grow into cultured red blood cells using a cocktail of growth factors. After labelling the cells so they could be traced, Douay's team injected 10 billion – the equivalent of 2 millilitres of blood – back into the original donor to see how they survived.

After five days, 94 to 100 per cent of the cells remained in circulation, while after 26 days, 41 to 63 per cent remained – a survival rate comparable to normal red blood cells. The cultured blood cells also gave every indication of being safe to use: they didn't transform into a malignant cell type, for example. Instead, they behaved like normal red blood cells, binding to oxygen and releasing it (*Blood*, DOI: 10.1182/blood-2011-06-362038).

"This is a huge step forward," says Robert Lanza, chief scientific officer at Advanced Cell Technology in Worcester, Massachusetts. In 2008, Lanza was a part of the team that grew red blood cells on a large scale in the lab for the first time.

Anna Rita Migliaccio of Mount Sinai Medical Center in New York City is equally impressed by Douay's work: "He showed that these cells do not have two tails or three horns and survive normally in the body."

"The results show promise that an unlimited blood reserve is within reach," says Douay. That blood reserve is needed urgently. Although blood donations are increasing in many developed countries, blood banks struggle to keep up with the demands of ageing populations who need more operations – often involving blood transfusions. And a source of HIV-free blood is essential in countries with high rates of HIV infection.

Earlier attempts to create blood substitutes have been disappointing. Several products have been rejected as a result of safety concerns or simply because they didn't work well (see "The road to artificial blood"). Besides blood derived from stem cells, alternatives include chemical blood – based on the high-oxygen solubility of perfluorocarbons – and oxygen carriers based on haemoglobin, which involve modifications to the red blood cell protein that transports oxygen.

"All aim to mimic, or in some cases enhance the oxygen-carrying ability of the red blood cells normally given as a blood transfusion," says Chris Cooper of

"The cultured blood cells behaved like normal cells and gave every indication of being safe to use"

The road to artificial blood

1818
First successful transfusion of human blood from a man to his wife, who had haemorrhaged after giving birth

1840
First successful whole blood transfusion to treat haemophilia

1901
Discovery of human blood types A, B, AB and O, allowing safer transfusions

1915
Demonstration that blood treated with anticoagulant can be stored in a fridge

1939
Discovery of the Rhesus blood group, makes transfusions safer

1989
First oxygen-carrying blood substitute (Fluosol-DA20) approved in the US. Withdrawn in 1994 because of side effects and limited benefits

2001
First haemoglobin-based blood substitute, Hemopure, approved for human use in South Africa

2005
Generation of fully mature red blood cells from hematopoetic stem cells

2006
Blood substitute, PolyHeme enters Phase III trials in the US. Results later suggest it is more likely to trigger adverse effects than real blood

2008
Generation of fully mature red blood cells from embryonic stem cells

2011
First lab-generated red blood cells injected into a human

Alien a

the University of Essex in Colchester, UK, who is developing a haemoglobin-based blood substitute that will be genetically modified to reduce its toxicity – haemoglobin is toxic in its unbound state. "The advantage of stem cell technology is that the product will much more closely resemble a red cell transfusion, alleviating some of the safety concerns that continue around the use of the current generation of artificial products," he says.

Thomas Chang at McGill University in Montreal, Canada, says that the success of Douay's stem-cell approach doesn't mean research into alternatives is any less worthwhile. Although blood grown from stem cells must be chilled, like fresh blood, "haemoglobin-based artificial blood does not need refrigeration", he says. This stability makes it more useful in remote areas or in the aftermath of natural disasters.

Douay's next challenge is to scale up production to a point where the cultured blood cells can be made quickly and cheaply in sufficient quantities for blood transfusions. The 10 billion cells his team made wouldn't go very far – a transfusion typically requires 200 times that number. With his existing technology, Douay estimates that a single transfusion would require 400 litres of culture fluid, which is clearly impractical. "We are still a long way from the vision of dropping a couple of stem cells into the broth and making endless units of blood," says John Hess of the University of Maryland in Baltimore.

Douay believes that it may take several years to scale up the technology. Another possibility is to use embryonic stem cells instead, as Lanza did in 2008. "We can generate up to 100 billion red blood cells from a single six-well plate of stem cells," Lanza says. He also claims to have made red blood cells through yet another technique: generating "induced pluripotent" stem cells from skin samples and coaxing those stem cells into becoming blood cells.

Lanza says he did this using skin from a person with type O blood. People with O negative blood are called "universal donors" because their blood doesn't trigger an immune reaction in recipients. "This is important for patients with massive blood loss where there isn't time for blood typing," says Lanza, who hopes to test both types of lab-made blood in people within the next two years. ■

SUPERSTOCK

Blood banks struggle to meet demand

Disease a an unholy

DOES the threat of rampant leave people more likely to murder? It's a provocative s that, if correct, should prov more incentive to improve the quality of public healthcare in countries where disease is rife.

Randy Thornhill, an evolutionary psychologist at the University of New Mexico in Albuquerque, has spent years amassing evidence for his "parasite stress" model of human society, which considers all disease to be a parasite on human society. He has already used it to predict that people in disease-ridden regions will be more xenophobic, and prefer to associate with relatives and close neighbours. These "collectivist" societies opt for strongly conservative values and autocratic governments, which Thornhill says minimises the risk of contracting diseases. By contrast, people in countries with low disease rates tend to be more individualistic and democratic, he says.

With Corey Fincher, also at the University of New Mexico, Thornhill has now found a link between disease and violence. The pair compared murder and disease rates from 48 US states and found that high disease rates correlated with high murder rates. The pattern held

"Reducing disease rates should cut murder rates in 20 years as a new healthier generation grows up"

even when they took into account economic inequality within the society, which also increases the murder rate (*Philosophical Transactions of the Royal Society B*, DOI: 10.1098/rstb.2011.0052).

The idea tallies with what we know about different countries' murder rates, says Martin Daly of McMaster University in Hamilton, Canada. A recent study identified a link between collectivist societies and murder rates, but did not look stress and violence," says Carlos David Navarrete of Michigan State University in East Lansing.

Others are not yet ready to accept the link, though. "It's fascinating and I'd like it to be true," says Val Curtis of the London School of Hygiene and Tropical Medicine, but she points out that there may be other factors at work. For instance, although the research takes into account relative economic inequalities within the society, it does not consider absolute wealth. Poverty itself may lead to higher murder rates – but because poor societies are likely to have relatively weak healthcare systems and higher levels of disease, there might still be a strong correlation between disease and murder.

If Thornhill's hypothesis is right, it should be possible to see a change in the murder rate as a society faces a reduced or heightened disease risk even as the levels of wealth in the society remained constant. The US data was not detailed enough to allow such an analysis. He predicts that simply investing in healthcare – but not necessarily any other aspect of society – could have an effect on the murder rates.

"If you clean up the diseases you'll reduce the rates of homicide," he says. He predicts that reducing disease rates should cut the murder rate within 20 years as a new generation grows up in a healthier environment.

"I'm not sure about that," says John Archer of the University of Central Lancashire in Preston, UK. He says social systems can linger for decades, even if the original cause disappears.

"The place to try this out is Africa," Curtis says. There are many projects underway to improve public health in disease hotspots, and it would be simple to track any effects on violence, she says. Michael Marshall ■