Meta-analysis torpedoes blood substitutes

Trials of hemoglobin-based blood substitutes have been dogged by clinical and regulatory setbacks and even attracted ethical spats over patient consent. But now a controversial meta-analysis published in the May 21 issue of the *Journal of the American Medical Association* (*JAMA* **299**, 2304–2312, 2008) threatens to cast a cloud over the entire field. The paper's authors, Charles Natanson and his colleagues at the US National Institutes of Health, conclude that current-generation blood substitutes pose a 30% elevated risk of death and a nearly threefold greater risk of heart attack than do standard products (e.g., saline) to correct volume. The meta-analysis includes data from 16 randomized, controlled clinical trials of products tested by five companies: Baxter International, Hemosol Biopharma, Biopure, Northfield Laboratories and Sangart.

The *JAMA* article elicited impassioned responses from blood-substitute companies that now find themselves in dire straits—falling stock prices, clinical trials in limbo and a barrage of negative press. A. Gerson, Greenburg, Cambridge, Massachusetts–based Biopure's vice president for medical affairs, fired off a letter to *JAMA*'s editors insisting the meta-analysis unfairly lumped the company's data with those from other firms, generating results he says aren't relevant to Biopure's own products. In response, Natanson claims the evidence for heightened risk of death and heart attack from the collective data is "overwhelming," and insists clinical testing should have been halted long ago.

The *JAMA* publication coincided with a two-day meeting cosponsored by the US Food and Drug Administration (FDA) and attended by nearly 350 people, including company representatives. At the meeting, agency officials concurred that current blood substitutes produce excess mortality and heart attacks. "For this reason, a careful weighing of potential risks and benefits will be needed to permit any future trials of the current products," writes Jay Epstein, director of the FDA's Office of Blood Research and Review, in an e-mail to *Nature Biotechnology*.

Alan Schechter, chief of molecular medicine at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland says, "Assuming the meta-analysis was appropriate and valid, [it] poses a big barrier to further clinical trials with current generation agents…and that's not good for the companies trying to develop these products."

Blood substitutes come in two forms: the widely available volume expanders—saline, Ringer's Lactate and D5W (a water-based 5% dextrose solution)—or oxygen therapeutics that mimic the blood's ability to transport oxygen. All current oxygen therapeutics, including those assessed in the *JAMA* study, are hemoglobin-based oxygen carriers (HBOCs). These products consist of free hemoglobin, the protein in red blood cells that binds oxygen in the lungs and releases it elsewhere in the body.

All HBOC companies aim to create an effective oxygen carrier that remains stable in storage at room temperature for long periods. So far, scientists have been unable to replicate blood's capacity to transport oxygen safely. The big hurdles come with managing free hemoglobin. In the body, hemoglobin is packaged into red blood cells, protecting the molecule from degradation and limiting its ability to interact dangerously with other molecules. But free hemoglobin readily breaks down into smaller molecular 'dimers' that rapidly wind up in urine. To avoid that problem, first-generation HBOCs cross-linked hemoglobins into larger molecules that would, in

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A safe, economic substitute could resolve blood shortages in the battlefield, emergency rooms and developing countries.

IN brief

UK passes hybrids

The UK Parliament has voted to allow the generation of human-animal hybrid embryos, creating the most liberal legal framework anywhere in the world for embryonic stem cell research. The move confirms that the Human Fertilisation and Embryology Authority acted within its jurisdiction when it gave permission in January to scientists at King's College London and Newcastle University to work on generating embryos by fusing enucleated animal oocytes with the nuclei of adult human cells (*Nat. Biotechnol.* **26**, 252, 2008). Embryonic stem cell lines produced as a result cannot be used in therapies but are expected to be useful as disease models. One immediate beneficiary was ReNeuron, of Surrey, UK, which saw its share price double, although its products are based on fetal stem cell lines. CEO Michael Hunt said, "Our hope is that the UK's reputation for supporting such pioneering early-stage stem cell research will be mirrored by further support for later-stage translational research activities." In Germany, researchers no longer have to fear a possible prison sentence for working on human embryonic stem cell lines created after January 2002. The German Federal Parliament voted in April to allow scientists to use up to 500 stem cell lines from abroad, as opposed to the 20 previously allowed, extending the qualifying date for importing lines to May 1, 2007. Brazil's Supreme Court ruled in May that scientists can lawfully conduct embryonic stem cell research, subject to certain caveats, such as not allowing the embryo to be destroyed. *—Nuala Moran*

Tighter gene tests

A report issued by the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) urges better oversight for genetic tests. The panel, commissioned by the US Department of Health and Human Services, identifies various gaps in the regulation of genetic testing and calls for better coordination between federal, state and other agencies to improve the oversight model. SACGHS members also recommend that public and private sectors adopt measures to assure public health and safety when conducting and interpreting results from clinical genetic testing. Although mandated to review the validity and utility of genetic testing, the panel recognizes that their recommendations "could well be applied more broadly to improve the quality of all laboratory tests." Indeed, they call on the US Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS)—the two federal agencies with principal regulatory authority over genetic testing—to overhaul clinical testing with "establishment of a mandatory test registry." The panel also urges the FDA "to strengthen monitoring and enforcement efforts against laboratories and companies that make false and misleading claims about laboratory tests, including direct-to-consumer tests." *—Jeff Fox*