Ebola virus RNA, was started in March 2015 and stopped 3 months later when an interim analysis of 14 patients showed the compound was unlikely to work. "We're struggling to publish informative, but not definitive data from trials," Horby says. But Johan van Griensven of the Institute of Tropical Medicine Antwerp in Belgium, who led the plasma study in Guinea, says his results, although far from iron-clad, will be published in a "top journal" on 7 January.

Questions surround the fate of several other studies. A trial of brincidofovir, an antiviral drug that had test tube activity against the Ebola virus, began in January 2015 and was stopped after enrolling just four patients because Chimerix, the company that produces the compound, pulled the plug. Horby, who led that study, too, says he never heard the full story. "We invested a huge amount of resources, time, effort, in very difficult circumstances," Horby says. "It should not have been stopped unless it was for a very good reason." A company spokesperson declined to answer detailed questions from *Science*.

Nor is it clear what happened to the very first clinical study, set up by Sierra Leonean scientists in the fall of 2014, which transfused Ebola patients with whole blood from survivors. Wiltshire Johnson of Sierra Leone's Pharmacy Board, charged with overseeing clinical trials in the country, told *Science* in May 2015 that 33 out of 44 transfused patients survived. The results have not been published, however, and its lead investigator, hematologist Sahr Gevao of the University of Sierra Leone in Freetown, did not respond to emails from *Science*. Even WHO isn't sure what became of the trial.

One last hope for an uplifting result remains: an ongoing study of ZMapp, an antibody cocktail that worked well in monkey experiments and famously was used to treat Kent Brantly and Nancy Writebol, two Americans who contracted Ebola in Liberia and recovered. Coordinated by the U.S. National Institutes of Health, the study began in Liberia in February 2015. After Ebola faded in that country, researchers began enrolling patients in Sierra Leone and Guinea and added one patient in the United States.

The study now includes about 70 patients, and because it has an RCT design, only half have received the antibodies. An independent panel has done several analyses of the trial, but Clifford Lane of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, says it's hard to conclude anything based on these interim assessments. "I'm hopeful that even if the data don't reach statistical significance, there might be at least a trend for efficacy," he says. Given the high hopes just 15 months ago, that's a most modest aspiration indeed. ■

EPIGENETICS

Sperm RNA fragments modify offspring metabolism

Molecules transfer mouse paternal traits to progeny

By **Mitch Leslie**

Male mice bequeath an unexpected legacy to their progeny. Two studies published online this week in *Science* reveal that sperm from the rodents carry pieces of RNAs that alter the metabolism of their offspring. The RNAs spotlighted by the studies normally help synthesize proteins, so the findings point to an unconventional form of inheritance. The results are "exciting and surprising, but not impossible," says geneticist Joseph Nadeau of the Pacific Northwest Diabetes Research Institute in Seattle, Washington.

"Impossible" is exactly how biologists once described so-called epigenetic inheritance, in which something other than a DNA sequence passes a trait between generations. In recent years, however, researchers have found many examples. A male mouse's diet and stress level, for instance, can tweak offspring metabolism. Researchers are still trying to determine how offspring inherit a father's metabolic attributes and physiological condition. Some evidence implicates chemical modification of DNA. Other work by neuroscientist Tracy Bale of the University of Pennsylvania Perelman School of Medicine in Philadelphia and colleagues has found that mammalian sperm pack gene-regulating molecules called microRNAs.

> ***"We've found another link that can connect the father and offspring."***
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> **Qi Chen**, University of Nevada School of Medicine

The new work highlights a different class of RNAs, transfer RNAs (tRNAs). In one study, genomicist Oliver Rando of the University of Massachusetts Medical School in Worcester and colleagues delved into a case of epigenetic inheritance in which the progeny of mice fed a low-protein diet show elevated activity of genes involved in cholesterol and lipid metabolism. When Rando's group analyzed sperm from the protein-deprived males, they uncovered an increased abundance of fragments from several kinds of tRNAs. The researchers concluded the sperm acquired most of these fragments while passing through the epididymis, a duct from the testicle where the cells mature.

In the second study, a team from the Chinese Academy of Sciences in Beijing and other institutions also homed in on tRNA fragments. After feeding male mice either a high-fat or low-fat diet, the scientists injected the animals' sperm into unfertilized eggs. They then tracked the metabolic performance of the offspring, which ate a normal diet. Although progeny of the fat-eating fathers remained lean, they showed two abnormalities often found in their dads and in people who are obese or diabetic: abnormal absorption of glucose and insensitivity to insulin. To determine whether tRNA fragments were responsible for the traits, the researchers inserted the fragments into eggs fertilized with other sperm. Fragments that came from fathers that ate the high-fat diet resulted in offspring that also showed impaired glucose absorption. "We've found another link that can connect the father and offspring," says reproductive biologist Qi Chen, a study coauthor, now at the University of Nevada School of Medicine in Reno.

Although tRNAs are best known for roles in protein synthesis, their fragments are turning up in other cellular situations. "Pieces of functional units that are pretty well understood can have interesting moonlighting functions," Rando says. Both studies suggest that the RNA bits alter gene activity. Rando and colleagues blocked one of the tRNA fragments inside embryonic stem cells and increased the activity of about 70 genes.

Bale says "both papers are really impressive" for digging deep into epigenetic mechanisms. And Nadeau says they should help overcome the challenge of identifying "the molecules that are responsible for inheritance outside of DNA sequences."

Researchers now need to ask "how permanent these changes are and how quickly they can be reversed by changing diet," says developmental endocrinologist Susan Ozanne of the University of Cambridge in the United Kingdom. The effects of the RNA fragments don't have to be harmful, Chen notes. "If a bad diet can influence us, I think a healthy diet can do it in the same way," he predicts. ■