

lier date, between 15 million and 13 million years ago, based in part on fossils found during the Panama Canal expansion (*Science*, 10 April 2015, p. 226).

At Urumaco, Luis Quiroz, a Venezuelan doctoral student at the University of Saskatchewan in Saskatoon, Canada, has found evidence that the later date may be correct. He studies trace fossils left by animals burrowing into beaches and coastal mudflats. The species he has identified live in nutrient-rich seawater, which Quiroz believes repeatedly submerged Urumaco during the early Neogene. The finding points not only to wildly fluctuating sea levels, but also to a source of nutrients, which most likely came from Pacific waters flowing into the Caribbean—dealing a blow to the idea of an earlier land bridge.

Just as its star is rising, Urumaco is becoming a destination for only the most daring scientists. “The last 2 years have been particularly challenging ... it’s truly putting in danger the possibility of doing fieldwork there,” says Marcelo Sánchez-Villagra, a paleobiologist at the University of Zürich in Switzerland who grew up in Venezuela. He plans to go to Urumaco in December, but has stopped bringing students.

Meanwhile, fewer paleontologists remain nearby, in Venezuela. Before moving to Brazil, Aguilera worked at Francisco de Miranda University in Coro, just a 35-minute drive from Urumaco. When the school’s budget was slashed, the administration forced him to retire. Now, he says, he’s lucky to get back to Urumaco once a year. Geologist Mauricio Bermúdez held on until 2015 at the Central University of Venezuela, Caracas, studying the Orinoco River’s ancient route. One day, on his way home from work, his bus was hijacked. Passengers were robbed and held hostage for 7 hours. Days after the ordeal, Bermúdez fled to Colombia with his family. “Many of the professors we work with ... they are already gone,” Jaramillo says, who hasn’t been back to Urumaco for 5 years. “It’s a massive migration of the educated people from Venezuela.” A local paleontologist maintains the collections and the museum in Urumaco, but he lost his government salary during the political upheavals. And as foreign researchers grow reluctant to travel to Venezuela, collaborations that might help Venezuelan scientists continue their work are dwindling.

But the Urumaco fossils are so important to the story of South America that Cadena and a few intrepid colleagues vow to keep coming back. Even after his equipment was stolen in Caracas, Cadena continued to Urumaco and unearthed a key fragment of a fossil he had long been hunting for. He’s heading back for more fieldwork in September. This time, he won’t tarry in Caracas. ■

## BIOMEDICINE

# Antiaging trial using young blood stirs concerns

## Company plans to charge volunteers \$8000 each for plasma transfusions from young donors

By **Jocelyn Kaiser**

It was one of the most mind-bending scientific reports in 2014: Injecting old mice with the plasma portion of blood from young mice seemed to improve the elderly rodents’ memory and ability to learn. Inspired by such findings, a startup company has now launched the first clinical trial in the United States to test the antiaging benefits of young blood in relatively healthy people. But there’s a big caveat: It’s a pay-to-participate trial, a type that has raised ethical concerns, most recently in the stem cell field.

The firm’s cofounder and trial principal investigator is a 31-year-old physician named Jesse Karmazin. His company, Ambrosia, in Monterey, California, plans to charge participants \$8000 for lab tests and a one-time treatment with young plasma. Volunteers don’t have to be sick or even particularly aged—the trial is open to anyone 35 and older. Karmazin notes that the study passed ethical review and argues that it’s not that unusual to charge people to participate in clinical trials.

But for some ethicists and researchers, the trial raises red flags, both for its cost to participants and for a design that they contend is unlikely to deliver much science. “There’s just no clinical evidence [that the treatment will be beneficial] and you’re basically abusing people’s trust and the public excitement around this,” says neuroscientist Tony Wyss-Coray of Stanford University in Palo Alto, California, who led the 2014 young plasma study in mice.

Decades ago, so-called parabiosis studies, in which the circulation of old and young animals was connected, suggested that young blood can rejuvenate aging mice. A

recent revival of the unusual approach has shown beneficial effects on muscle, the heart, brain, and other tissues, and some researchers are scrutinizing young blood for specific factors that explain these observations. The 2014 study, however, suggested that repeated injections of plasma from young animals were an easy alternative to parabiosis.

Wyss-Coray has since started a company, Alkahest, that, with Stanford, has launched a study of young plasma in 18 people with Alzheimer’s disease, evaluating its safety and monitoring whether the treatment relieves any cognitive problems or other symptoms. The company covers the participants’ costs. Wyss-Coray expects results by the end of this year. (Another trial at a research hospital in South Korea is examining whether cord blood or plasma can prevent frailty in the elderly.)

In Ambrosia’s trial, 600 people ages 35 and older would receive plasma from a donor under age 25, according to the description registered on ClinicalTrials.gov, the federal website intended to track human trials and their results. Karmazin says each person will receive roughly 1.5 liters over 2 days. Before the infusions and 1 month after, their blood will be tested for more than 100 biomarkers that may vary with age, from hemoglobin level to inflammation markers. The \$8000 fee—not mentioned on ClinicalTrials.gov—will cover costs such as plasma from a blood bank, lab tests, the ethics review, insurance, and an administrative fee, Karmazin says. “It adds up fairly quickly.”

Karmazin became interested in aging as an undergraduate. In medical school at Stanford, where he rotated through labs focused on stem cells and aging, he took note



A clinical trial will test whether blood’s plasma (yellow) has antiaging properties.

of the young plasma mouse study and other parabiosis research. While at Stanford, he says, he and colleagues began combing through hospital and blood bank donor records and found a preliminary association between transfusions of young blood and shorter hospital stays and lower mortality. Karmazin was also intrigued by the story of a Russian physician named Alexander Bogdanov who in the 1920s gave himself infusions of young human blood that he claimed boosted his energy level and bestowed a more youthful appearance. There is “overwhelming data” suggesting that young plasma will be beneficial to people, Karmazin says.

Last year, he co-founded a company called xVitality Sciences that aimed to offer plasma treatments at clinics overseas. The venture didn't pan out—Karmazin left, and the company is now apparently defunct. Karmazin then started Ambrosia with Craig Wright, a former chief scientific officer at a vaccine company, who now runs a clinic in Monterey. Ambrosia's study, which was reviewed by a commercial ethics board used by some for-profit stem cell clinics, doesn't need approval by the U.S. Food and Drug Administration, the pair says, because plasma transfusions are a well-established, standard treatment. Karmazin says he and Wright have now heard from about 20 prospective participants and have enrolled three, all elderly. Wright will likely transfuse plasma into the first person in late August.

To bioethicist Leigh Turner of the University of Minnesota, Twin Cities, the study brings to mind a growing number of scientifically dubious trials registered on ClinicalTrials.gov by private for-profit stem cell clinics. A trial's presence in the database confers “undeserved legitimacy,” he says.

The scientific design of the trial is drawing concerns as well. “I don't see how it will be in any way informative or convincing,” says aging biologist Matt Kaeberlein of the University of Washington, Seattle. The participants won't necessarily be elderly, making it hard to see any effects, and there are no well-accepted biomarkers of aging in blood, he says. “If you're interested in science,” Wyss-Coray adds, why doesn't such a large trial include a placebo arm? Karmazin says he can't expect people to pay knowing they may get a placebo. With physiological measurements taken before and after treatment, each person will serve as their own control, he explains.

Karmazin says he's filling a void, suggesting that most companies wouldn't be interested in developing human plasma as an antiaging treatment. “It's this extremely abundant therapeutic that's just sitting in blood banks,” he insists. ■

## U.S. RESEARCH MANAGEMENT

# NSF tries two-step review, drawing praise—and darts

Brief preliminary proposals can't do justice to innovative research, scientists complain

By Jeffrey Mervis

**A**s if getting a grant weren't hard enough already, the National Science Foundation (NSF) now requires thousands of conservation and environmental biologists to survive two rounds of peer review. The change, part of an experiment aimed at easing the strain on agency staff and outside reviewers, includes a first step in which three-quarters of applications are rejected.

NSF says that the two-stage process, which it launched 4 years ago as a pilot project in two divisions within its biology directorate, has resulted in a more manageable workload and fuller consideration of the highest quality proposals. Some scientists, however, aren't happy about the new procedures. They warn that the changes, notably a dramatically shorter initial application and only one chance a year to file applications rather than the previous two deadlines, could result in NSF funding less innovative research.

“You run out of room to describe anything that may be controversial or a little edgy,” says Peter Wainwright, president of the Society for Integrative and Comparative Biology and a professor at the University of California, Davis. “I suspect there are types of projects that don't get to the full proposal stage because it's just too hard to write them up in the

allowable space. It's a whole new ballgame.”

Last month, a congressional watchdog agency singled out the NSF project for praise and urged other major research agencies to be more aggressive in streamlining procedures that affect academic research. The study, released 22 July by the Government Accountability Office (GAO), was prompted by mounting concern that the the U.S. government's system for funding academic science is being stretched to the breaking point.

One reason is that scientists, with money tight, are submitting more grant applications. That creates more work for their universities, for the agencies that manage the grantsmaking process, and for the scientists who serve as reviewers. Ironically, the budget squeeze has also contributed to increased federal oversight to ensure those scarce dollars aren't being wasted.

The GAO report, which surveys a variety of approaches to the problem at four major research agencies, makes clear there are no simple solutions. And NSF's pilot project may seem counterintuitive: How could adding a second round of review actually reduce the burden on program officers and reviewers?

The answer lies in what NSF officials call binding preliminary proposals. Starting in 2012, scientists applying to core programs in the divisions of environmental biology (DEB) and integrative organismal systems could

## Shaking up the system

Applications rose and overall success rates dropped after the National Science Foundation's division of integrative and organismal systems required preliminary proposals. Applications that reached the full-proposal round faced better odds than in the past.

	2008	2009	2010	2011	2012	2013	2014	2015
Number of preliminary proposals					1824	1963	1973	1996
Percentage invited to submit full proposal					30%	22%	23%	24%
Number of full proposals	1364	1498	1379	1351	532	497	446	441
Number of awards	255	296	193	250	158	163	156	150
Percentage of full proposals funded					30%	33%	35%	34%
Overall success rate	19%	20%	14%	19%	9%	8%	8%	8%

# Science

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