Bacteria Sacrifice DNA Repair for Better RNA

Evolution is a game of trade-offs. Every trait an organism inherits may have benefits and drawbacks; what matters to natural selection is whether the trait is positive or negative on balance. But in a recent study, researchers described a balancing act that seems more counterintuitive than most: Bacterial cells prioritize transcription — the process of making RNA transcripts of genes as the first step in protein production — over repairing double-strand breaks in their DNA.

“We tend to think of DNA as the brains of the cell,” saiSusan Rosenberg, a biologist at Baylor College of Medicine in Houston. “If we push that analogy and think about parts of the cell competing for resources the way the parts of the body do, the brain should be getting whatever it needs at the expense of everything else.”

So when her Baylor colleague Christophe Herman approached her with the hypothesis that transcription might be more important than DNA repair, Rosenberg was ready to bet the other way. “And I was sure I would win,” she said.

Joe Nadeau, principal scientist at the Pacific Northwest Research Institute, found evidence that suggests eggs and sperm do not always combine randomly with respect to their genes — which, if true, violates one of the most enshrined tenets of Mendelian genetics.

J.H Kim

But she was proven wrong. Last month, she, Herman and their team published the results of their research in Nature: They found, using a series of experiments and intricate controls, that transcription can trump DNA repair in *E. coli*.

Rosenberg’s initial skepticism makes sense. DNA is the basis of heredity, after all, and a broken chromosome can be fatal. Errors in an RNA transcript, on the other hand, seem less grave. Such transcripts are temporary and short-lived, and the cell usually makes more than one copy. “When your house is on fire, you do not drop everything to make sure you took an accurate copy from one of your books in your home library,” said Andrei Kuzminov, a microbiologist at the University of Illinois who was not involved in the study. “You run for your life!”

But the story turns out to be much more complicated: A traditional DNA-centric perspective isn’t always best for explaining how complex processes like repair and transcription interact.

Transcription’s Rise to Power

Herman began to suspect that exaggerating the importance of DNA could be a mistake nearly a decade ago, when he found that errors made when copying DNA into RNA can lead to heritable changes in *E. coli* cells. (Those effects were epigenetic, meaning that the cells’ DNA was chemically modified while its base sequence remained the same.) Other research has also shown a correlation between transcription errors and diseases including cancer, multiple sclerosis and Alzheimer’s, although the link isn’t necessarily causal. And thefinal piece of the puzzle, according to Herman, dropped into place last year, when the J. Craig Venter Institute and Synthetic Genomics created a cell from scratch with the minimum genome an organism needs to survive. Herman noted that among the synthetic cell’s 473 genes, “very few coded for proteins involved in DNA repair.” But the major protein involved in maintaining transcription fidelity was there. “It was essential for life,” Herman said.

<img
class=”block fit-x fill-h fill-v is-loaded

mxa” alt=”Joe Nadeau, principal scientist at the Pacific Northwest Research Institute, found evidence that suggests eggs and sperm do not always combine randomly with respect to their genes — which, if true, violates one of the most enshrined tenets of Mendelian genetics.” src=”https://d2r55xnwy6nx47.cloudfront.net/uploads/2017/11/JoeNadeau_ByPacific-NorthwestResearchInstitute.jpg” style=”max-width:1000px;”/>

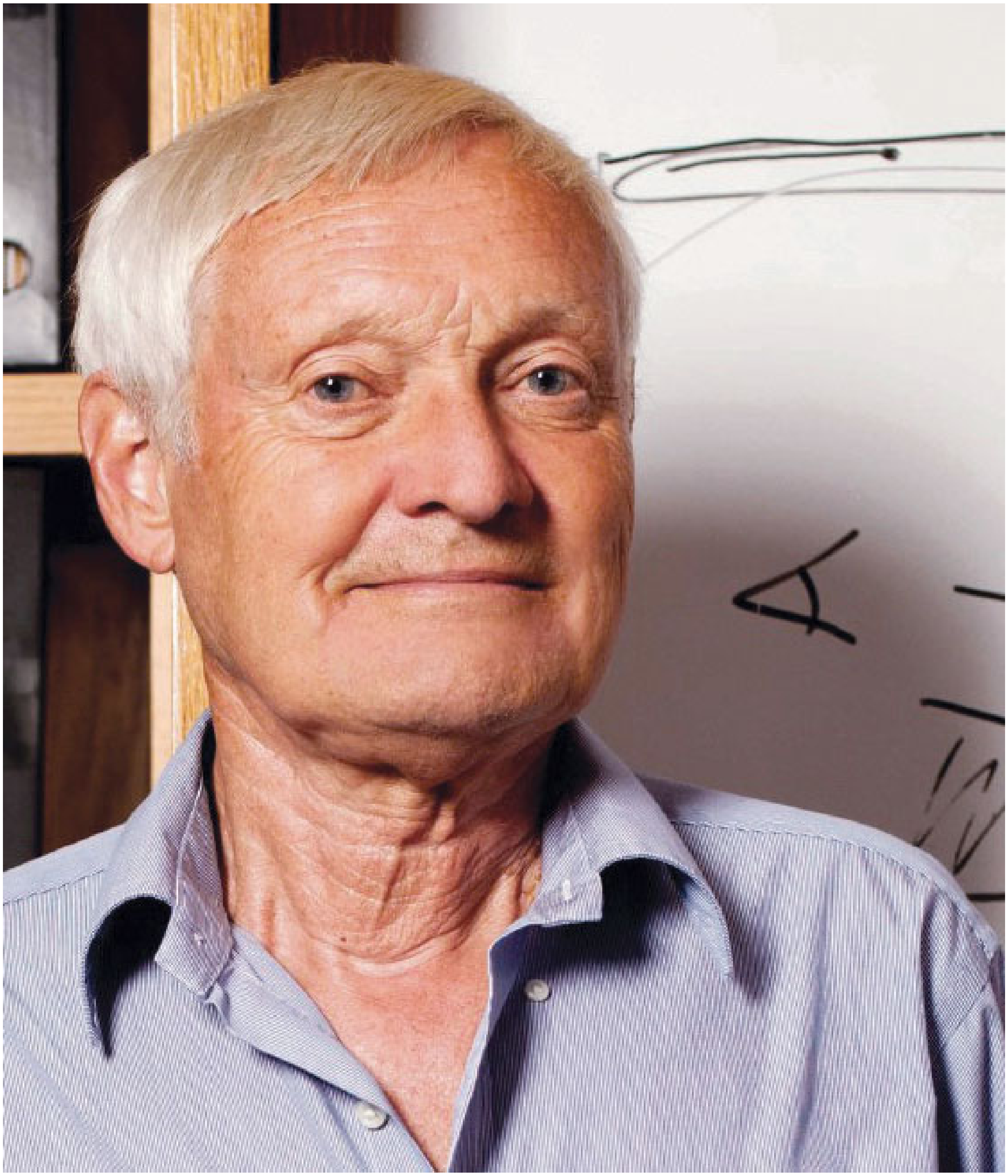
Joe Nadeau, principal scientist at the Pacific Northwest Research Institute, found evidence that suggests eggs and sperm do not always combine randomly with respect to their genes — which, if true, violates one of the most enshrined tenets of Mendelian genetics.

J.H Kim

Scientists had started digging deeper into ways that transcription processes might incidentally assist with the repair of DNA. But the Baylor team’s new findings suggest that those processes can also sometimes be an obstacle.

Herman, Rosenberg and their colleagues removed the gene in *E. coli* that encodes the transcription fidelity factor GreA, a type of proofreading protein that ensures cells make the correct RNA transcripts. The team then induced double-strand DNA breaks using a drug that mimics radiation. They found that in the absence of GreA, the cells became much more resistant to the drug’s damaging effects. In fact, the bacteria’s ability to repair their DNA improved 100-fold. “They went from being mild-mannered *E. coli* to being the champions of radiation repair,” Rosenberg said.

“I think most folks would not have guessed that cells would be dispensing with any of the possible DNA repair activity they could have,” she added, “particularly not in favor of a good-quality transcript.” But that seems to be what’s happening: A single transcription-related protein is hobbling a repair process that would otherwise work 100 times better than we see in nature.



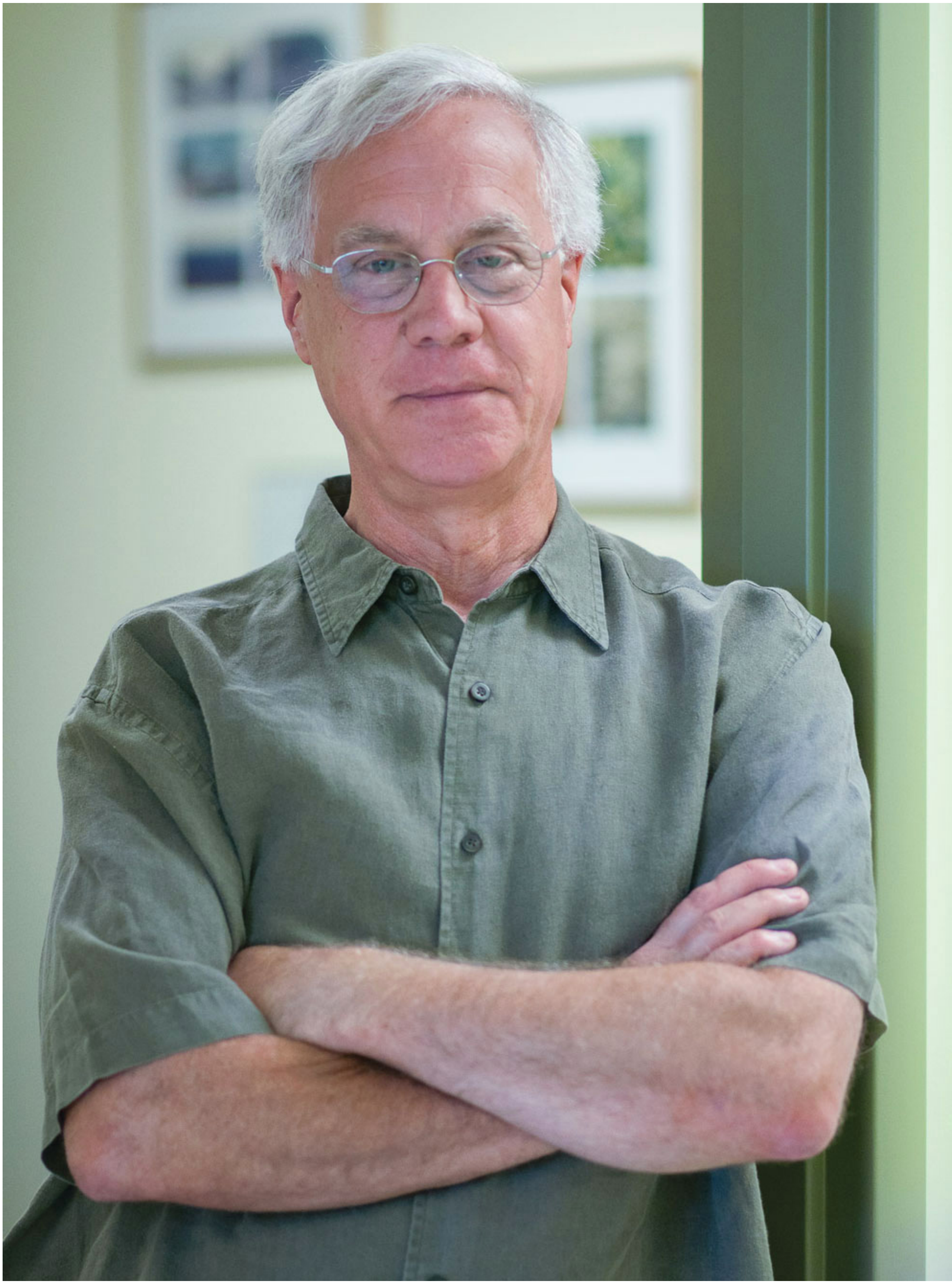
Joe Nadeau, principal scientist at the Pacific Northwest Research Institute, found evidence that suggests eggs and sperm do not always combine randomly with respect to their genes — which, if true, violates one of the most enshrined tenets of Mendelian genetics.

J.H Kim

Roadblocks and Collisions

Usually, when a chromosome experiences a double-strand break, an enzyme starts to degrade the adjacent DNA as a prelude to repair. In *E. coli* and other bacteria, when this enzyme reaches a sequence of nucleotides called a Chi site, it stops chewing up DNA and starts the repair process.

transcription and DNA repair. Instead, it found a way to ameliorate a different conflict — between transcription and DNA replication. Stalled transcription complexes don’t just lend DNA repair processes a helping hand; they can also end up causing double-strand breaks by interfering with the cellular machinery that replicates DNA.



Joe Nadeau, principal scientist at the Pacific Northwest Research Institute, found evidence that suggests eggs and sperm do not always combine randomly with respect to their genes — which, if true, violates one of the most enshrined tenets of Mendelian genetics.

J.H Kim

critical factor for the bacteria would be to express their genes accurately so that they can survive and flourish. “In a normal growing population,” Lloyd said, “the requirement of repairing DNA breaks would not be as great as the need to secure a competitive advantage against other species.” If the cells had evolved under extreme conditions that were more likely to break DNA, “they would have evolved different mechanisms to deal with that, and the efficiency of gene expression would no longer be the first concern.”

“This is not so much a conundrum as it is an inevitable advantage,” Lloyd said — a classic example of an evolutionary trade-off.

The discovery by Herman and Rosenberg paints a richer picture of how transcription can be involved with DNA metabolism, and the role transcription plays in ensuring the well-being of the cell, remarked

print