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Biology A (Salters Nuffield)

Advanced

PAPER 3: General and Practical Applications in Biology

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Scientific article for use with Question 8

How the DNA Revolution is Changing Us

1. The ability to quickly alter the code of life has given us unprecedented power over the natural world. The question is: Should we use it?

2. If you took a glance around Anthony James's office, it wouldn't be hard to guess what he does for a living. The walls are covered with drawings of mosquitoes. Mosquito books line the shelves.

3. Hanging next to his desk is a banner with renderings of one particular species – *Aedes aegypti* – in every stage of development, from egg to pupa to fully grown, enlarged to sizes that would even make fans of Jurassic Park blanch. His license plates have a single word on them: AEDES.

4. There are approximately 3,500 species of mosquito, but James pays attention to just a few, each of which ranks among the deadliest creatures on Earth. They include *Anopheles gambiae*, which transmits the malaria parasite that kills hundreds of thousands of people each year. For much of his career, however, James has focused on *Aedes*. Historians believe the mosquito arrived in the New World on slave ships from Africa in the 17th century, bringing with it yellow fever, which has killed millions of people. Today the mosquito also carries dengue fever, which infects as many as 400 million people a year, as well as such increasingly threatening pathogens as chikungunya, West Nile virus, and Zika.

5. In a widening outbreak that began last year in Brazil, Zika appears to have caused a variety of neurological disorders, including a rare defect called microcephaly, where babies are born with abnormally small heads and underdeveloped brains.

6. The goal of James's lab, and of his career, has been to find a way to manipulate mosquito genes so that the insects can no longer spread such diseases. Until recently, it has been a long, lonely, and largely theoretical road. But by combining a revolutionary new technology called CRISPR-Cas9 with a natural system known as a gene drive, theory is rapidly becoming reality.

7. CRISPR places an entirely new kind of power into human hands. For the first time, scientists can quickly and precisely alter, delete, and rearrange the DNA of nearly any living organism, including us. In the past three years, the technology has transformed biology. Working with animal models, researchers in laboratories around the world have already used CRISPR to correct major genetic flaws, including the mutations responsible for muscular dystrophy, cystic fibrosis, and one form of hepatitis. Recently several teams have deployed CRISPR in an attempt to eliminate HIV from the DNA of human cells. The results have been only partially successful, but many scientists remain convinced that the technology may contribute to a cure for AIDS.

8. In experiments, scientists have also used CRISPR to rid pigs of the viruses that prevent their organs from being transplanted into humans. Ecologists are exploring ways for the technology to help protect endangered species. Moreover, plant biologists, working with a wide variety of crops, have embarked on efforts to delete genes that attract pests. That way, by relying on biology rather than on chemicals, CRISPR could help reduce our dependence on toxic pesticides.

9. No scientific discovery of the past century holds more promise – or raises more troubling ethical questions. Most provocatively, if CRISPR were used to edit a human embryo's germ line – cells that contain genetic material that can be inherited by the next generation – either to correct a genetic flaw or to enhance a desired trait, the change would then pass to that person's children, and their children, in perpetuity. The full implications of changes that profound are difficult, if not impossible, to foresee.

10. "This is a remarkable technology, with many great uses. But if you are going to do anything as fateful as rewriting the germ line, you'd better be able to tell me there is a strong reason to do it," said Eric Lander, who is director of the Broad Institute of Harvard and MIT and who served as leader of the Human Genome Project. "And you'd better be able to say that society made a choice to do this – that unless there's broad agreement, it is not going to happen."

11. "Scientists do not have standing to answer these questions," Lander told me. "And I am not sure who does."

12. CRISPR-Cas9 has two components. The first is an enzyme – Cas9 – that functions as a cellular scalpel to cut DNA. (In nature, bacteria use it to sever and disarm the genetic code of invading viruses.) The other consists of an RNA guide that leads the scalpel to the precise nucleotides – the chemical letters of DNA – it has been sent to cut. (Researchers rarely include the term "Cas9" in conversation, or the inelegant terminology that CRISPR stands for: "clustered regularly inter-spaced short palindromic repeats.")

13. The guide's accuracy is uncanny; scientists can dispatch a synthetic replacement part to any location in a genome made of billions of nucleotides. When it reaches its destination, the Cas9 enzyme snips out the unwanted DNA sequence. To patch the break, the cell inserts the chain of nucleotides that has been delivered in the CRISPR package.

14. By the time the Zika outbreak in Puerto Rico comes to an end, the U.S. Centers for Disease Control and Prevention estimates that, based on patterns of other mosquito-borne illnesses, at least a quarter of the 3.5 million people in Puerto Rico may contract Zika. That means thousands of pregnant women are likely to become infected.

15. Currently the only truly effective response to Zika would involve bathing the island in insecticide. James and others say that editing mosquitoes with CRISPR – and using a gene drive to make those changes permanent – offers a far better approach.

16. Gene drives have the power to override the traditional rules of inheritance. Ordinarily the progeny of any sexually reproductive animal receives one copy of a gene from each parent. Some genes, however, are "selfish": Evolution has bestowed on them a better than 50 percent chance of being inherited. Theoretically, scientists could combine CRISPR with a gene drive to alter the genetic code of a species by attaching a desired DNA sequence onto such a favored gene before releasing the animals to mate naturally. Together the tools could force almost any genetic trait through a population.

17. Last year, in a study published in the *Proceedings of the National Academy of Sciences*, James used CRISPR to engineer a version of *Anopheles* mosquitoes that makes them incapable of spreading the malaria parasite. "We added a small package of genes that allows the mosquitoes to function as they always have," he explained. "Except for one slight change." That change prevents the deadly parasite from being transmitted by the mosquitoes.

18. "I'd been laboring in obscurity for decades. Not anymore, though – the phone hasn't stopped ringing for weeks," James said, nodding at a sheaf of messages on his desk.

19. Combating the *Ae. aegypti* mosquito, which carries so many different pathogens, would require a slightly different approach. "What you would need to do," he told me, "is engineer a gene drive that makes the insects sterile. It doesn't make sense to build a mosquito resistant to Zika if it could still transmit dengue and other diseases."

20. To fight off dengue, James and his colleagues have designed CRISPR packages that could simply delete a natural gene from the wild parent and replace it with a version that would confer sterility in the offspring. If enough of those mosquitoes were released to mate, in a few generations (which typically last just two or three weeks each) entire species would carry the engineered version.

21. James is acutely aware that releasing a mutation designed to spread quickly through a wild population could have unanticipated consequences that might not be easy to reverse. "There are certainly risks associated with releasing insects that you have edited in a lab," he said. "But I believe the dangers of not doing it are far greater."

22. The potential for CRISPR research to improve human medicine would be hard to overstate. The technology has already transformed cancer research by making it easier to engineer tumor cells in the laboratory, then test various drugs to see which can stop them from growing. Soon doctors may be able to use CRISPR to treat some diseases directly.

23. Stem cells taken from people with hemophilia, for example, could be edited outside of the body to correct the genetic flaw that causes the disease, and then the normal cells could be inserted to repopulate a patient's bloodstream.

24. In the next two years we may see an even more dramatic medical advance. There are 120,000 Americans on waiting lists to receive organ transplants, and there will never be enough for all of them. Thousands of people die every year before reaching the top of the list. Hundreds of thousands never even meet the criteria to be placed on the list.

25. For years, scientists have searched for a way to use animal organs to ease the donor shortage. Pigs have long been considered the mammal of choice, in part because their organs are similar in size to ours. But a pig's genome is riddled with viruses called PERVs (porcine endogenous retroviruses), which are similar to the virus that causes AIDS and have been shown to be capable of infecting human cells. No regulatory agency would permit transplants with infected organs. And until recently, nobody has been able to rid the pig of its retroviruses.

26. Now, by using CRISPR to edit the genome in pig organs, researchers seem well on their way to solving that problem. A group led by George Church, a professor at Harvard Medical School and MIT, used the tool to remove all 62 occurrences of PERV genes from a pig's kidney cell. It was the first time that so many cellular changes had been orchestrated into a genome at once.

27. When the scientists mixed those edited cells with human cells in a laboratory, none of the human cells became infected. The team also modified, in another set of pig cells, 20 genes that are known to cause reactions in the human immune system. That too would be a critical part of making this kind of transplant work.

28. Church has now cloned those cells and begun growing them in pig embryos. He expects to start primate trials within a year or two. If the organs function properly and are not rejected by the animals' immune systems, the next step would be human trials. Church told me he thinks this could happen in as few as 18 months, adding that for many people the alternative to the risk of the trial would surely be death.

29. Church has always wanted to find a way to provide transplants for people who aren't considered healthy enough to receive them. "The closest thing we have to death panels in this country are the decisions made about who gets transplants," he said. "A lot of these decisions are being made based on what else is wrong with you. Many people are rejected because they have infectious diseases or problems with substance abuse – a whole host of reasons. And the conceit is that these people would not benefit from a transplant. But of course they would benefit. And if you had an abundance of organs you could do it for everyone."

30. The Black-footed Ferret is one of ten most endangered mammals in North America. Twice in the past 50 years, wildlife ecologists assumed that the animals, which were once plentiful throughout the Great Plains, had gone extinct. They came close; every black-footed ferret alive today descends from one of seven ancestors discovered in 1981 on a cattle ranch near Meeteetse, Wyoming.

31. But the ferrets, inbred for generations, lack genetic diversity, which makes it harder for any species to survive.

32. "The ferrets are a classic example of an entire species that could be saved by genomic technology," said Ryan Phelan of the group Revive & Restore, which is coordinating efforts to apply genomics to conservation. Working with Oliver Ryder at the San Diego Frozen Zoo, Phelan and her colleagues are attempting to increase the diversity of the ferrets by introducing more variable DNA into their genomes from two specimens preserved 30 years ago.

33. Phelan's work can address two immediate and interlocking threats. The first is lack of food: Prairie dogs, the ferrets' main prey, have been decimated by sylvatic plague, which is caused by the same bacterium that gives rise to bubonic plague in humans. And the plague is also fatal to the ferrets themselves, which become infected by eating prairie dogs that have died of the disease. A vaccine against human plague developed in the 1990s appears to provide lifelong immunity in ferrets. Teams from the Fish and Wildlife Service have captured, vaccinated, and released as many of the ferrets (a few hundred exist in the wild) as they can. But such a ferret-by-ferret approach cannot protect the species.

34. A more sophisticated solution has been proposed by Kevin Esvelt, an assistant professor at the MIT Media Lab, who developed some of the CRISPR and gene drive technology with Church. Esvelt describes his work as sculpting evolution. "All you need to do is provide resistance," he explained – by encoding antibodies generated by vaccination and then editing them into the ferrets' DNA.

35. Black-footed ferrets are hardly the only endangered animals that could be saved through a CRISPR gene drive. The avian population of Hawaii is rapidly disappearing, largely because of a type of malaria that infects birds. Before whalers brought mosquitoes in the early 19th century, birds in the Hawaiian Islands had no exposure to the diseases that mosquitoes carry, and therefore no immunity. Now only 42 of more than a hundred species of birds endemic to Hawaii remain, and three-quarters of those are listed as endangered. The American Bird Conservancy has referred to Hawaii as "the bird extinction capital of the world." Avian malaria is not the only threat to what remains of Hawaii's native birds, but if it cannot be stopped – and gene editing seems to be the best way to do that – they will likely all disappear.

36. In February of this year, U.S. Director of National Intelligence James Clapper warned in his annual report to the Senate that technologies like CRISPR ought to be regarded as possible weapons of mass destruction. Many scientists considered the comments unfounded, or at least a bit extreme. There are easier ways for terrorists to attack people than to conjure up new crop plagues or deadly viruses.

37. The more rapidly science propels humanity forward, the more frightening it seems. This has always been true. Do-it-yourself biology is already a reality; soon it will almost certainly be possible to experiment with a CRISPR kit in the same way that previous generations of garage-based tinkerers played with ham radios or rudimentary computers. It makes sense to be apprehensive about the prospect of amateurs using tools that can alter the fundamental genetics of plants and animals.

38. But the benefits of these tools are also real, and so are the risks of ignoring them. Mosquitoes cause immense agony throughout the world every year, and eradicating malaria or another disease they carry would rank among medicine's greatest achievements. Although it is clearly too soon to contemplate using CRISPR in viable human embryos, there are other ways of editing the human germ line that could cure diseases without changing the genetic lineage of our species.

39. Children born with Tay-Sachs disease, for instance, lack a critical enzyme necessary for the body to metabolize a fatty waste substance found in the brain. The disease is very rare and occurs only when both parents transmit their defective version of the gene to a child. With CRISPR it would be easy to treat one parent's contribution – say, the father's sperm – to ensure that the child did not receive two copies of the faulty gene. Such an intervention would clearly save lives and reduce the chance of recurrence of the disease. A similar outcome can be achieved already through in vitro fertilization: implanting an embryo free of the defective gene ensures that the child won't pass the disorder on to a future generation.

40. When faced with risks that are hard to evaluate, we have a strong tendency to choose inaction. But with millions of lives at stake, inaction presents its own kind of danger. Last December scientists from around the world met in Washington to discuss the difficult ethics of these choices. More discussions are planned. There will never be simple answers, but without any regulatory guidance – and there is none yet for editing human DNA – the tremendous potential of this revolution could be overshadowed by fear.

41. "With gene drives and CRISPR we now have a power over species of all kinds that we never thought possible," says Hank Greely, director of Stanford's Center for Law and the Biosciences. "The potential good we can do is immense. But we need to acknowledge that we are dealing with a fundamentally new kind of power, and figure out a way to make sure we use it wisely. We are not currently equipped to do that, and we have no time to lose."

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