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CAPSULE

Bees play ball

Tool use is not limited to humans, primates and marine mammals as we know. According to a new study, published in the journal *Science*, invertebrates such as bees, too, can be trained in this skill. The experiment involved training bumblebees to roll a ball by offering them a reward.

Fear-free mice

Japanese researchers temporarily abolished fearful memories in mice by deactivating a neural protein. Such a feat is normally difficult to carry out, because the procedure would affect both the cell surface and the internal forms of the protein in question. The research is published in *Nature Biotechnology*.

'Smart' gut bacteria

Researchers have described the means by which infectious bacteria can sense that they are attached to our intestinal cells, and then remodel the expression of specific genes they possess, including those involved in virulence and metabolism, to exploit the cells of the person whose gut they inhabit and colonise the gut.

Autism and herpes

Women actively infected with genital herpes in early pregnancy had twice the odds of giving birth to a child later diagnosed with autism spectrum disorder (ASD), a study says. It is believed the mother's immune response to herpes simplex virus-2 could be disrupting foetal central nervous system development, raising risk for autism.

Drones and 'fuzzy logic'

Scientists, including one of Indian origin, are using artificial intelligence called 'fuzzy logic' to get drones to navigate and land themselves on moving platforms without any help. Researchers from the University of Cincinnati in the U.S. applied fuzzy logic, the kind of reasoning people employ subconsciously every day for the purpose.

ODD & END

Playway chemistry

Compared with conventional class-room learning, students may learn chemistry better through games despite receiving no formal in-class science instruction. This is what researchers from the University of Texas at Dallas found when 39 students from diverse fields played an enhanced version of the video game "Minecraft" and learned chemistry in the process, says a university press release. The game allows players to incorporate the properties of chemical elements and compounds into game activities. Using the model and instructions provided on a Wiki website, players can, for example, convert crude oil into a jetpack using distillation, chemical processes.

There is more to come in the CRISPR story

Though the verdict is out on the patent case, there are many reasons why the fight to own this gene editing technology will continue

NEW YORK TIMES

The U.S. Patent and Trademark Office recently issued a key verdict in the battle over the intellectual property rights to the potentially lucrative gene-editing technique CRISPR-Cas9.

It ruled that the Broad Institute of Harvard and MIT in Cambridge, Massachusetts, could keep its patents on using CRISPR-Cas9 in eukaryotic cells. That was a blow to the University of California, Berkeley, which had filed its own patents and had hoped to have the Broad's thrown out.

The fight goes back to 2012, when Jennifer Doudna at Berkeley; Emmanuelle Charpentier, then at the University of Vienna; and their colleagues outlined how CRISPR-Cas9 could be used to precisely cut isolated DNA. In 2013, Feng Zhang at the Broad and his colleagues – and other teams – showed how it could be adapted to edit DNA in eukaryotic cells such as plants, livestock and humans.

Berkeley filed for a patent earlier, but the USPTO granted the Broad's patents first – and last week upheld them. There are high stakes involved in the ruling. The holder of key patents could make millions of dollars from CRISPR-Cas9's applications in industry: Already, the technique has sped up genetic research, and scientists are using it to develop disease-resistant livestock and treatments for human diseases.

But the fight for patent rights to CRISPR technology is by no means over. Here are four reasons why.

1. Berkeley can appeal the ruling.

Berkeley has two months to appeal the USPTO's ruling – and may well do so. A key question is how confident Berkeley feels that its own patents, once granted, would cover the most lucrative applications of gene editing in eukaryotic cells, such as generating new crops or human therapies.

Prime contender Jennifer Doudna, right, and her lab manager, Kai Hong, working in her laboratory in Berkeley, California. AP

The Broad's victory centred on a key difference: that its patents specified how CRISPR could be adapted for use in eukaryotic cells and Berkeley's did not. This is why the USPTO ruled that the Broad's patents would not interfere with the granting of Berkeley's, and so should be allowed to stand.

Berkeley's team was quick to argue, in the wake of the decision, that its patent – if granted in its current state – would cover the use of CRISPR-Cas9 in any cell. That, the team says, would mean someone wanting to sell a product made using CRISPR-Cas9 in eukaryotic cells would need to license patents from both Berkeley and the Broad.

Yet the details of the USPTO's ruling could weaken Berkeley's chances of enforcing its patents in eukaryotic cells, patent scholars say. For example, much of the USPTO's 50-page decision argues that the use of CRISPR-Cas9 in eukaryotic cells – described in the Broad patent – required additional invention beyond that described in the Berkeley patent application.

So Berkeley may feel that it must still appeal. And its intellectual property is already licensed to several companies that intend to deploy CRISPR-Cas9 in eukaryotic cells. Those companies will probably prefer not to have to pay for a license from the Broad as well.

2. European patents are still up for grabs.

Both teams have filed similar patents in Europe and are still battling for patent rights there.

And the decision in Europe may not necessarily follow the same path as the USPTO, notes Catherine Coombes, a patent lawyer at the intellectual property specialists HGF in York, England.

On the basis of European case law, the European Patent Office could choose to assess whether the discovery of the general gene-editing system described in the Berkeley patent prompted "sufficient motivation" to try to make the leap to eukaryotic cells. If European judges find this to be the case, they could rule that the Berkeley patent covers eukaryotic applications of CRISPR-Cas9.

That could give Berkeley an edge that it lacked in the United States. "The fact that six groups got CRISPR-Cas9 to work in a eukaryotic environment within weeks of one another shows that in the field there was clear motivation to try," says Coombes.

Even so, there is likely to be no quick resolution to the European patent battle either: Coombes estimates that it could drag out for another five years or more.

3. Other parties are also claiming patent rights on CRISPR-Cas9.

Attention has focused on the Berkeley-Broad battle because their patents are fairly broad and are seen as being crucial to most commercial applications of CRISPR-Cas9. But there are 763 patent families (groups of related patents) that claim Cas9, according to the consulting firm IPStudies near Lausanne, Switzerland. Of those, some claim patent rights to certain aspects of CRISPR-Cas9 gene editing. Over time, holders of those patents may try to assert those rights.

That may not happen until companies that use CRISPR-Cas9 start to make money from their products. At that point, someone who owns a related patent may sue for infringement and ask for royalties.

When the time comes, look for plenty of patent holders to come calling, says Jacob Sherkow, an intellectual property scholar at New York Law School in New York City. "Everybody and their third cousin twice removed is going to be claiming they have some inventorship interest in the Broad's patent," he says. "The Broad is going to be fighting those battles for years."

4. CRISPR technology is moving beyond what the patents cover.

Researchers in academia and industry have been pushing CRISPR gene editing beyond the scope of the Broad and Berkeley patents.

Both patent families cover the use of CRISPR-Cas9, which relies on the Cas9 enzyme to cut DNA. But there are alternatives to Cas9 that provide other functions, and a way to sidestep the Berkeley-Broad patent fight.

One attractive alternative is Cpf1, an enzyme that may be simpler to use and more accurate than Cas9 in some cases. The Broad has already filed patents on applications of Cpf1 in gene editing, and has licensed them to the biotech company Editas Medicine in Cambridge (which also has licenses for some Broad patents on CRISPR-Cas9). In all, there are already 28 patent families that claim Cpf1, according to IPStudies, and not all of them are from the Broad.

Reports of other enzymes are trickling in. In December, researchers at Berkeley said that they had found two new Cas9 alternatives, CasX and CasY3. And some researchers may already be trying to patent unpublished alternatives – U.S. patent applications typically do not become public until 18 months after they are filed.

Sherkow likens the situation to the early days of PCR (the polymerase chain reaction), a technique used to amplify segments of DNA that quickly became a vital tool in molecular biology. Laboratories initially used just one enzyme, Taq1 polymerase, to carry out the protocol.

"Now if you go through the catalog, there's almost an Amazon warehouse of polymerases that you can use depending on the particular reaction that you want to do," he says.

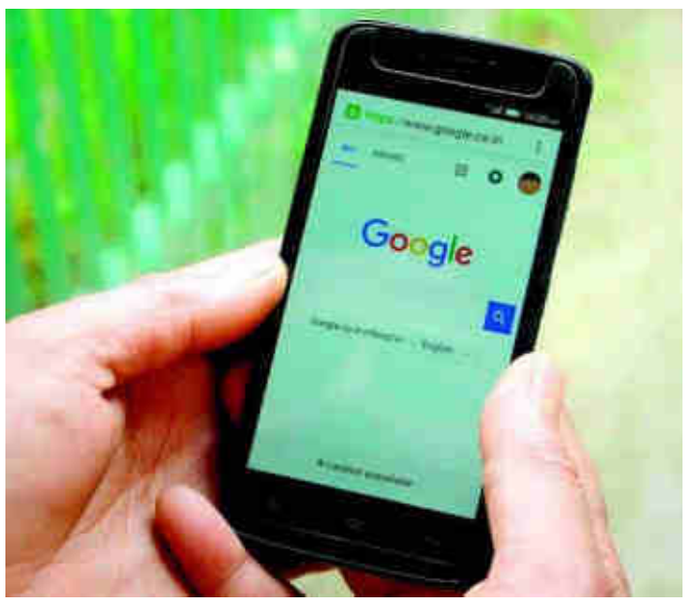
People are tethering the commercialization aspect of CRISPR to this particular patent fight, Sherkow says. "That's missing some of the broader picture."

Darknet robust for lack of "rich clubs"

The Darknet offers anonymity on the part of the surfer and the service provider

SHUBASHREE DESIKAN

Recent research analysing the structure of the Darknet in comparison with the Internet reveals that the former is, in fact, more robust against factors such as security breaches or systemic instabilities than the Internet. The analysis shows this is because of its peculiar topology that is different from that of the Internet. The Darknet's lack of a "rich club"-like core of highly connected nodes is one aspect that renders it robust against random crashes, targeted attacks and also cascading effects of failures of core nodes. This research is to be published in *Physical Review E*. "Internet is highly centralized around hubs, [has] highly connected nodes which are very interconnected each other. The Darknet is highly decentralized: we did not find a core of hubs. This [requires] much more effort to dismantle the network," says Manlio De Domenico, an author of the paper, in an email.



Ubiquitous network: Despite being widely used, the usual search engines probe only a tiny fraction of the Web. NISSAR AHMAD

The alter ego

The Internet and the Darknet have formed the subject of much research, especially regarding the higher robustness of the latter network. First created in the early 1990s by the US agencies - Defense Advanced Research Projects Agency (DARPA) and the Office of Naval Research - the Darknet is both resistant to eavesdropping and traffic analysis.

The Internet that we all know so well and can access using search engines like Google or Bing constitutes just a small fraction of the total of overlay networks; there is also the Darknet, the Internet's alter ego, which consists of the Web's non-indexed parts that cannot be accessed by search engines. What is more, this Darknet can be accessed only using onion routers like Tor or The Freenet Project- which are special browsers that ensure anonymity of the surfer as well as the service provider. While this is used by defence establishments for passing on sensitive and classified information, it is also, for instance, used by journalists who require utmost secrecy. Certainly it has a sinister side, with criminals also making full use of this technology.

From a network point of view, the structure of the Darknet is very different from that of the Internet. While in the Internet nodes that are central tend to connect more with each other, forming a "rich club" it is not the case in the Darknet. The centralised structure of the Internet makes it more vulnerable to attacks, because by hitting at the central nodes, one can destabilize the entire system. This can't be done with the Darknet which has a decentralised structure.

Dynamical instability

The Internet crashed for the first time in 1980 when it hosted thousands of users. The crash was due to a cascading effect of a mistake that originated in one router and not due to an attack on a central node.

This sort of cascade can propagate more easily through a network with rich club nodes, than a decentralised Darknet type structure.

Explaining the strength of the Darknet, Dr De Domenico says, "The fact that its network is highly decentralized makes [it] more efficient: if a node crashes, the load is redistributed almost equally among other nodes, with no super-nodes overloaded. This is true at the beginning of the process, and it is not the case with the Internet (where if a hub fails, it is likely to redistribute its load to other hubs thus overloading them)."

The researchers also predict that the Darknet is undergoing a transition from decentralised to centralised structure, based on observations over a span of a few years. This remains, however, to be checked by future studies.

Fast to reverse diabetes

A study on mice demonstrated reversal

INDO-ASIAN NEWS SERVICE

A type of fasting diet may reprogramme pancreas cells, promote the growth of new insulin-producing pancreatic cells and reduce symptoms of Type 1 and Type 2 diabetes, a study has shown.

In the study, led by researchers from the University of Southern California, mice were placed on fasting mimicking diet (FMD) for four days each week.

They showed remarkable reversal of diabetes.

The mice regained healthy insulin production, reduced insulin resistance.

They also demonstrated more stable levels of blood glucose – even in the later stages of the disease, the researchers said in the paper published in the journal *Cell*.

The genes normally active in the developing pancreas of embryonic/foetal mice are reactivated in diabetic adult mice when cycling FMD with normal diets.

This increases production of the protein neurogenin-3 (Ngn3) and, as a result, promotes the creation of new, healthy insulin-producing beta cells.

Researchers also examined pancreatic cell cultures from human donors and found that, in cells from Type 1 diabetes patients, nutrients mimicking fasting also increased expression of the Ngn3 protein and insulin production.

"These findings warrant a larger FDA trial on the use of the Fasting Mimicking Diet to treat diabetes patients," said Valter Longo from the University of Southern California.

"People with diabetes could one day be treated with an FDA-approved Fasting Mimicking Diet for a few days each month, eat a normal diet for the rest of the month, and see positive results in their ability to control their blood sugar by producing normal levels of insulin and improving insulin function," Longo added.

Question Corner

FOREIGN BLOOD CELLS?

Why does the immune system not attack blood that has been transfused?

■ A.P. SARADHI, VISAKHAPATNAM

When a foreign protein is introduced, the body reacts by producing antibodies. Some of these are protective and some could be hazardous to the body.

In blood transfusion, the patient's body receives "foreign" red blood cells, platelets, white blood cells and plasma containing proteins. Hence it is important to ensure maximum compatibility of the blood of the patient and that of the donor to prevent any hazardous reactions.

The major concern is about transfusing red blood cells which are not 100% compatible with the patient. When this happens the red blood cells of the patient are attacked by the incompatible antibodies in the transfused blood and vice versa resulting in lysis of red blood cells and dysfunction of organs in the patient. Hence, there is a compelling need for matching not only the major blood groups of the two (namely, A, B or lack of both "O" but also other red blood cell antigens which are not routinely done by most blood banks.

Since no compatibility tests are done specifically for platelets and white cells, in some patients the system recognises these as foreign and results in mild shivering and fever, which is referred to as non-haemolytic febrile transfusion reaction.

■ DR P SRINIVASAN, CO-FOUNDER & CHAIRMAN, JEEVAN BLOOD BANK & RESEARCH CENTRE, CHENNAI

THIS WEEK'S QUESTIONS

Can ageing be reversed or accelerated?

■ T.S. KARTHIK, CHENNAI

When you look at our nails, we see a white portion at the base, what is this?

■ P.J. ANISH, BENGALURU

Why is it that humans cannot tolerate water in their eyes even for a second, but fishes live in water for years?

■ NEERAD THANVI, BIKANER, RAJASTHAN

Readers can send their questions/answers to questioncorner@thehindu.co.in

Black rhinos on the brink of extinction

The species has lost 70% of its genetic diversity, finds study

DIVYA GANDHI

As the value of rhinoceros horn touches $65,000 per kg, poaching has begun to drive the African black rhinoceros to "the verge of extinction" - not just by reducing its population size, but by erasing 70% of the species' genetic diversity - says a research paper published recently in *Scientific Reports*.

Genetic variation is the cornerstone of evolution, without which there can be no natural selection, and so a low genetic diversity decreases the ability of a species to survive and reproduce, explains lead author Yoshan Moodley, Professor at the Department of Zoology, University of Venda in South Africa.

Two centuries ago, the black rhinoceros - which roamed much of sub Saharan Africa - had 64 different genetic lineages; but today only 20 of these lineages remain, says the paper. The species is now restricted to five countries, South Africa, Namibia, Kenya, Zimbabwe and Tanzania. Genetically unique populations that once existed in Nigeria, Cameroon, Chad, Eritrea, Ethiopia, Somalia, Mozambique, Malawi and Angola have disappeared.

Genetic erosion: The black rhino which roamed much of sub Saharan Africa is now restricted to just five countries.

The origins of the 'genetic erosion' coincided with colonial rule in Africa and the popularity of big game hunting. From the second half of the 20th century, however, poaching for horns has dramatically depleted their population and genetic diversity, especially in Kenya and Tanzania.

Museum collection

For the study, scientists used genetic data obtained from existing animals and museum samples (rhinoceros parts preserved in museum collections).

The paper calls for "a complete re-evaluation of current conservation management paradigms" for the black rhinoceros. "By identifying the genetic units remaining for surviving rhinos, we are effectively defining the boundaries within which management (be it translocations to increase genetic diversity or consolidation of populations for more effective protection) can be carried out without negatively affecting the gene pool," co-author Michael W. Bruford, Professor at Cardiff School of Biosciences, Cardiff University, U.K told *The Hindu*.

Greater the genetic diversity, the better is the population's ability to respond to pressures such as climate change and diseases, said Prof. Bruford. "Thus the loss of so much evolutionary potential in the black rhino is worrying for its future adaptability."