by the inventor. It also gave explicit patent protection to a modified form of DNA called complementary DNA (cDNA), which is made in the lab with an enzyme that creates DNA using an RNA template. Patents on cDNA are deemed more commercially valuable than patents on naturally occurring genes, in part because cDNA tends to be shorter and easier to work with in the lab than genes in their natural state. It can also be used for diagnostic tests if the mutations of interest are contained within the RNA template, as is often the case. But patents on cDNAs, at least for known genes, are largely a dying breed because making cDNA is a common practice that would be considered too obvious for a robust patent.

Increasingly, scientists define synthetic DNA as that which has been made from scratch by assembling the individual bases of DNA into a given sequence, often using machines. And the justices did not say whether synthetic DNA of this sort could be patentable if it exactly copied a naturally occurring sequence.

Lawyer Patrick Waller, of Boston firm Wolf Greenfield in Massachusetts, says that the decision could jeopardize patents on short stretches of synthetic DNA that are used to check whether the genome contains certain sequences, or to create multiple copies of particular DNA regions.

These issues now fall to the lower courts and to patent examiners who must interpret the Supreme Court opinion. Shortly after the decision was issued, Andrew Hirshfeld, a deputy commissioner at the US Patent and Trademark Office in Alexandria, Virginia, issued a memo suggesting that such patents would no longer be granted. That memo, intended to serve as interim guidance until the office updates its policies to incorporate the new ruling, is a sign that the patent office will be interpreting the Myriad decision strictly, says David Berry, a professor of intellectual-property law at the Thomas M. Cooley Law School in Lansing, Michigan. "Companies are just going to have to think up different approaches to claiming their inventions," he says.

Biotech companies might already be changing their approach. Simmons now tells clients to protect certain inventions as trade secrets, which are not publicly disclosed, rather than as patents. After the Myriad decision, he says, he may also instruct clients to introduce many modifications to the DNA or proteins they intend to patent, to make them as different as possible from naturally occurring forms. "There's no guidance here as to what is a sufficient amount of change to warrant a patent," says Simmons. "It's insane." ■

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LES HIRONDELLES/FLICKR/GETTY

**The issue of when or where canines were domesticated has geneticists in a tug of war.**

EVOLUTION

# Dog genetics spur scientific spat

*Researchers disagree over canine domestication.*

BY EWEN CALLAWAY

Scientists investigating the transformation of wolves into dogs are behaving a bit like the animals they study, as disputes roil among those using genetics to understand dog domestication.

In recent months, three international teams have published papers comparing the genomes of dogs and wolves. On some matters — such as the types of genetic changes that make the two differ — the researchers are more or less in agreement. Yet the teams have all arrived at wildly different conclusions about the timing, location and basis for the reinvention of ferocious wolves as placid pooches. "It's a sexy field," says Greger Larson, an archaeogeneticist at the University of Durham, UK. He has won a £950,000 (US$1.5-million) grant to study dog domestication starting in October. "You've got a lot of big personalities, a lot of money, and people who want to get their *Nature* paper first."

In January, Erik Axelsson and Kerstin Lindblad-Toh, geneticists at Uppsala University in Sweden, and their colleagues reported in *Nature*[1] that genes involved in the breaking down of starch seemed to set domestic dogs apart from wild wolves. In the paper and in media interviews, the researchers argued that dog domestication was catalysed by the dawn of agriculture around 10,000 years ago in the Middle East, as wolves began to loiter around human settlements and rubbish heaps (see *Nature* http://doi.org/mv4; 2013).

But Larson, who has worked with Lindblad-Toh on other projects, says that their claim is dubious. He notes that bones that look similar to those of domestic dogs predate the Neolithic revolution by at least several thousand years, so domestication must have occurred before then. "Why waste space [in a paper] saying something that is patently untrue?" he says.

Axelsson concedes that the changes in starch digestion in dogs could have occurred after they were domesticated. But he also counters that the Neolithic era lasted for thousands of years, and that dogs may have been domesticated during the earliest steps towards agrarian life — when human hunter-gatherers settled down and began eating more starch-rich wild plants.

A second study, published last month in *Nature Communications*[2], argues that dogs were domesticated 32,000 years ago when they began scavenging with Palaeolithic humans in southern China. A team led by Ya-ping Zhang at the Kunming Institute of Zoology in China drew that conclusion from studying the whole genomes of several grey wolves, modern European dog breeds and indigenous Chinese dogs.

But Larson says that there is no evidence to

suggest that wolves ever lived in southern China, "so how do you domesticate a wolf if there aren't any?" And Jean-Denis Vigne, an archaeozoologist at the National Museum of Natural History in Paris, agrees, noting that in earlier work, Zhang's team "completely ignored what has been published, even in the frame of genetics".

Peter Savolainen, a geneticist at the KTH Royal Institute of Technology in Solna, Sweden, who co-authored the *Nature Communications* paper, argues that Chinese scientific literature suggests that wolves did once live south of China's Yangtze River, but have since become extinct. But he acknowledges that the date that his team reported — like all molecular dating efforts — relies on several assumptions, such as the number of genetic mutations that develop in each generation.

A third paper[3] argues that a more probable date for domestication was 11,000–16,000 years ago. Posted to the arXiv preprint server on 31 May, the study, like Zhang's, compares the whole genomes of wolves and dogs. But the paper paints an even murkier picture, suggesting that wolves and the ancestors of modern dogs continued to breed together long after domestication, and that the wolf population that gave rise to dogs is extinct.

The authors, a team of geneticists co-led by John Novembre at the University of Chicago in Illinois, declined to comment on their work because it has not yet been published in a journal. But Larson and others say that the paper makes a strong point — that studying the genomes of long-dead dogs and wolves is the only way to settle the dispute. At least three other teams in the United States and several others in Europe are racing to sequence ancient dog and wolf genomes, but researchers say that many specimens will be needed to build a clearer picture of domestication. Still, "we're not in a position to be picky", says Adam Boyko, a dog geneticist at Cornell University in Ithaca, New York, who was involved in the arXiv paper[3]. "We're sort of going to be limited to which samples we can get DNA out of."

The move to look at ancient DNA could make the small field of dog genetics even pricklier, because archaeological bone samples are so precious. Novembre says that he finds the field more fractious than human genetics, and says that his experience has given him pause about future canine work. "It's really intense in the dog world," he says. But Boyko, who also collaborates with the Chinese group, says that although the field is competitive, it remains collegial. "At the end of the day, we sit back and enjoy a beer together when we see each other." ■

1. Axelsson, E. *et al. Nature* **495,** 360–364 (2013).
2. Wang, G.-D. *et al. Nature Commun.* http://dx.doi.org/10.1038/ncomms2814 (2013).
3. Freedman, A. H. *et al.* Preprint available at http://arxiv.org/abs/1305.7390 (2013).

PHARMACEUTICALS

# China drugs head fired over article row

*Researcher stands by results despite demand for retraction.*

**BY DAVID CYRANOSKI**

Jingwu Zang says he is baffled by the whole affair. Until last month, he was head of a neurodegenerative-disease research unit in Shanghai, China, for London-based drug firm GlaxoSmithKline (GSK). On 22 May, as he tells it, his boss told him that there would be an investigation. The next day, Chinese lawyers showed up at the company to interview him. On 31 May, he was told to hand in his computer and company credit card, and was escorted to his car. "Within a few minutes, I was outside the facility I built," he says.

On 9 June, he received a letter informing him of his official termination of employment.

The investigation has focused on a paper published in *Nature Medicine* that Zang co-authored on multiple sclerosis (MS), his speciality (X. Liu *et al. Nature Med.* **16,** 191–197; 2010). GSK is asking for the paper to be retracted; Zang stands by the results. The Chinese blogosphere is abuzz over the dispute, wondering what it signals for a centre seen as a bellwether for China's budding drugs industry.

Zang set up the global research and development centre in Shanghai in 2007. The centre was considered bold: of the many international pharmaceutical giants that had opened research operations in China in the previous five years, only GSK had given its branch wide autonomy, with control over global operations for an entire development sector, that of neurodegenerative diseases. "In Shanghai, we can make decisions that drive global studies," says Zang.

Now with some 400 scientific staff, the centre has several candidate neurodegenerative drugs in phase I and II clinical trials, Zang says, and he was eager to get one through phase III, to "demonstrate that we can do great science and move a clinical compound forward".

Four years ago, Zang's group started work on a protein called the interleukin-7 receptor (IL-7R). "It was a really exciting story," he says. IL-7R sits on the surface of certain immune cells, and a genetic variant of it had been linked to MS. Nobody knew what the underlying mechanism was, but Zang had a hypothesis — that the IL-7 pathway played a part in the pathogenic expansion of T-helper 17 ($T_H17$) cells, immune cells that, when present in excess, are thought to contribute to MS.

In 2010, the group published results in *Nature Medicine* concluding that this was indeed the case. But last month, the paper came under scrutiny from within GSK after the company and *Nature Medicine* were notified of a problem with some of the data. A GSK investigation has since concluded that human blood samples used to create a figure in the article — described in the caption as being taken from patients with MS — actually came from healthy subjects.

On 10 June, GSK posted a statement saying: "Regretfully, our investigation has established that certain data in the paper were indeed misrepresented. We've shared our conclusion that the paper should be retracted and are in the process of asking all of the authors to sign a statement to that effect."

Zang and Xuebin Liu, the paper's first author, both say that this was an unintentional mistake that does not change the paper's overall conclusion. Liu, whose group ran the experiment and compiled the data, says that the team had hoped to use data from cells of patients with MS and had drafted a manuscript with that wording. But although preliminary data from patients did reveal Zang's proposed link between the IL-7R pathway and $T_H17$ cells, staining in those images was inadequate — so the team turned to healthy subject data instead, Liu says. In a hurry to beat competition, they forgot to change the caption. Liu says that cells from either group can be used to show the effect.

***"Regretfully, our investigation has established that certain data in the paper were indeed misrepresented."***

Liu also addressed another problem, noted later on a pharmaceutical blog, after news of the investigation came out: two images, with captions describing different experimental conditions, are identical. Liu says that the mistaken duplication occurred during editing and layout of the article, and has asked *Nature Medicine* to check. The journal's chief editor Juan Carlos López says that he cannot comment yet.

The main thrust of the paper — that IL-7R is related to MS, and that blocking its function can ameliorate MS-like disease in a mouse model — largely agrees with results from other groups. But scientists have failed to replicate the specific mechanism proposed by Zang's team.

One of those studies, led by researchers at Stanford University in California and at Rinat, a subsidiary of the drugs giant Pfizer based in South San Francisco, California, found ▶