WES FERNANDES

compelling case. Pet dogs suffer from many of the same conditions as humans, from narcolepsy to arthritis. And the intensely inbred nature of dog breeds made it relatively easy to identify disease-causing genes: because there is little genetic variation within any particular breed, the genes that cause disease in affected individuals stand out.

Dogs had other advantages, too. The existence of kennel clubs, which maintain 'breed standards' and are full of enthusiastic pet owners and veterinary surgeons, helped dog geneticists to recruit subjects for study. "Given the resources they had, they were discovering new genetic diseases in breeds almost daily," says Niels Pedersen, a veterinary scientist at the University of California, Davis.

In fact, both cats and dogs offer insights into human disease, including those associated with old age. In 2004, a team led by geneticist Leslie Lyons of the University of Missouri in Columbia (and owner of two female cats, Withers and Figaro) discovered that mutations that cause polycystic kidney disease — a major cause of renal failure in older individuals — occur in the same gene in humans and cats[4]. Cat versions of type 2 diabetes, asthma, retinal atrophy and numerous other conditions have close similarities to human disease. Cats can also become infected with a virus that is closely related to HIV and experience symptoms similar to those of people with AIDS.

In the hopes of speeding up the discovery of genes related to these conditions last year, Lyons launched the 99 Lives cat genome sequencing initiative, playfully hosted on a site called Lyons' Den. She discussed the effort on 11 January at the Plant & Animal Genome conference in San Diego.

Lyons' team is cobbling together funding from anywhere it can find it. The researchers are asking private owners, breeders and even pet-food companies to donate the US$7,500 needed to sequence the genome of a single cat, which could be one of a donor's choice. "Any cat can participate. Any owner can participate," she says. All the data will be made public after the results are published.

"I would love to eradicate all genetic disease in cat breeds before we're done."

With the money raised so far, the team has sequenced the genomes of 56 cats, including fancy breeds such as Burmese; cats with specific diseases; and a kitten named Dragon and his parents Ares and Marcus — the hope is to use the feline trio to narrow down the genetic basis for traits they share, such as their silver, curly coats.

Even Robert Wayne, a canine geneticist at the University of California, Los Angeles, agrees that Lyons' effort is important. "I hope she raises money for it," he says.

Insights from cat genomics extend beyond disease. Razib Khan, an evolutionary geneticist at the University of California, Davis, wants to use genome sequences to chart the domestication and spread of cats throughout the world, and to determine how different domestic and wild cats are genetically. "There's always the question — are they domesticated at all?" he says. The 2014 publication that included Cinnamon's genome already identified differences between domestic and wild cats, including genes expressed in the brain that are possibly linked to the docility of (some) house cats. "Wild cats will hand you your behind if you get next to them and domestic cats will sit on your lap," O'Brien notes.

Lyons is also keen to see genomics help felines. "I would love to eradicate all genetic disease in cat breeds before we're done," she says. Her team's discovery of the cause of polycystic kidney disease has reduced its prevalence among Persians, by removing cats with the mutation from the breeding pool. Her lab is now developing drugs that could treat the terminal condition in cats — and perhaps in humans. But human health, Pedersen says, is not the only goal. "I'm in it, and Leslie's in it, for the good of cats." ■

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HEALTH

First biosimilar drug set to enter US market

But such cheaper, generic versions of biological drugs face scientific, regulatory and patent hurdles.

BY HEIDI LEDFORD

After years of debate, the US Food and Drug Administration (FDA) is poised to allow the sale of biosimilars, cheaper versions of complex and expensive biological drugs used to treat conditions such as cancer and autoimmune diseases. On 7 January, an FDA advisory panel decided unanimously that a drug made by Sandoz, the generics arm of Swiss pharmaceutical giant Novartis, should be accepted as a replacement for filgrastim (Neupogen), an immune-boosting drug for people undergoing cancer treatment made by Amgen of Thousand Oaks, California.

Such knock-offs are called biosimilars because the drugs that they mimic, dubbed biologics, consist of complicated molecules that are made in living cells and are impossible to copy exactly. Even copying them inexactly is immensely challenging — despite the expected approval of the Sandoz drug, the difficulties involved in creating and evaluating biosimilars may limit their infiltration of the marketplace. The field is also littered with patent issues, especially with regard to how the drug is manufactured. In the case of filgrastim, Sandoz is challenging some of the legal requirements for approval.

"We're starting from scratch," says Jordan Paradise, a specialist in technology law at Seton Hall University in Newark, New Jersey. "A lot of the scientific uncertainty is still there."

Unlike typical drugs, which are relatively small molecules made through biochemical processes, biologics are large protein molecules produced by genetically engineered organisms. Living cells may chemically modify the proteins they make by adding complex sugars and other compounds at certain positions. The exact conditions under which cells are grown can alter the pattern of these modifications, and thus the molecule's structure and behaviour. The result is a drug so complex that it is difficult — if not impossible — to fully characterize.

Because biosimilars are inexact copies, they are required to undergo more testing than an ordinary generic drug. The European Union has been evaluating and approving biosimilars for the past decade, but the United States did not have a way to do so until regulatory legislation was passed in 2010. Biotechnology companies have been waiting to find out how the FDA would evaluate the drugs.

Patient advocates hope that biosimilars can reduce drug costs by increasing competition. Biologics are expensive: researchers have calculated that treatment of metastatic colorectal cancer with bevacizumab (Avastin) costs about US$75,000 per year of life gained (V. Shankaran *et al. Oncologist* **19,** 892–899; 2014). A report last year by the RAND ▶

Corporation in Santa Monica, California, estimated that biosimilars could save $44.2 billion by 2024.

Filgrastim is relatively simple: it is a small protein with no attached sugars. Even so, Sandoz presented the FDA with clinical-trial data from 388 people with breast cancer and 174 healthy participants to show that its biosimilar breaks down in the body similarly to the original, and does not provoke an immune response.

The FDA is expected to make a final decision by May. But even as Sandoz prepares to sell its drug in the United States, it is embroiled in a patent fight with Amgen. By US law, Sandoz had to reveal the details of its manufacturing method to Amgen — a provision not present in Europe — so that Amgen could determine whether any of its patents had been violated. Sandoz refused. That is a disheartening precedent, says Paradise. "Here we've got the first biosimilar application and we've already got the manufacturers not working together."

Such concerns loom large among manufacturers, says Nicholson Price, a patent-law specialist at the University of New Hampshire School of Law in Concord. Drug firms often keep their manufacturing methods confidential, and production of complex drugs gives them ample opportunity to file patents on manufacturing techniques or ways of characterizing molecules. "The second company is attempting to feel its way in the dark to what the first company has done," says Price. "I suspect there are other biosimilars that are being deterred either by specific patents or just the worry that there may be patents lurking out there that they don't know about."

"We've got the first biosimilar application and we've already got the manufacturers not working together."

Even when a biosimilar makes it over these hurdles, it is unclear how consumers will react to a drug that is almost, but not quite, a copy of the original. At the advisory-committee meeting, a number of patient groups expressed support for biosimilars and the promise of relief from high drug prices. But they voiced concerns that biosimilars would be given the same generic names as the drugs they were meant to replace, creating confusion as to whether recipients were getting the original or the copy. Many will be watching the Sandoz drug's approval to see whether the FDA will let it be called filgrastim.

Committee member James Liebmann, an oncologist at the University of Massachusetts in Worcester, reacted to that concern with surprise. "This has been pretty clearly shown to be filgrastim," he said. "To name it anything else would be misleading." ■

MICROSCOPY

Inflated brains show nano detail

Diaper material expands tissue, enabling ordinary microscopes to reveal nanoscale features.

BY EWEN CALLAWAY

An innovative method could enable biologists to image an entire brain in exquisite molecular detail using an ordinary microscope.

The technique, called expansion microscopy, involves physically inflating biological tissues using a material more commonly found in baby nappies, or diapers. Edward Boyden, a neuroengineer at the Massachusetts Institute of Technology (MIT) in Cambridge, discussed the technique, which he developed with his MIT colleagues Fei Chen and Paul Tillberg, at a conference last month.

Conventional optical microscopes cannot distinguish objects that are closer together than about 200 nanometres. Although super-resolution microscopy can discern objects as close together as about 20 nm, they require expensive, specialized equipment, and struggle with thick structures such as sections of brains.

"What we've been trying to do is figure out if we can make everything bigger," Boyden told the meeting at the US National Institutes of Health (NIH) in Bethesda, Maryland. To do this, his team used a chemical called sodium acrylate, which has two useful properties: it can form a dense mesh that holds proteins in place, and it swells in the presence of water. The acrylate is the same substance that gives nappies their sponginess. When inflated, Boyden's tissues grow by a factor of about 4.5 in each dimension.

Before swelling, the tissue is treated with a chemical cocktail that makes it transparent, and then with fluorescent molecules that anchor specific proteins to the acrylate, which is then infused into the tissue. Just as with nappies, adding water causes the acrylate to swell. After stretching, the fluorescent-tagged molecules move farther away from each other; proteins that were previously too close to distinguish with a visible-light microscope come into crisp focus. In his presentation, Boyden suggested that the technique can resolve molecules that are as close as 60 nm before expansion.

Crucially, the process generally maintains the relative orientation and interconnection of proteins and keeps other cellular structures intact: it distorts the relative position of proteins by just 1–4%, Boyden's team calculated.

Viviana Gradinaru, a neuroscientist at the California Institute of Technology in Pasadena, says that Boyden's technique is another example of how scientists are bypassing hardware limitations by modifying biological tissue.

"This is certainly highly ingenious, but how much practical use it will be is less clear," notes Guy Cox, a microscopy specialist at the University of Sydney, Australia. "If this is to be of any serious use, I suspect it will be in collaboration with existing super-resolution techniques on small macromolecular complexes, to push the boundaries a bit further, rather than looking at whole cells." ■

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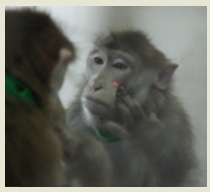

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