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Canine clues:

Dog genomes explored in effort to bring human cancer to heel

By Nala Rogers

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Joshua Schiffman had been searching for cancer-causing mutations in humans for years when his dog, Rhody, started limping in 2010. The shaggy Bernese mountain dog had histiocytic sarcoma, an aggressive tumor derived from immune cells. The condition, which can arise in various body parts such as the bone marrow and joints, is rare in humans but common in Rhody's breed. Schiffman started to read about Rhody's cancer, and he discovered the work of Matthew Breen, a comparative oncologist at North Carolina State University's veterinary school in Raleigh.

Breen was doing the same type of cancer research in dogs that Schiffman was doing in humans. Moreover, Breen had started to answer fundamental questions by comparing data from both species. "Before Rhody developed cancer, I never really considered cancer in dogs as something that could help us treat cancer in people," says Schiffman, a pediatric oncologist at the Huntsman Cancer Institute in Salt Lake City. Now, Schiffman collaborates with Breen to discover mutations

that cause the same types of cancer in humans and in dogs.

Dogs develop many of the same kinds of cancers as humans—often at higher rates—and they can receive treatment regimens similar to those used for people (*PLOS Med.*, doi:10.1371/journal.pmed.1000161, 2009). But dogs have more to offer in cancer research than just their treatment outcomes. Since the dog genome was first published a decade ago (*Nature* **438**, 803–819, 2005), research has increasingly shown that canine and human cancers are caused by aberrations in the same genes. Scientists at several labs have been comparing the genetic abnormalities in cancers from both species, and they have used this overlap to discover which mutations turn normal body cells cancerous. Now, this research is starting to bear fruit, yielding potential therapeutic targets that may help doctors to detect cancer sooner, to customize treatment and to develop new drugs (*Phil. Trans. R. Soc. B.*, doi:10.1098/rstb.2014.0231, 2015).

"The dog is actually starting to drive

biomarker discovery that is then being applied to human patients," Breen said in a presentation at a meeting of the US National Academy of Medicine (formerly the Institute of Medicine) in June in Washington, DC.

Sifting through chaos

By the time most cancers are detected, their DNA is in chaos. Whole chromosomes or large sections of the genome may have been duplicated, deleted or moved. Some genetic changes drive the disease, spurring growth or stopping cells from repairing DNA. The genes and pathways disrupted by these 'driver mutations' are often ideal targets for cancer-fighting drugs. But the driver mutations are hard to distinguish from the swarm of neutral changes that manifest as side effects of the broken machinery in cancer cells.

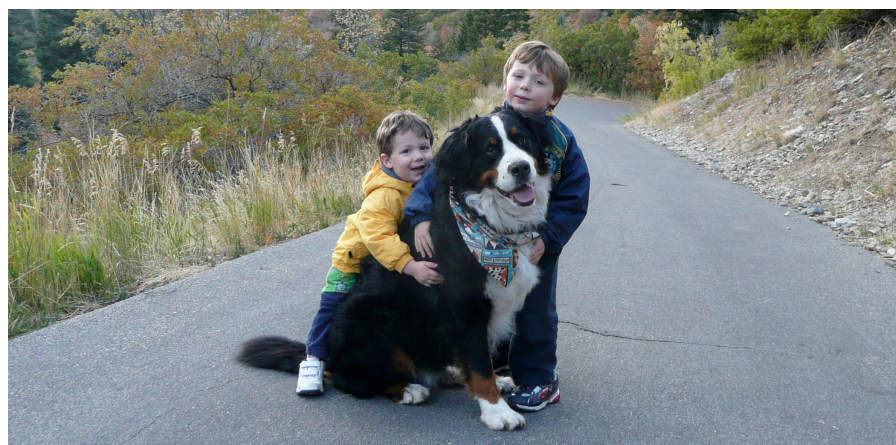
Research in dogs could help to sift through the noise. They have most of the same genes as humans, but these genes are distributed differently among the chromosomes, with different genes as neighbors. Thus, although

the same gene alteration may drive cancer in both species, the set of neutral mutations carried along for the ride will differ. “We use the dog data to filter through the human data and tease out those [cancer mutations] that are shared between humans and dogs,” Breen says. “The ones that are conserved—the shared ones—are most likely to be associated with initiation and early progression of malignancy.”

Human bladder cancers, for example, often have extra copies of the long arm of chromosome 8, a 100-megabase stretch of DNA that contains many genes. The equivalent region in dogs is broken into two sections that lie in different parts of the genome, only one of which is duplicated in canine bladder cancer. When Breen and Schiffman compared the parts that were duplicated most often in the two species, they were able to narrow the region of interest to a three-megabase stretch containing a single gene: poly(A) binding protein, cytoplasmic 1 (*PABPC1*). *PABPC1* helps to stabilize DNA, and in March, Breen and Schiffman highlighted duplications in *PABPC1* as a potential early driver of bladder cancer in both species (*Chromosome Res.* **23**, 311–331, 2015).

“It’s an incredibly powerful approach,” says Douglas Thamm, an oncologist at the Colorado State University Animal Cancer Center in Fort Collins, who is not involved in the project. “If you can take the same type of tumor from a dog and from a human, and see mutations that are conserved, the likelihood that that’s happening by chance becomes vanishingly low. It can really allow you to home in on the genes or pathways that might be the most important.”

Breen, Schiffman and their colleagues have identified shared genetic aberrations in dog and human cancers of the blood (*Chromosome Res.*, doi:10.1007/s10577-015-9475-7 2015; *Hum. Genomics*, doi:10.1186/1479-7364-7-2,



Joshua Schiffman

More than a pet: Schiffman's dog Rhody (pictured here) served as inspiration for his research. Opposite page: Breen (left) and Kelsey Poorman examine a chromosomal rearrangement.

2013), brain (*J. Neurooncol.* **94**, 333–349, 2009), skin (*Chromosome Res.* **23**, 171–186, 2015), bladder (*Chromosome Res.* **23**, 311–331, 2015) and bone (*Cancer Genetics* **205**, 572–587, 2012). Now they are conducting experiments *in vitro* to see which mutations really have a role in turning normal cells cancerous. In a few months, Breen says, they will present a short list of potential drug targets to pharmaceutical companies. They are also using the genetic signatures of cancers to develop diagnostic tests, such as urine tests for early-stage bladder cancers, for both humans and dogs.

Shaying Zhao, a cancer biologist at the University of Georgia in Athens, is also comparing the cancer genomes of dogs with those of humans. In studying the genomes of colorectal cancer from both species, Zhao's team has found several shared mutations in genes that help to keep epithelial cells facing in the right direction relative to other cells (*Oncogene* **33**, 814–822, 2013). Now, her team is investigating whether disrupting this cell polarity can trigger tumor growth (*Oncoscience* **1**, 854–865, 2014). “Canine cancer is a really important, underutilized resource,” says Zhao. “Without the dog-human comparison, I never would have studied cell polarity.”

Lots to filter

Despite the discovery of cancer mutations shared by humans and dogs, this approach has yet to yield a clear blockbuster hit for human medicine, and some researchers remain cautious. “What it boils down to is how useful or how transformative is the integration of dog and human genome information, and I think it’s hard to generalize,” says Levi Garraway, a cancer researcher at the Dana-Farber Cancer Institute and the Broad Institute in Boston. Garraway uses human cancer genomics to search for potential drug targets, but he has not

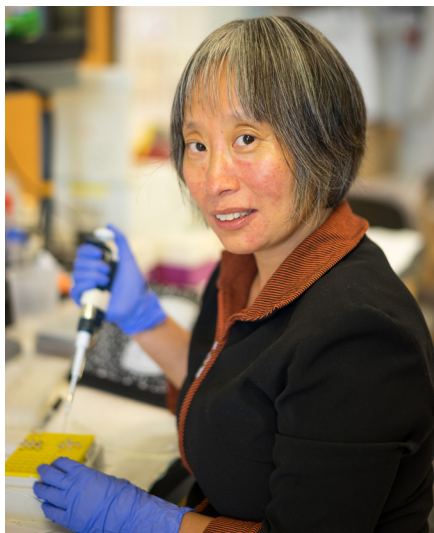
incorporated dog cancers into his research. The approach could be valuable, he says, especially when there are a lot of mutations to sort through. But not all cancer mutations shared by the two species will necessarily make good drug targets. “It’s just one cog in the wheel of drug discovery, and the extent to which it’s a major innovation will depend on the context,” he says.

Of all the work that Breen and Schiffman have done to highlight mutations by comparing genetic changes in dogs with those in humans, their work in lymphoma is the closest to helping humans, Breen says. In still-unpublished work, the researchers have identified a genetic signature that predicts how long dogs will survive after undergoing standard chemotherapy for lymphoma. Now, the scientists are analyzing biobanked samples of human lymphoma cells to see whether the signature seen in dogs could predict human response to treatment. They have already tested nearly 50 human samples, and they need about 100 more. So far, says Breen, the results are promising.

There is no shortage of pet dogs with spontaneous cancers to participate in research. Because of inbreeding, dogs develop cancer more than ten times as often as humans, Breen says, and certain breeds are exceptionally vulnerable to specific cancers. As many as one in four Bernese mountain dogs develops histiocytic sarcoma, the type that struck and ultimately claimed the life of Schiffman's dog, Rhody.

“Rhody really opened my eyes to this whole field of research,” says Schiffman. “Little did I know when my wife and I went to pick him out as a puppy that, six years later, he would change the entire course of my career, and hopefully, help people with cancer.”

Nala Rogers is a science writer based in Washington, DC.



Shaying Zhao

Mulling mutations: Zhao compares genomes.