Brain tumor research dog helps create gateway to help find human treatments

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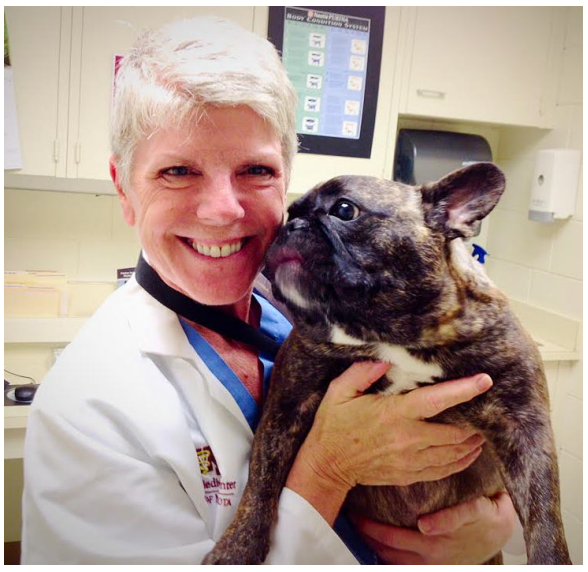

For Liz Pluhar and her U of M research team, there really is a superhero named Batman. And the “crime” that Batman helped fight is a form of brain tumor known as glioblastoma multiforme (GBM).

Glioblastoma multiforme tumors develop from glial cells, which provide the brain's structural backbone and support neuron or nerve cell function.

It all began around 2005, when Pluhar, DVM, PhD, Professor, Department of Veterinary Clinical Sciences, started working with the late John Ohlfest, PhD, who was an assistant professor at the university in Neurosurgery and Pediatrics. Ohlfest and Pluhar were members of the U's Masonic Cancer Center. The cancer center established a Brain Tumor Translational Working Group to bring together experts from basic science and clinical research to address site-specific cancers, foster collaborations, and provide the necessary scientific and clinical expertise to improve outcomes for patients with brain tumors.

The team also included neuro-immunologist Mike Olin, PhD, (pictured below left) who was doing his postdoctoral studies at the time. He is now assistant professor in the U’s Department of

Pediatrics, Division of Hematology/Oncology, and continues to work with Pluhar.

While the current team focuses on pet dogs like Chomper (being held by Pluhar in the picture at right), their ultimate goal is to develop targeted immunotherapy to help improve the standard of care for people with GBMs. The standard treatment if you have a high-grade (malignant) glioblastoma would typically be surgery followed by radiation and chemotherapy, whereas the current standard of care for dogs with GBM is radiation therapy alone.

“Based on what people who have had the treatment tell me, there is a lot of toxicity and adverse effects associated with it,” said Pluhar. “We want to find an alternative that can be used in conjunction with surgery that works as well as radiation and chemo but has few, if any, side effects.”

That’s where Batman came in. He was a black German Shepherd mix with bright brown eyes and enormous ears, hence the name. Batman had a glioma and his chances of living much longer were nil. “Dogs, like people, develop these tumors spontaneously,” Pluhar noted. “And the condition is similar, if not identical, to that found in people.”

In 2008, Pluhar partnered with Stephen Haines, MD, Neurosurgery Professor and Department Head, to surgically remove Batman’s tumor. Cells from the tumor were used to create what’s known as tumor lysate vaccines. The vaccines were designed to use Batman’s own immune system to help fight his tumor.

It worked. Instead of living for weeks or months, Batman lived for two more years, with none of the side effects from radiation and chemo.

Fast forward to today.

Pluhar now works with Associate Professor Matthew Hunt (pictured at right) of the Neurosurgery Department. Together they have successfully removed brain tumors from almost 200 dogs. Only a handful have not survived in the short term after surgery. That runs counter to the prevailing experience of other surgeons, who say one third of the animals die during surgery, one third die shortly after such surgery, and one third only live for a while, according to Pluhar.

“I don’t know what I’d do if I didn’t have Matt with me,” Pluhar said. “He has improved my surgical technique immensely. He also encourages me to accept dogs I probably wouldn’t have if I’d been working alone, which helps expand our case load.”

The surgical duo provides a steady supply of tumor cells that are used by Olin’s laboratory team to create tailor-made vaccines for each dog. “Mike is the one looking for new ways to modify or add things to the vaccines to improve the immune response and hopefully, to expand the disease-free and survival times for the dogs,” said Pluhar. “He’s an integral part of the team.”

Pluhar noted that the combination of surgery and immunotherapy isn’t a cure…yet. “All these dogs had their high-grade glioma come back,” she said. “As a result, we continue to look at different ways of stimulating the immune system.”

Olin explored such a path recently when he asked himself, “Why vaccinate in certain locations and not others?” Under grants awarded by the Children's Cancer Research Fund, Randy Shaver Cancer Foundation, and the American Brain Tumor Association, he conducted a study of the structures and functions of the proteins involved [proteomics] and ran some experiments. Then he discovered something.

“There is a soluble factor called CD200 that mounts a counter immune response to our vaccines,” Olin said. “When secreted by the tumor, it acts as a ‘checkpoint blockade’ and stops the vaccine from eliciting an immune response.” He developed a peptide inhibitor that overcomes the suppressive properties of CD200.[1]

“Using the inhibitor, we showed that we can go from zero to 50 percent survival in the mouse glioma model and up to 80 percent survival in the breast carcinoma model,” he added. During a pilot study (in which Chomper is participating), Olin worked with Christopher Pennell, PhD, Associate Professor, Lab Medicine and Pathology, Masonic Cancer Center, to cause regression of residual tumor after surgery in a dog with glioma using the new development. “That’s never happened before,” Olin said. The study is being funded by the Randy Shaver Cancer Research and Community Fund and the Skippy Frank Fund For Life Sciences and Translational Research.

The researchers now have two human candidates whose blood cells are being tested in vitro.

“We’re getting beautiful immune response,” said Olin.

In addition to Olin’s work with CD200, other approaches to immunotherapy have been developed from this work and brought to human clinical trials with Christopher Moertel, MD, Professor and Pediatric Neuro-oncologist and also a member of the Masonic Cancer Center. “We’re definitely progressing toward working on people,” Pluhar said.

Their work also led them to treating dogs with another type of brain tumor. Early on, the team would reach a preliminary diagnosis of the type of tumor using MRI and make a more definitive diagnosis with a surgical biopsy. “We started treated them with the glioma vaccine protocols and then discovered the dogs had high-grade, aggressive meningioma,” said Pluhar. “These dogs have done really well with the vaccines.”

In fact, unlike dogs with gliomas, most live the rest of their lives tumor-free. “Success is very high,” she said. “The combination of treatments is 85 to 90 percent effective. It’s really amazing.” Pluhar and Olin now have a meningioma vaccine program that treats dogs around the United States.

According to Hunt, people with meningioma typically start out with low-grade tumors that respond well to surgery, but eventually the tumors recur and become high-grade. This “unexpected spinoff,” as Pluhar describes the team’s work with meningioma, holds hope for these people.

A meningioma is a tumor that arises from the meninges — the membranes that surround your brain and spinal cord.

“Dr. Hunt is trying to get a clinical trial for people with high-grade, nonsurgical, or recurrent meningioma to see if what we’re seeing in the dogs translates to humans,” Pluhar said. “One of our early successes is just being able to grow these cells in culture,” Hunt added. “This breakthrough itself has opened the door to further work developing a vaccine.”

What might the future hold for this innovative research team?

“We’ll eventually get to the point where we’re overwhelming the people in Dr. Olin’s lab,” said Pluhar. The lab has to grow individual tumor cells for each dog and to obtain prolonged survival, booster vaccines are given every six to eight weeks. “They have to keep growing the cells for a long time until the tumor comes back,” she added.

A possible solution is to identify tumor cell lines that have all or most of the antigens the immune system needs to enable it to kill any remaining tumor or to prevent recurrences, according to Pluhar. Olin's lab would then make a replicable vaccine based on these cell lines.

"If we want to get regulatory approval on vaccines for dogs or people, each one has to be tested and meet certain criteria," said Pluhar. "It's easier to get approval if you have a tumor cell line that is used in every patient, instead of having the innate variability of using each dog's [or person's] tumor cells."

The dream remains the same…for people who have these tumors to be treated by surgery plus immunotherapy as the first standard of care. "We want quality of life to be much better and survival times to be longer," said Pluhar. Typically, humans with glioblastoma succumb to the disease within two years.

With robust, ongoing collaborations such as the one shared by Pluhar, Hunt, Olin, Moertel and their teams, that dream has a much better chance of becoming reality.

[1] *CD200 in CNS tumor-induced immunosuppression: the role for CD200 pathway blockade in targeted immunotherapy (/sites/neurosurgery.umn.edu/files/cd200_paper.pdf)*

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