

## First to Ask Question: What is Underneath Myelin?

# Chiu's Early MS Research Considered Classic Landmark Study

By Amanda Gasper

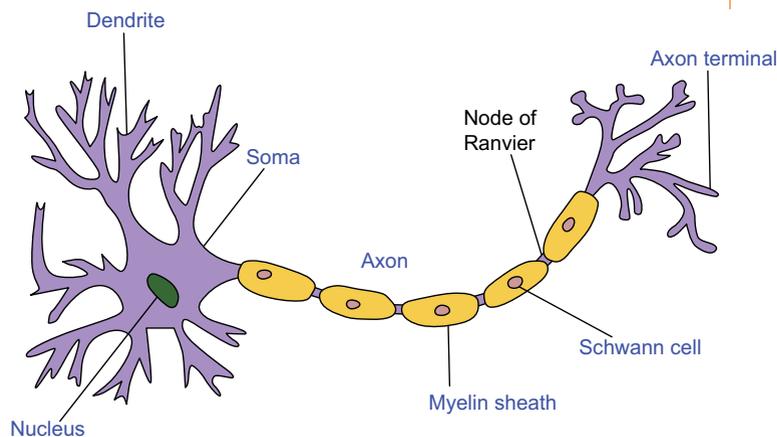
Shing-yan (Bill) Chiu's work is a good example of basic scientific research providing a client benefit.

In Chiu's case, the basic research he conducted 30 years ago ultimately played a role in the development of Ampyra™ – the new drug approved by the FDA in January for its ability to improve walking in people with any type of multiple sclerosis. Indeed, Ampyra™ is the first therapy to treat a symptom of MS.

Chiu is a professor with the department of physiology at the University of Wisconsin School of Medicine and Public Health. A resident of Wisconsin since 1985, Chiu received his Ph.D. at the University of Washington where he studied myelinated axons (also called nerve fibers). He got his start in MS research when he conducted his post-doctoral work at Yale University; where his mentor, J. Murdoch Ritchie, was funded by the National MS Society to study myelinated axons in MS. The National MS Society continues to support Chiu.

### Chiu's Classic Landmark Study

In 1980, two papers (one from England by Tom Sears and his colleagues, and the other from the United States by Chiu and Ritchie), appeared that directly influenced the development of Ampyra™. Chiu describes



*Chiu and his research partner "unrolled" myelin off the axon and exposed potassium channels.*

his work with Ritchie as a "classic landmark study," because it launched a new era of basic research on how ion channels are distributed on myelinated axons. Now,

30 years later, Ampyra™ has been developed based on that research.

Chiu added, "We were among the first to ask the critical MS question: if the myelin comes off the axon, what is underneath?" Chiu shared that he and Ritchie utilized a sophisticated technique to "unroll" the myelin off the axon. "It is like grabbing one corner of a carpet and quickly yanking it aside to see what lies underneath," said Chiu. "We took a peek at what's underneath and found a goldmine."



*Currently Bill Chiu is studying mitochondria, or what he describes as "mobile batteries."*

Chiu added, "A whole new era of basic research was born because of this peek. When we unrolled the myelin, we exposed potassium channels."

According to Chiu, ion channels (including potassium channels) are important because they allow the body's electric current to move along axons and signal the nervous system. However, when myelin is "unwrapped," as is the case in MS, the exposed potassium channels stop the nerve impulses so they are not propagated along the axons. "Now people can study these channels with unprecedented precision and they can use a marker to label them and see that they are underneath the myelin," Chiu said. "You can identify the genetic aspect of these channels and you can design drugs to block them in MS patients."

He explained, "The idea is that plugging these potassium channels would be like plugging leaking holes in a garden hose, so that nerve signals, like water, can travel long distances without leaking."

And that is just what researchers have done.

Chiu said: "For the past 30 years since that original discovery, the Society has continued to support

research on potassium channels in myelinated axons, both in my laboratory and others, with one important clinical goal: can we improve nerve transmission in MS patients with drugs that plug up these potassium channels? A major advance came in January of 2010, when the FDA finally approved the drug Ampyra™ that does just that: plugging up potassium channels so MS patients with all kinds of symptoms can benefit.”

Ampyra™, available this past March, is a symptomatic medicine to improve walking.

“It’s not a cure, but it gives you transient relief. It represents a big step forward for all kinds of MS patients, with all kinds of disabilities,” Chiu said. “This is a shining example of basic research supported by the Society that bears fruit 30 years later.”

### **New Focus on Mitochondria**

Chiu hopes the research he is currently conducting will also one day benefit MS patients. The National MS Society is supporting Chiu’s work with a \$568,425 grant. He said, “I’ve moved on to something that I hope is equally interesting: mitochondria.”

He described mitochondria as “mobile batteries.” They travel along axons to supply energy to the nodes of Ranvier, or tiny gaps between the myelin. At nodes of Ranvier, the axonal membrane is un-insulated and therefore capable of generating electrical activity for nerve signals.

“The node is important because it generates electricity,” he said. “You need to supply energy to the node to make it happy. And mitochondria are thought to pass through the node and unload energy to the node and move on. If there is a failure to supply energy, nerves cannot generate signals.”

According to Chiu, in the past five years or so, MS researchers have found that abnormalities in the mitochondria correlate with axons dying. Chiu said, “If we can find a drug or some manipulations, to make mitochondria become normal again in MS, the questions is: Will that prevent axons from dying?”

To study this correlation, Chiu watches the movement of mitochondria along axons with real-time imaging, like a movie.

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## **Wisconsin Resident Benefits From Drug Based on Chiu’s MS Research**

By Amanda Gasper

Difficulty with walking is a challenge for many individuals diagnosed with multiple sclerosis. Weakness, spasticity, loss of balance, numbness and fatigue can all hinder everyday life. But Ampyra, a new prescription medication available since March 2010, may help improve walking for those living with MS.

Ampyra is an FDA approved drug to improve walking for people with all types of MS. Ampyra works by improving nerve transmission along nerve axons (also called fibers).



*Francie White, left, says her husband Brian has gained mobility with Ampyra.*

It does this by plugging up potassium channels, which are exposed when the myelin is damaged. Wisconsin researcher and National Multiple Sclerosis Society grant recipient Shing-yan “Bill” Chiu and his mentor, J. Murdoch Ritchie, discovered the potassium channels 30 years ago while conducting MS research at Yale University.

Brian White thought he might benefit from taking Ampyra. White, a 45-year-old from the Antigo area, was diagnosed with relapsing-remitting MS in 1999. Since then, his strength, balance and walking longevity have declined.

“I couldn’t walk more than 100 feet without getting really tired,” he said. “And I wasn’t that quick.” His troubles walking were impacted by his inability to see cracks and unevenness in pavement. Because of his MS, White developed chronic optic neuritis and is legally blind. So White, who learned about Ampyra through an e-mail from the National MS Society and discussed it with his doctor (Dr. Loren Rolak, a member of the Wisconsin Chapter’s Clinical Advisory Committee), started taking the medication at the end of May.

“I wanted to gain a bit more mobility and make it a little easier to go up and down stairs. I wanted to feel a

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A single axon is very small. “You can’t even see it with the naked eye,” Chiu explained. “We inject a tiny droplet of marker, called “mito-tracker,” into the nerve. Then we use a sophisticated movie camera to look at how the mitochondria move through the nodes.”

He likened it to a helicopter keeping track of cars on the freeway. At night, the only way to see each car is by the headlights. The “mito-tracker” markers are like headlights sticking to the mitochondria. In the movies Chiu makes, he can see how the mitochondria move through the node because of the “mito-tracker” markers.

“**We took a peak at what’s underneath myelin, and found a goldmine.**”  
- Bill Chiu

Through his movies, Chiu can study the movement of the mitochondria; whether they are stopping, getting into traffic jams or turning the wrong way. He said, “We hope that this method will reveal interesting things about mitochondria and how they behave in multiple sclerosis. We are in a documentary phase. The first thing to do is capture these movies and then go home and study them.”

And hopefully this basic research will lead to clinical benefits, he said.

“It has no implications to MS, yet. But there are interesting things down the road, which I think will have implications,” Chiu said, emphasizing the importance of basic research.

“My previous research was done to ask a very basic question and it sustained thinking in the field for about 30 years – ultimately leading to translating basic research into clinical benefits. It shows the necessity and importance of basic research.” Concluded Chiu, “It has to be done.”

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little stronger doing that so it wasn’t quite so terrifying.” Within a week and a half, White started to notice a change in his walking, he said.

“I feel it’s easier to go up stairs and a little easier to go down stairs,” White said. “I’m more inclined to go walking. I still generally take the cane, more for balance and to push me along.”

His wife, Francie, has also noticed the change, especially while they are shopping.

“I have all the benches mapped out at Wal-Mart,” he said. “Now, I don’t have to use them as often. It helps me move around. I have a little strength, so the cracks in the pavement I can’t see aren’t as bad.”

Acorda Therapeutics, the maker of Ampyra, sponsored two phase III clinical trials. They found that people taking Ampyra had a more consistent improvement in walking speed compared to people who took a placebo. In the first phase III clinical trial, 35 percent of the people treated with Ampyra improved in walking speed, while eight percent of the placebo group improved. Patients who had the treatment also experienced increased leg strength, including some people who did not increase walking speed.

White, who had balance issues before taking Ampyra, noticed some extreme balance issues after starting it, but said they got better over time. He also experienced headaches and some insomnia.

In clinical trials, patients experienced back pain, headaches, dizziness, insomnia, fatigue, nausea, balance issues and urinary tract infection. A serious effect, seizures, was seen in some patients in the clinical trial.

It took about a month after White received his prescription to get Ampyra. According to White, the insurance company needed preauthorization. With his wife’s insurance and subsidization from Acorda Therapeutics, the drug costs him \$40 a month. Acorda Therapeutics has a team that provides support for access to the drug by working with insurance carriers. They also have patient assistance programs that limit copayments and offer financial assistance.

For more information on Ampyra, call Acorda’s Ampyra phone line, 1-888-881-1918 or visit the website [ampyra.com/home/](http://ampyra.com/home/).