



## Therapeutic Developed in United States Benefits Many in Asia

*Wayne State University*





***For a scientist with an idea that might make a difference to people's lives, the path from illuminating insight to world-changing reality can be dramatic and satisfying. Or it can be filled with financial obstacles, poor execution, and disappointing results.***

Since Wayne State University gastroenterologist Milton Mutchnick, M.D., first proposed using the hormone-like peptide thymosin alpha 1 to combat Hepatitis B in the mid-1980s, the drug has seen both outstanding success and somber letdown. Overseas, thymosin has become an important tool for fighting Hepatitis B, cancers and infections. Within the United States, its promise remains in doubt decades later.

Mutchnick, now Chief of Gastroenterology at Wayne State's School of Medicine, is a liver specialist who thinks the liver is a "really ugly-looking organ." But, he adds, "I have a great love for it. I find it fascinating. Among its functions, it secretes bile to help the body digest food. It filters toxins from the blood and metabolizes drugs. It has roles in blood formation and antibody creation. And it can regenerate itself."

Following his hepatology residency at Yale University, Mutchnick undertook a year of training in immunology at the University of Michigan - good preparation for an early focus on Hepatitis B and Hepatitis C.

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*— Fred Reinhart*



Both are infectious viruses that invade the liver. Some people's immune systems are able to clear their infections naturally. But for many, the diseases become chronic, lurking silently for decades, eventually inflaming the organ and causing the potentially fatal scarring of cirrhosis, possible liver failure or liver cancer. The B virus can be acquired through a number of routes, from sexual contact to infected drug needles. But the most common cause is being born to an infected mother.

It's estimated that in the United States there are two million Hepatitis B patients and four million Hepatitis C patients. Outside the U.S., the proportions are reversed: 350 million with Hepatitis B and 150 million with Hepatitis C. The B virus is epidemic in Asia, and it's estimated that 10 percent of China's population carries the infection. More than half of liver cancer cases worldwide occur in China.

### **Bringing Balance to the Immune System**

A vaccine that can prevent infection with the B Virus has been available since 1982, but when Mutchnick was beginning his career in the 1970s, he notes, it was a disease without an effective therapy. Although there are seven drugs now approved for B Virus treatment, including interferon, a sure-fire cure for Hepatitis B still doesn't exist (treatment begun early in the disease's course seems to be most effective).

Mutchnick's concept of using thymosin began with a visiting lecturer's talk on immune modulators in the mid-1970s. Allan Goldstein, Ph.D., suggested that a deficiency of the hormone thymosin alpha 1, produced by the thymus gland, was a factor in certain immunodeficiency diseases.

"I suspected that the issue wasn't that the B virus attacked the liver cells," Mutchnick says. "Apparently, once it invades the cells, it lives there without injuring them. The problem is that the host's immune system goes after the virus and kills the liver cell along with it."



“My thought was that perhaps thymosin doesn’t enhance or suppress the immune system but modulates it. I pursued this theory in lab research and found that, in the absence of thymosin, the immune system killed the cells, and that, when thymosin was added, it didn’t. In 1986, I was able to treat 10 patients – with promising results.”

The next steps were patents and further studies. “Thymosin showed good results and had few side effects,” says Fred Reinhart, who joined Wayne State’s Technology Transfer Office some years after Thymosin’s emergence. “We definitely get excited about a therapeutic that seems to be effective. We filed patents both in the U.S. and in a number of foreign countries.”

### **Differing Results, Expanded Uses**

The rights were licensed to two pharmaceutical companies for clinical trials. Rights in the United States and Europe went to a small biotechnology company. Rights to test and sell the drug outside the U.S. and Europe were licensed to SciClone Pharmaceuticals International, which focuses on drug distribution overseas.

In the U.S. tests, thymosin alpha 1 was given the brand name Thymalfasin and taken to multi-center trials in 1992. But there were problems – among them, funding difficulties, questions about protocols and too few patients involved. Results were positive – but too limited for definitive conclusions. Thymalfasin use went nowhere.

On a parallel track, under the brand name Zadaxin™, SciClone began trials throughout Asia and received its first approval from China in 1995. It began sales there in 1996. Other approvals followed. Today, Zadaxin is approved for use in 36 countries, from Argentina to Vietnam. Eventually, SciClone acquired the rights for Europe and, after that, the United States.

“Zadaxin’s original approval in China was for monotherapy treatment of Hepatitis B,” notes Randy McBeath, SciClone’s Vice President of Marketing. “That began in 1996 and continues today. Since then, Zadaxin’s value as an immunity enhancer has been built upon. Today it’s also used in China to treat liver cancer and problems of post-surgical infection.”

He adds: “Some Asian countries use it to fight Hepatitis C. In Italy, it is employed as an adjuvant drug with both flu and B Virus vaccinations – it lessens the risk of patients with compromised immunity systems developing the virus.”

SciClone has continued to seek Zadaxin applications within the U.S. and Europe. In late 2008 the company received FDA approval to begin Phase III trials of Zadaxin’s use for treating malignant melanoma – like liver cancer, a disease in which in which patients’ immune systems play key roles, McBeath notes.

As for Mutchnick, he’s moved on. “I’m out of the thymosin game,” he says. And despite thymosin’s heavy utilization in China, Wayne State University receives minimal royalties for Mutchnick’s thymosin work. “We file patent applications in many countries, with royalties from successful therapeutic products put back into research,” Reinhart says, “but in this case we didn’t get a patent in China. We’re very happy that research out of our university is helping people. I just wish we had filed in China.” 