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Ancient Chinese medicine unlocks new possibilities for cancer treatment

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Yung-Chi Cheng, Henry Bronson Professor of Pharmacology, a leader in drug development for hepatitis B, cancer, and HIV, is developing the first botanical drug to treat cancer. Credit: Andrew Hurley

More than 20 years ago, Yale pharmacology professor Yung-Chi Cheng, a leader in drug development for hepatitis B, cancer, and HIV, had a radical idea: What if he could unlock the therapeutic potential of ancient

Chinese medicines for treating cancer? What if he could design botanical drugs that would make traditional cancer treatments work better?

No one had done it before. The Food and Drug Administration didn't even have a process in place for approving multi-ingredient botanical drugs, and wouldn't until 2004, when the agency released botanical drug-specific guidelines.

Fellow researchers and drug development experts advised him to change course. Developing botanical drugs was too complicated, they said, too risky.

But the idea had taken hold, and Cheng, the Henry Bronson Professor of Pharmacology at Yale School of Medicine, was not going to let it go.

"Chinese medicine works by taking advantage of multiple chemicals, but also the capability of different organs in metabolizing these chemicals," he said, surrounded by careening stacks of paper in his office at Yale's Sterling Hall of Medicine. "It's a totally new paradigm. I've been met with a lot of suspicion, but I think the results will speak for themselves."

Now, in a landmark moment in cancer research, Cheng and research partners are launching the first international clinical trial for a botanical drug, YIV-906. The trial, involving patients with liver cancer and hepatitis B, will take place at 20 institutions across the United States, China, Taiwan, and Hong Kong. Lead sites include Memorial Sloan Kettering and Northwell Health Cancer Institute in New York, Taipei Medical University, the National Cancer Center of China, and Queen Mary Hospital in Hong Kong.

"He is a pioneer," said Jon Soderstrom, managing director of Yale's Office of Cooperative Research, who began advising Cheng in 1996.

"He is Lewis and Clark going into the Pacific Northwest without a map. By the sheer force of his personality and his empirical results, he made people pay attention to this space."

Major drug companies are watching Cheng's progress from the sidelines for now, said Shwu-Huey Liu, who began working in Cheng's Yale lab as a postdoctoral researcher in 1993, when his focus was on antivirals and traditional anticancer drugs. "They monitor us and come to meetings," she said, "but until we get approved, big pharma is not going to jump in."

Today Liu is cofounder and chief scientific officer of Yiviva, Cheng's biotech company, which is developing YIV-906. Combining Chinese and Spanish words, Yiviva translates as "long live medicine." It's a fitting slogan for a company that has resurrected an 1,800-year-old formula for stomach ailments to help fight cancer.

Old discoveries made new

In 1997, as Liu was finishing her postdoctoral work, Cheng mentioned his interest in Chinese medicine. "He said he thought it could be the future of medicine—especially in cancer," Liu said. She was a chemist with no background in Chinese medicine, but "he thought we could work together," she said. "My chemistry could help with quality control."

Liu connected with a librarian at Yale's Sterling Memorial Library, and was led to a tucked-away room on the third floor where few patrons ever set foot. She spent hours leafing through Sterling's collection of ancient Chinese texts, tracing the properties of Chinese herbs. Cheng had told her to look for herbs that were still in use, were not too rare, and had four or fewer elements.

Liu returned with about 20 formulations. One of them, an 1,800-year-old treatment for stomach ailments, was called Huang Qin Tang. It

combined licorice, dates, peonies, and skullcap, and was traditionally prepared as a tea. After lab testing, the Cheng team found that Huang Qin Tang had a high inhibitory property against the debilitating side effects of a chemotherapy drug called CPT-11 (later approved as irinotecan), including diarrhea, nausea, and vomiting. Cheng and team developed a drug based on the formula and tested it on one thousand mice.

The botanical drug YIV-906 (center) is developed from an 1800-year-old Chinese formula and relies on four naturally derived ingredients: licorice, skullcap, peony, and dates. Credit: Andrew Hurley

Not only did their drug, YIV-906, reduce the toxic GI side effects of the chemo drug, but it also enhanced irinotecan's anti-tumor activity—a major discovery that revealed YIV-906's powerful therapeutic potential.

"It was a surprise to us to see not only a reduction in the GI side effects of chemo but also an increase in the chemo action against tumors," Cheng said.

The rise of "WE" medicine

What followed were years of additional testing of the drug's effectiveness for a range of cancers—including liver, pancreatic, and colorectal—in multiple human studies involving over 200 patients. The positive effects were replicated again and again. YIV-906 not only diminished the side effects of chemo drugs and radiation therapy, but also led to a stabilization of cancer, faster recovery, and longer survival rates.

In 2019, Cheng and his research partners ran a study with Yale immunobiology professor Lieping Chen to test YIV-906's effectiveness with Chen's immunotherapy drug anti-PD1, and found that YIV-906 enhanced the immunotherapy drug's anti-tumor property. The combination of the drugs not only eradicated all tumors in mice, but when new tumors were implanted, the tumors did not grow. This suggested that YIV-906 with anti-PD1 "created a tumor-specific vaccine-like effect," they wrote in their study.

They called the new approach "WE" medicine, a melding of Western medicine—focused on microscopic and single-disease targets—and Eastern medicine, exemplified by traditional Chinese therapies.

A whole-system approach is needed to combat a complex adversary like cancer, Cheng said.

"The reason this drug works is because it has multiple chemicals which can work on multiple sites to alter the whole system of homeostasis," he said. "It triggers both innate immunity as well as adaptive immunity

within the cancer micro-environment."

All they need now are larger data sets. When the results of the international trial are available about three years from now, YIV-906 may find itself next in a long line of breakthrough drugs developed from natural products, a lineage that includes aspirin (from willow bark); Taxol (from pacific yew tree bark); Tamiflu (from star anise); and Artemisinin, a malaria treatment developed from the Chinese herb Artemisia annua, the discovery of which led to a Nobel Prize for chemist Youyou Tu.

It has been a long journey, but if Cheng and team are successful, it could yield a new approach for treating not only cancer, but for the prevention and treatment of age-related diseases and pulmonary diseases using adapted traditional Chinese medicine, Cheng said.

Said Soderstrom of Yale's Office of Cooperative Research, "This is an untapped potential people hadn't thought much about before."

Liu, who has stuck with Cheng since she first began studying in his lab over two decades ago, through multiple startups and lean times, said his belief in the massive potential of botanical drugs has sustained her.

"Dr. Cheng said, "If we get the first Chinese medicine approved as an FDA prescription drug, it will change human history,'" Liu said. "And I believe him."

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