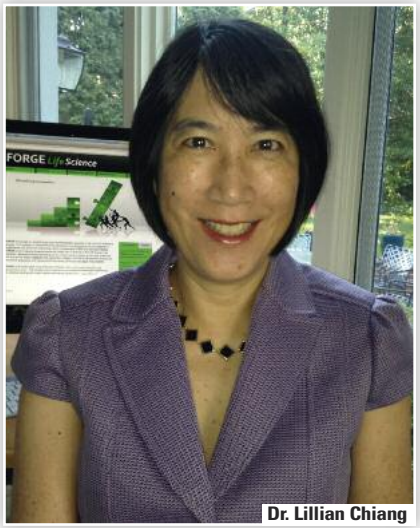
A Single Pill for Multiple Viruses

Lillian Chiang, Ph.D., President and CEO of Forge Life Science, talks about the company's efforts to develop a broad-spectrum antiviral by targeting cell metabolism.



Dr. Lillian Chiang

The treatment of viral infections is an unmet medical need. While many viruses such as rhinoviruses, which cause the cold, are not considered serious, others, such as ebola, are. There are more than 200 viruses that cause mild-to-severe diseases that have limited treatment options. And the antivirals that are available, while effective, unlike antibiotics, generally only treat a single virus type. This leaves major gaps in the ability to treat many illnesses.

Forge Life Science's founders discovered a way to create an antiviral that can target several distinct viruses with a single pill by tapping into a cell's metabolism. The company's breakthrough science is founded on forming new concepts around the control of infectious disease. The company is developing next-generation, host-targeted antivirals based on the discovery that human sirtuin proteins are innate viral restriction factors.

The company's technology stimulates sirtuin activity, which increases the host cell's ability to prevent viral growth. When viruses infect a human host cell, they take over and direct metabolism to serve the production needs of the virus. Forge's small molecule drugs modulate sirtuins to restore a metabolic state that favors the host cell in its battle against the virus.

"Some of the factors limiting our ability to manage viral infections include knowing which specific virus causes a disease and then developing culture conditions, the animal models, and the drugs that work," says Lillian Chiang, Ph.D., president and CEO of Forge Life Science. "Once we are able to get over the barriers of isolating, culturing, and developing preclinical models, there is a burst of activity, such as with HCV and HIV antivirals."

Dr. Chiang says there are other limitations in treating viruses.

"Resistance is also a challenge," she says. "The virus is clever. It can replicate rapidly and acquire mutations that render a traditional antiviral drug ineffective because that drug is directly interacting with the virus protein. This should not be a problem for sirtuin modulators, because they target proteins of the infected host cell."

Dr. Chiang says opportunistic infections is another area that is not well-served by existing direct-acting therapies.

"Immunocompromised patients, such as those with HIV, those who've had transplants, or those who are taking certain therapies for autoimmune disorders, such rheumatoid arthritis, are at risk for serious infections and are more susceptible to usually innocuous latent and community-acquired infections," she says. "For example, in the lung transplant arena, flu is a major risk to the graft organ. Our sirtuin modulators have strong potential to control a broad range of infections in immunocompromised patients."

Sirtuins' Role in Metabolism

Sirtuin research became a hot area a few years ago because of its potential for antiaging. It had been suggested that resveratrol, which is isolated from red wine, stimulates sirtuins, creating a life-enhancing effect that would be similar to calorie restriction. A 2007 study found that the resveratrol-activated sirtuins led to health benefits in mice.

But sirtuin-targeted drugs have yet to demonstrate sufficient efficacy in the clinic for chronic diseases, but research into the role of sirtuins in metabolism continues.

"Sirtuins are host proteins," Dr. Chiang says. "Humans have seven of them and they regulate other proteins, but what is special about sirtuins is that they use something called NAD, which is basically a metabolite that the cell uses to create energy. Sirtuins are master controllers of that process."

At Princeton University, Forge Founders Emre Koyuncu, Ph.D., Thomas Shenk, Ph.D., and Ileana Cristea, Ph.D., discovered that each of the seven human sirtuins normally functions as an innate viral restriction factor that inhibits the growth of multiple, diverse viruses. Dr. Koyuncu has joined the company as head of biology and continues to develop the technology.

"Because viruses have very few genes, they depend on the host for the building blocks that they need to reproduce," Dr. Chiang says. "But viruses are clever. After they infect a cell, they don't want the cell wasting its energy serving. The cell they redirect much of the metabolic process to support the growth of the virus."

Because sirtuins are host proteins, viruses cannot readily accumulate mutations that disrupt the sirtuin-targeted drug interaction, thereby minimizing the problem of acquired resistance associated with traditional direct-acting antivirals that target virus proteins.

Dr. Chiang says Forge's small-molecule drugs enhance the innate role of sirtuins to fend off diverse viral infections.

"It's also why we think it will be very difficult for the virus to mutate because the virus needs metabolic building blocks to make its own proteins in order to replicate," she says.

Forge's Research

Forge Life Science is working on a small-molecule therapy that would have broad-spectrum activity against several viruses. The company is working on two development programs.

The first is a single pill effective against multiple opportunistic infections, including cytomegalovirus, BK virus, and JC virus in immunosuppressed patients. The second is a broad-spectrum flu-antiviral with a reduced acquired resistance profile that will be effective against seasonal and pandemic influenza strains.

Both programs are in the lead optimization stage using both culture models and animal models, with the company working to improve potency.

The company, which has so far received $950,000 in investment funding and $450,000 in grants, is about three years from the clinic.

"If we meet the endpoints associated with these grants, the company could qualify for an additional $3 million in grants," Dr. Chiang says. "The U.S. Department of Health and Human Services is interested because of the public health concern about infections from pandemics and from a biodefense perspective."

The company has five employees, three of whom are full time, with the medicinal chemistry work being done through an outsourcing partnership in China. The company's vision is to build a pipeline of breakthrough anti-infectives that address the problem of acquired resistance and provide unique broad-spectrum treatment modalities. PV