

REPRINT FROM OCTOBER 20, 2016

## PRODUCT R&D

### SIRTUINS FORGE AHEAD

By Lauren Martz, Senior Writer

Since sirtuins hit the scene as modulators of numerous cellular pathways over 20 years ago, the enzymes have been implicated in metabolic diseases, aging and cancer. Now [Forge Life Science LLC](#) has licensed findings from [Princeton University](#) showing sirtuins have activity against a large number of viruses, and wants to create broad-spectrum antivirals that modulate sirtuins — analogous to the broad-spectrum antibiotics that revolutionized treatment of bacterial infections.

“There are roughly 115 different human viruses that have been sequenced and are known to cause disease in man, and we only have FDA-approved antivirals that can treat eight of them,” said Forge President and CEO Lillian Chiang. “If you add in vaccines, we can defend against only 15-20 viruses in a pandemic.”

She believes that modulating sirtuins will produce a more efficient treatment strategy than developing targeted therapies for each of the remaining viruses. The goal is to provide physicians with drugs that can be prescribed based on symptoms, rather than requiring timely and expensive diagnostic tests to identify the infectious agent.

Because sirtuins are targets on human immune cells rather than on viruses, Chiang believes Forge’s molecules are less likely to run into the problems of resistance that have arisen for some targeted antivirals and that are plaguing antibiotics.

Sirtuins constitute a family of seven enzymes with intracellular regulatory protein functions, including deacetylation. The most well known modulator is resveratrol, a natural compound found in red wine with anti-aging properties and metabolic benefits that indirectly activates [SIRT1](#). Forge is designing small molecule sirtuin modulators that have a combination of activating and inhibitory activity across the seven different sirtuins, with the mode of action of each compound tailored to best treat viruses that infect different tissues.

In 2008, [GlaxoSmithKline plc](#) acquired [Sirtris Pharmaceuticals Inc.](#) and its sirtuin modulators, including [SRT501](#), an orally bioavailable formulation of resveratrol. GSK discontinued development of [SRT501](#) after data from a 2010 Phase IIa trial showed the compound had minimal efficacy and increased the risk of renal complications in patients with multiple myeloma (MM). GSK spokesperson Mary Anne Rhyne told BioCentury that the pharma currently has undisclosed small molecule [SIRT1](#) activators in preclinical development.

### BIOCENTURY PRODUCT PROFILE

BIOCENTURY PRODUCT PROFILE	
INNOVATION STAGE	
Product	Sirtuin modulators as broad-spectrum antivirals
Concept	Inhibition and/or activation of one or more of the seven sirtuin enzymes can block replication of multiple viruses, providing a broad-spectrum antiviral
Disease	Viral infections
Competition	Antivirals targeting viral proteins; vaccines
Differentiation	Treats multiple viral infections with one compound without requiring specific diagnosis; avoids resistance by targeting human proteins; may have synergistic effects with other antivirals
Administration	Oral
Risks	Potential safety risks associated with targeting a pathway involved in metabolism and cancer
Development status	Preclinical
Patents	Patented
Company; lead investigator	Forge Life Science LLC; Thomas Shenk and Ileana Cristea; Princeton University

The connection with viral infections was published in 2014 by Princeton professors Thomas Shenk and Ileana Cristea, who showed all seven sirtuins have intrinsic, evolutionarily conserved antiviral properties and that sirtuin activation broadly inhibits replication of diverse viruses, such as cytomegalovirus (CMV) and influenza A. Shenk and Cristea are co-founders of Forge.

However, despite the broad activity, the company isn’t “proposing one pill to kill every infection out there,” said Chiang. Instead, it has created four programs: three around the key body systems of the respiratory system, CNS and liver; and one targeting the specific patient population of immunocompromised individuals.

“Ours is an orthogonal technique to targeting the virus directly, so we’re predicting a synergistic effect with other antivirals.”

Lillian Chiang, Forge Life Science

#### LEADING WITH THE LUNG

The company’s most advanced program is for respiratory infections and inhibits sirtuins in the lung and respiratory tract.

“During flu season, influenza A and B are responsible for maybe 20% of all respiratory infections, but there are a lot of other viruses that infect people — colds, SARS. Our vision is to target respiratory infections as a group,” said Chiang.

But the challenge is to tease out the subtle differences to find the optimal molecules to target.

“In general, every virus we’ve tested so far seems to be modulated by sirtuin activity, but there are differences in their relative sensitivity to one or more sirtuins,” said Chiang.

She added that designing sirtuin modulators is similar to designing kinase inhibitors. “It was once thought that selective kinase inhibitors were important, but oncologists are beginning to appreciate that the secondary effects of those non-selective kinase inhibitors often contribute to therapeutic activity.” Likewise, she added, “the key for us is to have compounds with the right mix of activity across the seven sirtuin enzymes.”

Chiang told BioCentury the company is experimenting with constructs that inhibit **SIRT1** and **SIRT2** — enzymes that deacetylate p53 — for respiratory infections.

“When the p53 hyperacetylation that occurs when we inhibit **SIRT1** and **SIRT2** is combined with a cellular stress, the cell undergoes apoptosis. In the case of an infection, the virus is that stress,” said Chiang.

The real benefit of this mechanism, she said, is that uninfected cells lack that stress signal and so are protected (see “Forging Sirtuin Inhibitors,” page 7.)

The lung program has benefited from a deeper literature on **SIRT1** and **SIRT2** inhibitors than Forge’s other modulators, and from optimized chemical constructs.

In addition, the program was well funded by grant money because of its potential public health impact, said Chiang. About

half of the \$5 million raised to date comes from four Small Business Innovation Research (SBIR) grants through NIH, and Chiang said the company has sufficient funding to complete the planned animal studies. The balance of the funding was received in July as seed funding from Mid-Atlantic Bio Angels.

Chiang expects to receive more support from Biomedical Advanced Research and Development Authority (BARDA) and the [U.S. Department of Defense](#) (DOD) through contracts to develop flu antivirals as the product advances through the clinic.

“Strategically, we realize taking advantage of these resources is a great way to grow an early company because we can continue to anticipate support from the government,” she said.

#### SIRTIIN MODULATOR BREADTH

In its CNS program, Forge is focusing on viral encephalitis caused by pathogens including measles, rabies and West Nile virus.

“Many of these infections are deadly, but on the other hand, many are very, very rare,” said Chiang, making the viruses unattractive targets for virus-specific drug development.

The company is not disclosing which sirtuins are the targets, but Chiang said the team has a chemical scaffold with high brain penetrance.

The liver program aims to treat infections such as CMV and hepatitis B virus (HBV).

The fourth program is designed to treat infections in immunocompromised patients, particularly transplant patients actively immune-suppressed to prevent graft rejection.

“The problem with infections in immunocompromised patients is that they don’t show symptoms like a fever because they aren’t mounting an immune response, so the infections are difficult to identify and treat, and ultimately most of the infecting viruses don’t have antivirals anyway,” said Chiang.

## FORGING SIRTUIN INHIBITORS

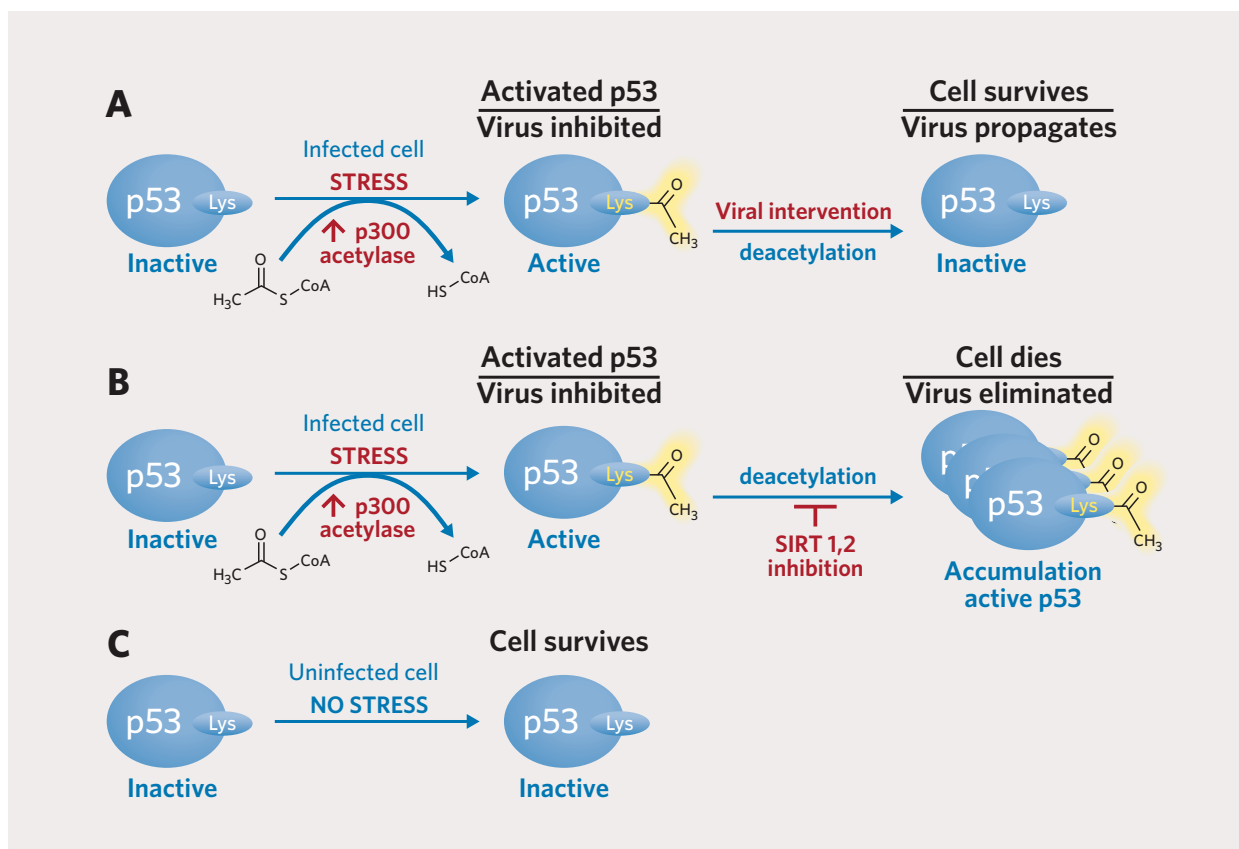
**Forge Life Science LLC** is developing a pipeline of small molecule sirtuin modulators with broad-spectrum antiviral activity. The company's most advanced program, which involves targeting compounds to the lung to treat a variety of viral respiratory infections, includes a dual SIRT1/SIRT2 inhibitor that kills infected cells by preventing sirtuin-mediated deacetylation of p53.

**A.** When a cell is subjected to stress, such as during viral infection, **p300** acetylates and activates **p53**, triggering a host process that inhibits viral replication and results in apoptosis of the infected cell. However, some viruses have evolved mechanisms for **deacetylation** of p53 -- such as up-regulation of the deacetylases SIRT1 and SIRT2 -- that render p53 **inactive**, allowing the cell to survive and the virus to propagate.

**B.** Forge's **SIRT1/SIRT2 inhibitor** blocks viral-induced deacetylation of p53, causing **accumulation of active p53** and ultimately **cell death** and **virus elimination**. By restoring a general host response, Forge's molecules have broad neutralizing activity against diverse viral infections.

**C.** In uninfected cells, the absence of cellular stress keeps p53 in an **inactive** state, preventing apoptosis. Because p53 is already deacetylated, Forge's SIRT1/SIRT2 inhibitor has no effect on survival.

p300 (EP300) - E1A binding protein p300; SIRT1 - Sirtuin 1; SIRT2 - Sirtuin 2.  
 Source: Forge Life Science LLC



The current treatment is usually to dial back immunosuppressive treatment and let the system recover on its own, but that puts the graft at risk of rejection, she said. “We think a broad-spectrum drug in this arena would be huge.”

The company has a portfolio of small molecules with good pharmaceutical properties, and is beginning preclinical testing on its initial molecules in animals this quarter. Preclinical proof-of-concept data are expected to read out by early next year.

Chiang said the goal is to submit an IND for a modulator from one of the four programs in 2018.

“In general, every virus we’ve tested so far seems to be modulated by sirtuin activity, but there are differences in their relative sensitivity to one or more sirtuins.”

Lillian Chiang, Forge Life Science

#### PARTNERING POSSIBILITIES

Although the programs are focused on single-agent therapies, Forge expects its molecules will have synergistic effects with antivirals, and already has some *in vitro* flu data to support the idea.

“Ours is an orthogonal technique to targeting the virus directly, so we’re predicting a synergistic effect with other antivirals,” said Chiang.

The company has unpublished data that show combining [Tamiflu](#) oseltamivir with Forge’s respiratory candidates prevents viral resistance. “[Tamiflu](#) develops resistance in two to three passages, but if you passage the cells in the presence of our compound too, resistance is prevented for much longer,” Chiang

noted. [Roche](#), [Gilead Sciences Inc.](#) and [Chugai Pharmaceutical Co. Ltd.](#) market [Tamiflu](#) to treat influenza.

The company is considering partnering on combos for all its programs, and thinks that HBV presents good opportunities. “The field is going after interferon pathways, so our molecules act with a distinct, possibly synergistic mechanism,” said Chiang.

Other possibilities for partnering that are further afield from Forge’s core expertise include bacterial and fungal infections, she noted.

“Our mechanism in general predicts that any infection involving a pathogen that undergoes an intracellular life cycle, as opposed to biofilms, for example, would be good candidates,” said Chiang. The company has unpublished data showing *in vitro* efficacy for its molecules against non-viral pathogens including chlamydia.

Although Forge’s IP doesn’t cover non-viral indications, Chiang said that doesn’t prevent the company from using its chemical structures for the broader set of indications.

The IP Forge licensed from Princeton covers the chemical scaffolds and the general use of sirtuin modulators to treat viral infections. ▀

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#### COMPANIES AND INSTITUTIONS MENTIONED

Biomedical Advanced Research and Development Agency (BARDA), Washington, D.C.  
Chugai Pharmaceutical Co. Ltd. (Tokyo:4519), Tokyo, Japan  
Forge Life Science LLC, Doylestown, Pa.  
Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.  
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.  
National Institutes of Health, Bethesda, Md.  
Princeton University, Princeton, N.J.  
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
U.S. Department of Defense, Washington, D.C.

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#### TARGETS AND COMPOUNDS

SIRT1 - Sirtuin 1  
SIRT2 - Sirtuin 2

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#### REFERENCES

Koyuncu, E., et al. “Sirtuins are evolutionarily conserved viral restriction factors.” *mBio* (2014)

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