A rare disease inspires a new way to attack cancer

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Postdoctoral fellow Ulla Gerling-Driessen, right, and her adviser, Carolyn Bertozzi, discuss their work on the NGLY1 molecule. Credit: L.A. Cicero

Some of the most promising new treatments for blood cancers, drugs called proteasome inhibitors, have a problem: For reasons that

researchers are still working to fully understand, cancer cells can build up a resistance to them. Now, researchers report in *ACS Central Science* how an investigation into a rare disease known as NGLY1 deficiency has revealed a way to outmaneuver one possible resistance mechanism.

For senior author Carolyn Bertozzi, a professor of chemistry, a faculty fellow of Stanford ChEM-H and HHMI investigator, it was an investigation unlike any she had embarked on before.

"I am very grateful, because when I moved to Stanford and joined ChEM-H, I hoped my new environment would enhance the impact of our research in medicine and human health," Bertozzi said. "And it was amazing how quickly that happened, and it started with a patient."

Her name is Grace Wilsey.

Going to war

Matt and Kristen Wilsey had known their daughter was ill even in utero, and that real challenges lay ahead. On the day Grace was born, her heart rate was low, forcing an emergency caesarean section. "The feeling was like shell shock," Matt Wilsey said. "The feeling was, 'my life is over.'

"But that sort of pity party lasts for about 10 minutes, and then it's like, OK, now it's time to go to war."

Eight years ago when Grace was born, however, no one knew what they were going to war against, other than a long list of symptoms: developmental delays, seizure-like activity, movement disorders and more. Stanford doctors eventually traced her illness to mutations in both copies of her NGLY1 gene, which governs the production of a protein molecule called N-glycanase 1, which gives NGLY1 its name.

Graduate student Fred Tomlin works in the lab with professor Carolyn Bertozzi. Credit: L.A. Cicero

Opportunities knock

Unfortunately, researchers didn't know much else at the time. Doctors only identified NGLY1 deficiency as a disease in 2012. Even today, there are just 37 people known to be living with it, Wilsey said. Back when Grace was diagnosed, there were fewer than five confirmed cases worldwide.

But there was one thing they did know, thanks to a Japanese scientist who had first studied the NGLY1 enzyme in the 1990s: the enzyme

strips sugars off of proteins, a process called deglycosylation – which just so happens to be one of Carolyn Bertozzi's specialties.

Bertozzi moved to Stanford in 2015, and it wasn't long after that a number of people recommended Matt Wilsey get in touch with her. By that time, he had already set up a foundation, Grace Science, to study his daughter's disease and search for cures, and he decided he wanted Bertozzi on board. That turned out to be easy to do, even if Bertozzi wasn't sure at first how she could contribute.

"At that point, the missing protein had been identified, but how its loss led to patient symptoms was somewhat of a mystery. For several months I stalled in submitting a proposal to the foundation for lack of a good idea,'" Bertozzi said. But then Bertozzi got a fortuitous tip from another HHMI investigator colleague that led her to a possible role for NGLY1 – and an idea for how to prevent cancer cells from becoming resistant to protease inhibitor drugs.

Rare disease with broad impact

That conversation took place at a conference in March 2016 where Bertozzi learned about a molecule called Nrf1. It turns out the molecule plays a role in regulating proteins inside our cells and it is very important for the health of neurons. Nrf1 is also responsible for limiting the effectiveness of proteasome inhibitor cancer drugs. When cancer cells are treated with these medicines, Nrf1 goes into overdrive and counteracts the protease inhibitor's effects.

For Nrf1 to do its job, it has to be in an active form – in particular, something has to strip off some sugar molecules that decorate its surface and prevent its activation. That something, Bertozzi, graduate student Frederick Tomlin and postdoctoral fellow Ulla Gerling-Driessen, and colleagues have now shown, is NGLY1.

Without NGLY1, the team found, Nrf1 winds up stuck with its sugar molecule and never reaches its active state. That finding could explain some of the problems that patients with NGLY1 deficiency experience. Basically, if a person can't produce NGLY1, then Nrf1 can't do its normal job of protecting neurons and other cells, and a wide range of symptoms can result.

Although the complete absence of NGLY1 has disastrous consequences, the team suggests that a little judicious depletion of the protein – just enough to prevent Nrf1 from counteracting the proteasome inhibitor's effects – could help the drugs be more effective.

Those findings, both Bertozzi and Wilsey said, demonstrate the promise of studying rare diseases like NGLY1 deficiency. "It's really hard to fix diseases," Bertozzi said. "But I want my students to know that everything they learn here, someone will build upon, and if it doesn't help today's patients, it will help tomorrow's patients, or maybe cancer patients."

Provided by Stanford University

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