ACS central science

EDITORIAL

Cite This: ACS Cent. Sci. 2017, 3, 1129-1130

# A Model for Accelerating Patient-to-Bench Research

Two years ago, just a month after setting up my new laboratories at Stanford, I was contacted by Matt and Kristen Wilsey, a family of Silicon Valley entrepreneurs and Stanford alumni. Their daughter Grace had been diagnosed with an ultrarare hereditary disorder a few years earlier—the second child ever identified with what we now call NGly1 deficiency, caused by mutations in the *ngly1* disease and concomitant loss of production of the enzyme *N*-glycanase. Grace's diagnosis came on the heels of a first patient, Bertrand Might, whose parents' journey was chronicled in his father, Matt Might's, blog and an article by Seth Mnookin in The New Yorker. Just under 40 patients have been identified since then, all with severe developmental delay as well as various neurological and secretory pathologies. Like the others, Grace was very sick and her parents were desperate to understand the root cause and to help the world find treatments and a cure. But because there was no known history of the disorder when Grace was born, her doctors couldn't even tell the Wilseys what to expect or how to help their daughter to thrive.

Though Matt Wilsey was an experienced tech entrepreneur, he and Kristen were new to the worlds of biomedical research and therapeutic development. The more they learned about how typical biopharmaceutical companies work—reluctant to work on ultrarare diseases like NGly1 without a clear business case—the more frustrated they became. Even if one got a pharmaceutical company interested, the long timelines and high attrition rates of clinical candidates were disheartening. Conversely, in the startup world, the fits, starts, and pivots of a company's mission under the influence of mercurial investors could render any gains rapidly null.

Matt wondered whether a different model could be realized—where top-notch researchers were mobilized as a team to understand the biology pathways underlying the pathologies of NGly1 disease, and where patients and their families were directly engaged in the research process. So they formed a nonprofit foundation, the Grace Science Foundation, to bring families and scientists together and support research into NGly1 disease that closes the loop from patient to bench, and hopefully back to patient. The organization is complemented by another called NGly1.org, launched by Cristina and Matt Might, that also promotes research and support for NGly1 patients and their families.

A benefit of studying monogenic diseases is that you know where to start in developing preclinical models. Guided by their clinical team at Stanford hospital, the Wilseys assembled a board of science advisors who could point them toward laboratories with the relevant expertise. Matt reached out to scientists one by one, in academia, institutes, and rare disease focused biotech companies, and built a worldwide team of researchers that would be the envy of any academic or biopharma enterprise. He mobilized them to generate critical materials such as disease-relevant cell lines and model organisms, that would be shared with any team interested in NGly1 research. The foundation also supports research into the biological functions of the *N*-glycanase, which were barely understood at the outset (see our recent publication in ACS Central Science for more insight into this), and in various therapeutic approaches including gene and cell therapies.

One of the most powerful resources provided by the foundation is a blood and tissue biobank—precious human research materials for probing mechanistic hypotheses and testing therapeutic notions. Last summer, the patients and their families were transported to Stanford to participate in the annual science conference, and also to donate blood and tissue samples that can further accelerate research. Their skin fibroblasts will be converted to induced pluripotent stem cells (iPSCs) for preclinical studies, and their blood analyzed for disease biomarkers. But beyond these critical samples, the event gave scientists, clinicians, and patients an opportunity to meet as a team and get to know each other. The scientists who spend most of their time at the bench found this to be a rare gift—a chance to meet the patients they hope to impact, to share with families the nature of their work, and to gain insight into the daily challenges that patients and their families would like to see prioritized.

Published: November 22, 2017






DOI: 10.1021/acscentsci.7b00540
ACS Cent. Sci. 2017, 3, 1129–1130

The experience of working on NGly1 disease, meeting Grace and her parents as well as other NGly1 families, has been one of the great privileges of my career in basic science. And it makes me wonder what else we can do to bring basic science researchers closer to the patients and families they can help. Clinicians are an important central glue, as they are a conduit of patients' unmet needs to scientists who can discover and invent. In most academic settings, these constituents spend precious little time in the same rooms. Perhaps it is time to think about how to improve that equation, to bring scientists onto a patient's health care team as part of the diagnostic and treatment journey. The Grace Science Foundation could be a model for much more than NGly1.

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DOI: 10.1021/acscentsci.7b00540
*ACS Cent. Sci.* 2017, 3, 1129−1130