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How Synthetic Biology Could Treat Celiac Disease

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Credit: Storyblocks [1]

By Dr. Ingrid Pultz

Synthetic biology is like genetic engineering on steroids. Using cutting edge computational design, synthetic biology aims to design novel biological molecules or even entire metabolic systems. However, because synthetic biology is a relatively new field, there are few real-world applications as of yet. Our plan is to change that.

Our story begins with undergraduate students at the University of Washington. In 2011, I led a team of students who entered the International Genetically Engineered Machine (iGEM) competition. During the course of a summer, the contest asks students to design, build, and test a new biological molecule or system – using the tools of synthetic biology and their imagination. In 2011, our team decided to develop a therapeutic for celiac disease.

Celiac disease is characterized by an inappropriate immune response to gluten, a protein found in any food containing wheat, rye, or barley. Individuals with this genetic condition suffer from gastrointestinal (GI) or systemic issues that can range from mild to quite serious. In celiac patients, gluten enters the intestines only partially digested. Immediately, these gluten fragments trigger inflammation, causing diarrhea and other symptoms associated with the condition. It is estimated that approximately 1% of Americans have celiac disease, though many remain undiagnosed.

An oral enzyme is the ideal therapy for celiac disease. The idea is that a celiac patient would take an enzyme, similar to the digestive enzymes already present in our GI tract, but capable of breaking down the problematic regions of gluten. If the enzyme is taken before a meal, hopefully any trace levels of gluten could be digested before they can trigger an immune response. Though simple in theory, developing such a therapy is difficult in practice.

The reason is because it is difficult for most enzymes to function in the human stomach. Anything that you swallow is subjected to the harsh reality of stomach acid. Enzymes are proteins, and most proteins meet their demise in the stomach. Thus, not only would the enzyme need to specifically digest gluten (we wouldn't want the enzyme to be distracted by other proteins), it would need to survive long enough in the stomach to accomplish its mission, which is to digest gluten to below the threshold that can trigger an immune response in people with celiac disease. Finding a naturally occurring enzyme that could do all this would be nearly impossible, which is why this puzzle presented a great opportunity for synthetic biology.

We began by making use of the pioneering computer software, the Rosetta Molecular Modeling Suite, that helps design novel proteins (such as enzymes). As a starting template, we chose a protein-digesting enzyme that was already known to have high activity in acidic conditions. But, it did not have the gluten-killing activity that we desired.

So using a video game-like interface to Rosetta called Fold-it, our iGEM team redesigned the enzyme on the computer in order to change its specificity from its original target to gluten. We then selected roughly 100 candidate theoretical enzyme designs. Next, we produced these engineered enzymes in the lab and tested them for their ability to break down gluten.

Lo and behold, some of the enzymes the students designed actually worked. By combining pieces from the best performing enzymes, we developed a prototype gluten-degrading enzyme. We named it KumaMax, which derives from the name of the starting template enzyme (kumamolisin).

As it so happens, not only did our iGEM team win the competition – defeating over 150 other teams – this work provided the foundation for a body of work that turned into a startup company.

After about five years of additional tweaking of the prototype enzyme at the University of Washington's Institute for Protein Design, the next step was to move towards commercialization, and we secured funding for Phase I clinical trials. We spun out a company from the University of Washington, officially launching on January 1, 2017, to bring this enzyme from the bench into humans.

Now the real experiment begins: Soon, we will be testing our product in actual celiac patients, hoping to forever change their lives using the power of synthetic biology.

Dr. Ingrid Pultz is Chief Scientific Officer at PvP Biologics.

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[1] https://www.storyblocks.com/stock-image/image-of-several-flasks-with-multi-color-liquids-s7hclvd7_zj6gt50we