Designing Away the Side Effects of a Former Wonder-Drug

Last week, we talked about how certain proteins can cause diseases like Alzheimer's and diabetes. Today, we'll talk about how designed proteins can cure diseases like anemia.

In 1989, **erythropoeitin** (Epo, pronounced ee-po) was promoted from a natural protein, that makes red blood cells, to a synthesized wonder-drug. It was used not only to treat anemia in cancer patients, but also as a supplement to enhance "quality of life" by increasing energy levels. The drug fell from grace, however, in 2011, when the FDA limited dosages, and therefore drug sales, after over-prescriptions and allegations of improper marketing resulted in several deaths from blood clotting side effects.

In April, researchers Jeffrey Way and Devin Burrill with the Wyss Institute eliminated Epo side effects by designing and creating a **protein-fusion** version of the drug.

Drug Design Philosophy

"We make drugs that look like what your body would make itself," says Dr. Way.

Epo is a naturally-occurring protein in the body which triggers red blood cell (RBC) production by binding to RBC stem cells in the bone marrow. The problem is that Epo in it's natural form can't tell the difference between an RBC stem cell or a platelet stem cell. If the dose is too high, it triggers the body to make too many platelets, causing blood clotting.

Way and Burrill, along with other collaborators, designed a drug that *is* able to differentiate between stem cells, thereby removing the side effect. Here's how they did it.

First, Make the Drug Less Reactive

The reactive surface of the drug is just a dozen or so atoms out of several thousand which make up the Epo protein. To prevent accidental stem cell interaction, researchers sought to make the reactive area smaller, but how?

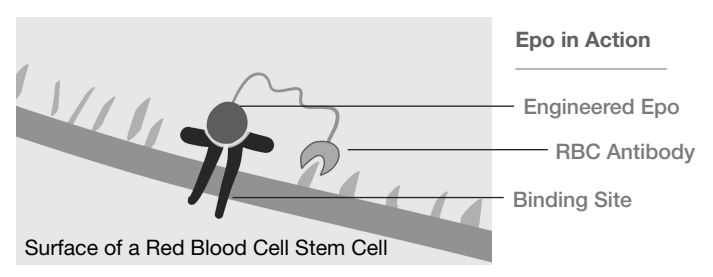
Over several decades, the pharmaceutical industry has contributed to research by creating public libraries full of different genetic mutations of proteins used in drugs.

The scientists combed through these libraries of genetic modifications, and found three suitable versions to test. Of those three, the mutation of changing one amino acid from an argenine to an alanine, successfully reduced the binding area of the Epo protein to around 10 atoms so that it is small enough to not bind to off-target sites, but large enough to still be effective.

Second, Control the Target

While Epo proteins on their own tend to attach to whichever stem cell happens to be around, antibodies attach only to very specific targets. Way and Burrill combined the natural ability of an antibody, which seeks and attaches *only* to red blood cell stem cells, with the reduced-reactivity version of Epo.

How did they combine these two objects? Kind of like how you or I would, with a piece of (molecular) string! Imagine two balls connected by a string, one ball seeks and finds the target, the other ball has the effect (see below).



Drug Design vs. Drug Discovery

Drug design is different from the current industry standard, which is **drug discovery**. In this case of selecting a genetic variation of the Epo protein, the current industry standard is to manufacture and test as many mutations as possible in phases until discovering desired proteins. This means thousands of tests starting from test tubes and Petri dishes, progressing to animal testing, and usually taking only one version to human testing.

Using computer modeling and taking a physics-based approach, the scientists at Wyss were able to select three mutations from several thousand for initial testing, thereby reducing time and cost.

Way and Burrill, with other collaborators, have started the company General Biologics to take their drug to market.

Up Next Week: Business in Medicine

Learn about companies on the cutting-edge that are bringing molecular simulations to the marketplace.

What is Compassionate Technologies?

Each Sunday we deliver to your doorstep an inspirational and educational piece describing a certain trend in technology and business.

We go from small to large throughout the year. This month focuses on Drug Design in Medicine, progressing up to topics in robotics, artificial intelligence, environmental and then space technologies.

Each month has four parts:

1st Sunday: Trends
2nd Sunday: Research
3rd Sunday: Technology
4th Sunday: Business

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While we're getting started, I'm doing free deliveries in my neighborhood for the month of June. Please enjoy and consider joining me on this journey!

Kindly yours,

Olivia Jeffers

Thoughts?

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"If you want to go fast, go alone. If you want to go far, go together."
- Unknown Origin