Rational Design Re-Emerges to Change Up Drug Discovery

"If we designed airplanes like we design drugs..." alludes Walter Woltosz, CEO and Chairman of Simulations Plus, then you probably wouldn't feel very safe on an airplane!

Rational drug design took the pharmaceutical industry by storm in the 1990s, a decade that spawned a series of fast and furious investments in the deserts of the Southwest.

The holy grail quickly turned into an elusive and dried up fountain of youth in the hot desert sands, leaving the area empty and desolate. The Billion-Dollar Drug was true, but mostly in cost and not in profits.

With new understanding from basic research and advances in molecular simulations, rational drug design now re-emerges, with the potential to shake up the pharmaceutical industry and provide benefits to both customers and drug developers.

The Old Way: Trial and Error in Drug Discovery

Most drugs were discovered through a series of trial and error, experimentation and desperation. Centuries before penicillin was accidentally discovered by Alexander Fleming in a petri dish in 1928, ancient Serbians, Chinese, and Greeks used moldy bread to rub into wounds to prevent infection.

Fast forward many hundreds of years, and scientists are still in the era of trial-and-error and accidental discovery, except that we've replaced humans with animals and biomarker experimentation.

It's important to draw the line between drug development and design. Common medicines used today, like Tylenol and penicillin, were never designed. We discovered and then manufactured them. In fact, we still don't know how these drugs work, but we can sure be grateful that they do.

A New Way: Drug Design

After a decade of Moore's law of computation rapidly increasing our ability to model complex systems, combined with nano-scale research on how molecules talk to each other, the trend of rational drug design re-emerges, poised to refine away the side effects of existing drugs and lay the groundwork for designing new ones.

Over the next 3 weeks we will discuss the trend towards design in drug discovery: first by reviewing basic research; second by exploring novel techniques used to design drugs more effectively; and finally by observing how biotech startups are working to bring these treatments to patients.

Before we dive in though, let's check the water level and take a look at the current state of the pharma industry.

One of the largest drivers of cost in the pharmaceutical industry is the high rate of failure and cost of experimentation. On average, 19 out of 20 drugs fail and a human clinical trial, the last step to market, can cost up to $100 million each. Successful drugs cost $1-500 million to develop; if you take the other 19 failed drugs into account, the cost rises to $2.6 billion per drug, with less than 20% of the cost dedicated to development of the successful drug itself. In general, the process often takes over 10 years in time, making drugs both a costly and high risk investment. The higher the risk, the higher the reward needs to be, which can lead to aggressive and hyper-competitive business behavior, often reflected back to consumers in terms of Shkreli-high prices for medicine.

Is there a way that we can reduce the experimentation phase by prefacing it with rational design? If only 2 out of 3 drugs fail, instead of 19 in 20, you can cut costs by a factor of 4, a savings of nearly $2 billion per drug, enough to bring almost three other drugs to market. It's a buy-one-get-three-free deal.

Where's the Catch?

Our ability to design drugs is limited by a lack of fundamental understanding of the structures of molecules and the physics of drug interactions. Our understanding is limited by how fine our vision is and how fast our brains work. Technological advances allow our vision to become finer, our hands smaller, and our brains faster with the aid of computational power and molecular simulations. By using design and simulations, researchers and drug manufacturers can know which drugs will fail before spending costly human-hours and dollars in development and testing.

Up Next Week: Research in Medicine

Learn about the new nano-scale research exploring the common molecular and structural roots of diseases like Alzheimer's and Type II diabetes.

How Alzheimer's and Diabetes Work at the Nano-Scale

Last week, we reviewed how rational drug design has the potential to lower drug prices by cutting the costs of failure in pharmaceutical experiments and development.

Today, we'll talk about the research that makes drug design possible. First, scientists must learn the language of the body, which at its most fundamental level, is the same as the language of the solar system: **physics**.

It might not seem that way because our bodies feel so unpredictable, but there is a sublime order underneath the chaos: how molecules talk to each other, what turns certain genes on and off, why some cells become blood cells and others platelets. Why some people get diseases and others don't.

The drugs that we use to treat disease also operate under the same laws of physics. After all, how else would we be able to mass produce medicines like insulin or Tylenol if there wasn't some sort of predictability?

Tying together the human body and drug reactions under the language of physics allows us to use computer simulations for faster, more effective drug designs.

Bringing It All Together: Nanobiotechnology

"Biology is nanotechnology that works," says Tom Knight, named the godfather of synthetic biology at MIT.

Known as the engineer's biology, synthetic biology "focuses on practical outputs," says Dr. Jeffrey Way with the Wyss Institute. It uses the same tools as biology; tools that were shaped over millions of years of natural evolution. For example, instead of harvesting the anti-malarial drug, Artemisinin, from the plant *Artemisia annua*, synthetic biologists use genetically modified yeast to ferment the drug in a lab, freeing supply from crop fluctuations.

In order to practice synthetic biology, we reduce the human body down to its most fundamental level; from groups of organs to bunches of molecules, proteins, and peptides, eventually down to the atomic realm of pinball and electromagnetic physics: a field called **nanobiotechnology**.

At the Micro-scale: Alzheimer's Disease and Diabetes

Many diseases occur on the macromolecule or protein level, which we can observe easily through microscopes. For example, we have known for the last dozen years that Alzheimer's disease and diabetes share in common large, sticky protein plaques called **amyloid** which collect in the brain and pancreas. An individual plaque is made of many proteins, which are made of even smaller peptides, which themselves are just a handful of atoms. To see at this nano-scale, you need a special electron microscope.

Into the Nano-scale: Self-Assembling Peptides

Dr. Ehud Gazit, a leader in the field of nanobiotechnology, has been studying how and why these amyloid plaques form for over 15 years. His research shows that these proteins self-assemble because it is energetically advantageous, meaning that they form naturally and on their own. Why is it advantageous? And how can we energetically motivate these plaques *not* to form?

To better understand **self-assembly**, imagine as if the king-sized bed that you ordered from IKEA has a new feature: automatic furniture assembly. You open the box and the bed just puts itself together. That's great, as long as one of your children doesn't peek inside and accidentally open it in the narrow hallway entrance of your home. Then you're stuck with a giant king-sized bed stopping anyone from entering or leaving, wondering if it's even worth your time to take it apart, or if you just want to start sleeping in the entryway.

Self-assembly isn't all bad, though. Let's take a look at **guanine**, one of the four peptides that encode our DNA. It also has a tendency to self-assemble. Imagine a primordial goop where suddenly guanine self-assembles and meets other characters of our DNA molecule, bumbling around until the primary building blocks meet in just the right orientation. Fast forward several million years and we have humans. It's not only in human DNA that guanine self-assembles, the process is also responsible for the beautiful and vivid color changes in the skin of a chameleon.

As we better understand self-assembly, disease, and drug interactions through the languages of biology and physics, we can begin to merge these two fields. For example, we can now create moulds for nanoscale semiconductor wires using drinking-straw-shaped amyloid nanotubes that self-assemble. Cool, huh?

Up Next Week: Technology in Medicine

Learn how scientists removed the side effects of a billion dollar drug using **rational drug design.**

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?

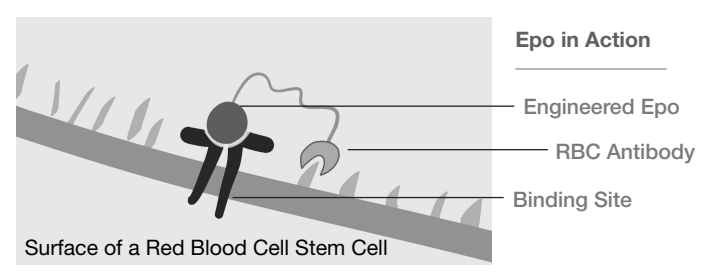
Over several decades, the pharmaceutical industry has contributed to research by creating public libraries full of different genetic mutations of proteins used in drugs.

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.

Taking Drugs from the Lab to your Nightstand

Last week, we discussed how rational drug design can hasten the discovery process and lower its cost. Today, we talk about the challenges that biotech startups face in taking these new drugs to market.

Often, drugs are borne from a university research lab, funded largely by government grants, such as from the National Institutes of Health (NIH). When a marketable drug emerges from the lab, it goes through a **tech transfer** process.

Tracing the journey from lab to marketplace, we follow the story of Drs. Nazneen Dewji and Jonathon Singer as they discover a molecule with potential for treating Alzheimer's disease and create the company Cenna Biosciences.

About Alzheimer's Disease (AD)

Over 1 in 10 people over 65 suffer from Alzheimer's, rising to 1 in 2 over the age of 90, affecting over 8 million people today. The disease is marked by cognitive degeneration and memory loss. Many families experience the emotional devastation of slowly watching their parents fade away. Currently, there is no safe and effective treatment.

Since the effects of amyloid plaques, which are implicated in the disease, are irreversible, there is a large market for a preventative drug. Currently, most Alzheimer's drugs inhibit gamma and beta-secretases, which affect 50-60 other chemical process in the brain.

Taking a drug with such a large off-target effect is not sustainable in the long run, says Dewji. What patients need is a preventative drug for the brain the "same way that you take statins for heart disease."

In the Lab: Discovering the Drug and Tech Transfer

In 1996, Dewji and Singer began researching pre-senelins, large molecules associated with amyloid beta reduction. They noticed that certain peptide groups prevented amyloid beta from forming. Over time, they narrowed down the peptide group to their most promising peptide, P8, with over 50% reduction in amyloid beta.

In the case of Dewji and Singer, their path to business followed the typical tech transfer process. In 2005, when their research became viable in industry, the University of California San Diego granted them exclusive license to the patent, allowing them to turn their research into a business opportunity.

Out of the Lab: Funding and FDA Approval

After receiving exclusive license, Dewji and Singer started Cenna Biosciences in 2006. The company is entirely owned by the two founders who invested $646,000 of their own money and raised $13.5 million, mostly in non-diluting NIH grants.

Currently in the process of seeking investigational drug application (IND) approval from the FDA, they have an added tailwind of a recent change at the NIH, that recently fast-tracked testing using biomarkers. They optimistically hope for 5 years between IND approval and reaching the market, hoping to partner with a major pharmaceutical company to assist with Phase II (small) and Phase III (large) human trials and marketing.

Deciding when to partner is a large and difficult decision for researchers. If they partner too early, the original researchers get diluted and receive a smaller payout for over 20 years of research. Most profit would go to the pharmaceutical company. If they partner too late, they run the risk of investing hundreds of thousands of their own money - into a drug that might not pass clinical trials or that might not succeed in the marketplace. For scale, a Phase III human trial for AD can cost over $200 million.

Dewji anticipates some trouble taking peptide drugs to market, since they cannot be ingested orally in pill form. Instead it will likely be administered via a nasal spray, allowing the drug to pass directly to the brain through the blood-brain barrier.

Either way it plays out, we can surely be grateful for the scientists doing the basic research that brings new therapies to light for many suffering people alive today and in the future.

Wrapping It Up: Drug Design in Medicine

The pharmaceutical industry is currently in the classical trial-and-error approach, passing along the high cost of experimentation in drug development to patients. Nanobiotechnology merges physics and biology, opening the doors for physics-based rational drug design. Many biotech startups then take these drugs to market.

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

To keep our doors open, fund interviews with top scientists and industry players, and to continue hosting local events, we charge $150 per year for 52 print weeklies.

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,

Thoughts?

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"Around here we don't look backwards for very long. We keep moving forward, opening new doors, and doing new things, because we're curious... and curiosity keeps leading us down new paths."
- Walt Disney, Film Producer, 1901-1966