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"Go where there is no path and leave a trail."
Katherine Johnson
Mathematician and NASA scientist

VIRTUAL ORGANS: Harnessing Math to Advance Science

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In 17th century Europe, physicians believed that the "Black Death" contagion traveled through poisoned air that could create an imbalance in a person's bodily fluids or humors.[1]

Today, many researchers believe that the Black Death pandemic was caused by a specific bacterium transmitted by rodents infested with plague-carrying fleas—an idea made possible by the development of germ theory. This is the theory that certain diseases are caused by microorganisms too small to be seen except through a microscope. In fact, germ theory is considered one of the most important advancements in medical science of the 19th century.

Humanity is now on the cusp of what many believe to be another great advancement in medical science and our ability to develop insights currently hidden due to the complexity that emerges from interactions of thousands of genes. That advancement is *in silico* biology.

The potential benefits of *in silico* research are multiple. Its methods can potentially contribute to cost- and time-efficient *in vivo* studies, enhance probabilities of successful results of these efforts, and reduce the consumption of certain resources, which may have multiple other beneficial ethical and environmental effects.

We spoke with **Joe Bender, Ph.D.**, Senior Director of the Computational Laboratory for *In Silico* Molecular Biology (**CLIMB**) at United Therapeutics (**UT**), and three of his team members—**Amy Smith, Ph.D.**, **Josua Aponte-Serrano, Ph.D.**, and **Pavan Pillalamarri, Ph.D.** to learn more about their work in this promising field of research designed to support UT's aim to manufacture 3D autologous printed lungs (**ULung™**)[2]. ULung is one of UT's four pre-clinical and clinical organ and organ alternative platforms designed to address the ongoing shortage of transplantable organs for patients with end-stage organ disease.

IN SILICO BIOLOGY AND UT

In silico biology refers to the use of computers to perform biological studies.[3] Growing out of a long history of mathematical discovery and computer science, the goal is to model and simulate biological processes to test hypotheses.

The mission of UT's CLIMB group is to digitize the lung anatomy and cell/molecular biology to create an *in silico* model of a lung that:

- responds to normal environmental stresses;
- predicts drug pharmacology and toxicology; and
- enables *in silico* trials of permutations of treatments and patients.

Data-driven discovery: The fundamental building block of the CLIMB group's work is data. Joe Bender explained the team's primary goal in practical terms. "My team and I—there are 13 of us today and we are growing—are trying to build a digital model of a human lung that is so faithful to the biology of an actual human lung that the U.S. Federal Drug Administration (**FDA**) approves its use to inform the design of our 3D printed lungs."

Nonetheless, the work does not always lead them to the answers they had hoped to find. "In research, you should be comfortable to sometimes be in a

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[1] Blakemore, Erin. (2020, March 12). *Why plague doctors wore those strange beaked masks.* National Geographic. Retrieved January 22, 2025. https://www.nationalgeographic.com/history/article/plague-doctors-beaked-masks-coronavirus

[2] ULung is a trademark of United Therapeutics Corporation. ULung is not approved for use in any jurisdiction.

[3] Palsson, Bernhard. (2000 November). *The challenges of in silico biology.* Nature Biotechnology. Retrieved January 22, 2025, from https://arep.med.harvard.edu/pdf/Palsson00.pdf

state of confusion," joked Pavan, a Senior Computational Engineer at CLIMB.

It's the kind of work that requires people who are resilient and nimble, able to move quickly to pivot to a new line of inquiry if needed.

"We tell people what we do is like predicting the weather," Joe shared. Meteorologists use mathematical models, large data sets, and their own knowledge to predict weather patterns. "We use similar techniques to model and predict biological processes. Like weather forecasting, which is difficult because some things in the atmosphere are unpredictable, validating the model of an organ is incredibly challenging because the proper function of an organ has so many variables," Joe said. "Still, our work is another tool that informs our colleagues' physical research."

Using math like a microscope: Lungs are composed of five lobes—three on the right, two on the left; they are covered by a slippery membrane and surrounded by fluid in the body to lubricate breathing; they have a system of airways called the bronchial tree; they have blood vessels, house a lymphatic system; and, they basically interact directly with the outside world, taking in the oxygen supply for the entire body and expelling carbon dioxide waste.

Cataloging a list of attributes of a lung helps us imagine the challenges of modelling its physical design and function. So, how does a team address the question of creating a virtual lung?

The short answer: break it down into smaller problem sets and do the math.

"I always knew I wanted to integrate technology and science. I was in my first year of undergrad when the Human Genome Project[4] completed its pilot phase of work. I changed my major to biology and have been pursuing this link between technology and biology since," said Amy, a Data Scientist in Computational Biology. She is leading efforts to identify gene interactions at CLIMB responsible for lung cell behavior, exploring whether UT could help encourage healthy functions and/or prevent disease growth in 3D printed organs recellularized with patient cells. "It's using math like a microscope," she explained.

Josua, a Computational Biologist in Cellularization at CLIMB, was a mechanical engineer who changed his major to philosophy and then circled back to biomedical engineering. "I wanted to understand the nature of science," Josua explained. Josua and the Cellularization team are trying to identify the essential cells needed for a lung to function. "You can't assume in this work that you will capture all the biology of a living lung. So, we must think like those who built the first aircraft. I imagine they asked themselves, 'What is the closest approximation to a bird wing that can enable humans to fly?' We ask ourselves a similar question. What is the equivalent 'minimal viable product' of a lung? That is what we are modelling."

Certain lung functions are somewhat more straightforward to compute and predict. "Fortunately, computational fluid dynamics principles help us create blood and air flow models that have high fidelity to what happens in a real-life lung," Joe explained.

The work is challenging, but promising, which is what drives the team forward. "The benefit of computational modelling is that you can do the experiment multiple times, changing parameters as you go. You can't do that in a cost and time effective way in a physical experiment," Pavan explained. "You still must do the real-life experiment, but our digital models might speed up the process. And that could help more patients sooner. That seems good."

We agree.

United Therapeutics converted to a public benefit corporation (**PBC**) in 2021—the first publicly-traded biopharmaceutical company to do so. Our **PBC purpose** has two parts: ***to create a brighter future for patients through the development of novel pharmaceutical therapies and technologies that expand the availability of transplantable organs.*** Our first purpose helps delay or avoid the need for an organ transplant, while the second purpose enables a patient to have a transplant when they need one.

[44] The Human Genome Project (1990-2003) was a landmark global scientific effort to generate the first sequence of the human genome.