Commercializing a Research Discovery: From the Bench to Business

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I am going to take you on a journey, a research journey of how my scientific career has come to be. It has evolved into creating two businesses. Although I once struggled to spell the word "business" and I knew nothing about business, now I'm a co-founder of two companies.

We'll start during my undergraduate career. The summer of junior-to-senior year, something happened to me: I found out I didn't want to be a doctor. I had worked really hard my first three years at Lafayette College studying biology. My dad is an orthodontist, and I thought that's just what biology majors do—we go to medical school. I didn't know why I was going to medical school; I just studied really hard. I had my 3.75, I was ready to take the Medical College Admission Test (MCAT), and then something hit me. I thought, "I don't know if this is for me," but what else could I possibly do? Because I had already gotten all my requirements done, I had my whole senior year to really just think about life, contemplate life in general—the universe. I started reading some of Carl Sagan's work. Some of you might know his book *Cosmos*. One of his famous quotes from that book really struck me: "The nitrogen in our DNA, the calcium in our teeth, the iron in our blood, the carbon in our apple pies were made in the interiors of collapsing stars. We are made of star-stuff."[1] This quote still really stimulates me to think about what a supernova looks like—all of this energy and these fusions happening. Two hydrogen molecules produce a form of helium, and then this stuff, this "star stuff," travels trillions of miles to the earth.

I began thinking: how does all this "star stuff" become life? I met with my research advisor (I had started doing a little bit of environmental research my senior year; I was passionate about the environment and wanted to save the world, as all senior undergrads want to do). When I posed these questions to her and started talking with her about some of this work I was reading, she replied, "Yeah, you shouldn't go to medical school. You should go to graduate school—you'd get to do this for a career."

Off I went to the University of Cincinnati to their Department of Environmental Engineering. It was quite a stark transition from little old Lafayette, a small liberal arts school with a cozy environment and everybody taking care of you, to this big university in a big city eleven hours from home. My first

semester, I was in Chemical Principles of Environmental Engineering. Here I am, a biologist—an environmental scientist—in all these engineering classes. I thought, "Oh, I didn't take enough math." In fact, I failed my first Chemical Principles of Environmental Engineering exam. I wasn't even close: it wasn't a 58 or 59, it was a 40— I still have the exam.

I'm thinking: "What the heck am I doing here? Maybe I'm not ready. Maybe I should have gone into the workforce first." And I thought, "Well, I'm just going to stick it out. Maybe if I just stick out my first semester, something good will happen." And actually, in this Chemical Principles of Environmental Engineering class, we finally talked about something I knew a little bit about: poop! Wastewater. We designed and came up with a series of equations that have to do with how wastewater gets treated. We visited a number of wastewater facilities, and the same pattern kept happening: you'd see this foamy poop, but what came out at the end of the process was nearly drinkable water.

I thought, "How does this happen?" We were deriving some engineering equations, with my professor writing long equations on the board, and I raised my hand. As a student, I asked a lot of questions. My professor said, "Yes, Ms. Lamendella, what can I help you with now?" I said, "What is that one variable?" He hadn't defined it. He said, "Oh, that's a variable for biomass—you know, the bugs." He could see me staring at him. "Yes, Ms. Lamendella? You don't seem satisfied with that." I said, "Well, what are these bugs? Who are they? Are there lots of different types? What are they doing?" He responded, "This is why we just have a parameter, one single parameter for them." I could tell I was getting under his skin.

That's where my excitement, my spark for microbiology, first happened. I had never taken a microbiology class as an undergraduate. It wasn't until graduate school that I started reading and taking coursework in microbiology because I wanted to know what those bugs were doing. It turns out that the bugs are doing biochemical transformations that turn carbon and nitrogen into less toxic forms and help create drinkable water.

EXCITED ABOUT MICROBES

Now I'm excited about microbes. I haven't yet started my research; I'm still taking some coursework and learning about microbes. They're everywhere. I'm reading about microbes that are in the air, or on surfaces, or in our bodies. I stumbled into some of Lynn Margulis' work; she developed the theory of endosymbiosis and revolutionized our understanding of evolution.[2] People actually didn't accept this theory right out of the gate, but she came up with the idea that, way back when, some sort of large bacteria—think of it as a proto-animal cell—engulfed a smaller bacterial cell, like an aerobic bacterium. Over evolutionary time, this actually became a good thing. The bacterium that got stuck inside of the bigger bacterial cell evolved into things like mitochondria, the powerhouses of our cells. Margulis

imagined that in the ancient soup of life, one bacterial cell engulfed another, and this chimeric result is the cell from which all fungal, plant, and animal life descended—even good old Carl Sagan, who was her first husband. It dawned on me then that not only are we covered in microbes, we *are* microbes . . . because all of these cells really are just bacteria stuck inside bacteria.

I had found the thing I wanted to study, but I needed a project. I wanted to become a scientist. I wanted to pose questions and hypotheses and design experiments to answer them. It's very fortunate that the regional office of the Environmental Protection Agency (EPA) was right across the street, and they had a training program with the University of Cincinnati (UC). So I did all my coursework at UC, and I did my research across the street. The field I ended up studying was in the Microbial Contaminants Control Branch within the EPA. There was an evolving field called Microbial Source Tracking, also known as "fecal source tracking." It's essentially figuring out who the culprit is. We know that there are a lot of sources of pollution that are affecting our groundwater and our surface water, but we need to figure out what those sources are. How do we identify if it's the leaky septic tank, the swine farm, or the chicken farm? We need to be able to identify and quantify the sources of fecal contamination. It's my two favorite things: studying poop and water and trying to keep poop out of water.

I was very excited that this was going to enable me to discover the microbial diversity associated with these organisms. My theory was that different hosts have all different types of guts—the environment that those bacteria are in. Those bacteria face lots of different environmental stressors. Microbes living inside of our gut are constantly co-evolving with the host and vice versa. I thought, "This might be really good in terms of coming up with a target that would be specific to a given host." I was on the hunt: what I tried to capture were specific microbes that, because of coevolution, are only found in specific hosts.

Each one of us in the division looked at a different host. I was the first-year graduate student, so I got the smelliest of all these animals; I was called the "pig-poop queen." My goal was to find bacteria that were specific to this one gut so that we could then target those host-specific bacteria. If we could find bacteria that are only found in the pig gut and if these targets made their way into the environment—into ground water and into surface water—we could develop a molecular tool to target them. That's what I did for about 4½ years.

You might be asking yourself: "How do you go about tracking bacteria in these different hosts?" The key is targeting DNA: using DNA to track whose poop is whose. DNA is the recipe book, the instructions for life. It's encoded by four different chemicals—adenine, thiamine, cytosine, and guanine—and it's the sequence or order of these four different chemicals that makes organisms different from one another. Based on this premise, we can actually use the DNA sequence. When they're sequencing your DNA—have you heard of 23andMe?—they're just decoding the list of letters that refer to the four DNA

chemicals. The pattern of these letters is a little bit different for each organism. It's kind of like a social security number for telling bacteria apart or a thumbprint for telling us who is there in a sample. My goal was to find which DNA sequences that represent these different bacteria are specific to swine.

For about a year, I collected as much poop as I could. I set out to a variety of different zoos. I went to a number of different Amish farms to collect as many types of pig-related samples as I could and samples from other non-target hosts, too. I wanted to develop a library of specific sequences and then extract the DNA from them. I think my library had over a thousand different fecal samples in it as well as water samples that we suspected might be impacted. We extracted the DNA from those samples; this means breaking open those bacterial cells to get the DNA out of them and then putting it into this fancy machine: a DNA-sequencer. I liken these to DNA printers. They're just generating that sequence for you.

The challenge really comes at the bioinformatic stage after you've generated all this data: to figure out what each of these sequences matches to in the database. Then, using some phylogeny, you can group those sequences based on their evolutionary history. What I was looking for were host-specific plaids, or groups of sequences, to design molecular targets against. It took me 4½ years, but I developed seventeen different molecular markers to track swine waste in water. It's not easy: the amount of data that these DNA sequencers produce is immense. We're talking millions and millions of sequences. Back when I was doing this analysis, circa 2005 and 2006, there weren't computational pipelines out there. I don't even think the "cloud" was really a thing. I gathered all the computers that nobody was using at the EPA and hoarded them, doing all the analysis in parallel on different computers, but I thought to myself: there's got to be a better way to do this.

A BETTER WAY

At the time, there really weren't bioinformatics programs out there, so I said, "I'd better beef up my computational skills." I applied for a postdoctoral position at the Department of Energy's Joint Genome Institute, which is affiliated with Lawrence Berkeley National Laboratory. The Joint Genome Institute is one of the institutes that first assembled and sequenced the human genome. I figured I should learn from the best of the best if I were to do this well. I headed out there for 2½ years and learned from incredible bioinformaticians on how to do this analysis.

When I went to Berkeley, I was excited. Not only was I going to be learning about bioinformatics, I was going to continue to work with poop, just in a different context. I moved my way up the alimentary canal, so to speak, and, instead of microbial tracking, I worked on inflammatory bowel diseases like ulcerative colitis and Crohn's disease. At the time that I moved to Berkeley National Lab, President Obama had poured money into science. One of the programs that was funded through the

National Institutes of Health is called the Human Microbiome Project (HMP). My research was part of that.

The HMP was trying to learn about the human microbiome. You can think of it as a microbial cloud that's following you around. It's all the bacteria on your skin, in your gut, everywhere throughout your body. Most of those organisms, the thirty-nine trillion that are on and in you, outnumber your actual human cells. They're mostly doing really good things for you. The human microbiome project was the first initiative to ask: "What does a healthy microbiome look like? What set of microbes does a healthy person have?" We can define that set of microbes that a healthy person has and then look at all different disease states, measure their microbiomes, and see if there are differences. There are certain microbes that they may have too much of or not enough of. It was the heyday for microbiome research and, really, the start of microbiome research.

When you think of the microbiome, it's really a question of who's there. There are from over 400 to, in some cases, over 1000 different bacterial species floating around just in your gut—very, very diverse. Different factors—host genetics, environment, diet, lifestyle, hormones, even industrialization—all of this affects and impacts the microbiome.

As I mentioned before, the microbiome does really good things for you. For example, the microbiome associated with your skin is helping fortify your immune system. In the colon, microbes are doing a ton for us in terms of digestion and vitamin production. You can see the wonderful things that microbes are doing for us. They're also outcompeting the bad ones, the pathogens. You want to have a really good, strong microbiome to outcompete any pathogens. What I did at Berkeley National Labs was study the role of the microbiome and the etiology of Crohn's disease and ulcerative colitis. We had a cohort whose microbiome we looked at over time and compared to healthy individuals. My post-doctoral supervisor let me come here to Juniata with all the data. As a result, the students here got to work on what may be the largest inflammatory bowel disease microbiome data set out there.

Again, the idea here is that we're trying to compare the healthy gut microbiota to what we call the dysbiotic gut microbiota. That's just a fancy word for an imbalanced, messed-up microbiota. We want to see what's wrong and then see how we might fix it. Are there certain prebiotics, probiotics, or changes in diet that we can intervene with? I'm only going to share a little bit of data from the inflammatory bowel disease (IBD) project, but you can see the whole host of other disease states that I'm working on with students (see Figure 1 below). We're looking at the role of the microbiome and things like diverticulitis, *C. difficile* infection, hypertension, anxiety. There's a super-highway that connects the gut to the brain.

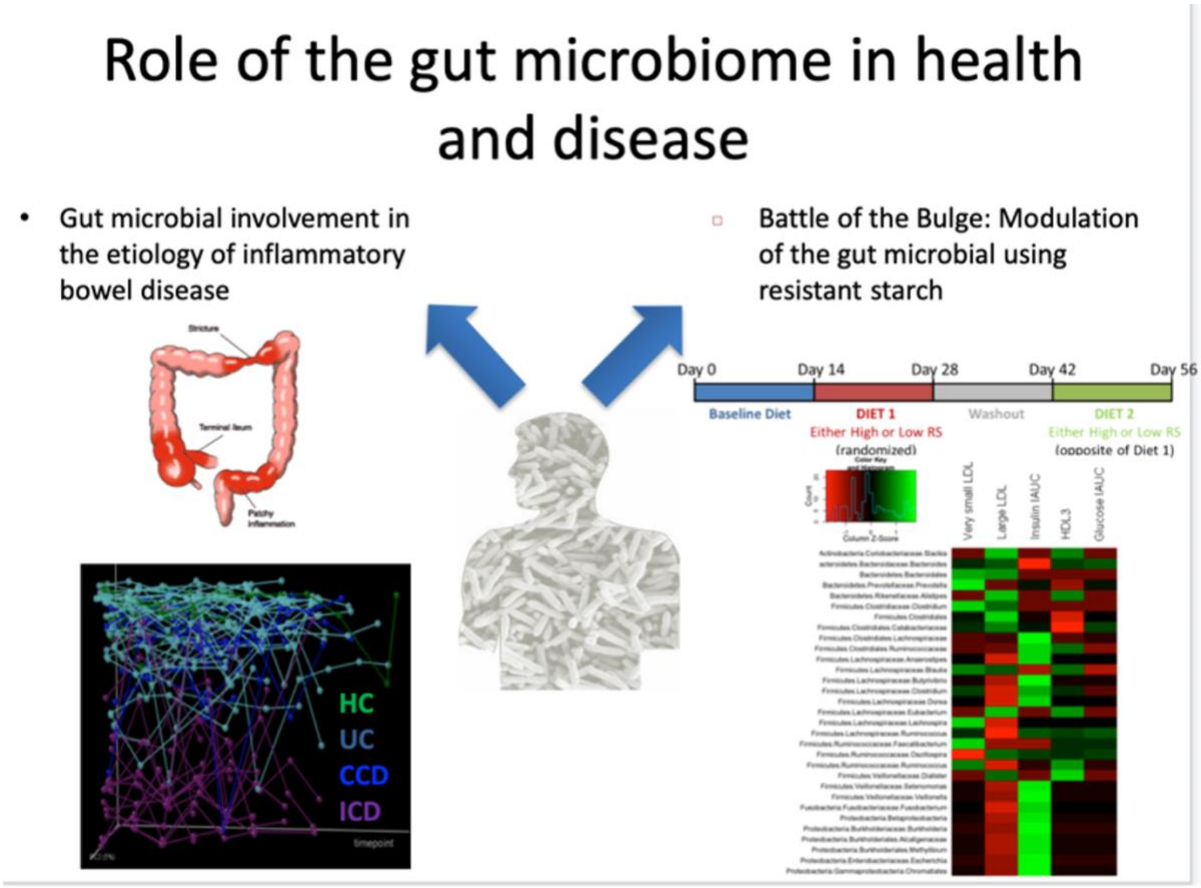

Figure 1. Role of the gut microbiome in health and disease. Image credit: Regina Lamendella.

Microbiomes can affect us in that way. We've also worked on a really neat cohort in babies. There's a disease called necrotizing enterocolitis; this disease has a really high mortality rate in infants. We've also worked on studies relating to obesity, heart disease, and Type 1 diabetes. This has been a really exciting time to be a microbial ecologist because the same set of skills can apply to virtually any disease that one wants to study.

What you're about to see is some of the data that we generated from this longitudinal cohort of individuals that have inflammatory disease. You'll see that individuals in orange are healthy individuals (HC), in yellow have ulcerative colitis (UC), individuals in pink and red have ileal Crohn's disease (ICD) or colonic Crohn's disease (CCD), and then purple and blue are other types of inflammatory bowel disease. What you'll see is how their microbiomes change over time. Each line is an individual. For some of these individuals, we had up to ten time-points (see Figure 2 below).

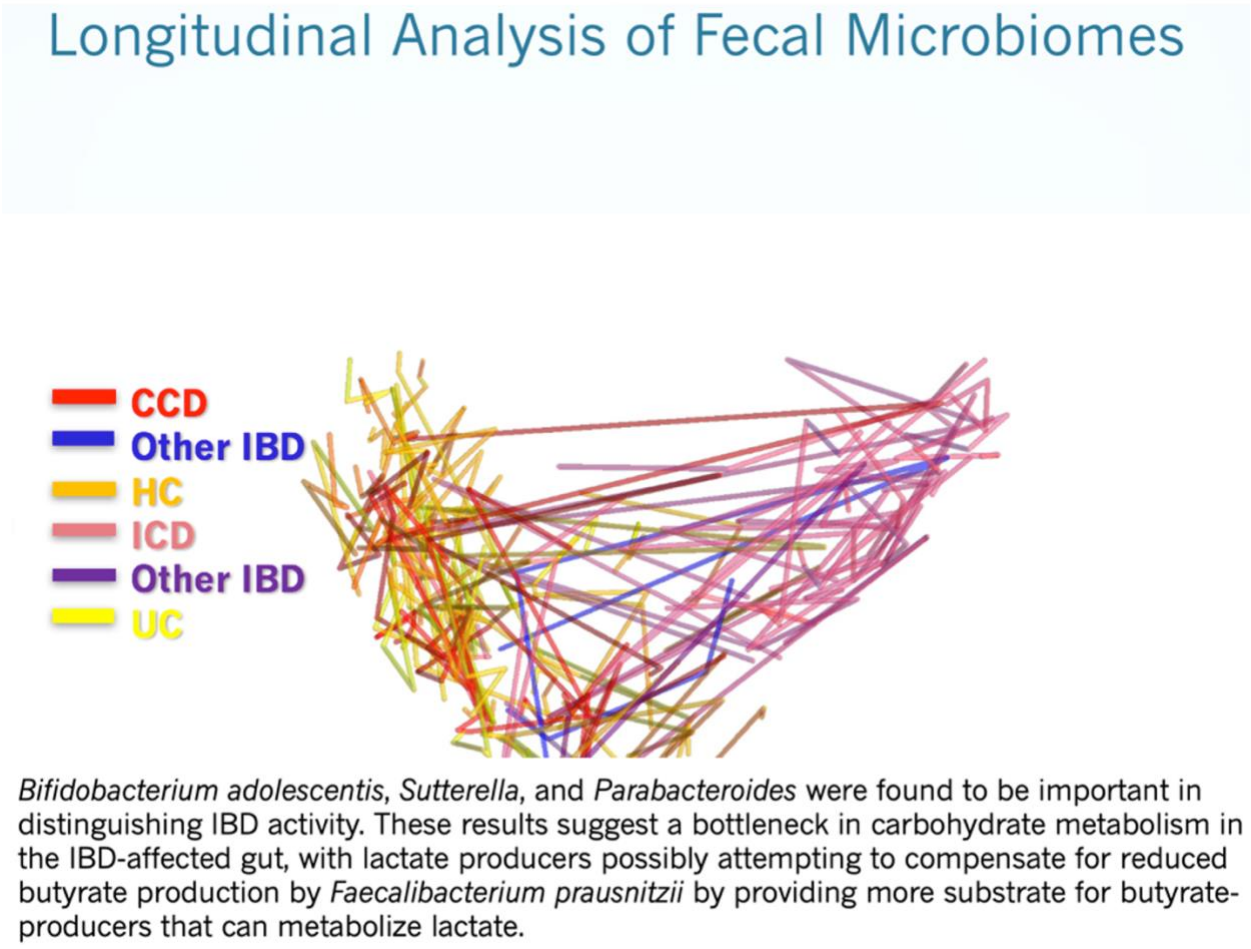

Figure 2. Longitudinal Analysis of Fecal Microbiomes. Image credit: Regina Lamendella.

It's all over the place, right? My student, Erin McClure, who graduated in 2013, used vector length as a way to look at variability in the microbiome. What you'll see between individuals that have ulcerative colitis and those that are healthy is that they fluctuate. The microbiome can change day to day. It can change actually hour by hour, based on what we're eating, etc. We noticed that individuals who are healthy stay, for the most part, in one plane. But individuals that have IBD? They are all over the map. We ended up defining the plane on the left side of the plot, designated by the yellow and orange lines, as the healthy plane, and, as one goes away from this healthy plane towards the right side of the plot, the person becomes more dysbiotic in terms of the microbes that are there (see Figure 3 below). What does this actually mean?

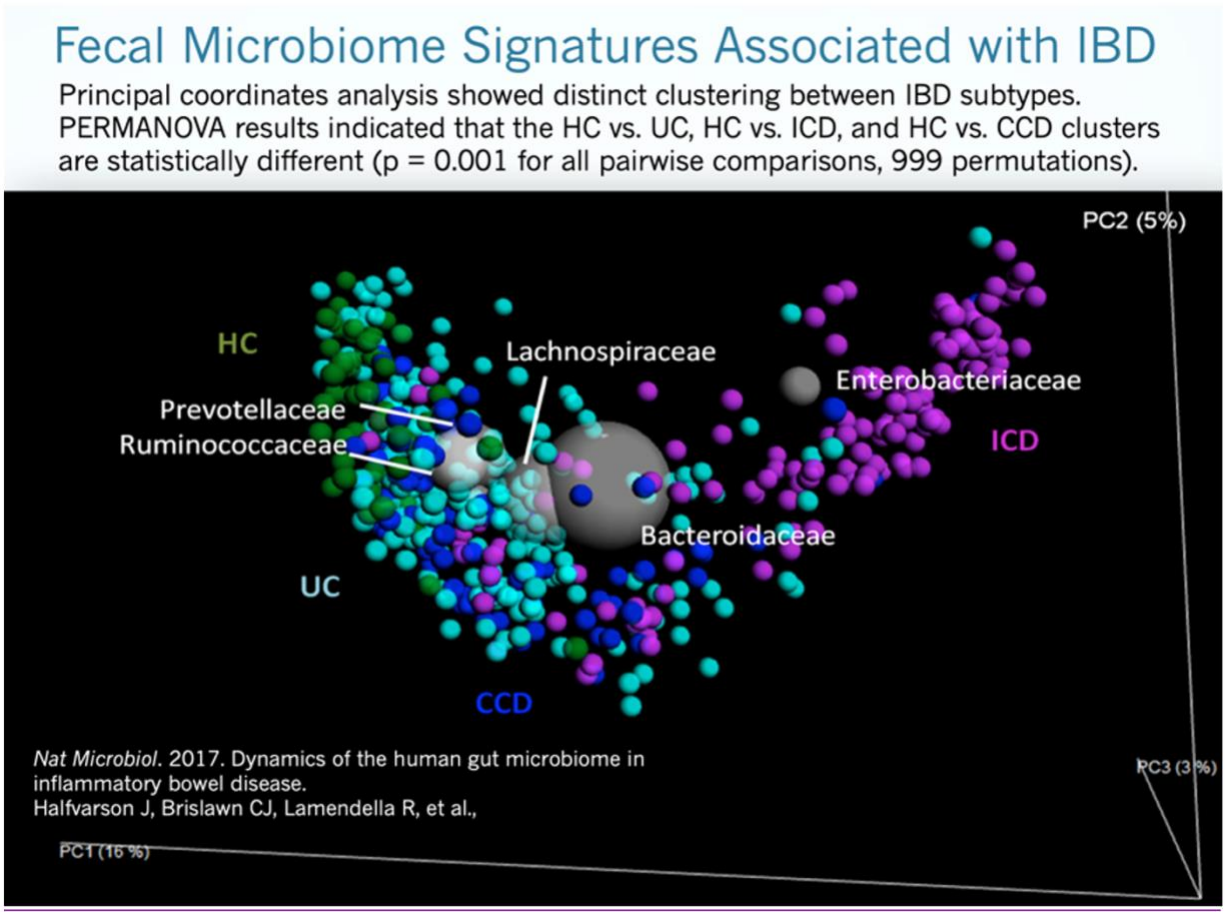

Figure 3. Fecal Microbiome Signatures Associated with inflammatory bowel disease.[3]

What students ended up doing was using some random forest modeling to ask, "Can we look at the microbiome as a predictive tool for when somebody's going to go into a flare-up?" Anybody who has ulcerative colitis or Crohn's disease knows that you might be okay for some time, but then, all of a sudden, you go into this flare-up state. So how could we predict and prevent that? With 92% accuracy, just by looking at these microbiomes, we can tell whether the individual is about to go into a flare-up. That's what gets me excited about the microbiome: using it as a tool to help inform us.

RESEARCH WITH UNDERGRADUATES

What's even more miraculous is doing this with undergrads. For me, that's been the most powerful part of this because I learned how to communicate better. I've also learned how extremely innovative our students are. I have had the honor of doing research with seventy-three students. For some, research has helped them discover themselves, their creativity, and their confidence.

We've created a research family. Some of my favorite memories are of us doing whitewater rafting, pizza nights, or pasta-making at my house. That's created a nice community here. Students have

not only contributed to but led the way in many of the thirty-one publications that we've had since I've been here at Juniata, with thirty-six unique Juniata students. With the exception of four or five of those publications, the students have been the primary authors. They're doing all the research, all the writing, and getting hands-on experience.

Not only is there the independent research that we've been doing, but, in the biology department, I lead a molecular microbiology course in which we do independent, student-designed projects. Sometimes they don't generate data that's publication quality, and that's fine because the skills that they are gaining in that course are really high impact. We use the Classroom Undergraduate Research Experience survey to measure student learning gains. The most significant are things like tolerance for obstacles faced in the research process, understanding the research process, and the ability to analyze data or information. It's all about confidence and learning to work independently.

HIGH-IMPACT PRACTICES

We need to put our money where our mouth is. I've done that by starting a research endowment that will be fully endowed this year. We want to pay forward our investments in research. It's changed me. I've seen it change students, and I want them to keep going. I always say our students have better ideas than us, and that's the truth. The innovation that they bring to the table is amazing. I'm about to share with you one of those examples.

In his senior year, Justin Wright was on his way to pursuing medical school. He decided it just didn't feel right. He came to me and asked if he could do some research. I said, "Sorry, I'm all filled up, but I've got a research course I'm running this semester. Why don't you take that, and we'll see how you do?" He did quite well. Justin stayed after his senior year to do some research with me. During that summer, he said, "Dr. L., we work on all these different diseases. Have you ever considered doing this as a business?" And I said, "Listen, man, I never even took a business class. I don't know where to start." With the guidance of Terry Anderson, who led the Juniata College Center for Entrepreneurial Leadership (JCEL), we asked: "How do we become an Limited Liability Company (LLC)?" Okay, now we need a tax guy. Now we need a business plan. "What's a business plan?" All these things sort of fell into place. Luckily, we had Terry to guide us. We're located on the second floor of JCEL's Sill Business Incubator.

We're able to help medical, clinical, and environmental scientists get to the biology faster. These are experts in their fields, but they don't know how to do microbiome research. They don't know how to do the bioinformatics. We've kind of become a consultant for them. We also have a slew of clients that we work with on things like biodegradation, how the microbes eat and transform compounds. We've been helping people like Dr. David Stewart, a famous colorectal surgeon, with the *Clostridium difficile* project for quite some time and making progress in terms of understanding the mechanism behind how *C.*

difficile infections occur and reoccur. We're also helping other medical doctors like Dr. Sridhar Mani at Albert Einstein School of Medicine. It feels really great to help them push their science forward.

We started in 2015. Justin came up the idea in 2014, and we came up with an actual LLC in March of 2015. Now we have over sixty different academic, governmental, and private institutions that we work with. Everybody asks me, "Well, how do you do this and be a professor?" I don't do it. I pull the projects in and have the connections, but this is being led full-time by seven recent Juniata alums. So far, we've funded twenty-one undergraduate research interns in the summers. It's just been wild beyond my dreams in terms of how it started. It really just started with a couple of grants. And then through word of mouth, it grew. People were saying, "Hey, these kids really know what they're doing. Send your samples this way."

Initially, I was paying Justin out of my pocket, and then we got the first sizable grant from the environmental firm CDM Smith. We were very excited. I remember Justin saying, "I can pay you now for real!" That was really a good feeling. When we got to year two and year three, we were increasing our revenue over time. Something that's been really neat is that the state of Pennsylvania has this Keystone Innovation Zone, which awards tax credits. Since the Sill Business Incubator falls within this Keystone Innovation Zone, we get these tax credits, which you can then essentially broker and utilize as you wish; we hire more individuals and continue growing.

CONTINUING TO GROW

In 2018, we started a second company called CSI: Contamination Source Identification. After we had been working in the clinical space for quite some time, we noticed a need for better diagnostic tools within that space, so we started a clinical version of Wright Labs called CSI. The reason they're two separate companies is that when you're working in a clinical space, you don't want to be wrong. You want to be right as much as you can. You have to get these clinical lab certifications so that you can actually work on clinically relevant samples.

CSI's goal is really to move diagnostics to detection. When a doctor is diagnosing an infection, they're looking at the symptoms that a person's coming in with and trying to figure out how to treat them. But we want to move away from diagnosis and directly to detection to really pinpoint that which is hidden. Diagnostics and detection are not an easy thing. When somebody is getting sampled for an infection, they do a blood draw. The current standard of care is culture: take the blood, inoculate it into media, and see what grows. It takes time: it takes twenty-four or seventy-two hours at least to grow organisms. You're looking for growth in little dots, or bacterial colonies, that you see on the Petri dish. The problem is that it's really hard to grow organisms. We can really only grow a couple percent of all the organisms out there. As it turns out, often the results come back, and it's culture negative. We know

an infection's there, but the test says no. As a doctor, as a clinician, what you do with that result? You're going to treat this patient with something. You probably give them a broad spectrum antibiotic. But what do you think that broad spectrum antibiotics do? They wipe out all the good organisms, too. It's also giving all those organisms a peek at what the antibiotic is. The organisms then develop resistance against the antibiotic.

One of the biggest hurdles clinicians face over the next several decades is antibiotic resistance. That's why we're moving towards phage therapy and other strategies. Because bugs are smart. They've been around over three billion years. They know what they're doing. If we could more accurately detect what that organism is, we could then select a more targeted therapeutic. You don't have to give that broad-spectrum antibiotic. We can select something to effectively kill exactly what organism or organisms are affecting an individual.

Right now, we're validated on blood and urine, but we would also like to validate other sample matrices like cerebral spinal fluid and synovial fluid. We will get there. For every type of sample matrix, we have to go through clinical and analytical validation. The idea is to take that sample and extract the DNA and RNA. Something I've worked on during my sabbatical is developing a patent application for what we're calling a "proprietary bacterial amplification technique." In a blood sample, it's mostly human nucleic acid. The bacteria that are floating around are the needle in the haystack. We would like to come up with a physical and chemical method to dampen the human signal so that we can actually identify the microorganisms. We then subject that sample to DNA sequencing and to analysis.

Justin and the team are also working on the Rapid DX pipeline. We'll be writing a patent to protect our rapid analysis pipeline. This stuff used to take forty-eight hours to analyze. We've now got it down to about thirteen minutes with the same accuracy. Then the results get compiled into a report that is sent through a hospital medical records system. We've been working the past eighteen months on automating this process.

We did a quick proof of concept study. We wanted to see whether this process that we had put together really could work. The first study we worked on was with the Rothman Institute on prosthetic joint infections with a really famous surgeon, Dr. Javad Parvizi. Prosthetic joint infections are a big problem. Joint replacement surgeries are increasing as the population is aging. We need hips and knees, but prosthetic joint infections cost our healthcare system a ton. While they only happen a couple percent of the time, when they do, it's pretty bad.

The five-year mortality rate following prosthetic joint infections is high: nearly 25%.[4] If you do get one, it's not a good thing. Those are not odds you want to be up against. So I met Dr. Parvizi for dinner, and I talked to him about our test system. He says, "Okay, hot shot, I'm going to give you some samples. You're going to be blinded. You tell me who is infected and who isn't." I gulped my wine down

and said, “All right.” So he sends us some samples. Some were individuals that were infected, and some were individuals that were not infected. With 100% accuracy, we were able to detect who was infected and who wasn’t.

I’m going to tell you one quick story because I think it proves the power of this technology. It was eye-opening for me, too, because I didn’t believe it until I saw it. Patient 15 came to Dr. Parvizi with a little bit of knee effusion. They suspected an infection, and they aspirated some synovial fluid, which was sent to us. We were blind: we didn’t know this individual was infected at the time. In addition to using our CSI-DX test, we subjected the sample to the current standard of care: culture, 16S rRNA gene sequencing, and metagenomics sequencing, which are state of the art right now. Although the CSI-DX test had a different result, the results of the culture, 16S, and what we call “shotgun metagenomics” tests all said, “The infection is a *Staphylococcus*.” So what will the doctor treat for? Staph.

The way physicians select antibiotics is based on their knowledge of how susceptible these different pathogens are to a given antibiotic. For example, we treat gram-positive and gram-negative organisms with different antibiotics. In this case, the doctor selected a standard antibiotic to treat *Staphylococcus* because that is what the culture, 16S, and metagenomics test results had all detected. Six weeks later, Patient 15 comes back to the operating room and his knee is a mess. Pus, everything. They take some samples. Seven of the seven samples showed that the actual organism causing the infection was a multidrug-resistant *E. coli*, which that antibiotic is not effective at treating. What ended up happening is, because the infection was so bad, his leg had to be amputated. You think to yourself, six weeks earlier, had we known it was an *E. coli*, could we have treated him differently? When we went back to what our test system had shown as the results six weeks earlier, we found an *E. coli* that actually had 33 different active antibiotic-resistant genes. Because the CSI-DX test is much more sensitive than the conventional tests, my hope is that we can get this test out there quickly.

We’re working really hard on another disease, especially since Pennsylvania is the number one state for this: Lyme disease. There are over 300,000 new cases a year.[5] Early diagnosis is key. If you catch the organism early, the antibiotics that are out there are very effective. The problem is when we get to mid- and late-stage Lyme. The organisms like to hide out in your tissues, brain, joints, etc. Other tick-borne diseases, like Rocky Mountain Spotted Fever, are also on the rise. During my sabbatical, we worked really hard on some proof of concept work. We took one of the organisms known to cause Lyme, which is *Borrelia*. We spiked *Borrelia* bacterial cells into blood and urine specimens at known concentrations all the way down to a couple cells to see “How low can we go?” We can detect this organism at around 3-4 cells per mL of blood, which is good because it’s not really found in a high concentration in blood. We’re also doing the same thing within urine for Lyme. We are now in our clinical testing and Institutional-Research-Board-approved study. We’re working with Dr. Timothy

Stonesifer and about forty other doctors in the Lancaster/Harrisburg-Hershey area. The results are looking really good. In individuals that have chronic Lyme, where the current standard of care test is saying there's nothing there, we are seeing Lyme-associated pathogens. We're also discovering unclassified organisms within the *Borrelia* species that are not known about. Because our test is untargeted, in that we're looking at the DNA and RNA from all organisms, we're able to see and capture things that other tests aren't looking for.

In our lab space, we have all the state-of-the-art equipment in terms of the sequencers, the robotics. We have a $310,000 robot that automates processing to ninety-six samples at a time. We've built and validated our protocol system to reduce the amount of variability that we would see person-to-person. We got the process down from forty-eight hours to about ten. Automation has helped us quite a bit, but don't worry, it's not going to replace student jobs. We still need people to code, for instance.

Here's my parting thought. Let's go back to the quote that I opened with: "The nitrogen in our DNA, the calcium in our teeth, the iron in our blood, and the carbon in our apple pies were made in the interiors of collapsing stars. We are made of star-stuff." I've made a revision: "We—and microbes—are made of star stuff." It's been a really exciting journey chasing this microbial star stuff, and I love doing that here at Juniata with our students. It's been a wild ride.

NOTES

1. Carl Sagan, Ann Druyan, and Neil deGrasse Tyson, *Cosmos* (New York: Ballantine Books, 2013).

2. Lynn Sagan, "On the Origin of Mitosing Cells," *Journal of Theoretical Biology* 14, no. 3 (March 1967): 225-74.

3. Jonas Halfvarson, Colin J. Brislawn, Regina Lamendella, Yoshiki Vázquez-Baeza, William A. Walters, Lisa M. Bramer, Mauro D'Amato, et al., "Dynamics of the Human Gut Microbiome in Inflammatory Bowel Disease," *Nature Microbiology* 2 (February 2017), https://doi.org/10.1038/nmicrobiol.2017.4.

4. Kyle M. Natsuhara, Trevor J. Shelton, John P. Meehan, and Zachary C. Lum, "Mortality during Total Hip Periprosthetic Joint Infection," *The Journal of Arthroplasty* 34, no. 7 (July 2019): S339. https://doi.org/10.1016/j.arth.2018.12.024.

5. "How Many People Get Lyme Disease?" Centers for Disease Control and Prevention, January 13, 2021, https://www.cdc.gov/lyme/stats/humancases.html.