iGEM 2019 Concordia

Concordia professor in synbio.
Interviewed by Lancia Lefebvre

Professor
The first thing you do as a grad student, and it's funny because students, when they come into the lab, the first thing that they want to do is go to the bench and start doing some experiments and then I always have to hold them back and say, look, you need to think this through, right? It's really easy to move DNA, clone things... Sit back and think carefully about your project, what you want to address and how you want to tackle the problem and what are the possibilities and avenues. It could easily take you three months, but to ask a freshly minted grad student to not do any in the lab work for three years, you know, it's torture. They say, 'I need to do something in the lab, do what?! It's part of the real process.

I mean, as professors we have to sit down and write research proposals all the time to get research funded. It's the same process. Yeah, here's a problem, right? Here's how I can think of to solve the problem. Designed some ideas and experiments, throw that out there. Great idea. Here's some money. Go for it, it's the same thing. If someone was to walk in there and dictate a project on you, then they would fail miserably at the iGEM process because we've taken away all of that part of creativity and critical thinking, debating ideas within groups, and building a project from scratch. If all that is done for you then it's not good.

Lancia
I know from writing experiments. Learning about the hydrogel, learning that there are all these properties you have to know about the gel, and how can we test them? The different approaches, studying for months, writing protocols on your own and having to case out which materials and amounts and why... What concentrations? How much? What equipment?

I think it gives you a lot of appreciation because we're just used to picking up research papers all the time and reading them. I had to read through a paper in half an hour. That's cool. And that gives you an appreciation for the amount of work that went behind that. I have students in the lab, it'll be four years they'll work hard before they can put out their first body or first paper. That's four years of plugging away and hammering it out before something comes out. It's tough. Come on. It's a bit of a race too, that's the part that I dislike. Science and technology are moving so fast now that you have this great idea, but it takes three, four years for the grad students to execute it. And there's like four other people that are working to do the same thing. So it's not, anymore getting an idea and getting it done. It's getting an idea of can I get done fast?

We've noticed talking to the other, iGEM teams, that most of the strong teams have huge collaborative networks. Some teams have a core of 15 people, but then they have a lot of volunteers working with people to accelerate those processes.

I think we have a tendency to do this here, we just need to bring that maturity to the iGEM program.

Next year alone, to have some structure to start from. What's really great about our team is most people want to see iGEM through. Everybody's really excited about making sure that there is a structure and that it's more successful.

What you just described there is another reason why it's important for the iGEM team to come up with their own idea and structure. Its ownership. 'That's my idea, we came up with it,' It's carried through as opposed to Dr. Martin

told me to do this. That ownership is so important.

We went in kind of blind, by the time we were supposed to present projects, I don't even think anybody knew what they could do, the potential. Offering the new students some structure.

My grad students used to coach the iGEM teams quite a bit. We had something called bootcamp. It the beginning, once the team got put together, one of the things you want to do very quickly is to overcome simple technical barriers like things everyone should know how to do. I should know how to do PCR. Let's get that over with. Within a month or so, all the basic molecular biology techniques were out of the way. And that doesn't become a limiting factor.

Well, then you start to see and think in ways that, cause like we did training a little later. At the same time, we were presenting projects. and getting feedback like, 'where is the synbio aspect of this project? Not everybody really understood what iGEM was either, the late start was challenging.

That would be a bit of an issue. This reflects too, and I see it all the time. So technique is not science and science is what comes out of the techniques, a lot of students when they come out of undergrad, they think that science is running a PCR and I think that science is really a protein gel and they think that science is really an enzyme... That's not science. Science is that information and the data that comes out of those things and what you do with it. So get PCR, just learn it and be done with it. The question is what can you do with PCR that's of value. I see it when undergrads that want to join my lab. There's grad students or undergrad students that send me an email. They say, I can do PCR, I can do SDS page, I can do this...
What can you do with those things? Right. The emails that pop out at me all the time are, 'I've looked at what your lab does. I've read your papers, I really like this. And I think that maybe here are some ideas and thoughts or directions that this could go. Most of the time they are way off, just because they're not deeply knowledgeable about this. But that email will catch my attention like that more than someone that sends me an email with skills. I go wait a minute, you're interested enough to spend the time to research the science and to think critically about the science and come up with what you think is a novel interesting idea, that's a scientific process.

If you're talking with grad students and they come in I'm thinking from the aspect of brainstorming an iGEM project, how do you help generate ideas to encourage the brainstorming process?

It's two or three different things, right? The first one is, and I guess in the years to come, it might be better. Right away when the grad student comes in I embed them into other people in the lab. The worst thing you can do is take a grad student, drop them in your lab and not have them collaborating or cooperating with other people. What I do is they spend the first two, three months looking and shadowing other grad students and postdocs, Learning about their science and projects. Reading the papers that have come out. By the first two or three months, we would expect them to do is understand what's going on in the lab.

And kind of mastered all the basic skills. Then personally what I do is I spend an hour or so every week or two weeks where I sit down with the student, we kick ideas around, I'll send them papers. I'll say read this. Let's talk about it next time you come back because I think there is some ideas in there. Because it's very difficult to brainstorm ideas and projects without a certain level of background information. If you just come in there cold Turkey, you haven't nothing to build on. I found for the iGEM project that I saw two, three years ago that was pretty

cool. The way they got around that problem is they first sat down and go, okay, time to brainstorm.

Okay, we have no ideas... Here are some preliminary topics and then everyone is an area or a topic or an idea or whatever. Go away, do your research, go read papers then we all come back here in a week and report back on what we found, possible ideas. What happens is you get feedback from the group brainstorming, go out finding information. What's out there? What are people doing, what's being done, what directions are these things going? Come back, share with the group again. They did that on a few cycles and eventually they choose. It's like, no, this has been done. This can't be done. This is impossible. That's cool. And then they sort of through their ideas, as they were reading and then came up with the project. What I find is inspirational sometimes to just look at the past iGEM projects. See what they've done and some of them are repetitive, some of them are boring or something. But it gives you an idea to the scale and the scope and the creativity. The kind of questions that are being asked. You can start wrapping your head around it.

That's something that people underestimate. Creativity is such an important aspect of science. People don't realize, but you have to be. There is a question or problem and there's so many different ways you can address that problem or question being creative about your approaches. I find some of the best scientists that I know are really creative people. They come up with these strange ways and approaches and experiments. It's like, 'wow I never would've thought of that.'

I have a classroom in systems thinking that could be super useful because it's taking a problem and seeing all the different ways you could solve it. It would be good to use that.

But the most important thing too is once you start thinking about the different ways to solve it, you need a certain level of background knowledge, right? Because you can't come up with things out of the blue. For an example like this, you have to understand what is in the realm of possibility, what are the tools and technologies that are out there and applying this information and tools and technology to address that problem in different ways. But if you don't know about these things... I find that in the early days in science, too much time spent in the classroom filling people's brains with the basic knowledge. Your argument is always well you need the basic knowledge so that you can apply it to in a creative way to solve problems. Yes, I understand that. I still feel that you have to start in much earlier in the process to use the critical creative thinking based on the knowledge you're acquiring as opposed to just shove your brain full of information and then hope that eventually, you'll use that information in creative ways.

I always dreamed that it would be more like a trade. I think it's more fun when it's more hands-on rather than when you learn the theory. It's better to learn about this as if it were a game, so it's more applied.

That's why this iGEM team is incredible. I've seen many of you go through the iGEM process. Some of them ended up in my lab and some of them are Masters students. They actually told me that six months later after working on iGEM, when they went back to their classes it was just a breeze. We had iGEM teams for a few years then Dr.A and Dr.B burned out a little bit and then didn't want to do it again and it took a season or two to get back on our feet with a supervisor. Get the team back up and going. What we've, what we found is, again, if you have a team every year, then there's a memory that stays there for members that were there the year before and materialism. If you stop and train them, you start from scratch.

What brought you into the field of genetic engineering?

It's kind of a convoluted story. I started off my graduate studies in a field called Bioremediation it was all about using microbes to clean up pollution. I spent five, six, seven years to that as it master's students and PhD student. When I finished my PhD, I kind of looked at this and I went, this is kind of silly? Cause the initiative should be trying to not create pollution instead. Trying to come up with the technology to clean up our messes. As I started thinking more about that and it kind of led me towards looking at more sustainable processes, for example, consumer products. Can we build a better whatever, better food, better chemistry...

So I ended up in a chemical engineering department for my post-doc and there they were, they had their vision was upside down and instead of deconstructing things, like bioremediation and cleanup. They were all about developing processes to make things in a cleaner, greener way. That's how I ended up in that space. You start digging a little bit in that space and realize that what nature kind of evolved is not necessarily the right biological systems to do that. So you need to do a lot of engineering, genetic engineering to get these biological systems to do what you want or need them to do.

Interesting, going from remediation to like building something from scratch. Is that why you call your microbes small green factories?

Yeah, that's exactly it. The premise was to try to, to try to reproduce initially petrochemistry but in microbes. Microbes have wonderful catalysts are coenzymes cause you don't need to have all these crazy reagents or high temperatures and toxic hydrocarbons, so you use sugar and whatever else in a microbe. You can actually reproduce a lot of the petrochemistry using these methods. Less energy, less pollution The idea is initially to reproduce what petrochemistry does. It's actually getting to the point now where we can actually build a better material than what petrochemistry can deliver, which is kind of cool.

Your opinion on the synthetic biology in the pharmaceutical industry?

The early days and I spent a bit of time in that space. It was all about getting access to those pharmaceuticals. It's kind of tricky transitioning or if we can say it has transitioned from small molecule pharmaceuticals. I was very much in those days very much still is to a certain extent inspired by natural products that you find in the environment. Grind and Find is what they call it, take a plant, grind, extract natural products find out whether it has any kind of amount of bio activity. What would happen very often in this space is grind and find an interesting molecule. But they would find it in some exotic sponge for which there's only like one species in coral reefs and you definitely don't want to harvest that.

They were getting a lot of hits of interesting molecules and structures, but traditional medicinal chemistry couldn't get access to those molecules and harvesting natural sources. We started thinking about how we can reproduce or build these biochemical pathways and microbes to make these natural products. In quantities or whatever it took to give pharma access to the market. That was the early days. There's still quite a bit of that going on in our lab. The next space really in pharma is really around therapeutic enzymes, antibodies, vaccines and all of these called biologics. So synthetic biology can actually have a pretty big role to play around in. If you want to create an antibody for whatever indication you can generate synthetic antibodies, there are very large libraries of synthetic antibodies today that you didn't have access to back then. And they're getting away from the small molecules into the biologics synbio has a huge role to play in there.

It's like accelerated the natural processes that you see in nature. What about scaling up? You're talking about making petrochemicals or antibodies or what about making it a larger industrial process?

It depends on which process and what the molecule is. You have to get a little bit more granular here. I'll give you an example, people have been selling the idea of making jet fuel to fly planes across the ocean on fuels that's made from the bio process. If you start calculating back and you look at the volumes, people don't realize that the volumes of fuel that a plane consumes when it crosses the Atlantic is huge. Multiply that by the number of flights and you go, is there any chance that we can actually build that capacity? That's one extreme, very large volume, very low value molecules but there here is a big range in between them. If you take a barrel of oil out of the ground, a portion, maybe two thirds of it goes to fuel, but one third goes to petrochemical. In terms of volume, the value is actually in the petrochemicals not in the fuel and the petrochemicals are smaller, so there's higher value but smaller volumes. There's a whole huge range from polymers to two lubricants to all of these different things. Household, even cosmetics. Those volumes are a little bit smaller, or mid scale between the jet fuel and that farmer kind of thing. Those are really accessible. There's the range.

You don't want to turn all of Brazil into sugar cane growing fields so you can put few planes across the ocean. There's other things that are smarter to do with it and if we can get the scale that cool. Synbio is not the solution to everything.
Synbio can actually address more things than people believe.

What is your opinion of using a biosensor to detect small molecules. For example, our project, whose goal is to detect small molecules of fentanyl to prevent overdosing.

It's got a huge application. Recently had a visit from the Canadian space agency and they're looking at long term, farther than high orbits. Visiting Mars or whatever. Once you start getting on these long distance flights, they need some sort of devices to tell them if they're getting sick, when they're getting sick and what they're getting sick from. They liked the idea of biological based systems. If I give you example, if I have a device that'll tell me, if this drug is better, when I have a disease. If I use a device I have to thrown it in the garbage, right? Then by the time I get to Mars, how many devices do I have to bring it with me?

But if I bring one cell or 10 cells or a vial of cells. That's basically a self reproducible device and anytime I need that biosensor with that drug, whatever, I just grew up a little bit of that vial. All I have to do is start with a little bit of bacteria and every time I need it I grow it as opposed to a crate full of devices that are one time use that you throw away that don't self-reproduce. There's a lot of value in these kinds of things, they're sensitive, there's self-replicating, they're specific.

I had a question about your experience with legislation while working on creating alkaloids. Working with Canada and the US did you see any difference , what are the biggest when it comes to policy and the production?

I don't know much about in the US but I can tell you in Canada it's been struggle. Mostly because the existing rules are not written for these kinds of things. When you present them with that, the perfect example is our example, in Canada, the regulations around controlled substances are product specific. Let's be specific, how much morphine am I allowed to hold? Here's the license, below the certain amount of you're a user, above a certain amount you're a distributor, with large amounts you're a producer. There's all the different licenses. It's easy to measure and know how much morphine you have. Now we show up to Health Canada, and say we have a yeast that can make

morphine. And they go, morphine, we know how to regulate that. How much morphine are you gonna make? We say, How much do you want? They say, 'What do you mean? How much do I want? '

Typically you use the morphine and you destroy it and its done. The yeast is different, right? Cause it's self replicating. If someone wants to get their hands on the yeast and take it with them, that could be problematic. They're looking at that and going, okay, are you a producer or not? The producers that we're used to be thinking about, they grew plants Papaver somniferum. We know how to regulate plants. We are allowed 200 plants. How do you regulate the microbe? Is it by volume? How do you dispose of the microbacteria? They're not quite sure how to handle this. When we were doing our research and were basically only producing small amounts of these opioids. Not a safety concern. But as things are getting better then we are producing grams of this stuff, they're like stop, we don't know how to deal with this, you're not allowed to do this.

That's basically what they told us. Mostly because they regulate around the risk. How much risk am I willing to take? So if I give you permission to hold a little bit of morphine. I know what that risk is, right? Cause you can't grow more morphine and if you have a little bit of morphine, you can't overdose on it. You can't sell it yet. There is a risk, I can really understand. To allow you to hold a vile of yeast that makes grams of morphine. That's a risk they don't know how to handle or control. They haven't put a risk value on that or processes to limit that risk and therefore they just say no. Risk averse Canadians. In the US I don't know how they're handling it. Other countries are handling it differently. Can tell you that Canada seems to be pretty risk averse.

With regards to your collaboration with Dr. Dueber, what was the structure, how did the collaboration proceed?

He was actually developing a biosensor for different molecules. For an enzyme that produces a molecule. It's a tyrosine hydroxylase and then we are building an entire pathway that was using this dopa in yeast. Hey, wait a minute, you have what I need and I have what you need and we came together.

Do you ship things to each other? Or share protocols?

In the world of controlled substances, if you look at opiates, you start with, glucose. You go up the pathway and then you get a molecule called reticuline. Particularly when you hit reticuline, it's not a controlled substance, the next step... if you could take reticuline into the next step, it is a controlled substance. Don't ask me how they qualify this, everything that we do stops at reticuline because it's not a controlled substance. They've refuse to give us any permission to do anything past reticuline, cause then we're in a controlled substance. So we ship things back and forth to California, but nothing about reticuline.

Do you think these regulations or have an effect on Canada's role in the industry with synthetic biology?

There's a perfect example, if you actually look at cannabis. The clarity around the rules and the not wanting to take risks, is a barrier to innovation. There's a reason why Canada is so big in cannabis and, and they basically wanted to become the world's supplier of cannabis is because the rules and regulations, I guess they're getting clearer, but they're their lax, right? You're allowed to do it in a controlled fashion. So people have to get licenses. Canada's the big, huge innovation in cannabis research. If they would have said no that innovation is going to go somewhere. If you put too many restrictions and regulations around these kinds of technologies, then you're putting a barrier to innovation and those things are gonna get done elsewhere.

Somebody else is gonna reap the benefits. It's a big problem with regulatory agencies because they don't want to stifle innovation by having too many rules, but you still need some rules. It can't be a free for all. Where's that line? Innovation and technology moves so much faster than regulation. The technology's moving over here and guys are doing crazy things, developing all these things, and the regulator is going Oh, I don't understand this. How do you put a risk around that? When they're lagging behind and if they are too far behind, you're going to stifle innovation. As innovators in the cannabis sector, that's what they do. They go, okay, what's the sense of me investing all this money in the greenhouse if I can't get my product to market because regulators won't allow me to do that. The clarity around the rules and the capacity to get licensed or distribution... If it's not there, people go somewhere else. It's kind of sad to say, but again, Canada we have a tendency, I find to be risk averse. Like take the chance, right? It's controlled risk to basically say I'm going to be able to put everything in a box and control everything. That's not going to happen.

So do you see any risks or challenges in the development of our project? For example, if this becomes a product?

The kind of question you're asking, the term they use for this is dual use. There can be a lot of benefits to this, but in the wrong hands there could be a lot of problems. If you're a fentanyl producer, could you use that sensor as a mechanism to improve the period of fentanyl you produce? It can be used for good and it can be used for bad to a certain extent. That's the dual use access. That's the question you have to ask yourself even before we start the project. What are the potential misuses of the technology that I'm moving towards and if I foresee some misuses, and sometimes you don't see coming.

To be honest, when we started this opioid project we were really a little bit naive until we got to the stage of, Oh my God, this is a serious business. Sometimes you can't see it coming. The people that work in risk assessment and dual use technologies, they always tell you that it's very, very often that it comes from nowhere and you're blindsided. You have to be prepared for surprises, I guess. If you're not sure if there's a dual use, then the best way is to start conversations, right? Because maybe you don't know, you don't understand what your technology could be used for, but somebody else might that works in a completely different field, like a medical device person or a drug prevention agency.

They can see all of these different things. I think that conversation is really important. The worst thing you can do when you're moving to a space like that is to try to hide it and keep it a secret because you're concerned that it might create problems. Then in the end, if it does, you're a drunk.

How do you do that with your projects?

We're in constant contact with healthcare. We tell them basically what we're doing all the time, which resulted in me being denied a license, but it's better that way. If we were to forge ahead not asking the questions, only to realize that we were outside the legal boundaries and half my grad students go to jail. Or that the Taliban broke into my freezer and took off with my opioid yeast.

I mean that's kind of silly, but you don't want to end up there. Right. You constantly have a conversation and that's how we ended up with the opioid stuff with John Dueber. I actually called the university and said, 'I think we're getting into this place here where it's getting a little questionable.' So the university, they call the RCMP and they

call Health Canada in terms of safety and security. They did the same thing in the US, they call the FBI and drug enforcement agency to let them know that it's there and happening in tech.

When you're around people who are like study or actively do genetic engineering, synthetic biology, to us it's a great thing. As you said there's like a lack of waste. Just keep it controlled. But to so many other people it seems like the worst thing ever. It's going to end the world...

Especially now with the addiction problem and overuse. I actually personally do worry about it. Growing yeast is not hard. Every time you make bread or beer or you're crossing yeast it's not hard. Earlier generations of our strains, they were making a few milligrams of stuff, and if you were to put that in beer, the generation of strains that we're at right now, they're making grams per liter. The standard dose of morphine is 10 milligrams. If you make an a gram per liter, you're making 100 does of morphine in a liter of beer, it's a hundred doses, sometimes more. You're overdosing.

Now we're in the realm of ‘this is serious business and don't want that to get out’. But of course academic labs are the least secure labs ever on the planet. Just imagine developing down in a pharmaceutical company somewhere locked up. Just security safety, it's all there. Here we have iGEM teams walking in and all, that's our biggest security threat [laughter]

Recently, something happened down at the Foundry. They went and looked up the log. Security went to everyone with an access card and asked people, so someone got into a computer and something happened and we'd just ask, did you go in there? No, no, no... Even with the cards and a little security... Sometimes the door is wide open. I personally have no problem with that. I'd rather have it wide open but now you're working in this wide open, freely accessible space. We have to start thinking about the potential risks.

Because it is a collaborative space, how do you feel about that versus traditional labs which are usually closed off?

I hate the traditional labs, they're terrible. I'm the generation of scientists who did all my training in traditional labs and I did get to experience towards the end of my training, how open labs function and I would never go back. It's really interesting because there's a clear break. If you actually just look in the genome center here and who's here and who is in the SP building and you can see that clear distinction. Everyone that's here is nine years or so except for maybe one or two exception, nine years or so as being professors in universities and they have no problem being an open space because that's how they view the best way to do science. That's probably how they were trained. Some of the labs and us and all the old farts kind of fall in that category are all in SP building in their little 10 by 10 space.

When I started at Concordia, I was in the SP building and I hated it because there was so little interaction between different labs if any at all. Then you have to start thinking about mechanisms to make that happen. Which becomes that extra effort. What you want is just natural collisions of two people, like what are you doing? So much healthier. The other thing I find is it's so much more fun to work in an environment that's really rocking and it's really happening. It's lively, there's people, there's science happening all the time, good science, bad science. There's someone there to help you anytime of the day and that is key to success. Just imagine if your supervisor has five grad students and you're going there on a Saturday morning to work and you're having trouble with a gel or with an assay and you're looking left and looking right, 'I'm just going to go home now. I'm just wasting my time.' As opposed to show up in an open space. People have to come in Saturdays and so there's almost someone here and it feels like something's happening all the time.

There's a huge trust issue that you said. Initially some people were scared like, so you have all these chemicals and

reagents in the shelf somewhere at any lab on the third floor can get access to our chemicals and reagents. They're going to sodium chloride or potassium phosphate! It's never happened. It happens so rarely.
It will happen. You'll deal with it. There's so much more benefits, but it has to be done in a kind of a smart way. Everyone that's in there is going to have to understand how the system works.

It's such a daunting task to start as a new prof, cause you have to find your grad students and buy all your equipment, get your reagents. It can take almost a year. You bring them in, you put them on two or three benches upstairs, all the equipment's there, all the reagents, there are senior postdocs, grad students, everything is there for your students to start being productive and active from day one. So for new profs, it's just a gold mine.

Is there anything with regards to our project for which you think we could improve upon?

That's a classic biosensor type thing. You're doing this in live cells? Eventually you want to have cell free. That would be a challenge. I don't think there are any products on the market with live cells. Because anything with live cells can self-reproduce and propagate. Anything cell-free it dies. There's all these processes and mechanisms that people are developing now for biosafety containment.

The classic bio containment would be, if you make your cells auxotrophic where it requires special nutrients to live. Then in your patch you supply that nutrient. But if the thing was ever to be released from the patch into the environment, the nutrients are not there for it to propagate. Life always finds a way. When you look at these bio containment processes, and that's why I said I have no idea... there's one chance in a million the cell may escape that containment mechanism. One in a million for bacteria is not a lot. So can you come up with a containment process where it's more than 200 million?