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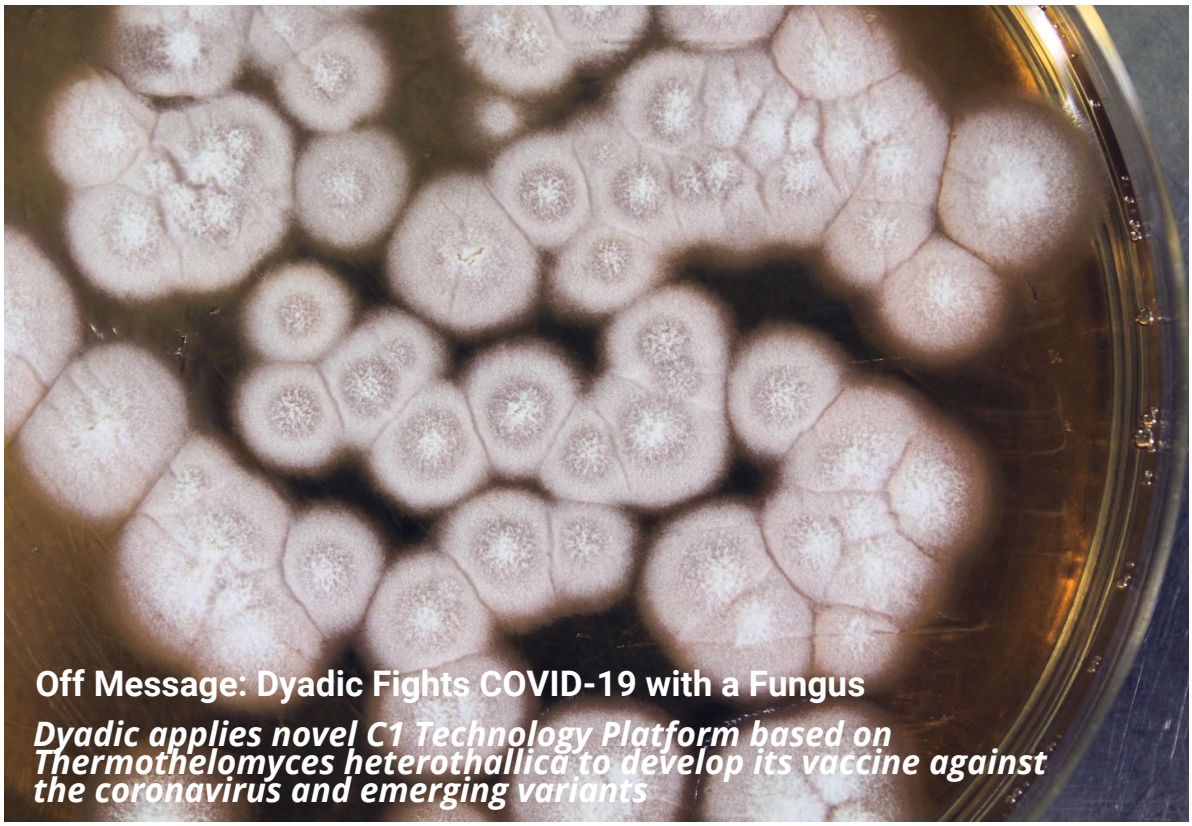

(https://www.genengnews.com/wp-content/uploads/2021/06/Dyadic-image-33333_Thermothelomyces-heterothallica-C1-fungus_184981_web.jpg)

By **Alex Philippidis (https://www.genengnews.com/author/AlexPhilippidis)** - June 8, 2021

Dyadic International has developed a gene expression platform for producing commercial quantities of industrial enzymes and other proteins, based on the Thermothelomyces heterothallica (formerly called Myceliophthora thermophila) fungus, which the company calls "C1." Dyadic is applying its platform toward the development of a COVID-19 vaccine, DYAI-100. [Anne Huuskonen, VTT Technical Research Centre of Finland]

Mark A. Emalfarb, Dyadic International founder, president, and CEO

While messenger RNA (mRNA) accounts for nearly all of the COVID-19 (https://www.genengnews.com/category/virology/coronavirus/) vaccines administered in the U.S. and worldwide, the developer of a fungal expression system based on *Thermothelomyces heterothallica* (formerly called *Myceliophthora thermophila*) insists that its technology can still play a key role in stopping the spread of COVID-19.

Dyadic International has spent some two decades developing its C1 Technology Platform, a fungal expression system intended to accelerate development, lower production costs, and improve the performance of biologic vaccines and drugs at commercial scales large or small. Since the pandemic, Dyadic has been working to apply its C1 platform toward development of COVID-19 therapeutics.

Earlier this year, Dyadic announced its own C1-based COVID-19 vaccine candidate—DYAI-100—with plans to advance it into a first-in-human Phase I trial during the second half of this year. In late May, Dyadic launched a partnership with India's Syngene International (part of Bangalore-based biotech Biocon) to produce a C1-based COVID-19 vaccine aimed at variants of concern, including the B.1.617.2 (Delta) variant that was first identified in India.

"Given the need for doses in the billion-plus range, this technology could make a real difference," Jason H. Kolbert, head of healthcare research for Dawson James Securities, commented in a May 26 research note. "Given the news that a candidate is now selected and advancing to trials, we are hopeful that the C1 platform will become part of a future COVID vaccine.

"However, we recognize that the landscape is maturing," Kolbert added.

mRNA-based vaccines accounted for nearly all (96%) of the 300 million doses of COVID-19 vaccines administered across the U.S. as of June 5, according to the U.S. Centers for Disease Control and Prevention (CDC). The worldwide percentage of mRNA jabs is not known because not all nations track such data, but is believed to be a majority of the 1.638 billion shots tallied globally by the World Health Organization.

Dyadic is also partnering to develop COVID-19 vaccines and/or boosters for South Korea and Southeast Asia with Medytox, whose Botulinum toxin type A (sold under Meditoxin® and other names) is an alternative to AbbVie-owned Allergan Aesthetics' Botox® (onabotulinimtoxinA)

Dyadic has numerous partnerships with research institutions and companies that include the European Union Zoonotic Anticipation and Preparedness Initiative (ZAPI) Project, the Israel Institute for Biological, Chemical, and Environmental Sciences (IIBR), Sanofi, and the Serum Institute of India, the world's largest vaccine manufacturer by number of doses produced and sold globally.

GEN Edge recently discussed Dyadic's development of C1, and its application against COVID-19, with Mark A. Emalfarb, the company's founder and CEO. (This interview has been lightly edited for clarity.)

GEN Edge: ***How long has Dyadic focused on C1?***

Mark Emalfarb: We came from industrial biotech where we made massive amounts of enzymes at massive scale very affordably. We sold our industrial business to DuPont on December 31, 2015, for $75 million, and refocused to C1 (the cell line) to go into the pharmaceutical industry for animal and human health.

GEN Edge: ***How did Dyadic come to apply its C1 cell line toward zoonotic diseases?***

Emalfarb: We've been involved with zoonotic diseases since 2015. We were involved in Europe in the Zoonose Anticipation and Preparedness Initiative (ZAPI). They had a competition of cell lines—*E.coli*, baculovirus, C1, etc. We won the competition by demonstrating hyperproductivity. We didn't just win by a nose. We won by being 300 times more productive than baculovirus cells.

C1 was more stable, we produced it in three days less time and we didn't have to do any inactivation because we're not putting in viruses like baculovoirus. We saved a step on the downstream, so there's no comparison. To use an insect cell in a pandemic is almost criminal.

The reason I say that is, you'd need billions of doses for people, and you'd need it affordable. Obviously, producing a magnitude times more in a shorter time is going to reduce your cost of goods.

ZAPI took our technology, produced an SBV antigen for Schmallenberg virus, put it into cattle, put it into mice. It worked excellently—challenge studies, efficacy, safety. Then they did it again for RVF, rift valley fever virus. In that particular case, we made 1,200 micrograms/liter in five days, and baculovirus couldn't do it at all. We were on

the goal line before they got to the starting gate. They then did cattle and sheep and mice studies for safety, efficacy, and potency or protection. And it was excellent—full challenge protection and everything else.

Through ZAPI, the Europeans were getting ready for a pandemic way ahead of the pandemic, like five years ahead. We worked with three of the top 20 coronavirus scientists in the world: Albert Osterhaus [PhD, Erasmus University Rotterdam], Berend Jan Bosch [PhD, Utrecht University], and Bart Haagmans [PhD, Erasmus Medical Center].

The crazy thing is, when the pandemic hit, they came to us and said, "Look, we're not getting funding from Europe." We were shocked. The European Union didn't even fund these people to actually solve the problem. And now they're pointing the finger at each other, they're pointing fingers at the pharma companies. I think they just need to look in the mirror and realize they spent the time to get ready, and when D-Day came, they didn't do anything about it.

GEN Edge: ***Dyadic is also partnering with the Israel Institute for Biological Research. What does that program entail, and what has it accomplished?***

Emalfarb: We've been involved with the Israel Institute for Biological Research in a similar plan to get ready for pandemics, combat infectious diseases—in their case also biothreats. We started that program in January 2018, two years ahead of the pandemics.

And in that program, we were doing the exact same thing, creating an improved C1 expression system to be ready for biological threats, pandemics, epidemics. We succeeded in making an enzyme to help combat against sarin and VX gas.

When the pandemic hit, the Israelis, like the Europeans, experienced firsthand the hyperproductivity of C1. They tried yeast and they tried CHO cells. I don't think they even bothered with insect cells because they already knew that would be almost a non-starter. C1 outshined all of them from a productivity standpoint. And then they took it and started moving into animal studies. Just like the Europeans, which proved with SBV and RVF virus safety, efficacy, potency and challenge, they did the same thing with the RBD SARS-CoV-2 for a vaccine.

At Dyadic, we listened to the Israelis and the Europeans and we made the RBD. We made it in two forms: By itself, and with a spy tag which allows you to make these nanoparticles. You use this spy tag, put it on a spy catcher, couple them together, but

we also made the full spike and the full spike with the spy tag. Then we made an RBD Fc as well, and a monoclonal antibody as well from C1. We did all this as a small biotech very rapidly, multiple vaccine candidates that we can provide people, and they can add their own adjuvants to it. We can make them at cGMP, large scale.

GEN Edge: ***What advantages does C1 have over mRNA for COVID-19 vaccines?***

Emalfarb: One of the benefits of C1 is we don't need fancy equipment. We run in standard E.*coli* fermenters, anywhere from one liter to 500,000 liters. We've been there—done that years ago, decades ago, reproduced it multiple times in multiple locations all over the world.

If we can run in a standard *E.coli* fermenter all over the world, you can go in India, China, Asia, Africa, Europe and America and pop this into a standard *E.coli* fermenter. But we can also grow in single-use bioreactors.

GEN Edge: ***Why was Dyadic able to successfully develop C1?***

Emalfarb: One of the benefits of C1 and the several hundred million dollars spent in the industrial biotech sector before we started moving into pharma is that we learned how to engineer it. We learned how to grow it and program it. We learned how to take genes and put them in a site-specific integration—one gene, one copy, same site, reproducible product, and high productivity.

If you take one gene and put it in one spot within seven weeks, we have a stable cell line that can be put into cGMP manufacturing. We can get there very rapidly. But just as importantly, with our cell line we can make billions of doses in a month. If mRNA wants to brag about what they can do it in six weeks and it takes us seven, I think we make up for lost time on the productivity side.

It should have anticipated this was going to be the case when you bring the power of industrial biotech, where we pump out massive amounts of things, compared to pharma, which does small amounts of expensive things too slowly, too expensively. It was obvious with synthetic biology that when you engineer a more efficient cell line, we were going to get to where we are today.

GEN Edge: ***How could C1 help address the world's need for COVID-19 vaccines and drugs?***

Emalfarb: Every day, people are complaining about people getting access to vaccines. And we had the answer, so we were ready. The Europeans got ready. We got ready with them and with the Israelis as well.

GEN Edge: ***In September 2019, shortly before the pandemic, then-President Trump issued Executive Order #13887 (https://www.federalregister.gov/documents/2019/09/24/2019-20804/modernizing-influenza-vaccines-in-the-united-states-to-promote-national-security-and-public-health), designed to promote faster and more scalable manufacturing platforms for influenza vaccines. Why did Dyadic view that Order as potentially helpful to its pandemic development efforts once COVID-19 emerged?***

Emalfarb: When that executive order came out, we felt that we had exactly what that order directed the government to do. We zeroed in on manufacturing capacity, shortages, problems, not being ready for pandemics. We pointed out that we needed to have more efficient cell lines, both cell-based like mRNA and recombinant-based like C1.

They had created this wonderful document just a little too late, because when the pandemic showed up, they didn't have time to actually effectuate making these wonderful cell lines that they know they needed for a pandemic.

Thankfully Moderna was there and Pfizer was there and mRNA was there, because it's making a difference today. It doesn't matter whether it solves the whole world's problem at the moment but it's making an impact in a positive way.

But when it came to recombinant technology, which is the other side of the executive order, we didn't need to develop it. We did it. We did it with the Europeans in ZAPI, and with the Israelis in the IIBR, so we were ready to go when this pandemic hit.

We brought that to the attention of some of the right people, including by the way, writing a letter to [then] Vice President [Michael] Pence on March 11, 2020. It's not that it fell on deaf ears. In fact, every one of the agencies supported the technology, from the FDA from BARDA [the Biomedical Advanced Research and Development Authority], from HHS [the U.S. Department of Health and Human Services]. But when it came to getting a check, we didn't get it.

GEN Edge: ***Why not?***

Emalfarb: The one issue that we hadn't done is that we hadn't been in [clinical trials in] humans yet. If we had been, I think they probably would have funded it. Yet Moderna had never been in man either, so is that a valid excuse? Not in my eyes, but anyway, I'm a little prejudiced towards this situation. I think the data speak for itself.

We have the ability to produce a lot of things for a lot of people because we're agnostic. We have a cell line. It grows quickly, it can be programmed fast, it can produce a lot with very low-cost media at flexible commercial scales, in small fermenters or large all over the world.

GEN Edge: ***What is Dyadic looking for from President Biden?***

Emalfarb: What I'm hoping is that the Biden administration focuses on science first, on data, and takes the opportunity to actually look at again something that's been validated as having the capability.

GEN Edge: ***In March, Dyadic announced a collaboration with South Korea's Medytox to develop COVID-19 vaccines based on C1. What progress have the companies made so far?***

Emalfarb: Medytox got access to C1 in July 2020. They've learned how to grow it so they now have mastered the productivity and the ability to reproduce the fermentation process, and now they just got to go reprogram.

Medytox are the fourth largest provider of botulinum in the world, so they have an incredibly skilled set of genetically engineered scientists, because to engineer a cell to produce botulinum is far more complicated than engineering C1.

So they're going to engineer these cells on their own, create different variants, and move it forward in collaboration with us. We have hands down the fastest, most efficient way to produce recombinant subunit proteins. It's like night and day. People are driving around in a Model T car that they've jerry-rigged and we're driving around in a Ferrari or a Tesla in terms of productivity and speed.

GEN Edge: ***How is Dyadic taking into account the COVID-19 variants as it develops DYAI-100? What will Dyadic do that Pfizer/BioNTech and Moderna didn't as they initially developed their vaccines for the original Wuhan strain?***

Emalfarb: It isn't that Pfizer and Moderna didn't do a great job. They did a great job of getting out a vaccine and getting them out fast that seemed to be effective. Hopefully long-term we don't have any health effects related to that. We don't know, not just because it's mRNA but the full spike has been a question mark in the past, maybe not present or the future.

We made the spike RBD; spike RBD with a spy tag; nanoparticles; the full spike. We even made the full spike with a spy tag to generate nanoparticles. We made the RBD Fc, and we made monoclonal antibodies. We did all this very quickly. Whatever sequence you want to put into a cell, we can do it fast, we can do it efficiently. We can produce it high levels of low cost in microbial fermenters to help really solve the problems of the world in a more efficient way. And more people are coming to us now with generation two or three.

There are all kinds of new gene sequences that people are coming up, new ideas and approaches. Not from the manufacturing. They realize we have a hyper-productive cell, but the cell just makes it more efficient—quicker, faster, cheaper—and the sequence is critical as well. What you put in determines the antigen coming out, whether it's a variant or a whole new approach. And people are now finding that as you do, the second time around usually works better than the first time around. We're open for business to help anybody and everybody that wants to put a gene in and make an antigen or an antibody.

This is an unsustainable model to be able to make all these vaccines and just give them away. The taxpayers are going to have to pay for this somehow—we didn't need to spend $17 billion to solve the problem if we use more efficient ways to do it. Whether it's big pharma, small biotech, governmental agencies, we're here and we work with them all. And not just, by the way, in COVID, but also in traditional antibodies, vaccines therapeutics—bispecifics, trispecifics. We need to make sure that this cell line C1 gets put into labs all over the world, so that we can make health care, affordable and accessible to everybody on the planet.

Scott Gottlieb [MD] said (https://www.fda.gov/news-events/press-announcements/remarks-fda-commissioner-scott-gottlieb-md-prepared-delivery-brookings-institution-release-fdas) when he was FDA Commissioner that while less than 2% of Americans use biologics, they represent 40% of total spending on prescription drugs. That was before COVID, so that was unsustainable. Now it's even worse.

We're happy to apply this. We have many people coming in, many programs in animal and human health, because C1 is also used for animal health—companion animals, chickens, pigs, cattle. Gorillas (https://www.sciencemag.org/news/2021/01/captive-gorillas-test-positive-coronavirus) are getting infected with COVID. Cattle (https://wwwnc.cdc.gov/eid/article/26/12/20-3799_article) and pigs (https://wwwnc.cdc.gov/eid/article/27/1/20-3399_article) can get infected with COVID—where's this all going?

If that's the case, how are we going to make all those vaccines or therapeutics? The world's burning, and we've got to help people, because every week's delay is a week delay that a shot is not getting into somebody in Africa or India or South America.