

Oragenics, Inc. using Genetically Modified Lactococcus Bacteria found in Yogurt and Milk to create Lantibiotics and Prevent Oral Mucositis



Alan F. Joslyn, PhD
President and Chief Executive Officer

Oragenics, Inc.
NYSE American: OGEN
www.oragenics.com

Interview conducted by:
Lynn Fosse, Senior Editor
CEOCFO Magazine

“We have taken a bacteria, a Lactococcus bacteria, that is found in yogurt and milk, and we have inserted the human gene for what is called human trefoil factor into the genome of the bacteria. Then, a patient takes this genetically modified bacteria to prevent their oral mucositis.”
- Alan F. Joslyn, PhD

CEOCFO: *Dr. Joslyn,, what is the premise and concept behind Oragenics, Inc?*

Dr. Joslyn: Oragenics is a biotechnology company located in Tampa, Florida with labs in Alachua, Florida. We actually utilize genetically modified bacteria and either use them to deliver protein therapeutics or use these genetically modified bacteria to make other potential compounds such as antibiotics through a process of synthetic biology.

CEOCFO: *Are genetically modified bacteria commonly used in solutions today?*

Dr. Joslyn: Actually, no. What we tend to read about, generally, are programs and companies that are developing microbiome type treatments for a variety of diseases, which are really blends of different types of bacteria that are already found in your GI tract. For example, we actually take an individual type of a bacteria; we go into the genetic makeup of that bacteria and manipulate it so that it can either deliver a human protein in the case of our oral mucositis product or we improve the bacteria’s own capability to produce a certain type of antibiotic, which is our other research program, lantibiotics.

CEOCFO: *When did you realize this could work?*

Dr. Joslyn: We have known about lantibiotics for a very long time. For example, they were discovered back in the late 1920s, much along the same time frame as penicillin. However, the issue has always been that bacteria never made enough of this type of antibiotic to make it therapeutically useful. Therefore, until now we have been unable to make enough to put lantibiotics into a pill or into a syringe and successfully treat an infection.

It took a lot of understanding and research to figure out how to manipulate the genes of a certain strain of bacteria *Streptococcus mutans* to improve the yields of a fermentation process. It took years and we finally, through this genetic manipulation, figured out what genes to turn on, what genes to turn off and can now, for example, use this genetically modified *Streptococcus mutans* bacteria to produce hundreds

of grams of this brand new class of antibiotics. Some of the knowledge around gene manipulation of bacteria goes back almost one hundred years, but we have not been able to harness the science of it, moving through the process to make them useful therapeutic agents in today's day and age.

CEO CFO: *Is it technology that has helped or is it just plain old brain power?*

Dr. Joslyn: Some of both! For example, our AGO13 program is actually a group of scientists in Belgium figuring out how to take a human gene that we have in our genome and insert it into the gene structure of a bacteria and have the bacteria do the work. It took not only the advancement of technology of how you can cut open genes and put human genes into bacterial genes and have the human protein produced by the bacteria's machinery.

It was coming up with that concept in the beginning to understand that this human gene would make a protein that, for example, regrows the lining of your mouth and that we could use a bacteria essentially as a drug delivery device, but just placing that bacteria in your oral cavity and let it do the work. Therefore, to answer your question, it is really a matter of both the science to conceptualize how we could treat a disease and then having the tools available to us to cut open DNA in a bacteria in a very specific place and put this human gene into that particular place.

CEO CFO: *What are you working on now at Oragenics?*

Dr. Joslyn: What we have in our company are really two separate programs. We have one program that prevents oral mucositis from occurring in patients who have cancer and are receiving chemo toxic treatments for their particular cancer, along with radiation therapy. We are specifically targeting head and neck cancer patients who are receiving, for example, Cisplatin plus radiation therapy to treat their cancer. The byproduct of the treatment of the cancer is the development of these really serious mouth sores that we call oral mucositis. When oral mucositis begins to occur in these patients they develop the inability to eat and drink. It is extremely painful for these patients. Many of them will be receiving opiates. They run the risk of having interruptions in their radiation therapy and their chemotherapy and it is just a bad outcome for patients once they develop this side effect of the chemo-radiation therapy. Therefore, we have taken a bacteria, a Lactococcus bacteria, that is found in yogurt and milk, and we have inserted the human gene for what is called human trefoil factor into the genome of the bacteria. Then, a patient takes this genetically modified bacteria to prevent their oral mucositis.

The patient, three times a day, takes a small amount of a dried powder which is the purified bacteria, and mixes it together with a raspberry flavored solution that we also provide, and this bacteria rehydrates and comes back to life. We have the patient swish it around in their mouth for about thirty to forty five seconds.

This reconstituted bacteria comes back to life and sticks to the inside of the lining off your mouth after you have swished it all around. It immediately begins to produce this protein called trefoil factor 1. What is so important about trefoil factor 1 is that it is actually a protein that your body produces all the time throughout the day. It is released from your salivary glands and it is always floating around in your mouth in small

concentrations. It is responsible for initiating the process for rapidly regrowing the lining of your mouth. If you have ever taken a sip of a hot cup of coffee or tea, or bitten down on a piece of hot food like a slice of pizza and you burned the roof of your mouth, generally by the next day that rough feeling, the pain, is gone. It was trefoil factor along with another protein called mucin that actually went and bound into that injured area and started a whole process to initiate regrowth of the lining of your mouth really, really quickly. Through this bacteria we are giving you back a much higher concentration of the protein than your body can generate naturally to regenerate the lining of your mouth. Why this is important is that in a cancer patient what happens is that the chemo radiation therapy begins to eat away at the lining of that mouth. We are trying to essentially stay ahead of the bad effects of the chemo by going ahead and resupplying much higher concentrations of that trefoil factor through the use of that bacteria. Patients this therapy on the very first day of their chemotherapy and they do this rinse three times a day for nine weeks, through their entire course of chemotherapy.

CEOCFO: *Where are you today with AGO13? What have you learned so far that surprised you?*

Dr. Joslyn: We have learned a couple of things. One, to answer your first question, we are actively enrolling head and neck cancer patients in this clinical trial. The clinical trial is being conducted in four different countries; the United States, the United Kingdom, Belgium and Germany. We have a number of health authorities around the world that are helping us with the whole process of advancing this particular program. We have learned that so far the side effects that we see are minimal and are what we would have expected to see in cancer patients receiving chemotherapy. Because this is a commonplace bacteria making a human protein there really have not been any side effects that you could speak to, other than what a cancer patient receiving, for example, Cisplatin experiences, such as low red blood cells, an occasional fever, some nausea and vomiting, but not anything that is specific to using a bacteria to actually treat an existing clinical condition. It is that aspect of this whole process that is unique, because we do not really think of bacteria in a general sense of being helpful, with the exception of maybe taking a probiotic for people who are really into the health and maintaining their microbiome.

Other than taking probiotics like that, we do not really think of bacteria as helping us treat disease. This is an example of us being able to do exactly that and to do it safely. Therefore, that is, I think, probably the biggest finding, at least so far. We will see how well it works here in a few months.

CEOCFO: *What has been the interest from the medical community that is aware of what you are doing?*

Dr. Joslyn: The interest from the medical community has been very positive because of a couple of different things. One is that it is an incredibly unique approach to treating disease, just because you are using a bacteria that is a carrier for creation of a human protein. However, the science is kind of new and sexy for investigators, for example, participating in our clinical trials. They have not seen anything like this before. What they usually do to treat oral mucositis is very involved with injections and other types of rinses and mucosal “tape” over the sores. This is something that is very unique and very intriguing to those investigators that are participating in our program.

The other thing is the simplicity of this. That is because all I do is grow this genetically modified bacteria in a giant fermenter. Then I go ahead and I collect all of that grown bacteria and I rinse it off and I freeze it and I put it in little vials. Therefore, it is incredibly simple as a method to deliver proteins to humans. On top of that it is extremely cost effective, because I am not trying to purify proteins and put them into vials and have to freeze them and all of the necessary steps to keep those proteins stable in a vial. I do not have to do any of that because I am using a bacteria, essentially as mini-factory to make the protein right where it is needed. It is the uniqueness of this science, coupled with it's simplicity, that has intrigued the investigators and people who know about this program so far.

CEOCFO: What else are you working on? What else is new?

Dr. Joslyn: We have a brand new class of antibiotics that were actually first discovered back in the late 1920s. They are called lantibiotics because they have special amino acids in the structure of these antibiotics. They are large proteins that are produced by certain strains of bacteria in our microbiome. We have identified this class of antibiotic, which is made by a non-pathogenic strain of *Streptococcus mutans*. It just kind of sits in our microbiome. In the microbiome each little bacteria strain has their own colony where they set up shop in the microbiome. It will be next to another colony of another bacteria and so on. What happens is that certain colonies, like these streptococcus strains, will put out tiny amounts of this lantibiotic, which is an extremely potent antibiotic, and it prevents their neighbors from coming into their particular space within the microbiome. It is kind of a regulator of bacterial overgrowth within the microbiome. Therefore, we know that they are very potent antibiotics.

In addition to that, we also know that if these streptococcus bacteria make too much of this antibiotic they will essentially kill themselves, because the concentration of the antibiotic would be too high within their little area in the microbiome. These streptococcus bacteria have very specialized genes which regulate production of the lantibiotic and only allow the bacteria to produce tiny amounts of the antibiotic. The easiest way to think about it is a skunk. For example, a skunk sits in hole, predators come nearby, and they put out a tiny spritz of the sulfur smell that we all know so well, and all of a sudden all the animals scatter. It is the same concept in the microbiome with lantibiotics, that this tiny little amount of antibiotic is put out there and all the other bacteria stop trying to approach in that streptococcus strain's space within the microbiome. How did we turn them into therapeutics is really the key question. Over the last several years we tried to improve the amount of lantibiotic that is produced by improving how you ferment bacteria to get them to produce more of these potent antibiotics. We were never able to get up beyond just a couple of milligrams of production in a fermentation vessel after years and years of research.

We actually began to work with a company called Intrexon back in 2012. What we did working with Intrexon is we went into the genome of the *Streptococcus mutans* strain and we found the regulator gene that regulates production of these lantibiotics and we turned it off, so that it no longer regulates production. Therefore, we now have a genetically modified strain of *Streptococcus mutans* that we put into a fermentation vessel at our contract manufacturing facility where they are able to run fifteen hundred meter size vessels, kind of what you would see in a craft

beer distillery, and we are able to make hundreds of grams now per manufacturing run to now do all of the toxicology and all of the microbiology that is needed to move this into our first clinical trial in humans. We are hoping that that happens in 2020 at some point.

CEO CFO: *What is your relationship with the University of Florida?*

Dr. Joslyn: Oragenics is a spin out of the University of Florida. In fact, some of our early patent work with these lantibiotics was licensed from that early work that was performed at the University of Florida. The founder of the company is a former professor of dentistry at the University of Florida, Dr. Jeffrey Hillman. One of his Postdoctoral fellows is actually our head scientist, Dr. Martin Handfield. Therefore, we have a very close working relationship with the University of Florida for our lantibiotics program.

CEO CFO: *Would you tell us about your current collaboration with Florida International University?*

Dr. Joslyn: It is really interesting, because Florida International University and Oragenics has just signed a research agreement where we are using their bio physics department to help us understand how our lantibiotics actually work as antibiotics, mechanistically. This collaboration will help us develop the next generation of antibiotics to treat very specialized infections. For example, now we know additional pieces of information that have not quite been published yet on how lantibiotics bind to the bacterial cell wall foundation called lipid II.

Every single bacteria strain has lipid II anchors for their cell walls. Lantibiotics bind to this particular foundational component of a bacteria's cell wall in a very unique way. They actually work different than other antibiotics to prevent bacteria from growing. Therefore, the work with Florida International University is twofold. One; to understand what these additional mechanisms of action are and then two; can we go into our library of approximately seven hundred different compounds and identify unique characteristics to be able to bring forward into very unique infections. Whether they be gram positive infections or gram negative infections, we would be able to use this library that we have with all of these different structural variations of lantibiotics and move forward and develop unique antibiotics, depending on the type of infection that you have.

CEO CFO: *Why pay attention to Oragenics, Inc?*

Dr. Joslyn: At Oragenics, right now our lead program, AGO13, is well into advanced clinical trials. We are approaching half way complete in our lead clinical trial in prevention of oral mucositis, which is a huge unmet need even today, around the world in patients who are receiving chemotherapy to treat their cancers. Therefore, there is this great potential through this particular product commercially. Now, we do not really have the intent to go out and build a sales force ourselves, because we are really a research and drug development oriented biotech.

We will be looking to do partnerships with other companies who would bring AGO13 for oral mucositis forward and commercialize the product in licensing deals, wherever those deals could be done around the world. The money that flows into the company from those licensing deals from our most advanced programs are what is going to fuel the expansion of our research capabilities in infectious disease. I say infectious disease, because you never know where that lantibiotic library will lead us or what

other opportunities will be put in front of us because of our knowledge in infectious disease. This is where, from a scientific perspective, we work with highly unique types of compounds as they relate to manipulation of bacteria genes and from investor perspective we have near term milestones that are really true value inflection points happening with the next year, that should be of interest to potential investors in the biotech space.

Executive BIO:

ALAN JOSLYN, PhD

Dr. Joslyn is currently the CEO and President of Oragenics. He previously was a co-founder of Lazarus Pharmaceuticals. Previously, in association with Care Capital, a life sciences venture capital firm, he was Chief Executive Officer of Sentinella Pharmaceuticals, a privately held antibiotic company and CEO of Edusa Pharmaceuticals, a privately held gastroenterology company. Prior to his association with Care Capital he served as the President and Chief Executive Officer of Mt. Cook Pharma from 2007 to 2009, and as Senior Vice President of Research & Development at Penwest Pharmaceuticals a specialty pharmaceutical company from 2004 to 2007. From 1995 to 2004, Dr. Joslyn held a number of leadership drug development positions within Johnson & Johnson. Before joining Johnson & Johnson, Dr. Joslyn was engaged in gastroenterology and oncology clinical research at Glaxo from 1988 to 1995. Dr. Joslyn also sits on the board of Synergy Pharmaceuticals, a publically traded gastroenterology company.

Dr. Joslyn received his B.S. in Medicinal Chemistry, B.A. in Biology and Ph.D. in Biochemical Pharmacology from the State University of New York at Buffalo.

