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Q&A with Dr. Isaac Cohen, CEO of Iaterion Pharmaceutical, Inc. Developing Novel Nuclear Receptors that is showing promise in the Fight against Cancer, Diabetes, Cardiovascular, Autoimmune, Metabolic Disorders and in treating Menopause

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CEOCFO: ***Dr. Cohen, what is the concept behind Iaterion Pharmaceutical, Inc?***
Dr. Cohen: We are following up on a discovery that was made by our Chief Scientific Officer, Dr. Leitman, of a new set of compounds that bind to nuclear receptors concurrently or simultaneously with the natural hormone and reprograms its effects. We call them coligands or nuclear receptor reprogramming agents. What they do is, unlike other drugs that were used as either agonists or antagonists; they actually change the course of the natural hormone in order to provide either a different function that was not there earlier or promote and restore normal function without some of the toxicities that the hormone generally generates. What we see is that when those compounds are applied simultaneously, for example, when you give them with estrogen, instead of causing cell proliferation which forms breast cancer and uterine cancer, they actually inhibit that process.

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CEOCFO: ***What are you replacing or enhancing? How are we treating some of the problems now that you can treat in a better way?***
Dr. Cohen: For example, in menopausal hormone therapy, right now if we give estrogen alone it results in uterine cancer. What people did was add progestin or progesterone to estrogen in order to abate the uterine cancer effect, but with the combination there is still an increase in the breast cancer effect. Therefore, although we mitigated one of the issues we are not able to mitigate the other issue. The other thing that people did was to add a selective estrogen receptor modulator to estrogen, drugs like tamoxifen. The selective estrogen receptor modulator competes with estrogen on the binding, so you have to use much more of it in comparison to the estrogen. What it results in is a mixed effect that sometimes it behaves like estrogen and sometimes it does not. For instance, on its own it increases hot flashes, so you have to give estrogen to mitigate that, but still there is the risk of clotting events and potentially stroke and other serious adverse events when you use it long term. Therefore, in the past decade or so women first dropped using hormone therapy because of the risks associated with it. Not only that, they are not able to reap the benefit of long term use of hormone therapies, which are the prevention of Type II Diabetes, the prevention of osteoporosis, reduction in weight and fat redistribution. What we are doing is trying to find a way where we can use hormone therapy for long term with a

completely new set of drugs that have no competition, but a change in how the natural hormone works, so you need much less of the hormone, number one, and number two; you can redirect it in pathways that, so far, we were able to mitigate all those risks. Of course, we still have to do the human clinical trials in order to prove that beyond the animal models.

CEOCFO: ***What is happening with your receptor when it is interacting with the hormone?***
Dr. Cohen: In simple terms, when estrogen binds to the hormone receptor it regulates about eight hundred genes. Some of them are genes that are important for human life at different stages that when you enhance them or inhibit them during menopause they can result in both positive and negative clinical effects. When you give our Coligand alone on the estrogen receptor it does not regulate the estrogen receptor. It does not turn genes on or off, so it is not functional on its own. However, when you give them together, all of a sudden it regulates thirteen hundred genes. Therefore, our compound plus estrogen regulates thirteen hundred genes. Only five hundred of them are common to the estrogen receptor. However, some of them are in the opposite direction. For instance, some genes that cause cell proliferation that will result in cancer are oppositely regulated. That means that instead of being activated they are inhibited or instead of being inhibited they are activated. That is how we think we will be able to really reprogram or change the direction in which estrogen works in the body. We believe we will be able to use the co-ligand + estrogen combination for near term effects like prevention of hot flashes, mood swings, night sweats, and changes in urogenital atrophy, which is vaginal dryness and difficulty in urination in early menopause and also the long term effects, like osteoporosis, Type II Diabetes and so on, without the risks of cancer.

CEOCFO: ***What are you working on specifically today?***
Dr. Cohen: We are still finalizing our preclinical package and we hope that within two years we will be able to enter the clinic with our drug combination, the Coligand plus estrogen. We are doing some confirmation structural studies to show what the precise mechanism. This is a bit complicated biology, because what we have to do is show how exactly the compounds are fitting in the binding pockets on the receptor as well as looking at what the downstream effects are of the machinery of the cell that results in this change. This is kind of a new idea in biology, that you can actually use two ligands with one receptor working in tandem, rather than one against the other.

CEOCFO: ***What gives you the confidence in your gut that this is going to work? From past experience and your history, how do you know?***
Dr. Cohen: This is a very, very good question! It has multiple layers of confidence. First of all, estrogen has a seventy year history with a lot of clinical research, both controlled and uncontrolled. Some of the largest human double blind, placebo controlled trials were carried with hormone therapy. The Women's Health Initiative is one of them. Therefore, we know a lot about how estrogen and how hormones effect the female body in the menopausal transition and in the long term after that when it is used for many years. We have that background when we assess what we are doing. The same is with the selective estrogen receptor modulators in breast cancer and osteoporosis that have been used for over twenty years. This is relatively a mature area of science and clinical science. So we have a lot of background in understanding how those work. Our new concept with the coligands actually came from asking more of epidemiological or anthropological questions, which is why is there, in different societies, that consume different nutritional products, significantly less breast cancer. This is mainly in Asian countries. Also, why is it that when Asian women immigrate to the West, and the second generation adopts Western diets, they get a significantly increased risk of breast of cancer similar to that of white Caucasians. We looked at some compounds that are in those diets and those were unusual compounds. A lot of people looked at flavinoids, like soy isoflavones, and they looked at either a direct effect like estrogen or an antagonistic effect. What we saw, which was very curious, is when given together with some of those nutritional compounds, we could see that there is a synergy with the estrogens and were pondering why that is. Now about five years of work we were able to delineate that there is not only xeno-estrogens or phytoestrogens coming from food, there are also those compounds that have that second layer, which is very different, that actually work in tandem with the natural receptor, but in a different fashion. They are not either agonist or antagonist to the receptor and they do not compete on the binding. They actually enhance the binding of the natural hormone. It is a very different concept which helps explain why people in those counties have had significantly less risks associated with the menopausal transition, especially in relation to cancer. Therefore, we have the confidence that both the history and knowledge that we have form estrogen and the selective estrogen receptor modulator used in medicine, as well as the epidemiological difference with Asian countries, and then our discovery of how that difference is really mitigated from a biochemical point of view. In summary, we have clinical science, epidemiological science, toxicology and molecular biology to support our development.

CEOCFO: ***Development is always expensive. Where do you stand in terms of funding?***
Dr. Cohen: So far, we have worked with NIH grants. We are now applying for a much larger NIH grant. In tandem, probably somewhere near January of February, we believe we will have enough data to really approach venture capitals

and go to pharmaceutical partners. We have practically utilized both academic and SBIR mechanisms to get funding. The reason why we did not go to investors at this stage is really multifold. One is that it is really difficult to get money for early stage development right now. The field of women's health is very much underserved by investors in the pharmaceutical industry. That is something you should definitely investigate and write a report about. There is little to no investment in women's health and there is no interest within pharmaceutical companies concerning women's health. The history of The Women's Health Initiative and drop of about eighty percent in use of menopausal hormone therapy led to a financial and regulatory concern when you are trying to develop something for women in that age group. Therefore, we felt we really should not go to investors unless we have a complete package, that is so compelling, and gives us a far greater chance to secure funding.

CEOCFO: ***Why pay attention to Iaterion Pharmaceutical? Why is the company and the concept important?***
Dr. Cohen: The discovery of the reprogramming agent could translate to, not only the estrogen receptor, but also to other receptors. Those are critical for both men's and women's health like the glucocorticoid receptor (GR), like the androgen receptor and there are several others. You can mitigate many aging diseases that are now critically pursued by major pharmaceuticals, but with strategies that are not preventative, they are treatment oriented. What we are doing is really potentially effecting the whole aging process in a very different way, whereby addressing some symptomatic changes can also lead to addressing the downstream diseases that occur during the aging process. Therefore, I think that not only do we have a very important discovery scientifically that can translate to various other fields, but it can translate to major change in public health and public expenditure. With the current debates, however you fall on that, with the rising expense of healthcare, it will be really important to start investing in those long term preventative measures, because otherwise we will not be able to afford healthcare. That is becoming more and more evident. Therefore, the strategy of pharmaceutical companies, to focus only on expensive drugs for very small orphan indications, has to change and that has to be really in tandem with public interest to try to not only to control the cost, but also affect health in a different way, which is more preventative. That requires a shift in thinking and I think we are at the forefront of that.