

Developing Therapies that Modulate Epigenetic Factors and Restore Normal Gene Expression in Mutated Cells, Imago BioSciences, Inc. is providing hope to Patients with Bone Marrow Cancers



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- Dr. Hugh Young Rienhoff, Jr.

CEOCFO: *Dr. Rienhoff, the first thing I see on the Imago BioSciences Inc site is, “Transforming medicine by translating science.” How so? What is the idea behind the company?*

Dr. Rienhoff: The original idea was that we wanted to be a science driven company in the sense that we had a solid foundation of scientific bench work that would support what you might call the clinical pieces, meaning that the various models and mechanisms that we understood would be those that would translate into some kind of disease modification or amelioration. That was the basic principal behind that statement.

CEOCFO: *What are you working on today? How does this translate day to day?*

Dr. Rienhoff: We are working in a family of diseases that are bone marrow cancers of sorts with varying degrees of aggressiveness. Our first clinical trials were involved in acute myeloid leukemia and high risk myelodysplastic syndrome, which are two myeloid types of cancer or pre-cancer in the case of myelodysplastic syndrome. There are a host of other less aggressive myeloid diseases, although many of them still ultimately result in significant morbidity and even mortality. One of those families of diseases is the myeloproliferative neoplasms, once called myeloproliferative diseases, because there is a proliferative or cell growing component to those, but not as aggressive as leukemia, but ultimately having some of the same effects leading to bone marrow failure. Currently, we are conducting a clinical trial in patients with myelofibrosis, one of the myeloproliferative neoplasms or so called MPM. Myelofibrosis is what it sounds like; fibrosis in the bone marrow that over time excludes the formation of normal blood cells, so the marrow gets crowded out. You can think of it as a chronic inflammatory disease in which there is progressive scarring of the bone marrow, which makes the bone marrow an inhospitable place for blood cells to develop and mature.

CEOCFO: *What is the science behind your technology?*

Dr. Rienhoff: Our drug targets an enzyme that regulates gene expression in blood cells. This enzyme is critical to the development of

mature cells in the marrow. By carefully inhibiting the enzyme, one can regulate the activity of cells in the bone marrow. Patients with myelofibrosis have acquired mutations that activate specific bone marrow cells called megakaryocytes, the cells that make platelets. Our drug, IMG-7289, slows down the production of megakaryocytes and the various growth factors and inflammatory proteins those cells make. The effect is that in the short term, patients feel better. However, our long term goal, our dream, is to have an impact on the national history of the disease, to increase overall survival. Can the drug slow the progression of the disease in patients enhancing longevity as it did in mice? That question remains to be answered.

CEOFCO: *What is happening with your drug? What is happening in the cell to shut down the receptiveness? What is the interaction?*

Dr. Rienhoff: Our drug actually interacts with an enzyme that is in the nucleus and that enzyme is responsible for modifying some of the proteins that regulate the transcription of these genes. It is a so-called epigenetic enzyme, in that it modifies the proteins that are bound to DNA, but it does not modify DNA itself. That is why it is called epigenetic. It is the proteins that assemble around DNA that really regulate whether a gene is expressed or not expressed. In this particular case, the enzyme is regulating the expression of growth factor expression and inflammatory hormones that are responsible for the signs and symptoms of myelofibrosis. By inhibiting the enzyme with our drug the expression of those genes goes down.

CEOFCO: *Do we know why it works? Does it matter if we know why as long as it does?*

Dr. Rienhoff: That is always a difficult question to answer. Do we know how gravity works? We have a pretty good sense of what is it all about and we have a lot of fundamental laws about Newton's second law, $F=MA$ and things like that. However, I do not think that we really, truly understand what is responsible for the force of gravity. I would say that is always true in biology, too. There is always another level that we do not understand. In this particular case we have a molecular understanding of how our target enzyme, called lysine-specific demethylase, or LSD1, binds to specific transcription factors that are bound to DNA, at very specific sites in the genome. However, the details of all of that are fuzzy. The actual mechanisms by which all of these proteins interact, I would say, is still a major unknown and not just for the enzyme that we study, but for many of these enzymes. That is because these protein complexes are incredibly complicated and very cell specific and dependent of the previous life of that cell. Therefore, I think there is a working understanding of what are doing but there is more to know. We are inhibiting an enzyme that regulates the methylation of histones, but beyond that I would say that the molecular details are a little bit fuzzier.

CEOFCO: *What have you learned so far?*

Dr. Rienhoff: Maybe one of the most important things that we have learned is that you can inhibit this enzyme safely and almost all the effects of inhibiting the enzyme are manifest in bone marrow cells and not anywhere else in the body. I think that is a majorly important observation, because there are many epigenetic targets in the nucleus, but they are functioning in many, many different types of cells; in the brain, the skin, the gut and the heart. In our case, it looks as though LSD1 is principally acting in the adult in the bone marrow cells.

Therefore, inhibition of the enzyme has so far a relatively favorable safety profile in animals and patients.

The other thing is that we were a little bit surprised to learn is how effective regulation of inflammatory hormones can be. Our empirical observation is that the patients with myelofibrosis feel better when taking the drug. I think that five years ago you would not have guessed that this would have happened. I do not think it was obvious that inhibiting the enzyme would have this kind of profound of effect on inflammation.

CEOCFO: *Would you tell us about your recent funding?*

Dr. Rienhoff: We were lucky to have a very capable venture capitalist named Dr. Dina Chaya from Omega take the lead. She did an extraordinary amount of due diligence, and it was her commitment and perseverance that deftly led the other investors to the close. She will bring to the board that same discipline. The other important factor was the current investors who committed to half of the financing. Without their on-going commitment to the company and its mission, there would be nothing.

CEOCFO: *What has been the interest from the medical community or at least the people who are aware of what you are doing?*

Dr. Rienhoff: I would say that in the myelofibrosis world, the enthusiasm is growing! Three years ago, when we showed people our animal data I think there was a healthy degree of skepticism that any mouse work would have a high degree of translatability to humans. However, now that we have treated patients and able to show that data to these very same clinicians, they have embraced the program. More gratifying in some ways than a nod from academics, is the enthusiasm the patients have shown and expressed to their fellow patients among patient groups about their experience being in the clinical trial. That has been particularly satisfying.

CEOCFO: *Is it relatively easy to get people for clinical trials in this area?*

Dr. Rienhoff: That is a great question! I would say that there is definitely competition for patients. I think some of that is because the current standard of care has been coupled with other drugs and there must be at least ten or fifteen or twenty studies where they take the standard of care, the one drug that is approved and are adding things to it. That has consumed a lot of the available patients who are not doing well on the standard of care alone. Therefore, I would say it is challenging, but not impossible. How effective we are at recruiting patients into the study will be partially based on patient enthusiasm, the desire to be in these studies. Secondly, the personal experience our investigators have with the drug and their growing enthusiasm for it will move them to enroll more patients. Those investigators that have a clear understanding of the shortcomings of the current standard and care and are willing to think beyond small incremental improvements in care are those that will embrace a drug such as ours that represents a distinctly different treatment paradigm.

CEOCFO: *What is the plan for the next year or so and then what is the plan overall as you continue to work in some different arenas?*

Dr. Rienhoff: Over the next year we will be expanding our Phase II study to include European countries and the UK in addition to more US sites. The goal is to fully understand how to use IMG-7289 for the

treatment of myelofibrosis. We will also start a study in patients with essential thrombocythemia and polycythemia. Those are two related MPN disorders where we think this drug will also be effective for some of the same reasons it is effective in myelofibrosis. Then there are a host of other studies in indications explored by individual clinical investigators. Over the next eighteen months, we could expect to see several of those studies initiated. We also have another program with a different compound we would like to use for some other non-malignant hematologic diseases.

CEOCFO: *From both sides, investment and healthcare, why pay attention to Imago BioSciences Inc?*

Dr. Rienhoff: Imago has a very deep focus on diseases of the blood. We have a drug that targets an enzyme not being targeted for these specific diseases by anyone else, and yet the drug is showing the kind of clinical results that could make this the standard of care in myeloproliferative neoplasms. In combination with other agents, there is a real possibility our drug could manage much more difficult diseases, like acute myeloid leukemia and even some solid tumors. We have been at this for seven years, almost to the day and have seen this program really make progress.

Much of drug discovery is predicated on the target you choose and then the molecule you elect to take into the clinic and then finally the disease that you hope to modify. It is not always in that order. Sometimes you pick a disease and you think you have got the right target and then you make a drug. In our case, we picked a target, we thought we knew about the disease that we wanted to go after and we developed a terrific inhibitor. However, we are finding that there are other opportunities that were not apparent when we first started. I think that is one of the most important things about drug development in general, which is to keep an open mind about what is the best use of the drug. It may not be what you originally thought. At Imago, we have been diligent about keeping our minds open and as a consequence these new opportunities made themselves available to us. I consider ourselves lucky in that regard.

