Maria Millan of The California Institute for Regenerative Medicine

Hall T Martin: [00:00:04] This is the Investor Connect Podcast Program, I'm Hall T Martin. I'm the host of the show in which we interview angel investors, venture capital, family offices, private equity, and many other investors for early-stage and growth companies. I hope you enjoy this episode.

Hall T Martin: [00:00:23] Well hello. This is Hall Martin with Investor Connect. Today we're here with Maria Millan, President and CEO of the California Institute for Regenerative Medicine called CIRM. CIRM is California's stem cell agency. Its mission is to accelerate stem cell treatments to patients with unmet medical needs by funding promising research in California. Maria, thank you for joining us.

Maria Millan: [00:00:43] Thank you, Hall.

Hall T Martin: [00:00:43] Can you tell us a little bit about your background? What did you do before CIRM?

Maria Millan: [00:00:48] So, I actually started off as a transplant surgeon in academia and I was always involved in research as well as in innovative solutions to healthcare. And, just recently - not that recently, it seems like just yesterday - but I did join the regenerative medicine sector because of the promise of the science and saw that it was a field that would require quite a bit to be built up in order to get the science out to patients. So, that was kind of a natural extension of what I did as a transplant surgeon in replacing organs that were damaged and treating life-threatening conditions, to now the novel field that's based on stem cell biology.

Hall T Martin: [00:01:36] So, what excites you right now about stem cell biology?

Maria Millan: [00:01:39] Well, I think we really are embarking on a new era because of the field of stem cell, regenerative medicine, cell gene therapy, precision medicine, all these words that have been used together and interchangeably, where we can develop definitive treatments for conditions for which currently there either is no cure or effective

treatment, or conditions that are just chronic and only have some symptomatic relief potentially but don't really impact the long-term effects of the disease.

Hall T Martin: [00:02:19] Well, great. So, we have a lot of investors that listen to the show and they're always trying to figure out how to invest in these great opportunities. What's your advice for people investing in startups in this sector that you see?

Maria Millan: [00:02:31] One of the things, the major kind of lesson - and I'll give a little bit of detail in terms of what I mean by this lesson - is that you just can't sidestep the biology and solid science, especially in the field of regenerative medicine, because the power of these type of products is it's actually entirely based on the biology and as opposed to kind of some of the chemistry-based and approaches in terms of the classical drug discovery where you kind of screen, you know, thousands of thousands of compounds, for instance, to see a potential effect and follow that, what happens with regenerative medicine products is, you know what you're targeting, for instance, a biology that you need to replace or fix and then you develop the product for that. And so, because it's entirely dependent on that, I would highly recommend that in the due diligence that investors definitely bring in the expertise to evaluate how real and how solid the data is to support their investment into the product. If I may, I'd like to describe how CIRM does that. CIRM, since it was formed, has funded over 1,000 programs and actually has funded 64 clinical trials and first-in-human clinical trials with these novel cell and gene therapy approaches. For conditions like Lou Gehrig's disease, diabetes, and most prominently severe combined immunodeficiency - also called bubble baby disease - you may recall that, a movie way back with John Travolta, where he was born without an immune system, and that's a really powerful example of where the biology is key, because in bubble baby disease, there is a lack of an immune system, and with several of our trials and then one specifically that's furthest along with ADA-SCID, the missing enzyme called ADA is replaced by gene therapy into the blood stem cells that are harvested under FDA-guided clinical trials and put back into the patient and these correctives stem cells give rise to the immune system. And the thing about that is you could actually measure that it works. You can measure corrected ADA because you can measure the enzyme, you can see immune cells where there weren't, and then you can correlate that with the efficacy. And so, 50 patients have already shown reversal of their disease with this approach, they were babies when they were transplanted. So, it's a really powerful example of why the biology matters and it can't just be a lot of kind of

promise. So, big advice I'd have is, if it looks too good to be true, it probably is, but counter that with the idea that actually regenerative medicine is offering real solutions that's evidence-based that actually are giving such dramatic effects. So, to distinguish the too-good-to-be-true and it really isn't, versus it-may-seem-too-good-to-be-true but it really could do something, is based on kind of a scientific due diligence. Another kind of area that is a major, I would say hurdle, is the manufacture of these types of products because these are very complex products, it's a new field. So, I think that an important thing for investors to look at is how solid is their path forward to bringing this toward commercialization? How scalable is it? How strong is their plan to transfer this out of the early-stage development and clinical trials toward the larger - not necessarily that large for regenerative medicine - toward the definitive trials, I should say, because there is a lot of potential there and a lot of excitement because the return on investment could be major in terms of financially an impact on health.

Hall T Martin: [00:06:38] So, what's your advice for startups to do that? It seems like there's a tremendous amount of biology here, lots of clinical trials. How do they prepare for that?

Maria Millan: [00:06:47] So, I just would like to kind of backtrack a little bit and just highlight that many of these programs, some of them have already made their way toward later stages, and I can give some examples of some of the programs that we funded at the bench then they spun out. We actually, 45 companies have spun out of CIRM-funded programs and there have been three IPOs that had occurred after CIRM had funded these programs initially. But, so the advice is that often these promising projects start in academia, and so, that is kind of the starting point and the home for many of these programs until often they are in Phase I clinical trials. So, the investors and then the management team who are starting up these companies need to be working with academia as well as then adapting it and scaling it toward their industry standards and getting it toward commercialization. So, the earlier that there's at least some familiarity with the technology and interaction with potential investments, we would highly encourage that. In fact, at CIRM, we have a program called the Industry Alliance Program where we help kind of broker that interaction between the academic teams and potential investors as well as other potential partners, that would be really key in terms of bringing their product forward and our IP partners include a variety of folks, including venture capital, like _____ Also, therapeutics companies like Novo

Nordisk, Bayer, BlueRock Therapeutics, which is an early-stage regenerative medicine company. Even incubator type entities such as ElevateBio, which was recently formed. So, we have industry alliance partners, but even outside of that, we've been really, the way we fund encourages our investigators that we de-risk early on by funding the science to find partners. So, one of the programs that has recently been acquired by Gilead started in the lab at Stanford on an idea that was initially so new that it was something that wasn't even getting funding by the NIH in the academic labs. And Irv Weissman, who's the scientist and his collaborator is Marcelle, just got CIRM funding, were able to bring this to the first-in-human trial, which CIRM funded, spun out a company called FortySeven Inc. FortySeven Inc. was also partnered with CIRM to support the early-stage trials, and then they were just acquired by Gilead this past year for $4.9 billion and that particular product did _____ achieve breakthrough therapy, so____designation. So, that's one of the examples out of many. Some of the programs that we funded in the very, very early stages, in the discovery stage, made their way through their own to later going and being acquired and now are marketed by Celgene, for instance. So, there are just different paths to get there. So CIRM, as an entity, I should say, was formed in 2004 by a state bond initiative to build a new field. At that time, stem cell sciences wasn't really a really solid field that wasn't the type of area of research even that people could get funding in, so CIRM was formed in 2004. Since then, not only has funded the research program, but created a funding model that takes it all the way through from basic translational to clinical, through our funding mechanism and providing advisory as well as infrastructure programs that we also fund to really give these programs a chance in a tough field, in a new field.

Hall T Martin: [00:10:56] Well, great. So, let's talk about the industry for a moment. How do you see it evolving at this stage?

Maria Millan: [00:11:03] I think we're in the beginning of a very exciting growth phase, just to let you, even with the CIRM experience. Five years ago, we could count maybe in the hundreds of millions, at most, of industry investment into the space, and now our cumulative is over $9.3 billion of partnership and investments into our portfolio programs and that's only of those that are publicly, that we track that are directly related to things we touched just before. But, so I think that the effect of that is even greater. So, there is a huge uptake now, it doesn't mean that it's totally without risk, obviously, so, the science still needs to be worked out, the early-stage development still needs to be

worked out, we need more specialized infrastructure in manufacturing and ancillary-type infrastructure needs to get these products toward commercialization.

Hall T Martin: [00:11:56] So, what role does stem cell research have in the COVID economy? How are stem cells being used in this particular case?

Maria Millan: [00:12:05] Oh, thank you for that question. So, in March of this year, when we were all adjusting to the COVID crisis and companies and labs were switching to remote work, our scientists and our team had identified that some of the science and some of the programs that we'd already had underway, could be relevant to the global effort to find solutions to the viral epidemic. And because of that, we, our board approved for us to allocate funds to taking these peer-review approach to identifying COVID programs and since then we've funded three clinical trials in the space, including stem-cell-derived NK cells which is a type of immune cell that is used to target the virus itself, a trial called _____which already had some scientific basis for showing that it could impact the lung damage caused by COVID - so-called ARDS - that led patients in the ICU on a ventilator. And the third program is something that's related to what people are now very aware of, the convalescent plasma. At that time we funded that in April, the convalescent plasma programs through the Mayo Clinic, et cetera, were just increasing and this program seeks to identify what the active ingredient is in the convalescent plasma for downstream like antibody therapies and candidates. Our earlier-stage programs are utilizing stem cells and stem cell models to identify new antivirals, as well as new vaccine approaches toward COVID. So, in a very, very short period of time, because of the funding model, the acceleration model we had in place, and because of the scientific community, we were able to deploy this and get 17 programs going within three months.

Hall T Martin: [00:14:08] So, what do you think is the biggest change we're going to see coming up?

Maria Millan: [00:14:12] I think that what we're going to see is, you probably know that there's a lot of excitement in terms of these novel platforms in the CAR-T therapies. So, they're cell therapies that are specifically geared toward attacking cancer. So, it's a cell therapy that is able to treat leukemias that were resistant to chemotherapy by having engineered on these immune cells, receptors that essentially seek and destroy the

cancer cells. So, the results have been remarkable and those products are in the marketplace. So the first two are out there by Gilead and Novartis and others are following. There also have been programs in gene therapy for correction. You may have heard of spinal muscular atrophy, which is a crippling disease babies are born with, where they continue to lose their muscular function because of degeneration. So, there is a gene therapy that was developed by Avexis and acquired by Novartis that now is out in the marketplace for these babies with this fatal neurodegenerative disease. And then the fourth that actually was approved before that was developed by Spark Therapeutics, which was to a blinding eye disease where a gene therapy is used to correct the mutation that results in blindness and that's now out in the marketplace as well. So, those are kind of the first instances of approved programs and I think what we're going to start seeing is many more of these gene therapies toward monogenic - meaning a single gene defect that's being corrected by gene therapy - are going to more of those for rare diseases and genetic diseases will be coming down the pike. And then eventually what are called more complex diseases, which can be tackled with gene therapy by targeting pathways. Another probably generation of products we'll see is a type of stem cell called induced pluripotent stem cell, which can be derived from skin and blood that are reprogrammed to be like embryonic stem cells, which then have this capacity to be differentiated into what you need them to be. So, those programs will allow you to differentiate them to the cells or the tissues that need to be fixed, but more than that, they could also be gene-modified to soup them up, to make them even more powerful in terms of their impact. So, kind of the next generation of programmes will probably include all of these, as well as other types of stem-cell-derived products.

Hall T Martin: [00:17:04] Are there particular subsectors or applications you think are good opportunities for investment today, and if so, what are those?

Maria Millan: [00:17:11] I think that the CAR-T space is pretty, there's a lot of activities, so probably a lot of competition there just because the companies have just exploded, so I think that those are probably attractive investments still, however, the space is probably crowded. I think gene therapy programs are still high risk, but potentially high-reward type of programs to be looking at, even if they are geared toward rare diseases. I think that the world is starting to realize that each rare disease when you're talking about being able to apply a platform to it, that an aggregate, it becomes a very large, larger number than looking at each individual indication on its own. So, there are

portfolio companies that are ready, that's the model, that's our business model, like Sangamo, for instance.

Hall T Martin: [00:18:04] Well, in the last few minutes that we have here, what else should we cover that we haven't?

Maria Millan: [00:18:08] I would say that there's a lot of, I think that I would look at the CIRM funding model just to show kind of what standards have led to approaches in terms of due diligence that points to kind of infrastructure that we've set up. And by the way, although we're a California-based state agency, our programs also span across the U.S. and the world just because of partnerships. One of our programs for instance, is in Israel, an ALS, and we have a partnership with the NIH to fund gene therapy for sickle cell, which is one of the prominent next indications in a cure-sickle-cell initiative. So, that's one. And then the second is, I would highly recommend the investors to be very aware of this topic of what's called stem cell tourism, direct-to-consumer, kind of bad actors that are out there that are peddling things that they're calling stem cells and regenerative medicine, but it's not backed by science and it's not, often they're not under firm FDA regulatory standards. Not only is it bad medicine because these are unproven without an evidence base and they're collecting money out of pocket from patients, so it's essentially taking advantage of these vulnerable populations, but also it's a bad investment because the FDA soon, and the world, is going to start cracking down. The FDA for sure, in terms of its enforcement and its standards for manufacturers, et cetera, will start closing these loopholes where some of these stem cell tourism, bad actor, direct-to-consumer, whatever you call it, have been acting and have been able to essentially gouge the public, unfortunately, while there's been legitimate, in parallel, legitimate progress with the science and with the field, there's been this sideline of snake oil salesmen. So, that is, I think, in terms of putting your money somewhere, that I would be highly watchful for that because they can be very, very slick, some of these entities. But doing really solid due diligence in terms of the business, in terms of the regulatory development package, and what the commercialization path looks like is a solid investment. Those are the steps that your investors will be going through anyway but just extra, an extra eye on some of these other issues as well. But I think it's a very, very promising area, I'd highly encourage investors to look at it, but to also realize that in the early stages, it is going to require a real partnership kind of with the folks who really know the science and the development,

and not to just bring in people who you think have had experience from other industries and bring into this because it's so unique, so, just make sure you really, truly get the right management team and that that management team knows who to really bring in to develop these very cutting edge, new, but somewhat complex programs.

Hall T Martin: [00:21:18] That's good advice. So, how best for listeners to get back in touch with you?

Maria Millan: [00:21:22] My email at CIRM is mmillan@cirm.ca.gov, and I'm also on LinkedIn, which is where I believe you, Hall and I got connected. Is that correct?

Hall T Martin: [00:21:39] That's right. Found you on LinkedIn. So, appreciate your sharing that with us. We'll put those details in the show notes. I want to thank you for joining us today and hope to have you back for a follow-up soon.

Maria Millan: [00:21:50] Thank you Hall. You have a good day.

Hall T Martin: [00:21:53] You too.

Hall T Martin: [00:21:55] Investor Connect helps investors interested in startup funding. In this podcast series, experienced investors share their experience and advice. You can learn more at Investorconnect.org.

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