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Dr Maria T. Millan, president and CEO of the California Institute for Regenerative Medicine (CIRM), shares the Institute's mission to advance basic and translational research in regenerative medicine in the State of California, their unique funding and operating model, and her perspective on the critical importance of investment in science and research.

Maria, could you introduce CIRM to our international audience?

CIRM was originally established in 2004 through a very unique mechanism. Californian citizens voted on a USD 3 billion bond initiative (Proposition 71) to fund the creation of this agency to jumpstart what was then a completely new field. Human embryonic stem cells had only just been isolated a few years prior to the passage of that 2004 proposition, and there was a lot of excitement but also controversy and uncertainty surrounding this new discovery initially. But the field of stem cells developed quickly, with other stem cells discovered, and then scientists developed technology to use gene therapies with stem cells, and CIRM fostered this momentum to grow this new emerging field of regenerative medicine.

The idea of CIRM was – and continues to be – the building of a regenerative medicine ecosystem in California for vital research opportunities to address unmet medical needs where traditional approaches and platforms have not succeeded. In 2020, Californian citizens voted again (in what

was called Proposition 14) to approve USD 5.5 billion to continue CIRM's research based on the value proposition that has been demonstrated since our establishment. For instance, in the past five years alone, over USD 13 billion in investment have entered the programs we work with.

In terms of what we do, it will help to clarify if I start with the activities we do *not* do. We do not ourselves own benches or laboratories. We do not conduct our own research or run our own clinical trials. We do not develop or commercialize products. We do not treat patients.

What we do is to work with researchers and clinicians to fund and design their development programs. We help them partner with the necessary players and we bring in experts to run their clinical trials. Essentially, we de-risk clinical programs by investing in the science and in the clinical trials to obtain the necessary data so that companies can obtain partnerships and additional funding from industry players or other investors.

We establish and foster the infrastructure and funding environment essential to bring basic research through translational research into programs that can be approved by regulators and subsequently successfully commercialized by companies and other industry players. We support companies to prepare dossiers for INDs (investigational new drugs, this is where the US Food and Drug Administration grants permission to start a clinical trial) and NDAs (non-disclosure agreements), and if our partners face challenges along the way, we bring in experts in disease areas, manufacturing or regulatory or other areas as needed. The CIRM team itself comprises trained scientists, former industry executives, and others with extensive industry experience. For instance, I was Associate Professor at Stanford University where I conducted bench and clinical research, directed the pediatric organ transplant surgery program and served on hospital and university leadership committees to drive strategy on education and hospital infrastructure and operations.

Our funding proposals are peer-reviewed through a very rigorous review process by experts external of the State of California before they are brought to our board for the final funding decision. We have established a robust funding model that allows funding to reach approved partners in fewer than 100 days after receipt of the original application. During COVID times, we shortened that further to 30 days for COVID-related programs but on average, it is around 80 days – still extremely rapid. The funding mechanism is very organized and based on a milestone payment system, and we see this as one of the main reasons for the general successful developments of our programs.

The bond issuer structure is certainly very interesting as an investment case in an area where we need a long view. How does CIRM recoup its investments? What are the benefits that CIRM brings to the State of California?

We do not own equity in the companies we partner with, we work with revenue-sharing provisions. The exact structure has evolved over the years but currently, there are two ways revenue sharing is triggered. Firstly, if a product becomes commercialized successfully and starts generating revenue, a percentage of that revenue up to a cap amount comes back to the State of California. Secondly, there is a loan conversion option that the IP holder can choose to exercise, in which case the loan plus interest returns to CIRM, where it is returned to our research budget to be deployed to other projects.

In addition, by law, our funding can only be provided for activities related to California. We have funded international companies and projects originating outside of California but only the parts of their programs related to California. This can be clinical research or manufacturing, for instance. What this does is, obviously, attract clinical research or manufacturing activity to the state.

For instance, we are working with the National Heart Lung and Blood Institute (NHLBI) for their ‘Cure Sickle Cell’ initiative. They were already aware of our portfolio and our successes before we even began discussions, and they also knew that we were a leader in cell and gene therapy translational research. Under this initiative, we funded a program by Dr David Williams at the Harvard Stem Cell Institute (HSCI), which uses gene therapy to help patients express a healthier form of haemoglobin that could be effective in treating sickle cell disease. Through our funding, this program was expanded to California from Boston, which, incidentally, has allowed it to benefit on the extensive cell and gene expertise in our state. For instance, two of our investigators – Dr Mark Walters at the University of California San Francisco (UCSF) and Dr Matthew Porteus at Stanford University – are using CRISPR-Cas9 technology to address the single mutation that causes sickle cell disease. Both programs use the gene-editing technology developed by the recent Nobel laureate, Jennifer Doudna of UC Berkeley and have reached the IND stage and will enter the clinic soon. This is just an example of how CIRM fosters partnerships and grows the regenerative medicine ecosystem here in California.

How have the research priorities of CIRM changed over the past 15 years? In 2006, very few companies were even interested in regenerative medicine or stem cell therapies, right? But today this is a very hot field and there are a lot of acquisitions. How has this

changed the types of programs that CIRM invests in?

We have certainly been working towards promoting industry uptake. Our five-year strategic plan (2016-2020) had increasing industry involvement as a major goal, and so we had designed our programs to be attractive to industry partners. This was not just to attract more investments but also to accelerate the development of our programs and to ensure that they can actually reach patients, at the end of the day.

We are certainly going to do the same over the next few years but perhaps counterintuitively, looking forward, we also want to focus on more early-stage programs. In the past few years, we have increasingly been investing in later-stage programs, mostly because when CIRM began, the majority of our investment was made in basic research, and then as these programs advanced, we continued investing in them as per our continuous funding model, and as a result, ten to 15 years later, many of our assets are now in late-stage.

With our new Proposition 14 funding, we are planning to restart the cycle and invest once again in basic research. There is still so much work that has to be done in terms of tackling tough healthcare challenges. For instance, brain diseases, particularly neurodegenerative disease, are one area of urgent medical need. With our new funding, out of the USD 5.5 billion, around USD 1.5 billion is earmarked for this area. By focusing on funding more basic research, we hope to continue building our pipeline and seeding new discoveries for the development of future innovative therapies.

Brain diseases have been such a challenging and intractable problem for a long time. What kind of approach will CIRM take?

We had invested significantly in brain diseases with our previous funds but looking back, I think our approach could have been more structured. We funded mostly early-stage programs that were, in retrospect, a little sink-or-swim. Moving forward, we want to take more of a consortium approach that gives us the opportunity to gain critical mass in terms of tackling this area.

I believe CIRM already serves the role of convener, dot connector and aggregator of science and innovative research in stem cell biology and genomics. We have the capabilities to build a knowledge network to gather genomics information and other generated data that can be leveraged in the use and development of various scientific models or technology platforms. We think that there are so many types of powerful research tools and data sets and so on out there –

that have not yet been brought together – that could generate powerful insights if put together.

We are still developing our strategic plan but our goal is to a create an integrated approach that fosters a knowledge network and thereby facilitate basic discovery while continuing to offer support for its translation into clinical programs that could be equitably delivered to the “real world,” to patients in need. There are practical aspects to commercialization, access and affordability that will need to be taken into account. CIRM has the opportunity to bring in these considerations along the way as we foster and support programs along with the discovery to translation to clinical development path. It all starts with strong science, however so the basic science piece is critical – and while the basic science we fund may not itself become a product candidate, but it may well unlock the door for future product candidates.

Regenerative medicine like CAR-T therapies and gene therapies have been game changers for the sector and certainly for patients. But they have typically come with extremely high price tags that have generated significant debate amongst payers and other stakeholders. Is CIRM adopting the *access & affordability* topic in the way it approaches its mission?

Firstly, I think we are still at the beginning of the journey. It took a long time before the first CAR-T therapy was approved and we still only have three CAR-T products approved by the US FDA, the third just approved recently. They are being reimbursed through different models so the whole sector is still in the process of learning.

In terms of CIRM, we do recognize this challenge, so Proposition 14 actually includes funding provisions for us to work on ways to make these treatments more accessible and affordable. An Accessibility and Affordability Working Group (AAWG) has been formed, which is chaired by CIRM’s Vice-Chairman Senator Arthur Torres, who has extensive health policy experience. We are still in the initial stages but we have made a commitment to this and we will figure it out. For instance, will we also fund studies to look at how we can increase access and affordability? Will we look at post-marketing studies and Real World Evidence (RWE)? We have always been an evidence-based, data-generating, science-driven organization but increasingly we also understand that there is science that goes beyond the lab or the clinic that relates to how patients can access the therapies they need. We need to ask the right questions so that we can provide policymakers and other stakeholders with the answers they need to make pricing and reimbursement decisions.

Relatedly, we have also incorporated aspects of diversity, equity and inclusion into our operations, strongly supported by our board. For instance, when we launched our emergency COVID funding last year, we made it a requirement for all funding applications to outline a plan for addressing diversity, equity and inclusion in their research programs, both in clinical trials and in basic research, for example, in terms of the types of cell lines used. We have now incorporated the same principle into our current call for funding applications, and we expect to continue refining this as we go along. We will also be tracking our progress on this.

When we interviewed Dr Peter Marks, director of the US FDA Center for Biologics Research and Evaluation (CBER), he highlighted that regenerative medicine was a priority for them and that CBER was actively working on growing the US's leadership position in gene therapy, particularly. How do you assess the agency's efforts in this space so far?

They have a great vision and I am very impressed with what the FDA has done with the 21st Century Cures Act and the creation of the Regenerative Medicine Advanced Therapies (RMAT) designation, in particular. CIRM programs have benefited from this RMAT program as it provides an opportunity for real time and frequent interactions with the FDA that account for the unique aspects of regenerative medicine programs in efforts to accelerate development while ensuring safety and an evidence-based approach. They are understaffed – especially with COVID these days – but they have been building expertise in this area and have provided both a lot of guidance as well as many opportunities for industry to work in partnership as the field of regenerative medicine grows.

How is CIRM investing in the next generation of talents in regenerative medicine? With such high demand, there is certainly a gap to bridge, correct?

As soon as CIRM was established, we recognized that we had to invest in building a workforce. We currently have two internship programs: the SPARK program targeting high-school students, and the Bridges program for college- and masters-level students that may otherwise not have the opportunity to get involved in stem cell research. Thousands of students have now gone through this program, a significant number of them are first-generation college graduates and many have gone into postgraduate research or have attained R&D positions in academia or industry.

We have also established the only clinical trial network in California focused on regenerative medicine, currently composed of UC San Diego, UC Los Angeles, UC San Francisco, UC Davis, UC Irvine and City of Hope. In addition to conducting regenerative medicine clinical trials, these networks have created an educational opportunity, for nurses, clinical fellows and other health care professionals to active clinical trials. With Proposition 14, we are also going to expand this network further.

The industry at large struggles with knowing when and how to invest in early-stage programs. What are some learnings you can share with our international audience?

The CIRM model has been a great demonstration of how regenerative medicine technologies could be evaluated. We have managed to bring in over USD 13 billion in industry funding because we de-risked promising programs in a very methodical and structured manner, with inputs from industry experts and external evaluators.

To me, one of the most attractive aspects of regenerative medicine is that even early-stage clinical trials give you positive or negative signals, even with the smaller clinical trial sizes, purely because of their mechanisms of action. Another attractive aspect is that it lends itself to platform technologies really well, which allows companies to potentially develop therapies for many different indications.

At the same time, there are challenges because it is still a young field. Consistency in therapeutic development and manufacturing is a major issue but I think this will resolve itself as the sector matures and becomes less siloed. It is widely recognized that we need specialized manufacturing infrastructure to build this new field and we believe this is best accomplished through public-private partnerships.

I would also like to emphasize again the critical importance of investment in basic science. Science is not a linear path to the clinic. The path is meandering and many things often converge serendipitously along the way of drug development. But there needs to be investment and a structure that facilitates such serendipities. I will close with this example. One of the first programs CIRM started when we were established was an education program to fund scientists so that they could explore what was then a brand-new area of research. One of the participants of that program was Derrick Rossi, co-founder of Moderna, a molecular biologist by training originally from Canada. With our funding, he went to work at the lab of Stanford’s Dr. Irv Weissman (a pioneer in stem cell biology) and later on, at Harvard where he actually developed mRNA technology for use in his stem

cell research. Subsequently, he spun out Moderna and of course, Moderna has been able to develop a COVID-19 vaccine in less than a year as a result of this mRNA technology. This mRNA technology, initially a stem cell project, has now revolutionized vaccine development.

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