Text: Louise Hagbard, Ph.D.

STEM CELL INNOVATORS

MARTIN F. PERA

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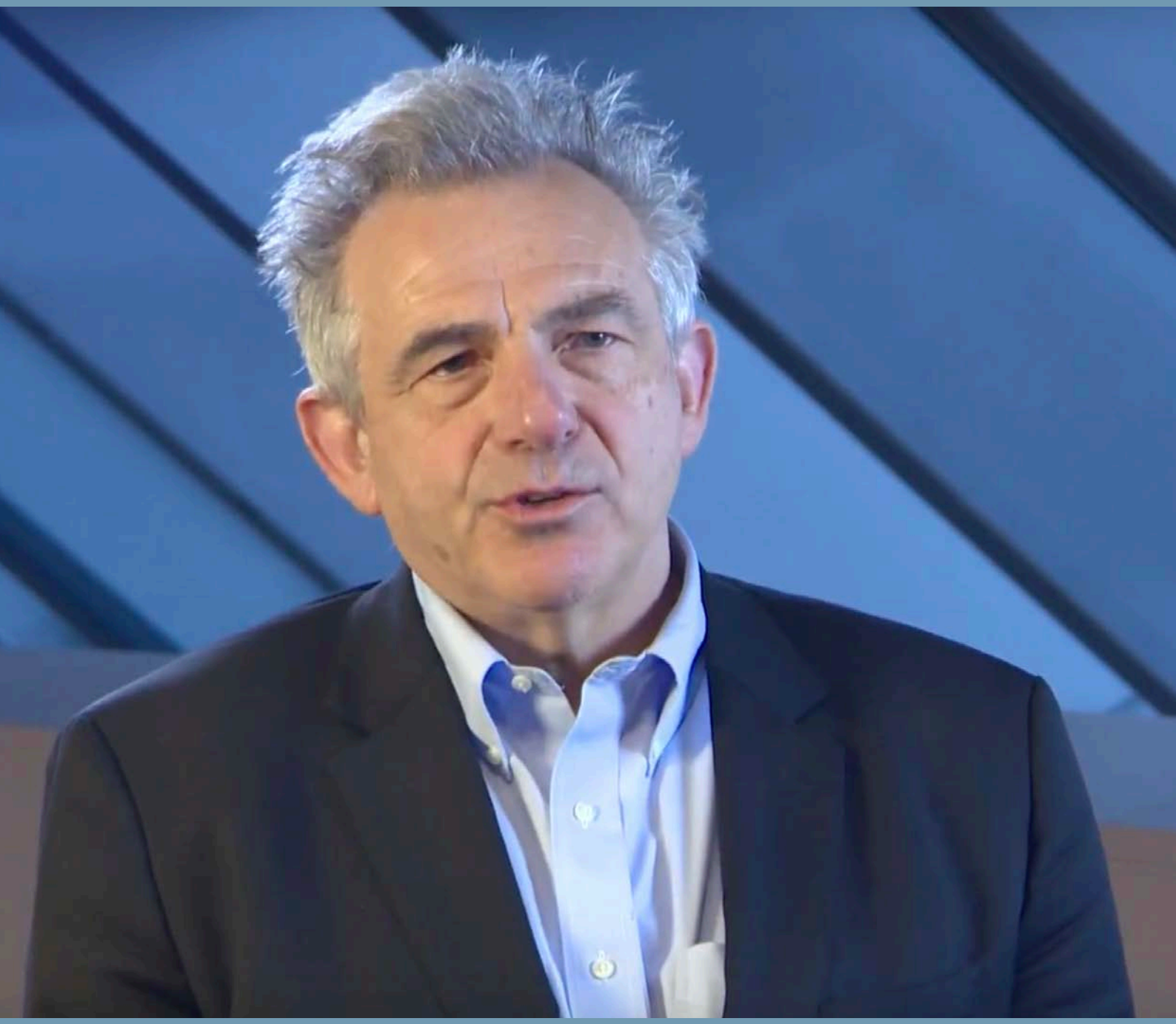
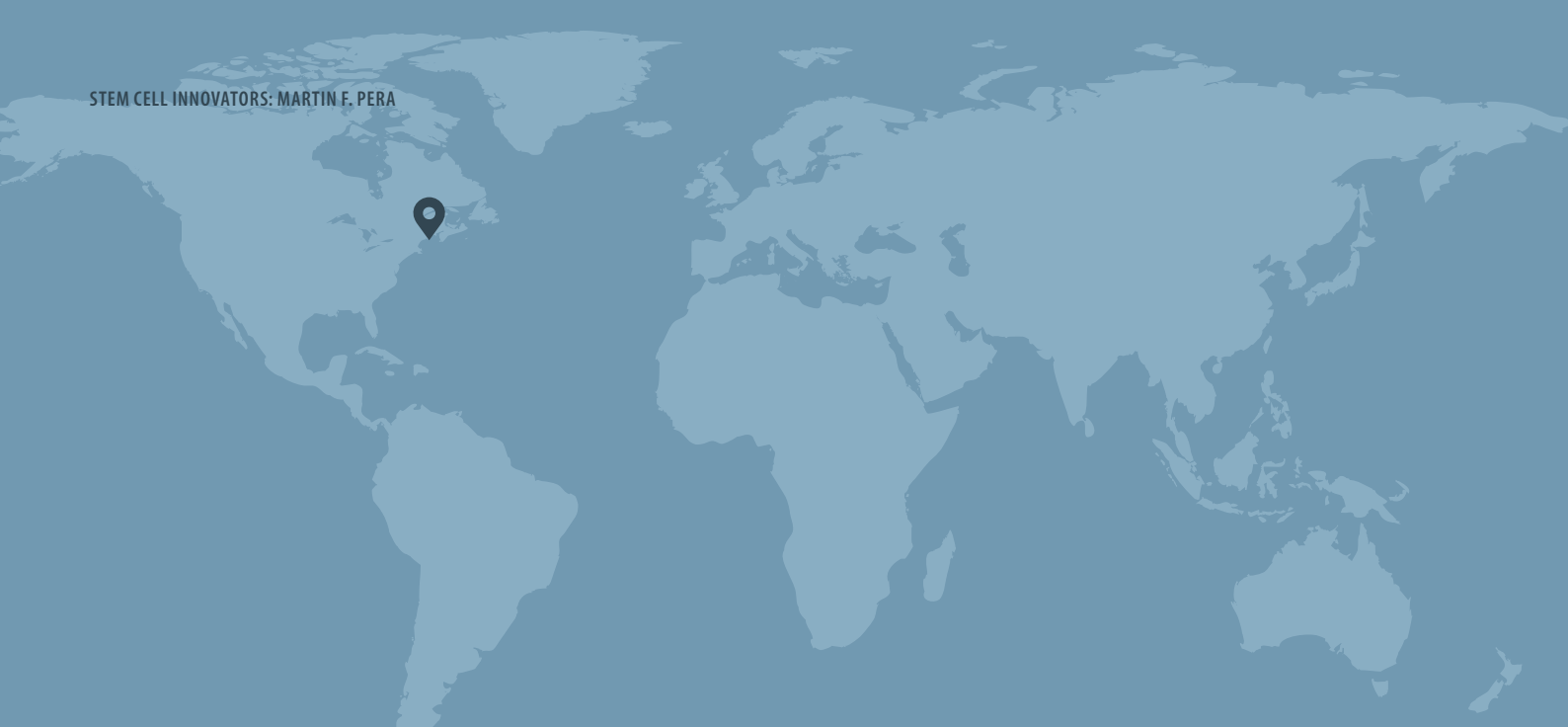




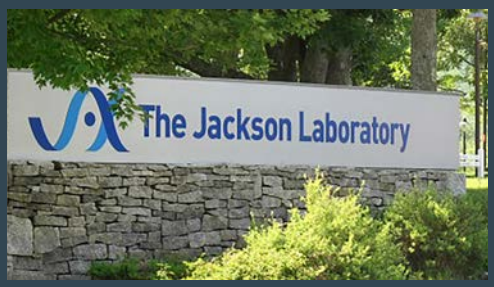
MARTIN F. PERA, Ph.D.

PROFESSOR AT THE JACKSON LABORATORY, BAR HARBOUR, MAINE, USA

ABOUT: **Professor Martin F. Pera is a pioneer and leading stem cell researcher with interests in neuroscience and regenerative medicine. His laboratory at Monash University was the second in the world to isolate embryonic stem cells from the human blastocyst, and the first to describe their differentiation into somatic cells *in vitro*. His work on neural differentiation of human pluripotent stem cells helped lead to the development of a new treatment for macular degeneration, which is now in clinical trials in Israel.**

Professor Pera received his Ph.D. from George Washington University. He held independent research positions at Oxford University before joining Monash University in 1996. In 2006 he moved to Los Angeles as the Founding Director of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at the University of Southern California. He returned to Melbourne in 2011 to become Professor of Stem Cell Sciences at the University of Melbourne and Program Leader for Stem Cells Australia, the Australian Research Council Special Research Initiative in Stem Cell Sciences. Professor Pera joined the Jackson Laboratory in 2017 where his research focuses on the biology and regulation of pluripotency and the genetic basis of individual differences in the response of the central nervous system to injury.

Professor Pera provides an authoritative voice within the stem cell research community and has provided extensive advice to state, national, international regulatory authorities and to the general public on the scientific background of human stem cell research, stem cell technologies, ethics, and legislation.



THE JACKSON LABORATORY

The Jackson Laboratory (JAX) is an independent, nonprofit biomedical research institution that employs more than 2,200 employees. JAX has its mammalian genetics headquarters in Bar Harbor, Main; a Genomic Medicine institute in Farmington, Connecticut; and facilities in Sacramento, California and Ellsworth, Maine. In May 2019, JAX celebrated its 90th anniversary.

Please tell us a bit about your research career

"I did my Ph.D. in pharmacology where I worked on a drug called Cisplatin. That drug became the mainstay of treatment for testicular germ cell tumors. It was part of a regimen that became a great success for those diseases, for which it is curative even at an advanced stage. After a while, I became convinced that the cells we were killing with the drug were more interesting than the drug itself, and I had an opportunity to join a clinical unit at the Royal Marsden Hospital in the UK. They had and still have the biggest testicular cancer clinic in Europe. So, we established cell lines from those cells which were pluripotent, and we studied the biology of those cells."

"Then I moved to Oxford University where we actually had permission from the UK embryology authority to try to derive stem cell lines from blastocysts. You know, Jamie Thomson's most important paper was not actually his human cell paper. It was a paper a few years before in which he describes stem cells from the rhesus monkey. Strangely, I don't think anyone much noticed the monkey paper. When we read this study, we realized immediately that these cells were very similar to our human embryonal carcinoma cells and we thought, we will be able to do derive normal ES cells in the human. However, access

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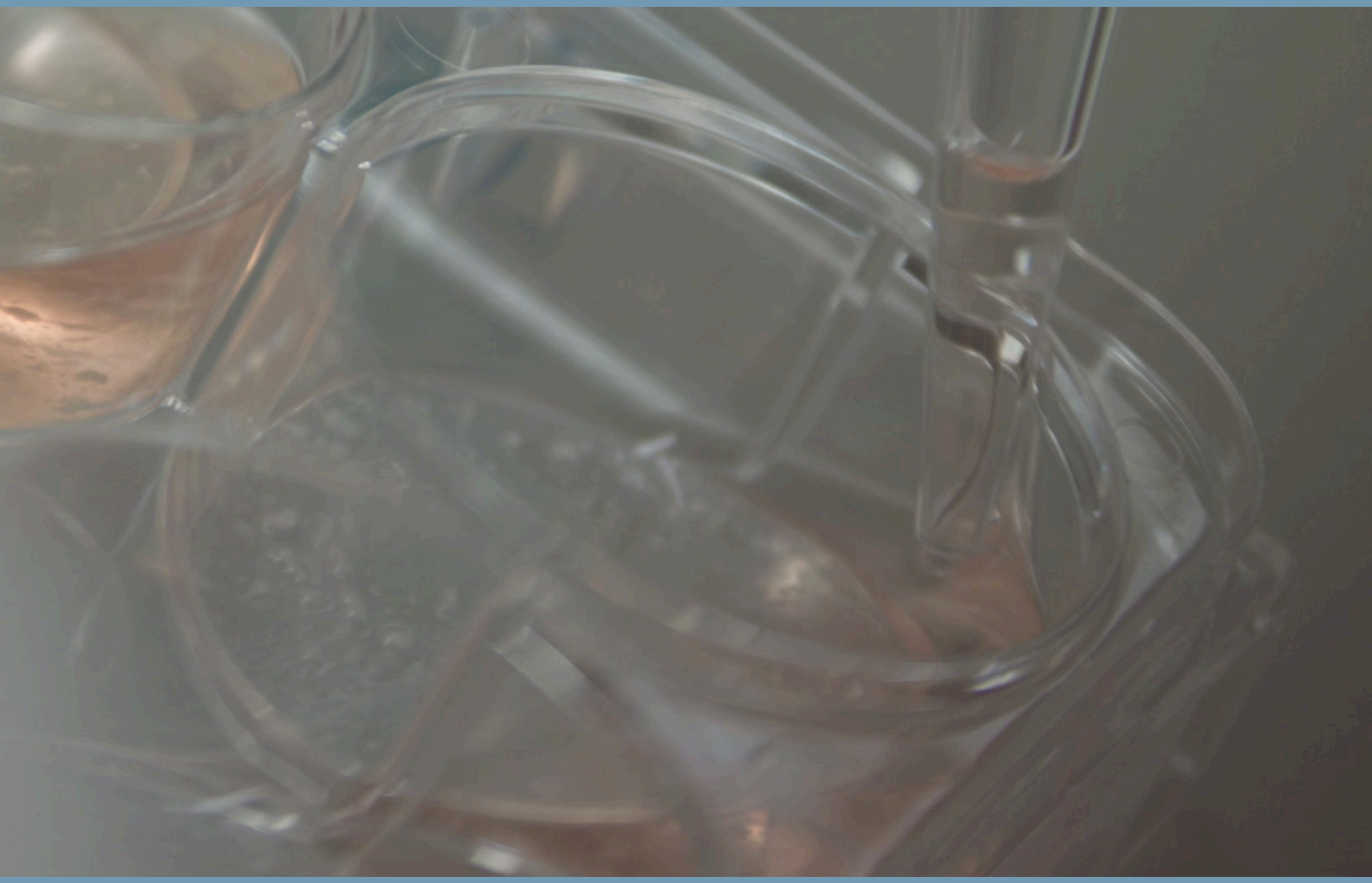

HIGHLIGHTED PUBLICATIONS

Embryonic stem cell lines from human blastocysts: somatic differentiation *in vitro*.
Reubinoff B.E. et al.
Nature Biotechnology, 2000, doi: 10.1038/74447

The authors describe the derivation of pluripotent embryonic stem (ES) cells from human blastocysts and are the first to describe their differentiation into somatic cells *in vitro*.

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to embryos was a bottleneck, and we didn't have a really close connection with a clinic at the time in Oxford and could not get hold of enough embryos of quality. We also tried to make cell lines from primordial germ cells, and really didn't get anywhere with that. So, when Alan Trounson offered me the opportunity to come down to Australia, we decided to have another go at deriving human ES cell lines. Alan had gone on a sabbatical with Ariff Bongso in Singapore, who was involved in this field from the early days and cemented a key collaboration there. Ariff is an outstanding IVF embryologist. So, I went to Australia, joined Alan's institute, and managed to get things off the ground with Alan, Benjamin Reubinoff and Ariff. We actually had a human embryonic stem cell line ready when Jamie published. I always tell people if you have to be second at something, it might as well be something like embryonic stem cells."

What were your aspirations for the field? What were your dreams at that time?

"I have always been interested in human development and developmental tumors. We also worked on the pluripotent cancer stem cells because we thought they provided a striking example of the fascinating connection between cancer cell malignancy, proliferation and differentiation. When Jamie Thomson published his paper on human embryonic stem cells, the degree of attention that that attracted was enormous. It confirmed that human pluripotent stem cells had more potential, and that they might be a powerful research tool for studying human development and disorders. I always felt then and still do that the research application for these cells, and what they can tell us about human biology, is probably as important as their potential for a curative cell therapy. Anyway, we went on to describe their conversion into neural progenitor cells."

"Of course, the idea and interest in the regenerative medicine applications of stem cells was there already from before Jamie's publication. There were even some clinical trials of cells made from teratocarcinoma stem cells. It seems crazy in retrospect, but people did it. No harm came from it, but no good came from it. Anyway, so that notion was already there."

At the time of the creation of the first cell lines, was there a big debate on the ethical implications of your research?

"In Australia, which is where I was at the time, we got very involved in the ethical and political discussions, because Australia is a large country with a small population, and at the time very few people were working in the field. There was an awful lot of objection at the time to the use of embryos in research. As always, when there is a discovery like this with a lot of excitement around it, there are also going to be people that say, 'Well, these applications are a long way off and these claims are nothing but hype.' At that time, we had a very conservative Prime Minister in Australia. But in the end, he accepted the research use

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of spare embryos from infertility treatments which were going to be discarded anyway. The potential benefits were seen to outweigh the limitations."

"I think research on human embryos will be always controversial. But it is much less of an issue today than it was 10 or 15 years ago. And that is for a couple reasons; First, we may have made enough embryonic stem cell lines for research purposes. Also, of course we now have an alternative to IVF as a source of cell material. However, the ethical controversies are far from over. Now the discussion is more about the various potential applications of these cells, like making embryo-like structures, making gametes, making chimeric animals with substantial human cellular contribution to many tissues. All of these are hugely complex and potentially difficult ethical issues. We and others have called for open public discussion on those types of questions, which I think is essential. Moreover, the ethical issues of our work do not respect national boundaries. Different regulations in different countries make it very difficult to collaborate and to conduct training. I think the international community must take these things on board, make it clear to the public what the benefits are, and why we want to do it, and try to get consensus."

Do you think that cell therapy will become as big as we hope it will be?

"I think it will. You only need to look at progress with the combination of gene and cell therapy and how powerful that is. That is an enormous growth area where there are already significant runs on the board. I just think that developing effective cell therapies is going to take a long time. We really do not know much about the fate of cell grafts *in vivo*. If we do not know the mechanistic details of how cell therapies fail or succeed, it is very hard to know how to go about improving them. So, I see great potential, but the current trials are unlikely to provide cures and will probably raise as many questions as they answer. There is much to learn about how cell grafts behave in a pathological environment, and how to improve their performance. Very diligent long-term follow up of clinical studies are going to be essential; then we will need to take these clinical findings back to the lab and refine our approaches."

What are your thoughts around the used of hESC- vs. iPSC-based protocols for clinical applications?

"I think the two cell types are likely to prove bioequivalent. The potential advantage of iPSC for building cell line panels for tissue matching is real, but banks will only be most helpful in populations that are relatively homogeneous genetically. I think it is still too early to know which cell type will be best for a given application, and the choice of a universal ES cellular platform or a tissue matching approach with iPSC also depends on how our ability to manipulate the immune system advances over the next ten years."

How do you interact with regulatory authorities? What sort of regulatory system would you envisage to balance scientific progress, ethical concern and public opinion?

"I think the involvement in regulatory issues, although a distraction from pure research, is very, very important. This engagement is essential, because bear in mind, we do not yet have much science behind our regulatory approach. We do not really know that much about how to look at efficacy and safety of these products in preclinical models. And if we in the scientific community do not have the right approach yet, the regulators certainly do not. We have to help educate them and bring them along. We have a project with the International Stem Cell Initiative now, around genetic stability, trying to understand what standards we should put forward to make sure

"For us to succeed with organoid we have to improve on reproducibility. In other words, companies like yours will have plenty of work ahead of you."

the cell lines we work with are free of acquired genetic lesions, which can have a drastic impact in research applications or cell therapy. Emerging areas in research - including production of human embryo-like structures *in vitro*, or human gametes from pluripotent stem cells, chimeras, human embryo and fetal tissue research - all of this, combined with gene editing, pose real challenges. We really need some form of international consensus on the ethics surrounding these areas, because the controversies do not respect national boundaries."

What do you think will be the most important developments for this field in the near future?

"We have an enormous opportunity now to learn about human development and its disorders. Looking at where we are in terms of our ability to model these processes, we have a fantastic new toolkit, including what we are learning from non-human primate embryology and from studies of the human embryo, from single cell technology, from organoid methodology, and of course from our ability to do precise gene editing in the human cells with CRISPR. I also hope that at least one of the pluripotent stem cell-based therapies currently under assessment for a half dozen or so essentially intractable medical conditions will be shown definitively to provide significant benefit to patients".

"Also, I think the use of organoid structures on an industrial scale for screening has a great future. For us to succeed with this new technology, we must improve reproducibility through refining the culture matrix and media and engineering the niche in 3D. In other words, you guys will have plenty of work ahead of you."

Can you tell us a bit about your current work?

"We are using mouse and human pluripotent stem cells to model how genetic background impacts on the how brain responds to injury. I think we have come an enormous way in terms of our capability to model development and pathology processes in a dish. Combining the two, we can achieve a new understanding of repair processes in adult tissues. I have also worked on retinal pigment epithelium for some time. I have participated in the early stages of cell therapy for macular degeneration at USC with the Doheny Eye Institute there, and also helped start a similar project with my colleague Ben (Benjamin) Reubinoff. Ben did some early neural differentiation work with us and went on to use this work to launch a project on stem cell derived RPE now in a clinical trial in Israel. But at the Jackson Laboratory, I am working with my colleague Patsy Nishina, studying some of the candidate susceptibility genes for macular degeneration using *in vitro* modeling, to see if we can understand some of the biology behind the early phase of this important disorder."

Being a PI and a scientific leader, how do you think you motivate younger students?

"I try to lead my group members along into interesting areas. I do not like to lean over people and tell them what to do every day. I try to find problems, that they will enjoy working on. However, in the end if the drive and inspiration do not come from within the individual, they are going to have a hard life in science."

What motivates you after this long career, a very successful career, in your daily work?

"I still find working with these cells fascinating. I learn something new about them every day. For me coming here to Jackson Laboratory has meant a return to more of a purely research role after over a decade of involvement in management and administration. I am in a great environment here with excellent faculty who are wonderful colleagues."

MARTIN F. PERA ON BREAKTHROUGHS

What do you think is the biggest breakthrough within the last 20 years of stem cell research?

"I would say the actual discovery of human ES cells. It had an impact that is hard to overstate. It opened peoples' minds to a whole different range of possibilities. And I would say it also triggered a lot of work on tissue stem cells in adults. If it were not for the discovery of IVF – which was an enormous breakthrough - we might not have produced human ES cell lines like we did and might not have been able to pursue it so quickly. The discovery of induction of pluripotency by defined factors is of course also a great achievement. Another huge development, without any question, is in the field of 3D organoids and co-cultures where I see enormous potential."


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