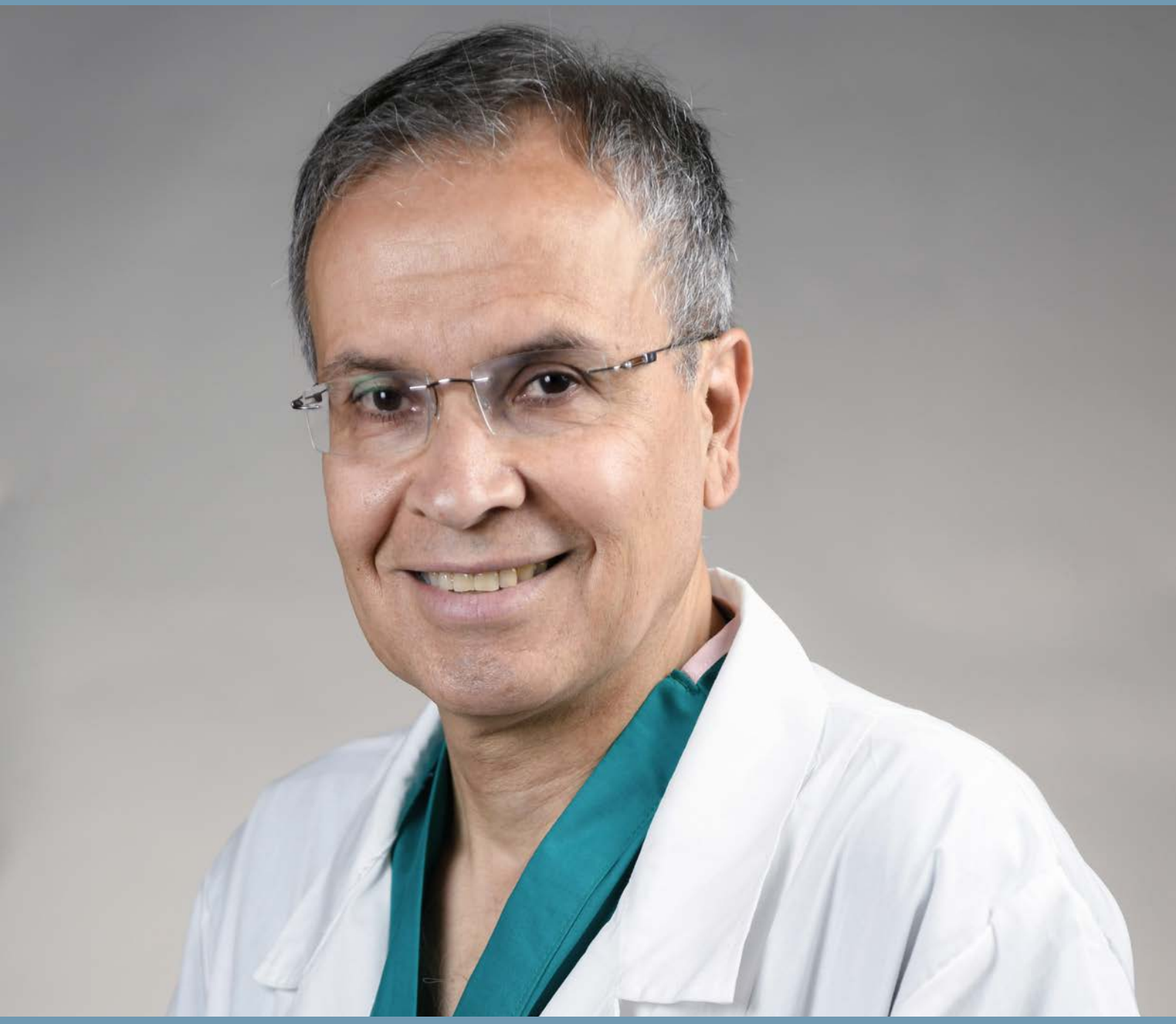
Text: Louise Hagbard, Ph.D. **Photo:** Avi Hayun

STEM CELL INNOVATORS

BENJAMIN REUBINOFF

"The key thing that changed my professional scientific career was the successful derivation of human embryonic stem cells. It's my life."



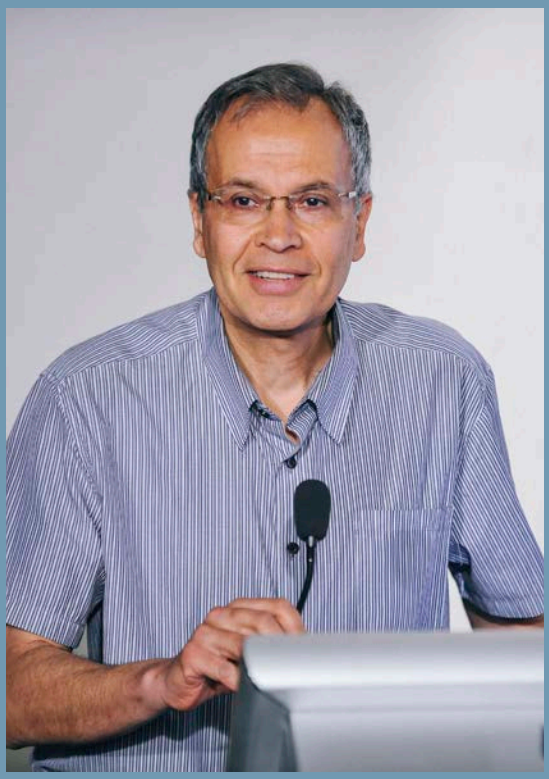
BENJAMIN REUBINOFF, M.D. Ph.D.

PROFESSOR, HADASSAH UNIVERSITY MEDICAL CENTER,
JERUSALEM, ISRAEL

ABOUT: **Prof. Reubinoff is one of the pioneers of human embryonic stem cell (hESC) research. In collaboration with scientists from Monash University in Melbourne and the National University of Singapore, he was the second in the world to derive human embryonic stem cell (hESC) lines and was the first to show somatic differentiation of the hESCs in culture.**

Prof. Reubinoff is the founder and director of the Sidney and Judy Swartz Human Embryonic Stem Cell Research Center and a full professor and chairman of the Department of Obstetrics and Gynecology at the Hadassah University Medical Center in Jerusalem. Prof. Reubinoff holds a Ph.D. degree in developmental biology from Monash University, Melbourne, Australia. He was the founder and has been the Chief Scientific Officer at Cell Cure Neurosciences Ltd. since 2006 and serves as a member of the Scientific Advisory Board at Kadimastem Ltd.

The focus of Prof. Reubinoff's research is the exploitation of human embryonic stem cells (hESCs) in regenerative medicine for the treatment of neural and retinal degenerative disorders. Other research areas include the derivation of new hESC lines from abnormal pre-implantation genetically diagnosed (PGD) embryos, the development of induced pluripotent stem (iPS) cells as models of human diseases, the study of hESC genetic modifications, and the characterization of hESC immunogenicity.



CELL CURE NEUROSCIENCES

Cell Cure Neurosciences (a fully owned subsidiary of BioTime, Inc.) is a biotechnology company focused on developing cell therapies for retinal and neural degenerative diseases based on human embryonic stem cells (hESCs). Their first product in development, OpRegen®, contains hESC-derived retinal pigment epithelial (RPE) cells to treat age-related macular degeneration (AMD), for which there is currently no FDA-approved therapeutic. A Phase I/IIa clinical trial of OpRegen® to treat the larger market of dry AMD, is currently ongoing.

↑ The 19-story Sarah Wetsman Davidson Tower is a new in-patient facility and is tangible example of Hadassah's commitment to the people it serves.

What is your background story? How did you end up in the stem cell research field?

"My clinical background is within obstetrics and gynecology and my area of specialty is infertility and IVF. Through this interest, I was looking for a topic for a fellowship period, something which would have broad horizons beyond the area of infertility. So, I approached Alan Trounson, a well-known embryologist and *in vitro* fertilization (IVF) expert from Monash University (Australia), with vast expertise in stem cell research. He offered me to work on the derivation of hESCs. I was very excited about the project because of its potential for applications in regenerative therapy, but it was a risky project because there had been attempts to derive human embryonic stem cells which had not been successful by that time. Nevertheless, I decided that I would devote myself to deriving human embryonic stem cells. After our success in deriving hESCs, I came back to Israel in the year 2000 and established the Human Embryonic Stem Cell Research Center at the Goldyne Savad Institute of Gene Therapy at the Hadassah University Medical Center. We have been focusing ever since on overcoming the barriers of developing human embryonic stem cells for clinical applications."

"After the first derivation of human embryonic stem cells which I did in Singapore, I flew back to Australia with the isolated ICM in a small flask in my pocket."

What are you most proud of?

"We, myself, Martin Pera, Alan Trounson, and Ariff Bongso were the second group in the world to derive human embryonic stem cells. We were working together in Australia at that time but since there were ethical constraints to perform any research on human embryos in Australia, we had to perform the initial derivations in Singapore. So actually, after the first derivation of human embryonic stem cells, which I did in Singapore, I flew back to Australia with the isolated ICM in a small flask in my pocket. These were the cells from which our first human embryonic stem cell line was derived and established. It was a very exciting adventure, I must say. It was covered within a review on the contribution of Israeli scientists to the field of human embryonic stem cells in Science Magazine."

"I am also proud of the work we do at the Hadassah University Medical Center. Our vision has always been to develop human embryonic stem cells for regenerative medicine. In the early days, the cell lines that were available were only suitable for research purposes, so the first step that we took was developing clinical-grade human ESC lines. We have spent years on deriving hESC lines here at Hadassah under GMP conditions. We were the first to develop GMP-grade, xeno-free human embryonic cell lines suitable for clinical applications, with the vision that they would serve the academic and medical communities worldwide as starting materials for clinical transplantation applications. It's very rewarding to see that our cell lines are performing well and that multiple groups worldwide are successfully using them. And just the fact that our cell lines are already in clinical trials with two projects; for macular degeneration at Cell Cure Neurosciences Ltd. and for ALS at Kadimastem, that is amazing."

What is the reason for your success?

"I must confess that, in the early days, when we derived the human embryonic stem cells, their utilization for clinical transplantation felt like a dream and not like something that would actually become a reality. Nevertheless, the fact that I am a physician, has inspired me to focus on developing the cells for clinical applications. The fact that we have been very focused and systematic from the start in our work on developing human embryonic stem cells for clinical applications has enabled us to be among the pioneers in reaching clinical transplantation trials with hESCs."

You have chosen to focus on neural and retinal degenerations and you are conducting a clinical trial in age-related macular degeneration. Why did you choose this research area?

"In the early days, I was looking for a direction and an indication where there had been initial clues or preliminary results suggesting that stem cell transplantation therapy may be beneficial. In age-related macular degeneration, there had been limited clinical data suggesting that transplantation of RPE cells could be beneficial. In the nervous system, there also have been studies of transplantation of fetal-derived dopaminergic neurons to Parkinson's patients that gave early indications of potential therapeutic effects. So, given these initial clues or proof of concept of stem cell therapy, I thought that we should focus on these directions. In addition, in those early days, directing the cells to differentiate into a particular cell type was a big challenge. Differentiation into retinal and neural lineages was relatively easier compared to other cell types."

"I must confess that, in the early days, when we derived the human embryonic stem cells, their use for clinical transplantation felt like a dream and not like something that would actually become a reality."

Our clinical-grade hESC lines are already used in two clinical trials projects; for macular degeneration at Cell Cure Neurosciences Ltd. and for ALS at Kadimastem."

What have been the biggest challenges to get to clinical trials?

"There have been multiple challenges and barriers that we had to overcome on the route to clinical trials. An initial challenge of course was to have the appropriate starting material, which is the clinical grade human embryonic stem cell line of high quality. Progress that has been made along the years in understanding pluripotent stem cell biology and differentiation has really been important and helpful in developing the hESCs for clinical applications. It helped us to overcome manufacturing hurdles, such as growing on a larger scale in the GMP facility, and to better understand the biology of differentiation, and to be able to control it."

"A great challenge was getting pure populations of functional, differentiated cells. It was crucial also to show safety and efficacy of the differentiated cells in animal models. Developing the regulatory structures for application to regulatory agencies was a challenging but necessary opportunity to focus all of the material we had collected during the manufacturing, preclinical and testing phases. Thankfully, we met these challenges and are successfully well on the way to completing our Phase I/IIa clinical trial."

If you had an unlimited amount of funding, what would you do with that money?

"I would broaden my efforts to develop hESCs for regenerative therapy. I would focus on three areas: neuronal degradation, the retinal indication, and diabetes."

How has your relationship with the regulatory agencies been? Has it been a good interaction?

"We have had very close communication with the FDA and with the Israeli Ministry of Health and I must say that the relationship has been very positive. They have been mutual learning partners because the field is also new to the regulatory agencies. It was thrilling to see that the regulatory agencies' main motivation was really to try and promote the field, learn about the problems, and to think about ways to overcome the issues of safety and efficacy."

How is the situation for you as a stem cell researcher in Israel? Are there ethical discussions around derivation of new ES cells?

"Actually, the ethical atmosphere in Israel towards hESC derivation and research has been very positive already from the very early days. The reason is that according to Jewish tradition, the embryo is not considered a human being when it's not in the mother's womb. So Jewish orthodox rabbis in Israel were actually in favor of hESC research because they saw the huge potential medical benefits and the possibility of saving human lives. The public opinion has also been positive, and Israel was actually the first country in the world that established law in parliament that allowed the derivation of human embryonic stem cells."

Will it be as big as we hope? Do you think regenerative medicine will be an off-the-shelf treatment in the future?

"Yes, I am optimistic that there will be ready-made, off-the-shelf products that will come from pluripotent stem cells, but it's not going to happen tomorrow. There is still a way to go. I think that the big challenge for the next 5 to 10 years will be to cross the barrier of phase 2 and 3 clinical trials. If proof of efficiency and therapeutic effects will be demonstrated in these clinical trials, the vision of off-the-shelf products for regenerative therapy will become a reality." •

BENJAMIN REUBINOFF ON THE BIGGEST ADVANCE

? If you look back on these 20 years since you were one of the first to derive an embryonic stem cell line, what do you think has been the biggest advance in the stem cell research field since then?

! "There really has been a tremendous advancement and monumental progress, but it's hard to point out one particular achievement. I think that during these 20 years there have been many, many small steps forward where we have learned more and more about the biology of pluripotent stem cells and how to successfully control them. All of this information has helped make a big change, and if you look back, there has been a revolution in the way of culture of pluripotent stem cells, in our abilities to direct differentiation, and how we now are able to genetically modify them. We could hardly keep the undifferentiated cells ongoing in culture in the early days, up to the stage we are at today where we are taking our protocols through to clinical trials."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