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Natural Selections

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Natural Selections interviews Ali Brivanlou, Principal Investigator Laboratory of Stem Cell Biology and Molecular Embryology, the Rockefeller University

Guadalupe Astorga

Together with his team, Ali investigates the molecular pathways underlying cell communication during development. Notably, his team was recently able to preserve human embryos in culture for up to 14 days. This revolutionary achievement will illuminate unknown information about our own origins that may be crucial to understanding and reversing neurodegenerative diseases, repairing diseased tissues, and growing human organs *in vitro*.

NS: What differentiates a stem cell from any other cell type?

AB: Stem cells come in different flavors: embryonic stem cells (ESCs) and adult stem cells (ASCs). The former are derived from the early embryo, a few days after fertilization, while adult stem cells are continuously present in almost all tissues of our body, and allow for regeneration. The big difference between these two groups is their range of ability. A human or a mouse ESC can give rise to all the organs of the body. As time moves forward, their potential decreases. So, i.e., an adult hematopoietic stem cell can only give rise to blood derivatives, and bone stem cells will give rise to bone. This difference is intense, because ESCs are the only cells that can mimic a fertilized egg and give rise to a whole organism. They contain all the information sufficient and necessary to create all the organs and their organization. These are very unique properties that put ESCs on top of the hierarchy of decision-making that allows all the fates to be established. This is really exciting because we can use human stem cells in clinical settings to repair or replace tissues; and also because it teaches us, at the most fundamental level, how cell fate is established.

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NS: What gives a stem cell the information to form a whole individual?
AB: This is a very old biological problem. About 2,300 years ago, Aristotle described the development of a bird inside an egg and created the foundation of current embryology. At the end of the 19th century and beginning of the 20th there were two schools of theories. One defined by the British school of embryology, suggesting that fate is based on lineage – you know who you are based on who your parents and grandparents are. The other is the American school, suggesting that [it] is not the lineage that determines your fate, but your neighborhood – you know who you are depending on where you end up being and who your neighbors are. It ends up that the American school was correct, not the British. Fate in an embryo is determined by where a cell finds herself. I figured out that this is mediated by cell-cell communication, cells have a dialogue. As the embryo grows and the number of cells increases, their neighborhood becomes more complex and their fate more refined. This is mediated by receptors and secreted factors. Ligands come out of the cells and bind receptors in the recipient cell that sends the signal to the nucleus. An extrinsic piece of information becomes an intrinsic response in transcription. This allows cells to gradually figure out what they will be. We learned their language and how to manipulate it to change their fate. Many people in the stem cell field are interested in the applications of this knowledge. I am still interested in learning more about this communication.
When I was a graduate student at Berkeley and during my postdoc at Harvard, it was still questionable whether the American school was right. So I asked, "If the neighborhood defines your fate, what kind of fate would you have if you don't have any neighbors?" Cell communication as a fate determination mechanism is conserved over millions of years. So, I took a frog embryo, which is a ball of 2,000 cells, and I dissociated them so they could no longer communicate. Any ligand sent was diluted to infinity in the medium so other cells could not "hear" it. The result was very surprising. All embryonic cells: those going to become gut, or kidney, liver, muscle, bone; every single one converted to a brain cell. Not receiving any signals pushes a cell towards a brain fate. This was very controversial when I published it because one thinks that this is the most sophisticated organ, but how can this sophistication arise from zero communication? At some point, a group of cells in the embryo decide to no longer listen to their neighbors. They close all communications and give rise to the dorsal anterior part of the nervous system. In order to generate other fates, cells have to say "Do not close your windows or your doors, listen". This complexity is something I'm still trying to dissect.

NS: Before it was possible to obtain embryonic stem cells only from embryos. Now they can be taken from different tissues. How is this done?
AB: In 2012, a Nobel Prize was given to two of my heroes: John Gurdon and Shinya Yamanaka. They showed different things with a common denominator: that biological time can go backwards. Yamanaka showed that any adult cell can be reprogrammed to behave like an ESC. John Gurdon, who mentored both my postdoc and graduate student advisor, was the first to clone an animal. He showed that [it] is possible to create a whole individual from the nucleus of a skin cell of a tadpole (that is ahead in time) placed in an egg. But it took more than 50 years to recognize John Gurdon for his contribution. If you ask people which one was the first animal to be cloned, they always say Dolly, never the frog. But Dolly was cloned decades after the frog, people didn't care the same. It was only when it got closer to humans that people started to really get interested.

NS: Usually embryos are implanted in women about one week after fertilization. Before you were able to keep embryos in culture for 14 days, nothing was known about this second week of development. What are the potential implications of these discoveries?
AB: It has tremendous implications. Mammalian development post implantation has always remained a mystery. The architecture and geometry of the embryo changes as it attaches to the walls of the uterus and it becomes invisible. We showed what happens after implantation in humans, unveiling, for the first time, our own origins. This was spectacular and unexpected because we showed that the human embryo has all the information to sustain its development at least for 14 days in the absence of maternal inputs. It was mesmerizing to see that self-organization occurs in the embryo, cells decide their fate and they organize in a specific structure of concentric circles, generating waveforms from the center to the edge. We stopped at 14 days because there's a guideline in the United States, called the 14-day rule.

NS: If there was a reevaluation of the 14-day rule, where would you set the new limit and why?
AB: We are in discussions with the National Academy of Science, the National Academy of Medicine and the National Academy of Bioengineering. A lot of this work is done in collaboration with my physics colleague Eric Siggia from RU. We are trying to answer questions like "Do we want to move further than 14 days?" If the answer is yes, "How far do we want to go?". I'm very happy and proud to initiate the debate so we can create a dialogue regardless of our background, culture, language, or religion and together discuss how the new technology available can [help us] reevaluate this rule. This is a great question and the debate will resolve by itself. My personal opinion is that if we can double the 14 days, if the embryo survives, that would be a great advance for the 21st century, and we could get important information about

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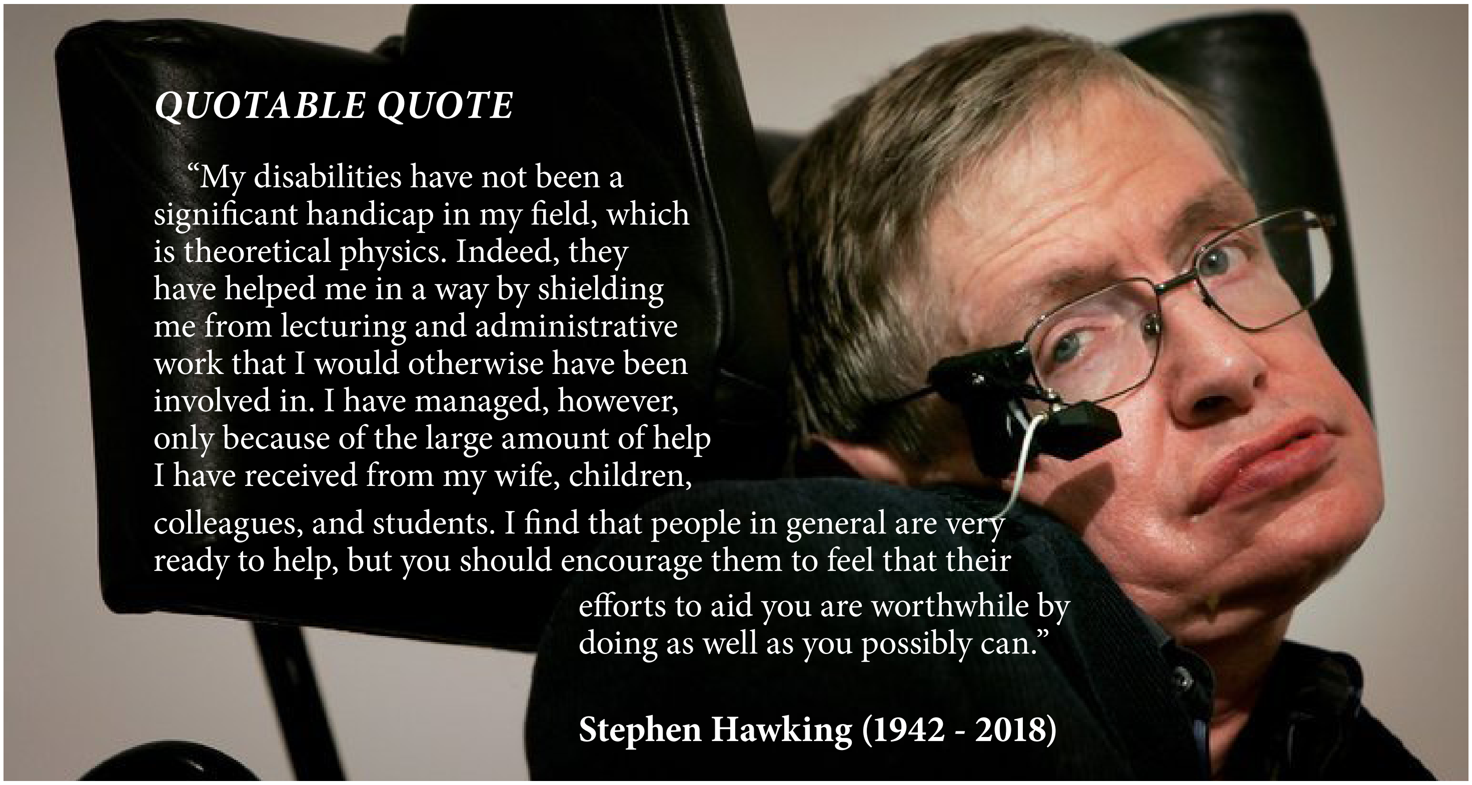
organ formation, or organogenesis, because it happens during this time window.

NS: How far are you from creating human organs from stem cells?
AB: Very close actually. This work is in review in *Nature* now. Once you can make a human embryo, the mother of all the organs, you can make organs by [the] hundreds. If you know the language being used among cells to distinguish fate, then I can assure you, it's a matter of [a] short term.

NS: What other passion do you share with science?
AB: The passion of curiosity, pushing the boundaries of the limit of what's beyond. This is a human tradition, from Christopher Columbus wanting to see what is on the other side, to the pioneers of the West Coast wanting to see the boundaries of the land. It's a natural phenomenon in us, to be attracted to the unknown. When I look down that microscope, my eyes send signals to my brain that tell me, "I want to know where I come from." Where does that need derive from? That need of self-understanding, I think is very human. What drives it? I don't know, but for me it's a necessity, not a choice. I need to know, I don't know why, but I need to know.



Life on a Roll

Qiong Wang

Morocco Log #1

Stepping straight onto the tarmac of Casablanca Mohazammed V International Airport after a 6 hour flight with the Royal Air Morocco, I am officially on the continent of Africa!

The reputation of Casablanca would be overrated if it were not for the magnificent Hassan II Mosque by the Atlantic Ocean. Marrakesh, on the other hand, is what I imagined Morocco would be like – vibrant colors, ancient history, and exotic culture blended with chaos everywhere. Djema Square at the heart of the old medina is the biggest outdoor marketplace in Marrakesh. Every day, when the sky dims into a scarlet sunset and the square is re-lit with a sea of tent light bulbs, when the delicious smell of BBQ travels to your nose through clouds of smoke that rise above vender stalls, when the boisterous crowd and circus animals pour into the square from all directions, you can't help but realize that this place has just woken up and the show is about to begin.