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A Shadow of Knowledge in Stem Cell Science

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Abstract

"Theory of Forms" implies that a genuine version of creatures exists beyond the shapes in this world. Stem cell technology has adopted developmental cues to mimic real life. However, the functionality of the lab-made cells is far from primary ones. Perhaps it is time to switch from analytical to systematic perspective in stem cell science. This may be the way to define new horizons based on the systematic perspective and convergence of science in stem cell biology, bridging the current gap between the shadows of real knowledge in current research and reality in future.

Keywords: Theory of Forms, Stem Cell Science, Systems Biology

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Greek philosopher Plato implies that beyond all creatures and shapes in this world, there is a far more genuine version of them. How we appear physically is merely an image and a fairly unwitting imitation of the original forms in the "realm of forms" or the "Realm of Ideas". This philosophical theory is named "The theory of Forms or the theory of Ideas" (1, 2).

Human life begins when a fertilized egg passes through the different developmental stages followed by the differentiation of embryonic stem cells to a great number of different cells with varied physiological functions (3, 4). Thanks to the rapid advances in stem cell research during the past four decades, scientists were able to successfully generate a variety of somatic cells by applying the knowledge gained from embryo development. Experimental stem cell differentiation protocols have adopted developmental cues and mimicked micro-environmental and spatiotemporal conditions required for natural development that control most of the cell's fates (5, 6).

However, the functionality of the experimentally generated somatic-like cells is far less than that observed from primary cells both *in vitro* and in living organisms. Hence, the lab-made cells should be considered as tentative, simple, and superficial replicas of the original cells. For instance, stem cell-derived neurons have many similarities with primary neurons in terms of morphological features and they can recapitulate basic physiological functions such as electrical conductivity. However, they lack the advanced capabilities of primary neurons (7). Human activities are controlled by the nervous system; neurons perceive specific stimuli and fire signals that regulate all of a being's actions. Although activation of lab-made neurons does produce an electrical action potential, it does not generate philosophy, critical thinking, rational conclusions, feelings, emotions, intellectual pondering, and many other complicated actions when we pile up billions of them. More specifically, tiny neurons located in the pre-frontal cortex of the human brain, generate concepts and reflect them as meaningful words and emotional fluctuations such as love, passion, misery, grief, and other empathic and mental connections that are tangible and transparent to others. All this convoluted relativity is something that is not present in *in vitro* generated nerve cells (8). We are all aware of limitations of a single cell to perform a distinct physiologic function and we admire the fact that combination of cells in certain clusters enable them to do physiologic activity."

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Since 1998, despite massive efforts to propose pluripotent stem cell (PSC) technology as a promising platform in regenerative medicine, few translational studies reached clinical trials. The heterogeneity of PSC-derived cells in terms of maturity, possible terato-/tumorigenicity, and their poor physiological performance are the main obstacles to reaching their broad application (9). Thus, two major questions can be highlighted:

1. Is it time to summarize our achievements and to reconsider our perspectives and expectations in stem cell research?

2. Could a different standpoint serve as a game changer in this regard?

From a philosophical point of view, current research is based on breaking down complex processes into smaller parts in order to easily understand them, which is called "analytical approach" (10). Therefore, cells were studied as microscopic units of living organisms to understand life's complexity. On the other hand, "systemic approach" enables scientists to handle complex systems with a global perspective without focalizing on details in order to reach equivalent complexity, and without oversimplifying the reality. From a philosophical perspective, this approach corresponds to the holistic school of thought (11).

Thus, there is a philosophical dilemma as to whether the cells represent the whole living thing or if the living system can only be comprehended by the holistic view. Certainly, both views are logical to some extent, however, the pivotal question remains unanswered. Does the living system as a whole, as parts or as cells contain other components that we are not able to understand using the present methodologies and techniques? In other words, does life at molecular or cellular level or even the whole organism itself have any other esoteric forms? Or simply, does the living organism as a "whole" have properties that are more than "the sum" of its components?

Historically, "reductionism" was a step ahead of the subjectivity and holistic views of ancient philosophers. This improved human observation and its confirmation but it also led to a paradox because it relied on parts and not the whole. The historic disagreements between Plato and Aristotle were mostly because of the subjective nature of their observations and their holistic views without experimental confirmation due to lack of modern tools.

After years of research, current knowledge enables scientists to create an environment mimicking reality which is a demo version of real life with living cells. Thus, the situation is like the shape of words drawn by an under-the-school-age child without having any insight into the meaning or the actual message behind them.

Comprehending the complexity of inter- and intracellular reactions and the dynamic cross-talk between the living cells and their microenvironment would provide a new horizon for a better understanding of life. "Systems biology" and "optimization approaches" such as "artificial intelligence" (AI) are interdisciplinary fields in science that can process big data and simplify complicated phenomena (12-14). Both advanced technologies, and their related databases are constantly being expanded and updated. High-tech instruments and in-use software packages generate big data and enable researchers to focus more on data-driven hypotheses rather than idea-driven ones (15). This approach enables scientists to investigate precise hypotheses followed by an exact analytical process in order to reach accurate results/answers without any prejudice and bias.

If systems biology is complemented with a holistic view and philosophy of existence, as well as a reductionist approach, it may present a realistic picture of natural phenomena. Then, stem cells will be viewed as biological substrate for the perfect growth/repair of an organism. The reductionist approach will describe the roles of individual mechanisms in the whole organism and system biology could have its missing puzzle solved with this.

Organoid technology (16-18), microfluidics (19, 20), and OMICS approaches (21) have provided reliable models to investigate the complexity and translation of vast data pools of biological molecules into structures and physiological functions. Human on a chip is a great example for this approach. All these modules together, can on one hand, open new windows for the better understanding of real life and on the other hand, bridge the gap between analytical and systemic approaches.

At present, interdisciplinary approaches and networking in form of collaborating across traditional disciplinary boundaries may help scientists to envisage different perspectives in order to solve their challenges. This, in turn, will help scientists save time and money as well as redefine current challenges beyond their limitations, which may provide innovative solutions based on a new understanding of complex phenomena.

However, even the modern technologies and approaches, in the future, will face the central challenge of "control volume". Does the smallest entity studied in the Petri dish or the highly complex whole organism have other unknown or hidden facets beyond their reach? Is there any other form or realm of existence like that mentioned by Plato some thousand years ago?

In summary, significant progress has been made in the field of stem cell research throughout the years. Still, we are facing the same limitations as for the other configurations in *in vitro* cell culture. Thus, lab-made cells still cannot describe a character in the frame of an overall physiological function like metabolism regulation. Still acting as shadows of their real-life counterparts, these cells are a preliminary version of primary cells in Mother Nature. Thus, lab-made cells cannot describe a character in the frame of a complex activity such as writing a poem or generating images as a result of the excitement of photoreceptor cells in the retina.

In the big data era, scientists need to collaborate more on systematic approaches to understand the complexities of

life and think beyond the current box of knowledge using advanced approaches such as AI to facilitate analysis and interpretation of big data and validate them. What scientists have achieved until now is of great value, but it should not be forgotten that there could be shadows or frames far away from the actual physical forms that exist in the realm of nature. Perhaps it is time to reconsider our current analytical approach in stem cell science to better design the strategy of their applications in regenerative medicine. This may be the way to define new horizons based on the systematic perspective and convergence of science in stem cell biology, bridging the current gap between the shadows of real knowledge in current research and reality in future.

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Authors' Contributions

S.O.-S.; Drafted manuscript and contributed in development of the concept. A.K.N., M.H., M.N.; Developed and discussed the idea. M.V., A.K.N., M.H., M.N.; Critically edited manuscript. M.V.; Conceived the idea, developed and discussed the subject and finalized the manuscript.

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