Embryos, fetuses, and neonates form perfectly functional tissues and organs every day. Despite fevered efforts over the past 30 years, there has been very modest progress toward achieving the bewitching goal of organ replacement with embryonic or iPSCs. What is the basis of this humbling status quo? Surely one reason is our enduring ignorance of mechanisms governing development in any organ or cell. For organs like pancreatic islets, developmental studies have revealed dozens of crucial conditions or factors required to create a functional islet. It is likely there are thousands more to discover from integrated studies of organ development and physiology.

Embryology, developmental and transplant biology, genetics, physiology, and other disciplines fostered the invention of iPSCs and embryonic stem cells. We should re-dedicate ourselves to the unfinished work that the pioneers in these disciplines, like Morgan, Spemann, Mangold, Jacob, Monod, Medawar, and Claude Bernard, have thus far advanced. We should avoid an impatient, jackpot mentality that has adapted what little we know to generate imperfect replacement organs from renewable sources.

What would Dr. Bernard suggest? Perhaps that, to achieve the lofty goal of functional organ replacement with stem cells, it would be useful to remain patiently dedicated to our basic scientific foundations.

The stem cell field exploded this past decade with the discovery that fully differentiated somatic cells can be reprogrammed into pluripotent stem cells. The true pluripotency of iPSCs from mouse cells was subsequently verified by the gold standard tetraploid complementation test. However, no such gold standard has been set to assess the full pluripotency of embryonic stem cells (hESCs) or iPSCs in humans. The primed state of hESCs or hiPSCs (human iPSCs) is not fully pluripotent, and female cell lines face risk of X chromosome erosion in long-term culture. Despite recent efforts, whether we have been able to truly recapitulate the pluripotency of the inner cell mass in the human blastocyst remains to be determined. The very definition of naïve and the means to achieve and maintain a naïve state is under debate. In this regard, the present so-called “naïve” hESCs or hiPSCs (human iPSCs) are not exactly perfect. By using comprehensive approaches, especially genome-wide sequencing, it will be exciting for the field to delve deeper into the mystery of induced reprogramming at the molecular level. Assessing the quality and safety of iPSCs is another task. Finding a robust marker associated with true pluripotency in these cells, along with efforts to improve the chemical culture system to stably maintain pluripotency, will be the foremost issue to facilitate clinical application of iPSC technology.
Breaking New Ground

Christa Bücker
Max F. Perutz Laboratories

The fact that reprogramming actually works, is still fascinating and amazing, even 10 years later. That a cell’s fate can be easily overruled by simple exogenous expression of a combination of transcription factors raised eyebrows. But early skeptics were won over by the reproducibility and simplicity of the process.

While much work has focused on the underlying mechanism, we still don’t understand how reprogramming works at the molecular level: why is it successful in some cells and not in others? What are the steps that lead from loss of one cellular identity to the acquisition of pluripotency? And what exactly is the pluripotent stem cell state? Combinations of single-cell technologies and screening tools will hopefully shed more light on the epigenetic barriers that protect a cell fate. These mechanistic insights will help to reduce variability between iPSC clones and improve reprogramming efficiencies. Moreover, we will gain knowledge about developmental and differentiation processes and cellular identity.

Besides the insights into basic biology, the first 10 years of iPSC research have led into diverse and unexpected areas: disease modeling, drug development, and even clinical applications. The next decade will massively expand upon that: directed differentiation and organoid culture systems from iPSCs will help us understand complex diseases and hopefully find new ways of treatment.

Ground-State Curiosity

Malin Parmar
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The discovery of iPSCs revolutionized the field of regenerative medicine and pushed the horizons of our knowledge and curiosity, opening up new and unanticipated possibilities towards the generation of patient-specific stem cells and personalized medicine. The first clinical trials for macular degeneration are under way, and as we learn more about the genetic stability, safety, and immunogenicity of these cells, the predictions are for them to reach the clinic for other diseases. Where donor-cell rejection is a major complication, iPSCs offer possibilities for autologous or allogenic matched donors that greatly surpass human embryonic stem cells, their natural biological counterparts. In essence, we have become living reservoirs of spare cells with the potential to repair any organ in our body. But perhaps beyond even this, the very notion of iPSCs has expanded our conceptual grasp of what is possible in biology. Waddington’s epigenetic landscape was challenged by showing how transcription factor delivery can fundamentally reprogram the identity and function of somatic cells. Now, 10 years after this remarkable discovery, studies have shown that it is possible to directly convert one mature cell type into another and that this can be done in vivo. These discoveries will inevitably change the landscape of regenerative medicine and of our scientific minds, propelling further innovations and leading to new treatment strategies.

Patient in a Dish

Nissim Benvenisty
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Reprogramming patient cells by defined factors generates iPSCs carrying specific disease mutations. The robustness of this process and availability of somatic cells from effectively any human disorder give an advantage to iPSCs over ESCs in disease modeling. The ability to differentiate human iPSCs into a variety of somatic cells enables analyzing phenotypes for multiple diseases, such as neurological and cardiac disorders. The initial success with such models triggered the establishment of several national and international initiatives aimed at deriving disease iPSCs, generating thousands of iPSC lines for the scientific community. One major aim in establishing such disease iPSCs is to better understand the molecular and cellular basis of the disease’s phenotypes, especially in cases where mouse models failed to recapitulate patient phenotypes. The other major aim is finding therapies for human disorders either by candidate drug testing or high throughput screening. However, disease iPSCs face many challenges; e.g., the most common human disorders with a genetic component are polygenic and appear late in life, and it is still unclear whether these embryonic-like cells would robustly show phenotypes related to such disorders. It can be expected that, in 10 years’ time, we would have iPSC models for practically any monogenic and polygenic disorder and, even with multiple mutations for each disease, in parallel to many clinical trials based on these patient cells in a dish.