What is Regenerative Medicine?

Regeneration is a well known biological term and phenomenon. According to the popular Webster dictionary, biological regeneration can be defined as “the restoration or the growth by an organism of organ or tissue, that have been lost, removed or injured.” Dr. William Haseltine believes that regenerative medicine is about assisting the body to heal itself. He is the father of regenerative medicine and the editor of the e-journal Regenerative Medicine. Dr. Helen Blau from Stanford University, US, wrote that the goal of regenerative medicine is to restore form and function to damaged tissues. Dr. David Stocum, from the University of Indianapolis, US, believes that the ultimate goal of regenerative medicine research is to be able to restore structure and function to damaged human tissues and organs that are incapable of regeneration. He is another prominent specialist in regenerative biology.

We suggest an “operative” definition of regenerative medicine as an engineered or assisted form of tissue regeneration. We also argued that, in its essence, regenerative medicine is an applied stem cell and developmental biology. There is a tendency to reduce or associate regenerative medicine with stem cells only. This is an obvious misconception. The phenomenon of regeneration in the adult organism is much more complex. Regenerative medicine cannot be related only to the mobilization and recruitment of resident, circulated or transplanted stem cells. From another point of view, mechanical artificial organs, ceramic or synthetic non-biodegradable biomaterials and prostheses would definitely be a misinterpretation of this field and its original meaning.
The Ten Commandments of Regenerative Medicine

In order to describe the evolving basic conceptual understanding of regenerative medicine and also to prevent persistent misconceptions, we tried to formulate the “Ten Commandments of Regenerative Medicine” as presented below:

1. Regenerative medicine is a biomedical technology, not a science.
2. Regenerative medicine is about minimally invasive cost-effective medical technology. It is about the regeneration and repair of the body. It is not about replacement of body parts with prostheses or artificial mechanical organs.
3. Regenerative medicine is a biology-based or/and biology-inspired technology.
4. Regenerative medicine must be based on solid basic science—regenerative biology, stem cell and tissue biology. Regenerative medicine, in essence, is an applied stem cell, developmental and regenerative biology.
5. Regenerative medicine is not only about isolation, propagation, “stemness” and multipotentiality and directed differentiation of embryonic and adult stem cells. It is also about tissue regeneration, in broad terms, including cell proliferation and apoptosis, differentiation, dedifferentiation, transdifferentiation and extracellular matrix remodeling.
6. Regenerative medicine is about “engineered,” “directed,” “assisted” or “enhanced” tissue and organ regeneration.
7. Regenerative medicine must be based on maximally deep knowledge about evolutional, developmental, physiological and pathological aspects of damaged or injured tissue regeneration as well as on detailed knowledge about histo- and organogenesis, tissue turnover and plasticity, regenerative and histogenic potential and its regulation.
8. In regenerative medicine, the most underestimated aspect is cell delivery.
9. The second most critical issue for future success or failure of regenerative medicine is an efficient functional integration of mobilized or transplanted stem cells.
10. Finally, success or failure in regenerative medicine technologies depends not so much on technological feasibility but rather on selection of commercially sound and profitable business models. Economic restraints (cost effectiveness) is an integral part of intellectual challenges in regenerative medicine.
Scientific Foundations of Regenerative Medicine

There are at least five recent discoveries which built the foundations for the emerging field of regenerative medicine.

- The isolated culture of human embryonic stem cells.
- The discovery of adult cell reprogramming with nuclear transplantation (so called “therapeutic cloning”).
- The discovery of embryonic stem cells and validation of their “stemness” (proliferative potential and multipotentiality of adult stem cells).
- The discovery of “transgerminal plasticity” of tissue and organospecific stem and mature cells (sometimes called “transdifferentiation”).
- The discovery of new mechanisms of tissue turnover in adult organism tissue (based on recruitment of resident and circulated adult stem cells).

In short, a series of these remarkable recent discoveries demonstrated that there are previously unknown mechanisms of the human organism and its tissues. These potential for regeneration can be enhanced and explored for therapeutic purposes.

The Main Challenges in Regenerative Medicine?

Besides many optimistic promises, regenerative medicine still has many challenges. Regenerative medicine, like any other emerging biomedical technology and biotechnology business, is a subject to substantial technology, manufacturing, clinical trials, financial, regulatory and political risks. There is a growing consensus that in order to be successful, cell therapy will have to be based on “off the shelf” products, not on autologous transplants. Thus, the main challenge is to figure out how to bypass histocompatibility barrier and to avoid immune rejection. Potential strategies to overcome the immune rejection of allogenic stem cells include allogeneic transplantation with pharmacological immunosuppression, nuclear reprogramming, genetic manipulation of major histocompatibility genes and induction of immune tolerance through the establishment of immune chimerism.

The recent paper with a very intriguing title: “Mesenchymal stem cells avoid allogeneic rejection” described at least three mechanisms of avoiding immune rejection by stem cells and it suggests strong optimism and indication of feasibility of the future “off the shelf” product approach. Mesenchymal stem cells appear to use a surprising array of mechanisms to avoid immune rejection by the host, including hypoimmunogenicity, modulation of immune cell function and creation of a immunosuppressive microenvironment. However, many other challenges remain before regenerative medicine. Future basic science and translational research is likely to focus on improving our ability to isolate, propagate and guide the differentiation of stem cells; control their survival and proliferation; indentify factors that mediate their homing and modulate the immune, inflammatory and fibrotic responses.
Evolving Business Models for Regenerative Medicine

The key to commercial success is to choose the right time for investment and to select the right business model. It can be a service, a product-based or a tool-proving business model. It is logical to assume that the selling of stem cells for research is not a very profitable business. From another point of view, one unit of umbilical cord blood or bone marrow, if transfused or transplanted into patient, usually costs US$20 000 to US$25 000. This seems like an economically sound business. However, in regenerative medicine, there is a strong belief that the “service model” will not work and there is a strong imperative from existing structure of biotech business to adopt the “off the shelf” or the “product-based” business model. A product-based business model maintains good manufacturing practice facilities to reduce profit margin due to high manufacturing costs. “Off the shelf” product-based model also implies using allogeneic not autologous cells. Finally, there is still no cost effective way to isolate, propagate cells and assemble tissues or organs in the operating rooms of the hospitals. This assumption (although it sounds very reasonable) can be mistaken. Bone marrow transplantation can be another prototype business model. But this model implies that hospitals, not biotech companies, will mostly benefit economically from such business model. If true, this view would suggest to health care providers to invest in the necessary regenerative medicine infrastructure (stem cell banks, GMP facilities, cell sorters, bioreactors and so on), in their hospitals. Small closely-operated automatic units placed inside or close to the operation room can replace expensive plants producing “off the shelf” allogenic products. Thus, one can argue that the insight for future successful business model in regenerative medicine must be taken not only from powerful big pharmaceutical and medical device industry, but also be from well established routine hospital business of blood transfusions, bone marrow and organ transplantations. Only time will tell us what business model will actually work.
Conclusion

We agree with a realistic view of the venture capitalist Mr. Giebel who recently wrote that “stem cell research needs to be incubated in the academia longer before it is ready to graduate into business that can commercialize the technology and deliver real products. Undoubtedly, when the time is right, venture capitalists will follow, to enable companies to commercialize and realize this promise.”

References:


5. Ryan JM, Barry FP, Murphy JM, Mahon BP. Mesenchymal stem cells avoid allogeneic rejection. J Inflamm (Lond). 2005 Jul 26; 2(1), 8

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