Fundamentals of Tissue Engineering and Regenerative Medicine

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(Eds.)

Fundamentals of Tissue Engineering and Regenerative Medicine

Springer

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Preface

The man-made creation of tissues, organs, or even larger organisms was for a long time a matter of myth and dream throughout the history of medicine. It now comes into clinical reality. Tissue engineering and regenerative medicine are the terms that are nowadays used to describe the approach to generate complex tissues and organs from simpler pieces. Both are multidisciplinary, young and emerging fields in biotechnology and medicine, which are expected to change patient treatment profoundly, generating and regenerating tissues and organs instead of just repairing them. There is much promise and expectation connected to this biomedical discipline regarding improved treatment possibilities, enhanced quality of the patient's life, and the ability to overcome in a future perspective the need for major grafting procedures. It is anticipated that this biotechnology has also a high economical impact on clinical medicine. To fulfil these expectations several challenges concerning scientific, technological, clinical, ethical, and also social issues need to be met. Basic research still requires the evaluation and elaboration of fundamental processes and procedures in multiple research fields. However, first bioengineered products have already been introduced in the markets, and much more are in the preclinical stage, and many companies are involved in this area.

In addition to having a therapeutic application, where the tissue is either grown in a patient or outside the patient and transplanted, tissue engineering can have diagnostic applications where the tissue is made in vitro and used for testing drug metabolism and uptake, toxicity, and pathogenicity. The foundation of tissue engineering/regenerative medicine for either therapeutic or diagnostic applications is the ability to exploit living cells in a variety of ways. Whereas tissue engineering is a more technical concept of tissue and organ reconstruction by the use of cells, scaffolds, and biomolecules, the term regenerative medicine is more focused on the support of self healing capabilities and the use of stem cells. Medicine-oriented stem cell research includes research that involves stem cells, whether from human, non-human, embryonic, fetal, or adult sources. It includes all aspects in which stem cells are isolated, derived, or cultured for purposes such as developing cell or tissue therapies, studying cellular differentiation, research to understand the factors necessary to direct cell specialization to specific pathways, and other developmental studies. In this sense it does not include transgenic studies, gene knock-out studies, nor the generation of chimeric animals.

Both concepts (tissue engineering and regenerative medicine) of cell, tissue, or organ regeneration and reconstruction are based on an multidisciplinary approach bringing together various scientific fields such as biochemistry, pharmacology,

material science, cell biology, and engineering and clinical disciplines. The promising biotechnology, now introduced as a new clinical tool in the restoration of lost tissues or the healing of diseases, is assumed to change treatment regimes and to contribute significantly to clinical medicine in future decades. A lot of current limitations seem most likely be overcome in the near future, suggesting that tissue engineering as well as regenerative medicine strategies will replace other therapies in routine clinical practice.

The fast growth of the tissue engineering and regenerative medicine discipline is mirrored by the high number of excellent research papers covering all aspects of these fields. Additionally, numerous high quality books are available describing in detail different aspects of tissue engineering or regenerative medicine. Despite the fact that such literature is already available, we decided to edit a book on tissue engineering and regenerative medicine. There were three reasons for this decision: during our experimental and clinical work on tissue regeneration and reconstruction, with our main focus on bone and cartilage engineering, which we have done for more than a decade in our clinics as well as in our interdisciplinary biomineralization and tissue engineering research group, we observed that many specialists of the different fields, involved in approaching this area, had difficulties in overviewing the complexity of the field. We therefore intended to edit a comprehensive book covering all major aspects of this field. Secondly, during the last decade a shift and, at the same time, interdentation was seen between the tissue engineering field and the field of regenerative medicine (with a main focus on stem cell research). In recent years stem cell research and use was applied with tissue engineering techniques and the border between both areas therefore blurred. This fusion is mirrored also by the emergence of new societies (for regenerative medicine) or the renaming of the most influential society (Tissue Engineering and Regenerative Medicine Society, formerly the Tissue Engineering Society International). Therefore, there was a need to integrate both aspects in one book. Thirdly, as tissue engineering brings together basic researchers, mainly having a biological, biophysical, or material science-oriented background, with clinically oriented physicians, we found that they differed in the used "language." In this text book the contributors tried to use an uniform terminology as a common platform for discussions across the borders of medical subspecialities.

Fundamentals of Tissue Engineering and Regenerative Medicine is intended not only as a text for biomedical engineering students and students in all fields of tissue engineering and cell biology, and medical courses at basic and advanced levels, but also as a reference for research and clinical laboratories. In addition, a special aim of this book was to define the current state of tissue engineering and regenerative medicine approaches which are applied in the various clinical particualar specialities. We have therefore conceptualised the book according to a methodological approach (social, economical, and ethical considerations; basic biological aspects of regenerative medicine; classical methods of tissue engineering (cell, tissue, organ culture, scaffolds, bioreactors); and a medical discipline-oriented approach (application of these techniques in the various medical disciplines). Since during the last years these therapeutic options have been introduced in clinical treatment decisions, this book gives profound basic tissue engineering information (as how to generate and regenerate tissues and organs) and at the same time the medical specialist will find detailed information on the state of regenerative medicine in his/her discipline. The text of this book is supported by numerous

tables, schematic illustrations, and photos in order to provide a better understanding of the information offered in this book. As the recent detailed knowledge in tissue engineering and regenerative medicine far exceeds the content of a book, we have tried to find a compromise between a comprehensive depiction of this new biomedical field and one that is manageable for the reader.

The expertise required to generate this book far exceeded that of it editors. No single expert, to date, is able to have detailed insight into all aspects of this fast growing and complex biomedical field. The content of the book represents the combined intellect and experience of more than one hundred researchers and clinicians, all of them outstanding specialists in their field. Their fundamental work has not only set the basis for the tremendous advances in this biotechnology field but has also given patients new and fascinating treatment options in clinical medicine.

Finally, we believe that, especially today, it is important to understand and reflect the current limitations of the field. The expectations must be aligned with scientific and, perhaps more importantly, ethical considerations and reflections. Given that stem cell use is a mainstay in regenerative medicine, a special focus is given to ethical as well as theological considerations. In addition to the impressive speed with which the advances in tissue engineering and regenerative medicine during the last decade have made a clinical impact on the treatment of many diseases, a fascinating aspect of this area of biotechnology is that it is a model of how basic biology is closely connected with and directly transferred to clinical medicine.

We hope this book will add further stimulus for all basic researchers and clinicians who are involved in investigating and applying tissue engineering and regenerative medicine techniques and will contribute to make this an attractive and reliable alternative treatment option in medicine.

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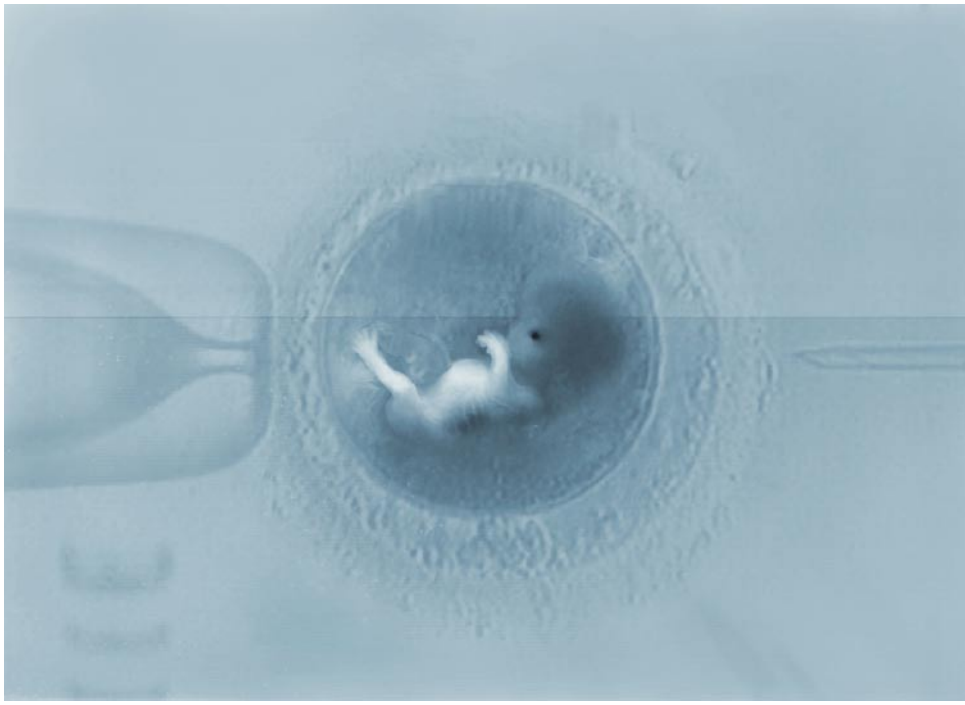
Part A

General Aspects

I General and Ethical Aspects



The History of Tissue Engineering and Regenerative Medicine in Perspective

1

U. Meyer

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1.1 History

The artificial generation of tissues, organs, or even more complex living organisms was throughout the history of mankind a matter of myth and dream. During the last decades this vision became feasible and has been recently introduced in clinical medicine. Tissue engineering and regenerative medicine are terms for the field in biomedicine that deal with the transformation of these fundamental ideas to practical approaches. Several aspects of generating new tissues and organs out of small pieces of living specimens are now scientifically solved, but at this point it is unknown how much impact these new approaches will have on clinical medicine in the future. In this respect it seems important to recapitulate from where the visions and the work came, in order to speculate or predict where tissue engineering and regenerative medicine will head.

The concept of tissue engineering and regenerative medicine as measures to create more complex organisms from simpler pieces is deeply embedded in the people's imaginary world. A change in the vision, hope, and believe of how to create or regenerate complex organs or organisms can be observed during history as a mirror of the cultural history of mankind. Even the early history of men is related to the idea that independent life can be created without sexual reproduction. Stories from Greek mythology [the creation of persons without sexual reproduction, e.g., the generation of Prometheus (Fig. 1.1)] may be considered as early reports representing the idea of creating living creatures from living or nonliving specimens. The Biblical tale of Eve created from Adam's rib is a further and perhaps the most well-known

Fig. 1.1 The generation of Prometheus

Fig. 1.2 Healing of Justinian

Fig. 1.3 Theophrastus von Hohenheinm

example of this concept [1] (in a modern view a kind of hybrid cloning). A multitude of examples in literature and the arts mirrors the desire of humans to be able to create by themselves living individuals or at least parts of individuals. The envisioned measures to create life are influenced by the social, cultural, and scientific background of individual persons at that time.

The famous painting "Healing of Justinian" (Fig. 1.2) a visualization of the legend of St. Cosmas and St. Damien (278 AD) depicting the transplantation of a homograft limb onto an injured soldier, is one early instance of the vision of regenerative medicine. As humans progressed in the understanding of nature and as they developed more advanced culture techniques they envisioned the generation of living creatures by applying physicochemical or biological techniques. During the transformation from the Middle Ages to the Renaissance in Europe, there was the hope and belief by a number of scientists that through alchemy living organisms could be generated. Theophrastus von Hohenheim, better known as Paracelsus (Fig. 1.3), tried (and failed) to find a recipe to create human life by a mixture of chemical substances in a defined environment.

Johann Wolfgang von Goethe (1749–1832) deals in his fundamental work of literature *Faust* [2] with the relation of an individual (Faust) to knowledge, power, morality, and theology. One central theme in the struggle of Faust to be powerful is the deeply embedded wish to create life. The creation of the artificial being Homunculus in Goethe's *Faust* is a central part of the drama, by which Goethe reveals various transformational processes working in the human soul. In the famous laboratory scene of *Faust (Part II)* he describes the vision of men being able to create life by alchemy (Fig. 1.4), representing the irrepressible human dream of "engineering" life:

Look there's a gleam! – Now hope may be fulfilled,
That hundreds of ingredients, mixed, distilled –
And mixing is the secret – give us power
The stuff of human nature to compound
If in a limbeck we now seal it round
And cohobate with final care profound,
The finished work may crown this silent hour

Fig. 1.4 Depiction of Dr. Faustus and his Homunculus

It works! The substance stirs, is turning clearer!
The truth of my conviction passes nearer
The thing in Nature as high mystery prized,
This has our science probed beyond a doubt
What Nature by slow process organized,
That have we grasped, and crystallized it out.

The description of the creation of Homunculus is also of special concern today, since it is suggestive of many contemporary "Faustian" technologies, such as cloning, genetic, or stem cell techniques in modern tissue engineering and regenerative medicine. With respect to an historical view of tissue engineering, Faust is a representative of Northern European humanity striving for evolution from the scientific and ethical limitations and strictures of the 16th century Reformations to the new aspirations of humanity that Goethe saw developing during the 18th century Enlightenment era. He was attracted to the idea of creating life by adding substances to nonliving specimens, similar to visions of how God created Adam, visualized by the famous painting of Michelangelo (Fig. 1.5). Goethe struggles to weave the personal inner journey of Faust towards some enlightenment (described in the prologue):

I've studied now Philosophy,
And Jurisprudence, Medicine,
And even alas! Theology
All through and through with ardour keen!
Here now I stand, poor fool, and see
I'm just as wise as formerly.
Am called a Master, even Doctor too,
And now I've nearly ten years through
Pulled my students by their noses to and fro
And up and down, across, about,
And see there's nothing we can know!

thereby being in the context of the collective social forces that are undergoing transformation through the historical processes of that time. As Faust deals with nearly all aspects and questions that arise in tissue engineering and regenerative medicine (and that are discussed in the first chapter of this book), it can

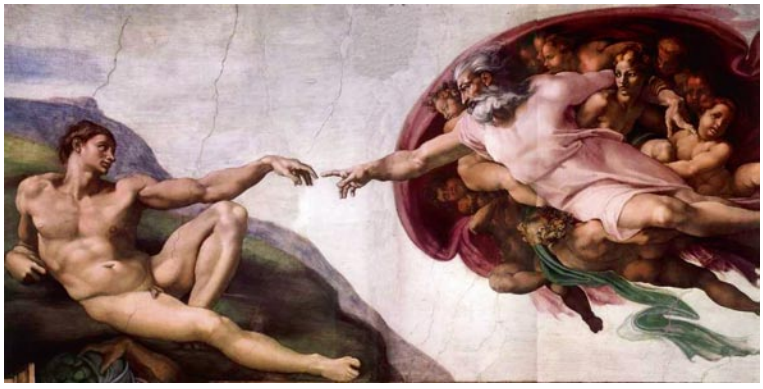

Fig. 1.5 Michelangelo's painting The Creation of Adam

be considered to be a timeless and always relevant consideration on the field of biomedicine.

Later on, as science and medicine progressed, a multitude of stories, reports, paintings, and films dealt with the idea that humans could create life by modern "scientific" measures. A prominent newer example in literature and film is the story of Frankenstein, written by Mary Shelley in 1818 (Fig. 1.6), describing the vitalization of a creature, reassembled from different body parts.

Parallel to the mythological, biblical, and fictional reports, various persons performed pioneering practical work to generate, heal, or regenerate body parts. The emergence of tissue engineering is, through their work, closely connected with the development of clinical medicine (prosthetics, reconstructive surgery, transplantation medicine, microsurgery) and biology (cell biology, biochemistry, molecular biology, genetics).

The mechanical substitution of body parts by nonvital prosthetic devices (metallic and ivory dentures, wooden legs) can be considered as early efforts to use biomaterials in reconstructive medicine. The first attempts to replace teeth in the sense of modern dental implantology seems to go back as early as in the Galileo-Roman period. The anthroposophic finding of a human skull, containing a metallic implant in the jaw [3], is indicative of early attempts of humans to regain lost function by tissue substitution. Leading areas of reconstructive medicine in clinical use were evident in the age before modern dentistry and orthopedics. Ambroise Pare` (1510–1590) described in his work *Dix livres de la chirurgie* [4] measures to reconstruct teeth, noses, and other parts of the body. A common method in the 18th century to replace teeth was the homologous transplantation of teeth in humans. John Hunter (1728–1793) investigated in his pioneering work the effect of transplantation not only at a clinical level (he claimed, that homologous transplanted teeth lasted for years in the host) but also performed animal experimental work on the fate of transplants, thereby setting the basis for a scientific approach on transplantation medicine [5].

A milestone in the modern view of tissue engineering was the use of skin grafts. The use of skin grafts is closely related to the work of the famous surgeon Johann Friedrich Dieffenbach (1792–1847). As he performed animal experimental and clinical work on skin transplantation (described in *Nonnulla de Regeneratione et Transplantatione* [6]), and as he also established ways to use pedicled skin flaps (since most of the clinical skin transplantation treatments failed), Dieffenbach is one of the modern founders of plastic and reconstructive surgery and can also be considered to be an early practitioner in transplantation medicine. Breakthroughs in the clinical use of skin grafts were made by Heinrich Christian Bünger, first successful autologous skin transplantation [7]; Jaques Reverdin (1842–1929), use of small graft islets; and Karl Thiersch (1827–1895), split thickness grafts [8, 9]. The high number of failures were overcome by the observation of Esser (1877–1964) that immobilization of transplants through the use of dental impression materials improves the fate of transplants in facial wound reconstruction. The clinical efforts reached through the combined use of surgical and dental techniques in reconstructive surgery and transplantation medicine led to the evolution of the dental- and medical-based Maxillofacial and Plastic Facial Surgery discipline. The foundation and establishment of this new specialty at the Westdeutsche Kieferklinik in Düsseldorf and the extensive experience in this center with injured soldiers during the

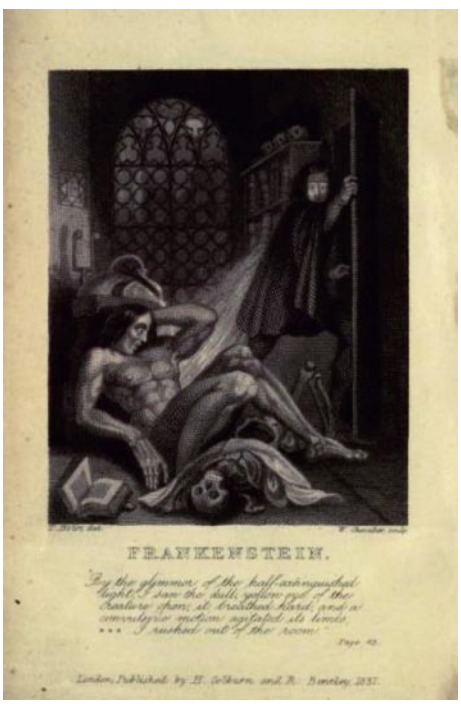

Fig. 1.6 Book cover of Frankenstein (Edition 1831)