Molecular and Translational Medicine

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As we enter into this new era of molecular medicine with an expanding body of knowledge related to the molecular pathogenesis of human disease and an increasing recognition of the practical implications for improved diagnostics and treatment, there is a need for new resources to inform basic scientists and clinical practitioners of the emerging concepts, useful applications, and continuing challenges related to molecular medicine and personalized treatment of complex human diseases. This series of resource/reference books entitled Molecular and Translational Medicine is primarily concerned with the molecular pathogenesis of major human diseases and disease processes, presented in the context of molecular pathology, with implications for translational molecular medicine and personalized patient care.

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Dwaine F. Emerich • Gorka Orive
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Cell Therapy

Current Status and Future Directions

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I would like to dedicate this book to a collection of people. First, and foremost, to my wife (Renee), son (Julian), and daughter (Simone) who have tolerated this crazy biotechnology life for 30 years and have always made me want to be a better person. Secondly, to Dr. Gorka Orive, co-editor of this book. We have had a nearly decade old, very fruitful, collaboration and the funny thing is-we have never met. Here's looking forward to that beer when we finally get together. Lastly, I would like to thank Mastery Martial Arts for adding years to my life following a life-threatening illness. Special thanks to Mr. West, a gifted instructor, for physical and mental guidance together with effective arm (and sometimes leg) twisting.

Dwaine F. Emerich

I would like to dedicate this book to my wife (Raquel), my two sons (Ander and Mikel), my parents (Ramón and Araceli) and my brother (Ibon). I am very fortunate to have them always by my side, receiving all their support and love. I also would like to thank my co-editor in this book, Dwaine Emerich. We have been working together "virtually" for more than 10 years and he has always been and remains being a benchmark for me. Dwaine inspires me and helps me to improve everyday. Last but not least, I would like to thank my instructors and my closest friends for their friendship.

Gorka Orive, Ph.D.

Preface: A Brief Introduction to the Span of Cell Therapy

Cell-based therapy is a very old concept dating back thousands of years. Today's modern concepts of cell therapy can be traced to studies by researchers such as Claude Bernard and Alexis Carrel in the early 1800s to 1900s to Dr. Paul Niehans in the 1930s who successfully treated a patient with a damaged parathyroid by macerating an ox parathyroid gland injecting it into a patient's pectoral muscle. Contemporary cell therapies are more targeted than the "general revitalizing whole body therapies" envisioned by these early investigators and, as illustrated in this, volume span a virtually unlimited range of therapeutic applications with cells derived from an equally diverse range of sources. Most cell therapies are experimental or are in early stage clinical trials with some notable exceptions including hematopoietic stem cells, dendritic cells (Provenge®), cartilage-derived chondrocytes (ChondroCelect® and MACI®) and corneal stem cells (Holoclar®). Together with rapid advances in many fields these therapies illustrate how recently intractable translational challenges have been overcome and how we can anticipate cycles of research and clinical development to lead to an acceleration in product approval.

It is impossible to classify all of the cell types under investigation for cell therapy or to list all of the possible indications that those cells could be applied to in an easily digestable format. But to give a flavor of the breadth of the field we list a few general approaches here.

1. Non-modified, somatic cells have been used as general medical practice for many years. Blood transfusions and bone marrow transplants are routine and other cells types including mesenchymal stem cells are under intense pre-clinical and clinical investigation. The reasons behind their routine use are based on the relatively easy ability to isolate and manipulate the cells into a reliable product without any associated significant co-technologies. Other cell types, especially immune cells for oncology, can also be considered under this classification but the complexity of manipulation and difficulties in cost-effective manufacturing and clinical translation make their use more challenging. It is also likely that in many cases, adjunct technologies for modification of immune cells will be needed to optimize their benefit. It is also likely, however, that these cells will not benefit in the near term from currently transformative immortalization technologies. Despite decades of basic research these technologies still remain unproven.

2. Viral manipulation of cells can be, in principle, carried out in vivo or ex vivo. This is really a subset of gene therapy and involves directly administering genes into the desired portion of the body. Commonly, this involves the use of viral vectors and can be applied to a vast range of indications including cancer, brain diseases, and cardiovascular diseases. Still the translation from animal model to human has been hampered somewhat by uncertainty over the ability to regulate or discontinue gene expression once the virus is injected. Ex vivo gene therapy involves transferring genes in culture prior to reintroducing the modified cells into the patient. This is also an area where the technology might be applicable for a variety of cell types, although the most common cell type are T cells where the cells are isolated and modified to activate the cells for selective destruction of cancers. This is one of the few areas where large pharmaceutical companies have invested considerable resources into developing large scale capacity.
3. Stem cell technologies hold the promise of a holy grail of an unlimited supply of an infinite repertoire of cell types. Beginning with the development of mouse and human embryonic stem cell lines the field has now been set on fire with the discoveries of transdifferentiation (or lineage reprogramming) and human induced pluripotent stem cells (iPS). It is difficult to understate the impact of the iPS revolution. While still in its infancy and still controversial, the field is developing rapidly in areas including using iPS cells to recapitulate neurodegeneration in vitro to understand disease pathogenesis and is hurtling towards clinical evaluation. Reprogramming approaches allow investigators to generate stem cells from poorly defined or accessed progenitor pools. As exciting as this field is it is still unknown whether iPS-based cell treatments will provide significant therapeutic benefits. As of now, nearly 2000 clinical trials are open and registered at www.clinicaltrials.gov. so many answers will be forthcoming. As a note of caution, such a large number of clinical trials can easily form unrealistic expectations. After all, clinical trials with these cells will still need to elucidate the optimal means of utilization including suitable trial designs, manufacturing processes that control cell composition, genetic stability/drift, optimal dosing and route of administration, and potency: all considerations that other cell therapies must traverse.
4. Biomaterials are increasingly being combined with cells to provide three–dimensional constructs that are otherwise unachievable with conventional approaches. Biomaterials initially were used as simple scaffolds for promoting cell growth, providing controlled drug delivery, or protecting cells from immunological destruction but have evolved considerably to provide support for tissue regeneration, control of cell fate, three-dimensional scaffolds for developing complex tissue and organ constructs. Even more contemporary materials are so–called "smart" and are capable of combining all of the above advantages with complex receptor-ligand profiles, thermo-responsive properties, and self-assembly.

5. In the future gene editing may become a viable means of targeted and efficient genetically engineering live cells by inserted or deleting DNA using engineered nucleases. The field has rapidly run through meganucleases, zinc finger nucleases, transcription activator-like effector-based nucleases and most recently the CRISPR-Cas system. CRISPR-Cas9, in particular, has moved into a mainstream technological method with enormous potential. Initial target indications will likely be blood cell and monogenetic diseases.

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