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Annu Navani · Sairam Atluri ·
Mahendra Sanapati *Editors*

Essentials of Regenerative Medicine in Interventional Pain Management

Second Edition

Springer

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Editors

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Manchikanti's Essentials of Regenerative Medicine in Interventional Pain Management, 2nd edition, *is dedicated to my grandmother, the late Gopamma Manchikanti, who was responsible for my entering into a medical career and who taught me the value of education and giving back; to my parents, the late Yadagiry and Laxmamma Manchikanti for their unconditional love and support; to my wife, Chandrakala, for her dedication and unceasing support; to our children, Anu and her husband, Alvaro, Sunil and his wife, Neena, Kavita (an interventional pain physician); and our grandchildren, Nikhil and Mehr, who have provided us the true meaning of life with pleasure.*

I also dedicate this book to all interventional pain physicians and regenerative pain medicine physicians across the globe and patients who suffer from chronic pain seeking relief, and, finally, the great staff of the American Society of Interventional Pain Physicians (ASIPP), Pain Management Centers, and Ambulatory Surgery Center.

Laxmaiah Manchikanti, MD

Editor-in-Chief

Foreword by Steven E. Sampson

Following my PM&R residency in 2006 and venturing into the unknown realm of clinical practice, I was introduced to the concept of Platelet-Rich Plasma. My journey began at an orthopedic practice in Santa Monica, CA, working with the United States men's national soccer team. We had word of a new treatment emerging from Spain using one's own blood to heal soft tissue, tendon, and ligament injuries. Since that time, the field of orthobiologics or more popularly termed regenerative medicine has rapidly evolved beyond my expectations.

After being disenchanted with the limitations of medications and corticosteroids, the promise and fundamental basic science behind cell therapy as a natural remedy for pain and musculoskeletal conditions were encouraging. At the same time, technology was rapidly advancing with musculoskeletal ultrasound and fluoroscopic image-guided delivery.

Eager to explore this realm and seek resources to build a solid foundation, I quickly found there were limited options. There were no orthopedic medical conferences or societies focusing on Platelet-Rich Plasma (PRP) and cell therapies. Therefore, I created TOBI (The Orthobiologic Institute) to gather multiple specialties to collaborate and promote best practices. The conference echoed the field's growth from 20 physicians at the initial meeting to hundreds of physicians attending from over 40 countries.

In 2006, there was a single PRP dental and craniofacial textbook available by Robert Marx. This resource described the premise behind platelets and growth factors affecting tissue and wound healing. This foundational textbook was a helpful resource providing the confidence to further explore orthobiologics. There was no regenerative medicine textbook or comprehensive literature reviews for common musculoskeletal conditions available for support.

Nowadays following the efforts of many pioneering colleagues and friends, editor-in-chief Laxmaiah Manchikanti, MD, and editors Annu Navani, MD, Sairam Atluri, and Mahendra Sanapati, MD, have provided a complete resource for practitioners at all skill levels. As a visionary, Laxmaiah Manchikanti, MD, founded ASIPP (American Society of Interventional Pain Physicians) and cultivated interventional pain management as a specialty. Dr. Manchikanti recognizes the vast potential and future trajectory in orthobiologics and, with a herculean effort, has produced this critical resource.

This essentials textbook of regenerative medicine in interventional pain management contains 34 chapters from leading authorities in the field. Its topics vastly cover critical subjects from autologous PRP, bone marrow concentrate, and adipose, to allogenic products, regulatory guidelines, ethical considerations, and more. It is a must-have for anyone practicing orthobiologics and applicable to multiple specialties confronting patients suffering from pain and musculoskeletal disease.

Orthopedic regenerative medicine is an exciting and rapidly changing field with potential to reshape the treatment of musculoskeletal injuries and pain management. There remain many challenges ahead from standardization, protocols, regulatory compliance, data collection, and vetting new technology. Having this bedside textbook resource available for clinicians is a major step forward as the field continues to move closer to mainstream.

The achievement of producing this comprehensive textbook will inspire the next generation of practitioners and hopefully heal the next generation of patients.

Pomona, CA, USA
Los Angeles, CA, USA

Steven E. Sampson

Foreword by Gabor B. Racz

In our daily life as physicians, one hears about successes, hopes, and failures, but also an undeniable generally accepted willingness to learn and find out more. Upon reading the updated version of *Manchikanti's Essentials of Regenerative Medicine in Interventional Pain Management*, 2nd edition, by Laxmaiah Manchikanti, MD, Annu Navani, MD, Sairam Atluri, MD, and Mahendra Sanapati, MD, I find an amazing knowledge base presented in a manner that finds the reader wanting to learn even more. The presentation is clear, the composition of sentences is anything but tiring, and it provides answers even to topics that the reader failed to consider. The body of knowledge comes from way over 2725 references, 34 chapters over 333 figures and 76 tables, through the diligent works of more than 57 authors.

To overcome the resistance to write another book, Laxmaiah Manchikanti, Annu Navani, Sairam Atluri, and Mahendra Sanapati deserve real credit because they recognized the need for broad-based multidisciplinary physician involvement. The field is large including other science-based disciplines such as engineering, molecular sciences, researchers, and healthcare-related national and international organizations getting into providing guidance in the last decade. It may have started as prolotherapy that organized medicine could not completely accept; however, determination of prolotherapy continues to take what was being gradually accepted not as prolotherapy but evolving into regenerative medicine. The separation and the regenerative powers of platelet-rich plasma, stem cells, and *mesenchymal stem cells* focusing on the ability to change function and repair, reconstruct even regrow, not just groups of cells but structures, are finding a way to broader and broader acceptance, basic science, and clinical information.

No question, the 34-chapters book effectively gathers the pertinent information without omitting any details for the reader, fulfilling its purpose as the Essentials of Regenerative Medicine for Interventional Pain Management. Truth has a way of winning and regenerative medicine is not necessarily the precursor or first step before surgery. Interventional pain with neuroplasty and lysis of adhesions is also growing and producing long-lasting results with inhibited fibroblast and reduction of inflammation through the use of hypertonic saline and hyaluronidase that can address multi-level pain and complement regenerative procedures. The notion of repairing, re-growing, and reforming body parts is very attractive, and the evolution of the knowledge, when one looks at the description of responding and nonresponding cell types, ensures that the outcome is not assured with any single patient. But as we know more, we recognize which therapies must have roles, when to consider neuromodulation, functional restoration, or other procedures based on evidence, and when surgery is the solution.

The big attraction is also through the figures and tables that lend themselves to a quick way of presenting lectures to others that have not had the opportunity to get to the essentials that really should be part of the armamentarium of decision-making on how to treat patients. The medical, legal, and ethical considerations are beautifully presented, and I feel that this book should be part of the personal library of all physicians in interventional pain management and other related fields.

The authors deserve our gratitude for the beautiful work that *Manchikanti's Essentials of Regenerative Medicine in Interventional Pain Management*, 2nd edition, has become.

Austin, TX, USA
Winston-Salem, NC, USA
Paducah, KY, USA
Frisco, TX, USA
Carrollton, TX, USA

Gabor B. Racz

Prologue

Having been an early adopter and innovator in Musculoskeletal Regenerative Medicine since my first PRP injection in 2008, I have witnessed rapid advancements in understanding and the complexity of Orthobiologics. However, there are still significant barriers to adoption and controversies in the field. These barriers exist in scientific, political, and clinical aspects. We are entering an era where an incredible amount of literature is published, for example more than 43 Randomized Controlled Trials for PRP, yet surprisingly slow adoption by institutions and insurers. The reasons are multifactorial and complex. In addition, we are seeing a dilution of research by studies that on paper have excellent methodology, yet utilize poor quality equipment and suffer from poor characterization of final orthobiologic product. These subtleties are not discerned by the beginner in this field, nor insurance and regulatory decision makers. Likewise, a trend towards "Assembly Line" regenerative medicine does not meet the highest standard of care, and threatens the whole field, with potential for poor outcomes at scale. We are in a time of desperate need to bring clarity and ethics into our field. This textbook is an attempt to lay a foundation in this regard. The authors collectively make up a passionate, disciplined, and ethical group, many of whom are driving the field forward with seminal research, development of new procedures, and equipment, as well as teaching on the national and international stage, and in active discussions with regulatory bodies. With additional time, research, adoption, and regulatory clarity, it is my hope that these therapies may be much more available to the masses, as an accepted way to meet the challenge of treating those in the treatment gap between conservative care and major surgical intervention. Until then, please enjoy learning with this comprehensive textbook, as a first step to competency in this field.

Rowan Paul
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San Francisco, CA, USA

Preface

Manchikanti's Essentials of Regenerative Medicine in Interventional Pain Management, 2nd edition, is an updated version of the book published in 2019 to bring concise, collective, and comprehensive information to all physicians practicing regenerative medicine, including interventional pain physicians and others with its applications in managing pain. Regenerative medicine is an integral part of interventional pain management within the definitions of interventional pain management and interventional techniques. Interventional techniques are defined as minimally invasive procedures including percutaneous precision needle placement, with placement of drugs in targeted areas or ablation of targeted nerves, and some surgical techniques such as laser or endoscopic diskectomy, intrathecal infusion pumps, and spinal cord stimulators for the diagnosis and management of chronic, persistent, or intractable pain. Interventional pain management is defined as the discipline of medicine devoted to the diagnosis and treatment of pain-related disorders principally with the application of interventional techniques in managing subacute, chronic, persistent, and intractable pain, independently or in conjunction with other modalities of treatment. While interventional pain management has been recognized as a specialty of its own since 2001, its origins date back to 1901 when the first caudal epidural injection was administered to manage low back and lower extremity pain. Interventional pain management continues to be an evolving and dynamic specialty. More recently entering the scene, regenerative medicine was defined in 1992 by Leland Kaiser as, "a new branch of medicine that attempts to change the course of chronic disease and in many instances will regenerate tired and failing organ systems." Subsequently, numerous authors with widespread literature have established the unique ability of stem cells to differentiate into all the cell types of the human body (pluripotency) and envisioned the immense potential to develop a new kind of regenerative therapy; at the same time, inevitable growth of regenerative medicine, at times dynamic, has also led to chaos and uncertainty creating multiple ethical and legal issues, and leading to an uncertain regulatory atmosphere.

Regenerative medicine by definition is a multidisciplinary specialty and a branch of translational research in tissue engineering and molecular biology, which encompasses the process of replacing, engineering, or regenerating human cells, tissues, or organs to restore or establish normal function. Consequently, regenerative medicine offers a transformative approach to health care, with the promise of engineering damaged tissues and organs by stimulating the body's own repair mechanisms to functionally heal previously irreparable tissues or organs. In the modern era, two major components of regenerative medicine in managing chronic pain include platelet-rich plasma and stem cell therapy. There is increasing literature in support of these modalities in managing spinal and musculoskeletal disorders. Enthusiastic support for the evidence-based practice of regenerative medicine continues to emerge. Even then, along with optimism and future directions, substantial controversy, misuse, abuse, and regulatory impact have taken center stage in recent years.

The goal of this comprehensive text is to provide an evidence-based approach to the application of principles of regenerative medicine in managing chronic pain of spinal, neurological, and musculoskeletal origins. While this is the first comprehensive text on the application of principles of regenerative medicine with appropriate descriptions of technical aspects for inter-

ventional pain physicians, we were committed to ensuring that this text was neither too long nor too cumbersome, and, yet, we have striven to make this work encyclopedic in its coverage. With this book covering the entire field of regenerative medicine applicable to interventional pain physicians it provides not only didactic materials but also focuses on technical aspects. From across the globe, leading experts in their respective fields have contributed chapters on specific topics following a single format: to present a cogent and integrative understanding of the field of regenerative medicine as applicable for interventional pain physicians.

We have maintained the overall unique structure of this text to our previous publications with an introduction of the subject, historical context, pathophysiology, applicability of regenerative medicine with its evidence base, indications, anatomy, technical aspects, complications, and precautions for each topic when available and applicable. This comprehensive book consists of 34 chapters, more than 333 figures, and 76 tables under the main sections of:

Part I: Basic Considerations

Part II: Regenerative Medicine in Musculoskeletal Disorders

Part III: Regenerative Medicine in the Spine

Part IV: Miscellaneous Applications

The development of this monumental task in the form of a book publication is attributed to the administrative and logistical expert eyes of the editors and staff of the American Society of Interventional Pain Physicians (ASIPP). This has placed a substantial burden on all involved and their families. The editors wish to thank all the contributors for their time, efforts, and development. In addition to the significant work by editors and contributors, an insurmountable effort has been forwarded by Tonie Hatton, Diane Neihoff, Savannah Gold, and Vidyasagar Pampati, MSc. We are also indebted to many of the world leaders in regenerative medicine and ethics and their families, without whose guidance and patience, this work would have been impossible. We are grateful to a world leader in interventional pain management, Gabor Racz, MD, and a world leader in regenerative medicine, Steven E. Sampson, DO, for writing the foreword.

This second edition will serve as a unique text for regenerative medicine physicians, including interventional pain physicians—a work in progress, which will see continued developments and changes. The overall focus continues to be patient safety in all applications of regenerative medicine to reduce pain and suffering. It is our goal to expand the evidence base and curb misuse and abuse, while at the same time reducing controversy by the implementation of appropriate regulations and guidelines. In this way, we can be optimistic about the future.

Paducah, KY, USA — Laxmaiah Manchikanti
Campbell, CA, USA — Annu Navani
Cincinnati, OH, USA — Sairam Atluri
Evansville, IN, USA — Mahendra Sanapati

Important Notice

The information provided in this book is based on the best available evidence and does not constitute inflexible treatment recommendations. Due to the changing body of evidence, this document is not intended to be a "standard of care." The material and guidance in this book are meant to provide a basis for the understanding behind the role of biologics in healing, to provide a source of appropriate indications for the use of biologics, to facilitate and help standardize biologic therapy, and to encourage the performance of high-quality studies in an effort to document outcomes and advance this field.

This book has been prepared with utmost care and diligence. Appropriate care has been taken to confirm the accuracy of the information presented and to describe generally accepted practices. However, the authors, editors, and publishers are not responsible for errors or omissions or for any consequences from application of the information in this book and make no warranty, expressed or implied, with respect to the contents of this book.

Readers must apply standard safety precautions and perform the techniques described only with appropriate experience. As new research and clinical experience broaden our knowledge of interventional pain management, changes in interventional modalities in regenerative medicine arena and drug therapy become necessary and appropriate. Readers are advised to keep abreast of the latest developments by staying informed about Food and Drug Administration (FDA) regulations, by reading journals, and checking the product information provided by the manufacturer of each drug to be administered to verify the recommended dosage, the method and duration of administration, and the contraindications. Some biologics presented in this publication may have FDA approval only for limited use. It is the responsibility of the healthcare provider to ascertain the FDA's approval status for each biologic, drug, or device planned for use in his/her clinical practice. This book will only provide guidance; however, it does not provide any standards. It is the responsibility of the treating physician, relying on individual experience and technical expertise, along with appropriate history, physical examination, and laboratory investigations of the patient to determine the appropriateness of regenerative medicine and drugs administered for each individual patient.

Neither the publisher, the editors, nor the contributors assume any responsibility for any injury and/or damage to persons or property arising from this publication.

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About the Editors

Laxmaiah Manchikanti is a physician specializing in interventional pain management, a professor, philanthropist, and author.

He is the founder of American Society of Interventional Pain Physicians, Society of Interventional Pain Management Surgery Centers, multiple state societies, American Board of Interventional Pain Physicians, as well as *Pain Physician* and *Pain Medicine Case Reports* medical journals.

He has been credited with advancing the evolution and development of interventional pain management as a specialty. Interventional pain management was recognized as a specialty in 2002 by the Centers for Medicare and Medicaid Services. In March 2005, interventional pain management was provided with mandatory representation on the Medicare Carrier Advisory Committee.

He founded the MGM scholarship fund, the Manchikanti Charitable Trust, Chandrakala and Laxmaiah Manchikanti Foundation, and sponsored the Manchikanti Library at McCracken County High School. In addition, he also founded and operates the Manchikanti Gopamma Primary School, Manchikanti Gopamma High School, and Manchikanti Yadagiry Junior College, donated fully equipped facilities for Manchikanti Yadagiry Memorial welfare residential school, and sponsored multiple other activities in Bodangparthy, Nalgonda District, Telangana state, and other areas. He is cofounder of the Gandhi Medical College Global Alliance and sponsored Manchikanti Auditorium at Gandhi Medical College, Hyderabad, Telangana state.

Dr. Manchikanti has been serving as Clinical Professor of Anesthesiology and Perioperative Medicine at the University of Louisville, Louisville, KY, since 2012, and Professor of Anesthesiology-Research, Department of Anesthesiology, School of Medicine, at the LSU Health Sciences Center, New Orleans and Shreveport, LA, since 2017.

He is serving as Chairman of the Board and Chief Executive Officer of American Society of Interventional Pain Physicians (ASIPP) and Society of Interventional Pain Management Surgery Centers (SIPMS). He has also served as President of ASIPP and SIPMS before being named Chairman of the Board of both ASIPP and SIPMS.

He is subspecialty certified in pain medicine by the American Board of Anesthesiology, Diplomate of American Board of

Interventional Pain Physicians and American Board of Pain Medicine, and competency certified in regenerative medicine.

He has been in practice in Paducah, KY, since completion of a fellowship in anesthesiology and critical care medicine in 1980. He graduated from Gandhi Medical College, Osmania University, Hyderabad, India. He completed his internship and residency in anesthesiology at Gandhi Hospital, Youngstown Hospital Association (Northeastern Ohio School of Medicine), Allegheny General Hospital, and his fellowship in anesthesiology and critical care medicine at the University of Pittsburgh School of Medicine.

Dr. Manchikanti has published over 600 publications and serves on several editorial boards. He is also the editor of 14 books designed for interventionalists.

Dr. Manchikanti has been recognized for his dedicated efforts by several prestigious organizations, including:

AAPI Presidential Recognition Award, 2023

Trailblazer Award, World Institute of Pain, 2019

Giants in Pain Management Award, American Society of Interventional Pain Physicians, 2017

Distinguished Alumni Award, Gandhi Medical College Global Association, 2016

Becker's Healthcare Leadership Award, Becker's Hospital Review

Interventional Pain management Visionary Award, National Spine & Pain Centers, 2015

Distinguished Service Award, Osmania, Gandhi and Kakatiya Medical Alumni Association of America, 2006

House of Representatives Presented in honor of Dr. Laxmaiah Manchikanti, MD, by Congressman Ed Whitfield, 109th Congress First Session, 2005–2006

Annu Navani is the Founder and CEO of Comprehensive Spine and Sports Center, the leader in interventional and interdisciplinary spine and orthopedic care. She founded Comprehensive Spine and Sports Center in 2008 with the vision of bringing evidence-based, cutting-edge therapies to the community. She also serves as the Medical Director of Le Reve Regenerative Wellness where she offers conventional and regenerative medicine therapies along with her team of interdisciplinary medical providers.

Dr. Navani completed her Anesthesiology residency from Medical College of Wisconsin, Milwaukee, and fellowship in Pain Medicine from the University of California, Davis. She is board certified by the American Board of Anesthesiology in Anesthesiology along with subspecialty certification in Pain Medicine (ABA) and through American Board of Interventional Pain Physicians (ABIPP). She is board certified in Regenerative Medicine by American Board of Regenerative Medicine and competency certified by American Board of Interventional Pain Physicians.

She is widely published in the field of Interventional Spine and Regenerative Medicine and has contributed via several

peer-reviewed journal articles, visionary editorials, and book chapters including the first-ever clinical practice guidelines for Spine Regenerative Medicine. Her clinical and research activities involve spine and orthopedic biologics, with a special interest in the application of biologic therapies for the restoration of structure and function of disrupted discs.

Her vision is to forward the field of regenerative medicine by rigorous research in biomedical engineering and cellular regeneration in an effort to offer it as a standard treatment to create a functional and fulfilling life for people.

Sairam Atluri is the founder of StemCures and medical director of Tristate Pain Management Institute in Cincinnati, Ohio. He has been practicing interventional pain medicine for more than 20 years after completing anesthesia residency and pain management fellowship at the University of Cincinnati. Dr. Atluri is board certified in anesthesia and pain medicine. He is certified in regenerative medicine by the American Society of Interventional Pain Physicians (ASIPP) along with certification in Pain Medicine by the American Board of Interventional Pain Physicians (ABIPP). Additionally, he is also a Fellow in Interventional Pain Practice (FIPP).

Dr. Atluri has published many articles in the field of Regenerative Medicine including the first and the largest controlled trial using bone marrow stem cells to treat severe chronic low back pain. He has written numerous chapters in four regenerative medicine textbooks. Dr. Atluri is recognized as one of the top 70 pain management physicians in the US by Becker Review.

Dr. Atluri's interest is in using stem cell therapy to treat chronic spine and joint pain. He is an instructor for the cadaver courses conducted by ASIPP and a speaker at the annual meetings of ASIPP and Ohio Society of Interventional Pain Physicians regarding stem cells. He is also a speaker at the top regenerative medicine organizations like TOBI (The Orthobiologic Institute) and IOF (Interventional Orthobiologics Foundation).

Mahendra Sanapati is Director of the Pain Management Centers of America and Medical Director of Pain Management Centers of America, Evansville, IN, and the Advanced Ambulatory Surgery Center, Evansville, IN. He is the founder of Advanced Pain Care Clinic in Evansville, IN, and the Global Scientific Innovations, Evansville, IN.

He is the Executive Vice President of the American Society of Interventional Pain Physicians, President of the Indiana Society of Interventional Pain Physicians, as well as Vice President of the Society of Interventional Pain Management Surgery Centers. Dr. Sanapati completed his residency at New York Medical College Affiliated Hospitals in Valhalla, NY, and a Fellow in Pain Management.

He has board certifications as a Diplomate with the American Board of Anesthesiology and American Board of Interventional

Pain Physicians, and a subspecialty certification in Pain Medicine from the American Board of Anesthesiology. He is also certified in regenerative medicine.

Dr. Sanapati has authored multiple manuscripts and has been a presenter and panelist for multiple meetings, covering a variety of topics in pain management. He is a member of the American Society of Interventional Pain Physicians, Kentucky Society of Interventional Pain Physicians, Indiana Society of Interventional Pain Physicians, the International Neuromodulation Society, the American Medical Association, and the American Society of Regional Anesthesia and Pain Management.

Part I

Basic Considerations

1 Evolution of Regenerative Medicine in Managing Musculoskeletal and Spinal Disorders

Laxmaiah Manchikanti, Annu Navani, and Mahendra Sanapati

Introduction

Regenerative medicine is the science of repair, restoration, and regeneration of diseased or injured cells, tissues, or organs to restore homeostasis. This multidisciplinary specialty includes advanced research leading up to clinical applications from the art of tissue engineering all the way to the science of cellular biology producing a variety of injectates, implants, scaffolds to simulate normal morphology and function in tissues [1–3]. In addition, regenerative medicine offers a transformative approach to health care, with a promise of engineering damaged tissues and organs by stimulating the body's own repair mechanisms to functionally heal previously irreparable tissues or organs [4]. Cell biology is *the branch of biology that studies the structure, function, and behavior of cells,* the structural, functional, and biological unit of all organisms. Tissue engineering, on the other hand, is the use of a combination of cells, engineering and materials, methods, and suitable biochemical and physical chemical factors to improve or replace biological tissues. The term regenerative medicine is often used synonymously with tissue engineering, even though scientists and practitioners involved in regenerative medicine place more emphasis on the use of multiple techniques beginning with prolotherapy, platelet-rich plasma (PRP), and stem cell therapy.

In the modern era, two major components of regenerative medicine in managing chronic pain include PRP and stem cell therapy. An increasing number of physicians believe that the injection of PRP or stem cells are an effective treatment for various spinal and musculoskeletal disorders [5–10]. Even though these treatments have not been well established, and the literature continues to emerge, there is enthusiastic support for the evidence-based practice of regenerative medicine [11]. Even then, along with optimism and future directions, substantial controversy, misuse, abuse, and regulatory impact has taken center stage in recent years [12–26].

Historical Context

The concept of regeneration dates to 2000 years ago when Aristotle recorded Initial observations on the regeneration of the tail in lizards, as reported in his book, *History of Animals*, cited by Dinsmore in his publication [27].

In 1992, Leland Kaiser [28] in an article describing future technologies utilized the term regenerative medicine stating that, "a new branch of medicine will develop that attempts to change the course of chronic disease and in many instances will regenerate tired and failing organ systems" [29]. Subsequently, the wide-spread use of the term regenerative medicine has been attributed to the founder of human genome sciences, William A. Haseltine [30]. Speaking on the isolation of human embryonic stem cells, Haseltine recognized that unique ability of these cells to differentiate into all the cell types of the human body (pluripotency) and envisioned that there was a potential to develop a new kind of regenerative therapy [31–34]. Consequently, he used the term "regenerative medicine" in the way that it is used today describing an approach to therapy that employs human genes, proteins, and cells to re-grow, restore or provide mechanical replacements for tissues that have been injured by trauma, damaged by diseases or worn by time and offering the prospect of curing diseases that cannot be treated effectively including those related to aging [30].

In a breakthrough in 1908, Russian histologist Alexander Maximow [35, 36] proposed the term "stem cell" for scien-

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tific usage. After a hiatus of a few decades, a series of discoveries led to renewed interest and acceleration in research focused on clinical applications. The scientific evidence of adult neurogenesis in ongoing stem cell activity in the brain was presented by Joseph Altman et al. in 1960 [37]. In 1963, McCulloch and Till illustrated the presence of self-renewing cells in mouse bone marrow [38] and in 1968, bone marrow transplant was first used between 2 siblings to treat severe combined immunodeficiency. In 1981, mouse embryonic cells were derived from inner cell mass [39] and in 1992, neural stem cells were cultured in vitro as neurospheres [36]. Then in 1981, embryonic stem cells were first identified in mice and soon the first artificial animal clone, Dolly the sheep, took birth in 1997 [40]. Soon researchers claimed that similar hybrids could be made by fusing human embryonic stem cells with adult cells from a particular person to create genetically matched tissue and organs. From 1995 to 1998, Michael D. West, PhD, organized and managed the research between Geron Corporation and its academic collaborators, James Thomson at the University of Wisconsin, Madison, and John Gearhart of Johns Hopkins University, that led to the first isolation of human embryonic stem and human embryonic germ cells, respectively [41].

In 1998, Thomson et al. isolated human embryonic stem cells [42]. In 2006, Shinya Yamanaka of Kyoto University announced the arrival of "induced pluripotent stem cells;" adult cells that were genetically induced to revert to embryonic-like cells [43]. In 2007, Martin Evans shared the Nobel Prize for medicine with Mario Capecchi and Oliver Smithies for work on genetics and embryonic stem cells [44]. In 2012, Yamanaka won the Nobel prize for creating induced pluripotent stem cells, which he shared with John Gurdon of the University of Cambridge [45, 46].

A new type of stem cell was discovered by scientists of Wake Forest University and Harvard University led by Dr. Anthony Atala in early 2007 [47]. In the same year (2007), research reported by three different groups showed that normal skin cells can be reprogrammed to an embryonic state in mice [48]. On September 12, 2014, Masayo Takahashi at the Riken Centre at the Institute of Biomedical Research and Innovation Hospital in Kobe, Japan, transplanted a 1.3/3.0-millimeter sheet of retinal pigment epithelium cells, which were differentiated from induced pluripotenti stem cells (iPS) cells through directed differentiation, into an eye of an elderly woman, who suffered from age-related macular degeneration [48]. The scientific work in this field is progressing rapidly, opening new frontiers to solving some of the greatest medical challenges in history.

Regenerative medicine is also described interchangeably as tissue engineering aiming to regenerate damaged tissues, instead of replacing them, by developing biological substitutes that restore, maintain, or improve tissue function [49]. The term "tissue engineering" was officially coined at the National Science Foundation workshop in 1988 to mean, "the application of principles and methods of engineering and life sciences toward the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve tissue function." The field of tissue engineering is multidisciplinary, drawing expertise from engineering and life sciences including clinical medicine, materials science, genetics, mechanical engineering, and other related branches. Tissue engineering relies extensively on the use of scaffolds—artificial three-dimensional frame structures that serve as a mimic extracellular matrix for cellular adhesion, migration, proliferation, and tissue regeneration in three dimensions. The scaffolds essentially act as a template for tissue formation and are typically seeded with cells and occasionally growth factors or subjected to biophysical stimuli on the form of a bioreactor; a device or system which applies different types of mechanical or chemical stimuli to cells [50]. Thus, cell-seeded scaffolds are either cultured in vitro to synthesize tissues which can then be implanted into an injured site or are implanted directly into the injured site using the body's own systems, where regeneration of tissues or organs is induced in vitro.

Interventional pain management is defined as, the discipline of medicine devoted to the diagnosis and treatment of pain related disorders principally with the application of interventional techniques in managing subacute, chronic, persistent, and intractable pain, independently or in conjunction with other modalities of treatment [51]. In addition, interventional techniques are defined as, minimally invasive procedures including, percutaneous precision needle placement, with placement of drugs in targeted areas or ablation of targeted nerves; and some surgical techniques such as laser or endoscopic diskectomy, intrathecal infusion pumps and spinal cord stimulators, for the diagnosis and management of chronic, persistent, or intractable pain [52]. Regenerative medicine has significant potential for interventional pain physicians to incorporate into daily practices of chronic pain management. The past 20 years have seen a tremendous growth of interventional pain management to a level of explosive increases until 2009, followed be deceleration through 2019 and decreases due to COVID-19 pandemic providing minimally invasive, interventional techniques in managing chronic pain [53–61]. However, recent data and analysis have shown a reversal of growth patterns from 2009 to 2016 [53–61]. Further, interventional pain management has suffered with reimbursement issues [62–65], coverage policies, and finally debate on the effectiveness of interventional techniques [64, 65]. Consequently, regenerative medicine has offered a potential for growth with research and applications in interventional pain management.

Consequently, the therapeutic application of cells or cell-based therapy, forms a fundamental part of the landscape of

regenerative medicine or tissue engineering and the attendant exploding applications, development, revenues, and associated regulations, fraud, and abuse [12, 66]. While regenerative medicine has extensive applications, its applications in managing chronic pain and musculoskeletal disorders are of paramount interest for interventional pain physicians.

Evolution

Once the discovery started, the adaptation and growth of Regenerative Medicine was inevitable. The existing short-lived surgical solutions for musculoskeletal and spine conditions were now open to a minimally invasive solution that would have the potential for lasting a lifetime [66]. Also, efforts went into conceptualizing solutions that would be healing while offering efficacy and sustainability. There was also a consumer driven interest towards natural and holistic solutions that could preserve and heal native tissues to restore homeostasis as opposed to the traditional concept of excision and replacement of the damaged tissues. In vitro and animal studies have appealed to researchers and clinicians alike who have exponentially moved the field forward over the last decade. The last few decades have seen a tremendous growth in clinical trials around the world as shown in Fig. 1.1 [67]. These can be further traced to identify the variations of publications between different countries of the world.

Figure 1.2a, b depict the global trends of worldwide clinical trials for mesenchymal stem cells (MSCs) (Fig. 1.2a) and stem cells in general (Fig. 1.2b) [68]. It is interesting to note that most MSC trials are being conducted in China (35%) followed by the U.S. (21%) and Europe (23%). In contrast, the U.S. (61%) is by far the world leader in stem cell clinical trials, followed by Europe (23%), China (7%), followed

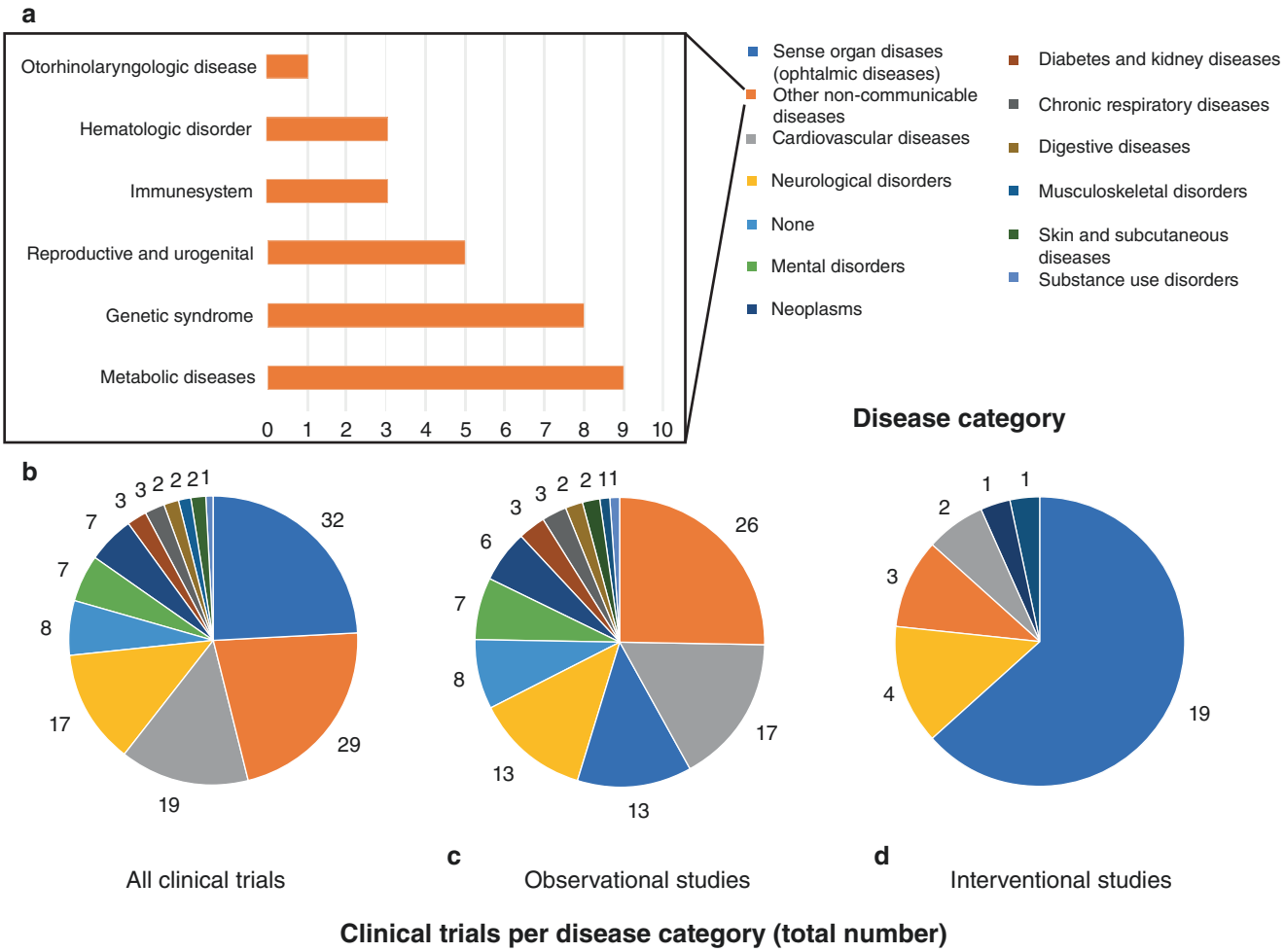

Fig. 1.1 Disease categories targeted in clinical trials involving human pluripotent stem cells. The legend shown on the top right is color coordinated with all three pie charts. (**a**) Sub-classification of the category "non-communicable diseases". (**b**) Distribution of clinical trials involving pluripotent stem cells dependent on the targeted disease. (**c**) Distribution of observational clinical trials dependent on the targeted disease. (**d**) Distribution of interventional clinical trials dependent on the targeted disease. Source: Deinsberger J, Reisinger D, Weber B. Global trends in clinical trials involving pluripotent stem cells: A systematic multi-database analysis. *NPJ Regen Med* 2020; 5:15 [67]

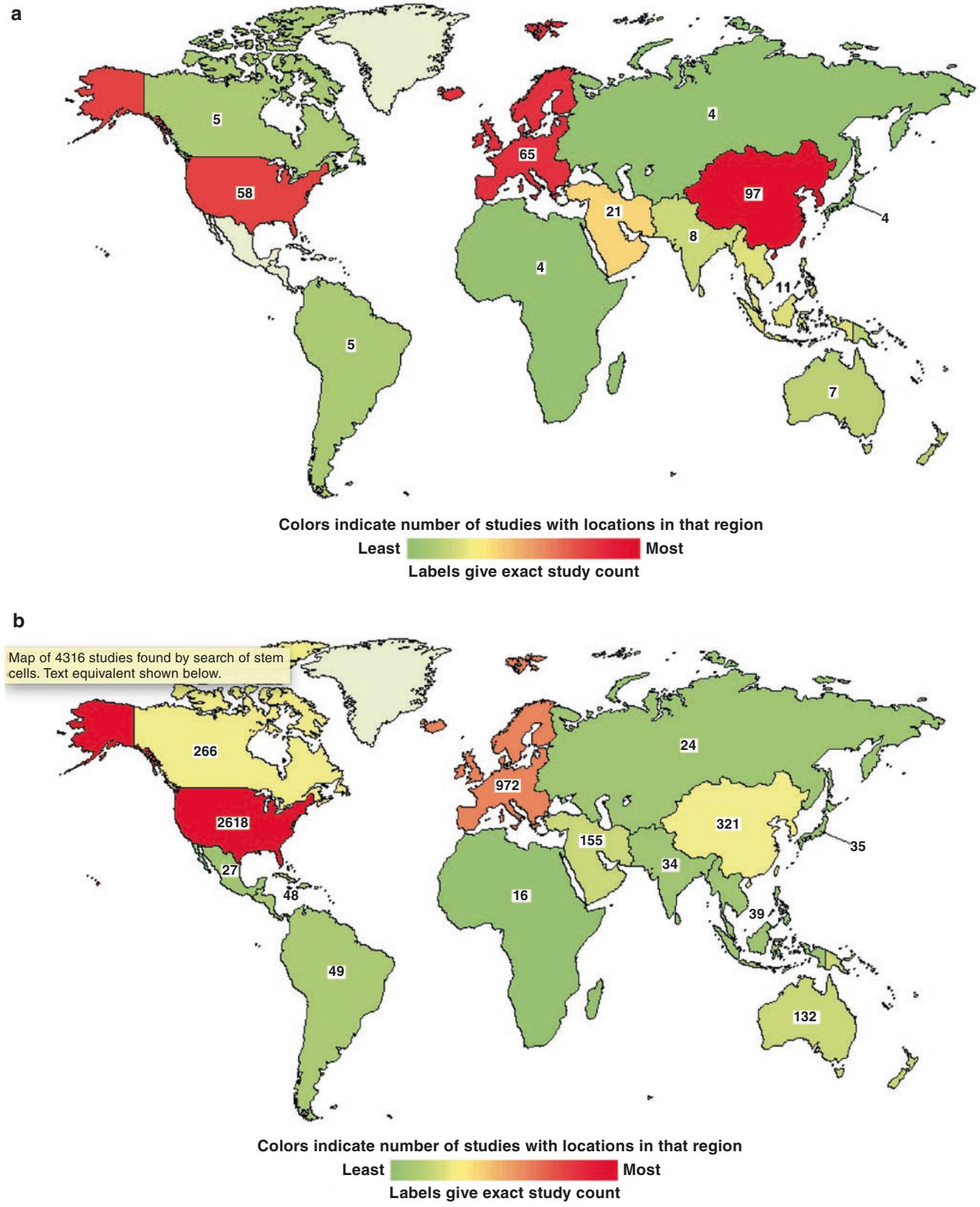

Fig. 1.2 Global trends of worldwide clinical trials for mesenchymal stem cells (**a**) and stem cells in general (**b**). Mapping global trends in MSC & stem cell clinical trials: Unexpected findings by Professor Paul Knoepfler, Ph.D/2 Comments/December 10, 2012/Blog, stem cells

Fig. 1.3 World stem cell policy map showing countries with permissive (dark brown), flexible (light brown), or restrictive or no policy on ES cell research. Permissive policy allows various laboratory techniques to create embryonic stem cell lines, including nuclear transfer/research cloning and the extraction of stem cells from embryos that remain unused after IVF treatments. Flexible policy allows the creation of stem cell lines from donated embryos unused after IVF treatments. Countries colored in brown represent about 3.5 billion people, more than half the world's population. Reproduced from: scmap.html (reprinted with permission of William Hoffman, MBBNet, University of Minnesota)

closed by Canada, with India and Australia after that [68]. These trends in growth have been dictated by politics and policies around the world. Figure 1.3 outlines the world stem cell policy map showing countries with permissive (dark brown), flexible (light brown), or restrictive or no policy on embryonic stem cell research [69].

In 2016, the search of PubMed database for scientific publications containing the term "mesenchymal stem cell" or "mesenchymal stem cells" results in nearly 30,000 results as reported by Bioinformant Inc. [70]. Of those, 62% i.e., 17,804 of those MSC articles were released between 2011–2016 noted in Fig. 1.4 [70] and more than half of the total publications, i.e., 15,808 of all MSC publications pertain to "Humans," rather than "Other Animals" as noted in Fig. 1.5 [70]. A current analysis through June 2023 showed rapid increase in publications in the last 7 years (Fig. 1.6).

The trends in the total number of newly registered trials that increased linearly in each year from 2007 to 2012, and more than quadrupled during this period is depicted in Fig. 1.7a thereafter slowing in 2018. When newly registered trials are divided by phase, the number of new phase 2 trials increased through 2011, after which they appear to have plateaued Fig. 1.7b. The number of phase 3 trials increased transiently in 2012–2014 to a peak of ~12% of all trials reported but only accounted for ~6% of all trials since 2015 [71].

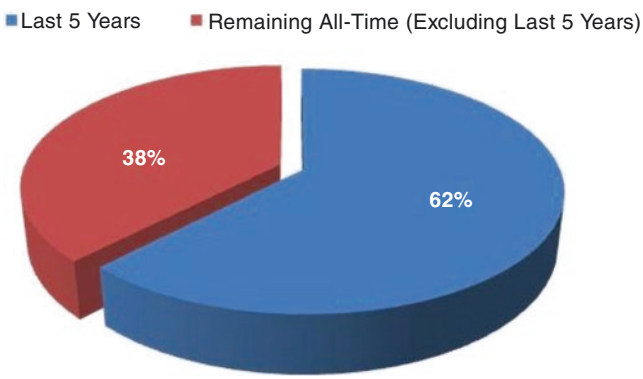

Fig. 1.4 Percentage of MSC scientific publications released in the last 5 years. Source: Hildreth C. Two-thirds of all mesenchymal stem cell (MSC) publications were released in the past 5 years. *BioInformat*. 2016. https://bioinformant.com/two-thirds-of-all-mesenchymal-stem-cell-msc-publications-were-released-in-the-past-5-years/ [70]

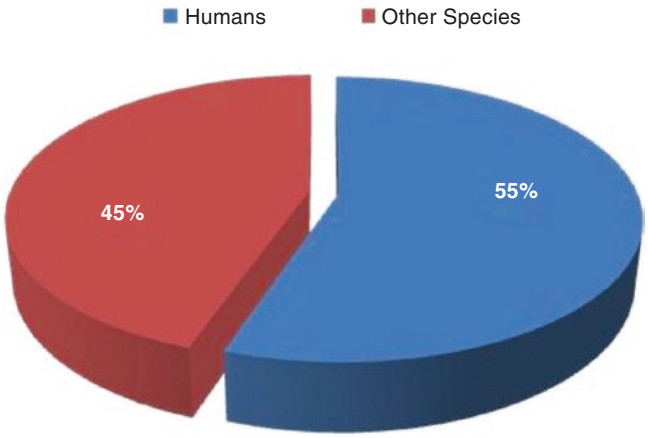

Fig. 1.5 Breakdown of MSC publications by species. Source: Hildreth C. Two-thirds of all mesenchymal stem cell (MSC) publications were released in the past 5 years. *BioInformat*, July 15, 2016. https://bioinformant.com/two-thirds-of-all-mesenchymal-stem-cell-msc-publications-were-released-in-the-past-5-years/ [70]

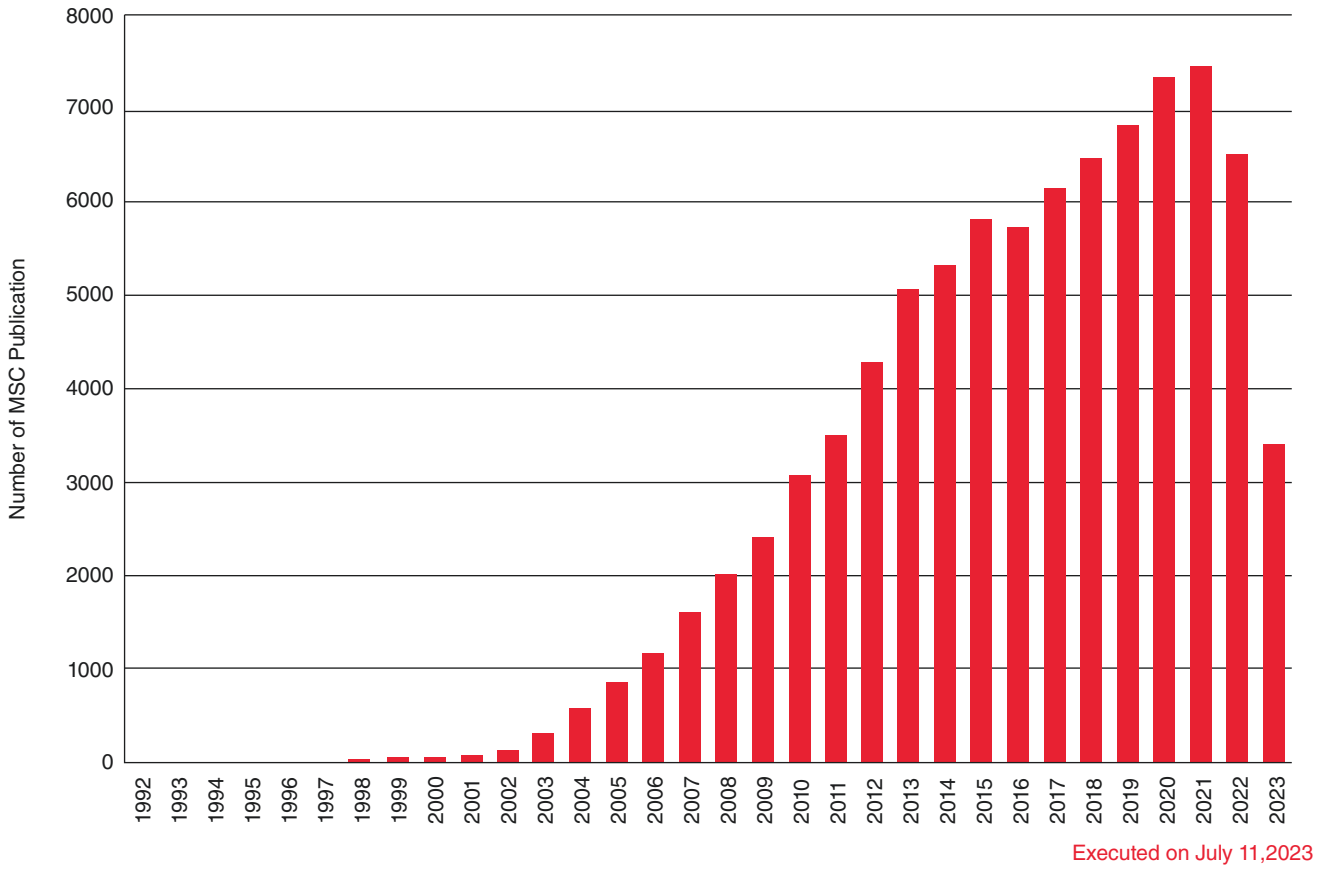

Fig. 1.6 Half of all mesenchymal stem cell (MSC) publications on PubMed were published in the past 7 years

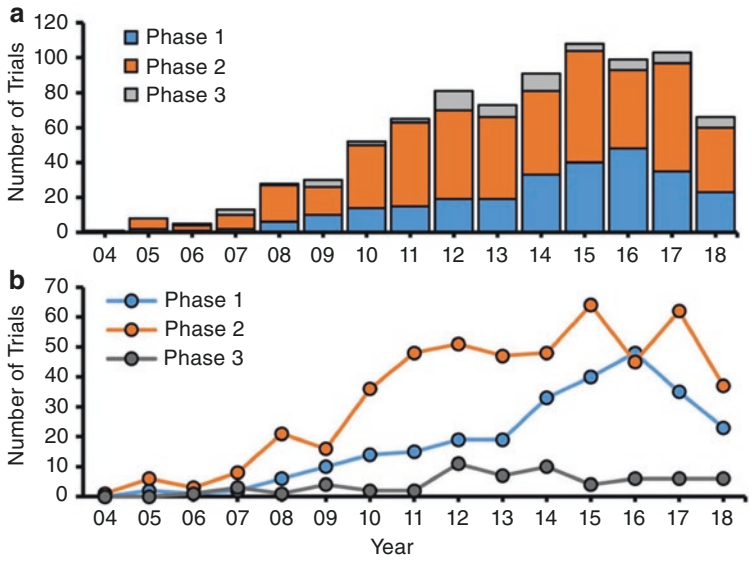

Fig. 1.7 Trends in the total number of newly registered trials increased linearly in each year from 2007 to 2012, and more than quadrupled during this period. (**a**) The rate of increase in new trial listings slowed thereafter and dropped dramatically in 2018. When newly registered trials are divided by phase, the number of new phase 2 trials increased through 2011, after which they appear to have plateaued (**b**). Source: Bergel S. Uber wirkungen des fibrins. *Deutsche Medizinische Wochenschrift* 1909; 35:663 [71]

Origin and Types of Regenerative Medicine

The present focus on regenerative medicine is based on therapy with (PRP) and adult stem cell therapy in chronic pain, even though, a multitude of other biologicals have been described and utilized.

Platelet-Rich Plasma (PRP)

After the initial descriptions of prolotherapy, the use of PRP has been popularized [72–76]. PRP is defined as, "a sample of autologous blood with concentrations of platelets above baseline values [72]." PRP has been used since 1909 for its potential for clinical use as autologous fibrin glue [66, 72]. Since 1950, PRP has been used to manage dermatologic and oral maxillofacial conditions [72]. Over the years, PRP gradually has been studied and used in several branches of medicine including musculoskeletal medicine, orthopedic surgery, and specifically spine [5–8, 72, 75].

The nomenclature of PRP products is confusing with multiple terms used including platelet concentrates, autologous growth factors, plasma rich growth factors, platelet gel, and platelet-rich fibrin matrix [76, 77]. In addition, classification categorizing PRP formulations based on the presence of leukocytes and the fibrin architecture of the formulation have been described [78]:

- Pure platelet-rich plasma (PPRP) referring to leukocyte-poor PRP.
- Leukocyte- and platelet-rich plasma (LPRP) referring to PRP that contains leukocytes and has a low-density fibrin network after activation.
- Pure platelet rich plasma fibrin (PPRPF) which designates preparations without leukocytes and with a high-density fibrin network, which are also called leukocyte-poor platelet rich fibrin.
- LPRF designated to describe the preparations that contain leukocytes in a high-density fibrin network.

Another classification system described by DeLong et al. [79] also known as the PAW Classification System of PRP is based on the absolute number of platelets (P), the way platelet activation (A) occurs, and the presence of absence of leukocytes (W).

Platelets are a nuclear 2–3 μm diameter fragments of megakaryocytes from the bone marrow and contain an abundance of growth, chemotactic, and clotting factors (Fig. 1.8) [80–82]. Platelets are capable of adhering to and pulling together torn tissue using their tentacle-like filopodia with an internal network of actin and myosin (Fig. 1.9) [82, 83]. PRP is simply a platelet concentrate, platelets in plasma concentrated 3–5× or higher than in whole blood [73, 84].

Platelets are activated to adhere to collagen and release their growth factors. Platelet activation depends on external stimuli such as thrombin, adenosine diphosphate (ADP), calcium [85–87], or the presence of certain structural proteins that are not present in the endothelium such as collagen [88]. Platelet degranulation involves the fusion of alpha and dense (delta) granules to their membranes with release of growth and anabolic factors [89].

Platelet degranulation results in inflammation [90, 91], recruitment and proliferation of several cell types including leukocytes (days 0–2) [92, 93], promotion of neovascularization (days 2–3), migration and division of fibroblasts, synthesis of collagens type I and III, and new tissue formation (days 3–5) [91].

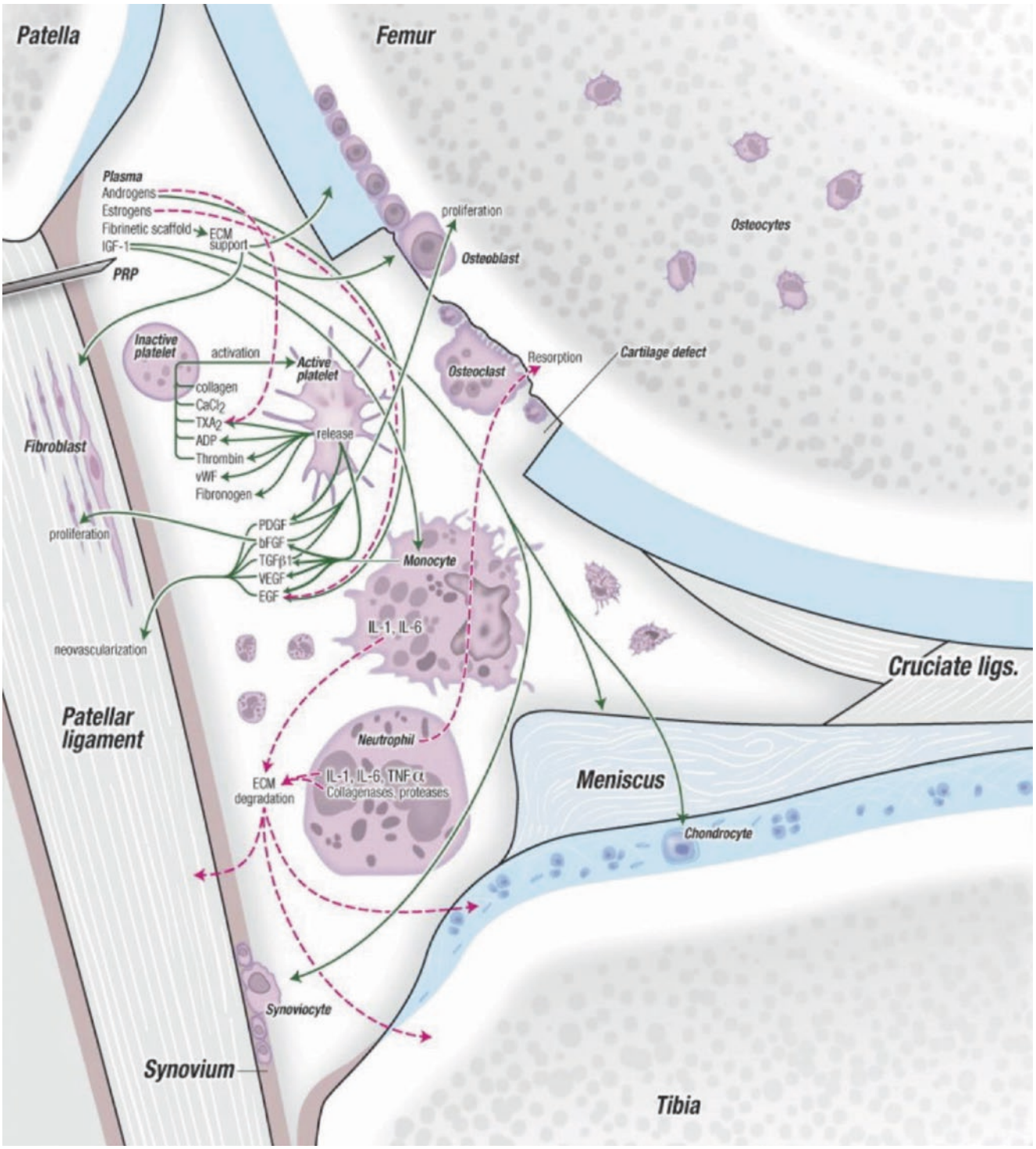

Fig. 1.8 Platelets and their growth factors upon PRP injection into the knee. PRP has leukocytes to a variable degree, including neutrophils and monocytes. Soluble hormones such as IGF-1 and target cells such as synovial, meniscal, and ligamentous fibroblasts, chondrocytes, and osteocytes are shown. Arrows indicate positive (green) and negative (red) effects. *ADP* adenosine diphosphate; *$CaCl_2$* calcium chloride, *ECM* extracellular matrix, *EGF* epidermal growth factor, *IL-1* interleukin 1, *IL-6* interleukin 6, *ligs* ligaments, *TNF* tumor necrosis factor, *VEGF* vascular endothelial growth factor, *vWF* von Willebrand factor. Source: Boswell SG, Cole BJ, Sundman EA, et al. Platelet-rich plasma: A milieu of bioactive factors. Arthroscopy 2012; 28:429–439 [80]

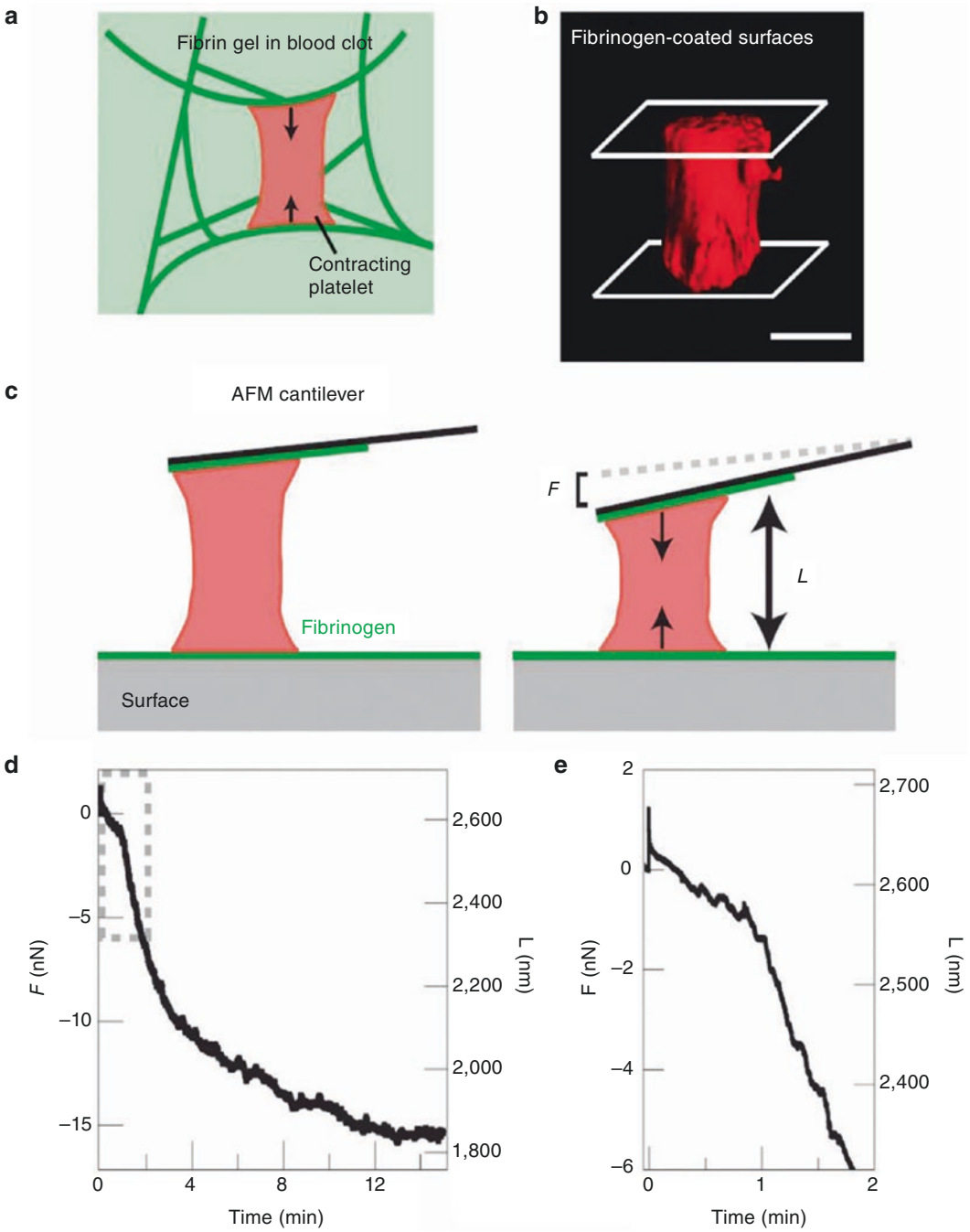

Fig. 1.9 Measuring contraction of single platelets using an atomic force micrometer (AFM). Diagrams of (**a**) platelet contraction in a blood clot, (**b**) platelet within experimental set-up, (**c**) AFM cantilever measuring platelet contraction force. Graph (**d**) of activated platelet force (nN) and displacement (nm) versus time (min), and (**e**) close-up of left upper corner of (**d**). Reproduced from: Lam WA, Chaudhuri O, Crow A, et al. Mechanics and contraction dynamics of single platelets and implications for clot stiffening. Nat Mater 2011; 10:61–66 [82]

Platelets release platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor beta-1 (TGF-B1), interleukin 1B (IL-1B), ADP, and histamine [94, 95]. These factors stimulate leukocytes to release inflammatory cytokines (IL-1B, TNF-á, IL-6) [96], enhance the expression of degradative enzymes of the matrix metalloproteinase (MMP) family [97], and prepare tissue for repair and regeneration [97].

Platelet-related growth factors and neovascularization stimulate fibroblast homing and proliferation in tendons and ligaments [81]. Fibroblasts orient at the site of injury marked by platelet aggregates and neovessels and synthesize collagen [98].