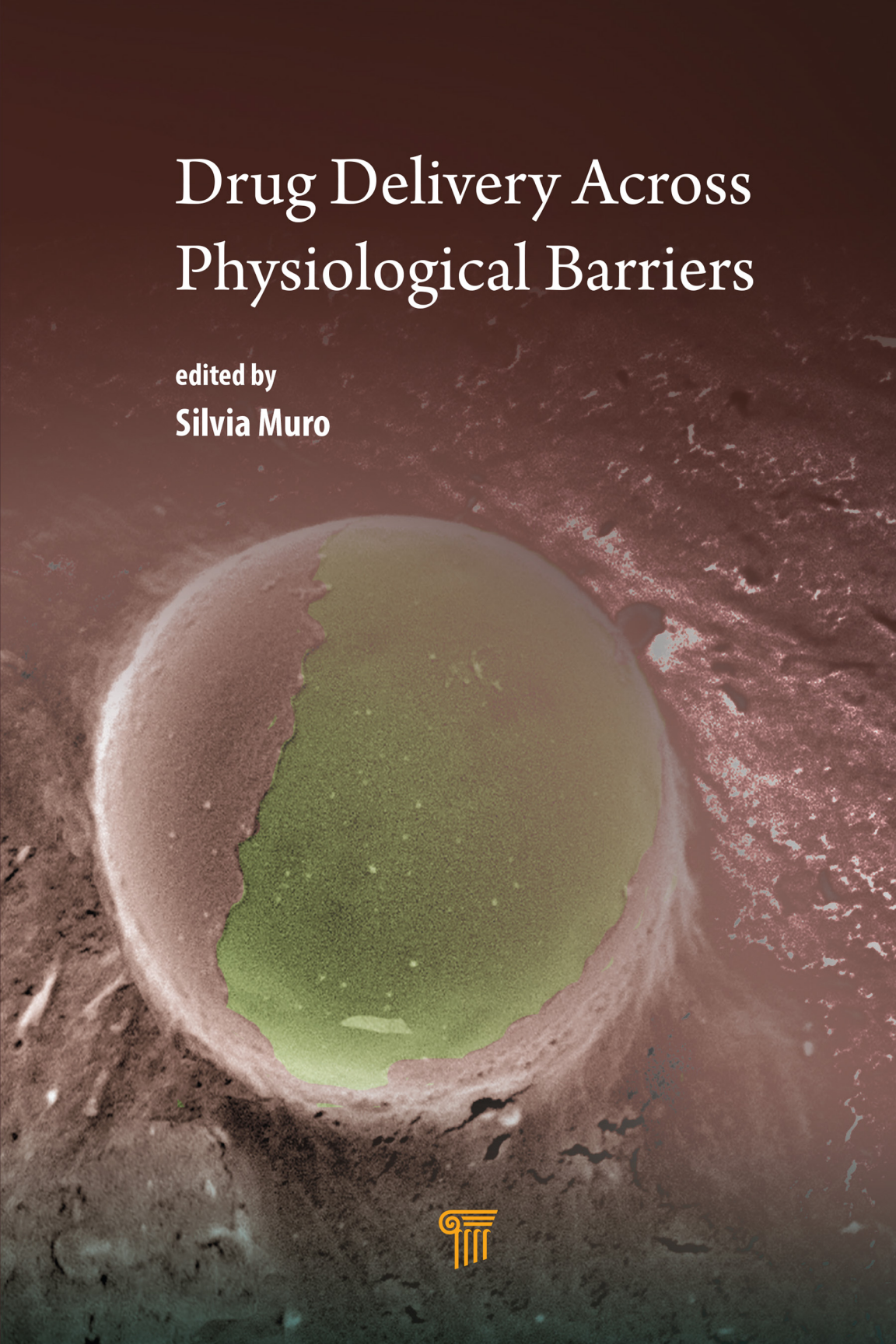
Drug Delivery Across Physiological Barriers

edited by

Silvia Muro



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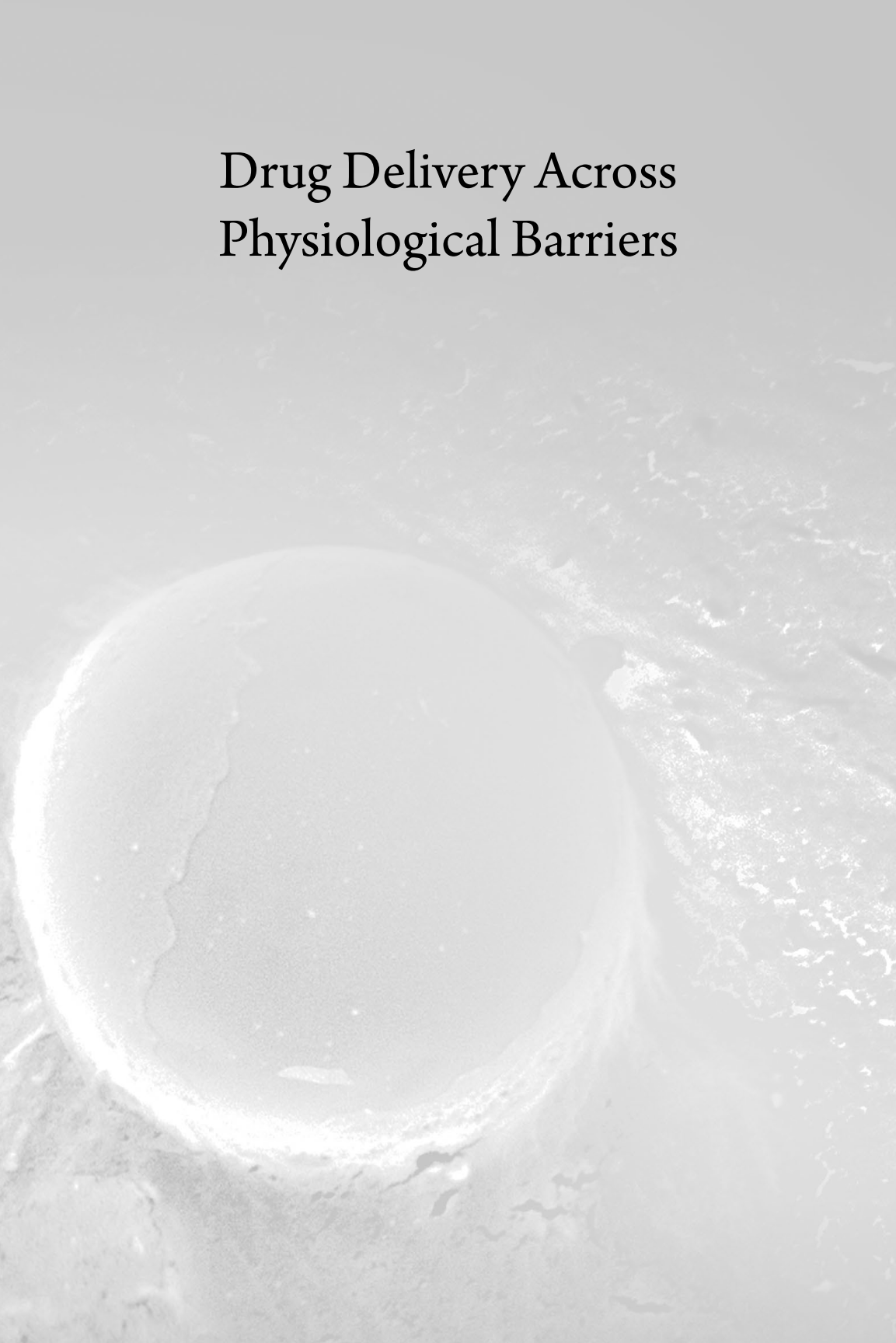

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Preface

Optimal drug delivery in the body is paramount to maximizing the therapeutic efficiency of pharmaceutical compounds while minimizing their potential toxicity. In this regard, numerous advances in the last decades have rendered considerable improvement in drug delivery strategies, thereby increasing the bioavailability of therapeutic agents. These systems help solubilize pharmaceutical drugs, protect them from premature degradation, control their circulation, target them to sites of disease, and optimize their release rate. In addition, for most therapeutics, access to their targets of intervention requires penetration across body compartments, extracellular matrices, cellular linings, and/or different intracellular environments. Therefore, the design of strategies capable of improving transport of pharmaceuticals through these physiological barriers has become an imperative yet a challenging need in the quest for better therapeutics. This book aims at providing an overview of current advances in the field of drug delivery from the perspective of transport across the said physiological barriers. This is pursued by discussing fundamental knowledge pertaining to the biological function and natural mechanisms regulating these barriers, as well as by focusing on drug delivery strategies that facilitate transport of drugs and their carriers at the tissue, cell, and subcell levels.

With this in mind, the book has been divided into three independent yet complementary sections. **Section A** covers the background biological information regarding the structure, function, and regulation of constituents of the said physiological barriers, offering the reader an overview of the challenges and opportunities they pose. Within this section **Chapter 1** introduces the concept of cellular barriers or linings, which arise as a result of the

physiological need to develop selective compartments within the body. They are established by epithelial or endothelial cells, which strongly adhere to each other, forming polarized linings that separate apical and basolateral compartments, such as those which coat hollow organs, glands, blood vessels, etc. These cellular linings most often act as barriers to passive transport of substances between the compartments they separate, regulating passage in a minutely controlled manner. From a drug delivery perspective, they regulate absorption or penetration of therapeutics across the inner layers of the skin, the gastrointestinal wall, passage from the bloodstream into subjacent tissues, etc., which pertains to drug access from the administration point to the intended body compartment. Subsequently, **Chapter 2** covers fundamental aspects of the cellular plasma membrane. This is important because, once in the appropriate body compartment, penetration into cells of the affected tissues requires passage through the plasmalemma that separates and permits communication between the intracellular environment and the extracellular milieu. The composition and regulation of this semipermeable barrier are described, including passive and active mechanisms of transport involving diffusion, ion and molecule channels, endocytosis, or exocytosis. Further, **Chapter 3** touches upon subcellular organization and offers a detailed overview of the biological mechanisms by which macromolecules (e.g., proteins, lipids, etc.) are naturally sorted and trafficked to their final subcellular destinations with exquisite precision. The cellular machinery, signaling cascades, and pathways employed in these events are finding valuable translational applications in the field of drug delivery. To end this section, **Chapter 4** discusses how pathogens have evolved remarkable means to overcome all these physiological barriers in order to infect their hosts. A main focus is paid to how such invasive bacteria and viruses gain access inside cells of the body, for example, by recognition and binding to particular cell-surface markers leading to endocytic uptake, disruption of the plasmalemma or the membrane of endolysosomal vesicles, hijacking the cytoskeleton and molecular elements promoting vesicular fusion or fission, etc. Mimicking such strategies and pathways established by nature is becoming a main practice in order to advance drug delivery.