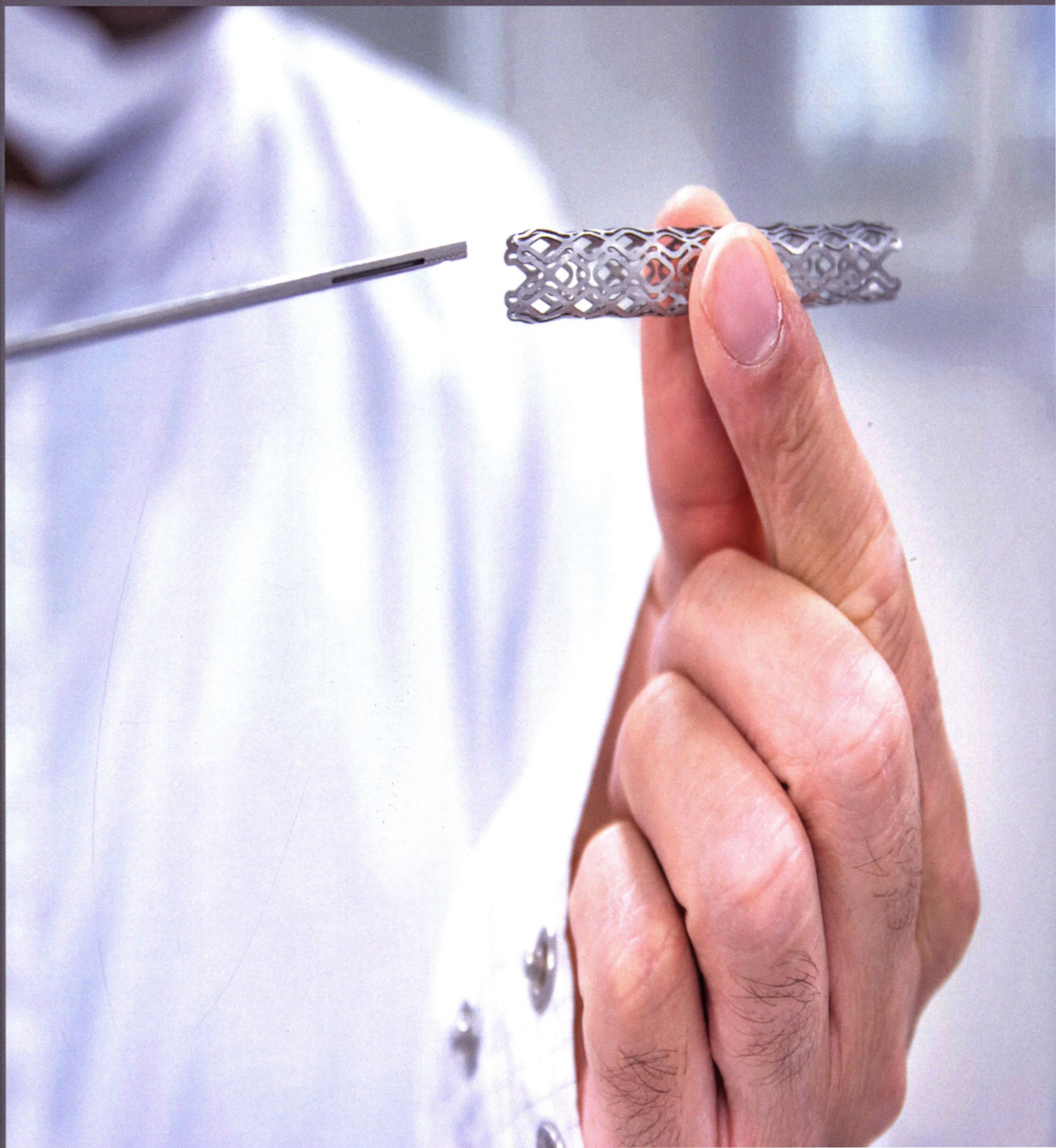
Functional Biomaterials for Medicine and Healthcare

Contributors: Darya Hadavi, André A. Poot, et al.



About the Book

The field of biomaterials has recently been focused on the design of intelligent materials. Toward this goal, materials have been developed that can provide specific bioactive signals to control the biological environment around them during the process of materials integration and wound healing. In addition, materials have been developed that can respond to changes in their environment, such as a change in pH or cell-associated enzymatic activity. In designing such novel biomaterials, researchers have sought not merely to create bio-inert materials, but rather materials that can respond to the cellular environment around them to improve device integration and tissue regeneration. Biomaterial is a nonviable substance used in a medical device intended to interact with biological systems. Their usage within a physiologic medium needs the characteristic features such as efficient and reliable. These characteristic features have provided with a suitable combination of chemical, mechanical, physical and biological properties. Nowadays, biomaterials are commonly used in various medical devices and systems; synthetic skin; drug delivery systems; tissue cultures; hybrid organs; synthetic blood vessels; artificial hearts; cardiac pacemakers; screws, plates, wires and pins for bone treatments; total artificial joint implants; skull reconstruction; dental and maxillofacial applications.

Functional Biomaterials for Medicine and Healthcare, a compilation of review articles, is designed from a medical perspective and is aimed at academics as well as medical and biomedical engineering students who want to become involved in the design, development, manufacturing or use of prostheses or medical devices. It covers basic information on the complexities of implant and medical device development. The design process, technology assessment, animal experiments, histocompatibility, tissue compatibility and infections are described. It is an essential reading for scientists, engineers, and clinicians, and a useful reference tool for undergraduate and postgraduate students.

Functional biomaterials made of natural building blocks can offer significant advantages over purely synthetic systems, and the use of human proteins, functional peptides or nucleic acids as the precursor materials is common for the minimization of the immunogenicity of the delivery materials. However, the biocompatibility and biodegradability of functional structures with desired properties is affected by the biomaterials' structural characteristics and building block assembly pathways. Moreover, the elevated sensitivity of natural building blocks to environmental changes makes structural analysis of such biomaterial systems challenging.

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Preface

The field of biomaterials has recently been focused on the design of intelligent materials. Toward this goal, materials have been developed that can provide specific bioactive signals to control the biological environment around them during the process of materials integration and wound healing. In addition, materials have been developed that can respond to changes in their environment, such as a change in pH or cell-associated enzymatic activity. In designing such novel biomaterials, researchers have sought not merely to create bio-inert materials, but rather materials that can respond to the cellular environment around them to improve device integration and tissue regeneration. Biomaterial is a nonviable substance used in a medical device intended to interact with biological systems. Their usage within a physiologic medium needs the characteristic features such as efficient and reliable. These characteristic features have provided with a suitable combination of chemical, mechanical, physical and biological properties. Nowadays, biomaterials are commonly used in various medical devices and systems; synthetic skin; drug delivery systems; tissue cultures; hybrid organs; synthetic blood vessels; artificial hearts; cardiac pacemakers; screws, plates, wires and pins for bone treatments; total artificial joint implants; skull reconstruction; dental and maxillofacial applications.

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1

BIOMATERIALS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Keywords: Alzheimer's disease, biomaterials, delivery systems, nanoparticles, liposomes, scaffolds

Alzheimer's disease (AD) as a progressive and fatal neurodegenerative disease represents a huge unmet need for treatment. The low efficacy of current treatment methods is not only due to low drug potency but also due to the presence of various obstacles in the delivery routes. One of the main barriers is the blood–brain barrier. The increasing prevalence of AD and the low efficacy of current therapies have increased the amount of research on unraveling of disease pathways and development of treatment strategies. One of the interesting areas for the latter subject is biomaterials and their applications. This interest originates from the fact that biomaterials are very useful for the delivery of therapeutic agents, such as drugs, proteins, and/or cells, in order to treat diseases and regenerate tissues. Recently, manufacturing of nano-sized delivery systems has increased the efficacy and delivery potential of biomaterials. In this article, we review the latest developments with regard to the use of biomaterials for the treatment of AD, including nanoparticles and liposomes for delivery of therapeutic compounds and scaffolds for cell delivery strategies.

INTRODUCTION

Neurological diseases, such as frontotemporal dementia, stroke-induced vascular dementia, and Alzheimer's disease (AD), are characterized by the impairment of memory and cognitive functions (Han et al., 2015). More than 80% of dementia cases are caused by AD, which is categorized as one of the most occurring neurodegenerative diseases in the world (Anand et al., 2014). Moreover, AD is considered as a slow pandemic disease. Whereas currently, 3 out of 1000 individuals worldwide are suffering from AD, this is expected to increase to 12 per 1000 by the year 2050 (Brookmeyer et al., 2007).

Alzheimer's disease can be classified as familial AD or sporadic AD, while they share clinical and pathological features, including progressive cognitive impairment, plaque deposits in the brain, axonal transport defects, synapse loss, and selective neuronal death. Only 5% of the AD cases are of familial type, whereas 95% belong to sporadic AD (Kim and Tsai, 2009; Thal and Fandrich, 2015). Another classification system for AD is based on the age of emerging.

Whereas 1–6% of the AD cases emerges in 30- to 60-year-old people, which is known as early-onset AD, late-onset AD occurs in people older than 60 years with 90% prevalence (Mullane and Williams, 2013).

Alzheimer's disease is characterized clinically by progressive decline in mental and cognitive ability. The disease begins with impairment in the part of the brain, which is responsible for learning, memorizing, thinking, and planning. This mental decline negatively affects the patients' work and social life because they have difficulties in expressing themselves and organizing their thoughts (Alzheimer's Association, 2012). As the disease progresses, more changes occur in the personality and behavior of the patients and they need extensive help with daily activities. Shrinkage of the brain over time results in more signs of AD, such as decline of thinking and reasoning skills, inability to respond to the environment or to control movement (Alzheimer's Association, 2012).

Since Dr. Alois Alzheimer did observe the presence of amyloid plaques [extracellular deposits of amyloid-beta (Aβ) peptide] and intracellular hyperphosphorylated neurofibrillary tangles (NFTs) in the brain as pathological features, many hypotheses concerning causative factors for AD have emerged (Armstrong, 2013; Kumar et al., 2015). Three main causes of AD have been proposed. It can be due to dysregulation of the cholinergic system, which is related to cognitive impairment of the patient. Alternatively, AD can be due to accumulation of NFTs or deposition of Aβ peptide in the brain (Anand et al., 2014). NFTs are paired helical filaments resulting from hyperphosphorylation of tau proteins. These proteins are mostly found in the axons, and their hyperphosphorylation is caused by internal cell dysregulation. NFTs severely harm neurotransmitter transport and axonal integrity (Sun et al., 2003). The formation of Aβ peptides is the result of cleavage of amyloid precursor protein (APP). APP is a type I transmembrane protein, which is highly expressed in the central nervous system (CNS) and suggested to be responsible for synapse formation, neurogenesis, axonal transport, cell signaling, and plasticity. During two enzymatic steps by β-secretase and γ-secretase, Aβ peptides mainly consisting of 40 or 42 amino acids are liberated from APP, forming Aβ oligomers, Aβ polymers, and eventually Aβ plaques (Thinakaran and Koo, 2008). The presence of NFTs and Aβ plaques in the brain causes shrinkage pressure, which leads to nerve cell apoptosis. This cell death process starts from the memory and learning regions of the brain and then spreads to other regions *via* transfer among nerve cells that are along anatomical pathways (Gunawardena and Goldstein, 2001; Brunholz et al., 2012). Currently, the pathophysiology of AD is subject to changes. Recent studies claim that Aβ peptide and phosphorylated tau proteins are the reflection of damage in neurons rather than being responsible for the disease (Hardy and Selkoe, 2002). It has been suggested that formation of NFTs is due to an adaptive strategy of cells to oxidative stress over the long term. Nevertheless, among all hallmarks of AD, Aβ deposition is the prevailing one for more than two decades and considered as an important causative factor of AD (Hardy and Selkoe, 2002).

It has been shown that Aβ oligomers are the primary structures leading to damage of normal functions of the brain (Gu et al., 2009; Orive et al., 2009). Based on studies on familial AD, mutations were only seen in APP and presenilin genes (PS1 and PS2), and no mutations were reported for tau protein. This finding suggests that hyperphosphorylation and aggregation of tau protein in the form of NFTs result from the direct effect of Aβ peptides on tau protein (Ranka et al., 2002). The involvement of Aβ oligomers in synaptic impairment suggests that they have negative effects on postsynaptic structure and plasticity of the excitatory glutamatergic synapse (Shankar et al., 2008). As amyloid plaque formation is a rather late process (Orive et al., 2009), more insight in the formation of Aβ peptide is needed in order to get a comprehensive understanding of the etiology of this disease.

CURRENT TREATMENT

The enormous financial and emotional burden of AD on patients, community and caregivers as well as increasing numbers of AD patients raise the essential need for an effective treatment. About a century after the discovery of this disease, only five drugs have been approved by the US Food and Drug Administration (FDA): acetylcholinesterase inhibitors rivastigmine (Exelon), galantamine (Razadyne and Reminyl), tacrine (Cognex), donepezil (Aricept), and NMDA receptor antagonist memantine (Namenda) (Musardo et al., 2013). These drugs are only able to target symptoms of AD and decrease the speed of progression of the disease. However, many patients do not respond to these drugs or the drugs have no profound effects on alteration of the process of AD (Han et al., 2015).

From 1998 to 2011, approximately 100 therapeutic compounds were tested in clinical trials for the treatment of AD, but they all failed. Among others, agents included inhibitors of γ-secretase and Aβ oligomer/fibril formation, as well as antibodies against Aβ (Mullane and Williams, 2013). This raised doubt on the causality of Aβ in the development of AD (Armstrong, 2014). Moreover, it was suggested that patients were treated too late, having irreversible brain damage 10–20 years after onset of the disease, explaining the discrepancy with promising studies using animal models of AD (Mullane and Williams, 2013). Importantly, clinical failure of therapeutic agents was explained by low bioavailability in the CNS due to restriction by the blood–brain barrier (BBB) (Lauzon et al., 2015).

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