Preamble

The relation between mankind and the surrounding environment began as soon as the first man stood upright. The development of tools commenced soon after. Wherever man has lived, tools have been found that were made from materials of biological origin.

Bones, animal skins, animal hair, horns, shells, wood, plant fibers, plant leaves, straw, for all of them man found a use and discovered novel applications.

The transformation of these collected biomaterials also began very early in man's development. Fire was used to harden wooden spears; animal hair and plant fibers were transformed into clothes or used to make baskets.

Much later, around 7500 BC, man discovered the possibility of extracting new materials from the earth, such as mud, which could be transformed by blending it with straw and sun drying. Later, c.5000 BC, bricks started to be made in kilns, giving rise to one of the strongest and cheapest building materials.

Modified kilns were used to extract metals from rocks and the hegemony of organic materials began to fade over the following centuries.

This situation changed dramatically in the 19th century, when several scientists became interested by in strange properties of several natural substances.

Around 1834, Hancock in Great Britain and Goodyear in the United States successfully improved the structural properties of latex rubber by adding sulfur.

In addition, cellulose was isolated from plant material in 1838 by the French chemist Anselme Payen, who determined its chemical formula. Soon, several materials derived from cellulose were made, namely, nitrocellulose, celluloid, cellulose acetate, cotton powder. The starch composition was shown to be identical to that of cellulose, the same being the case for glycogen.

One aspect remained, however, without explanation, that is, if starch and glycogen have exactly the same chemical composition, then why are starch and glycogen so different from cellulose as far as behavior and function are concerned? The answer to this enigma was given by Hermann Staudinger in 1920, who published work that opened up a new world for organic chemistry (Staudinger, 1920). Not only did he proved that rubber and other biomolecules, such as starch, glycogen, cellulose and proteins, which he named macromolecules, are long chains of repeating molecular units linked by covalent bonds, but also he showed that different ways of covalent bonding were responsible for different properties, even when the global chemical composition was the same. He also coined the term polymers. During his career he developed several methods to determine the molecular weight of polymers. As a result of this groundbreaking work, Staudinger won the Nobel Prize of Chemistry in 1953.

We can say that Staudinger's work was inspired by the biomaterials he worked with: cellulose, starch, glycogen, and rubber. If so, we can accept that the first bioinspired materials were the synthetic polymers that are so widely used nowadays.

The developments in molecular biology opened up further doors within this area. More and more macromolecules were discovered that were linked to very specific functions inside cells. Another landmark was setup when Watson and Crick disclosed the complex structure of DNA and how it could explain the mechanism of hereditary conservation of characteristics from parents to children (Watson and Crick, 1953). DNA is not a single polymer chain as many polymers are. DNA is a double-stranded molecule with hydrogen bonds between nitrogen bases, these bases being placed in a strict matching mechanism.

The accuracy of Watson and Crick's description of how the DNA double helix unfolds to replicate and self-assemble afterwards provided another exciting tool for bioinspired materials, namely a way of controlling self-assemblage. The possibility of controlling the assembling and disassembling cycles of DNA molecules became a reality with the introduction of the polymerase chain reaction (PCR) as a way to synthesize novel DNA molecules. With a very small amount of DNA, we are now able to replicate it billions of times in a machine called a thermocycler and use the synthetic DNA to transform living cells or to produce completely different materials. Kary Mullis won the Nobel Prize of Chemistry in 1993 for the invention of PCR.

The combination of new methods for DNA sequencing and PCR gave rise to astounding breakthroughs; one of the most striking examples being the in vitro/in silico (ie, by exocellular means combined with powerful computational methodologies) synthesis of an artificial bacterium, *Mycoplasma mycoides* JCVI-syn1.0, by the Craig Venter's group. As the authors stated:

> *We report the design, synthesis, and assembly of the 1.08-mega-base pair* Mycoplasma mycoides *JCVI-syn1.0 genome starting from digitized genome sequence information and its transplantation into a* M. capricolum *recipient cell to create new* M. mycoides *cells that are controlled only by the synthetic chromosome. The only DNA in the cells is the designed synthetic DNA sequence, including "watermark" sequences and other designed gene deletions and polymorphisms, and mutations acquired during the building process. The new cells have expected phenotypic properties and are capable of continuous self-replication.*
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> *(Gibson et al., 2010)*

The frontier of synthetic biology was wide open. An exciting new field was offered to researchers.

On the other hand, researchers from the area of materials were moving fast. A number of new methodologies to characterize macromolecules were developed in the last decade. Advanced techniques address molecular weight determination, molecular and structural characterization by spectroscopic techniques, morphology and structural characterization by microscopy and diffraction, thermal analysis, in addition to techniques such as atomic force microscopy, and circular dichroism, XPS, micro-FTIR, MALDI-TOFF, NMR, micro-CT, among others.

However, new problems arose when bioinspired materials started to be assayed to tackle real-world issues. We can say that, in most cases of materials science, macromolecules have a primary orientation axis. In turn, in the real world of tissue engineering, macromolecules are not oriented in the same direction, since we have many different macromolecules coexisting and interacting. As a matter of fact, each organic tissue has its own preference, but in the vast majority of cases, organs in general present different cell-layer arrangements depending not only on their function (eg, lung, heart, bone, liver, kidney, among others) but also on their location in the human body (eg, skin, brain, eye).

Take an apparently simple example. Skin is a multilayered tissue, the outermost layer being the epidermis, which is indeed composed of four distinct layers: the one directly in contact with the outside world is called the stratum corneum, and going inside the body, we have the stratum granulosum, the stratum spinosum and the stratum basale. We now know that skin barrier capacity is controlled by lipids filling the extracellular space of the skin's surface layer—the stratum corneum.

Then comes the dermis, which is mainly connective tissue harboring a great number of cells, mainly fibroblasts, but also a number of organelles of different kinds—hair follicles, oil glands, sweat glands, nerves, etc., where the outer layer (ectoderm) is rather different from the medium layer (mesoderm) and from the innermost layer (endoderm). In other words, organs are far from being homogeneous.

In general terms, when you have a tissue you will have a simplified 2D organization, whereas when you are working with an organ you will have a multilayered 3D organization, as is the case of the skin where the ectodermis, endodermis and mesodermis will be present, or a quite intricate and even a rather corrugated structure, as in the case of the bones, lung, or brain.

For these reasons we are still far from being able to create artificial organs from scratch. The best way to produce tissues will be, for quite a while, the use of stem cells. The reason is simple. Stem cells have inscribed in their genome all the information needed to synthesize the right tissues and to coordinate the self-assemblage, on the one hand, and the 3D organization on the other.

Nevertheless, bioinspired materials are already under very active investigation and are proving their usefulness in many fields.

This is why we present this book, which is organized in distinct topics.

The first topic is composed by six chapters that present a general overview and discuss sensitive subjects such as *Design and preparation of biomimetic and bioinspired materials*, *Preparative methods and devices of bioinspired materials in drug-delivery systems*, *Metamorphic biomaterials*, *Molecular signaling mechanisms of host–materials interactions*, *Multifunctional biomaterials and their bioinspired systems for bioactive molecules delivery*, and the *Perspectives of bioinspired materials in regenerative medicine*.

The second topic is devoted to methodologies, tackling subjects such as *Advanced techniques for characterizing bioinspired materials* and *Imaging strategies for bioinspired materials*.

The third topic deals with biomaterials that are already on the market or are on the verge of being purchased in view of the clinical phases they are undergoing. In this topic we can find five chapters on *Injectable hydrogels as a delivery system for bone regeneration*, *Therapeutic proteins in bioactive materials for wound healing*, *Smart devices: micro and nanosensors*, *Smart devices: Lab-on-a-chip*, and *Electronic tongues and aptasensors*.

Finally, a set of three chapters discuss the challenges and the opportunities that recent advances in biology can offer to bioinspired materials. This is the case of *Advances on nucleic acid delivery with nonviral vectors*, *Artificial virus particles*, and *Synthetic Biology strategies towards the development of new bioinspired technologies for medical applications*.

Notwithstanding the impossible task of covering all of the exciting themes around this subject, there is still the need to point out future developments, including:

1. The feature of identification and spontaneous assembly present in several biomolecules might be explored to the benefit of a number of bioinspired materials. Spontaneous assembly involves two stages, namely the identification of the target and the attachment to the target at a special site that may be called the docking site. Spontaneous attachment has been recognized for many years, because this is what explains, for instance, the activity of antibodies, which identify and attach to antigens, or the activity of phages. The news is that we now know which are the molecules directly involved in a particular attachment mechanism, and we also know there are sticky molecules of various kinds. The first to be discovered were the nucleic acids, as we saw with the work of Watson and Crick. But soon after, many nucleic acid-binding proteins were described. Following these came the description of carbohydrate-binding molecules, called lectins. Although we have been aware of lectins since the 19th century, they have been increasingly used in the affinity separation of sugar mixtures. Lectins display a high affinity for sugar moieties and, as a result, they stick to a pure carbohydrate or to the carbohydrate part of a glycoprotein or a glycolipid. They are used in the most common assay to identify the different blood types by simple agglutination. Nowadays, injectable hydrogels are being used for bone regeneration. Many of the injectable hydrogels are composed of carbohydrate parts, as is the case of hyaluronic acid, an anionic, nonsulfated glycosaminoglycan, or of hydroxypropyl-methylcellulose. We may speculate that the decoration of these hydrogels with lectins might prevent a fast biodegradation or dampen the immune response.
2. Recently, specifically around 1999, the discovery of sillafins brought to light the role of these peptides in the templating process of exquisite diatom silica skeletons. The same happened with sponges, organisms that have also a silicious skeleton, though they are quite different from diatoms. In both cases, the involvement of proteins in the control of the silification process was unveiled. For example, sillafin-R5, a 19-aminoacid cationic peptide very rich in lysine and serine residues is able to induce precipitation of silica in seconds, at room temperature and at pH 5 or more. On the other hand, the spiculas from sponges are formed via the enzyme sylicatein involving a different mechanism. What is interesting is the potential utilization of the biosilica for bone regeneration. Indeed, both silaffins and silicatein have potential utilization in stimulating the growth of osteocytes (Gough et al., 2004). This is another aspect that needs to be more deeply explored in the future. Additionally, the flexibility brought about by the control of silica templating at a micro and nano scale opens up new possibilities in the design of smart devices, micro- and nanosensors and lab-on-a-chip (Rai and Perry, 2010; Miles et al., 2012; Otzen, 2012).

3. If, as expected, the number of surgical implants increases exponentially, then there will be an opportunity for the development of small, inexpensive and portable devices, able to monitor the postsurgical recovery process.
4. The fast development of the new tools discovered in the recent years for genome editing, as well as emergent approaches to assemble DNA parts will certainly foster the development of new bioinspired materials for medical applications.

As editors of this book, we have tried to organize it in an order that raises the readers' interest, by making it as easy to understanding as possible. This is why we have a comprehensive list of terms, abbreviations and acronyms for each chapter. The chapter sequence was also set out in such a way that similar subjects are assembled.

We hope that, by putting together a set of different fields, pertaining, all of them, to the domain of bioinspired materials, several novel ideas will spark and give a new thrust to this exciting subject. If so, we think we have done our job, by contributing to efforts to make the life of millions of people suffering every day from many health issues less painful, providing relief, if not a cure, with the help of novel, durable, biocompatible biomaterials applicable in less invasive ways. Enjoy your reading.

The Editors
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