Chapter 4
Biobased Materials for Medical Applications

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4.1 Biobased Materials: An Introduction

We live in a world of materials where every facet of our lives is influenced by an ever-widening network of interdependent materials based phenomena. The materials-driven technologies that we use on a daily basis to conduct business, communicate information, pursue leisure and entertainment activities, and monitor and promote health play a very important role in enhancing our quality of life. However, there is a marvelous materials domain that exists within living organisms and which orchestrates all the physiological processes that facilitate life. The orchestrated processes originate at the subatomic level and progress in scale from molecular level to macroscale phenomena. These processes encompass vital life functions such as protein synthesis, genetic information transfer, and neural signal processing and brain function. These processes also produce and utilize a uniquely functioning hierarchy of biobased materials that interact in an elegant fashion to facilitate life functions.

At a fundamental level, biobased materials can be thought of as materials that are produced by living organisms to facilitate life processes. It is a natural extension that biobased materials play an important role in medical and healthcare technologies. There is no shortage of novel applications for biobased materials in healthcare and beauty products, pharmaceutical compositions, vitamins and nutritional supplements, food, and natural food preservatives. Biobased materials also can be used as components in diagnostic tools and preventative therapies in rapidly developing fields including biomaterials, tissue and organ engineering, and genetic engineering. The future of biobased materials in medical applications for enhanced healthcare holds exciting possibilities as we transition from reactive to more proactive approaches to treat medical conditions. In reactive medical approaches, symptoms
are the central focus, and we try to fix problems after they occur. Proactive medical approaches put the focus on the underlying root problem and promote the development of more effective biobased materials and therapies for earlier diagnosis and treatment to facilitate more positive health results. Henry David Thoreau encapsulated the value of this sentiment in his famous quote “For every thousand hacking at the leaves of evil, there is one hacking at the root.” May we develop effective strategies to wisely use biobased materials to destroy the root causes of disease and poor health among our people worldwide.

Many factors need to be considered to fully define and understand biobased materials in the context of past performance, present capabilities, and future possibilities in healthcare. A number of relevant factors related to biobased materials are depicted in Fig. 4.1. The diagram highlights the importance of structure – properties – processing considerations from the field of materials science and links these concepts with other characteristics that help to broaden the expansive domain of biobased materials. These developments are catalyzed as more details regarding the complex interrelationships in materials design are uncovered. The design matrix can be expanded to include modeling and performance optimization and even recycling/upcycling of unique biobased waste products which possess unforeseen benefits for advancing the degree of care and the scope of the medical conditions that we can effectively treat and cure. The atomic structure and microstructure of a material determines its properties and how it can be used. New considerations related to sustainability and the impact that modeling can have on optimization bring a new level of intrigue to biobased materials. In the past, biobased materials were limited to compounds or components that were carefully extracted from the initial source. Examples include cellulose-based cotton fibers harvested from *Gossypium hirsutum* (the cotton plant), chitin harvested from *Callinectes sapidus* (the blue claw crab),

![Fig. 4.1](image-url)
coal and oil that was produced from ancient biomass and harvested from modern oil fields, or cells and tissues harvested from a donor source or grown in vitro using tissue engineering strategies. Current efforts in biobased materials search for ways to utilize materials with minimal processing.

This helps to promote the green materials chemistry revolution which seeks to minimize our footprint on Earth’s diminishing resource pool. These important efforts can be augmented by higher levels of recycling, upcycling, and responsible manufacturing to minimize waste and promote better natural resource management. In essence, an essential component can be harvested from its biobased source, while the remaining constituents can be used in additional ways to minimize waste. This is the biobased equivalent of using “… everything about the hog except the squeal” as quoted in *The Jungle* by Upton Sinclair [110].

In order to attain the full potential that is inherent with biobased materials, we need to expand our view of biobased materials to include a broader vision of cells and tissues and cellular by-products as biobased materials. The basic function of cells can also be used as bioreactors to produce biobased therapeutic agents in recombinant DNA-based technologies to produce insulin and other large-scale medical products. Another biobased material approach involving cells uses selective cultivation and/or separation of cells and cell-derived materials which serve as a foundation for the harvest, cultivation, and seeding of biobased material products for tissue and organ engineering. The intrinsic behavior of cells can be utilized to construct functional tissue-engineered tissues and organs that can be seamlessly integrated into the body. One promising approach involves “mini beating heart cluster” that was made by culturing chicken cardiac cells on chitosan and cellulose acetate scaffolds. The mini beating hearts were cultured at Howard University in Dr. Winston Anderson’s Lab as part of a Senior Research Lab for Catholic University of America students studying the development of heart patches in 2006. Figure 4.2 highlights another promising approach towards developing cardiac implants. Novel procedures were developed to produce full replacement hearts based on “ghost heart” protocols. The name “ghost heart” aptly captures the appearance of the decellularized heart structure that remains after washing cells from the heart with a soap detergent solution, typically sodium dodecyl sulfonate (SDS). The heart structure contains all the biobased extracellular matrix proteins and collagen framework from the heart. The procedure was first developed for rat hearts [86] and subsequently developed for pig hearts and other whole organ systems [4]. Ghost hearts can be transformed into a viable heart by repopulating the structure with appropriate cardiac cells under proper conditions. In the future, fully functioning hearts can be tailor-made for a person in need of a new heart by using the person’s own cardiac cells to minimize host rejection issues. These approaches can be applied towards generating other tissues and organs and will one day soon replace traditional organ harvesting and implantation procedures.

Food science encompasses a very unique and interesting category of biobased materials. An expanded view of food and nutrition will contribute to breakthroughs in medical treatments and technologies based on what we eat and how it influences our body’s health. On one end of the food biobased materials spectrum, alternative
Fig. 4.2 Decellularized ghost heart scaffold. (Courtesy of Dr. Doris Taylor)

food products that encompass nutritional additives or vegetarian/vegan meat analogues to promote healthier lifestyles are having a major impact on food choice. On the other end of the spectrum, phenomenal breakthroughs in our understanding of the human gut microbiome (HGM) and the many ways that it can impact health will lead to the future ability to tailor the profile of the gut microbiome to treat and prevent a host of medical maladies. Diet can be an effective tool in tailoring the profile of the gut microbiome and impacting various aspects of health [122]. A study in early 2020 highlighted evidence that the Mediterranean diet influences the gut microbiome in the elderly population by promoting a higher level of microbial diversity that can contribute to longevity [43]. More positive benefits from the Mediterranean diet include improved cognitive function, memory, immunity, and skeletal health. Additional studies show that dietary impacts on the gut microbiome influence youth across geographic boundaries. Collaborative studies in China and Canada indicate that the gut microbiome may hold the key to the “Fountain of Youth.” This study by Bian et al. [8] revealed that the gut microbiome of the healthiest elderly people in the study (90–100 years old) was very similar to the gut microbiome of young people in their 30s. Intermittent fasting also plays a role in promoting a healthy gut microbiome as well as promoting the transformation of white adipose tissue to healthier brown adipose tissue [73]. Hence, a host of factors influences our
gut microbiome composition from the time of its initial population at birth through its continued modification and change across the whole aging spectrum.

There are a number of riddles and puzzles that are presented by biobased materials and dietary-based fuel sources. Here is one riddle that highlights the unique similarities among widely differing organisms: “How are termites, cows, and baleen whales related?” In addition to being living biobased organisms that utilize biobased materials on many different scales, these organisms also have a predominant food source that their bodies cannot digest. The gut microbiome of termites, cows, and baleen whales plays a key role in this unfolding story. Specific families of bacteria play an important role in converting the cellulose in wood which is a termite’s favorite food source into simple sugars that provide sustenance and fuel for the termite. Cows have symbiotic bacteria that exist in their digestive systems to convert the cellulose from the grass and straw that they eat into compounds that provide nutrition for life. It turns out that filter-feeding baleen whales also have bacterial microbiome species that help convert the chitin exoskeletons from their main food source (krill and plankton) into simple sugars and other compounds for sustenance [104]. People can be added to this unfolding story related to the symbiosis of organisms and their gut microbiome. Humans eat fiber which is a cellulosic biobased material that is undigestible without the help of HGM species. Specific HGM species synthesize short chain fatty acids (SCFA – acetate, butyrate, and propionate) during the anaerobic fermentation of fiber and starch in the colon [106]. The resident microbes in the gut microbiome of termites, cows, filter feeding whales, and humans serve as biobased refineries that are responsible for digesting polysaccharide biobased feedstocks to produce critically important simple sugars and other biologically active molecules to fuel life processes. SCFAs have been linked with a host of health benefits ranging from regulating neuroimmunoendocrine function across the gut brain axis [108], alleviation of stress-induced brain-gut axis alterations [127], Alzheimer’s prevention, and anticancer properties, especially in regard to colorectal cancer [47].

A unique discovery regarding the gut microbiome of wax moth (Galleria mellonella) larvae presents another opportunity for environmental resource management and waste reduction. This concept highlights the hidden potential of the gut microbiome in addressing technological challenges that are indirectly linked with health. Wax moth larvae have the ability to eat plastic waste. The gut microbiome of these worms contains microbes that are effective in the biodegradation of polymers with a preference for polyethylene. In the wild, the wax moth larva is a parasite in bee colonies because it eats honeycomb wax. An amateur beekeeper and scientist in Spain discovered the unique ability of the wax moth larvae to eat polyethylene in 2017. Dr. Bertocchini removed wax moth larvae from her beehives and placed them in a plastic bag. The larvae quickly escaped by eating their way to freedom [10]. The edible degradation method of wax moth larvae is more effective than current polymer degradation methods. There is another species of insect beetle larvae called the superworm that is able to eat polystyrene. With the assistance of its resident gut microbiome, the ingested polystyrene is converted into simpler polymers and carbon dioxide as depicted in Fig. 4.3 [143]. It may be possible to tailor the gut micro-
biome of other organisms and use them as living plastic composters similar to how earthworms compost leaves and other organic detritus matter and transform it into nutrient-rich soil [37].

The repercussion of this effect can propagate even further in making connections with health because disease-related links between a number of commercial polymers are being established. Melamine is a nitrogen-containing organic compound that can be synthesized from urea. It is used in polymers, fertilizers, and fabrics. Its high nitrogen content was exploited by the unfortunate use of melamine as an adulterant in milk to falsely portray higher protein levels. Research has shown that exposure to melamine results in an increased incidence of kidney cell damage and pathological mineralization via kidney stone formation [51]. The formation of kidney stones in infants and children in China who consumed melamine-tainted milk was an unfortunate side effect. Novel microfluidic devices have been employed to probe the mechanism of how melamine catalyzes kidney stone formation in finer detail [46].

The purpose of this chapter is to expand our understanding of biobased materials and investigate some novel developments in this fascinating field of study. The question of what is meant by biobased materials will be further addressed in a comprehensive fashion by defining the term and providing a view of the scope of biobased materials. The important role of energy, material inputs and outputs, and fundamental phenomena and models will be integrated into our consideration of biobased materials. Specific topics within the broad category of biobased materials will be highlighted to provide a comprehensive view of the field by covering traditional as well as some uniquely new and developing areas. Bone tissue inspiration will serve as a scaffold to help build key concepts in our exploration of biobased materials. Rich and robust examples from these unique areas will provide valuable guidance as we seek to develop a broader vision for what we can achieve in medical diagnostics and health based on a deeper understanding of biobased materials. The new perspective and vision for near-term and long-term medical health and treatment breakthroughs from biobased materials will help us to develop more predic-

Fig. 4.3 Superworms have the unique ability to eat polystyrene with the assistance of their resident gut microbiota. (Reprinted with permission from Ref. [143])
tive and adaptive medical treatment approaches where targeted data metrics can be used more effectively to monitor and improve health. This will facilitate the timely implementation of appropriate intervention strategies that can be administered pro-actively to restore health balance.

### 4.1.1 Definitions

What is entailed within the term *biobased materials* and how can we adequately define it with regard to breadth and depth and scope? At its most fundamental level, biobased means life based, and this can be interpreted to mean having a foundation in life. Biobased materials have an intimate connection with life at some point in time and within its historical timeline. Some biobased materials are still living, while others have ceased to carry out life processes, but they can still be used to benefit or promote living organisms or life processes. A regulatory-based definition for biobased products was developed for the United States Farm Security and Rural Investment Act (USFSRIA) of 2002, also known as the 2002 Farm Bill. In the Act, biobased products are defined as a commercial or industrial product (other than food or feed) that is composed, in whole or in part, of biological products or renewable domestic agricultural materials (including plant, animal, and marine materials) or forestry materials or an intermediate feedstock. This definition for biobased materials stemmed from a federal government effort to promote green technologies and environmentally friendly products.

Biobased materials were further defined by Curran [25] as “… products that mainly consist of a substance (or substances) derived from living matter (biomass) and either occur naturally or are synthesized, or it may refer to products made by processes that use biomass. Following a strict definition, many common materials, such as paper, wood, and leather, can be referred to as bio-based materials, but typically, the term refers to modern materials that have undergone more extensive processing. Materials from biomass sources include bulk chemicals, platform chemicals, solvents, polymers, and biocomposites (some materials may fall under more than one category). The many processes to convert biomass components to value-added products and fuels can be classified broadly as biochemical or thermo-chemical. In addition, biotechnological processes that rely mainly on plant breeding, fermentation, and conventional enzyme isolation also are used. Bio-based materials are perceived as potentially greener alternatives than their petroleum-based counterparts; however, this claim is being scrutinized closely. New bio-based materials that may compete with conventional materials are emerging continually, and the opportunities to use them in existing and novel products are just beginning to be explored.”

Currently, all federal agencies are required to give preference to products that are predominantly made from biobased materials [24]. The US Department of Agriculture (USDA) manages the BioPreferred Program which was birthed from the 2002 Farm Act. The BioPreferred Program was reauthorized and expanded in
the Agricultural Act of 2014 (the 2014 Farm Bill). The aims of the Agricultural Act of 2014 include increasing the development, purchase, and use of biobased products in order to reduce US dependence and reliance on petroleum, increase the use of renewable agricultural resources, and contribute to reducing adverse environmental and health impacts. More information about this program can be found at the BioPreferred Program website (www.biopreferred.gov). Small business entities who wish to obtain government contracts with federal agencies are informed about these important regulations and must attest to their understanding of biobased provisions and requirements as part of the business registration process. The term biobased in this context focuses on the amount of new or recent organic carbon that is in an object compared to the amount of old organic carbon that it contains. The amount of biobased C can be calculated according to Eq. 4.1.

\[
\text{biobased content} = \left(\frac{\text{new organic } C}{\text{new organic } C + \text{old organic } C}\right) \times 100
\]

Calculations of biobased content only consider organic carbon. This consideration highlights the intimate link between biobased materials and the most important component of biobased materials: carbon. All modern materials are arguably biobased and either directly or indirectly derived from biobased materials due to the ubiquitous nature and presence of carbon in all materials as either a direct component or as a necessary processing aid. The oil which is used to produce petroleum-based products is derived from ancient biomass. The early development of metallurgy was catalyzed by heat energy that was generated by burning biomass in the form of wood or coal. Additional contributions of biomass include the important role of carbon in coke furnaces to reduce ores into pure metals. Molecular integration of carbon in iron is also used to influence the formation of economically useful steel products such as the series of stainless steel grades that are used for biomedical implants and tools.

Further consideration of carbon in all of its myriad forms begs the question: “How can we best describe carbon as it is intimately and creatively linked and utilized within the vast biobased network of our living biosphere Earth and the universe that it resides in?” It can be useful to further define categories of biobased materials based on the unique relationships among carbon in its many forms. Primary biobased C (1 °C) is carbon that is used to form the structural framework of a living organism, and it is fully integrated into its fundamental makeup. Secondary biobased C (2 °C) consists of biobased carbon materials that are biosynthesized by a living organism and used to carry out vital life functions. Tertiary biobased carbon (3 °C) can be considered the residue or leftover biomass from 1 °C and 2 °C biobased materials. Examples of 3 °C include coal and fossil fuel petroleum. Quaternary biobased carbon (4 °C) may be categorized as products that are derived from fossil fuels. These can encompass materials that are used after minimal processing such as by-products from petroleum processing like petroleum jelly.
The medical benefits of petroleum jelly were discovered on the oil fields when oil workers found that wounds healed faster when they were covered with the jelly like substance that was found on oil pipes. Value-added products that are synthesized through intricate processes to modify the atomic architecture of the carbon to yield advanced materials can also be classified as 4 °C. There are a number of biobased materials that can be grouped in this category including high surface area carbon adsorbents, C nanoparticle and nanotubes (single and multiwall), graphite and graphene, synthetic diamonds (for cutting, grinding, and polishing), and diamond thin films (for thermal-based microelectronic applications).

4.1.2 Scope

It is fascinating how the lines that separate different categories of biomaterial and biotechnology enhanced fields of research are blurring and morphing into unique interdisciplinary fields of research endeavor. We are on the precipice of great advancements in healthcare treatments as our ability to fully utilize biobased materials increases. A lot of these advances are energized by the more sophisticated lenses that we can use to uncover the underlying biologically active constituent components and their chemical and physical properties to unlock the mechanisms that give rise to their specific biological function. We can envision the progress that has been achieved from the early discovery of the microscope by Von Leeuwenhoek in the 1600s. Robert Hooke and others contributed great improvements to the resolving power of the microscope to enhance our view. Electron microscopy really opened up a new world with the introduction of the transmission electron microscopy (TEM) in the 1930s. Biobased materials could now be viewed with a much higher level of resolution, and we were on the pathway to view the atom. Advances in optical microscopy such as confocal and fluorescence imaging modes coupled with new types of microscopy including atomic force microscopy enhanced the span over which biobased materials can be viewed. This span ranges from subatomic to subcellular to cellular to tissue and organ sections.

There are many ways that the subject of biobased materials can be approached in order to gain a more fully developed understanding of this broadly applicable term. There are many nuances which can be applied to the term biobased to further delineate it from the broader parent field of biomaterials science. A definition for biobased materials was presented earlier in this chapter that focused on “new” carbon. This definition is relevant but somewhat limited, so we would like to expand the definition and scope of biobased materials to encompass the following considerations. Biobased materials can be (1) biological in origin, (2) derived from biological sources, (3) involve aspects of biomimetics and bioinspiration, and (4) encompass materials that are necessary for life.
4.1.2.1 Biological Origin

On the most fundamental level, biobased materials are types of matter that result from specific biological processes. Hence, biobased materials are biological in origin and can be thought to originate from some action on living matter or by living matter to form some unique reaction product (i.e., produced by some living organism). Primary and secondary biobased C (1 °C and 2 °C) are the main carbon components in biobased materials with biological origin. Biobased materials can encompass a broad range of source systems including plant or animal resources, single cell or multicellular clusters, and single cell-derived molecular products or produced via the collective action of multiple cells or specialized tissue. Time also plays a key role in determining the utility of biobased materials. Some biobased materials such as food items have a limited shelf life and must be used before perishing. Spices have played a very important historical role in food preservation [48]. In modern times, a lot of synthetic chemicals are used to extend food shelf life, but the long-term health effects of synthetic preservative compounds are in question. It is estimated that 1.3 billion tons (approximately one third) of all food produced worldwide is wasted due to spoilage [49]. In a unique application of biobased materials, extracts from plants are being used to help preserve foods based on specific antimicrobial or chemical effects [11]. Rosemary-based extractives are a great alternative to synthetic preservatives such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and tert-butyl hydroquinone in functioning as antioxidants to prevent oil and fat spoilage and rancidity. BHT has been linked to cancer in test rodents. Rosemary’s key anti-spoilage ingredients are carnosic acid and rosmarinic acid. These natural antioxidants are also found in sage and act to increase shelf life of foods by inhibiting the free radical chain reactions that cause fat and oil oxidation. Additional benefits from these compounds include a possible link to suppression of Alzheimer’s disease [50].

At the other extreme, some biobased materials reach the end of their life cycle and undergo decomposition processes to yield products such as organically rich compost soil. If the time horizon is much longer, oil, coal, and other fossil fuels (3 °C – tertiary carbon) can be the biobased output that results from plant and other biobased organic material inputs. It is interesting how in this case, the energy that went into growing the initial biobased feedstock materials is stored and can be released during combustion or used to develop a life-preserving component in a biobased medical therapy.

4.1.2.2 Derived from Biological Sources

Biobased materials that are derived from biological sources retain the essence of the original biological material, but some aspects have been altered to accommodate specific needs or constraints based on the intended application. Ghost hearts are an
exciting example of this category where residual collagen and extracellular matrix proteins are retained within the architectural framework of the heart, while the cell entities are removed to minimize host rejection issues as shown in Fig. 4.2. This becomes even more important when porcine-based tissue products are considered. Pig cells have an extra surface glycoprotein/polysaccharide complex that triggers the host body rejection response when porcine cell-based biomaterials are implanted in humans.

4.1.2.3 Biomimetics and Bioinspiration

Biomimetic is derived from the root word *bio* (life) and *mimere* (to mimic). The intended goal of biomimetic design and processing is to utilize information gathered from the study of biological systems to improve material’s processing technology. It is a natural extension to utilize biomimetic design principles gathered from natural biological materials synthesis and systems function to enhance the level of control that can be exerted over the development of biobased materials. The field of biomimetics was originally divided into two focus areas by Sarikaya et al. [105]: biomimicry and bioduplication. Biomimicry looks for alternative processing routes to achieve the unique structures and functionalities that are exhibited by biological materials, while bioduplication refers to the direct adoption of biological processes to synthesize advanced biobased materials. Design principles used in nature can be harvested and reinvested to synthesize bioimplants with tailored functionalities that are more effectively integrated into the body to treat the underlying medical issue in a more efficient and effective manner. One approach to achieve the next generation of bone implants involves adopting biomimetic processing strategies. The successful bioduplication of bone combines aspects of tissue engineering with fundamental studies of the structural and cellular biology of bone tissue in order to integrate unique design principles with advanced processing strategies to fabricate bone-inspired nanocomposites.

Bioinspiration and biomimicry are more recent additions to expand the field of biomimetics. Biomimicry principles can be applied to a wider palette of materials to broaden the range of properties that can be achieved to emulate biobased materials. Nanolaminated materials have been developed that exhibit enhanced properties on par with nacre in terms of strength and fracture toughness. These materials are made from engineered materials that replace the protein, chitin, and calcium carbonate biobased materials that are used in natural laminated nacre [82]. Natural nacre is composed of a chitin protein sandwich interlayer structure (20–50 nm thickness) with calcium carbonate platelets (300–500 nm thickness) that use nanoasperities and interlayer bridges to further enhance the mechanical properties and damage tolerance [112].
4.1.2.4  Required for Life

The last case for biobased materials entails materials that are critical for life. This requirement broadens the scope of biobased materials to include elements, molecules, and substances that are necessary for life. This class of biobased materials includes the main building blocks of cells and tissues. Lipids, carbohydrates, nucleic acids, and amino acids interact in a phenomenal manner to form hierarchical structures including the cell membrane, DNA and RNA, proteins, and hybrid polysaccharide-protein complexes for life continuation and replication. These important molecules are carbon based. Additional biobased materials that are considered in this category include food and other fuel sources. It is interesting to note that some biobased materials occupy niches in multiple categories, while other materials such as water and O₂ are examples of non-carbon-based molecules that are not biobased under traditional considerations but are necessary for life.

4.1.3  Interpretation

The interrelationships among biobased materials and health are like a giant puzzle with an enormous amount of detailed pieces that need to be deciphered in terms of their basic and active components. Once this is completed, the task of understanding how the pieces fit together to influence health using elegant control mechanisms and nested feedback loops must be uncovered to yield optimum health outcomes that can be tailored for individual patient needs and intended outcomes. With the information incorporated in the definition and scope for biobased materials, we can start to interpret biobased materials in a new light. This view includes aspects of biology, chemistry, and physics with math and engineering concepts. Biobased materials provide a multilevel foundation on which life is built. Biobased materials encompass architectural concepts based on the structural role of materials like cellulose, chitin, and collagen in building the “skeletal” framework for plants, arthropod, and mammalian organisms. Biobased materials also encompass the food components which serve as the fuel and source of energy for the continuation of life processes. The developing and expanding field of food science provides a novel and exciting perspective to view biobased materials for health. Food sources are converted into essential, value-added resources to promote health. Fiber is a base substrate for the biosynthetic production of SCFA and other biologically active compounds.

As we move to integrate biobased materials within the field of biomaterials in a more wholistic fashion, we can anticipate designing and tailoring a broader spectrum of materials to elicit specific interactions within the body to enhance health on multiple levels. Biobased materials will serve multiple roles as therapeutic, diagnostic, predictive, and preventative agents in medical devices and therapies. This multilevel progression will give birth to some extremely versatile and valuable advanced materials where we can draw special inspiration from Robert Newnham who revolutionized the field of smart materials with his phenomenal work on piezoelectric
materials. A piezoelectric material can interconvert mechanical and electrical stimuli and have widespread use in robotics, very accurate positioning systems for remotely focusing telescope mirrors, and a host of other microelectronic applications. Dr. Newnham popularized the concept of smart materials. A smart material possesses the ability to change their properties in response to environmental stimuli, and they also have the dual ability to perform both sensing and actuating functions and can be viewed as imitating life in a rudimentary fashion. Many biobased materials exhibit piezoelectricity such as the bone (Fukada and Yasuda, [40]) and its components hydroxyapatite and collagen, respectively, wood [39] and nanocellulose and chitin. Dr. Newnham was able to envision an even greater development in materials technology by predicting that smart materials may one day have the potential to surpass the level of intelligent materials and become wise materials [83]. The concept of wise materials implies the ability to select the appropriate material’s response to accommodate a specific situation and make the best decision after considering many factors and possible outcomes. This enhancement in material’s behavior will be supported by advances in artificial intelligence (AI) and the concerted efforts that are being conducted to integrate AI with biological systems. Some aspects of this adaptive capability are already exhibited in a number of biobased materials and systems that exist within living organisms. The classic large-scale example is our brain, central nervous system, and neural networks and how they coordinate specific body functions. The nucleus and its associated chromosomes within the cell provide a smaller-scale example of genetic code and intelligent information transfer.

4.2 Classes of Biobased Materials

The field of biomaterials is subdivided into four classes of materials which include metals, polymers, ceramics, and composites. Each class of materials has its own set of unique characteristics that make them suitable for addressing needs within the medical and biomedical area. We can also classify biobased materials into specific groups based on unique characteristics. This chapter will focus on the following classes of biobased materials as shown in Table 4.1: biobased elements and molecules, biobased polymers, biobased minerals, biobased composites, biobased liquids, and biobased wastes.

4.2.1 Biobased Elements

Atoms are the critical building blocks from which all materials in the universe are constructed. Protons, neutrons, and electrons (and the quarks that are the constituents of the proton and neutron) are the three basic components which are arranged in increasingly more sophisticated patterns to build the raw elemental materials of
Table 4.1 Overview of biobased materials classes and selected medical applications

| Biobased material                 | Applications                                                                 |
|-----------------------------------|-----------------------------------------------------------------------------|
| **Biobased elements**             |                                                                             |
| C                                 | High surface area adsorbent, compounding agent                              |
| H                                 | Fuel (fusion)                                                               |
| O                                 | Respiration                                                                 |
| Ca                                | Ca signaling                                                                |
| Fe                                | Oxygen transport                                                            |
| Si                                | Microelectronics (substrate and components)                                 |
| **Biobased molecules and polymers**|                                                                             |
| Lipids                            | Building blocks for cell membranes, energy storage                         |
| Amino acids/proteins              | Building blocks for proteins and polypeptide chains                         |
| Collagen                          | Tissue engineering, skin grafts, and augmentation                           |
| Chitin                            | Source of chitosan, composite reinforcement                                |
| Chitosan                          | Wound dressing, scaffold, gene transfection                                 |
| Cellulose                         | Paper, sterile bandages, tissue engineering scaffolds                       |
| Casein                            | Paints                                                                      |
| Nucleic acids (DNA, RNA)          | Gene transfection, CRISPR                                                  |
| Proteins                          | Nutrition, targeted therapies                                              |
| **Biobased minerals**             |                                                                             |
| Hydroxyapatite                    | Mineral storage, hard tissue component, protein adsorption                  |
| Calcium carbonate                 | Hard tissue reinforcement                                                   |
| Iron oxide                        | Oxygen transport                                                            |
| Silica                            | Bone component, bioglass component, gene influencer                         |
| Clay                              | Biotic substrate and catalyst                                               |
| **Biobased composites**           |                                                                             |
| Bone                              | Bone transplants (auto-, Allo-, xenograft)                                  |
| Nacre                             | Bone tissue engineering                                                    |
| Crab shell                        | Bone tissue engineering                                                    |
| **Biobased liquids**              |                                                                             |
| Water                             | Transport, solvation                                                       |
| **Blood**                        |                                                                             |
| Umbilical cord blood              | Source of stem cells (cord blood bank)                                     |
| Horseshoe crab blood              | Limulus bacterial test                                                     |
| **Milk**                          |                                                                             |
| Breast milk                       | Source of nutrition                                                        |
| **Biobased cells and tissues**    |                                                                             |
| Red blood cells                   | Oxygen transport                                                            |
| White blood cells                 | Immune system surveillance                                                  |
| Osteoblasts                       | Build new bone matrix, repair                                               |
| Osteoclasts                       | Remove unneeded bone, bone remodeling                                       |
| Skin                              | Insulation and cooling, first line of defense against pathogens             |
| Bone                              | Structural framework for body, ca storage, support                          |
| Heart                             | Necessary for circulation of blood                                          |
| **Biobased waste**                |                                                                             |
| Stool/feces                       | Fecal microbiome transplants                                                |
| Urine                             | Source of stem cells, urea (hair care)                                     |
the universe. These patterns allow us to distinguish the fundamental characteristics of matter and group the elements in the periodic table. The manner in which the elements interact and react to form higher-level molecular compounds is governed by atomic bonding rules and fundamental principles that are covered in chemistry and physics courses.

4.2.1.1 Organic Elements (C, H, O, N, S)

Most biobased elements can be classified as organic due to the presence of carbon. This means that they are composed predominantly of the elements H, O, N, and S in addition to C. H is the simplest element, and it serves as the major fuel source in the fusion reactions that produce light. O is a critically important element for breathing and respiration in living organisms. O is an important component in many organic and inorganic molecules. In addition, O plays a very important role in combustion and oxidation processes. Our understanding of the critically important roles of these organic compounds in the chemistry and structural features of key biobased materials including collagen, cellulose, and chitin is expanding due to discoveries in complementary scientific fields of endeavor such as astronomy and astrophysics.

Let There Be Light

One major discovery has literally shed new light on the fundamental fusion processes which contribute to the continuous creation of the elements. Scientists have recently claimed to have glimpsed the first light that illuminated the universe in the early dawn of the beginning of creation. This initial light has been attributed to the fusion reactions that gave birth to the first stars [5, 16]. The full story of this phenomenal discovery includes theorized contributions from dark matter, one of the most mysterious subjects in the field of physics and astronomy. All stars that we see in the sky undergo fusion reactions. These fusion processes provide the driving force for change and developments in our universe ranging from subatomic particle phenomena involving quarks, neutrons, and neutrinos to gigantic quasars which exist at the center of massive black holes. Most galaxies host massive black holes in their centers which play an important function in recycling matter and destroying as well as giving birth to stars.

The Cauldron of Chemical Creation for Biobased Elements

Fusion occurs when small atoms combine to form larger atoms and release large amounts of energy in the process. It is the opposite of fission reactions in which large atoms such as uranium (U) are broken apart into smaller atom reaction products. Hydrogen (H) is not only the simplest element in the universe and the first element on the periodic table, but it is also the most abundant. H undergoes fusion...
to make helium (He). H and He make up about 90% of the normal matter in the known universe. H consists of one negatively charged electron (e) that travels around the single positively charged proton (P) in the H nucleus. The He atom consists of two e that travel around the He nucleus. The He nucleus consists of two protons and two neutrons (N) which have no charge. In one of the more interesting transformations in chemistry, a P combines with an e to yield a neutral or non-charged N as shown in Eq. 4.2.

$$P(+) + e(-) \rightarrow N(0) \quad (4.2)$$

In a very simplified description of this fundamentally important energy generating reaction, four H atoms react in a specialized fashion to achieve the proper number of P, N, and e to form one He atom. Two of the four H atoms remain unchanged, while the e and P from the other two H atoms combine to form 2 N. The final simplified reaction is shown in Eq. 4.3.

$$4H \rightarrow He + energy \quad (4.3)$$

This fundamental reaction is the basis for the generation of the massive amounts of energy that our Sun produces.

One of the most exciting discoveries related to our Sun was reported in January of 2020. Some of the highest resolution images of the Sun have been recorded using the newly installed Daniel K Inouye Solar Telescope in Hawaii. The amazingly detailed images show convection cells on the Sun’s surface that are caused by the flow of matter in the convection zone which extends from the surface of the Sun to about 200,000 Km below the Sun’s surface. The convection is driven by the temperature differential between the sun’s core which is about 15,000,000 °C and the sun’s surface which is about 6000 °C. Hot plasma rises within the Sun to the surface. As the plasma rises, it gradually cools, becomes denser, and sinks back down to be reheated in a thermal convection cycle. The individual convection cells are the size of the state of Texas. Based on the size of Texas (695,662 km$^2$ (Google Map Data)) and the surface area of the Sun (6,078,747,547 Km$^2$ (NASA.gov)), there are over 8.7 million convection cells covering the surface of the Sun.

Solar fusion energy is the starting point for biobased materials, and it is intricately linked with all life on planet Earth. Life as we know it would not be possible without light energy. Biomass benefits from solar energy to power its growth via photosynthesis. As the energetic fusion processes that produce elements in stars continue, He is fused under the proper conditions to produce heavier elements which include C, N, and O which are also critical for life.

Carbon is the critically important building block for biobased materials. It is the fourth most abundant element in our solar system and most likely in the universe. Carbon forms through the high speed/high temperature collision and fusion of three He-4 nuclei (alpha particles) which transform into carbon 12 in what is known as the triple-alpha process. In this process, two He-4 nuclei fuse to create Be-8 nuclei and one He-4 nuclei fuses with the Be-8 nuclei to create a C-12 nucleus. Hoyle
proposed that the C-12 nucleus must exist in an excited state [59]. The energy considerations necessary for this excited state to exist were discovered shortly thereafter and highlighted in an ab initio computer simulation by Epelbaum et al. [33]. Oxygen forms via a similar process. However, four He-4 nuclei combine to form oxygen. While oxygen is heavier than carbon, oxygen is more abundant than carbon. This may be due to symmetry considerations where it may be somewhat easier (and more energetically favorable) for two Be-8 nuclei to fuse and create O-16 than for one Be-8 nuclei and one He-4 nuclei to fuse and create C-12.

The formation of carbon is useful as a single element compound as well as an important partner with oxygen and hydrogen and other elements to make various molecules that are essential for life. Carbon plays a very important role in developing areas of advanced technologies encompassing high surface area adsorbents and carbon nanotubes for structural, sensing, and biomaterial applications. The specific surface area ($SA_{sp}$) is a very important physical characteristic of materials. It can be measured by the adsorption of molecules of known size on a known mass of the powder of interest. The method of Brunauer, Emmett, and Teller (BET) is widely used to measure $SA_{sp}$. In this method, a powder sample is degassed to remove any surface impurities, and a N$_2$ gas stream is flowed over the surface of the powder at a known pressure. The sample is immersed in liquid nitrogen which causes N$_2$ molecule to adsorb onto the powder surface. The number of N$_2$ molecules that adsorb can be determined by the change in pressure, and the area of the powder sample can be determined by knowing the amount of N$_2$ adsorbed and the size (footprint) of the N$_2$ molecule. The SAsp can be calculated based on Eq. 4.4.

$$SA_{sp} = \frac{SA}{V \rho} = \frac{3}{rr} \text{(for a spherical particle)} \quad (4.4)$$

where $SA$ is the surface area (based on the particle geometry) in m$^2$, $V$ is the volume of the particle (based on geometry), $r$ is the particle diameter, and $\rho$ is the particle density.

High surface area adsorbents are important for filtration and selective adsorption of molecules in respirator applications. High surface area carbon adsorbents also serve an important role in poison control to chelate toxic agents in the event of accidental ingestion. High surface area materials typically start at 1000 m$^2$/g. Comparable surface areas are typically achieved by heating a carbon source in a controlled fashion to form high levels of porosity. Ultra-high surface area carbon with surface area of 3532 m$^2$/g has been produced using the hydrothermal carbonization of chitosan gels [60]. As a point of reference, the theoretical limit for the specific surface area for a special class of materials known as metal organic framework (MOF) molecules is 14,600 m$^2$/g as reported by Farha et al. [36]. In this work, they achieved a BET gas adsorption measured specific surface area greater than 7000 m$^2$/g for a copper-based MOF using a supercritical carbon dioxide extraction method to maintain structural integrity and prevent pore collapse. As of early 2020, the highest reported surface area is 7800 m$^2$/g for a zinc-based MOF by Hönicke et al. [57].
Since the discovery of the pencil in England in the 1500s, carbon in the form of graphite has served as a critical resource for recording the creative energies of humans. This tool has been used to record important information and artwork and even medical and scientific records on paper. This fact is often overlooked in our modern electronic age of email and electronic data storage. Of course, these new resources are important, but should be celebrated along with the pencil precursor that made these developments possible. Petroski [90] and Tinney and Hammond [120] highlight key points and features of pencils and their contribution to historical developments and the newer more focused role of pencils in inspiring creativity in the age of the computer.

4.2.1.2 Biobased Inorganic Elements (Ca and Fe)

There are a number of supplementary elemental components that play critical roles in the function of biobased materials. Ca and Fe are two of the most important biologically active metals due to their important roles in our skeletal system and in oxygen transport in blood. Ca serves as a main component in the hydroxyapatite mineral reinforcing phase that is integrated within the collagen-based matrix phase. In addition to calcium’s important role in bone tissue and teeth, Ca plays an ubiquitous role in most biological signaling processes ranging from appetite to conception to birth and muscle contraction. Fe is stored in protein-based apoferritin cages within hemoglobin in red blood cells in order to carry out its important role in oxygen transport for cells. More information about Ca and Fe is included in the following section on biobased minerals.

4.2.2 Biobased Minerals

It is reasonable that most biologically relevant nanoparticles include calcium and iron in some form. Ca and Fe are prominently featured in nanoparticle based systems and therapies in the form of calcium phosphates and iron oxides. The following section will provide a brief introduction to hydroxyapatite, iron oxide in the form of magnetic nanoparticles, silica, and clay materials as biobased minerals.

4.2.2.1 Hydroxyapatite

Hydroxyapatite (HAp) is the premier calcium phosphate that occurs in mammalian hard tissues. HAp makes up approximately 70% of the bone by mass. The idealized chemical formula for stoichiometric HAp is $Ca_{10}(PO_4)_6(OH)_2$. A Transmission electron micrograph of nanoscale hydroxyapatite crystals is shown in Fig. 4.4. Biologically based HAp is liberally substituted by a variety of ions and molecules including Mg, Na, Si, K, F, and carbonate. Some of the unique features of natural
bone mineral that have been reported in the literature include low degree of crystalline order [140], the absence of OH, and the resulting influence on bioactivity [89], deviation of calcium to phosphate ratio from 1.67 [74], and substitutional incorporation of carbonate and its influence on solubility and bioactivity. Carbonate is a very important molecule in biologically based HAp, and it can substitutionally replace either phosphate or hydroxyl groups in the HAp structure, resulting in a decrease in degree of crystalline order and morphological changes [68–70]. Bone mineral chemistry plays an important role in influencing the overall bioactivity of nanocomposites [54, 102]. Biologically active HAp has a variable composition that is usually monitored via the calcium to phosphate (Ca/Pi) ratio. The ratio is 10/6 or 1.67 for stoichiometric HAp. There are a variety of anions and cations that can substitutionally incorporated within the HAp lattice including carbonate ion and a host of beneficial, neutral, and detrimental metals. In essence, apatite has an appetite for foreign ions, and this predilection can be both a blessing and a curse in terms of the biological functionality of HAp. Hydroxyapatite has a wonderful capacity for adsorbing biologically relevant compounds. HAp serves as an important mineral storage site for Ca, Pi, and other biologically relevant ions and molecules. Excess Ca that is stored in the bone can be retrieved as needed to facilitate Ca-dependent physiological processes. On the detrimental side, heavy metals such as Hg and in particular, Pb, can substitute for Ca in the HAp crystal lattice and lead to neurotoxic effect due to long-term exposure and release from bone tissue into the blood and incorporation into the brain. Pb can be removed via chelation therapies using ethylenediamine tetra acetic acid (EDTA). Flouride is an example of a beneficial element that can integrate into the crystal structure of HAp and impart a higher degree of insolubility to dental enamel [69]. The higher solubility helps to prevent bacterial action that leads to erosion of the enamel layer and tooth decay. Flouride ion has been added to municipal water systems and also toothpaste to help fight cavities and tooth decay.
Silica (SiO$_2$)

Silica plays a very important role in a widening number of biological processes. Most of the Earth’s crust is aluminosilicate based and silica is very abundant on beaches throughout the world. Silica also possesses some very important biological properties. Carlisle [19] found that silica was present in the bone tissue of young rats and that the silica concentration in the bone tissue was elevated during the early stages of bone formation. A very important development in the use of silica in bio-based materials occurred with the creation of Bioglass by Hench in the late 1960s. Bioglass revolutionized the field of bioceramics and provided inspiration for a large number of researchers. Bioglass incorporates calcium and phosphorous into a sodium silicate-based glass to develop a bioactive material. Bioglass develops a tailored surface chemistry to promote bone bonding interactions due to the presence of phosphorous, calcium, and sodium in the glass matrix. In the body, the calcium, phosphorous, and sodium leach out of the glass matrix leaving a silica-rich surface layer. The sodium ion regulates the pH in the vicinity of the Bioglass surface, and an amorphous calcium phosphate layer forms that subsequently crystallizes and recruits osteoblast cells for bone tissue formation and bonding [52]. Bioglass is considered the first synthetic bioceramic that was designed to exhibit tailored bioactivity and introduced the concept of designing nonviable materials so that they recruit appropriate cells for bone tissue healing and remodeling. There were further developments in Bioglass and supporting studies on the unique role of silica in the bone. Since the introduction of Bioglass, the idea of developing bone-inspired materials and composites has greatly expanded, and silica still plays a unique role. Silica exhibits the ability to regulate gene expression for specific genes related to bone tissue growth, remodeling, and function ([53, 141]. Silica has also been employed as a multifunctional surface modification agent for hydroxyapatite [14, 15]. In this role, silica has the potential to enhance interfacial bonding, level of bioactivity, and pH stability of hydroxyapatite for the development of enhanced bone inspired implants.

Iron Oxide

Fe imparts the wonderful capacity for magnetic properties and the ability for in situ manipulation of magnetic nanoparticle assemblies via the use of an external magnetic field. The important role of iron in imparting magnetic properties provides another host of applications for iron in biological systems. A few examples include cell sorting, magnetic nanoparticle-based hyperthermia treatments for cancer, enhanced contrast agents for magnetic resonance imaging, and as a force transduction agent to develop models for the role of mechanical stresses in cancer metastasis [1].
Clays

Clays are aluminosilicates that have occupied an important role in the history of materials development and the establishment of society. This is due to (1) relatively easy access mining where some sources can be collected near river beds; (2) plasticity, formability, and processing ease; (3) ability to render permanently hard through sintering; and (4) improved resistance to microbial growth with glazes and coatings to minimize porosity. The plasticity of clay is due to its plate-like particle morphology that allows water layers to be entrained between clay particles, and this allows shear-induced plasticity behavior. Removal of water leads to hardening of the clay body shape and plasticity can be restored by the re-addition of water. Sintering is a solid state process that converts the clay green body into a permanently hard piece due to atomic level diffusion processes that bond individual particles into a solid mass with densities that approach 100% theoretical. Clays exhibit multilayer phenomena for life due to the ability to enhance the level of sanitation with glazes that protected clay-based plates and drinking cups from bacterial colonization. Hence, many traditional clay-based or ceramic objects are called sanitary ware for plumbing and toilet fixtures to draw attention to this important benefit. Interlayer chemistry of clays have been linked to catalyzing chemical reactions for life and serving as substrate for important chemical reactions for life. Clays also have important use in bioimplant scaffold development [64].

4.2.3 Biobased Polymers (*Collagen, Cellulose, Chitin/Chitosan*)

4.2.3.1 Collagen

Collagen is a structural protein that is the main component of the organic matrix of the bone. Collagen also serves as the main component in most tissues and organs in our bodies with over 28 different types. The basic building blocks of proteins are amino acids. There are approximately 20 amino acid types that are routinely encountered in mammalian species. Each amino acid has a similar base structure composed of a carboxyl and an amino end group. Amino acids form peptide bonds in a condensation type polymerization reaction that results in long molecules that are called polypeptide chains. Three polypeptide chains orient in a helical fashion along the axial chain length to form the collagen molecule. The collagen molecule is a cigar-shaped structure that is approximately 300 nm in length and about 1–2 nm in diameter. Five collagen molecules assemble in a quarter stagger pattern along their axial length to form the collagen macromolecule. This quarter stagger pattern arrangement results in the characteristic 67 nm banding pattern that can be seen in Fig. 4.5a, and additional features of collagen structure can be seen in Fig. 4.6. The collagen macromolecule is the basic building block that forms the foundation for tissues in the body including skin, cartilage, bone, blood vessels, muscle, the heart, and the eye.
Fig. 4.5 Scanning electron micrograph of (a) collagen (from chicken bone) and (b) chitin fibrils from *Callinectes sapidus* (blue claw crab). Note the appearance of the quarter stagger collagen bands with 67 nm spacing in (a). The bar in each photo represents 1 μm (1000 nm).

Collagen Type I

- Molecular unit
- Peptide bonds
- Glycosidic bonds
- 3-chain coiled helix
- Linear Crystals
- Nanofibrils
- Aggregation of fibers
- Fibrous Bundles
- Hierarchical Structure

α-Chitin

Fig. 4.6 Hierarchical structural development for collagen-based bone and chitin based (crab shell). (Diagrams for cab shell microstructure are from Chen et al. [21])
4.2.3.2 Cellulose

There are a number of unique approaches which employ the liquid crystalline and self-assembly characteristics of cellulose and nanocellulose to control the fiber orientation and texture in paper. The development of ordered phases in cellulose has been studied in detail [98] and share similarities with Bouligand structures (Kaushal, Walker, and Drummond; 1951). Bouligand structures exhibit unique patterns of nested arcs which originate from the liquid crystalline and self-assembly characteristics of chitin, cellulose, and even collagen and can be seen in various biological tissues including bone, crab shell, and plants ([52, 53] Wilson et al. 2012; [45]; Giraud-Guille 1994, 1996, 2005). Chitin and collagen share similar structural features with cellulose in that all three molecular building blocks are elongated molecules approximately 300 × 2–5 nm in diameter.

4.2.3.3 Chitin/Chitosan

Chitin was first isolated from mushrooms in 1811 by the French scientist Henri Braconnot. In 1823, Odier found the same compound in the cuticles of insects and named it chitin [84]. At least 10 gigatons (1 × 10¹³ kg) of chitin are synthesized each year making chitin the second most abundant natural polymer on Earth. It is found in the exoskeleton of crustaceans, cuticle of insects, and cell wall of fungi [62]. Three polymorphic forms of chitin (α-, β-, and γ-chitins) have been identified. α-Chitin, the most abundant form found in nature, is arranged in an anti-parallel configuration. β-Chitin is organized in a parallel configuration, and γ-chitin is a mixture of α- and β-chitin. The anti-parallel configuration gives a highly ordered crystalline structure with strong hydrogen bonding between chitin chains, leading to the rigid and insoluble properties of α-chitin [78]. α-Chitin types vary in terms of the length of their N-acetylglucosamine chains, the degree of crystallinity, and the dependence on the presence of accessory inorganic compounds or proteins. As a consequence, the consistency of the chitinous layers in organisms like arthropods differs considerably [62]. A chitinous exoskeleton is diagnostic of the crustaceans. It is secreted by a single layer of cells (the epidermis) and gains its stiffness and structural complexity mainly by being folded and curved in many complex ways [130]. Chitosan is deacetylated chitin. The deacetylation process imparts limited solubility to chitosan in slightly acidic aqueous solvents. A scanning electron micrograph for chitin from blue claw crab shell is shown in Fig. 4.5b. There are a number of similar features that are shared by chitin and collagen related to biosynthetic processes as well as structural characteristics. An overview of these features is shown in Fig. 4.6.
**4.2.4 Biobased Composites and Bone Inspiration**

Biobased composites integrate an organic protein and/or polysaccharide-based matrix with an inorganic mineral-based reinforcing component that imparts enhanced mechanical and bioactive properties. There are a number of novel opportunities for the adoption of innovative design features and processing techniques harvested from biobased composite materials. The biomimetic inspiration can be utilized to exert more control over the microstructure, hierarchical architecture, and functionality of biobased materials that can be used in a wide range of medical applications. Natural biobased materials such as bone, teeth, and ivory have been used in various cosmetic and medical applications since the earliest days of recorded history. Dental bridges were made by fastening carved ivory and/or discarded human teeth with gold as early as 500 BC. Some of the more exotic materials that have been used for dental implants include walrus, hippo, and elephant tusks and seashells. Problems with these implants, such as discoloration and disintegration in the body, motivated people to develop improved biomaterials. The study and improved adaptation of biobased nanocomposites can provide key insights and inspiration to fabricate functionally advanced biobased material implants that overcome the limitations of some of the earlier biobased implants.

Nature has an extraordinary way of constructing elaborate composite structures with exceptional properties from relatively simple compounds. Design concepts such as hierarchical nested design and self-assembly phenomena are utilized in fascinating ways to synthesize biological nanocomposites by the controlled nucleation of an appropriate inorganic phase in the presence of a functionalized organic matrix. The matrix exerts a high degree of control over the development of the inorganic phase by regulation of ion flux at the matrix interface, growth, and morphology modification of the inorganic phase by adsorption/complexation interactions with soluble polymer macromolecules and functional group mediation of molecular interactions at the polymer/matrix interface [18]. Biomineralization processes result in elaborate, multifunctional architectures that display an extraordinary degree of control over the phase distribution, size, interfacial structure, morphology, and crystallographic orientation of the inorganic phase.

The process of mineral phase formation is governed by solubility, surface and complexation chemistry, and bioavailability of important elemental and molecular species such as calcium, carbonate, phosphate, magnesium, and silica. Specific aspects of nanocomposite design related to matrix phase chemistry, degree of crystalline order and orientation, phase distribution, and microstructure are uniquely controlled during the birth, healing, and remodeling of the bone. There are many lessons that we can learn from bone structure and biology to improve our ability to synthesize nanocomposites for various applications.

What does bone inspired mean? Inspiration can be thought of as an intangible element that enables one to envision, achieve, or bring into existence something that was previously unknown or undeveloped. The overall goal of using bone as a biomimetic subject is to draw inspiration from the unique structure and function of
hard tissue to make materials to improve bone health [88]. Biomimetic lessons and inspiration from bone can be utilized on three different levels. The first aspect of bone inspiration deals with the development of materials for bone tissue repair based on biomimetic lessons from bone. A number of bone implant material were developed to try to mimic the basic composition of the bone. Polyethylene with 20 volume percent hydroxyapatite was found to exhibit a high level of bioactivity with mechanical properties on the lower range of the levels exhibited by the bone [13]. Another aspect of bone inspiration involves using insights gained from the structure and function of the bone and other biological hard tissues to synthesize novel nanocomposites for various technological applications. Bone inspiration can also be utilized for the development of models and strategies to address critical issues in education and mentoring. While all three aspects of bone inspiration are important, the first one related to bone-inspired nanocomposites to enhance the healing and remodeling of bone will serve as the focus for this section. Key aspects of the structure and properties of bone will be highlighted to show unique ways of adopting and adapting these features to design functionally advanced bioimplants to improve bone healing and remodeling. Additional insights from nacre and crab shell are included as additional representative examples of biobased composites.

4.2.4.1 Bone

The bone is one of the most important and fascinating biomineralized composite structures in nature. The bone exhibits unique self-healing properties. It has a functionally graded architecture that forms via liquid crystalline phenomena exhibited by the collagen matrix, and this hierarchical development characterized by Bouligand structures promotes optimization of its mechanical and chemical properties. On a macroscopic scale, the bone provides structural support for our bodies, protects our internal organs, serves as an attachment site for muscle and tendon, and provides a reservoir for bone marrow tissue that facilitates the production and storage of hematopoietic and mesenchymal stem cells. On a microscopic scale, the bone serves as a storage site for calcium, phosphate, and other biologically relevant ionic species. The bone also provides a framework for the activities of osteoblasts, osteoclasts, and osteocytes to orchestrate the production of extracellular matrix proteins (ecm), resorb excess bone, and help coordinate cellular and tissue interactions. The nanoscale features of the bone make this material truly remarkable from a material’s design viewpoint. The bone is composed of a cell-derived collagen matrix that works in conjunction with ecm and matrix vesicles to influence the in situ nucleation and growth of hydroxyapatite (HAp) crystals [2]. The HAp crystals appear as thin platelets that are intimately incorporated within and on collagen fibrils [134]. The bone is a very important tissue in the body due to its structural and metabolic importance in overall body homeostasis. The bone is also a unique tissue because it integrates HAp, a hard calcium phosphate-based mineral phase, with a protein-based organic matrix to form a strong and tough nanocomposite. The bone
derives its properties from the multilevel hierarchy which is built in during the growth, development, and remodeling of this tissue.

The main constituents of the bone include HAp, the collagen matrix, various ecm proteins, water, and cells as shown in Fig. 4.7. There is a great deal of interactions between each of these critical building blocks for the bone. The major cells in the bone include differentiated cells such as osteoblasts, osteoclasts, and osteocytes and progenitor cells including hematopoietic and mesenchymal stem cells. The role of osteoblasts is to build new bone. The osteoblasts are considered specialized fibroblasts [30] that have the ability to express structural proteins such as collagen and ecm components such as osteopontin, osteonectin, alkaline phosphatase, bone sialoprotein, and bone morphogenetic protein that contribute to the organic matrix of bone. The ecm components are glycoproteins which serve various roles in regulating cell activities and biomineralization. Osteoclasts serve an important role in bone remodeling. Osteoclasts are drawn to areas of the bone that are no longer needed and remove bone by forming resorption pits. The mechanism of osteoclast bone removal is via enzymatic and pH modulation. Osteocytes are osteoblasts that become entombed in bone tissue and serve a signaling/sensory role in bone tissue health. Osteoblasts and osteoclasts have a very interesting origin and lineage [30, 117]. The intramedullary cavity of long bone houses the bone marrow which produces the mesenchymal and hematopoietic stem cells that have very important roles in promoting and protecting our skeletal system. Mesenchymal stem cells are pluripotent cells that under appropriate conditions can differentiate into specialized cells to produce connective tissue such as bone, muscle, tendon, cartilage, and adipose (fat). Hematopoietic stem cells can differentiate into cells related to the blood

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**Fig. 4.7** Hierarchical structural levels for bone tissue. (Used with permission from [134] (a) and [84] (b))
and immune system such as red and white blood cells, macrophages, monocytes, T cells, B cells, and other cells that help protect our bodies from invading pathogens. While the osteoblasts originate from mesenchymal stem cells, the osteoclasts come from the hematopoietic stem cell lineage.

A number of other structural features need to be considered in bone tissue. The major acellular components of the bone are HAp, collagen, and ecm. Bone tissue is supplied with oxygen and nutrients via numerous blood vessels. Concentric layers of bone matrix (lamella) enclose a central blood vessel within Haversian canals. Osteocytes are interspersed between the lamella in very small spaces known as lacunae. Lacunae and Haversian canals are connected via microscopic channels (canaliculi) that provide a pathway for tissue fluid to reach the bone cells. There are two types of bone that typically occur. Compact bone is characterized by closely spaced Haversian canals and lamellae; hence it is the densest type of bone. Cancellous bone contains many open spaces between trabeculae. The trabeculae are thin processes of the bone that join together in different arrangements in different bone types to give structural integrity and strength along the lines of strain in individual bone.

Advances in bone inspired nanocomposites tend to follow technology trends. For the longest time, mechanical properties were considered the most important factor in orthopedic implants because these properties could be monitored and modified as needed. There were many successful implants made of metals that helped improve the quality of life for many with skeletal problems (hips, long bones, etc.). But problems associated with stress shielding (i.e., bone atrophy due to improper stress distribution), corrosion, implant density differences, and the inherent static nature of metallic implants drove efforts to improve bone implant design. There was a fundamental shift away from monolithic metal implants because of metal’s inability to grow, change, and adapt with native bone tissue to something more similar to the bone. One of the first considerations in biobased bone implant design is that bone tissue is living and vibrant, so an ideal replacement should exhibit these characteristics also.

Autologous bone is the gold standard for bone graft-based materials to replace diseased or damaged bone. Autologous bone is harvested from the patient, typically from the hip region. While this material performs on a superior level because it contains all the key factors required for successful integration and stimulation of bone healing and remodeling events with no autoimmune issues, autologous bone harvesting results in a new wound site where risks associated with compromised healing and infection may occur. We are not yet able to generate biobased bone implants that rival autologous bone, especially from the aspect of being fully living and vibrant as healthy bone tissue. However, there have been a number of ingenious developments in bone tissue implants that have brought us much closer to being able to produce materials that approach the performance of autologous bone in orchestrating bone healing and remodeling.

Researchers have utilized aspects of bone inspiration to give birth to a host of biobased materials that attempt to capture the essence of bone and restore functionality to damaged bone tissue. Foundational studies on the osteoinductive properties
of demineralized bone matrix (DBM) were performed by Urist et al. [125]. The implantation of DBM underneath the skin or within muscle tissue initiated a series of reactions that ultimately produced viable bone tissue with marrow. These studies demonstrated that demineralized bone matrix (DBM) possesses the ability to induce new bone formation in regions that were remote from bone tissue such as subcutaneous zones or intramuscular regions. Whole bone was found to be ineffective at inducing bone formation in similar regions. Further studies by Reddi and Huggins [96, 97] and Reddi and Anderson [95] on the osteoinductive properties of DBM showed that the bone induction process proceeded via an endochondral mechanism in which the implanted DBM was transformed to a cartilage type plaque by the action of macrophages and fibroblasts which transformed to chondroblasts to facilitate cartilage tissue formation. The chondroblasts were in turn transformed to osteoblasts and the cartilage mineralized to complete the endochondral bone formation process. Later studies by Reddi [93, 94, 103] revealed that DBM contained a family of osteogenic extracellular matrix (ECM) proteins which came to be known as bone morphogenetic proteins (BMP) which promoted various activities that are necessary for bone formation. The removal of mineral phase in DBM exposed these osteogenic proteins so that they could more readily function in orchestrating new bone formation.

Questions at the Interface of Biobased Bone Implants

Our understanding of the intricate processes that orchestrate the healing and remodeling of the bone has greatly expanded in recent years. New insights in areas such as osteoblast and osteoclast lineage and function [30, 138], the ability to grow and sustain osteoclasts in culture, and identification of novel ECM proteins and elucidation of their roles in cell signaling and biomineralization [79, 136] have enhanced our ability to synthesize functionally advanced biobased bone implants that incorporate key aspects of bone architecture and functionality. There are still a number of questions that remain unanswered on both sides of the implant/bone tissue interface. The questions on the biobased implant side relate to the optimum bulk and surface chemistries for the mineral phase and the organic matrix and the overall structure/architecture that best promote seamless integration of biobased bone implants into bone tissue. The questions on the bone tissue side involve how growth factors, ECM, cells, and biomineralization phenomena work to orchestrate the bone healing and remodeling response. On a more fundamental level, the questions involve the key surface and interfacial characteristics of biobased bone implants that best predict and determine optimum hard tissue bioactivity. These key interfacial characteristics relate to factors such as surface charge, chemical composition [44, 54], adsorption capacity, matrix orientation and feature size [38, 139], particle size effects [41, 133], degree of crystalline order [140], porosity [55], solubility, etc. Another important question involves how synergistic effects influence materials performance. The answers to these questions will help in designing biobased bone
implants that elicit the optimum bone healing response and expand the range of hard tissue conditions that can be treated.

Nacre

One of the most unique resources for the development of bone implants comes from the chemistry and architecture of biomineralized hard tissues such as coral and nacre. Coral has been used as a material to help guide the regeneration of bone tissue since the mid-1970s. The porous CaCO3 coral exoskeleton exhibits a unique ability to bond with the bone due to the bioactivity of CaCO3 and the presence of pores (>100 μm) which allows vascularized bone tissue to grow into the coral for implant fixation [81, 138].

The “rediscovery” of nacre as a bioactive material for bone healing and remodeling occurred in the 1990s. The ancient Mayan people used nacre as a biobased implant material, and this work was inspired by the Mayan practice of using nacre to replace missing teeth and the subsequent integration of nacre into the jawbone. Nacre is a layered nanocomposite composed of calcium carbonate, chitin, and protein that makes up the inner portion of the shell of deep sea mollusk species such as *Haliotis rufescens* (Fig. 4.8). Archaeological specimens of Mayan skulls showed

![Beautiful iridescent coloration in red abalone nacre pairs well with incredible strength and toughness and unique bioactivity for bone tissue engineering. (Photo credit from Dr. Pupa Gilbert)](image)
evidence of the ability of implanted nacre to physically bond to the jawbone [137]. The work of Lopez et al. has demonstrated that nacre-induced osteoblasts to generate new bone in osteoblast cell cultures in vitro [75, 109] and that this biobased material could be used to generate new bone in human patients in vivo [3, 137]. The series of studies included culturing osteoblasts in the presence of nacre chips [75], observing the inducement of osteoblasts to produce a bone “bridge” between neighboring nacre and bone chips with a 1 mm gap [109], and the implantation of crushed nacre into periodontal defects in human adult females [3]. Westbroek and Marin [137] pointed out interesting implications regarding common features and chemical factors in the biomineralization processes that developed for the various biomineralized tissues over time. The idea of a kinship between biomineralized tissues seems plausible due to the observation that the implanted nacre produced no detrimental effects in the female patients and resulted in the growth of new healthy bone tissue in the defect regions [3]. Later research on the mechanism for the osteoinductive properties of nacre revealed that nacre contains water-soluble matrix proteins that stimulate osteoblast activity and even promote the differentiation of cells to the osteogenic line [80]. At least one of the nacre matrix proteins, Perlustrin, has been found to share a number of similarities with human insulin like growth factors [135].

Crab Shell

Crab shell is unique composite consisting of a chitin protein matrix that is mechanically fortified by calcium carbonate. It shares a number of similarities with bone as highlighted in Table 4.2.

Table 4.2 Similarities between the biomineralized hard tissues bone and crab shell

|   |   |
|---|---|
| 1. | Biomineralized composites |
| 2. | Ca\(^{2+}\) based inorganic phase |
| 3. | Each inorganic phase (hydroxyapatite, calcium carbonate) contains 40% Ca\(^{2+}\) by mass |
| 4. | Textured, crystallographic orientation of inorganic phase |
| 5. | Highly loaded inorganic phase (50–70 wt.%) |
| 6. | Relatively hard and damage tolerant |
| 7. | Organic polymer matrix phase |
| 8. | Protein and mucopolysaccharide constituents |
| 9. | Liquid crystalline behavior of the organic matrix |
| 10. | Structural support role |
| 11. | Cellular control |
| 12. | Self healing behavior |
| 13. | Piezoelectric properties (ability to convert mechanical stress) |
uid crystal nature of chitin and the respective roles that it plays in the self-assembly and mineralization processes of crustacean shell [2]. Bouligand structures are present in crab shell also as shown in Fig. 4.9. The chitin matrix in crab plays a critical role as a framework for the orchestrated activities of macromolecules and cells to coordinate cellular and tissue interactions for shell formation and repair. The chitin-protein matrix in crab shell functions as a framework for the activity of specialized epidermal cells to produce and secrete organic matrix for maintenance of integument integrity and function through various molt cycles and survival events.

4.2.5  Biobased Liquids

4.2.5.1  Water

Mix one part oxygen gas with two parts hydrogen, and the simple yet elegant liquid that forms between the temperature regime of 273–373 K (0–100 C) at standard temperature and pressure makes life as we know it possible. Water is the liquid vehicle that makes all other biobased liquids possible (Table 4.1); hence water is the ultimate biobased liquid. Water is in fact the liquid of life. This is due to its ability to interact with biologically important molecules in thermodynamically driven processes which orchestrate hydrophilic (solubility and dissolution) and hydrophobic (phase separation and sequestration) interactions. The major component of our bodies and source of life in terms of origins from sea (reference article) and creation stories from many cultures.

A literature survey on the subject water reveals a very interesting trend. While water is necessary for life, there is not an abundance of articles that highlight water
as a stand-alone compound entity. It is mostly portrayed in a support role, and in this role as a behind-the-scenes supporter, water truly shines in its role as the solvent that carries the vitally important ions and biologically active molecules that support life. Water has unique interactions with various species in terms of solubility and insolubility, conductivity, hydration and hydration spheres, anomalous freezing behavior, oxygen and gas permeability, and electrolyte strength moderation related to the transfer of Na/K across cell membrane. All of these factors make water in its simple embodiment of two hydrogens and one oxygen the greatest liquid in universe.

Water is the main constituent of the other vitally important biobased liquids which include the natural systems blood, plasma, breast milk, and urine and the synthetically produced biobased liquids simulated body fluid, simulated infant formula, and artificial blood. One of the most interesting artificial blood systems is based on the leguminous plant synthesized hemoglobin analogue leghemoglobin which has recently been receiving rave reviews in vegetarian meat substitutes such as the Impossible Burger.

### 4.2.5.2 Milk

Milk is the first food that sustains the life of many mammalian species including humans. Our early introduction and lifelong association with milk and its dairy derivatives provides milk with a very high status in our lives and culture. Milk is equated with abundant food when used in idioms such as “a land flowing with milk and honey” to epitomize abundant food and rich resources.

Milk is a colloidal suspension of protein stabilized fat globules that are impregnated with nanocrystalline calcium phosphate in an aqueous solvent. The main protein constituent in milk is casein. Casein is a phosphoprotein that has been used as the basis for glue and paint binders. The early artwork of Walt Disney and his prolific gallery of talented artists features casein-based paints. Calcium phosphate crystals exist in milk with other proteins that contribute to the nutritional value of milk for the young of many species [72]. Milk (and in particular breast milk) also hosts a rich supply of stem cells and microbes which help boost the immune system of the young offspring through introduction and population of the gut microbiome. *Bacteroides* are uptaken into the gut of babies during birth and can also be supplied in breast milk. This occurrence highlights the intrinsic benefit of breast milk in promoting and maintaining health of developing babies gut microbiome and indicates a potential opportunity for optimizing baby formula with probiotics. Milk also serves as the biobased feedstock for “cultural” transformation to produce a myriad of cheese and yogurt products under controlled bacterial fermentation conditions. These milk based products can contribute to health by providing a rich source of protein and calcium and contribute to gut microbiome diversity and health.

The fat content of milk continues to be an important consideration with proponents arguing for the benefits of whole milk vs others who argue that reduced fat milk products are better for health. The topic of milk fat content and a potential relation between telomere length has received attention. Telomeres are the end
strands of chromosomes that function as a cell clock by shortening after each cell division. When the telomere reaches a certain length, cell division ceases. These studies report that there may be a link between drinking lower fat content milk and longevity because data showed that telomere length seemed to decrease more slowly for participants who drank lower fat milk [121]. In another study, data is presented that indicates that children who drink whole milk at an early age are less likely to become obese later in life. How can these studies be reconciled to address the question of which type of milk is healthiest? More careful studies to pinpoint exact causes and mechanisms for the observed phenomena need to be conducted in order to find the best conditions for optimum health. We also need to enhance our understanding of fat and understand how all fats are not bad based on the fascinating studies that highlight the metabolic and health differences between white, brown, and even gray fat [9]. Brown fat is the optimum fat that our bodies can develop and it is similar to baby fat and the fat that bears develop as they prepare to hibernate. It is easier to burn and provides cleaner energy transfer. Brown fat formation seems to be catalyzed by exposure to colder temperatures.

4.2.5.3 Blood

The blood that courses through your veins contains plasma and transports red blood cells, white blood cells, and platelets. The plasma component contains water, ions/electrolytes, proteins, blood gases, glucose, amino acids, and waste products such as urea. The importance of blood as a biobased material cannot be emphasized enough and its vital role in medical products in both natural and synthetic forms is covered in a vast number of references.

4.2.5.4 Urine

The sports drink industry is a $10 billion dollar per year industry, and Gatorade is the leading brand with a market share of about 70% based on data from 2013. The history of Gatorade can be traced back to a curious question asked by a college football coach in 1965, “Why aren’t my football players urinating more?” The very hot condition under which the players were practicing was causing their bodies to retain as much water as possible due to sweat-induced dehydration. The players were also losing important salts from their body. A solution to this problem was posed by a physician, Dr. Robert Cade, and his team who came up with an elegant solution modeled after urine. The athletes were given a rehydration solution that contained water, salt, and sugar. Dr. Cade’s wife suggested the addition of lemon juice after players complained about the taste, and with that simple recipe, Gatorade was born to support the University of Florida Gator’s football team.

Urine is a very important fluid that is produced in the kidneys and contains a host of biobased components including urea, nitrogen, phosphorous, proteins, and specialized cells. Urine contains water (about 95%), urea (from amino acid metabo-
lism), inorganic salts, creatinine, ammonia, and pigmented products of blood breakdown (urochrome) which gives urine its characteristic yellowish color (www.Britanica.com/science/urine). The yellow color of urine may be an indication that the individual should drink more water. Urine serves as a carrier for stem cells and can be used as a source for human urine-derived stem cells for improving urinary health [7]. Due to its unique chemical composition, urine has been proposed as a source of fertilizer to help with terrestrial plant growth for beets [91] and also for space colonization efforts (https://www.livescience.com/58254-growing-tomatoes-in-urine-for-mars-missions.html). Urine has even been the subject of a study for which the lead investigator was honored with an Ig Noble Prize. The research study on the hydrodynamics of mammalian urination revealed that it typically takes 21 seconds for animals to empty their bladder. This is pretty amazing because despite bladder sizes that can range from the elephant (whose bladder can hold 42 gallons of urine) to the greyhound (0.4 gallons) to the mouse (approximately 1/2 ounce), the 21 s rule seems to hold universal [142].

4.2.6 **Cells as Biobased Materials**

Most descriptions of biobased materials focus on a range of natural materials which include structural elements such as collagen from mammalian organs and tissues and cellulose and chitin from plant-based cells. A large number of biobased materials are derived from cellular metabolic products. Proteins and the genes that encode protein synthesis encompass many more possibilities to identify materials that have great utility for treating a host of medical conditions. With this foundation, we can easily envision cells as biobased materials that have extraordinary applications that are currently in use as well as a myriad of potential transformative therapies that are just on the horizon. More information about these developments can be found on the National Cell Manufacturing Consortium webpage [http://www.cellmanufacturingusa.org/about-national-cell-manufacturing-consortium] and in the Cell Manufacturing Roadmap to 2030 document http://www.cellmanufacturingusa.org/sites/default/files/Cell-Manufacturing-Roadmap-to-2030_ForWeb_110819.pdf.

Now as we move along the pathway of natural biobased materials, it is obvious that many of the biobased materials that we encounter are structural elements from plant- and animal-based tissues and cells. This constitutes most of the biomass that is broken down and repurposed to enrich soil and serve as a foundation for future coal and oil deposits. The cellular metabolic products, proteins, and the genes that encode protein synthesis can only be made by the most basic and fundamental unit for the synthesis of biobased materials – the cell. The cell is the actual biological entity that conveniently and efficiently hosts all the components that play key roles in the ongoing synthesis and proper functioning of the many biomolecules that are required for life. Cells are biobased material “biorefineries” that have extraordinary
applications for their role in the directed synthesis of products that can be harvested for medical use. Cells also serve as a foundation for myriad therapies that are currently in use as well as a host of potentially transformative treatments that are in the development pipeline.

Recent years have seen the development of a large-scale competition for meatless analogues as well as tissue-engineered meat products for people who are against the practices in the traditional meat industry. There are a number of companies who are producing cell manufactured meat products including chicken, beef, and fish. Cells are harvested from the donor animal without harm and expanded in culture in a controlled manner to develop cell and tissue engineered meat products. The expanded cell meat products can be tailored to mimic meat through the co-culture of adipose, cartilage, and muscle cells with added components to modulate texture, taste, and tenderness. These products are in the pipeline to make an appearance on consumer plates in the next few years, and a number of companies are making headlines including Memphis Meats, Finless Foods. Ben-Ayre and Levenberg [6] provide a comprehensive review of animal cell culture technology applied towards tissue engineering for the production of clean meats.

4.2.6.1 Cell and Tissue Reactors for the Production, Modification, and Storage of Biobased Materials

A wonderful world exists beneath the boundary surface of the bilayer lipid membrane of the cell. The mystery of the inner workings of the cell has been unraveled in an exciting manner since the discovery of the microscope and the first inspiration to call these units of life “cells” by Robert Hooke in 1665. The four basic molecular building blocks of the cell include lipids, carbohydrates, amino acid, and nucleic acids from which membranes, molecular polysaccharide complexes, polypeptides and proteins, and DNA/RNA are constructed.

The organelles of the cell provide the power (mitochondria), structural integrity and framework (actins), packaging and storage (endoplasmic reticulum), and control center (nucleus). The inner workings of the cell have been captured in a phenomenal way by the Harvard BioVisions Project (biovisions.mcb.harvard.edu). The old saying that “A picture is worth a thousand words.” can be updated to describe the amazing visualization that can be achieved through the medium of animation: “If a picture is worth a thousand word, a great animation can be worth more than a million words.” The web page for BioVisions is shown in Fig. 4.10. An engaging TED Talk from 2007 presented by Dr. David Bolinsky describes the origin and captures the vision for this extraordinary project. The video can be viewed at the following web address: https://www.ted.com/talks/david_bolinsky_visualizing_the_wonder_of_a_living_cell.
Pirated Cell Bioreactors: COVID-19

As the whole world grapples with the COVID-19 pandemic, it is important to take some time and devote a portion of this chapter to convey a message of hope in the face of such a dire emergency. This pandemic unfolded at the beginning of 2020. It is an unprecedented event, and its scope is very pervasive as whole countries are shutting down, schools are closing, and the largest exodus from in-person classes to online education has occurred within a time span of less than 2 weeks. The culprit which has caused all this mayhem is a very small coronavirus variant that basically takes control of the cell nucleus and forces the cell to make replicas of the virus and propagate the infection process. The COVID-19 virus is believed to have jumped from an animal species, possibly a bat, to humans. In contrast to other coronavirus of the past such as SARS from 2002 and MERS from 2012, the COVID-19 virus is extremely infectious in human to human transmission. In an even more deadly twist, patients can be infected and spread the virus for up to 14 days before showing any symptoms. The COVID-19 virus can stay alive on surfaces for days if not weeks, and there is a concerted effort to find effective cleaning agents. Lysol and Chlorox brand products are taking the lead in cleaning surfaces to limit spread of the virus. Antiviral agents such as silver and copper are interesting biobased material agents that may become effective tools for combating COVID-19. In particular, copper shows a high level of promise in inactivating coronavirus species that are closely
related to COVID-19 such as the coronavirus 229E [132]. There is a frantic scramble to find a vaccine for COVID-19, and as of March 16, 2020, human trials started in an expedited process to find a relevant therapy to slow down its spread. May a number of these efforts prove successful as people worldwide rise above this situation and show solidarity and support and sympathy for the families who are grieving the deaths of loved ones.

4.2.6.2 Plant-Based Reactors

Specific biobased components that are produced within plant hold the key to health and longevity. These cell-produced compounds have a host of names including flavonoids, vitamins, phytochemicals, phytonutrients, and carotenoids. New additions are constantly being incorporated into this vivid palette to unlock higher levels of health since the first home remedies were cultivated from plants from community healers. One of the first biobased material pharmaceuticals that was produced on a large scale was salicylic acid or aspirin. Also known as \( o \)-hydroxybenzoic acid, this compound was known to Hippocrates as early as 400 BC, and it is produced from extractives from willow tree bark [118].

Cannabis and Cannabis Oil

One of the biggest plant-derived compounds that is receiving a lot of attention is cannabis or CBD oil. CBD took the stock market by storm in 2018–2020 as marijuana became legalized in many states and investors got wind of its marketed appeal as a biobased medicinal substance. Marijuana has long been used to help patients deal with long-term pain and glaucoma. CBD is a derivative oil from marijuana plants that lacks the psychotic effects of its sister compound from marijuana, THC. CBD presents a promising intervention for a host of conditions ranging from Parkinson’s disease to chronic pain. Research studies continue to provide evidence for its effectiveness in treating epilepsy and depression and as a resource to help people recover from drug addiction [32]. The August 28, 2019, issue of Nature Outlook, vol 572 provides a great overview of various aspects of cannabis and CBD including green methods for growing and producing cannabis, the pros and cons of cannabis, the use of cannabis to enhance exercise workouts, regulatory issues, and cutting edge research into its medicinal uses and synergistic effects in health.

Apples

The wise idiom, “An apple a day helps keep the doctor away.” is a saying that is ingrained in US culture. Many people know this saying anecdotally and may take its truth for granted. However, scientific research is providing evidence on many fronts to strongly support the claims behind the reputation of apples as being healthy.
Since the time of the legendary naturalist and apple connoisseur John Chapman, also known by his more popular name Johnny Appleseed, apples have been commercially produced, and today, there are over 3000 varieties worldwide. Apples are a wonderful biobased food product that contains many biobased material compounds that have direct links with healing. Apples contain phytochemicals, fiber, and a unique biobased compound called ursolic acid. Ursolic acid is found in apple peels, and this compound has been linked with muscle fiber repair and development as well as promoting the transformation of white fat to brown fat [67].

Dandelions: The Tooth of the Lion

Dandelions are a very widely spread plant that is often considered a nuisance weed for those who do not know about its wonderful health benefits. It occurs on every continent, and in some regions of Europe it is a value-added agricultural food crop. The name dandelion comes from the French dente de leon which means tooth of the lion for the characteristic ridges that appear on to edge of its flowerette leaves. The title tooth of the lion is appropriate because full utilization of the health benefits of the dandelion can take a lion’s size bit out of health problems and challenges. The white dandelion is edible. Its vitamin- and mineral-enriched green leaves can be used as salad greens or sautéed like spinach. The flower can also be eaten as well as the stem. The dandelion is sometimes referred to as the piss or pee weed roots because some say that dandelions grow wherever dogs pee. This nickname is actually quite appropriate for another reason. The dandelion root can be used to make a tea that acts as a diuretic to help flush the kidneys. The dandelion flower actually consists of multiple flowers where each “petal” is in fact a separate, individual flower. Dandelions also provide a rich source of inulin which is a rich prebiotic source of fiber.

Dandelions have also received attention from a biomimetic perspective. The seed or “papus” of the dandelion exhibits unique aerial flight characteristics that allow it to travel far distances on wind currents. An unusual vortex wind pattern is generated below the seedling that creates very interesting vortex patterns that may be useful for advancing flight and the development of wind-powered flying mini drones [23]. As if the wonders of the dandelion could not be explored further, the white milky substance that flows from the broken stem of the dandelion is latex rubber. Rubber has been used as a biobased material medical product for a long time in various products. Natural rubber was very valuable for making gloves, tourniquet bands, and other medical products as well as tires for transportation prior to the development of synthetic rubber. There is an interesting story regarding dandelion-derived rubber. Dr. George Washington Carver collaborated with Henry Ford during World War II to develop alternate sources of rubber in the event that the Malaysian rubber supply chain was disrupted. They investigated sweet potatoes, golden rod, and dandelions. Current interest has returned to dandelion as a source of rubber for the tire industry [12, 129].
Spices

Spices have exhibited numerous health benefits in preventing and treating a wide variety of diseases such as cancer, aging, metabolic, neurological, cardiovascular, and inflammatory diseases [76]. New research continues to uncover new therapies and more effective delivery platforms for the active agents within spices. Curcumin is the active ingredient in turmeric which is used in curry. While curcumin has a lot of potential benefits including enhancing the gut microbiome [107], the bioavailability of curcumin is low. One way to address this is to encapsulate curcumin within nanoparticles. Research efforts along this pathway are gaining traction with promising results for HSV-2 Infection and Alzheimer’s [123, 131].

4.2.6.3 Tissue Origami Engineering

Nature provides many examples of folding across multiple length scales which can serve as sources of inspiration. There is a wide variety of macro-scale folding and unfolding events such as the unfolding of a leaf, shoot, or flower petals to reveal its hidden beauty. Sulci are localized creases or furrows on the surface of soft materials that form by a compression-induced instability [56, 117]. Many macro-scale folding events can be classified as sulci such as skin wrinkles and folds in the brain. There is an amazing level of folding hierarchy in living systems in which macro-scale folds are the large-scale manifestation of nanoscale events. Skin wrinkling in response to moisture occurs due to swelling and rearrangement of keratin fibers in corneocyte cells which make up the outer layer of mammalian skin [35]. Higher level curvature and folding is evident in the brain, and this folding is postulated to be related to the level and type of neuronal connections [99]. Flowers contain microscale pollen which is able to fold in response to dry conditions and preserve the pollen until it can rehydrate, unfold, and play its role in propagation [63]. The cells within the plant exhibit folding at the micro and nanoscale. Subcellular phenomena within cell organelles include organelle directed processes such as the folding of cristae in mitochondria, the convoluted structure of the endoplasmic reticulum (ER), and the function of chaperones in ER to monitor protein folding. At the nanoscale, macromolecules such as DNA and proteins fold into an almost infinite array of functional structures to facilitate life functions at the cell, tissue, and organ levels. DNA topology and folding research has already yielded a rich source of inspiration for DNA origami. The most relevant examples of bio-origami for TOE include embryogenesis [128] and organogenesis [29] in which cell sheet folding occurs via mechanical and molecular cues.

Paper has occupied a very important niche in society since its humble beginnings in Egypt as papyrus to the discovery of modern paper in China around 105 AD. Paper has faithfully served as a medium for recording thoughts, ideas, stories, and pictures to help preserve our history. One of the most exciting developments in paper technology occurred when someone discovered that you could put a creative wrinkle in paper by folding it. In origami, the expressed or implied form of an animal or object
in nature is captured by a series of folds that transform the single sheet of paper into a finished three-dimensional design. The final form can be obtained either by free form folding which in its most basic form is crumpling or by following a specified set of folding instructions or a crease pattern. The physical and chemical properties of cellulose make paper well-suited for folding. While thin sheets of cellulose paper, metal, and plastics can be folded to produce a crisp crease, only paper can be folded in the opposite direction along the same crease line without producing buckling of the material. A number of specialized origami papers have been developed including hand- or machine-made papers, tissue paper laminated metal foil, animal manure-based papers, and fibers including wood, mulberry bark, and rice or specialized components such as exogenous plant fibers. Michael LaFoss is an origami artist who uses fibers from his subjects to make specialty papers including cactus fiber-based paper used to make a cactus. There are even different classifications of origami that have developed over the years including traditional, modern, wet folding, tessellations, crimping, modular, and kirigami where cutting is allowed.

The creative potential of origami design principles has been used to develop a host of new materials and technologies including stents, telescopes, and airbags. The integration of mathematics into origami has resulted in a tremendous shift in the level of complexity and creativity that can be designed and folded into a sheet of paper. Origami enthusiasts have developed models to make multi-legged and segmented insects, scorpions, and crabs which seem to take on a life of their own including birds with feathers, complex sea creatures such as an octopus and squid, asymmetric leaves and flowers, all manner of human and mythological figures, and even human organs. The only limit to what can be achieved through paper folding is the level of inspiration and creativity of the designer. One of the most inspirational aspects of origami is the implied perception that folded objects can take on a life of their own. The famous 1819 Japanese woodcut entitled “A Magician Turns Sheet of Paper into a Crane” by Hokusai and the famous Japanese children’s story The Paper Crane by Molly Bang (a story about a paper crane given as a gift that comes alive) share interesting and literal examples of this idea. These examples lead us to ask the questions: (1) What are the limits to what can be folded from paper in terms of complexity, length scale, size, and function? and (2) Can origami objects transform into living things? This question is taken to a possible end in Fig. 4.11, where a heart is folded from a specially designed paper and seeded with appropriate cardiac cells to yield a fully functioning heart. Progress on both sides of this novel tissue engineering approach is being made in traditional cell and tissue engineering studies as well as unique approaches towards the folding of three-dimensional objects with high levels of intricate details [27].

The immense potential that can be derived from improving our conceptualization of paper and designing paper and/or paper derivatives to directly address health issues and medical needs on a broad and versatile scale led to the concept of creating biologically inspired origami (BIO) Paper. The main inspiration for BIO Paper is the delicately crafted extracellular matrix (ECM) that serves as the framework for tissues and organs to facilitate cell adhesion, cell patterning, and function. The ECM orchestrates cellular process by serving as an instructive substrate while providing
cues that accompany and modulate gene-based signals. The ECM also serves as an active sensing and compliant substrate in collecting chemical information and transmitting mechanical cues for cell signaling. The integral role of mechanical signals in activating and directing cellular activities has been placed on par with genetic-based control mechanisms [29] and has been highlighted in a number of studies since the classic work of Thompson [119]. Cellulose and other types of paper can be used to develop a creative palette for enhancing the bioactivity of substrates which are fashioned to help direct the intricate processes involved in cell interactions, tissue formation, and organ regeneration. Cellulose and cellulose-based papers have a rich history in serving as cell and tissue substrates with expanded activity. Derda et al. [28] used paper as a support structure for growing cells in a Matrigel matrix. Subsequent studies showed that this technique could be used to culture/grow cells in a multilayer system [29]. Additional work in this area has been conducted using hydrogel-coated paper scaffolds for origami-based bone tissue engineering [65]. The concept of paper can be expanded to include spinach leaves that can be decellularized and recellularized with endothelial cells [42]. Key aspects of this fascinating work are highlighted in Figs. 4.12 and 4.13. In the ultimate utilization of biobased paper for tissue origami engineering, whole tissues and organs are being converted into dynamic paper that includes all the key extracellular matrix biobased components including growth and signaling factors [61]. These “Tissue Papers” uniquely combine aspects of paper and tissue and organ extracellular matrix components to broaden the developing field of tissue origami engineering. The developmental folding processes in the biology regime integrate with the inspiration of traditional and modern origami to fuse into tissue origami engineering (TOE) and

Fig. 4.11 Tissue origami engineering (TOE) development cycle from imagination to reality
provide many possibilities for creative advances in tissue engineering. This is especially evident when these efforts include key aspects of 3D additive manufacturing and cell and tissue printing.

One very unique feature of paper is that it is possible to control its physical and chemical characteristics such as paper chemistry and composition, fiber diameter, fiber orientation, texture, and hierarchical effects. Unique compositions and levels of bioactivity can be achieved by integrating biologically active matrix molecules and growth factors with paper to design biologically inspired origami (BIO) Paper. BIO Paper is an important component for achieving the dream of tissue origami engineering as depicted in Fig. 4.14. Most papers consist of randomly oriented cellulose fibers. Kimwipes serve as the support structure to support the growth of MC3T3-E1 cells. In Fig. 4.14a, the cells are stained with fluorescein isothiocyanate
(FITC) and DAPI (4',6-diamino-2-phenylindole, dihydrochloride) is used to stain the cell nuclei in Fig. 4.14b.

Smart paper-based medical diagnostics are revolutionizing many aspects of healthcare and diagnosis. Martinez et al. [77] bring the convenience and versatility of biobased-enhanced paper diagnostic systems that integrate microfluidics and antibody-antigen interactions on paper with smart phone-enabled analysis. The
paper based analytical devices (PADs) have the ability to revolutionize healthcare in developing countries due to the low cost and adaptability for remote diagnosis using smart phones and colorimetric detection.

4.3 Biobased Materials Come Full Circle: Medical Treatment Treasure from Biobased Waste

The origins of food as fuel aspects of biobased materials stem from hunger and need-based inspiration, creativity, and experimentation from our ancestors. Nomadic hunter gatherers developed skills that allowed them to put down more permanent roots and progress to agricultural-based civilizations. The ability to grow a wider variety of plant and animal-based foods in larger quantities was supplemented with the knowledge and technology to produce more extravagant food accompaniments such as fermented food products and exotic spices. These new foods were used to unleash new flavor profiles and promote health via improved food preservation as well as enhancing intrinsic nutritional profiles.

While progress in biobased materials related to food production occurred through collective efforts across the globe over many thousands of years, one recent development has been both a blessing and curse to producing sufficient quantities of food for a hungry world. The initiation of modern biotechnology and using engineering concepts for food production has been attributed to [34]. Ereky was a Hungarian agricultural engineer who in 1919 coined the term biotechnology to harness the great potential that could be achieved by merging biology and modern technology. He is considered the founding father of biotechnology for his contributions to the field. In his book, “Biotechnology of Meat, Fat, and Milk Production in an Agricultural Large Scale Farm” (translated from German), he proposed a large-scale process to convert waste-based raw material inputs into more useful food products [19]. He built a fattening farm and slaughterhouse for pigs which became the largest and most profitable meat and fat operation in the world. The blessing came in terms of achieving large-scale food production by converting trash (waste) to treasure (food), whereas the curse has been unfolding over time as revealed in improper human labor practices that have been highlighted in reports and literature such as The Jungle by Upton Sinclair. These works highlight both animal and human suffering through unjust labor practices and inhumane care and handling of animals in efforts to squeeze out maximum profits. The results of some of these wrongful practices are starting to be reaped in terms of poorer consumer health and has driven a lot of the shift in dietary preferences towards organic produce and a lower reliance on meat products as vegetarian and vegan options become more popular. This darker side of biotechnology needs to be acknowledged as we move towards more humane practices which mitigate and can potentially eliminate any trace of abusive practices in food production. Examples of this include tissue engineered meat proteins (Ben-Arye and Levenberg [6]) and potentially healthier alter-
natives to meat proteins such as plant-based meat analogues such as the Impossible Burger. The saying you are what you eat has drawn important attention to the choices that people make regarding healthy foods and the impact that choice makes in long-term health as disease statistics highlight increases in preventable medical conditions. There is no greater area for improved health related to dietary inputs and outputs and how they impact the gut microbiome.

4.3.1 Gut Microbiome (Influence on Overall Health)

The microbiome project (https://www.genome.gov/27549400/the-human-microbiome-project-extending-the-definition-of-what-constitutes-a-human) was initiated in 2007 as an important offshoot of the human microbiome project to uncover the microbial living universe that exists on and within us. The microbiome encompasses oral, nasal, pubic, and digestive regions of the body. Collectively, the number of distinct species of commensal bacteria, virus, and fungal populations outnumber the cells in our bodies by at least tenfold. While the human microbiome project was concluded in 2012, the initial spark that the work generated has grown into a full blown fusion reaction that is providing great energy to move our understanding of the human genome and the gut microbiome with its associated genome forward. The gut microbiome has been compared to an exotic garden containing a metagenomic complex consortium of trillions of microbes flourish with a collective genome that contains at least 100 times as many genes as the human genome. There is evidence of cross communication between the HGM and the native human genome [92]. Additional evidence related to a specific role for microbiome-mediated training of immune cells for wound healing was reported in 2019 for skin microbiome species and mucosal-associated invariant T (MAIT) cells ([22, 85, 71]). The microbiome cells play a mentoring role by training the specialized T cells while residing in the thymus during the early weeks of their developmental life. The combined influence of the gut microbiome has a profound influence on human physiology, nutrition via vitamin supplementation and energy harvest, and conversion of ingested feedstocks into vital compounds such as short chain fatty acids. Changes in the gut microbiome have been associated with health issues related to bowel diseases, infections, and obesity. It is a fascinating idea that the gut microbiome holds the key to treating a large number of health conditions directly related to the digestive system. However, evidence is being uncovered through numerous studies that indicates the healing properties of the gut microbiome may also encompass the immune system, brain health and learning, and metabolic conditions including diabetes and cancers.

The gut microbiome is a veritable treasure chest that contains a wealth of bio-based substances that hold the key to long-term health and success. The fact that this treasure is renewable based on an individual’s input (i.e., food source) and output (energy, waste) becomes the source of inspiration for tailoring the population of microorganisms that constitute the gut microbiome. The food-based input for the
GM provides the raw materials for the gut microbiome to manufacture various bio-based output products that influence a host of biological processes. These processes contribute to healthy living including metabolism and weight regulation, immune system response, vitamin synthesis, and mood and executive function. A lot of these interactions are controlled through the gut microbiome-brain axis. The establishment of a unique connection between HGM and our brains opens up wonderful opportunities for developing effective therapies to treat mental and emotional imbalances such as depression, stress disorders, and even Alzheimer’s disease [66]. We have just begun to scratch the surface of the impact that elucidation of the exact nature of the gut microbiome and its various interactions within the digestive system environment will provide. This information will inspire the development of a host of responsive and preventative therapies to help optimize healthcare and lead society into greater levels of health and prosperity. In this section, questions related to what is the gut microbiome and our current understanding of it, how it functions, what are the conditions that determine the health status of the gut microbiome, what is it composed of, and how wide its influence can spread will be addressed. A number of questions that can serve as an initial starting point or point for continued ponderings regarding the gut microbiome and its wide influence on health are listed in Table 4.3.

The compositional profile for the human gut microbiome (HGM) contains approximately 30–100 trillion individual microbes that can be classified within 500–1000 distinct bacterial species. The HGM mass is about one kilogram which is comparable to the mass of the human brain. While the presence and prevalence of distinct microbial species in the HGM is important, the compositional profile of the HGM may prove to be more important in achieving long-term health advances. There are a number of factors that influence the HGM compositional profile including diet, exercise, environmental factors, and age. [26, 58, 111, 124, 126] Intermittent fasting is becoming more popular, and it also plays a role in HGM composition [20].

Table 4.3 A series of gut microbiome questions

| Question                                                                 |
|--------------------------------------------------------------------------|
| How does the gut microbiome change as people age?                        |
| What can be done to tailor the gut microbiome composition for optimized health and fitness? |
| How does the specific foods and its specific components (spices, fiber, etc.) impact microbiome compositional profile and overall health? |
| Can microbiome of people with different diseases be analyzed to prescribe medical treatments or auxiliary treatments to enhance the effectiveness of traditional treatments? |
| Can a personalized gut microbiome profile be developed and maintained for individuals? |
| How is the gut microbiome influenced by different disease processes?      |
| How can we use gut microbiome data to develop comprehensive health profile analytics that informs a higher level of effective treatments and move more fully to preventive medicine? |
| What is the full extent of health benefits (mental, physical, psychological, emotional, etc.) that can be achieved by proper maintenance of the gut microbiome? |
| What are the key questions that need to be asked and answered in order to understand the interrelationships and interactions between the gut microbiome and the brain? |
These represent only a few of the many factors that are the subject of a large number of ongoing studies that will continue to help uncover the vast potential of utilizing the HGM to treat medical pathologies.

Shifts in the gut microbiome compositional profile can have beneficial or detrimental effects on various aspects of health depending on how the profile shifts. It is not just one species but a whole microbial ecosystem that has far ranging influence on health. Developing the ability to create Gut Microbiome Maps (GMMs) and how they can be plotted and charted to influence overall health is an important goal in HGM studies. The GMMs can map the spatial organization and compositional profile within GI tract and will yield rich resources for optimizing distribution of beneficial microbial species in terms of time sequence effects and location effects and even open the possibility for predictive effects. This will allow us to see how different factors impact the HGM and how targeted shifts will impact overall health.

Each of the distinct microbes that make up the HGM play a crucial role in promoting health or contributing to disease processes which is referred to as dysbiosis. In some cases, dysbiosis is directly linked with leaky gut syndrome where the inner lining of the intestines becomes disorganized and permeable. This state allows microbial products to leak out of the gut and cause problems with host body functions. Bacteroides is a species of beneficial bacteria that populate a healthy gut microbiome. There are over 40 species of Prevotella, and it seems to be both beneficial and harmful. Prevotella species can be present in some infections and linked with arthritis.

The diversity of the gut microbiome plays a clear cut role in obesity. Less species abundance in the gut microbiome has been linked with higher level of obesity, indicating an inverse relationship. This has been shown for studies linking gut microbiome diversity and health for people who immigrate to the USA from other countries [17]. Firmicutes is another prevalent HGM species that has an interesting link with obesity. The firmicutes to bacteroides ratio has related to obesity where a higher level of Firmicutes is better than higher levels of Bacteroides Humanized mice models are being developed by introducing human stool into germ free mice to study these phenomena and other HGM related effects on a deeper level [22].

4.3.1.1 Nonconventional Transplants Yielding Extraordinary Results

Novel applications for biobased waste have been developed and utilized over time. The science and technology related to the use of stool in the field of biomedical research can be affectionately called “poo poo” ology. Some of the highlighted features include digestive products ranging from Kopi Luwak coffee (poo poo coffee from civet) to donated stool that is repurposed into a powerful therapy for treating microbial infections such as Clostridium difficile (C dif) [31, 87]. This is arguably the ultimate recycling and further highlights the wonders of the gut microbiome and how our wonderful bodies are composed of a host of symbiotic organisms that contribute to our overall health when in balance or homeostasis. Fecal microbiota transplant (FMT) is an effective therapy for treating a number of conditions that involve
changing the gut microbiome profile by introducing fecal matter into the body in order to reestablish a healthy balance [113]. The first fecal transplants occurred in the fourth century. The possibility of fecal banking is raised based on a study where stool was removed from patients prior to heavy antibiotic therapy and reintroduced after treatment [116]. Results showed restoration of gut microbiome to original state for all 14 patients in study compared to 11 who did not have stool reintroduced. The precedent for FMT has been set in the historic development of vaccines in which dead or attenuated forms of virus are introduced into body to help the host develop protections against the virus through activation and training of the immune system.

Stool/Feces

It is fascinating how beneficial gut microbiota can be introduced into the human body by embedding the healthy bacteria within food products. Yogurt is a time-tested method of introducing healthy gut bacteria into people in a way to maintain a healthy gut microbiome profile. Newer options for introducing healthy gut bacteria into our bodies are in the development pipeline. Is anyone hungry for pooperoni? This food product is in fact being developed with fermented meat products to help provide options for people who are lactose intolerant. Selected species of bacteria from baby stool are harvested and used to ferment meat [100]. In the future, it may be possible to purchase such food products as poop tarts, poop corn, and poopsicles to tailor the profile of our gut microbiomes.

4.4 Future Possibilities for Biobased Materials

This chapter presented a number of examples of different ways that biobased materials are being used to support advances in the way that we treat medical conditions. Some of the examples relate to traditional uses, while a number of the more recent developments present some very exciting possibilities where we may be able to treat the majority of medical conditions using biobased materials strategies. One of the most promising aspects of biobased materials involves our growing understanding of the HGM and how it impacts various aspects of our immune system, metabolism, and a range of other physiological functions including vitamin synthesis. These unique breakthroughs highlight the interconnections that exist between biobased materials. Our studies of biobased materials will continue to usher in a world where we have a fuller understanding of how pathologies develop in the body, and it will be possible to design strategies for early detection and focused interventions to prevent diseases from occurring. We can envision tangible biobased materials as well as the influence of physical processes, such as exercise and diet on gut microbiome function to eradicate disease. Not only does exercise cause the release of endorphins that help to improve mood [144]; exercise also has an impact and influence on our nervous system. Exercise induces platelets to release blood-derived neurotrophic
factors (BDNF) that stimulate production of new neurons [145]. There are a number of direct interrelationships between the human gut microbiome and human health issues, but the trillion-dollar question is related to how the data can be mined adequately to produce viable treatments and therapies. Formative and summative evaluation of gut microbiome can be applied towards tailoring its composition to promote better health. A traditional engineering-based approach can be used based on inputs and outputs in which food is the main input and waste products is the output. If the optimum output profile can be determined, then the input could be adjusted to accomplish the intended goal.

References

1. Alshehri AM, Wilson OC Jr, Dahal B, Philip J, Luo X, Raub CB. Magnetic nanoparticle-loaded alginate beads for local micro-actuation of in vitro tissue constructs. Colloids Surf B: Biointerfaces. 2017;159:945–55.
2. Anderson HC. Molecular biology of matrix vesicles. Clin Ortho Rel Res. 1995;314:266–80.
3. Atlant G, Balmain N, Berland S, Vidal B, Lopez E. Reconstruction of human maxillary defects with nacre powder: histological evidence for bone regeneration. C R Acad Sci Paris/ Life Sci. 1997;320:253–8.
4. Badylak SF, Taylor D, Uygun K. Whole organ tissue engineering: decellularization and recellularization of three dimensional matrix scaffolds. Annu Rev Biomed Eng. 2011;13(1):27–53.
5. Barkana R. Possible interaction between baryons and dark-matter particles revealed by the first stars. Nature. 2018;555(7694):71–4.
6. Ben-Arye T, Levenberg S. Tissue engineering for clean meat production. Front Sustain Food Syst. 2019;3(article 46):1–19. https://doi.org/10.3389/fsufs.2019.00046.
7. Bharadwaj S, Liu G, Gong A, Jia C, et al. The gut microbiota of healthy aged Chinese is similar to that of the healthy young. mSphere. 2017;2(5):e00327–17.
8. Bian G, Gloor GB, Gong A, Jia C, et al. The gut microbiota of healthy aged Chinese is similar to that of the healthy young. mSphere. 2017;2(5):e00327–17.
9. Blumenfeld NR, Kang HJ, Fenzl A, Song Z, et al. A direct tissue-grafting approach to increasing endogenous brown fat. Sci Rep. 2018;8(7957):1–12. https://doi.org/10.1038/s41598-018-25866-y.
10. Bombelli P, Howe CJ, Bertocchini F. Polyethylene bio-degradation by caterpillars of the wax moth Galleria mellonella. Curr Biol. 2017;27(6):PR292–3.
11. Bomgardner M. Extending shelf life with natural preservatives. Chem Eng News. 2014;92(6):13–4.
12. Bomgardner M. Dandelions, the scourge of lawns, may be a fount of rubber. Chem Eng News. 2016;94(30):28–9.
13. Bonfield W, Grynpas MD, Tully AE, Bowman J, Abrham J. Hydroxyapatite reinforced polyethylene: a mechanically compatible implant material for bone replacement. Biomaterials. 1981;2(3):185–6.
14. Borum L, Wilson OC Jr. Surface modification of hydroxyapatite: I Dodecyl alcohol. Biomaterials. 2003a;24(21):3671–9.
15. Borum L, Wilson OC Jr. Surface modification of hydroxyapatite: II Silica. Biomaterials. 2003b;24(21):3681–8.
16. Bowman JD, Rogers AEE, Monsalve RA, Moudzen TJ, Mahesh N. An absorption profile centered at 78 megahertz in the sky-averaged spectrum. Nature. 2018;555(7694):67–70.
17. Brooks AW, Priya S, Blekhman R, Bordenstein SR. Gut microbiota diversity across ethnicities in the United States. PLoS Biol. 2018;16(12):e2006842. https://doi.org/10.1371/journal.pbio.2006842.

18. Calvert P, Mann S. Synthetic and biological composites formed by in situ precipitation. J Mater Sci. 1988;23:3801–15.

19. Carlisle EM. Silicon: a possible factor in bone calcification. Science. 1970;167:279–80.

20. Catterson JH, Khericha M, Dyson MC, Vincent AJ, Callard R, Haveron SM, Rajasingam A, Ahmad M, Partridge L. Short-term, intermittent fasting induces long-lasting gut health and TOR-independent lifespan extension. Curr Biol. 2018;28(11):1714–1724.e4. https://doi.org/10.1016/j.cub.2018.04.015.

21. Chen PY, Lin AYM, McKittrick J, and Meyers A. Structure and mechanical properties of crab exoskeletons. Acta Biomaterialia. 2008; 4(3):587–596.

22. Constantinides MG, Link VM, Tamoutounour S, Wong AC, et al. MAIT cells are imprinted by the microbiota in early life and promote tissue repair. Science. 2019;366(6464):445.

23. Cummins C, Seale M, Macente A, Certini D, Maestropaolo E, Viola IM, Nakayama M. A separated vortex ring underlies the flight of the dandelion. Nature. 2018;562:414–8. https://doi.org/10.1038/s41586-018-0604-2.

24. Curran M. Do bio-based products move us toward sustainability? A look at three USEPA case studies. Environ Prog. 2003;22(4):277–29.

25. Curran M. Biobased materials. In: Othmer K, editor. Encyclopedia of chemical technology; 2010.

26. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini PG, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. PNAS. 2010;107(33):14691–6. https://doi.org/10.1073/pnas.1005963107.

27. Demaine ED, Tachi T. Origamizer: a practical algorithm for folding any polyhedron. In: Proceedings of the 33rd international symposium on computational geometry (SoCG 2017), Brisbane, 4–7 July 2017; 2017, p. 34:1–34:15.

28. Derda R, Laromaine A, Mamamoto A, Tang SKY, et al. Paper-supported 3D cell culture for tissue-based bioassays. Proc Natl Acad Sci. 2009;106:18457–62.

29. Derda R, Tang SK, Laromaine A, Mosadegh B, Hong E, Mwangi M, Mamamoto A, Ingber DE, Whitesides GM. Multizone paper platform for 3D cell cultures. PLoS One. 2011;6(5):18940. https://doi.org/10.1371/journal.pone.0018940.

30. Ducy P, Schinke T, Karsenty G. The osteoblast: a sophisticated fibroblast under central surveillance. Science. 2000;289:1501–4.

31. Edmond M. The power of poop: fecal microbiota transplantation for Clostridium difficile infection. Trans Am Clin Climatol Assoc. 2016;127:71–80.

32. Eisenstein M. From Menace to medicine. Nature. 2019;572:S2–4.

33. Epelbaum E, Krebs H, Lee D. Ab initio calculation of the Hoyle state. Phys Rev Lett. 2011;106:192501.

34. Erecky K. Biotechnologie der Fleisch-, Fett-, und Milcherzeugung im landwirtschaftlichen Grossbetrieb: für naturwissenschaftlich gebildete Landwirte verfasst. Berlin: P. Parey; 1919.

35. Evans ME and Hyde ST. From three dimensional weavings to swollen corneocytes. J. R. Soc. Interface. 2011; 8:1274-1280.

36. Farha OK, Eryazici I, Jeong NC, Hauser BG, et al. Metal–organic framework materials with ultrahigh surface areas: is the sky the limit? J Am Chem Soc. 2012;134(36):15016–21.

37. Fierer N. Earthworm’s place on Earth. Science. 2019;366(6464):425–6.

38. Flemming RG, Murphy CJ, Abrams GA, Goodman SL, Nealey PF. Effects of synthetic micro and nano-structured surfaces on cell behavior. Biomaterials. 1999;20:573–88.

39. Fukada E. Piezoelectricity of wood. J Phys Soc Jpn. 1955;10(2):149–54.

40. Fukuda E, Yasuda I. On the piezoelectric effect of bone. J Phys Soc Jpn. 1957;12(10):1158–62.

41. Gao H, Ji B, Jager IL, Arzt E, Fratzl P. Materials become insensitive to flaws at nanoscale: lessons from nature. Proc Natl Acad Sci U S A. 2003;100(10):5597–6000.
42. Gershlak JR, Hernandez S, Fontana G, Perreault LR, et al. Crossing kingdoms: using decellularized plants as perfusable tissue engineering scaffolds. Biomaterials. 2017;125:13–22.
43. Ghosh TS, Rampelli S, Jeffrey IB, Santoro A, et al. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. Gut. 2020;1–11. https://doi.org/10.1136/gutjnl-2019-319654.
44. Gibson IR, Bonfield W. Preparation and characterization of magnesium/carbonate co-substituted hydroxyapatite. J Mater Sci Mater Med. 2002;13:685–93.
45. Giraud-Guille MM. Liquid crystalline order of biopolymers in cuticles and bones. Micros Res Tech. 1994; 27(5):420–428.
46. Gombedza F, Evans S, Shin S, Boadi EA, Zhang Q, Nie Z, Bandypadhyay BC. Melamine promotes calcium crystal formation in three-dimensional microfluidic device. Sci Rep. 2019;9(875):1–14. https://doi.org/10.1038/s41598-018-37191-5.
47. Gomes SD, Oliveira CS, Azevedo-Silva J, Casanova M, Barreto J, Pereira H, Chaves S, Rodrigues L, Casal M, Corte-Real M, Baltazar F, Pretto A. The role of diet related short chain fatty acids in colorectal cancer metabolism and survival: prevention and therapeutic implications. Curt Med Chem (E-pub ahead of print); 2018. https://doi.org/10.2174/092987325666180530102050.
48. Gottardi D, Bukvicki D, Prasad S, Tyagi A. Beneficial effects of spices in food preservation and safety. Front Microbiol. 2016;7 https://doi.org/10.3389/fmicb.2016.01394.Spices.
49. Gustavsson J, Cederberg C, Sonesson U, van Otterdijk R, and Meybeck A. Global Food Losses and Food Waste: Extent, Causes, and Prevention. Report based on a study conducted for the International Congress Save Food at Interpack2011, Düsseldorf, Germany, Food and Agriculture Organization of the United Nations, (FAO) Rome, 2011.
50. Hase T, Shishido S, Yamamoto S, Yamashita R, et al. Rosmarinic acid suppresses Alzheimer’s disease development by reducing amyloid β aggregation by increasing monoamine secretion. Sci Rep. 2019;9:8711. https://doi.org/10.1038/s41598-019-45168-1.
51. Hau AK, Kwan TH, Li PK. Melamine toxicity and the kidney. JASN. 2009;20(2):245–50. https://doi.org/10.1681/ASN.2008101065.
52. Hench LL, Splinter RJ, Allen WC, and Greenlee TK. Bonding Mechanisms at the interface of ceramic prosthetic materials. J. Biomed. Mater. Res. A. 1971; 5(6):117-141.
53. Hench LL and Jones JR. Bioactive glasses: Frontiers and challenges. Front. Bioeng. Biotechnol. 2015; 3:194.
54. Hing KA. Bone repair in the twenty-first century: biology, chemistry or engineering? Philos Trans R Soc Lond A. 2004;362:2821–50.
55. Hing KA, Best SM, Bonfield W. Characterization of porous hydroxyapatite. J Mater Sci Mater Med. 1999;10:135–45.
56. Hohlfeld E, Mahadevan L. Unfolding the sulcus. Phys Rev Lett. 2011;106:105702.
57. Hönicke IM, Senkovska I, Bon V, Baburin IA, et al. Balancing mechanical stability and ultra-high porosity in crystalline framework materials. Angew Chem. 2018;57(42):13780–3.
58. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. Science. 2001;292(5519):1115–8. https://doi.org/10.1126/science.1058709.
59. Hoyle F. On nuclear reactions occurring in very hot stars. I. The synthesis of elements from carbon to nickel. Astrophys J Suppl Ser. 1954;1:121.
60. Huang J, Liang Y, Hu H, Liu S, et al. Ultrahigh-surface-area hierarchical porous carbon from chitosan: acetic acid mediated efficient synthesis and its application in superior supercapacitors. J Mater Chem A. 2017;5:24775–81.
61. Jakus AE, Laronda MM, Rashedi AS, Robinson CM, et al. “Tissue papers” from organ-specific decellularized extracellular matrices. Adv Funct Mater. 2017;27(34):1700992.
62. Jolles P, Muzzarelli R. Chitin and Chitinases. Boston: Birkhauser Verlag; 1999.
63. Katifori E, Alben S, Cerda E, Nelson DR, Jacques DJ. Foldable structures and the natural design of pollen grains. Proc Natl Acad Sci. 2010;107(17):7635–9. https://doi.org/10.1073/pnas.0911223107.
64. Katti KS, Ambre AH, Peterka N, Katti DR. Use of unnatural amino acids for design of novel organomodified clays as components of nanocomposite biomaterials. Philos Trans R Soc A Math Phys Eng Sci. 2010;368(1917):1963–80. https://doi.org/10.1098/rsta.2010.0008.
65. Kim S, Lee HR, Yu SJ, Han M, et al. Hydrogel-laden paper scaffold system for origami-based tissue engineering. PNAS. 2015;112(50):15426–31.
66. Kowalski K, Mulak A. Brain-gut-microbiota axis in Alzheimer’s disease. J Neurogastroenterol Motil. 2019;25(1):48–60.
67. Kunkel SD, Elmore CJ, Bongers KS, Ebert SM, Fox DK, Dyle MC, Bullard SA, Adams CM. Ursolic acid increases skeletal muscle and brown fat and decreases diet induced obesity, glucose intolerance and fatty liver disease. PLoS One. 2012;7(6):e39332. https://doi.org/10.1371/journal.pone.0039332. Published online 2012 Jun 20. PMCID: PMC3379974
68. LeGeros RZ. Effect of carbonate on the lattice parameters of apatite. Nature. 1967;4982:403.
69. LeGeros RZ, Tung MS. Chemical stability of carbonate and fluoride containing apatites. Caries Res. 1983;17:419–29.
70. LeGeros RZ, Trautz OR, LeGeros JP, Klein E, Schirra WP. Apatite crystallites: effects of carbonate on morphology. Science. 1967;155(3768):1409–11.
71. Legoux F, Bellet D, Daviaud C, El Mor Y, et al. Microbial metabolites control the thymic development of mucosal-associated invariant cells. Science. 2019;366(6464):494–9.
72. Lenton S, Nylander T, Texeira SCM, Holt C. A review of the biology of calcium phosphate sequestration with special reference to milk. Dairy Sci Technol. 2015;95:3–14.
73. Li G, Xie LS, Nichols RG, Tian Y, Li L, Patel D, Ma Y, Brocker CN, Yan T, Krausz KW, Xiang R, Gavriloa O, Patterson AD, Gonzalez FJ. Intermittent fasting promotes white adipose tissue browning and decreases obesity by shaping the gut microbiota. Cell Metab. 2017;26(4):672–85. https://doi.org/10.1016/j.cmet.2017.08.019.
74. Liou SC, Chen SY, Lee HY, Bow JS. Structural characterization of nano-sized calcium deficient apatite powders. Biomaterials. 2004;25(2):189–96.
75. Lopez E, Vidal B, Berland S, Campprasse S, Camprasse G, Silve C. Demonstration of the capacity of nacre to induce bone formation by human osteoblasts maintained in vitro. Tissue Cell. 1992;24(5):667–79.
76. Lu QY, Summanen PH, Lee RP, Huang J, Henning SM, Heber D, Finegold SM, Li Z. Prebiotic potential and chemical composition of seven culinary spice extracts. J Food Sci. 2017;82(8):1807–13.
77. Martinez AW, Phillips ST, Whitesides G, Carrilho E. Diagnostics for the developing world: microfluidic paper-based analytical devices. Anal Chem. 2010;82(1):3–10.
78. Meyers MA, Chen PY, Lin AYM, Seki Y. Biological materials: structure and mechanical properties. Prog Mater Sci. 2008;1–206.
79. Midura RJ, Wang A, Lovitch D, Law D, Powell K, Gorski JP. Bone acidic glycoprotein-75 delineates the extracellular sites of future bone sialoprotein accumulation and apatite nucleation in osteoblastic cultures. J Biol Chem. 2004;279(24):25464–73.
80. Mouries LP, Almeida MJ, Milet C, Berland S, Lopez E. Bioactivity of nacre water soluble matrix from the bivalve mollusk Pinctada maxima in three mammalian cell types: fibroblasts, bone marrow stromal cells and osteoblasts. Comp Biochem Physiol B Biochem Mol Biol. 2002;132(1):217–29.
81. Muller-Mai C, Voight C, De Almeida Reis SR, Herbst H, Gross UM. Substitution of natural coral by cortical bone and bone marrow in the rat femur. J Mater Sci Mater Med. 1996;7:479–88.
82. Munch E, Launey ME, Alsem DH, Saiz E, Tomsa AP, Ritchie RO. Tough, bio-inspired hybrid materials. Science. 2008;322(5907):1516–20.
83. Newnham R. Smart, very smart, and intelligent materials. MRS Bull. 1993;18(4):24–6. https://doi.org/10.1557/S0883769400037313.
84. Odier A. Memoire sur la composition chimique des parties cornees des Insectes [Thesis on the chemical composition of the horny parts of insects]. Mem. Soc. Hist. Paris. 1823;1:29-42.
85. Oh J, Unutmaz D. Immune cells for microbiota surveillance. Science. 2019;366(6464):419–20.
86. Ott HC, Matthiesen TS, Goh SK, Black LD, Kren SM, Netoff TI, Taylor DA. Perfusion-decellularized matrix: using nature’s platform to engineer a bioartificial heart. Nat Med. 2008;14:213–21. https://doi.org/10.1038/nm1684.
87. Palmer KH. Are you ready to swallow a pill full of poop? 2016.; Retrieved from www.wired.com/2016/11/microbiome-therapy-making-fecal-transplants-better
88. Palmer LC, Newcomb CJ, Kaltz SR, Spoerke ED, Stupp SI. Biomimetic systems for hydroxyapatite mineralization inspired by Bone and Enamel. Chem Rev. 2008;108(11):4754–83.
89. Pasteris JD, Wopenka B, Freeman JJ, Rogers K, Valsami-James E, van der Houwen JAM, Silva MJ. Lack of OH in nanocrystalline apatite as a function of degree of atomic order: implications for bone and biomaterials. Biomaterials. 2004;25(2):229–38.
90. Petroski H. The pencil: a history of design and circumstance. New York: Alfred A Knopf, Inc; 1989.
91. Pradhan SK, Holopainen JK, Weisell J, Helvi H-TH. Human urine and wood ash as plant nutrients for red beet (Beta vulgaris) cultivation: impacts on yield quality. J Agric Food Chem. 2010;58(3):2034–9.
92. Qin J, Li R, Raes J, Arumugam M, et al. A human gut microbial gene catalogue established by metagenomics sequencing. Nature. 2010;464:59–65.
93. Reddi AH. Cell biology and biochemistry of endochondral bone development. Coll Relat Res. 1981;1:209–26.
94. Reddi AH. Morphogenesis and tissue engineering of bone and cartilage: inductive signals, stem cells, and biomimetic biomaterials. Tissue Eng. 2000;6(4):351–9.
95. Reddi AH, Anderson WA. Collagenous bone matrix-induced endochondral hemopoiesis. J Cell Biol. 1976;69:557–72.
96. Reddi AH, Huggins CB. Biochemical sequences in the transformation of normal fibroblasts in adolescent rats. Proc Natl Acad Sci U S A. 1974a;69:1601–5.
97. Reddi AH, Huggins CB. Cyclic electrochemical inactivation and restoration of competence of bone matrix to transform fibroblasts. Proc Natl Acad Sci USA. 1974b;71(5):1648–52.
98. Revol JF, Bradford H, Giasson J, Marchessault RH, Gray DG. Helicoidal self-ordering of cellulose microfibrils in aqueous suspension. Int J Biol Macromol. 1992;14(3):170–2.
99. Ronan L, Pienaar R, Williams G, Bullmore E, Crow TJ, Roberts N, Jones PB, Suckling J, and Fletcher PC. Intrinsic curvature: A marker of millimeter-scale tangential cortico-cortical connectivity? Inter. J. Neur. Sys. 2011; 21(5):351-366.
100. Rubio R, Jofre A, Martin B, Aymerich T, Garriga M. Characterization of lactic acid bacteria isolated from infant faeces as potential probiotic starter cultures for fermented sausages. Food Microbiol. 2014;38:303–11.
101. Rujitanapanawich S, Kumpapan P, Wanjanoi P. Synthesis of hydroxyapatite from oyster shell via precipitation. Energy Procedia. 2014;56:112–7.
102. Salgado AJ, Coutinho OP, Reis RL. Bone tissue engineering: state of the art and future trends. Macromol Biosci. 2004;4(8):743–65.
103. Sampath TK, Reddi AH. Dissociative extraction and reconstitution of extracellular matrix components involved in local bone differentiation. Proc Natl Acad Sci U S A. 1981;78(12):7599–603.
104. Sanders J, Beichman A, Roman J, Scott JJ, Emerson D, McCarthy JJ, Girguis PR. Baleen whales host a unique gut microbiome with similarities to both carnivores and herbivores. Nat Commun. 2015;6:8285.
105. Sarikaya M, Liu J, Aksay IA. Nacre: properties, crystallography, morphology and formation. In: Sarikaya M, Aksay IA, editors. Biomimetics: design and processing of materials. New York: American Institute of Physics; 1995.
106. Scott K, Gratz SW, Sheridan PO, Flint HJ, Duncan SH. The influence of diet on gut microbiota. Pharmacol Res. 2013;69(1):52–60.
107. Shen L, Liu L, Ji HF. Regulative effects of curcumin spice administration on gut microbiome and its pharmacological implications. Food Nutr Res. 2017;61(1361780) https://doi.org/10.1080/16546628.2017.1361780.
108. Silva YP, Bernardi A, Frozza RL. The role of short chain fatty acids from gut microbiota in gut-brain communication. Front Endocrinol. 2020; https://doi.org/10.3389/fen-do.2020.00025.
109. Silve C, Lopez E, Vidal B, Smith DC, Camprasse S, Camprasse G, Couly G. Nacre initiates biomineralization by human osteoblasts maintained in vitro. Calcif Tissue Int. 1992;51(5):363–9.
110. Sinclair U. The jungle. New York: Doubleday; 1906.
111. Sonnenberg JL, Sonnenberg ED. Vulnerability of the industrialized microbiota. Science. 2019;366(6464):444.
112. Sun J, Bhushan B. Hierarchical structure and properties of nacre: a review. RSC Adv. 2012;2:7617–32.
113. Sunkara T, Rawla P, Ofosu A, Gaduputi V. Fecal microbiota transplant – a new frontier in inflammatory bowel disease. J Inflamm Res (JIR). 2018;11:321–8.
114. Takahashi T. Atlas of the Human Body. Collins Reference, Scranton PA, 1994.
115. Tallinen T, Chung J, Rousseau F, et al. On the growth and form of cortical convolutions. Nat Phys. 2016;12:588–93. https://doi.org/10.1038/nphys3632.
116. Taur Y, Coyte K, Schluter J, Robilotti E, et al. Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. Sci Transl Med. 2018;10:460,. eaap9489. https://doi.org/10.1126/scitranslmed.aap9489.
117. Teitelbaum S. Bone resorption by osteoclasts. Science. 2000;289:1504–8.
118. Thomas MR. Salicylic acid and related compounds. In: Othmer K, editor. Encyclopedia of chemical technology; 2006. https://doi.org/10.1002/0471238961.1901120920081513.a01.pub2.
119. Thompson DW. On growth and form. Cambridge: Cambridge University Press; 1917.
120. Tinney M, Hammond A. The secret life of the pencil: great creatives and their pencils. London: Laurence King Publishing; 2017.
121. Tucker LA. Milk fat intake and telomere length in U.S. women and men: the role of the milk fat fraction. Oxidative Med Cell Longev. 2019;2019(2019):1574021,. 12 pages. https://doi.org/10.1155/2019/1574021.
122. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomics analysis in humanized gnotobiotic mice. Sci Transl Med. 2009;1(6):6ra14. https://doi.org/10.1126/scitranslmed.3000322.
123. University of South Australia. Curcumin is the spice of life when delivered via tiny nanoparticles: treatment for Alzheimer’s and genital herpes. ScienceDaily. 2020; Retrieved 18 Mar 2020 from www.sciencedaily.com/releases/2020/03/200305132144.htm
124. University of Western Ontario. ‘Ridiculously healthy’ elderly have the same gut microbiome as healthy 30-year-olds. ScienceDaily. 2017, October 11; Retrieved 18 Mar 2020 from www.sciencedaily.com/releases/2017/10/1710111123728.htm
125. Urist MR, Silverman BF, Buring K, Dubuc FL, Rosenberg JM. The bone induction principle. Clin Orthop Relat Res. 1967;53:243–83.
126. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018;361:j2179.
127. Van de Wouw M, Boehme M, Lyte JM, Wiley N, et al. Short chain fatty acids: microbial metabolites that alleviate stress induced brain-gut axis alterations. J Psychol. 2018;596(20) https://doi.org/10.1113/jp276431.
128. Varner VD, Voronov DA, and Taber LA. Mechanics of head fold development: Investigating tissue-level forces during early development. Development.
129. Venkatachalambin P, Geetha N, Sangeetha P, Thulaseedharian. Natural rubber producing plants: an overview. Afr J Biotechnol. 2013;12(12):1297–310.
130. Vincent JF. Arthropod cuticle: a natural composite shell system. Compos Part A. 2002;33:1311–5.
131. Vitali D, Bagri P, Wessels JM, Arora M, Ganugula R, Parikh A, Mandur T, Felker A, Garg S, Kumar MNVR, Kaushic C. Curcumin can decrease tissue inflammation and the severity of HSV-2 infection in the female reproductive mucosa. Int J Mol Sci. 2020;21(1):337. https://doi.org/10.3390/ijms21010337.
132. Warnes SL, Little ZR, Keevil CW. Human coronavirus 229E remains infectious on common touch surface materials. mBio. 2015;6(6):e01697–15. https://doi.org/10.1128/mBio.01697-15.

133. Webster TJ, Seigel RW, Bizios R. Biomaterials. Osteoblast adhesion on nanophase ceramics”. 1999;20:1221–7.

134. Weiner S, Wagner HD. The material bone: structure-mechanical function relations. Annu Rev Mater Sci. 1998;28(1):271–98.

135. Weiss IM, Gohring W, Fritz M, Mann K. Perlustrin, a Haliotis laevigata (abalone) nacre protein, is homologous to the insulin-like growth factor binding protein N-terminal module of vertebrates. Biochem Biophys Res Commun. 2001;285(2):244–9.

136. Wendel M, Sommarin Y, Heinegard D. Bone matrix proteins: isolation and characterization of a novel cell-binding keratan sulfate proteoglycan (osteoadherin) from bovine bone. J Cell Biol. 1998;141(3):839–47.

137. WestBroek P, Marin F. A marriage of bone and nacre. Nature. 1998;392:861–2.

138. White EW, Weber JN, Roy DM, Owen EL, Chiwoff RT, White RA. Replamineform porous biomaterials for hard tissue implant applications. J Biomed Mater Res. 1975;9(4):23–7.

139. Wilkinson CDW, Riehle M, Wood M, Gallagher J, Curtis AS. The use of materials patterned on a nano- and micro-metric scale in cellular engineering. Mater Sci Eng C. 2002;19:263–9.

140. Wopenka B, Pasteris JD. A mineralogical perspective on the apatite in bone. Mater Sci Eng C. 2005;25:97–104.

141. Xynos ID, Edgar AJ, Buttery LDK, Hench LL, Polak JM. Ionic products of bioactive glass dissolution increase proliferation of human osteoblasts and induce insulin-like growth factor II mRNA expression and protein synthesis. Biochem Biophys Res Commun. 2000;276:461–5. https://doi.org/10.1006/bbrc.2000.3503.

142. Yang PJ, Pham J, Choo J, David L, Hu DL. Urination time does not change with body size. PNAS. 201402289. 2014; https://doi.org/10.1073/pnas.1402289111.

143. Yang Y, Wang J, Xia M. Biodegradation and mineralization of polystyrene by plastic-eating superworms Zophobas atratus. Sci Total Environ. 2020;708:135233.

144. Yeager A. How exercise reprograms the brain. 2018.; Retrieved from https://www.the-scientist.com/news-opinion/a-new-role-for-platelets%2D%2Dboosting-neurogenesis-after-exercise%2D%2D65630. 

145. Zimmer K. A new role for platelets: boosting neurogenesis after exercise, (The scientist. com). 2019; Retrieved from https://www.the-scientist.com/news-opinion/a-new-role-for-platelets%2D%2Dboosting-neurogenesis-after-exercise%2D%2D65630.