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Lifelike Transformative Materials for Biohybrid Implants: Inspired by Nature, Driven by Technology

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Today's living world is enriched with a myriad of natural biological designs, shaped by billions of years of evolution. Unraveling the construction rules of living organisms offers the potential to create new materials and systems for biomedicine. From the close examination of living organisms, several concepts emerge: hierarchy, pattern repetition, adaptation, and irreducible complexity. All these aspects must be tackled to develop transformative materials with lifelike behavior. This perspective article highlights recent progress in the development of transformative biohybrid systems for applications in the fields of tissue regeneration and biomedicine. Advances in computational simulations and data-driven predictions are also discussed. These tools enable the virtual high-throughput screening of implant design and performance before committing to fabrication, thus reducing the development time and cost of biomimetic and biohybrid constructs. The ongoing progress of imaging methods also constitutes an essential part of this matter in order to validate the computation models and enable longitudinal monitoring. Finally, the current challenges of lifelike biohybrid materials, including reproducibility, ethical considerations, and translation, are discussed. Advances in the development of lifelike materials will open new biomedical horizons, where perhaps what is currently envisioned as science fiction will become a science-driven reality in the future.

1. Nature as a Blueprint for Lifelike Implants

The close examination of the simplest living organisms (i.e., bacteria) reveals a high degree of structural and functional complexity packed into a cell barely a few micrometers across. Somehow, these tiny organisms can assemble complex molecular machines such as flagella, which feature a molecular motor 20–30 nm in diameter[1] that rotates more than 1700 times every second in order to generate motive force.[2] At progressively smaller scales, finer and finer degrees of organization are revealed, down to the molecular level where crisscrossing layers of polymer strands provide strength and integrity to the cell wall. In more complex eukaryotic cells, additional layers of organization allow the subdivision of the cell into discrete membrane-bound compartments with different functions. Many such cells are arranged into tissues in multicellular organisms, with different cells adopting different functional roles. At all these scales, various principles of natural biological

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design are apparent, including self-assembly, hierarchical organization, pattern repetition, specialization, adaptation, and above all, transformation. Structures at the molecular, nano, and micro scales can work together to coordinate the functions of even the largest and most complex living organisms, including ourselves.

Nature builds living organisms from the bottom up, starting from the expression of genetic information on a cellular level, resulting in the proliferation and differentiation of cells and their self-organization into tissues and organs, as observed during development and in specialized processes such as metamorphosis and wound healing.[3] Nature harnesses this construction strategy to convert chemically simple building blocks into sophisticated structures that function cooperatively in living systems.[4] Cells form tissues and secrete an extracellular matrix (ECM) of polysaccharides and fibrous proteins that fill the intercellular space, providing physical support, nutrients, biochemical gradients, and appropriate signaling molecules to guide cell behavior. Accordingly, many tissues display natural anisotropy, with the cells and ECM organized in distinct spatial patterns that are both adaptable and dynamic. Native tissues are dynamic structures that exhibit not only a mere continuous turnover of the molecular and cellular components, but are also endowed with the ability to grow, remodel, and adapt. In other words, they are gifted with the power of self-transformation.

One of the main challenges of tissue engineering (TE) and implant development is to mimic the complexity of native tissues, including their ability to self-organize and adapt to their surroundings.[5] Current engineered constructs are rather basic, often containing the major cell type or types of native tissues in a biodegradable scaffold, but unable to replicate the full cellular and extracellular profile of native tissues. Ideally, we should seek to generate lifelike materials that embrace all these requirements and provide an ideal microenvironment to guide cells in predictable manner, thus orchestrating native-like tissue development.

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2. Biohybrid Implants as Lifelike Materials

2.1. What are Lifelike Biohybrid Implants?

The term biohybrid is used extensively in the context of material science and implant development but it does not have one precise definition and is used in different ways by different authors.[6] Many authors define biohybrid materials as a combination of organic and inorganic components, others as a combination of living entities with inert substances, and still others as a combination of synthetic and natural polymers. Some so-called biohybrid materials do not contain any natural components at all, but rather use synthetic materials to accomplish a biomimetic design. In other words, the system is inspired by nature (bioinspired) but the materials are provided by technology.[7] Yet another interpretation is the integration of biological materials into machines[8] including the combination of cells or tissues with mechanical parts as an example of soft robotics.[9]

Despite the lack of a unified meaning, one common underlying idea prevails in all biohybrid systems: the combination of matters with different, contradictory, or complementary properties to produce a system that integrates the best of each component. Paraphrasing Aristotle, virtue is an excellent medium between the extremes of excess and defect. This understanding applies also to the biohybrid concept as understood by us, where the extremes would be purely technological and purely biological alternatives. In the absence of a strict definition, we consider biohybrid implants to refer to any system based on a combination of technical and biological or biomimetic components that exploit synergy to achieve a performance of functionality that cannot be accomplished using either of the single components alone.

2.2. Technological Approaches for the Development of Biohybrid Implants

One of the main drawbacks of current biohybrid implants is their limited mimicry of natural structures. This is because it is difficult to replicate the small-scale organization of native tissues in larger (macroscale) biohybrid constructs. It is possible to approximate the structure of a tissue on the microscale by combining appropriate cell types with a scaffold that provides physical support and contacts for cell adhesion. On this small scale, nutrients, growth factors and other molecules can be supplied by diffusion from the surrounding medium. But scaling such a device to the size of an entire organ is much more challenging. At larger scales, diffusion is no longer sufficient for the transfer of nutrients and waste products, and it becomes impossible to provide appropriate concentrations of growth factors and other signaling molecules.

Nature solves this problem via the dynamic spatial organization of different structural molecules and cell types in tissues, including the migration and infiltration of immune cells, and by providing a fully developed vascular system. In natural tissues, the vascular system develops under the control of regulatory proteins that influence cell division, expansion, migration, and morphology, resulting in a continuous net of capillaries that are placed at the ideal intervals between cells to ensure a sufficient supply of oxygen and nutrients. Similarly, the spatial organization of cells such as neurons and immune cells is guided by a combination of developmental cues and chemotactic signals to

direct the migration and activity of those cells in a tissue-wide context. These cues include the network of proteinaceous fibers, such as collagen and elastin, which form the ECM. These not only maintain the tissue structure but also provide tracks along which motile cells can migrate as they follow concentration gradients of chemokines and other signals. The tissue mechanical properties imparted by the hierarchical disposition of the ECM components are actively sensed by the cells (mechanotransduction) and critically determine cell function, differentiation, and overall tissue homeostasis.[10]

For the production of lifelike biohybrid implants, this complex cellular and extracellular organization must be imposed, either from the top down, from the bottom up, or from a combination of both. We are only just beginning to find technological solutions to address the challenges of top-down and bottom-up TE, but progress thus far has been encouraging.[11] This progress should parallel the fundamental understanding of cell–material interactions, critical to the success of any tissue-engineered construct.[12]

One of the key developments in bottom-up TE is the ability to exploit the intrinsic self-assembling and self-organizing nature of biological materials and combine this with nanofabrication and microfabrication methods to develop functional biohybrid constructs.[8] Self-assembly is the prime example of bottom-up organization found in nature and we can now design novel self-assembling materials, often based on protein subunits that spontaneously assemble and disassemble in different environments.[13] The material can be designed in a manner that enables self-shaping and self-folding even in the absence of cellular control.[14] However, self-assembly is not a complete solution on its own because such hierarchically ordered structures are difficult to expand to the macroscale.[15] We can rely on self-assembly to control structural organization on the molecular scale, but to bridge the gap between the nanoscale and the macroscale to obtain functional tissue replacements constitutes a major challenge. There are, though, some encouraging examples in which self-assembling peptides have been used as molecular "chaperons" to guide protein assembly into hierarchical structures.[16] For example, the co-assembly of an elastin-like polypeptide (ELP) and an oppositely charged peptide amphiphile led to a multilayered tube.[17] The tube featured a millimeter-range size and formed at a liquid-liquid interface that keeps the two solutions separate. The system enabled the generation of more complex tubular structures by simply touching and pulling the membrane. In a follow up study, a similar multicomponent self-assembling approach, using this time ELP in combination with graphene oxide, was exploited to create more robust hybrid systems.[18] Still, the application of these systems is not universal and requires a narrow window of frame conditions.

The challenge of bottom-up microscale to macroscale organization can be addressed by the fabrication of building blocks such as microgels, microspheres, and other microcarriers (beads, rods, and fibers) that are subsequently integrated into higher-order structures.[19] This often involves the microencapsulation of cells within spherical[20] or rod-shaped[21] microgels[22] or the growth of cells on the surface of other microcarriers that are then assembled into larger structures via physical and/or chemical linkages, either randomly or in a defined pattern. The latter allows microcarriers seeded with different cell types to be arranged in a tissue-like configuration.[23] On the other hand, microgels produced using microfluidic technology can be assembled and interlinked to form macroporous constructs in which cells can more easily infiltrate.[24] Compared to spherical microgels, the interlinking of rod-shaped microgels leads to the formation of larger pores with less microgel volume.[25] The use of thinner and higher-aspect-ratio microgels produced by in-mold polymerization showed that pore size increases proportionately with the aspect ratio (up to 20), producing scaffolds with porosities of up to 90% and a mean pore size of up to 82 μm. The constructs supported rapid, extensive filling by fibroblasts within one week.[26] Furthermore, magneto-responsive microgel rods containing superparamagnetic iron oxide (SPION) nanoparticles were fabricated using a similar approach and dispersed into a biocompatible hydrogel precursor. The application of a weak magnetic field induced unidirectional ordering of the rods, which was preserved by crosslinking of the hydrogel precursor to form a hierarchical structure called an Anisogel. These structures can induce the orientation of cells either by functionalization with RGD [27] or when they are non-bioactive, acting instead as a physical barrier.[28] In fully synthetic Anisogels, the most efficient cell alignment was observed for non-bioactive microgels in a bioactive surrounding gel based on polyethylene glycol. The combination of magnetic nanoparticles with lifelike materials opens new horizons for the shape morphing of functional hydrogels.[29]

To ensure reproducibility and low batch-to-batch variation during the fabrication of the microcarriers described above, microfluidics imposes control over the synthesis of individual particles and improves overall yields. Indeed, microfluidics has also been used to facilitate the continuous, high-throughput production of microgel rods with uniform size, stiffness, and aspect ratio.[30] A microfluidic setup was also used to produce monodisperse collagen gel beads (<300 μm in diameter) that can be used to encapsulate or anchor cells, followed by molding in a silicone chamber that forms the scaffold of the 3D tissue construct.[31] Gelatin methacryloyl beads have also been produced using a microfluidics-assisted approach, followed by heat-induced physical crosslinking to form a scaffold structure and then photochemical annealing to increase mechanical resilience.[32]

Many of the approaches discussed above represent a combination of bottom-up and top-down strategies, i.e., they involve the design of small units that are built up into a larger construct (bottom-up concept), but those units are converted into macroscale scaffolds by molding, casting, or sedimentation (top-down approaches). An appealing strategy to assemble small units into a whole, following a bottom-up strategy, is offered by additive manufacturing.

The application of additive manufacturing technologies such as 3D printing [33] enables small building units (e.g., beads, spheroids, and vesicles) to be placed precisely within organotypic architectures, as shown for the placement of cell-like units.[34] The resulting multi-vesicular structures were further interconnected between them, resulting in synthetic tissues with diverse functionalities (storing and releasing reagents, logic operations, responding to magnetic fields, and interacting with living cells).[34b] In another interesting example, the bioink was composed of i) cell-encapsulated microgels and ii) a hydrogel precursor that forms a second polymer network and integrates the microgels.[35] This strategy represents an interesting platform for printing heterogeneous tissue constructs with high shape fidelity.

Current efforts to precisely control the geometry and hierarchy of 3D-printed implants must be accompanied by a thorough evaluation of the resulting mechanical properties.[36] Both aspects are critical to the overall performance, functionality, and fate of the implants.

3D printing is also a powerful tool to advance the development of centimeter-scale tissues, in which the development of a perfusable or vascularized network is critical for preserving cell viability within the cm-scale tissue.[37] 3D printing offers the possibility to build structures containing micro-channels or in which blocks of hydrogel can be evacuated by printing channels with sacrificial inks that can be removed.[38] An excellent example of complex cell-laden constructs is presented by Kim and colleagues, in which they produced skeletal muscle constructs by bioprinting human muscle progenitor cells and human neural stem cells. The bioprinted constructs facilitated rapid innervation and matured into organized muscle tissue in vivo in a rodent model of muscle defect injury.[39]

Reproducing the complex, heterogeneous, and hierarchical architecture of functional tissues and organs requires knowledge of how the native tissue is built and organized. The acquisition of this information in a patient-specific manner and its subsequent integration into the biohybrid implant design are promising paths toward personalized medicine. Importantly, the use of 3D printing also allows the integration of information from (clinical) imaging techniques for the creation of customized implants according to the patient's unique anatomy and specific needs.[40] By using post-processing algorithms, clinical imaging data (e.g., obtained from CT or MRI) can be transformed into a 3D CAD model of the target tissue construct. The CAD model is then converted into a motion program that controls the movement of printer nozzles and the dispensing of bioink.[41]

As an alternative to rather spheroid units, many researchers are focusing on microfibers as building blocks for biohybrid systems. The predominance of fibrous proteins such as collagen and elastin in the ECM elevates fibers as the biomimetic building block of choice to replicate the features of native tissues. Collagen and elastin are protein polymers that align to form protein fibers, which can assemble into larger bundles and in turn form higher-order net-like structures. This creates an interesting overlap between the fields of TE and textiles. Indeed, fiber and textile-based approaches have been exploited for engineering a wide variety of tissues, [42] including skin, cartilage, tendon, ligament, muscle, oesophagus, trachea, and cardiovascular tissues.

The fundamental basic units of textiles are also polymer fibers with a high degree of alignment, often facilitated by flow-induced shear stress and drawing (or stretching) during production.[43] The fibers are bundled into yarns that provide strength, and the yarns can be deposited as nonwovens, or can be converted into planar textiles, for example by weaving or knitting.[43] Textiles often feature seemingly contradictory properties (e.g., both flexibility and strength) that are rarely achieved in other material structures. This is possible due to the strength of the individual fibers and yarns, combined with the relative independence of inter-fiber and inter-yarn movement, thus conferring structural elasticity. Accordingly, a twisted yarn composed of 100 fibers achieves a flexural rigidity 100 times greater than that of a single fiber. However, if these fibers are glued together, the flexural rigidity increases to 10 000 times greater than that of a single fiber.[43]

Most native tissues are composites featuring a water-based matrix reinforced by an anisotropic fibrous support. Therefore, a promising approach for the development of lifelike biohybrid implants is a combination of fibers and/or textiles that confer mechanical properties analogous to native tissues (including anisotropy) with hydrogels that have an inherent capacity to absorb water.[44] For example, vascular grafts have been prepared from PVDF knitted textiles embedded within a fibrin hydrogel matrix to provide a suitable environment for cellular remodeling.[45] In a further step, such textiles were functionalized with ultra-small superparamagnetic iron oxide (USPIO) nanoparticles. This enabled noninvasive imaging of the grafts following implantation in sheep as arteriovenous shunts[46] and as interpositional grafts in the systemic circulation.[45b] The imaging data can be gathered in a continuous manner, enabling the same implant to be monitored through its lifetime, thus eliminating the noise and artefacts created by comparing data from different implants.

Whereas the implants discussed above are constructed, populated with cells, and cultivated in vitro until they evolve a form and functionality similar to native tissue, the strategy of in situ TE relies on the colonization of cell-free implants by cells in vivo. This attracts a lower regulatory burden because the implant does not contain living cells when it is first introduced into the body. The absence of cells also increases the potential for off-the-shelf availability. However, the design must ensure that the implant can integrate with existing tissues in the absence of an in vitro maturation step. Fiber-reinforced biohybrid implants are promising in this regard because a well-designed textile scaffold guarantees long-term stability in vivo, while the biobased hydrogel matrix promotes tissue remodeling by attracting the surrounding cells in situ. Essentially, this approach uses the human body as a bioreactor to transform the biohybrid implant into an autologous native-like tissue. For example, these design principles have been applied to a genetically engineered elastin-based matrix to develop vascular grafts,[47] venous valves,[48] and heart valves[49] (**Figure 1**).

In addition to traditional fiber and textile fabrication approaches such as spinning, weaving, and knitting, more recent approaches for the development of fiber-based biohybrid implants have adopted microfluidics[50] and 3D printing technologies.[51] Reasonable approximations of woven and knitted structures can be produced by techniques such as selective laser sintering,[52] which features unique capabilities to manufacture precisely complex geometries, although it is limited to thermoplastic polymers.[53] Alternatively, small printed components can be interlocked in a modern equivalent of chainmail.[54] Such materials have yet to be mass-produced and it is unclear whether they match the mechanical properties of traditional fiber-processing technologies. The latter is an important requirement in TE constructs that are subject to considerable stress, such as cardiovascular implants. Therefore, another promising approach is to take advantage of the mechanical reliability of conventional textile manufacturing methods and the versatility of 3D printing by using the latter to deposit polymers onto the surface of existing textiles, thus modifying their structure and functionality.[51b,54]

Currently, we are witnessing emerging technologies that encompass, in a synergistic way, the fundaments of already-existing

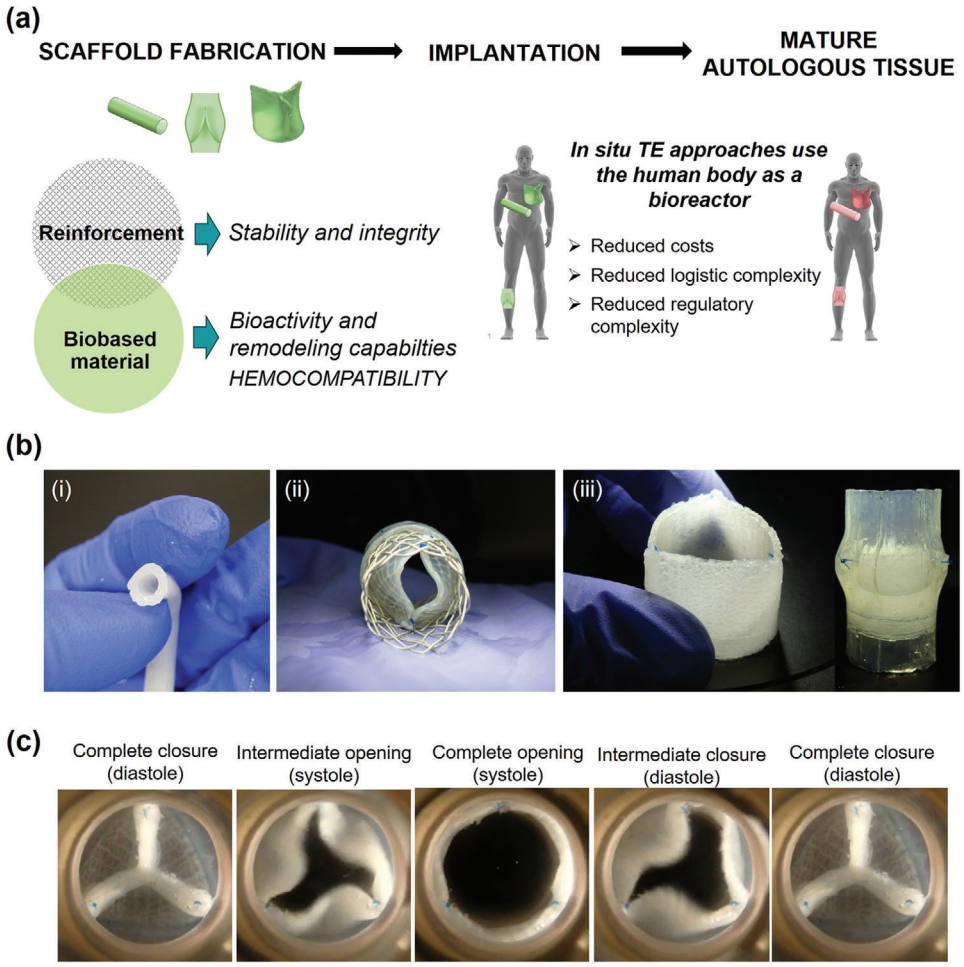

Figure 1. Fiber-reinforced biohybrid implants for in situ TE. a) Schematic of the in situ TE workflow. b) Examples of cardiovascular implants based on a hydrogel matrix of engineered elastin reinforced with textile/fibers: i) vascular graft, reproduced under the terms of the CC-BY 4.0 license.[47] Copyright 2019, The Authors. Published by Frontiers; ii) venous valve, reproduced under the terms of the CC-BY 4.0 license.[48] Copyright 2022, The Authors. Published by Frontiers; iii) heart valve, reproduced with permission.[49] Copyright 2022, Wiley-VCH GmbH. c) Snapshots of the opening-closing cycles of the aortic biohybrid heart valve under aortic conditions simulated in a mock circulation system, reproduced with permission.[49] Copyright 2022, Wiley-VCH GmbH.

ones. Perhaps one of the most exciting examples is melt electrowriting (MEW), in which the advantages of 3D printing converge with traditional fiber electrospinning. MEW is an additive manufacturing technology in which the polymer fiber jet is digitally controlled. This enables the accurate (sub-microscale resolution) and tailored deposition of microbiomimetric fibers according to tissue requirements or even patient-specific anatomic features.[55] Recently, an aortic heart valve was developed based on heterogeneous PCL-fibrous structures fabricated by MEW and embedded in a genetically engineered elastin matrix,[49] representing a step forward in the field of fibrous scaffold fabrication and in situ heart valve engineering (Figure 1). So far, the number of materials explored and optimized for MEW is rather limited, in contrast with the many different polymers investigated for traditional electrospinning. PCL is currently considered the gold standard polymer for MEW due to its low melting temperature and rapid solidification.[56] Nevertheless, several polymers beyond PCL have already been implemented in MEW schemes, including poly(propylene) (PP), poly(vinylidene fluoride) (PVDF), and poly(2-oxazoline)s (POx).[56] Improvements in current printers (e.g., to achieve the required melt temperature) can contribute significantly to widening the range of polymers processable by MEW.[56]

3. Reproducibility and Translation

3.1. Reproducibility of Biohybrid Lifelike Materials: To Seed or Not to Seed?

Medical products require a high level of reproducibility and standardization throughout production, but the biological part present in some biohybrid implants inevitably introduces some variability. The realization of this has prompted a tendency to move from classical TE to in situ TE.

There are three main categories of in situ TE approaches: i) those in which the implant is cell free during the whole produc-

tion process ("culture free") and do not rely on any donor material ("tissue free"); ii) those that still use cells to render a matrix in vitro, which is then decellularized prior implantation to obtain a cell-free implant; and iii) those that rely on decellularized native tissues. Therefore, in situ TE based on decellularization involves either cell culture and in vitro conditioning or tissue harvesting.

An implant developed following a truly in situ "culture free" and "tissue free" approach benefits from off-the-shelf availability, a lower regulatory burden for clinical translation, and no need for tissue harvesting and/or cell isolation. In such an approach, the in vitro cell culture phase is omitted, eliminating issues caused by the sometimes unpredictable behavior of cells during the production phase. However, even if the implant is developed as a cell-free system, it will interact with cells in vivo. Therefore, we cannot eliminate the cellular component as a key determinant of an implant's fate, even if the implant is developed as cell-free scaffold. An example to illustrate these considerations is the study of Bouten and colleagues, where a cell-free vascular graft intended for in situ TE and implanted in rats evidenced the difficulties to predict graft development and performance in vivo.[57] The study points to the influence of several factors affecting the subject-implant interface, including the surgical procedure and the inter-individual variabilities, among probably others yet to be identified, and highlights the need for further progress in personalized medicine.[58] While in situ TE presents a priori several advantages when compared to classical TE, there is still much to be learned about the remodeling that an implant will experience when localized in a patient in vivo. To gain insight into the underlying phenomena, in vivo noninvasive (molecular) imaging constitutes an indispensable tool, which should go hand-in-hand with the development of materials able to adapt to the patient´s needs.

3.2. The Regulatory Landscape for Biohybrid Materials and the Challenge of Translation

3.2.1. Regulatory Landscape

Biohybrid materials used for TE may or may not contain natural biological substances (including bioactive molecules) and may or may not contain cells and/or tissues (which may or may not be genetically modified), thus placing such materials at the interface between the major regulatory categories: drugs, biological medicinal products, and medical devices.[59] To address this complexity, the regulatory agencies in the USA, EU, and other jurisdictions have established offices to deal with so-called combination products (defined as products containing two or more regulated components in different categories). They have created specific regulations for products containing cells and/or tissues, including TE products, thus helping to define a clearer regulatory pathway for innovative products that would otherwise challenge the rather inflexible regulatory framework.[60] In the EU, classical TE materials are designated as advanced therapy medicinal products (ATMPs) and may be classed more specifically as i) TE products (TEPs) if they are not combined with a medical device, or ii) combined advanced therapy medicinal products (CATMPs) if they are. In the US, the FDA includes such materials as a class of biologics known as human cell, tissue, and cellular and tissue-based products (HCT/Ps) that are stratified into three risk groups. TE products are classed as high-risk products and follow the same regulatory pathway as other biologics, unless they are combined with a medical device, in which case they are regulated as combination products. The regulators acknowledge that the designation of a given product may not be obvious, especially given that the distinction between a biologic and a medical device is not always clear cut.[61] If product categorization is uncertain in the EU, the sponsors of a product may ask for an optional ATMP classification procedure, which is overseen by an expert Committee for Advanced Therapies (CAT). In the US, such products are evaluated by the Office of Combination Products (OCP), which makes a decision on the product classification and then assigns it to the corresponding center based on the primary mode of action (drug, biologic or device). Other jurisdictions have their own regulatory frameworks that do not align precisely with either the EU or US systems.[62] The same product can therefore be registered as a TEP or CATMP in the EU, an HCT/P or combination product in the US, a drug in Canada, a biologic in Australia, and a cell therapy product in South Korea, all subject to different procedures and development timescales.[63] There are ongoing efforts to harmonize the various international regulatory systems.

3.2.2. The Challenge of Translation

Translational research aims to convert basic research results into applications with a direct benefit to humans. In medicine, this generally means the clinical development phase and any follow-up research that reduces new clinical innovations to everyday practice (point-of-care patient applications). Regulatory pathways evaluate the benefits and risks of a given product, so translational research should focus on both sides of this equation: the desired efficacy of a product and its safety in patients with variability in risk patterns. Therefore, the development of biohybrid materials for medical applications should focus, from the outset, on how patient variability affects the efficacy and safety of the medicinal product in situ. This includes a thorough study of the interface between the patient and product (and how the variability of the interface affects efficacy) as well the potential for graft-versus-host reactions that can compromise patient safety. The pre-clinical development of innovative products must therefore include regulatory research involving the collection of data to support risk evaluation. The analysis of such data may lead to changes during product development to increase the product's efficacy and safety. This part of research–termed as regulatory research–is mandatory and parallels the development of the product from the very beginning. In addition to an effective risk management strategy, other aspects, such as standardization, scalability, and competitiveness against current therapies, must also be addressed in the early stages of translation. This will help to build a solid basis for product development and prevent a promising academic idea from ending up in the translational "valley of death".[64]

4. Computational Modeling as a Tool for Optimizing the Design of Biohybrid Implants

Computational simulations of lifelike materials can facilitate the high-throughput screening of different material compositions

under diverse conditions in order to optimize biohybrid implants for specific applications. However, this is a significant challenge because it requires the accurate simulation of material behavior, kinetics, and hemodynamic responses. The virtual high-throughput screening of implant designs can be facilitated by methods based on model order reduction and machine learning. Both types of methods reduce the degrees of freedom in the computation to such an extent that real-time simulation becomes feasible. For example, innovative nonintrusive model order reduction methods can be used to couple existing physical and biological knowledge about new materials with data-driven techniques in system identification.[65]

New simulation methods not only seek to accomplish simulation in real time but also to achieve sophisticated, multi-scale descriptions of lifelike materials and systems[66] (**Figure 2**a). Complex interactions between scaffolds and the living components of implants occur at the cell, tissue, and organ levels, which must be understood and then applied to the manufacturing process in order to achieve significant advances in novel implant design. Biological components ranging from endothelial and smooth muscle cell to certain growth factors and biologics/drugs can influence the behavior of the biohybrid material in many different ways, including the degree of anisotropy.[67]

Biohybrid devices such as heart valves and stents are characterized by complex geometries, making it difficult to model their non-linear structure and mechanical behavior even when using well-established approaches like the finite element method. It is particularly important to simulate the contact between the device and the surrounding material/blood flow accurately[66b] (Figure 2b). Emerging methods such as isogeometric analysis, virtual elements, and physically/biologically informed networks are promising alternatives to solve the boundary value problems of the simulation model in future.[68]

The reliability and accuracy of numerical simulations depend on the quality of the underlying models, including the use of verified and validated parameters. This requires close cooperation between researchers working on the physical materials and those running computer simulations because the challenge is not the lack of data but the means to intelligently structure and exploit the data.

Computational simulations can be used not only to test new materials but also to predict the effect of cells, materials, and their interactions in order to optimize tissue engineering approaches. This typically involves iterative rounds of model construction based on initial experimental observations, model calibration, or fitting to set parameters based on experimentally recorded values, and model validation by testing the resulting predictions.[69] Computer models can be used to predict cell behavior such as growth and differentiation[70] or cell–cell and cell–matrix interactions during tissue formation.[71] They can also be used to predict the relationship between tissue structure and function,[72] the flow of nutrients, bioactive molecules and waste,[73] and the optimal properties of tissue scaffolds,[74] biomaterials,[75] and microfluidic devices.[76]

Examples of models and simulations used to predict cell behavior include those describing signaling pathways and gene regulatory networks that determine cell fate, such as stem cell differentiation.[77] Models of cell behavior are particularly useful in the context of biohybrid constructs when the parameters include the effect of synthetic scaffolds.[78] In one recent example using a model that accommodates the effects of the immune system and mechanical factors on of tissue formation,[79] the appearance and spontaneous reversal of stenosis was predicted in tissue-engineered vascular grafts.[80] Other models have been used to predict how cell behavior influences tissue remodeling, particularly by simulating the reorganization of cytoskeletal fibers and their effect on the extracellular matrix in vitro.[81] One of the most important advantages of computational models is that they can address parameters that cannot be tested directly in experiments, such as the degree of shear stress experienced by individual cells[82] or spatiotemporal gradients of different sugars in a bioreactor.[83] Finally, computational models can be used to optimize processing methods for the development of biohybrid constructs, including bioreactor-based processes.[84]

5. Noninvasive Imaging

Biohybrid implants are transformative, which means they are subject to maturation and remodeling in vivo. These dynamic maturation processes involve complex interactions between cells, biohybrid scaffolds, and natural tissues and do not always proceed without problems. For example, cells may remain in a prolonged inflammatory state, they may differentiate incorrectly, or they may initiate fibrosis causing the system to lose function. The synthetic components of the system should integrate with the body and remain stable as the natural tissue regenerates or repairs and then should degrade harmlessly over time. To ensure that such events unfold as envisaged, it is useful to monitor post-implantation cell behavior and implant integrity, ideally by noninvasive imaging. This enables the early detection of dysfunctions and the prompt deployment of countermeasures.

Clinically established noninvasive imaging modalities, such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound, can be used to assess morphological features and the functionality of biohybrid implants. The option of repeated measurements allows intra-individual observations and thus the detection of small recipient-specific changes. However, imaging can do much more. For example, diagnostic markers can significantly improve the localization of biohybrid systems, as demonstrated by the CT imaging of biohybrid scaffold materials labeled with gold[85] and barium nanoparticles,[86] and MRI with manganese-loaded porphyrins,[87] ferritin derivatives,[88] and SPIONs.[46,89] Furthermore, ^{19}F-containing markers are often used for MRI labeling because fluorine is not usually found at significant concentrations in human soft tissues. Examples include fluorinated hydrogels[90] and vascular biohybrid scaffolds constructed from thermoplastic polyurethane and visualized by hybrid ^{1}H/^{19}F MRI.[91] Imaging markers can facilitate the visualization of material degradation in vitro and in vivo, as shown for SPION bound to collagen scaffolds[92] or incorporated into PLGA filaments[93] (**Figure 3**) as well as for radiopaque iodinated thermo-reversible hydrogels.[94] The next level of theranostic scaffold materials will be able to report interactions with cells or newly transformed tissue matrices. Alternatively, these materials can also carry drugs that are released by internal or external triggers, such as the release of basic fibroblast growth factor from acoustically responsive scaffolds to trigger angiogenesis.[95]

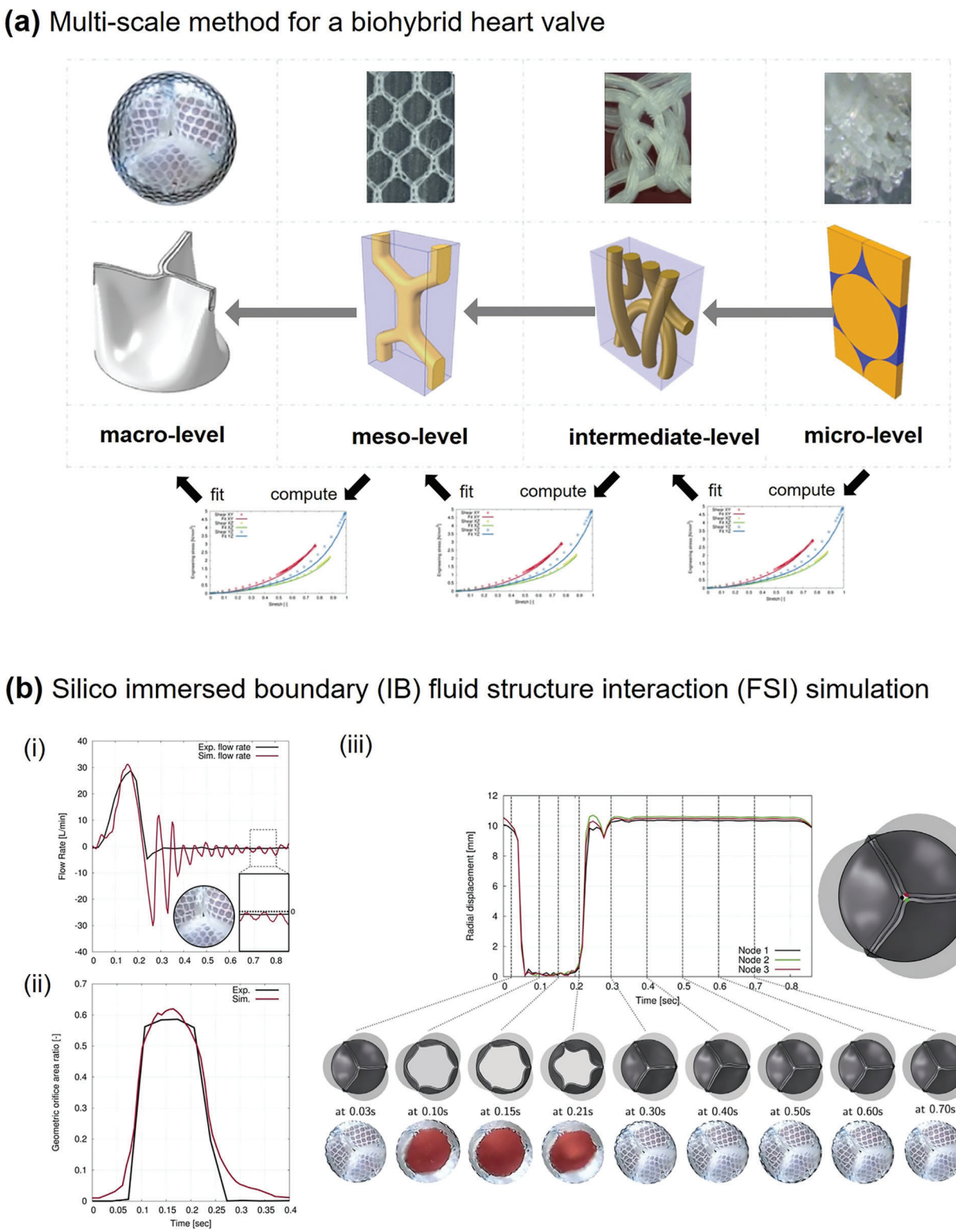

Figure 2. a) Schematic representation of the multi-scale method, in which the biohybrid valve is divided into four structural levels to predict the material parameters. b) The fluid structure interaction (FSI) simulation. i) Comparison of the flow rate in vitro and in the fluid FSI simulation, and close up view of the biohybrid valve showing a gap at its geometric center resulting in continuous backflow corroborated by a negative flow rate recorded in the experiments during the diastolic phase. ii) Geometric orifice area ratio obtained by FSI simulations, in good agreement with the in vitro results during the systolic phase. iii) Radial displacement of three points on center of the free edges of the tubular valve leaflets plotted over one beat cycle and comparison of the valve deformation state at nine different time points in a normalized beat cycle. Reproduced with permission.[66] Copyright 2018, Elsevier.

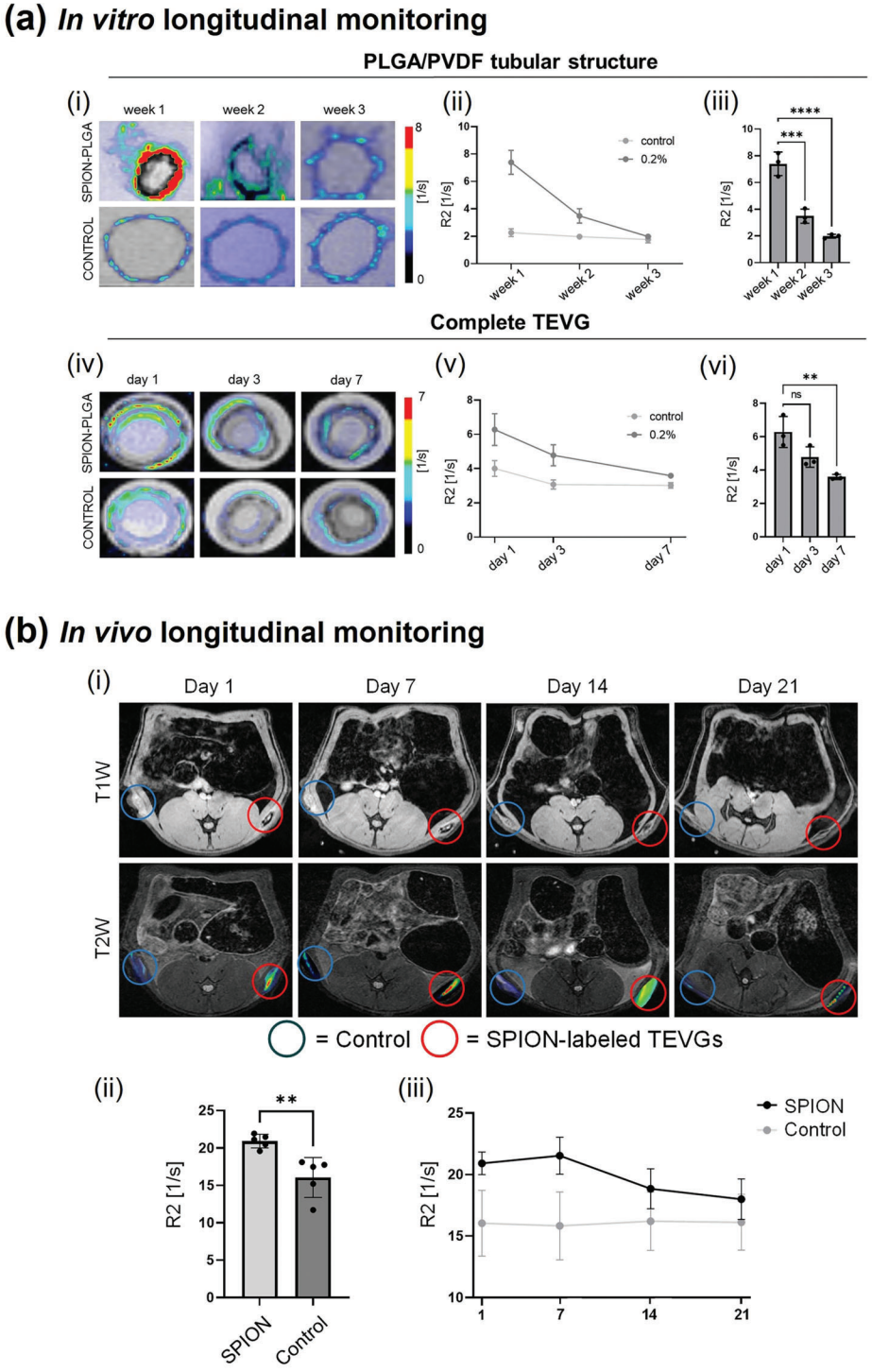

Figure 3. Monitoring of PLGA fiber degradation by MRI. a) In vitro monitoring of SPION-labeled PLGA degradation. i) R2 color maps superimposed on T2 weighted images of SPION-labeled PLGA fibers combined with the PVDF tubular scaffold (top) and of unlabeled controls (bottom) in PBS. ii) R2 relaxation rates of 0.2% SPION-labeled PLGA fibers compared to the unlabeled control. iii) R2 values of 0.2% SPION-labeled PLGA fibers decrease due to fiber degradation. iv) T2 weighted MRI images of the complete TEVGs with SPION-labeled (top) and unlabeled PLGA fibers (bottom), with corresponding superimposed R2 color map. v,vi) R2 relaxometry confirms the degradation of 0.2% SPION-labeled PLGA fibers compared to the unlabeled controls and their faster degradation in the presence of SMCs and ECs. b) In vivo longitudinal monitoring of SPION-labeled PLGA degradation. i) T1- and T2-weighted MRI images of subcutaneously implanted SPION-labeled TEVGs (red circles) and unlabeled controls (blue circles) for 21 days. R2 color maps of both samples superimposed on the grayscale T2-weighted images highlight PLGA fiber degradation over time. ii) Comparison of the R2 relaxation rate of SPION-labeled TEVGs and unlabeled controls. iii) R2 relaxation rate of SPION-labeled and unlabeled TEVGs over 21 days. Data are means ± SD ($n = 3$; ns > 0.05, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$). Adapted under the terms of the CC-BY 4.0 license.[93] Copyright 2022, The Authors, published by Wiley-VCH GmbH.

When synthetic fibers degrade they are replaced by the endogenous ECM to ensure the stability of biohybrid transplants. Molecular imaging can be used to monitor the production of elastin, collagen, or enzymes that are involved in matrix remodeling, including examples such as a gadolinium-containing elastin-binding MR probe[96] as well as reagents targeting collagen and fibrin developed for MRI and positron emission tomography (PET) imaging.[97] The elastin/collagen-binding MRI probes were later used to monitor the maturation of biohybrid vascular implants in vitro.[93] A clinically attractive alternative for collagen imaging is multispectral optoacoustic imaging, although further evaluation for sensitivity and robustness is required.[98]

Imaging the cells in biohybrid systems is even more challenging. The three main approaches are the use of imaging biomarkers, reporter genes, or indirect labeling with targeted diagnostics.[99] Direct labeling is disadvantageous because the label becomes diluted as cells proliferate and can be transferred from dead cells to endogenous macrophages. Bioluminescent and fluorescent reporter proteins are not limited in this manner, but they are difficult to apply in clinical settings. Indirect labeling methods tend to have low sensitivity, making it difficult to observe individual or scattered cells. Another important diagnostic demand is the assessment of the tissue response at the implantation site. Here, numerous molecular imaging methods are available to follow processes such as angiogenesis, inflammation, and apoptosis.[100] Furthermore, the PET label ^{18}F-FDG has been used to detect inflammation at the site of biohybrid vascular grafts.[45b]

Noninvasive imaging therefore provides many opportunities to characterize biohybrid implants in vitro and in vivo. Identifying and refining the most robust, affordable, and clinically-applicable approach is a significant challenge but is essential for the clinical translation of biohybrid systems.

6. Noninvasive Control of Transformative Materials for Biohybrid Implants in vivo

Lifelike materials for biohybrid implants must have the ability to transform their properties in vivo in order to adapt to their dynamic environment. Research has recently focused on the development of smart, responsive biodegradable biohybrid implants for both diagnosis and therapy.[101] Although current materials can response to multiple stimuli,[102] they do not behave as truly autonomous systems. A truly autonomous transformative material should simultaneously serve i) as a sensor for the precise detection of the environment in vivo, and based on this information, ii) as an actuator to enable the accurate transformation of material properties according to the required output. This demands a very precise interaction loop at the interface between the material and in vivo environment to maintain tissue functionality. To control that these events proceed as planned, it is imperative i) to monitor implant performance after implantation, ideally by noninvasive imaging (as highlighted in Section 5), and ii) to be able to rectify the implant, if necessary, in a noninvasive manner by remote control.

New promising approaches for the accurate on-demand transformation of material properties include magnet-based imaging techniques such as MRI[103] and the magneto-thermal effect for actuation.[104] For this, magnetic nanoparticles are linked to the respective biodegradable scaffold material, allowing a magneto-thermal environment to be generated by applying an alternating magnetic field.[105] The heat generated by magnetic actuation can be exploited as a tool to accelerate the degradation of the materials, thus triggering the release of the drug cargo.[106] Magnetic fields have also been used to control the deformation of macroporous ferrogels remotely and subsequently promote the release of biological agents caused by water flow through the interconnected pores.[107] These examples illustrate how magnetic materials can be harnessed for the release of therapeutic agents on demand by remote control. Besides on-demand drug release, magnetic hydrogels can also be actuated to perform many other responses, including heterogeneous and complex movements, locomotion, and navigation.[29b,108]

Magnetic hydrogels also provide a platform for the remote stimulation of cells.[109] Together with the potential to modify the architecture [107] and mechanics[109,110] of biohybrid materials remotely, this opens new horizons for the noninvasive control of implants in vivo. The full potential of materials functionalized with magnetic nanoparticles can be exploited in combination with their use as tracers for magnetic particle imaging, a novel preclinical imaging technique. This promises the unprecedented advantage of image-guided therapy on a molecular level.[111]

7. Final Remarks

The scientific community has always been fascinated by biological structures and has striven to develop materials that replicate or even improve on nature.[112] In this perspectives article, we have highlighted the design principles of natural structures in living cells and tissues and how these can be harnessed to engineer biohybrid lifelike materials in the laboratory. The design of biological systems has been shaped and refined through the process of evolution. The potential knowledge acquired by unravelling the rules governing the construction of living organisms offers the possibility to create new materials and systems, not just copying nature (biomimetics) but even improving it and creating completely new functions. Ongoing and disruptive technological developments in microscopy,[113] molecular imaging, computational simulation, and biofabrication are essential to, i) understand nature's ability to build complex structures, ii) exploit this knowledge to build transformative biohybrid implants, and iii) follow and control the behavior of such implants in vivo. Efforts in all these areas need to be sensitive to ethical principles. Alongside a thorough consideration of medical and technical risks, it is necessary to consider the impact on the human self-image and on what is perceived as human nature (and potential threats thereto). Research into biohybrid implants must be accompanied by ethical discussions focusing on biohacking, enhancement, and human-technology relations, to allow medical progress that is truly desirable and justifiable. The integration of these aspects has the potential to open new horizons in biomedicine.

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Conflict of Interest

The authors declare no conflict of interest.

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