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Dielectric Elastomer Actuators, Neuromuscular Interfaces, and Foreign Body Response in Artificial Neuromuscular Prostheses: A Review of the Literature for an In Vivo Application

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The inability to replace human muscle in surgical practice is a significant challenge. An artificial muscle controlled by the nervous system is considered a potential solution for this. Here, this is defined as a neuromuscular prosthesis. Muscle loss and dysfunction related to musculoskeletal oncological impairments, neuromuscular diseases, trauma or spinal cord injuries can be treated through artificial muscle implantation. At present, the use of dielectric elastomer actuators working as capacitors appears a promising option. Acrylic or silicone elastomers with carbon nanotubes functioning as the electrode achieve mechanical performances similar to human muscle in vitro. However, mechanical, electrical, and biological issues have prevented clinical application to date. Here materials and mechatronic solutions are presented which can tackle current clinical problems associated with implanting an artificial muscle controlled by the nervous system. Progress depends on the improvement of the actuation properties of the elastomer, seamless or wireless integration between the nervous system and the artificial muscle, and on reducing the foreign body response. It is believed that by combining the mechanical, electrical, and biological solutions proposed here, an artificial neuromuscular prosthesis may be a reality in surgical practice in the near future.

1. Introduction

Our inability to replace human muscle in surgical practice is still a major issue to solve. We currently can use joint arthroplasty, bone bank allograft, artificial ligaments, vascular prosthesis and dermal substitutes for treating the respective tissue defect, but there are no solutions for dealing with muscle or nerve loss. Artificial muscle is considered to be the potential solution for this. However, this approach is not used in surgical practice yet, because of mechatronic and biological issues. The term artificial muscle is used to describe materials/devices that mimic the performance of natural muscle by contracting, expanding, rotating, and relaxing. The activation of the artificial muscle directly via the nervous system would guarantee the best replacement of natural muscle. Here we define "neuromuscular prosthesis" as an artificial muscle directly activated by the patient's nervous system. Current mechanical, electrical, and biological issues have prevented clinical application to date and these are presented here. The aim of this review is to define which materials and mechatronic technologies would be the most suitable for clinical application of a neuromuscular prosthesis. The endeavor to develop a clinically effective neuromuscular prosthesis requires a multidisciplinary approach including material science, mechanical engineering, electrical engineering, chemistry, and medical expertise.

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Muscle loss and severe muscle dysfunction related to musculoskeletal oncological impairments, neuromuscular diseases, traumas, and spinal cord injuries could be potentially treated through an artificial muscle implantation. For these applications, the ideal neuromuscular prosthesis should be activated by the will of the patient through the nervous system and should reproduce the performance of natural muscle. This is based on activation of the electrical and mechanical components of the prosthesis by the patient's nervous system; here we define it as mechatronic compatibility. The mechatronic compatibility is determined by the mechanical and electrical properties of the patient-prosthesis system. The signal must be sufficient to activate the electrical components of the device and it must guarantee sufficient voltage to trigger and sustain mechanical actuation. To date, no efficient neural communication has been reached for implanted devices and the actuation voltage needed for the artificial muscles proposed in the literature limits clinical application. On the other side, we define biocompatibility as the biological compatibility of the prosthesis with patient tissue. The device must not be harmful for the patient and it should avoid a foreign body response (FBR). Researchers in materials science have proposed different solutions for creating a device mimicking human muscles properties. Since the development of the first pneumatic artificial muscles in 1948 to the braided muscle development by Dr. O. Häfner and the further development by Dr. J. L. McKibben of the McKibben pneumatic actuator muscle in 1952, a wide range of devices have been engineered. Actuators (pneumatic, dielectric elastomer based, electrostatic, nanocomposites, photoexcited, piezoelectric, photostrictive, electrostrictive, and magnetostrictive), fiber polymers (highly oriented semicrystalline polymer fibers, and twisted nanofiber yarns), ionic composites, alloys with shape memory thermally activated, and stimuli-responsive gels are some of the materials and structures used to date in the field of artificial muscles. Pressure, temperature, voltage, and light are the most common external sources used to stimulate contraction. Robotics, exoskeletons, smart windows, drug delivery systems, and energy harvesting systems are amongst the wide range of applications of the different devices. In order to reproduce human muscle, the dielectric elastomer actuator (DEA) with nanostructured carbon electrodes is to date considered the best solution, due to mechanical performances and voltage based actuation. As the aim of this work is to present which solutions could be suitable for an artificial muscle in clinical applications, it will be focused on reviewing properties and limitations of the DEA with nanostructured carbon electrodes and possible solutions for an in vivo use. To separately analyze the mechanical, electrical, and biological issues, we divided the review into three different sections treating the contracting component, the neuromuscular interface, and the different approaches used to avoid FBR of the implanted material.

2. The Artificial Muscle Today

2.1. The Contracting Component

Different biomaterials have been used during the years for reproducing natural muscle biomechanics and function.[1] Loss of muscle tissue related to oncological surgery and trauma or muscle dysfunction as encountered in neuromuscular diseases and spinal cord injuries results in severe impairment for the patient. The objective to restore a damaged muscle needs to tackle the issue of the performance of the implanted muscle. The implanted muscle should ideally restore the mechanical effectiveness of the original muscle. For this, materials must guarantee the ability to move and use objects in everyday life. In this section we will focus on the devices that seem more suitable for reproducing the human muscle function:[2–5] the DEA.

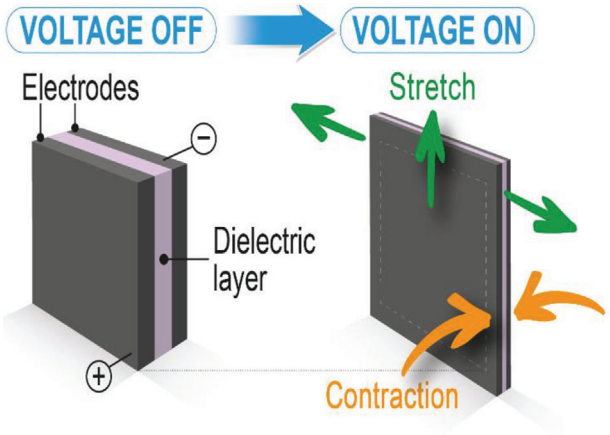

Figure 1. Dielectric elastomer contraction schematic.

DEAs are capacitors with elastic properties. They consist of a thin elastomer coated with compliant electrodes on both sides. Attraction between the opposite charges in the electrodes is generated when a voltage is applied. This electrical attraction forces the film to contract in thickness and expand in area simulating a human muscle (**Figure 1**).[2] DEAs are to date considered one of the leading solutions in reproducing human muscle performance with regards to fast response, large strains, and stresses attainable, long lifetimes, good reliability, and high energy efficiencies, similar to the human muscle (**Figure 2**).[3,4]

Perlrine et al. discovered that dielectric elastomers can exhibit a strain of over 100% when an electric field is applied.[2] Since that discovery a range of application in multiple fields like soft robotics and prosthetics have emerged. The thin membrane dielectric elastomer is the most important component of the DEAs. To be effective it must fulfill mechanical and electrical properties with appropriate elastic modulus, strength, breakdown resistance, low viscosity and high dielectric constant.[6] Three major materials used today for dielectric elastomers are polyurethanes (PU), acrylics, and silicones.[4] According to Peine et al. acrylics seems the most promising. One reason is that the 3M VHB acrylic elastomer (such as the most used VHB 4910 and VHB 4905) are commercially available at low cost. However, acrylics exhibit strong viscoelasticity, a property that can compromise the performance of DEAs.[7,8] Compared to acrylics, silicone DEAs exhibit less viscoelasticity operating with lower losses at higher frequencies, but with less actuation strains attainable, still outperforming PU.[4,9] Another favorable characteristic of the silicone elastomer is the resistance to stress softening with ageing (progressively decreasing elastic properties and performance due to mechanical actuation) enabling activation over more than 400 million cycles without breaking, compared to acrylics.[10–13] The disadvantage of the silicone based elastomer is the higher

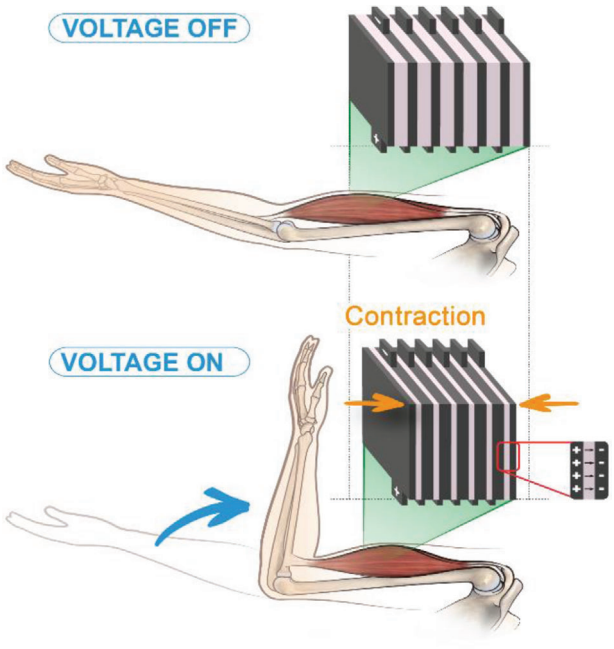

Figure 2. DEA working as artificial muscle.

electrical field needed to activate contraction, due to the low dielectric permittivity.[5] The actuation of a dielectric elastomer is given by the Maxwell pressure:

$$p_r = E^2 \varepsilon_0 \varepsilon_r \quad (1)$$

where E is the electrical field applied, $\varepsilon_0 = 8.854 \times 10^{-12}$ F m^{-1} is vacuum permittivity and ε_r is the relative dielectric permittivity of the thin elastomer calculated as $\varepsilon_r = \varepsilon'/\varepsilon_0$, where ε' is the real part of material's dielectric permittivity. This means that lower dielectric permittivity needs higher electrical field applied for the contraction. In fact, the dielectric permittivity of current dielectric elastomers ranges from 2 to 8. Dielectric permittivity of silicone elastomers is typically ≈2–3. This means that silicone elastomer, while it possesses superior mechanical properties compared to other dielectric elastomers, does not reach full potential due to the energy density being too low (low dielectric permittivity). The result is that the actuation strain of unstrained silicone dielectric elastomer is usually less than 15%, while elongations up to 300% should be realizable (if the elastomer electrically survives).[5] This can be compared to the human muscle strains of 5–30%.[14] Duduta et al. found that by stacking multiple layers of elastomers (UV-curable strain-stiffening elastomers) with ultrathin carbon nanotubes (CNT) the DEAs performance is close to the human muscle performance (0.4–40 J kg^{-1}) with an energy density peak of 19.8 J kg^{-1}.[14] This principle was reproduced by Behboodi et al. who produced an alternative robotic exoskeleton using stacked DEAs (SDEAS).[15] Kovacs et al. report that free-standing SDEAs without rigid support, have a performance similar in strain to human muscle without load (30%) and 10% with 1 kg load;[16] so, as the tensile load increases, the maximum contraction decreases. On the other hand, if DEAs are in different configurations, they reach less strain performances without load: 3% tubular,[17] 8% helical,[18] and folded 5%.[19] The analysis of the SDEAS produced by Kovacs made by Behboodi et al. reported that Kovacs's SDEA has similar performance to skeletal muscle from the point of view of the electromechanical delay (21 ms vs 54 ms of the skeletal muscle), power to mass (429.1 W kg^{-1} vs 200 W kg^{-1}), strain rate (660% s^{-1} vs 500% s^{-1}).[15] The cycle life appears to be sufficient at least for the specific application of the study (exoskeletons); however, according to Behboodi et al., the main issue of inferiority of Kovacs's SDEAS compared to skeletal muscle are the maximal longitudinal strain reached (>40% in the skeletal muscle and 3.3% with 80 g load, importantly lower than that reported by Kovacs et al). The difference may be attributed to the testing machines used, as stated by Behboodi,[15,16] and to the axial Young's modulus (0.87 mPa vs 10–60 mPa for the skeletal muscle);[15] this suggests to solve the problem through different design or pre-straining the DEAs that compose the SDEAS for improving isotonic contraction. Previous work focuses on the important issue of the high-voltage required for the contraction of this kind of actuator and how that limits clinical application;[20] they show how with thin slices of silicone (0.3 mm) an actuation strain of 7.5% of the total length of the actuator is obtainable with 245 V, with a ratio of 125% kV^{-2}, the highest reported for DEA. This is an important result if compared to other DEAs like the one proposed by Nam et al. guaranteeing a strain of 20% even working at low voltages (10 V μm^{-1}) has a ratio of 7% kV^{-2} using high molecular weight polymethylvinylsiloxane as the actuator material.[21] The solution of using thin slices composing the SDEA seems to be confirmed when using 0.1 mm thick acrylic layers obtaining a contraction up to 35% with 500 V (**Table 1**).[22] A 50% DEA focal length change was reached in a 2020 study using a dielectric elastomer combined with an ionogel composing the conductive part, to reproduce a human eye.[23] Despite application in the optical field there was a lack of data on mechanical performance with loads applied as required for artificial muscle.

2.2. The Neuromuscular Interface with Nanostructured Carbons

A human muscle contracts in response to an impulse transmitted from the nervous system to the muscle fibers through the neuromuscular interface. If the muscle or the nerve is lost or dysfunctional, the neuromuscular interface needs to be restored. Nanostructured carbons are considered a potential solution for this;[24,25] nanostructured carbons are carbon allotropes that include fullerene, graphene/graphene oxide, CNTs, carbon quantum dots, and nanodiamonds. They show promising properties for being used in different applications including biomedicine for biosensing, bioimaging, and drug delivery.[24,25] Considering potential application for simulating a human neuromuscular interface, CNTs offer an efficient electrical contact to transfer impulses to trigger muscular prosthesis contraction.[26] CNTs are made of graphene arranged in a series of rolled up tubular structure of condensed benzene rings. They can be single walled (SWCNT) or in multiple coaxial tubes (MWCNT).[27] Considering a muscular prosthesis, Duduta et al. showed that silicone based dielectric elastomers with integrated CNT composite electrodes deliver similar performances to the human muscle in peak energy density contraction: 19.8 J kg^{-1} (0.4–40 J kg^{-1} in human).[14] In order to reach significant electromechanical performance, the electrodes for DEAs must be highly conductive, stretchable,

Table 1. Actuation properties of different types of artificial muscles compared with human muscle.

	Actuation strain [% of length/actuation voltage]	Energydensity [J kg^{-1}]	Electromechanical delay [ms]	Axial Young modulus	Power to mass [W kg^{-1}]	Strain rate [% s^{-1}]
Silicone DEA non-stacked	Up to 15%[5]	–	–	–	–	–
SDEAs	30%/3.5 kV,[16] 7%/245 V,[20] 20%/10 V um^{-1},[21] 35%/500 V[22]	19.8 J kg^{-1}[14]	21 ms[16]	0.87 mPa[16]	429.1 [W kg^{-1}][16]	660 [% s^{-1}][16]
SDEAs with loads	10% with 1 kg load,[16] 3.3% with 80 g load[15]	–	–	–	–	–
Tubular DEAs	3%[17]	–	–	–	–	–
Helical DEAs	8%[18]	–	–	–	–	–
Folded DEAs	5%[19]	–	–	–	–	–
Human muscle	5–30%,[14] >40%[15]	0.4–40 J kg^{-1}[14]	54 ms[16]	10–60 mPa[16]	200 [W kg^{-1}][16]	500 [%/s][16]

compliant, and capable of sustaining a large number of actuation cycles.[28] The electrode has to remain functional at high grade strain to be effective. SWCNT composite electrodes have been reported to conduct up to 700% linear strain,[25] making them suitable for use as the electrode for muscular prosthesis. It has been shown that prestraining the film further improves the performance of silicone and acrylic based actuators.[26] Pelrine et al. reached dielectric membrane length deformation up to 117% with silicone elastomers and up to 215% with acrylic elastomers using biaxial and uniaxial prestrained films. The strain, response time and pressure of silicone elastomers overcame those of natural muscle; specific energy densities were greatly higher than those of other field-actuated materials.[29] An analysis of CNTs silicon rubber composites used as compliant electrodes has been published by Kim et al. showing that treating the SWCNTs with nitric acid can lower the sheet resistance (Rs) of the silicon rubber composite; the lowest Rs value (50 Ω sq^{-1}) exhibited by samples with 4 wt% of SWCNT content. This sheet resistance corresponds to a conductivity value of 63 S cm^{-1}. In addition, the composites maintain high conductivity after several tensile strains are applied. Stretching the composite sample up to 300% of its original length made the Rs value increasing to 320 Ω sq^{-1} (19 S cm^{-1}), showing that the strain of the treated silicone rubber decreases the conductivity of the material. Even after the 20th stretch/release/stretch cycle, the conductive properties of the composite containing nitric acid treated CNTs remain constant at a value of 18 S cm^{-1}, thus better than the untreated sample (≈5 S cm^{-1}). These results provide a scalable route for preparation of highly stretchable and conductive SWCNT composite with low concentrations of SWCNT.[30] In 2019, another study investigated the use of graphene and CNT composites for artificial muscle; in this case the authors used coiled graphene/CNT yarn; they showed that tensile actuation of these artificial muscles is 19%, two times larger than coiled bare CNT muscles, having a work capacity of 2.6 J g^{-1}.[31] In another 2019 study the authors used sheath-run artificial muscles (SRAMs) made of cheaper polymers other than using just CNTs (commercial nylon 6, silk, and bamboo yarns as the muscle core as well as electrospun polyacrylonitrile nanofibers) for comparing to CNTs hybrid yarns artificial muscle (HYAMs) performances (CNTs HYAMs are a type of artificial muscle composed by CNTs and polymers coiled together in order to produce contraction when activated).[32] The key finding was that comparing SRAMs made of PEO-SO3/CNTs to CNTs HYAMs, the former reached higher tensile strength. In this study SRAMs generated 1.98 watts g^{-1} of mean contractile power, that is, 40 times the average contractile power of human muscle.

2.2.1. Electro-Mechanical Integration

The promising results obtained regarding the mechanical properties and the electrical conductivity of nanostructured carbons composite electrodes must be coupled with effective electromechanical integration with the nervous system. This is a very important issue and solving the mechatronic integration problem might be the turning point for artificial muscle applications in the clinical setting. Despite the lack of in vivo results, the problem of a suitable contraction following a nervous system stimulation is nowadays addressed through two possible strategies in vitro: the seamless integration of neural tissue with conductive biomaterials and the wireless telemetric control using sensors recognizing residual muscles or nerves activation.[33]

Seamless Integration: Directly connecting an artificial muscle to the nervous system of a patient would restore the normal functional anatomy of the human body. Here we present strategies for directly connecting a nerve to a nanostructured carbon material. Nerve regeneration studies offer a range of options useful for studying the result of integration between the nervous system and nanostructured carbon materials. In combination with polycaprolactone (PCL) CNTs have been used for improving sciatic nerve repair showing good properties for nerve restoration (**Figure 3**).[34] Similar results have been obtained by Yu et al. showing that, without causing body rejection or severe chronic inflammation, the MWNT-enhanced collagen/PCL conduit could effectively promote nerve regeneration of a sciatic nerve defect in rats and as well preventing muscle atrophy.[35] Gupta et al. produced a scaffold of aligned MWCNT/chitosan stating that it could be considered a reliable option for peripheral nerve repair or in spinal cord injuries.[36] In the study reported, the scaffold allows HT-22 hippocampal neurites to regrow in an aligned manner. Aligned

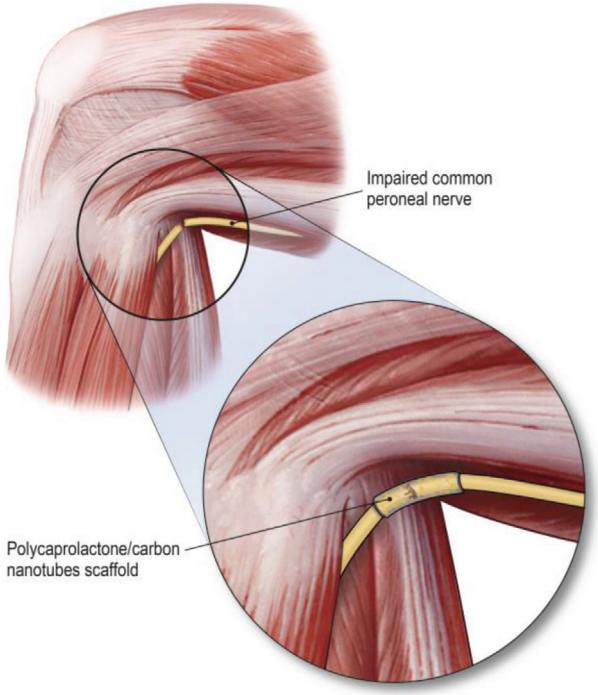

Figure 3. In human representation of how the PCL/CNT scaffold suggested by Assaf et al. could restore common peroneal nerve injury.[34]

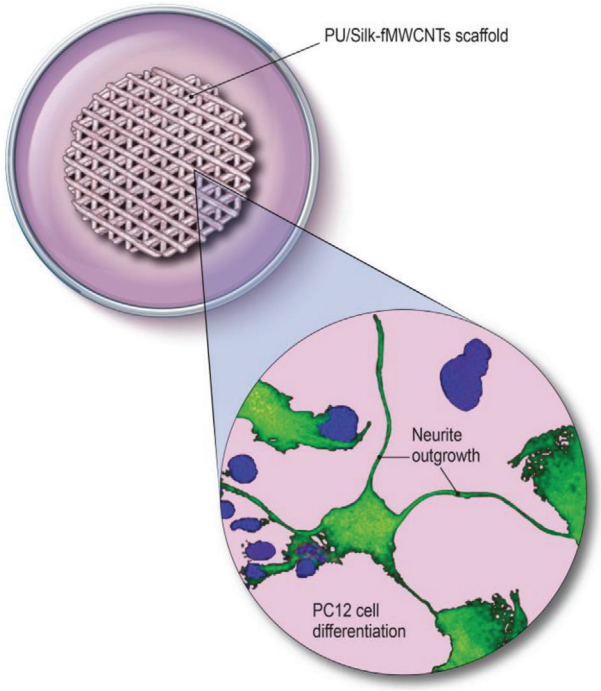

Figure 4. Schematic in vitro representation of PU/Silk-fMWCNTs scaffold inducing neurite outgrowth in rat pheochromocytoma PC12 cells.[37]

scaffolds have also been investigated by Shresta et al., finding an improvement in neural expression in vitro with success in axonal regrowth. They developed an electrospinning technique a fibrous scaffold, assimilating PU and silk fibroin in combination with functionalized multi-walled CNTs (fMWCNTs). The in vitro tests showed that the aligned scaffolds (PU/Silk-fMWCNTs) significantly induces the growth and proliferation of Schwann cells (S42) and the differentiation with spontaneous neurite outgrowth of rat pheochromocytoma (PC12) cells, guided along the axis of the aligned fibers (**Figure 4**).

The conductive scaffold made of PU/Silk-fMWCNTs significantly induces neural expression in vitro with success in axonal regrowth, that has been confirmed by qRT-PCR analysis and immunocytochemistry.[37] Another study compares two different kinds of scaffolds, showing that combining SWCNTs/Silk scaffolds with fibronectin, improves biocompatibility, nerve regeneration, and nerve conduction if compared to the SWCNTs/Silk scaffold alone.[38] Using the SWCNTs/Silk/Fibronectin nerve guide conduit in rats with impaired sciatic nerve, a nerve conduction velocity of 25 m s^{-1} was observed. This value is less than in a healthy animal (39.4±3 m s^{-1}), but clearly better than a conduction in an impaired nerve without a nerve guide conduit (5 m s^{-1}).[38] Fabbro et al. confirmed these results by finding good properties in neural tissue regeneration in vitro in organotypic spinal slices reproducing multilayer tissue complexity with CNTs.[39]

In a 2020 study,[40] the Authors integrate graphene with a 3D engineered skeletal muscle tissue using a 3D printed soft polyethylene glycol diacrylate (PEGDA) as the structural material. The use of PEGDA allows the electrical stimulus to be conducted from graphene to the muscle with various voltage and frequencies.[40] Graphene electrodes seems to be a reliable substrate for seamless neuronal integration by affecting neuron activity at a single-cell level; this provides an electrical coupling with natural nervous system, having an impact even on glutamatergic and GABAergic synaptogenesis, as well as on short-term synaptic plasticity.[41–43] Thus, graphene provides useful properties for use in a neuromuscular artificial interface. In particular its electrical conductivity can recognize and conduct the potential difference of the neuronal axon.[41–44] This could provide electrical communication between the natural nerve and the DEA with CNTs electrodes. To date, the gold standard for peripheral nerve injury reconstruction is the sensory nerve autograft, a technique in which nerve gap is bridged through microsurgical grafting of a donor nerve (usually, the donor nerve is the saphenous nerve, the medial cutaneous antebrachialis nerve or the sural nerve).[45–47] Normal function can be restored with less than 2 cm of gap, in patient younger than 25 years old and in reconstructions made no further than 2–3 months after trauma, due to the difficulty of promoting a proper axonal regrowth with grafting techniques.[46] Because of this, nanostructured carbons have been studied for nerve regrowth as well. This is useful because surgical techniques like neurorraphy can be used for treating just <5 mm nerve gaps,[36] and nanostructured carbons are nowadays investigated for treating larger gaps. For their electrical and mechanical properties they can be useful for seamless integration between the artificial muscle and an injured nerve for trauma's muscle and nerve injuries. The device-nerve system would benefit through nerve regeneration if the active part of the damaged nerve is too distant from the device for seamless communication. The effectiveness of these potential solutions may be compromised by the FBR following implantation. Pathophysiology of FBR and its

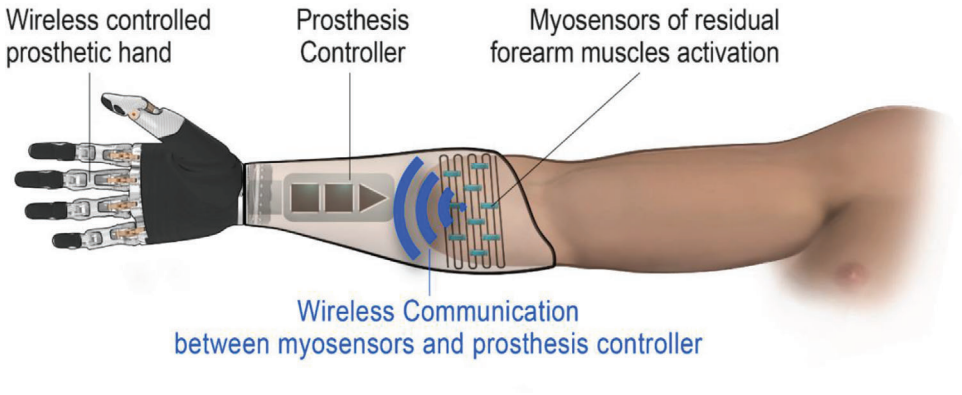

Figure 5. Wireless controlled external prosthesis schematic illustration.

consequences on device failure are presented in the section of the paper: 2.3. Strategies for avoiding FBR.

Wireless Control: To date wireless communications have been most widely used to control external prosthesis (**Figure 5**). An excellent demonstration is the study of Weir et al. who developed an external prosthesis for trans-humeral amputees.[48] They used biocompatible intramuscular implantable sensors (IMESs) to recognize the contraction of the amputated residual muscles. The activated sensor communicates via telemetric wireless control with the prosthesis controller providing contraction of the part of the prosthesis corresponding to the activated muscle. The telemetric communication of the sensor with the controller is possible through a transcutaneous magnetic link that eliminates the problems of the transcutaneous electrodes, mainly linked to infections; the same magnetic link wirelessly charges the sensor. The presence of an amplifier circuit allowed the electromyography (EMG) sensor signal to be amplified for providing a stronger prosthetic muscle contraction; for avoiding tissue lesions due to the increased voltage a tissue protector on the EMG sensor has been provided. The Authors tested the device by surgically implanting IMESs in the anterior tibialis and in the lateral gastrocnemius of cats that communicated with an external instrumented jacket covering the lower limb. After four months they still reported complete functionality of the prosthesis. Another study,[49] shows how intramuscular electrodes inserted into selected muscles can reduce the problems of external electrodes in recognizing and amplifying the signal of residual muscle contraction. In this case the electrodes were powered from an external source wirelessly. A reliable amplification multichannel system for implantable intramuscular sensors has been suggested in this paper in which application specific integrated circuit (ASIC) amplifiers provide a wireless amplification of the muscular contraction signal in dogs avoiding the crosstalk problem of external electrodes for myoelectric prosthetic control.[50] Important breakthroughs in prosthetic advancement have been made by DEKA Integrated Solution Corp. (DEKA) in developing more advanced prosthetics for limb amputee veterans. The DEKA arm uses external myoelectric sensors as electrodes;[51] the electrodes' signals are provided by residual muscle activation through EMG sensors. One of the most interesting strategies used for amplifying the muscle contraction signal is the targeted muscle reinnervation. This is a surgical technique in which residual nerves of the amputated muscles are attached to residual functional muscles providing a higher activation input, thus increasing the EMG signal for a better control of the prosthesis.[52] This surgical technique can be useful for the management of neuroma pain in amputee patients.[53] Considering clinical use for the neuromuscular artificial prosthesis and thus an internal implantation, the problem of charging the battery of the prosthesis is a major issue. One useful approach can be provided by cardiothoracic surgery, wherein charging the ventricular assisting devices without transcutaneous cables (increasing the risk of infection) is achieved using the transcutaneous energy transfer system.[54–56] This a transcutaneous energy transmission system that provides power to the internal Li-ion battery of the device; in this study it guarantees the set output driving voltage actuation of 40 V.[54] The same system found application in powering an artificial anal sphincter system.[57] The ASIC system has been used by others to implement an implantable wireless neural stimulator.[33] This work shows how an implantable neural stimulator can provide muscle contraction through external wireless telemetric control: the Authors encapsulated a 16 channel electrode into a nerve cuff attached to the rats' sciatic nerve providing muscle activation through sciatic nerve stimulation. Efficacy in telemetric communication and muscle activation was preserved even after 5 months of implantation.[58]

2.3. Strategies for Avoiding Foreign Body Response (FBR)

An artificial muscle implant will be exposed to a FBR. This needs to be tackled in order to preserve artificial muscle efficiency. Different biological reactions constitute the host reaction following the interaction between tissues and the implanted device: injury, provisional matrix formation (fibrin rich polymer with interspersed crosslinked fibronectin), acute and chronic inflammation, granulation tissue formation, and fibrosis/fibrous capsule development.[59–61] Blood-based transient provisional matrix formation on the surface of the device is the first reaction following implantation. The initial thrombus/blood clot surrounding the device involves systems of extrinsic and intrinsic coagulation, fibrinolysis, kinin-generating, and platelets. Despite the biomaterial is not vascularized, this phenomenon is triggered by the inflammatory response of the innate immune system following

injury to the blood supplied connective tissue by the implanted device.[62] Together these processes, that ultimately involve adsorption and desorption of proteins resulting in provisional matrix formation, are known as the Vroman Effect.[63] Due to the interaction between the surrounding tissues and the implanted device and the subsequent provisional matrix formation, acute and chronic inflammation occur.

Acute inflammation is mediated by neutrophils and by mast cells. They reabsorb fibrinogen and degranulate with release of histamine, interleukine-4 (IL-4), and interleukine-13 (IL-13); this mediates the acute response to the implanted biomaterial, with an important role in the subsequent FBR.[64,65] Chronic inflammation is on the other hand identified by the presence of mononuclear cells, that is, monocytes and lymphocytes, at the implant site. It's usually of short duration and it is confined to the site of implantation. Acute and chronic inflammation usually last no longer than two weeks if a biocompatible materials is used. If it lasts longer than three weeks this usually indicates an infection.[62] The resolution phase of acute and chronic inflammation is indicated by the presence of granulation tissue composed of macrophages, fibroblasts, and neovascularization in the new healing tissue. Granulation tissue is the precursor of the fibrous capsule that is forming at the surface of the device. A one- to two-cell layer of FBR cells consisting of monocytes, macrophages, and foreign body giant cells separates the granulation tissue from the implant or biomaterial.[62] The activation of macrophages involves the production of a large array of bioactive agents such as cytokines, interleukins, chemokines. A privileged microenvironment between the cell layer and the surface of the implanted materials is produced by the adhesion of macrophages and foreign body giant cells. As described by Henson with the definition of frustrated phagocytosis, those adhering cells release oxygen free radicals, degradative enzymes, and acid (mediators of degradation) in the microenvironment between cell layer and the surface of the device.[66,67] Even in this privileged microenvironment, materials are susceptible to high concentrations of these degradative agents with the resulting pH of the phagolysosome as low as 4.[68] The impact of these mediators of degradation on the material depends on composition and surface chemistry.[62] One of the problems in this cascade of events is that adherent cells are exhausted and incapable of further producing bactericidal molecules, due to the respiratory burst occurring after macrophage and foreign body giant cell adhesion. Moreover, the macrophages can be incapable of attacking foreign organisms that may be adherent to the biomaterial as the implant's surface can cause adherent cell apoptosis.[62,69] In cardiovascular devices, adherent inflammatory cell apoptosis has been described as a leading mechanism for the persistence of infection: in this case it's the shear stress given by the cardiovascular devices' surface to induce apoptosis.[70] Analyzing the impact of FBR on the functionality of the device, the molecular adhesion of macrophage and FBR giant cells results in clinical device failure.[62] Studies on PU have shown that at the basis of FBR and the subsequent device failure there is chronic inflammation with production of reactive oxygen free radicals as principal mediators of the device damage and failure; the use of corticosteroids in in vivo models was associated with increasing biostability of the device.[71] Other studies show antioxidants in PU can act as inhibiting agents to the oxidation process that occurs with the foreign body reaction.[72–75]

Many strategies have been studied to avoid or at least reduce FBR and subsequent clinical failure of implanted medical devices. In 2019 Farah et al. developed a formulation allowing long-term anti-inflammatory controlled-release.[76] High drug density formulations and very slow surface dissolution guaranteed by the compact lattice structure suppressed the FBR in both rodents and non-human primates for at least 1.3 years and 6 months, respectively. In particular, the colony stimulating factor 1 receptor inhibitor GW2580 has been used. They used it in various medical devices: muscle-stimulating devices, human islet microencapsulation systems and electrode-based continuous glucose-sensing monitors. They found that this approach inhibits fibrosis around the devices and concluded that local, long-term controlled release with the crystal formulations described provide a suitable solution to the FBR limitations improving and temporally extending functionality of implanted devices.[76] Blood glucose concentration sensors are a great example of long-term implanted devices. In previous work masitinib (inhibitor of mast cell-targeting tyrosine kinase) has been used to decrease the mast cell activation to prevent fibrosis of such devices and to preserve efficiency of performance;[77] masitinib was released from degradable polymer microspheres delivered from the surfaces of the implanted continuous glucose monitoring (CGM) system. The evaluation of the activity of the devices in a rat population over 21 days has indicated an improvement in performance with the masitinib treated group compared with non-treated, suggesting that activity of local tissue mast cell and fibroblast is affected by drug pharmacokinetics and dynamics. Similar results have been achieved during the acute phase of inflammation through the release of masitinib from the sensor implant to target tissue resident mast cells, considered as leading mediators of the FBR. A composite polymer hydrophilic matrix has been used to coat implanted CGM sensors. The polymer rapidly dissolves to release slower-degrading polymer microparticles containing masitinib. Compared to control implant sites, the resulting FBR in vivo, at 14, 21, and 28 days, displays statistically significant reduction in capsule thickness and inflammation cell density if masitinib-releasing composites were used.[78] Chung et al. in a review,[79] show how different biomaterials have different immunomodulatory effect on specific cells; for example, extracellular matrix (ECM) gel coating reduces macrophage activation,[80] or chitosan (useful for producing aligned CNTs scaffolds for nerve regeneration)[36] prolongs neutrophils recruitment through IL-8 pathway.[81] This study even considers the potential implication of the gut microbiome in FBR in distant site, hypothesizing an interaction between gut microbiome and the microenvironment surrounding the foreign body.

Recent advanced in materials and drug delivery are now providing solutions for reducing FBR.[82]

Size and shape of the material are important in modulating the immune response as underlined by Mariani et al.[83] Usually, sharp edges with no acute angles are more biocompatible and reduce inflammation: triangular shapes produce more enzymatic activity and circular shapes have the lowest enzymatic activity.[84,85] Considering shape and size, implanted spheres in rodents and non-human primates, show that larger spheres show reduction in FBR and fibrosis if compared with spheres with smaller diameters.[86] Considering the surface, this study concludes that the thickness of the capsule of the FBR depends on

the material and that increased porosity of the surface is linked with a reduced capsule thickness.[87] Madden et al. found an interesting correlation between porosity and macrophage switching to M2 anti-inflammatory type (instead of M1 pro-inflammatory type) in cardiac tissue engineering: after 4 weeks, pHEMA-co-MAA scaffolds, with ≈30 µm diameter of defined pore size, polarized macrophages to a M2 phenotype, thus reducing reaction capsule thickness and improving neovascularization;[88] however, it's not reported if this effect depends just on the density of pores on a given surface or also on the size of the pores. Increasing M2/M1 ratio is important in tissue remodeling and other studies found correlation between surface porosity of the material, M2 switching and reduced capsule thickness.[89–91] A previous work has been conducted on silicone elastomers and is relevant to the clinical application of muscular prosthesis.[91] Other studies analyze how nanoscale changes in the biomaterial's surface can influence the immune system;[92,93] M. Hulander et al. found that surface bound hydrophilic gold nanoparticles on the surface of the biomaterial seem to reduce immune-complement activation by suppressing the activity of IgG to activate the complement; this effect is diminished with increased hydrophobicity.[94]

Another strategy used to minimize FBR is immune isolation of the implant by "hiding" it in the ECM. In previous work polypropylene mesh covered by ECM had a reduced FBR, M1 macrophage and FB giant cells, with an increase ratio M2/M1 in macrophages;[80] also this study suggests a reduced foreign body reaction effect is obtained when implanted biomaterials are coated with ECM.[95] Sandor et al. coated tissue expanders with decellularized ECM; after implantation in subcutaneous space for nine months in non-human primates minimal capsule formation was identified.[96]

A drug delivery-based strategy has been proposed in different studies as already described above.[76–78] In other work the corticosteroid based therapy has been shown to inhibit TGF-beta formation, thus preventing fibrosis and neoangiogenesis.[97] In particular, dexamethasone has been used in drug-releasing devices designed to release over extended periods of time (3 months), reducing device fibrosis.[98,99] Reducing FBR through vasoconstrictor effect of epinephrine with subsequent decrease of neoangiogenesis, myofibroblasts concentration and capsule thickness has been investigated by Dolan et al. with dynamic actuation drug delivery in a rodent model. This system comprises an implanted drug delivery system that cyclically actuates release of epinephrine, with reduction of peri-implant capsule thickness if compared to the control group having the non-actuated drug delivery system implanted.[100] The use of Pirfenidone, a drug used in idiopathic pulmonary fibrosis, resulted in a 50% collagen reduction around the implant in a submammary implanted prosthesis study.[101] Another strategy used small interfering RNA (siRNA) for targeting major component of fibrosis capsule (COL1) showing reduction in capsule formation after 2 and 4 weeks in rodents and for targeting mTOR (a phosphorylating enzyme encoded by MTOR gene), but these in vitro were not sustained in vivo.[102,103]

Another new approach for reducing FBR consists in coating implanted biomaterials with zwitterionic materials to obtain very low fouling rates.[82] These studies present reduction in FBR rates in mice, using in particular carboxybetaine chemotype.[104–106] Another formulation with good results in vivo in reducing fibrosis and capsule formation was produced by coating CGM sensors with a dopamine conjugation.[107] It showed importantly higher levels of accuracy without any need for recalibration if compared to non-coated sensors over a three day period; usually CMG sensors remain accurate for just six days, because of the negative effect of the FBR on their function.[108]

Table 2. Comparison between acrylic and silicone rubber properties.

	ACRYLIC (VHB kinds)	SILICONE RUBBER
Cost	Lower	Higher
Viscoelasticities non linearities	Higher	Lower
Actuation strain	Higher	Lower
Stress softening with ageing	Higher	Lower
Dielectric permittivity	Higher	Lower

3. Combining Current Technologies for a Clinical Application

In order to reproduce a human muscle with an artificial neuromuscular prosthesis for a clinical application, a DEA with compliant CNT electrodes provides fast response times, long lifetime, good reliability, high energy efficiencies and large strains.[2–5,14,26,27] This technology comprises a layer of expandable biomaterial, coated by electrodes of opposite polarity on the two opposite sides of the layer (Figures 1 and 2). When a voltage is applied, the electrodes are attracted to each other, causing the compression of the layer in the tangential plane of the electrical attraction and expansion in the perpendicular plane (Figures 1 and 2). The key discussion at this point is about the material used as the expandable layer. The two main materials used are acrylic and silicone and their properties are summarised in **Table 2**.[4,7–14]

Despite having minimal viscoelastic nonlinearities,[7,8] silicone attains a lower actuation strain because of its lower dielectric permittivity.[5] For the Maxwell pressure equation: $p_r = E^2\varepsilon_0\varepsilon_r$, ε_r is the dielectric permittivity of the biomaterial and the lower that is, the higher the electrical field E required, to reach the same pressure. So silicone needs higher electrical field to attain the same actuation strain as acrylic materials, as it has a lower dielectric permittivity. Usually, the actuation strain of silicone is lower than 15%, compared to the 5–30% for human muscle.[14] This data suggests that acrylic and silicone are both suitable for reproducing human muscle and considering the comparison of all their properties no one of them seems to be clearly better than the other even if silicone appears to have more reliable mechanical properties over longer actuation periods.

As suggested in Table 2, currently produced DEAs exhibit strains lower in comparison to human muscles, moreover, needing high voltages to actuate (Table 2). These performances make currently produced DEAs unable to reproduce human muscle efficiency. To improve mechanical properties in actuation and to lower the electrical voltage needed for actuation of the DEA the use of stacked multiple layers interspersed with electrodes (Figure 2) has been investigated.[14–16] The electromechanical compression of the different single layers creates the contraction on the length of the definitive DEA, simulating the contraction of

the human muscle. This can be explained by the capacitance law in which every single layer can be considered a single capacitor:

$$C = \varepsilon \cdot \frac{A}{d} \tag{2}$$

where C is the capacitance, so the property of accumulating electrical charge at the opposite faces of the layer. In a dielectric elastomer this causes the compression of the layer due to the attraction of the opposite charged electrodes. A is the area of the layer, d is the distance between the electrodes (the thickness of the layer) and ε is the dielectric permittivity of the layer. It is clear that the smaller the distance between the electrodes, the easier it is for the layer to contract; so reproducing this principle with 3 mm stacked layers composing the DEA, instead of having just one single layer, enables mechanical performances similar to human muscle.[14] The high voltages needed for current DEA could result in harmful conditions for soft tissue and for the patient. An important potential solution for addressing this important issue is the insulation of the conductive materials of the prosthesis. A recent 2018 study suggest interfaces made of polyethylene/metal oxide nanocomposites for high voltage insulation materials with promising results. This may be useful even for a neuromuscular prosthesis due to the biocompatibility of polyethylene and metal oxide.[109] A liquid silicone rubber filled with SiC particles has also been used for high voltage cables insulation and it could be considered a reliable solution for use in neuromuscular prosthetics.[110] These solutions, apart being useful for clinical safeness of the device, could allow to reach higher voltages if needed for appropriate actuation.

The loss of the muscle or its dysfunction needs the restoration of the neuromuscular interface to be tackled. Literature reports on the high conductivity of CNT based electrodes and that they can be used as a reliable technology for artificial muscle functioning as artificial neuromuscular interface are promising.[14,24,26,27] These electrodes remain conductive even at high strain and this is relevant if we consider that prestretching acrylic or silicone layers improves the mechanical properties of the DEA.[25,26] It is not yet clear if single-walled CNTs have better performances than multi-walled CNTs, but single-walled CNTs have been used in more studies compared to multi-walled,[14,26,27,31,32] with authors positive about their application in artificial muscle. Two potentially useful technical aspects involved in production of DEAs using CNTs seem to be the doping of the SWCNTs by nitric acid and using SRAMs instead of HYAMs.[27,32] The first approach significantly lowers the sheet resistance (Rs) of the silicon rubber composite when it has to contract and this is important to improve the contractile performance of the DEA; the other technique, using SRAMs, allows more tensile strength compared to using HYAMs and this can be relevant to consider during the production of the DEA; in particular SRAMs made of PEO-SO3/CNTs reached 40 times the contractile power of a human muscle.

So, stacking multiple elastomers to create the DEA,[14–16,20] as well as prestretching each layer,[26] doping the silicone with nanosilica,[24] or using CNTs as compliant electrodes,[14,24,26,27] can improve the mechanical properties of the DEA, thus requiring lower voltages to actuate. This is of great importance because the electromechanical compatibility and integration between the electrical system and the DEAs is probably the main issue to face for an in vivo application. Actuators in silicone, despite having the most suitable mechanical properties for reproducing human muscle,[10–13] suffer of low dielectric permittivity due to the intrinsic properties of silicone thus requiring high voltage for their actuation.[5] The operating driving voltages needed for dielectric elastomers of 10–100 µm in thickness range from 500 V to 10 kV,[9,111] thus limiting DEAs' application. It is clear that the driving voltage generated in the artificial muscle electrical system by the potential difference of the nerve must be greater than the driving voltage threshold required for functional actuation. This study provides clear data that silicone elastomers 3 µm thick can actuate at voltage values lower than 300 V,[20] however strategies like stacking the elastomers, prestretching the layers, doping the silicone and using CNT electrodes may allow the driving voltage to be even lower. On the other side, other than working on elastomer properties, an amplification of the voltage could be useful for providing a sufficient driving voltage. In a clinical setting, in terms of completely substituting a human muscle keeping the possibility to contract the artificial muscle under the cerebral cortex activation, the driving voltage is primarily provided by the natural peripheral nerve. Two potential ways for linking the natural nerve to the DEA's CNTs electrodes have been suggested: seamless integration or wireless communication. The seamless biological and electrical integration of graphene with peripheral nerve is technically possible,[30,31,37–39] the nerve potential difference (ranging between −40 and −90 mV) is insufficient to actuate a dielectric elastomer. The amplification systems used in external prosthesis may provide reliable solution. As shown, they work through internal myoelectric sensors for recognizing nerve activation more precisely than with external electrodes.[30,31,37–39] There are no data in using electroneuronography (ENG) instead of EMG in external prosthesis control; for completely substituting a muscle, ENG could be more useful if the natural muscle must be surgically excised making impossible to have an EMG signal; in this case, ENG sensors should be used.[112,113] As described previously, use of a wireless amplification system to communicate with an external prosthesis (residual muscle activation signal–sensor–wireless communication with amplifier–signal amplification–external prosthesis controller) can reach a sufficient voltage to actuate the external myoelectric prosthesis.[48–51] This same approach should be applicable to artificial muscles implants. It would shift the challenge from mechanoelectrical compatibility and integration to a biocompatibility issue. The latter as dealt with in the next section "Strategies for avoiding FBR". Thus, if this system is applied to internal prosthesis, it should be able to make an internal artificial muscle contract under cerebral cortex stimulus.

The use of a DEA as an implantable artificial muscle requires an energy source. The circuit connecting the battery and the electrodes needs to be in parallel as shown.[14] For charging the implantable battery, an external charger can provide wireless charging as suggested in previous studies through a magnetic field creating a voltage in a solenoid battery.[48–50] When the nerve activation is recognized by the internal ENG sensor, the wireless communication activates the controller. The controller then keeps the circuit of the battery closed for the whole duration of the nerve activation. When the patient no longer needs to activate that specific muscle, the ENG sensors stop activating the

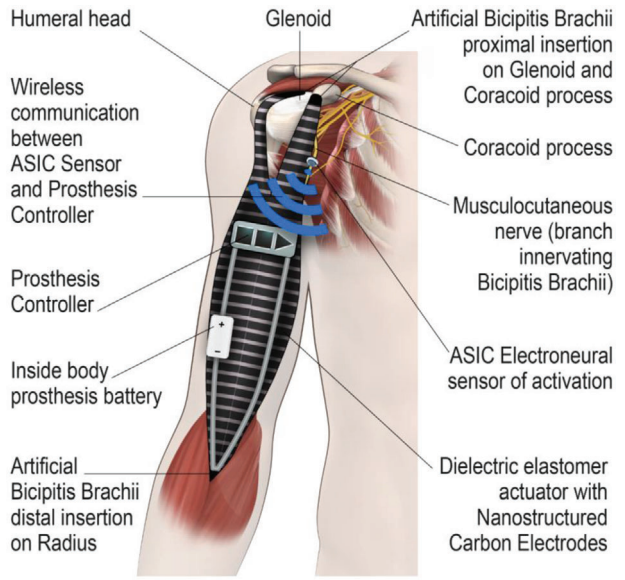

Figure 6. Wireless controlled neuromuscular prosthesis schematic illustration through peripheral nervous system activation.

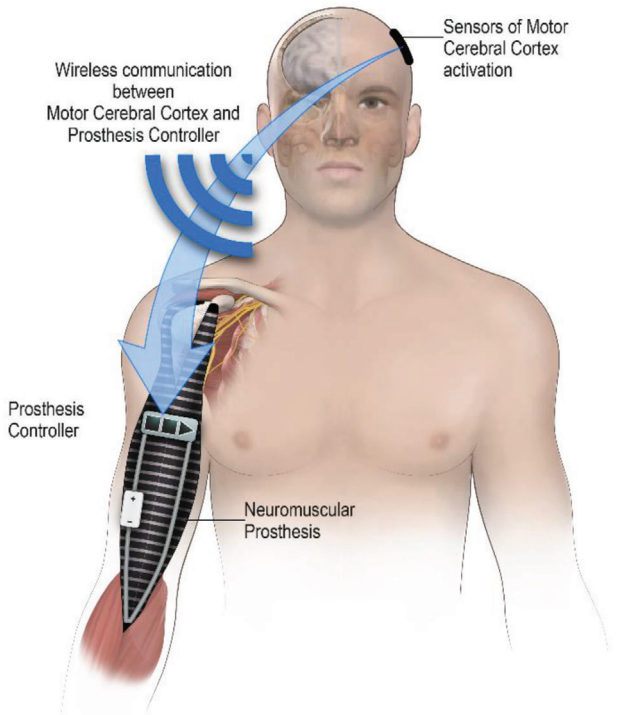

Figure 7. Wireless controlled neuromuscular prosthesis schematic illustration through direct central nervous system activation.

controller; and the circuit in the battery is open again, resting the DEA contraction (**Figure 6**).

Other than being used as electrodes for artificial muscles or as electrical component at the opposite faces of the layer in a DEA that works as a capacitor, CNTs have been proposed as biomaterials for nerve tissue restoration. This is a key point for this review: the neural restoration properties of CNTs might allow communication between impaired human tissue and artificial neuromuscular prosthesis in future. Impaired nerve conduit guides based on CNT scaffolds, combined with PCL,[30,31] PU,[37] silk,[37,38] and fibroin/fibronectin,[37,38] allow nerve regrowth and improve nerve conduction.[30,31,37–39] To avoid random neurite regrowth, directional regrowth can be reached by using aligned MWCNT scaffolds.[36,37] All these results show how CNTs, other than having good properties for DEAs compression and expansion, can be useful for regenerating peripheral impaired neural tissue.

CNTs can even be used in the future to completely bypass the peripheral nervous system. Actually, they show suitable properties for recording neural activity of cerebral cortex neurons.[114–118] Through a pattern recognition system of cerebral cortex activation, this could be useful for wireless communication with other peripheral muscle actuation devices, thus providing actuation of a muscle bypassing the peripheral nerve activation or wireless activating the residual peripheral nerve as shown by Ortega et al.[33] This approach could be useful in spinal cord injuries, peripheral neuropathies and for controlling prosthetic limbs in amputee patients (**Figure 7**), in which the clinical problem is not the muscle itself, but the impaired communication for receiving the signal to contract. Emerging trends of wireless implantable neural interfaces for neuromodulation and/or neuroprosthetics are also presented in a 2020 paper by Won et al.: free-battery electrodes operating for data transmission or stimulation on nervous system, functioning through wireless or Bluetooth, could potentially be a suitable neural interface for peripheral prosthetic control.[119]

A pioneering 2019 study shows how the epidural recording of cerebral cortex activity with the use of artificial intelligence and wireless communication with peripheral exoskeleton actuators can be a reliable brain-machine interface; in the study, a quadriplegic is able to move by controlling the external total body exoskeleton with the cerebral cortex.[120]

With the aim of developing an artificial neuromuscular prosthesis for a human clinical application the FBR to the implanted device/structure is an issue to be confronted. There are three main strategies for reducing FBR to implanted biomaterials and they should be considered for producing devices that generates less FBR and eventually combined for producing a biocompatible neuromuscular prosthesis:

1) Different sizes and shapes produce different FBR and prosthesis design should follow these principles: usually edges without acute angles are more biocompatible and reduce the inflammation response, maybe due to the tissue damage caused by the friction against an acute edge.[84,85] If the biomaterial is spherical, larger diameter reduce FBR.[86] The porosity of the material influences capsule thickness: increasing the porosity of the biomaterial reduces the FBR.[87–91] This should be considered in the manufacturing process of dielectric elastomers. In this study,[91] results were found in silicone elastomers, so that they can be considered suitable results for developing DEAs that produce less FBR in neuromuscular prosthesis. Adding gold particles to an elastomer surface, as proposed in this study,[94] could be another solution for reducing

FBR for clinical useful DEAs, but it is not clear if gold particles can affect the electrical activity of the DEA.

2) Implanted devices can be hidden in different ways to minimize the FBR: coating the device with ECM shows minimal capsule fibrosis in three separate studies and this should not interfere with actuation if applied to dielectric elastomers;[80,95,96] this can be considered a good solution for clinical use of DEAs, as the coating with ECM should not impair the performance of the elastomer, preserving the ability to contract and expand. Sandor et al. studied performance over a nine month period. Other studies should analyze longer period of implantation with ECM coating; anyway, in this study a minimal capsule formation was found after nine months. Considering that the capsule usually forms in the first weeks after the implantation and that the ECM matrix should remain coating the device without being reabsorbed, the results obtained in the nine months observation period of the Sandor et al.'s study can be reasonably extended to a longer period. ECM should not be reabsorbed as natural component of microenvironment external to tissues; in alternative to ECM, zwitterionic biomaterials have been studied for device coating for their property to show very low fouling rates.[82] Carboxybetaine chemotype seems a suitable zwitterionic material in three separate studies,[104–106] and other results in vivo showed reduced fibrosis and capsule formation after coating CGM sensors with a dopamine conjugation.[107] These studies provide results that zwitterionic biomaterials can be a suitable solution for coating implantable devices and further studies could investigate any potential interfering effect of zwitterionic materials on actuators.
3) Anti-fibrotic drugs and pharmaceuticals can be released or administered in different ways for reducing FBR: GW2580 and masitinib have been studied through crystal polymers or microspheres coating the surface of the biomaterial slowly releasing the drug.[76–78] These studies show how the delivery of pharmaceuticals and biomolecules on the surface of the biomaterial succeeds in reducing FBR in murine and primate models; but If we think about a long term in vivo application for neuromuscular prosthesis implantation in human they lack of results in long term periods (maximum 1.3 years, 21 days, and 28 days, respectively and maximum 6 months in Farah et al.'s primate model); moreover, they considered static devices, not contractile like a muscular prosthesis has to be, making fibrosis of it a severe impairment for its functionality. Considering dexamethasone delivered on the surface of the device by PLGA (polylactic-co-glycolic acid) microspheres/PVA (poly-vinyl alcohol) hydrogel composites, even Bhardwaj et al.'s study suffers of a short period analysis and the reduction of FBR is limited to the period of drug administration;[98] anyway in three months observation period fibrosis has been prevented on the surface of the devices confirming that drug slow release can be a good strategy to develop for reducing FBR in a neuromuscular prosthesis. The same results in preventing fibrosis have been reached by this study with pirfenidone in murine models;[101] the problem of this strategy, although the good property of inhibiting fibrosis, is that the drug has not been slowly released on the surface of the device through microspheres or hydrogel, but administered systemically. Considering a long term implantation, a systemic treatment with a drug for preventing fibrosis can have collateral effects due to the drug itself. So, a local drug release seems to be a more suitable option to choose, but literature lacks of comparison between the two strategies on the long term period. A different strategy suggested in this study had good result in preventing fibrosis through the use of siRNA targeting COL1 (the major component of fibrosis capsule). It is an interesting approach because siRNA should hypothetically act without having the side effects of the drugs, but the study has been conducted over a maximum period of 4 weeks, too short for understanding if it can be reliable for inhibiting FBR in a long term implanted muscular prosthesis in human.[102]

3.1. Clinical Scenarios

This review has been presented with clinical applications in mind, so here we suggest different clinical scenarios and future perspectives in which neuromuscular prostheses could be used to replace the function of natural muscle and provide a therapy for different neuromuscular diseases.

3.1.1. Bone Tumors

For patients with distal femur osteosarcoma invading vastus intermedius and rectus femoralis the standard treatment is a resection total knee arthroplasty (TKA) following the excision of the affected part of the femur. For oncological reasons, the two invaded muscles need to be resected; they usually are resected with safety margins of at least 2–5 cm from the affected part, with severe impairment of extensor function. So, in a neuromuscular prosthesis implanting scenario, after the implantation of the resection TKA, the two affected muscles are detached from their insertion (on the anteroinferior iliac spine for rectus femoralis and from the femur diaphysis for vastus intermedius proximally and on the superior part of the patella distally). After being detached, and before being completely excised, the two muscles need to be deafferented from the femoral nerve branches that innervate them. In this case just the rectus femoralis needs to be replaced to provide a good extensor function. So, a silicone made neuromuscular prosthesis with CNT electrodes, coated with ECM matrix is attached with trans osseous stitches to the anteroinferior iliac spine and to the superior margin of the patella. Internal ENG sensors are placed in proximity of the previously deafferented femoral nerve branches for signal recognition and activation. The artificial muscle battery is placed superficially to the muscle, under the subcuticulous tissue to be as near as possible to the external wireless charger. After this, the surgical replacement of a natural muscle with a neuromuscular prosthesis is completed. From now on, the patient, activating the part of the cerebral cortex implied in the extension of the knee, would produce a potential difference in the femoral nerve branches recognized by the internal ENG sensors; the sensors activate the prosthesis controller closing the circuit of the battery-artificial muscle systems providing the extensor actuation needed.

3.1.2. Traumas

Consider blunt trauma in the anterior part of a patient's arm with complete impairment of the flexor muscles of the arm, in particular bicipitis brachii and brachialis. The surgical procedure would follow the same principles presented in the first case, with complete excision and deafferentation from the musculocutaneous branches of the impaired muscles and the implantation of the neuromuscular prosthesis for re-establishing flexor function. In this case the proximal insertion of the DEA should be on the anterior and superior structures of the scapula or in the anterior face of the humerus and the distal insertion on the proximal part of radius or ulna.

3.1.3. Muscular Genetic Disorders

Duchenne muscular dystrophy causes muscle dysfunction for a genetic mutation in dystrophin, present in muscle fibers. One of the group of muscles more affected are the pelvic girdle stabilizers, in particular the gluteus muscles, causing the impossibility for patients to walk since the early adolescence. Replacing the gluteus muscle group with a neuromuscular prosthesis could be a suitable solution for keeping the ability to walking to these patients. In this case the proximal insertion of the artificial muscle should be on the lateral and posterior part of the iliac crest or of the iliac bone until the lateral margin of the sacrum, and the distal insertion on the lateral part of greater trochanter of the femur and on the gluteal tuberosity in the posterior part of the femur.

3.1.4. Sarcopenia in Elderly Patients

The progressive muscle atrophy with ageing is linked with disability problems due to the difficult to keep moving and walking. The replacement with artificial muscle of pelvic girdles stabilizers and feet plantar flexors, for their important role in lower limb biomechanics, could improve the disability problems linked to muscle atrophy.

3.1.5. Iatrogenic Nerve Impairment

In orthopedic surgery, one of the major nerve complications is the lesion of the common peroneal nerve in its superficial location under the peroneal head. Its motor function is to innervate tibialis anterior, extensors digitorum, and peroneal muscles, providing dorsiflexion and pronation of the foot. A lesion of the common peroneal nerve results in the impossibility to dorsiflex and pronate the foot. A graphene scaffold coating the impaired nerve could be a suitable therapy for re-establishing functionality.

3.1.6. Spinal Cord Injury

Patients suffering spinal cord injuries can potentially have their motor function restored with the wireless communication between the cerebral cortex external activation sensors and the peripheral sensors implanted in the impaired muscles triggering muscle contraction. Every impaired muscle should have at least a sensor contraction trigger wirelessly connected with the cerebral cortex external activation sensor specific for the activation of that muscle. In this case the leading problem is nerve connections, so a replacement of the muscle would not be needed, unless the muscle is atrophic for disuse.

3.1.7. Amputations

Sarcoma of the thigh muscles invading femoral vascular-nerve bundle. The standard orthopedic treatment in this case would be the amputation of the thigh at a proximal level from the lesion or the hip disarticulation. Replacing the whole amputated anatomical part with a 3D printed bone structure and with muscular tissue functioning as a neuromuscular prosthesis could be a suitable solution in the future. As in the previous case, the neuromuscular prosthesis could receive the wireless actuation input through cerebral cortex activity recording sensors.

4. Conclusion

As we strive to reproduce the mechanical performance of human muscle silicone DEA with CNT electrodes provide an attractive possibility. The electromechanical performance is impressive and in some studies the results obtained are similar to those with human muscle. CNT-based electrodes provide effective integration with the dielectric elastomer layer ensuring optimal performance. Further optimization of elastomer composition and the use of a wireless amplification system of natural nerve activation voltage provide avenues to allow the voltage needed for DEA actuation to be reduced and electrical compatibility to be enhanced. Every biomaterial used in vivo will suffer from a FBR. Choosing the right size and shape of the device, hiding the biomaterials with ECM or zwitterionic materials and releasing antifibrotic agents are strategies used to reduce the FBR. Considering the state of the art, an artificial neuromuscular prosthesis could be an effective solution for replacing natural muscle in musculoskeletal oncological related impairments, neuromuscular diseases, traumas, and spinal cord injuries. Mechatronic compatibility between the natural nerve and the DEA is still the major limitation for a clinical application. Despite this, we believe that combining the mechanical and electrical solutions proposed here, the artificial neuromuscular prosthesis may be a reality in the surgical practice in the very near future.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

artificial muscles, carbon nanotubes, dielectric elastomer actuators, foreign body response, graphene

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[1] S. M. Mirvakili, I. W. Hunter, *Adv. Mater.* **2018**, *30*, 1704407.
[2] R. Pelrine, *Science* **2000**, *287*, 836.
[3] Y. Qiu, E. Zhang, R. Plamthottam, Q. Pei, *Acc. Chem. Res.* **2019**, *52*, 316.
[4] G. Y. Gu, J. Zhu, L. M. Zhu, X. Zhu, *Bioinspiration Biomimetics* **2017**, *12*, 011003.
[5] F. B. Madsen, A. E. Daugaard, S. Hvilsted, A. L. Skov, *Macromol. Rapid Commun.* **2016**, *37*, 378.
[6] S. Bauer, S. Bauer-Gogonea, I. Graz, M. Kaltenbrunner, C. Keplinger, R. Schwödiauer, *Adv. Mater.* **2014**, *26*, 149.
[7] W. Hong, *J. Mech. Phys. Solids* **2011**, *59*, 637.
[8] C. Chiang Foo, S. Cai, S. Jin Adrian Koh, S. Bauer, Z. Suo, *J. Appl. Phys.* **2012**, *111*, 034102.
[9] P. Brochu, Q. Pei, in *Electroactivity in Polymeric Materials*, (Ed: L. Rasmussen), Springer, Boston, MA **2012**, p. 1.
[10] R. D. Kornbluh, R. Pelrine, Q. Pei, R. Heydt, S. Stanford, S. Oh, J. Eckerle, in *Smart Structures and Materials 2002: Industrial and Commercial Applications of Smart Structures Technologies*, SPIE, Bellingham, WA **2002**.
[11] L. Maffli, S. Rosset, M. Ghilardi, F. Carpi, H. Shea, *Adv. Funct. Mater.* **2015**, *25*, 1656.
[12] R. Kornbluh, A. Wong-Foy, R. Pelrine, H. Prahlad, B. McCoy, *MRS Online Proc. Libr.* **2010**, *803*, 1262.
[13] S. Rosset, M. Niklaus, P. Dubois, H. R. Shea, *J. Microelectromech. Syst.* **2009**, *18*, 1300.
[14] M. Duduta, E. Hajiesmaili, H. Zhao, R. J. Wood, D. R. Clarke, *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 2476.
[15] A. Behboodi, S. C. K. Lee. *IEEE Int Conf Rehabil Robot*. June **2019**, pp. 499–505.
[16] G. Kovacs, L. Düring, S. Michel, G. Terrasi, *Sens. Actuators, A* **2009**, *155*, 299.
[17] R. Sarban, R. W. Jones, B. R. Mace, E. Rustighi, in *Int. Conf. on Noise and Vibration Engineering 2010 (ISMA 2010)*, Leuven, Belgium, September **2010**.
[18] F. Carpi, A. Migliore, G. Serra, D. De Rossi, *Smart Mater. Struct.* **2005**, *14*, 1210.
[19] F. Carpi, C. Salaris, D. De Rossi, *Smart Mater. Struct.* **2007**, *16*, S300.
[20] A. Poulin, S. Rosset, H. R. Shea, *Appl. Phys. Lett.* **2015**, *107*, 244104.
[21] S. J. Dünki, Y. S. Ko, F. A. Nüesch, D. M. Opris, *Adv. Funct. Mater.* **2015**, *25*, 2467.
[22] S. Rosset, H. R. Shea, *Appl. Phys. A: Mater. Sci. Process.* **2013**, *110*, 281.
[23] B. Chen, W. Sun, J. Lu, J. Yang, Y. Chen, J. Zhou, Z. Suo, *J. Appl. Mech.* **2020**, *88*, 031016.
[24] T. K. Gupta, P. R. Budarapu, S. R. Chappidi, S. S. Y. B., M. P., S. P. Bordas, *Curr. Med. Chem.* **2019**, *26*, 6851.
[25] H. Wang, Q. Chen, S. Zhou, *Chem. Soc. Rev.* **2018**, *47*, 4198.
[26] B. Wang, A. Facchetti, *Adv. Mater.* **2019**, *31*, 1901408.
[27] M. I. Sajid, U. Jamshaid, T. Jamshaid, N. Zafar, H. Fessi, A. Elaissari, *Int. J. Pharm.* **2016**, *501*, 278.
[28] Z. Yu, X. Niu, Z. Liu, Q. Pei, *Adv. Mater.* **2011**, *23*, 3989.
[29] R. Pelrine, R. Kornbluh, Q. Pei, J. Joseph, *Science* **2000**, *287*, 836.
[30] T. A. Kim, H. Kim, S. S. Lee, M. Park, *Carbon* **2012**, *50*, 444.
[31] J. S. Hyeon, J. W. Park, R. H. Baughman, S. J. Kim, *Sens. Actuators, B* **2019**, *286*, 237.
[32] J. Mu, M. J. De Andrade, S. Fang, X. Wang, E. Gao, N. Li, S. H. Kim, H. Wang, C. Hou, Q. Zhang, M. Zhu, D. Qian, H. Lu, D. Kongahage, S. Talebian, J. Foroughi, G. Spinks, H. Kim, T. H. Ware, H. J. Sim, D. Y. Lee, Y. Jang, S. J. Kim, R. H. Baughman, *Science* **2019**, *365*, 150.
[33] P. Troyk, S. Bredeson, S. Cogan, M. Romero-Ortega, S. Suh, Z. Hu, A. Kanneganti, R. Granja-Vazquez, J. Seifert, M. Bak, in *2015 7th Int. IEEE/EMBS Conf. on Neural Engineering (NER 2015)*, Annu Int Conf IEEE Eng Med Biol Soc, Montpellier, France, April **2015**.
[34] K. Assaf, C. V. Leal, M. S. Derami, E. A. de Rezende Duek, H. J. Ceragioli, A. L. R. de Oliveira, *Brain Behav.* **2017**, *7*, e00755.
[35] W. Yu, X. Jiang, M. Cai, W. Zhao, D. Ye, Y. Zhou, C. Zhu, X. Zhang, X. Lu, Z. Zhang, *Nanotechnology* **2014**, *25*, 165102.
[36] P. Gupta, D. Lahiri, *Neural Regener. Res.* **2016**, *11*, 1062.
[37] S. Shrestha, B. K. Shrestha, J. Lee, O. K. Joong, B.-S. Kim, C. H. Park, C. S. Kim, *Mater. Sci. Eng., C* **2019**, *102*, 511.
[38] F. Mottaghitalab, M. Farokhi, A. Zaminy, M. Kokabi, M. Soleimani, F. Mirahmadi, M. A. Shokrgozar, M. Sadeghizadeh, *PLoS One* **2013**, *8*, e74417.
[39] A. Fabbro, A. Villari, J. Laishram, D. Scaini, F. M. Toma, A. Turco, M. Prato, L. Ballerini, *ACS Nano* **2012**, *6*, 2041.
[40] Y. Kim, G. Pagan-Diaz, L. Gapinske, Y. Kim, J. Suh, E. Solomon, J. F. Harris, S. W. Nam, R. Bashir, *Adv. Healthcare Mater.* **2020**, *9*, 1901137.
[41] N. P. Pampaloni, D. Scaini, F. Perissinotto, S. Bosi, M. Prato, L. Ballerini, *Nanomedicine* **2018**, *14*, 2521.
[42] G. Cellot, F. M. Toma, Z. K. Varley, J. Laishram, A. Villari, M. Quintana, S. Cipollone, M. Prato, L. Ballerini, *J. Neurosci.* **2011**, *31*, 12945.
[43] G. Cellot, E. Cilia, S. Cipollone, V. Rancic, A. Sucapane, S. Giordani, L. Gambazzi, H. Markram, M. Grandolfo, D. Scaini, F. Gelain, L. Casalis, M. Prato, M. Giugliano, L. Ballerini, *Nat. Nanotechnol.* **2009**, *4*, 126.
[44] E. Abbasi, A. Akbarzadeh, M. Kouhi, M. Milani, *Artif. Cells, Nanomed., Biotechnol.* **2016**, *44*, 150.
[45] T. Matsuyama, M. Mackay, R. Midha, *Neurol. Med. Chir.* **2000**, *40*, 187.
[46] D. P. Kuffler, C. Foy, *Int. J. Mol. Sci.* **2020**, *21*, 1808.
[47] D. P. Kuffler, *Prog. Neurobiol.* **2014**, *116*, 1.
[48] R. F. Weir, P. R. Troyk, G. A. DeMichele, D. A. Kerns, J. F. Schorsch, H. Maas, *IEEE Trans. Biomed. Eng.* **2009**, *56*, 159.
[49] P. A. Lichter, E. H. Lange, T. H. Riehle, S. M. Anderson, D. S. Hedin, in *Ann. Int. Conf. of the IEEE Engineering in Medicine and Biology Society*, IEEE, Piscataway, NJ **2010**, p. 5074.
[50] D. McDonnall, S. Hiatt, C. Smith, K. S. Guillory, in *Ann. Int. Conf. of the IEEE Engineering in Medicine and Biology Society*, IEEE, Piscataway, NJ **2012**.
[51] L. Resnik, S. L. Klinger, K. Etter, *Prosthet. Orthot. Int.* **2014**, *38*, 492.
[52] T. A. Kuiken, G. Li, B. A. Lock, R. D. Lipschutz, L. A. Miller, K. A. Stubblefield, K. B. Englehart, *JAMA, J. Am. Med. Assoc.* **2009**, *301*, 619.
[53] J. M. Souza, J. E. Cheesborough, J. H. Ko, M. S. Cho, T. A. Kuiken, G. A. Dumanian, *Clin. Orthop. Relat. Res.* **2014**, *472*, 2984.
[54] H. Miura, A. Yamada, Y. Shiraishi, T. Yambe, in *Ann. Int. Conf. of the IEEE Engineering in Medicine and Biology Society*, IEEE, Piscataway, NJ **2015**.
[55] Y. Fu, L. Hu, X. Ruan, X. Fu, *Artif. Organs* **2015**, *39*, 378.
[56] H. Miura, I. Saito, F. Sato, Y. Shiraishi, T. Yambe, H. Matsuki, in *Ann. Int. Conf. of the IEEE Engineering in Medicine and Biology Society*, IEEE, Piscataway, NJ **2013**.
[57] L. Ke, G. Yan, S. Yan, Z. Wang, X. Li, *Artif. Organs* **2015**, *39*, 615.
[58] S. Bredeson, A. Kanneganti, F. Deku, S. Cogan, M. Romero-Ortega, P. Troyk, in *Ann. Int. Conf. of the IEEE Engineering in Medicine and Biology Society*, IEEE, Piscataway, NJ **2015**.

[59] J. M. Anderson, *Annu. Rev. Mater. Sci.* **2001**, *31*, 81.
[60] D. T. Luttikhuizen, M. C. Harmsen, M. J. A. Van Luyn, *Tissue Eng.* **2006**, *12*, 1955.
[61] E. G. Pamer, M. Kastellorizios, N. Tipnis, D. J. Burgess, J. D. Lambris, K. N. Ekdahl, *Immune Responses to Biosurfaces*, (Eds: J. D. Lambris, K. N. Ekdahl,D. Ricklin, B. Nilsson), Springer, New York **2015**.
[62] J. M. Anderson, A. Rodriguez, D. T. Chang, *Semin. Immunol.* **2008**, *20*, 86.
[63] B. D. Ratner, A. S. Hoffman, in *Biomaterials Science*, Academic Press, London **2004**.
[64] J. Zdolsek, J. W. Eaton, L. Tang, *J. Transl. Med.* **2007**, *5*, 31.
[65] L. Tang, T. A. Jennings, J. W. Eaton, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 8841.
[66] P. M. Henson, *J. Immunol.* **1971**, *107*, 1535
[67] P. M. Henson, *J. Immunol.* **1971**, *107*, 1547
[68] A. Haas, *Traffic* **2007**, *8*, 311.
[69] W. G. Brodbeck, J. Patel, G. Voskerician, E. Christenson, M. S. Shive, Y. Nakayama, T. Matsuda, N. P. Ziats, J. M. Anderson, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 10287.
[70] M. S. Shive, M. L. Salloum, J. M. Anderson, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 6710.
[71] E. M. Christenson, J. M. Anderson, A. Hiltner, *J. Biomed. Mater. Res., Part A* **2004**, *70A*, 245.
[72] R. S. Labow, Y. Tang, C. B. McCloskey, J. P. Santerre, *J. Biomater. Sci., Polym. Ed.* **2002**, *13*, 651.
[73] L. A. Matheson, R. S. Labow, J. P. Santerre, *J. Biomed. Mater. Res.* **2002**, *61*, 505.
[74] J. P. Santerre, K. Woodhouse, G. Laroche, R. S. Labow, *Biomaterials* **2005**, *26*, 7457.
[75] R. S. Labow, E. Meek, L. A. Matheson, J. P. Santerre, *Biomaterials* **2002**, *23*, 3969.
[76] S. Farah, J. C. Doloff, P. Müller, A. Sadraei, H. J. Han, K. Olafson, K. Vyas, H. H. Tam, J. Hollister-Lock, P. S. Kowalski, M. Griffin, A. Meng, M. McAvoy, A. C. Graham, J. McGarrigle, J. Oberholzer, G. C. Weir, D. L. Greiner, R. Langer, D. G. Anderson, *Nat. Mater.* **2019**, *18*, 892.
[77] M. Avula, D. Jones, A. N. Rao, D. McClain, L. D. McGill, D. W. Grainger, F. Solzbacher, *Biosens. Bioelectron.* **2016**, *77*, 149.
[78] M. N. Avula, A. N. Rao, L. D. McGill, D. W. Grainger, F. Solzbacher, *Biomaterials* **2013**, *34*, 9737.
[79] L. Chung, D. R. Maestas, F. Housseau, J. H. Elisseeff, *Adv. Drug Delivery Rev.* **2017**, *114*, 184.
[80] M. T. Wolf, C. L. Dearth, C. A. Ranallo, S. T. LoPresti, L. E. Carey, K. A. Daly, B. N. Brown, S. F. Badylak, *Biomaterials* **2014**, *35*, 6838.
[81] C. J. Park, N. P. Gabrielson, D. W. Pack, R. D. Jamison, A. J. Wagoner Johnson, *Biomaterials* **2009**, *30*, 436.
[82] O. Veiseh, A. J. Vegas, *Adv. Drug Delivery Rev.* **2019**, *144*, 148.
[83] E. Mariani, G. Lisignoli, R. M. Borzì, L. Pulsatelli, *Int. J. Mol. Sci.* **2019**, *20*, 636.
[84] B. F. Matlaga, L. P. Yasenchak, T. N. Salthouse, *J. Biomed. Mater. Res.* **1976**, *10*, 391.
[85] T. N. Salthouse, *J. Biomed. Mater. Res.* **1984**, *18*, 395.
[86] O. Veiseh, J. C. Doloff, M. Ma, A. J. Vegas, H. H. Tam, A. R. Bader, J. Li, E. Langan, J. Wyckoff, W. S. Loo, S. Jhunjhunwala, A. Chiu, S. Siebert, K. Tang, J. Hollister-Lock, S. Aresta-Dasilva, M. Bochenek, J. Mendoza-Elias, Y. Wang, M. Qi, D. M. Lavin, M. Chen, N. Dholakia, R. Thakrar, I. Lacík, G. C. Weir, J. Oberholzer, D. L. Greiner, R. Langer, D. G. Anderson, *Nat. Mater.* **2015**, *14*, 643.
[87] W. K. Ward, E. P. Slobodzian, K. L. Tiekotter, M. D. Wood, *Biomaterials* **2002**, *23*, 4185.
[88] L. R. Madden, D. J. Mortisen, E. M. Sussman, S. K. Dupras, J. A. Fugate, J. L. Cuy, K. D. Hauch, M. A. Laflamme, C. E. Murry, B. D. Ratner, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 15211.
[89] B. N. Brown, R. Londono, S. Tottey, L. Zhang, K. A. Kukla, M. T. Wolf, K. A. Daly, J. E. Reing, S. F. Badylak, *Acta Biomater.* **2012**, *8*, 978.
[90] E. M. Sussman, M. C. Halpin, J. Muster, R. T. Moon, B. D. Ratner, *Ann. Biomed. Eng.* **2014**, *42*, 1508.
[91] B. D. Ratner, *J. Cardiovasc. Transl. Res.* **2011**, *4*, 523.
[92] P. E. Scopelliti, A. Borgonovo, M. Indrieri, L. Giorgetti, G. Bongiorno, R. Carbone, A. Podestà, P. Milani, *PLoS One* **2010**, *5*, e11862.
[93] P. Roach, D. Eglin, K. Rohde, C. C. Perry, *J. Mater. Sci.: Mater. Med.* **2007**, *18*, 1263.
[94] M. Hulander, A. Lundgren, M. Berglin, M. Ohrlander, J. Lausmaa, H. Elwing, *Int. J. Nanomed.* **2011**, *6*, 2653.
[95] P. X. Ma, *Adv. Drug Delivery Rev.* **2008**, *60*, 184.
[96] M. Sandor, D. Singh, R. P. Silverman, H. Xu, P. G. De Deyne, *ePlasty* **2014**, *14*, e7.
[97] M. Miller, Y. C. Jae, K. McElwain, S. McElwain, Y. S. Jung, M. Manni, S. B. Ji, D. H. Broide, *Am. J. Physiol.: Lung Cell. Mol. Physiol.* **2006**, *290*, L162.
[98] U. Bhardwaj, R. Sura, F. Papadimitrakopoulos, D. J. Burgess, *Int. J. Pharm.* **2010**, *384*, 78.
[99] U. Bhardwaj, F. Papadimitrakopoulos, D. J. Burgess, *in J. Diabetes Sci. Technol.* **2008**, *2*, 1003.
[100] E. B. Dolan, C. E. Varela, K. Mendez, W. Whyte, R. E. Levey, S. T. Robinson, E. Maye, J. O'Dwyer, R. Beatty, A. Rothman, Y. Fan, J. Hochstein, S. E. Rothenbucher, R. Wylie, J. R. Starr, M. Monaghan, P. Dockery, G. P. Duffy, E. T. Roche, E. T. Roche, G. P. Duffy, *Sci. Rob.* **2019**, *4*, eaax7043.
[101] M. Gancedo, L. Ruiz-Corro, A. Salazar-Montes, A. R. Rincón, J. Armendáriz-Borunda, *Aesthetic Plast. Surg.* **2008**, *32*, 32.
[102] P. O. Rujitanaroj, B. Jao, J. Yang, F. Wang, J. M. Anderson, J. Wang, S. Y. Chew, *Acta Biomater.* **2013**, *9*, 4513.
[103] H. Takahashi, Y. Wang, D. W. Grainger, *J. Controlled Release* **2010**, *147*, 400.
[104] S. Jiang, Z. Cao, *Adv. Mater.* **2010**, *22*, 920.
[105] B. Cao, Q. Tang, G. Cheng, *J. Biomater. Sci., Polym. Ed.* **2014**, *25*, 1502.
[106] L. R. Carr, Y. Zhou, J. E. Krause, H. Xue, S. Jiang, *Biomaterials* **2011**, *32*, 6893.
[107] X. Xie, J. C. Doloff, V. Yesilyurt, A. Sadraei, J. J. McGarrigle, M. Omami, O. Veiseh, S. Farah, D. Isa, S. Ghani, I. Joshi, A. Vegas, J. Li, W. Wang, A. Bader, H. H. Tam, J. Tao, H. J. Chen, B. Yang, K. A. Williamson, J. Oberholzer, R. Langer, D. G. Anderson, *Nat. Biomed. Eng.* **2018**, *2*, 894.
[108] Y. Wang, S. Vaddiraju, B. Gu, F. Papadimitrakopoulos, D. J. Burgess, *J. Diabetes Sci. Technol.* **2015**, *9*, 966.
[109] A. M. Pourrahimi, R. T. Olsson, M. S. Hedenqvist, *Adv. Mater.* **2018**, *30*, 1703624.
[110] N. Shang, Q. Chen, X. Wei, *Materials* **2018**, *11*, 403.
[111] H. S. Wang, J. Cho, D. S. Song, J. H. Jang, J. Y. Jho, J. H. Park, *ACS Appl. Mater. Interfaces* **2017**, *9*, 21998.
[112] M. Aman, K. D. Bergmeister, C. Festin, M. E. Sporer, M. F. Russold, C. Gstoettner, B. K. Podesser, A. Gail, D. Farina, P. Cederna, O. C. Aszmann, *Front. Neurosci.* **2020**, *13*, 1442.
[113] H. Huang, S. Su, N. Wu, H. Wan, S. Wan, H. Bi, L. Sun, *Front. Chem.* **2019**, *7*, 399.
[114] K. Wang, C. L. Frewin, D. Esrafilzadeh, C. Yu, C. Wang, J. J. Pancrazio, M. Romero-Ortega, R. Jalili, G. Wallace, *Adv. Mater.* **2019**, *31*, 1805867.
[115] F. Vitale, S. R. Summerson, B. Aazhang, C. Kemere, M. Pasquali, *ACS Nano* **2015**, *9*, 4465.
[116] T. D. Yoshida Kozai, N. B. Langhals, P. R. Patel, X. Deng, H. Zhang, K. L. Smith, J. Lahann, N. A. Kotov, D. R. Kipke, *Nat. Mater.* **2012**, *11*, 1065.

[117] M. A. Moffitt, C. C. McIntyre, *Clin. Neurophysiol.* **2005**, *116*, 2240.
[118] M. Jorfi, J. L. Skousen, C. Weder, J. R. Capadona, *J. Neural Eng.* **2015**, *12*, 011001.
[119] S. M. Won, E. Song, J. T. Reeder, J. A. Rogers, *Cell* **2020**, *181*, 115.
[120] A. L. Benabid, T. Costecalde, A. Eliseyev, G. Charvet, A. Verney, S. Karakas, M. Foerster, A. Lambert, B. Morinière, N. Abroug, M. C. Schaeffer, A. Moly, F. Sauter-Starace, D. Ratel, C. Moro, N. Torres-Martinez, L. Langar, M. Oddoux, M. Polosan, S. Pezzani, V. Auboiroux, T. Aksenova, C. Mestais, S. Chabardes, *Lancet Neurol.* **2019**, *18*, 1112.

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