

# Recent Advances for Improving Functionality, Biocompatibility, and Longevity of Implantable Medical Devices and Deliverable Drug Delivery Systems

Neta Kutner, Konda Reddy Kunduru, Luna Rizik, and Shady Farah\*

The great majority of medical devices elicit foreign body response (FBR) postimplantation. FBR is a major hurdle to develop a successful device for impaired organs, leading to failure of devices/treatments. In recent times, several advantageous technologies have been developed based on either surface modifications or localized drug delivery systems (DDSs) in order to overcome the FBR limitation, which enhanced the success of implantable medical devices. The recent advances for improving the functionality, biocompatibility, and longevity of implantable medical devices and deliverable DDSs are discussed here. It is believed that these advances will further guarantee the improvement of existing implants and deliverable entities while enabling the development of new therapy technologies. Such technologies are anticipated to be long-term patient-friendly and thus lead to a higher quality of life.

## 1. Introduction

Human body of multiple organs is a biological machine. To improve the functioning of an organ when it fails to do its job, biomedical implants and devices are required. Depending on the needs of the human body, so far, various biomedical implants and devices have been manufactured.<sup>[1]</sup> Implanted medical devices are commonly used for many purposes such as diagnostic, therapeutic, and even for regenerative action, suggesting a long-lasting solution for many medical cases.<sup>[2]</sup> These implantable devices can be classified into three main categories, according to their implantation site: orthopedic implants, cardiovascular implants, and implants for different use.<sup>[3]</sup> Orthopedic implants include bone replacers<sup>[3,4]</sup> and spinal implants.<sup>[3]</sup> Cardiovascular implants include stents and<sup>[3,5,6]</sup> electronic pacing.<sup>[2,3]</sup> Implants for different use include controlled drug release platforms<sup>[2,3]</sup> and biodegradable scleral plugs.<sup>[3]</sup>

N. Kutner, Dr. K. R. Kunduru, Dr. L. Rizik, Dr. S. Farah  
 The Laboratory for Advanced Functional/Medicinal Polymers & Smart Drug Delivery Technologies  
 The Wolfson Faculty of Chemical Engineering  
 Technion-Israel Institute of Technology  
 Haifa 3200003, Israel  
 E-mail: sfarah@technion.ac.il

Dr. S. Farah  
 The Russell Berrie Nanotechnology Institute  
 Technion-Israel Institute of Technology  
 Haifa 3200003, Israel

 The ORCID identification number(s) for the author(s) of this article can be found under <https://doi.org/10.1002/adfm.202010929>.

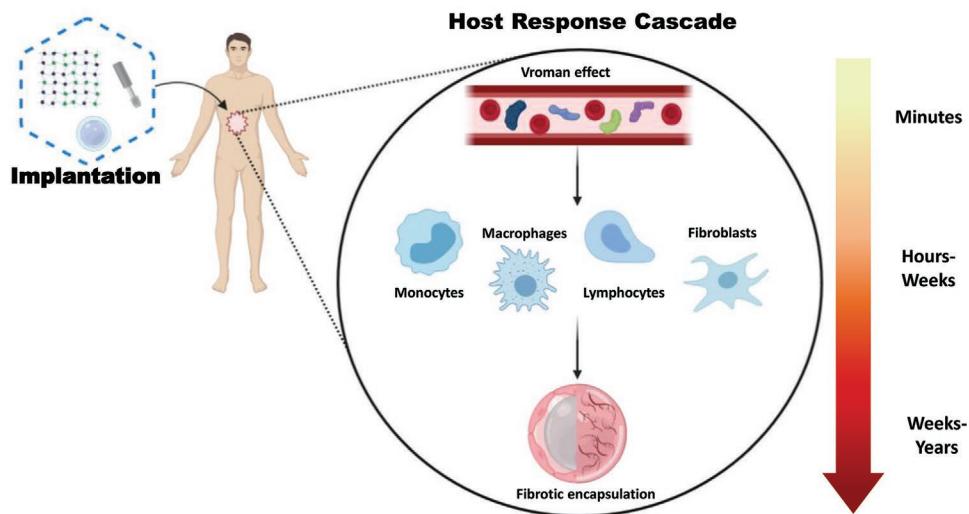
DOI: 10.1002/adfm.202010929

The demand for the medical implants and devices is being increased year by year and will also be expected to keep increasing annually and in the long-term future. However, the placement of these biomedical implants/devices within the body determines what kind of requirements, such as designs and material types, are necessary toward the preservation of human lives.<sup>[1]</sup> Although their characteristics have great importance, the fate and the success of the devices will eventually be determined by the host immune response.<sup>[2,7]</sup> Since the host response could limit materials, the device might change its properties and even lose its functionality.<sup>[7]</sup> The caused damage to the

tissues during the implantation provokes the innate immune system response.<sup>[7,8]</sup> The first defense line is known as Vroman effect, and it is mainly composed of the coverage of the device with plasma proteins, and it is the start of the inflammatory response.<sup>[7,8]</sup> The formed protein layer provides the linkage between the host tissues and the biomaterial. Later, neutrophils start to aggregate and respond, recruiting more immune component of the innate system. Then, depending on the size of the implant, the macrophages response will commence.<sup>[7]</sup> As macrophages have a phagocytic ability, they will try to clear debris and eliminate any foreign element.<sup>[8]</sup>

For nondegradable devices, the next steps are followed. As the body tries to heal the injury or to remove the foreign object, it will try to clear it out. Since the phagocytosis of nondegradable element will fail, the immune response will eventually lead to the inflammation and device encapsulation, as part of the foreign body response (FBR).<sup>[9]</sup> The FBR is composed of different immune factors such as macrophages, fibroblasts, foreign body giant cells (FBGCs), etc., depending on the device's surface characteristics. This FBR will last as long as the device is in the body,<sup>[7]</sup> usually leading to fibrosis: isolation of the devices from the nearby tissues by creating a buffer multi-component layer on top of the device. This fibrous capsule is mainly created by myofibroblast and fibrocytes, forming collagen and extracellular matrix (ECM) layer around the device (**Figure 1**).

For biodegradable implant the FBR is less expected and mainly depends on the surface of the implant and the degradation of the products.<sup>[2]</sup> Different materials present different degradation rates and products that could affect the immune response.<sup>[10]</sup> Usually, the clearance of the degradation products is possible. In case that the degradation products are not



**Figure 1.** Demonstration of the post implantation host response. Implant could be made of different types, such as hydrogels, capsules, and metallic devices. Implantation causes local injury that provokes an immune response, initiating the Vroman effect in the blood vessels and promoting the inflammatory process. Afterward, different immune factors such as monocytes, macrophages, lymphocytes, and fibroblast act against the device. The inflammation could lead to a fibrotic encapsulation of the device, isolating it from the nearby tissue environment. Created with BioRender.com.

evacuated, leading to their further accumulation at implant's microenvironment, or if the implant does not fully degrade, this might provoke an immune response and FBR.<sup>[10]</sup>

Generally, the host response and the fibrotic encapsulation specifically are blemishing the device's functionality and longevity.<sup>[7,8]</sup> One such example is the case of continuous glucose monitoring (CGM). In the last years, diabetic patients are using this device more frequently, allowing them to not only monitor their glucose blood levels, but also control insulin injection and to receive data like the trends and warnings before hypoglycemia episode.<sup>[11]</sup> Nevertheless, the device functionality is limited by the FBR, in which macrophages accumulation around the sensors decrease the accuracy of the sensor, thus affecting the device's reliability.<sup>[11]</sup> Another known FBR related issue is cochlear implant among deaf patients. The platinum and platinum/iridium electrodes were studied and found to be encapsulated in a fibrotic envelope. This reaction may lead to the degradation of some of the implant components, and it also limits the performance of the device.<sup>[12,13]</sup> One additional problem caused by the FBR is among intraneural electrodes.<sup>[14]</sup> In the last few years, a neural prosthetic limb has become a revolutionary solution for amputated patients, improving the patient abilities and performances.<sup>[14]</sup> The system is composed of the prosthesis itself, with microelectrodes that are implanted in the peripheral neural interface.<sup>[14,15]</sup> Together, they transduce the signal to the nervous system that causes the prosthesis to act. Although this device is a state-of-the-art engineering, it is also limited by the FBR. The fibrotic encapsulation of the microelectrodes is causing an increase in the electrical impedance of the electrodes,<sup>[14,16]</sup> which leads to their failure. This directly affects the device functionality and longevity.<sup>[14]</sup> This raises the question how to cope with the host immune response, preserving the device functionality without significantly destabilizing the immune system of the implanted patient.

The main approach for postimplantation is administrating immune suppressive drugs, such as corticosteroids, rapamycin,

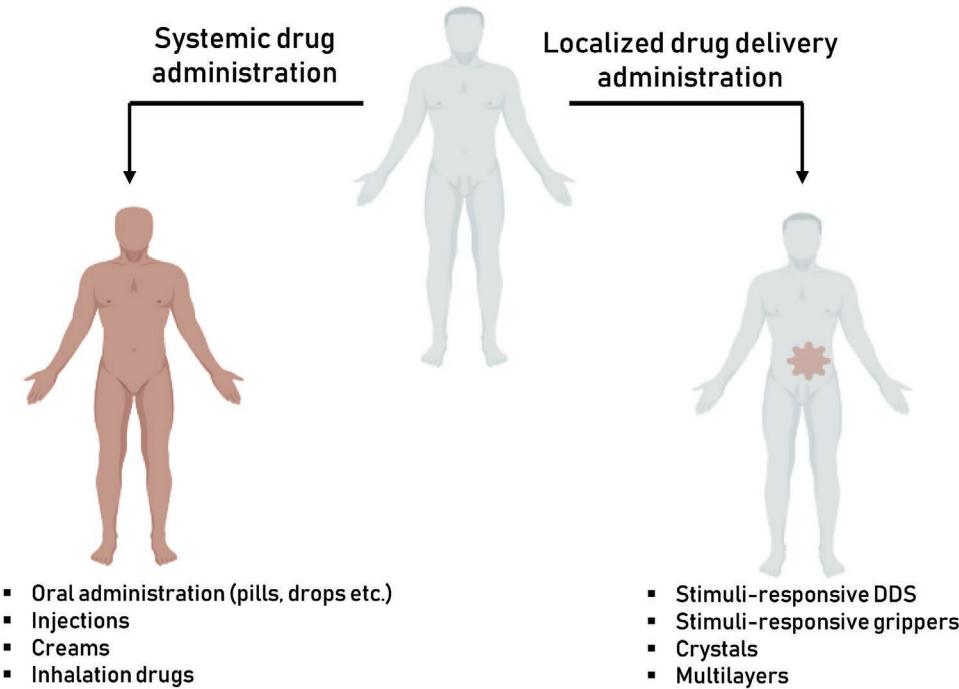
dexamethasone, etc.<sup>[17]</sup> However, this administration method causes a systemic effect, leading to a systemic weakening of the patient's immune system, putting the host in risk for infection.<sup>[18]</sup> In the recent years, the approach for localized therapy has been extensively investigated.

As the biomedical field is evolving, several approaches are currently investigated to enhance biocompatibility and ensure a safe implantation. To overcome this problem, appropriate markers are required on the surfaces of the device. In the following sections we will discuss two common approaches for dealing with implants rejection: enhancing biocompatibility through a diffusive effect of localized drug delivery systems (DDS) and contact activity of surfaces modifications.

## 2. Localized Therapy Using Drug Delivery Systems

Oral administration holds some great advantages to the end user and the care provider: it is easy to administrate independently, thanks to the known portion, painless and noninvasive method.<sup>[19,20]</sup> Given these advantages and the fact that swallowing is a very basic action, it is no surprise that oral administration is the most preferred and commonly used method.<sup>[19]</sup>

Nonetheless, as a systemic treatment, oral administration holds several serious drawbacks. First, a relatively low bioavailability which is caused by the first-pass metabolism and elimination and gastrointestinal tract degradation.<sup>[19,21]</sup> These bioprocesses decrease the available drug fraction for the targeted tissue, making this method less effective than desired to be. Second, the drug effect is systemic, meaning the drug effect is not selective, affecting many tissues and organs and not just the relevant one. Systemic delivery may cause serious adverse effects due to the treated healthy tissues/organs. It is also decreasing the availability of drug molecules for the targeted location since the drug is widely distributed (Figure 2).



**Figure 2.** An illustration of the differences between the systemic effect and the targeted therapy effect on the human body. Created with BioRender.com.

These limits strengthen the need of more acceptable approach of localized drug delivery. Drug delivering is the action of directing the drug/therapy agents to the target site, with minimal distribution to other irrelevant sites.<sup>[22]</sup> DDSs should be able to persist a series of bioreactions inside the patient's body, while accomplishing the delivery of the drug molecules to the target site.<sup>[23,24]</sup> DDSs are believed to hold a great improvement to the known oral systemic care. They hold the ability to shift the pharmacokinetic of a dosed drug, improving the bio-distribution and by that enhancing the bioavailability and efficacy.<sup>[24,25]</sup> DDSs are also able to minimize the toxicity of many drugs that are known for their adverse effects.<sup>[24]</sup> As a multidisciplinary interest, it is a very popular field of research, which is broadly explored from different scientific perspectives.<sup>[19]</sup>

One of the most important aspects in designing a DDS is biocompatibility of the material. Since the implant is eventually destined to therapy, it is of great importance that it will not cause any major immune response, toxicity, or cancerous effect. There are several approaches to meet this requirement, and here we present several leading mechanisms for DDS development for enhancing medical implants biocompatibility, functionality, and longevity of implantable medical devices and DDSs (Figure 3).

## 2.1. Stimuli-Responsive Platforms

An intriguing approach for designing DDS is using stimuli responsive materials. These materials uniqueness is within their ability to change their properties or behavior in respond to a signal.<sup>[23,26]</sup> The signal could be internal, from a physiological condition/reaction, or it could be external, rising from an initiated source.<sup>[23,24]</sup> These devices are able to exploit the physi-

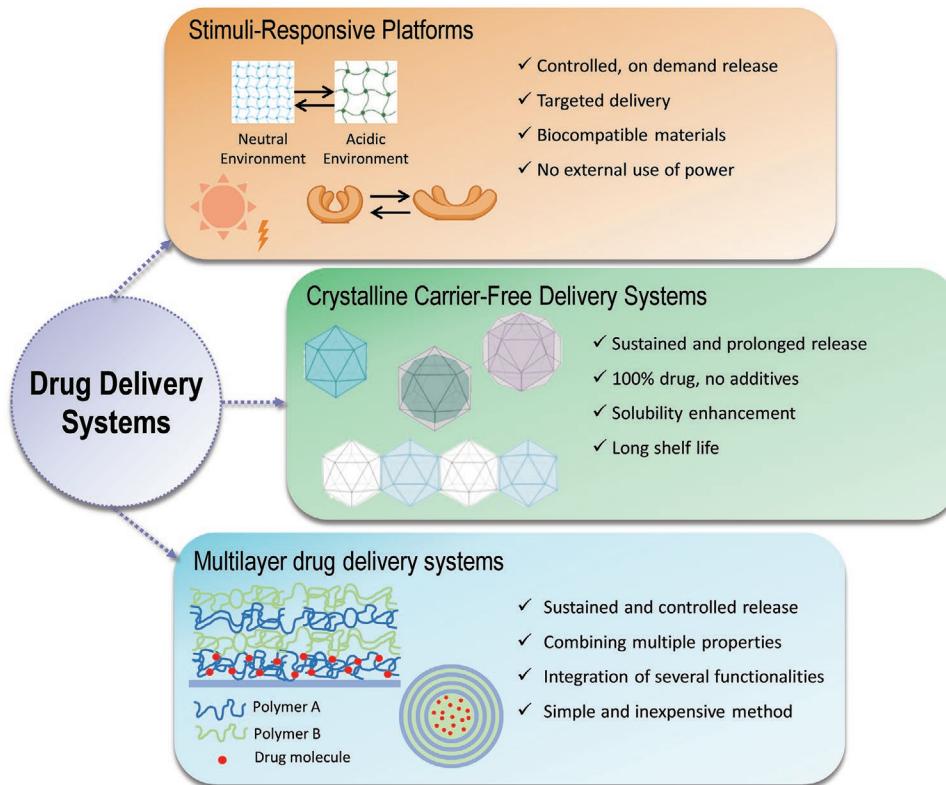
ological conditions in certain medical status in order to monitor, treat, and impact them, suggesting an accurate live therapy and diagnostic platforms. This category of materials also includes stimuli-responsive polymers, which are often named as smart or intelligent polymers, and they could experience a structural or morphological change in response to a variety of stimuli, such as pH, light, temperature, electrical or magnetic field, etc.<sup>[27]</sup> Since stimuli-responsive materials topic is very broad, in this section, we consider elaborating on three widely explored and commonly used stimuli: pH-, light-, and stimuli-responsive grippers.

### 2.1.1. pH-Responsive DDSs

One of the most commonly used triggers is a pH alternation.<sup>[28]</sup> Materials in this subgroup are able to alter their chemical or physical characteristics when experiencing a change in the acidity of their microenvironment. There are two mechanisms for pH-responsive platform activations: one is based on the protonation of a certain chemical element, and the second is based on the degradation of a chemical bond which is sensitive to acid.<sup>[26]</sup> As there are many pH-responsive polymers, each one reacts differently to a pH alternation,<sup>[27]</sup> for example swelling, precipitation, chain collapse extension etc.<sup>[27]</sup> These polymers contain a moiety like carboxyl group, pyridine, sulfonic, phosphate, and amine, which could be protonated and advance a conformation change.<sup>[27]</sup>

An acid cellular external environment is characteristic for several pathological issues such as inflammatory, where the most targeted ones are cancerous cells.

Pu et al. used the inflammatory environment characteristics, which include oxidative stress and low pH levels (Figure 5I).<sup>[29]</sup> They used an *N*-palmitoyl chitosan (NPCS) that contains a Cy3



**Figure 3.** Recently reported approaches of DDSs for improving functionality, biocompatibility, and longevity of implantable medical devices and DDSs and their main advantages. Created with BioRender.com.

moiety to create nanoparticle (NP)-based DDS which releases curcumin under oxidative and acidic environment. Curcumin is the active ingredient of turmeric, and a highly potent anti-inflammatory agent. However, its distribution in the human body is very limited, since it is poorly soluble in aqueous phase, therefore has low bioavailability.<sup>[30]</sup> The performance of the platform was tested under pH 5.5 and  $1 \times 10^{-3}$  M H<sub>2</sub>O<sub>2</sub>, which characterize the inflammation site. Under physiological condition of pH 7.4, the NPs were shrinking. In this condition, the curcumin molecules are tight with the Cy3 groups, which enable energy transfer between them. When applying the acidic conditions, the NPs were swollen, so the curcumin molecules are not close enough to the Cy3 groups, which allow them to be released. This platform was compared with free curcumin injection among healthy and acute-inflammatory-induced mice. Results revealed that the curcumin levels of the free form drug were decreased in both mice types.<sup>[29]</sup> The curcumin-loaded NPs exhibited a constant drug levels among healthy mice, and an increasing level among the inflammatory induced mice. This demonstrates the controlled release manner of the drug, while the signal is applied.<sup>[29]</sup> This example is a good demonstration of how the inflammation site could serve as a stimulus for drug release, and also to improve the curcumin bioavailability.

Another study that aims to use a unique pH level was conducted by Ninan et al., who tried to exploit the pH alternation in a wounded environment (Figure 5II). Researchers developed a pH-responsive carboxylated agarose hydrogel loaded with tannic acid (TA),<sup>[31]</sup> which has antioxidant, antimicrobial,

and anti-inflammatory activities.<sup>[31,32]</sup> Results show that under low pH, the hydrogel swelling was significantly larger compared with higher pH values, correlated with the accelerated TA release under acidic pH. The hydrogel was also proven as cytocompatible in a test conducted with 3T3 fibroblast cells. It also demonstrated an ability to reduce nitric oxide levels, which is a pro-inflammatory mediator.<sup>[31]</sup> These described abilities present a potential DDS for treating a local FBR.

While normal cells have extracellular pH 7.4, the cancer cells have higher acidity of pH 6.8–7.<sup>[28]</sup> This distinctive difference was used by Liang et al. to develop a localized DDS based on chitosan-grafted dihydrocaffeic acid (CSDA).<sup>[28]</sup> Chitosan is a natural polysaccharide made from chitin monomers,<sup>[28,33]</sup> produced from insects, crustacean and fungi.<sup>[33,34]</sup> Chitosan holds some great advantages that make it a highly suitable polymer for biomedical application: high biocompatibility,<sup>[28,33,34]</sup> easily conjugated amine functionality,<sup>[35]</sup> low immune response including minimal FBR,<sup>[34]</sup> biodegradability,<sup>[28]</sup> ability to act against microorganisms,<sup>[28]</sup> and good production cost thanks to its abundance.<sup>[34]</sup> Since chitosan is not well dissolved, grafting it with dihydrocaffeic acid improves its solubility.<sup>[28]</sup> The formed hydrogel was loaded with the doxorubicin (DOX), a well-known anticancer drug administrated for treating various kinds of tumors.<sup>[36]</sup> Due to its unfortunate cardiotoxicity, many attempts were made to make the therapy targeted.<sup>[36]</sup> Results show that at pH 5.5, the crosslinked hydrogel swelling level was higher compared to the swelling in pH 7.4. In a more acidic environment, the amine groups of the chitosan are protonated and become

positively charged, therefore repulsing away from each other. Also, the Schiff base chemical bonds are weakened, decreasing the crosslinking.<sup>[28]</sup> The release profile showed that the DOX is released in a prolonged manner, and the kinetics is faster in acid environment. This happened due to the enlargement of the pores in low pH, and thanks to the DOX protonation that makes it more hydrophilic.<sup>[28]</sup> This kind of development holds a tremendous potential to become a DDS for cancer treatment, and even for other pathological conditions. Due to the pH selectivity it demonstrates, and the ability to carry a therapeutic loading, it is possible to develop such platform that would increase the efficacy and safety all at once.

Chitosan could also be combined with mesoporous silica nanoparticles (MSNs) to achieve a different loading capability. In the research of Popat et al., they formed a phosphonate functionalized MSNs loaded with ibuprofen.<sup>[37]</sup> The particles were coated with chitosan, by the covalent bond of the chitosan's amine group and the phosphonate moiety. The drug release was examined for chitosan coated MSNs and noncoated particle, under 37 °C at pH 5 and 7.4. These pH levels correlate with the endosome and in normal tissues, respectively. For the non-coated particles, the drug was completely released after 3–4 h, independent on the pH of the medium.<sup>[37]</sup> Yet, for the chitosan-coated particles the release profile changes. In pH 7.4, the chitosan has low solubility, so only 20% of the drug is released. In pH 5, about 90% of the loaded ibuprofen is released after 8 h.<sup>[37]</sup> Ibuprofen is widely used and known for its anti-inflammatory capabilities.<sup>[38]</sup> Also, inflammatory environment is characterized with low pH levels.<sup>[29,39]</sup> Therefore, such platform might be useful for treating chronic inflammation, which is one of the FBR stages.

Additional usage of chitosan as a pH-responsive DDS was developed by Qu et al., describing a self-healing, pH-responsive, DOX-loaded hydrogel for hepatocellular carcinoma (HCC) treatment.<sup>[40]</sup> Chemotherapy is considered as the primary standard treatment for HCC, which is the sixth most common cancer worldwide.<sup>[41]</sup> HCC is considered as a chemo-resistant tumor; therefore, treating it with chemotherapy is not a promising approach. DOX is one of the most commonly used drugs for HCC therapy,<sup>[40,41]</sup> yet tumor resistance may occur.<sup>[40,41]</sup> Therefore, the need for a targeted HCC treatment is essential in order to improve the results. Here, researchers used a solubility-improved chitosan by using *N*-carboxymethyl chitosan (CEC), combined with dibenzaldehyde-terminated poly(ethylene glycol) (PEGDA) to hydrogel formation.<sup>[40]</sup> The hydrogel was loaded with DOX, and tested for a self-healing drug releasing platform. The hydrogel was proved to be injected easily through a catheter with 0.8 mm diameter and 10 cm length, demonstrating the ability to be minimally invasive with rapid healing, minimal scaring, and pain.<sup>[40]</sup>

Due to the enhanced glycolytic metabolism and increased production of lactic acid in the tumor environment, the microenvironment that surrounds it becomes acidic.<sup>[40]</sup> Near acidic environment, the amino group of the chitosan is protonated, weakening the bond with the –CHO group, and breaking the crosslinking of the CEC/PEGDA. This allows the swelling and the DOX diffusion.<sup>[40]</sup> The release and degradation were evaluated in acidic environment (pH 5.5) and physiological environment (pH 7.4), revealing that indeed

the degradation is enhanced in the acidic environment compared with the physiological environment: 40% mass loss compared with 14% mass loss, respectively. The size of the pores was evaluated by SEM, demonstrating a decrease in the pore size as the PEGDA percentage increases,<sup>[40]</sup> which is correlated with the PEGDA a crosslinker, causing a denser network and smaller pores. Also, as the swelling increased under acidic conditions, the pores continue to grow, as the largest diameter under pH 5.5 for 10% (w/v) of PEGDA with CEC of  $238 \pm 6 \mu\text{m}$ . Also, it was demonstrated that the release rate is increased with the decrease of pH values.<sup>[40]</sup> It is important to mention that under acidic condition the DOX might be protonated as well, increasing its hydrophilicity and promoting its diffusion ability in the PBS.<sup>[40]</sup>

In a direct contact cytotoxicity test, the hydrogel showed no toxic effect on L929 cells, demonstrating their biocompatible applicability.<sup>[40]</sup> The therapeutic activity of the DOX-hydrogels was evaluated on human hepatocellular liver carcinoma (HepG2) cells, compared with free DOX in low concentrations (0.025, 0.05, and 0.1  $\mu\text{g mL}^{-1}$ ) and higher concentrations (0.25  $\mu\text{g mL}^{-1}$ ). Test showed that the encapsulated DOX had greater influence on the cell viability, presenting an improved anticancer effect even for the lower concentrations. Finally, an *in vivo* gel formation was proven by injecting the precursor solution to rats, proving the hydrogel ability to form in the physiological environment.<sup>[40]</sup> This research demonstrates the ability of hydrogel-based DDS to improve the therapeutic effect, while minimizing the invasiveness and pain accompanied with many anticancer therapies.

To conclude, pH-responsive platform attracts great attention in the DDS field and implantable medical devices. Its ability to rapidly change its conformation in response to an acidic environment, which is characteristic for many pathological conditions such as inflammation, could be widely useful for medical usages, specifically for a localized immunosuppressive effect. This will enhance the safety of the postimplantation, minimizing the immune vulnerability of the patient while administering immunosuppressants.

### 2.1.2. Light-Responsive DDSs

An interesting physical stimulus is light, which is a fundamental stimulus for many biological systems.<sup>[42]</sup> Light as a stimulus holds many advantages: it does not require a direct contact with the target area,<sup>[42]</sup> has a high safety profile since it is a noninvasive approach<sup>[24,43]</sup> and has the ability to cause conformational shifts rapidly.<sup>[42–44]</sup> Also, light is considered as an easy to apply trigger, that gives good robustness.<sup>[24]</sup> Materials should be light-absorbing, as the commonly used mechanism in light-responsive platforms are chemical bonds cleavage,<sup>[42]</sup> conformation shift,<sup>[42,43]</sup> or a decrease in the hydrophobicity of the platform.<sup>[42]</sup> When comparing the light stimulus to a pH stimulus, the main advantage of light is almost no adverse effects to the physiological environment is made.<sup>[24]</sup> In addition, the high resolution of the delivery enhances the precision, therefore increasing the efficacy.<sup>[24]</sup>

Since light is an external stimulus, the applied light must be able to penetrate the tissues to reach the DDS. UV light

has a poor ability to do that,<sup>[44]</sup> and it also might harm some of the biological elements due to a carcinogenic effect that might occur with prolonged treatment.<sup>[24,42]</sup> These drawbacks led researches to search for another way to use light triggering. For example, in a recent study reported by Kim et al. describes a bioluminescence resonance energy transfer (BRET) system, based on luciferase-rose bengal conjugates for photodynamic therapy (PDT).<sup>[42,45]</sup> The emission peak of the donor luciferase (535 nm) is correlated with the absorption peak of the acceptor rose bengal (550 nm). The reaction between the luciferase and its ligand CTZ generates single oxygen.<sup>[2,45]</sup> The conjugate successfully harmed C126 murine colon carcinoma cells, suggesting a new innovative approach for cancer therapy that does not include irradiation.<sup>[42,45]</sup>

Another common approach is using NIR radiation, which poses a decreased phototoxicity compared to UV radiation, and also presents a better ability for tissue penetration.<sup>[24]</sup> One example of NIR-responsive platform was presented by Zhao et al., who created intra-articular DDS composed of chitosan-modified molybdenum disulfide nanosheets (Figure 5III).<sup>[46]</sup> The sheets were loaded with dexamethasone, which was released once an NIR radiation was applied. Dexamethasone is a synthetic glucocorticoid with anti-inflammatory activity.<sup>[47,48]</sup> The ability to control the drug concentration by manipulating the release could improve the treatment,<sup>[46]</sup> and also serves as a localized delivery system of a well-known anti-inflammatory drug.

Another usage of NIR for liposomes decomposition is described in the recently reported study of Spring et al. where a photoactivable multi-inhibitor nanoliposomes (PMIL) able to release multiple molecules were generated for anticancer treatment (Figure 5IV).<sup>[42,49]</sup> Liposomes were made with incorporated lipophilic benzoporphyrin (BPD) derivative in the lipidic bilayer. The Liposomes were loaded with the multikinase inhibitor XL184, which was encapsulated in PLGA.<sup>[42,49]</sup> This formed structure protects the XL184 particles from being hydrolyzed, keeping them unreleased until a light stimulus will occur.<sup>[49]</sup> Once NIR radiation was applied, the BPD broke allowing the disruption of the lipidic bilayer, leading to the XL184 release and the inhibition of the tumor proliferation process such as angiogenesis, metastasis etc. This mechanism was also tested on mice with pancreatic cancer, demonstrating a prolonged therapy effect for 10 days.<sup>[49]</sup> PDT holds a great potential, as many researchers are exploring the opportunities that this method holds.

A different application of NIR radiation was made by Nazari et al. who investigated an NIR-responsive DDS, made from optical fibers coated with 5-fluorouracil (5-FU) loaded UiO-66, an archetypal metal-organic framework (MOF).<sup>[43]</sup> In this research, the scientist created a UiO-66-coated optical fiber, using the ability of the fiber to deliver light to the targeted site.<sup>[43]</sup> The UiO-66 was loaded with the chemotherapy drug 5-FU, to test the accepted release profile when applying different wavelength: 800, 1050, and 1550 nm.<sup>[43]</sup> The results revealed that at 1050 nm the UiO-66 has sufficient energy to overcome the drug absorption enthalpy, enabling the 5-FU release.<sup>[43]</sup> Although 11–186 optical fibers are needed to reach the commonly administrated dosage of 5-FU, this research demonstrates the principle and feasibility of using light-responsive materials.

Although NIR radiation demonstrated several promising application, it is still limited in its energy, therefore not always sufficient for photoactivation of some chemical reactions.<sup>[24]</sup>

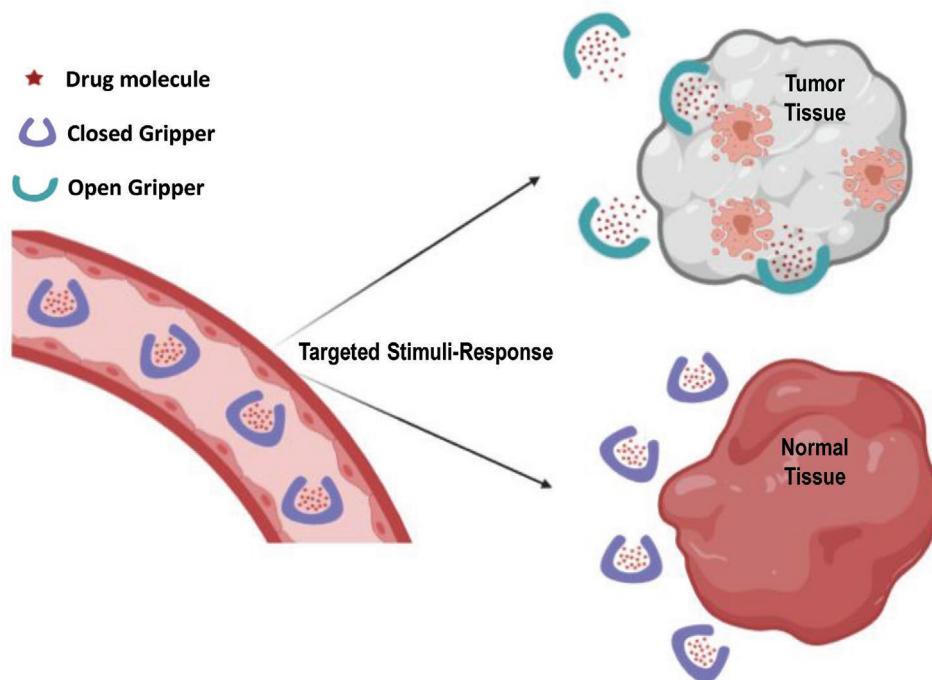
An interesting material for a DDSs is MSNs, which are colloidal silicas.<sup>[50]</sup> MSNs are characterized with increased biocompatibility, and are easy to design.<sup>[24,51]</sup> Their porosity enables cargo loading, which is capped with agents that promotes the cargo release with different stimuli such as light, depends on their characteristics.<sup>[24,51]</sup> Studies compared the in vitro toxicity of different silicon-based devices found that MSN presents a higher cell viability compared with fumed SiO<sub>2</sub>.<sup>[50]</sup> The porosity of MSN provides a reduced contact with the cell's membrane, therefore demonstrating a reduced hemolytic effect.<sup>[50]</sup> MSNs are used for oral application for an improved systemic treatment, due to their ability to deliver poorly soluble agents, therefore increasing their bioavailability.<sup>[50]</sup>

In a research conducted by Chang et al. an NIR-responsive platform for DOX release from gold nanorods (AuNR) core, coated with MSN shell. The MSN was capped with double stranded DNA (dsDNA) or siRNA.<sup>[51]</sup> Once NIR radiation was applied, the photothermal effect on the AuNR caused the detachment from the polynucleotides, and their denaturation. This provoke the reveal of the pores, leading to the drug release.<sup>[51]</sup> In vitro test on lung cancer cell line was conducted. After the colloids were taken, the cells were exposed to NIR irradiation, which was on-off switched. The Dox-releasing colloids demonstrated a lower cell viability, which is correlated with the released Dox in the dark field scattering images.<sup>[51]</sup> This is a good demonstration of combining MSN with an inorganic agent creating a light-triggered platform for drug releasing, using the photothermal effect of NIR radiation on AuNRs along with the loading and biocompatibility of the MSN.

### 2.1.3. Stimuli-Responsive Based Gripps Implants

Many of the surgical and medical procedures are advancing to the noninvasive approach. These includes untethered robots that are remotely controlled to reach the target site in the patient body.<sup>[52]</sup> Gripps are one such device that could be used for a variety of tasks from biopsy to drug delivering, named theragripps.<sup>[52]</sup> Theragripps are mainly based on polymers and hydrogels, thanks to their stiffness, which is in the same range as tissues.<sup>[52,53]</sup> They also hold the ability to swell/shrink under different pH levels, dismissing the need for external intervention of power supply.<sup>[53]</sup> The combination of stimuli-responsive materials with theragripps creates a unique platform of an untethered devices, that could be navigated to the target tissues and fulfil its task in a precise manner<sup>[52]</sup> (Figure 4).

One such example is presented in the work of Li et al. about a pH-responsive polymer bilayer micro-robot for drug delivery purposes (Figure 5V).<sup>[54]</sup> The device is made from poly (ethylene glycol) acrylate (PEGDA) which gives the motion ability, and 2-hydroxyethyl methacrylate (PHEMA) which is pH-responsive.<sup>[54]</sup> At the basic pH 9.58, the PHEMA was swelled, and the device demonstrated maximal trapping, while at acidic pH 2.6 the deswelling caused an unfolding motion.<sup>[54]</sup> Motion was enabled by inducing a magnetic field, reaching the velocity of 600 μm s<sup>-1</sup>. The device cytotoxicity was tested



**Figure 4.** Targeted drug delivery systems based stimuli responsive grippers. The grippers become open and release the drug near the target tissue. Created with BioRender.com.

by using mammary carcinoma cells (4T1). Along with the control untreated group, the test groups included cells with the theragrippers alone, and with polycaprolactone (PCL)-docetaxel (DTX) microbeads loaded theragrippers. Results showed that the theragrippers alone treated group had cell viability similar to the control, proving that the theragrippers are not cytotoxic. The group with the PCL-DTX had lower cell viability percentage, confirming the release and activity of the anticancer drug.<sup>[54]</sup> One such device that is able to be navigated to the target area in the patient body and remain there, while releasing drug in a specific environment is of great need.

More stimuli could be the basis for additional theragrippers. A light responsive soft microrobot device, loaded with alginate microbeads is described in Fusco et al. paper.<sup>[55]</sup> The device was made owing to their ability to open under short exposure to NIR radiation or thermal signal. Alginate was loaded with iron oxide particles, creating ferrogel microparticles with the ability to be navigated.<sup>[55]</sup> Examination showed that the devices decomposed at 40 °C, meaning it will remain stable under physiological temperature, responding to the external NIR signal. Testing the ability for D1 mouse mesenchymal stem cells demonstrated that cells remained viable while being encapsulated in the device for at least 7 days.<sup>[55]</sup> The advantages of light-response principal were previously discussed, and this work emphasizes them, especially when combined with gripping ability.

fumarate (PPF), segment which is known for bone filling purposes.<sup>[56]</sup> By integrating iron oxide in the polymers, the designed device could be navigated through an induced magnetic field, as used in the previous examples. The PNIPAM-AAC is thermo-responsive, allowing the swelling and shrinking of the polymer that promotes the folding to both directions. The self-folding threshold temperature was determined as 36 °C. Above it the PNIPAM-AAC is shrinking, so the device fold with the PPF is the external layer, and under it the PNIPAM-AAC is swelled so PPF is the internal layer. These heating–cooling cycles were tested for 50 successful times.<sup>[56]</sup> Incorporation of drug molecule in one of the device's layers could serve as a drug delivery platform, which is tight with the target site in the patient body, allowing a localized treatment.<sup>[56]</sup>

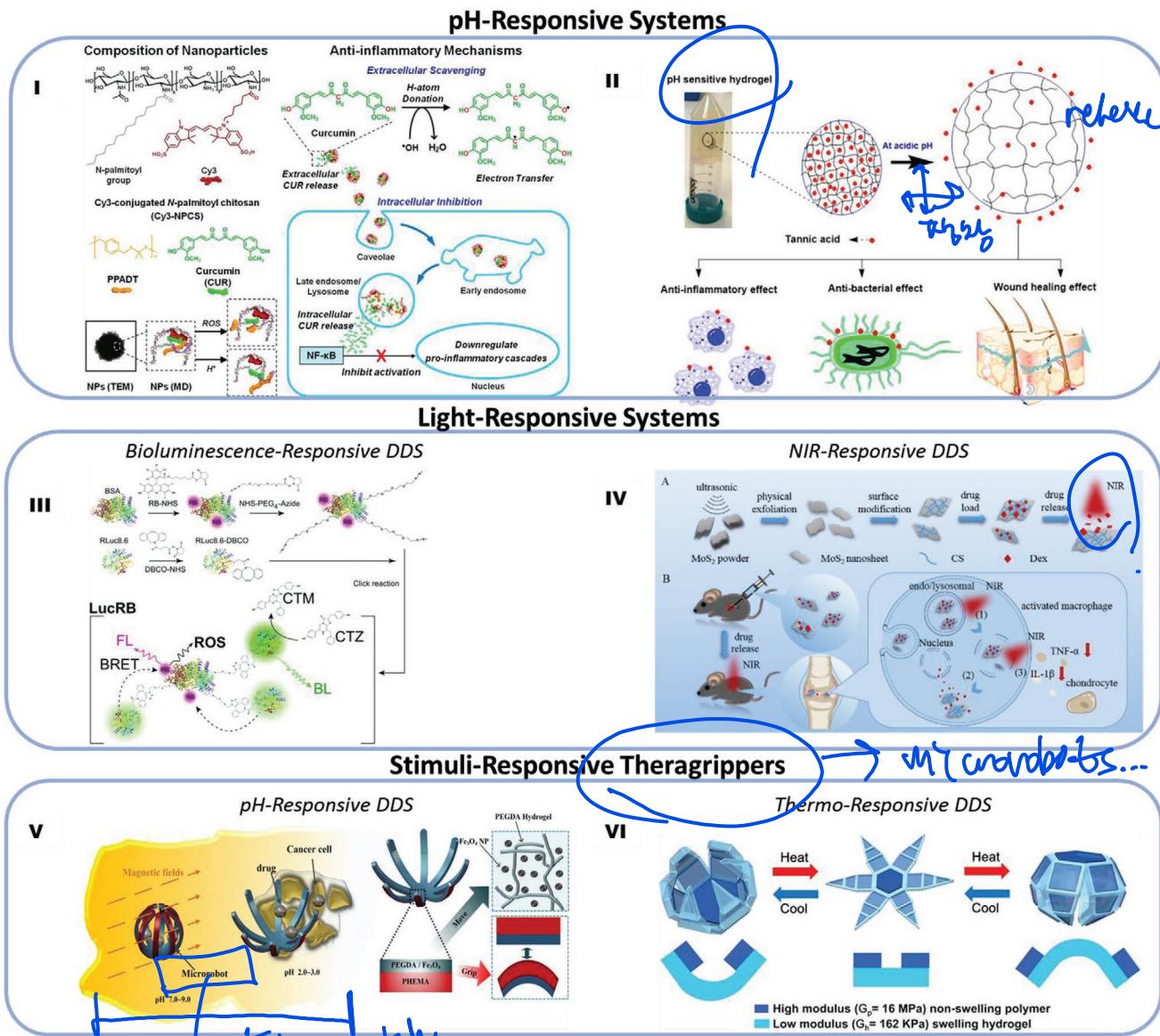
### how (decomposition)

#### 2.1.4. Other Stimuli-Responsive Platforms

We chose to elaborate only about three promising and intriguing stimuli, yet there are more intriguing and highly promising stimuli that might be suitable for biomedical application, which are currently investigated for potential medical devices and treatments. For example, glucose-responsive materials could be used as a small and continuous insulin administration platform or as glucose monitoring system.<sup>[26]</sup> Redox sensitizers might be useful as well, as ROS are characteristic for several pathological conditions such as cancer, injured tissues etc.<sup>[26]</sup>

Although the use of stimuli-responsive materials appears to be very promising, attracting the attention of many biomedical researchers, most of the developed technologies become a used product in clinics. Many of the developed DDS are failing at the

3. Thermo-responsive theragrippers are also widely investigated. One such device was described in Breger et al.'s work on self-folding microgrippers which are thermo-responsive (Figure 5VI).<sup>[56]</sup> As many stimuli-responsive hydrogels lack the needed stiffness for gripping quality, PNIPAM was incorporated with acrylic acid which is stiffer, creating PNIPAM-acrylic acid (AAC). The PNIPAM-AAC was formed over a polypropylene



**Figure 5.** Representative examples of pH-responsive DDS, light-responsive DDS and stimuli-responsive theragrippers. I) NPCS nanoparticle-based DDS for curcumin release under oxidative and acidic environment. Adapted with permission.<sup>[29]</sup> Copyright 2014, American Chemical Society. II) pH-responsive carboxylated agarose hydrogel loaded with tannic acid. Adapted with permission.<sup>[45]</sup> Copyright 2016, American Chemical Society. III) Bioluminescence resonance energy transfer (BRET) system, based on luciferase-rose bengal conjugates for photodynamic therapy. Adapted with permission.<sup>[46]</sup> Copyright 2017, Royal Society of Chemistry. IV) NIR-responsive intra-articular DDS composed of chitosan-modified molybdenum disulfide nanosheets. Adapted with permission.<sup>[46]</sup> Copyright 2019, American Chemical Society. V) A pH-responsive polymer bilayer micro-robot for drug delivery purposes. Adapted with permission.<sup>[54]</sup> Copyright 2016, IOP Publishing. VI) Thermo-responsive self-folding microgrippers. Adapted with permission.<sup>[56]</sup> Copyright 2015, American Chemical Society.

scale-up process, due to the system complexity, which lack the feasibility to become a commercialized product.<sup>[26]</sup>

## 2.2. Crystalline Carrier-Free Delivery Systems

Though carrier-based DDS appear as highly potentiate, at specific cases, carriers may provoke immune response and rejection cascade. An innovative methodology should include carrier-free DDSs, which are a stand-alone platform for localized therapy without the aid of additional carriers.<sup>[57]</sup> This type of

DDSs are not carrier-dependent and significantly less expected to provoke toxicity or immune-response.<sup>[58]</sup> Here, we describe a promising DDS platform based on crystals. Although crystals are usually considered as a product of separation process,<sup>[59]</sup> in the recent years they became an interesting method for drug formulation.<sup>[60]</sup>

Crystal-based carrier-free delivery systems offer unique properties, making them a very suitable method to develop innovative drug formulations and biomedical implants function improving. First, many of the drugs are poorly soluble and unable to persist in physiological environment, therefore

posing an unsatisfying low bioavailability.<sup>[20,61]</sup> When drugs are formulated in crystalline phase, it increases the effective dosing while simultaneously increasing its stability thanks to the dense compact structure.<sup>[59,62]</sup> Second, drug release from a crystalline phase suggests a continuous and elongated manner.<sup>[59,63]</sup> Achieving such properties may contribute to decreasing adverse effect, since it enables a lower concentration usage.<sup>[57,60]</sup> One of the greatest advantages of the crystalline-based carrier-free delivery systems is the increased drug efficiency thus patient is administrated with DDS with up to 100% drug composition.<sup>[20,57,59,60]</sup> Dismissing the need for an external carrier enable simultaneously avoiding the immunogenicity and also getting the desirable concentration within the targeted tissue.

In addition, when considering the potential of drug crystals as a DDS or as part of biomedical implant, it is worthy to mention that the production process is relatively cheap, and relatively easy one to scale-up for commercializing purposes.<sup>[61]</sup> Also, it has the capability to be administrated orally, intravenous, through ocular route or in a pulmonary method,<sup>[61]</sup> suggesting a unique opportunity to develop a therapy approach for a variety of diseases and pathological conditions.

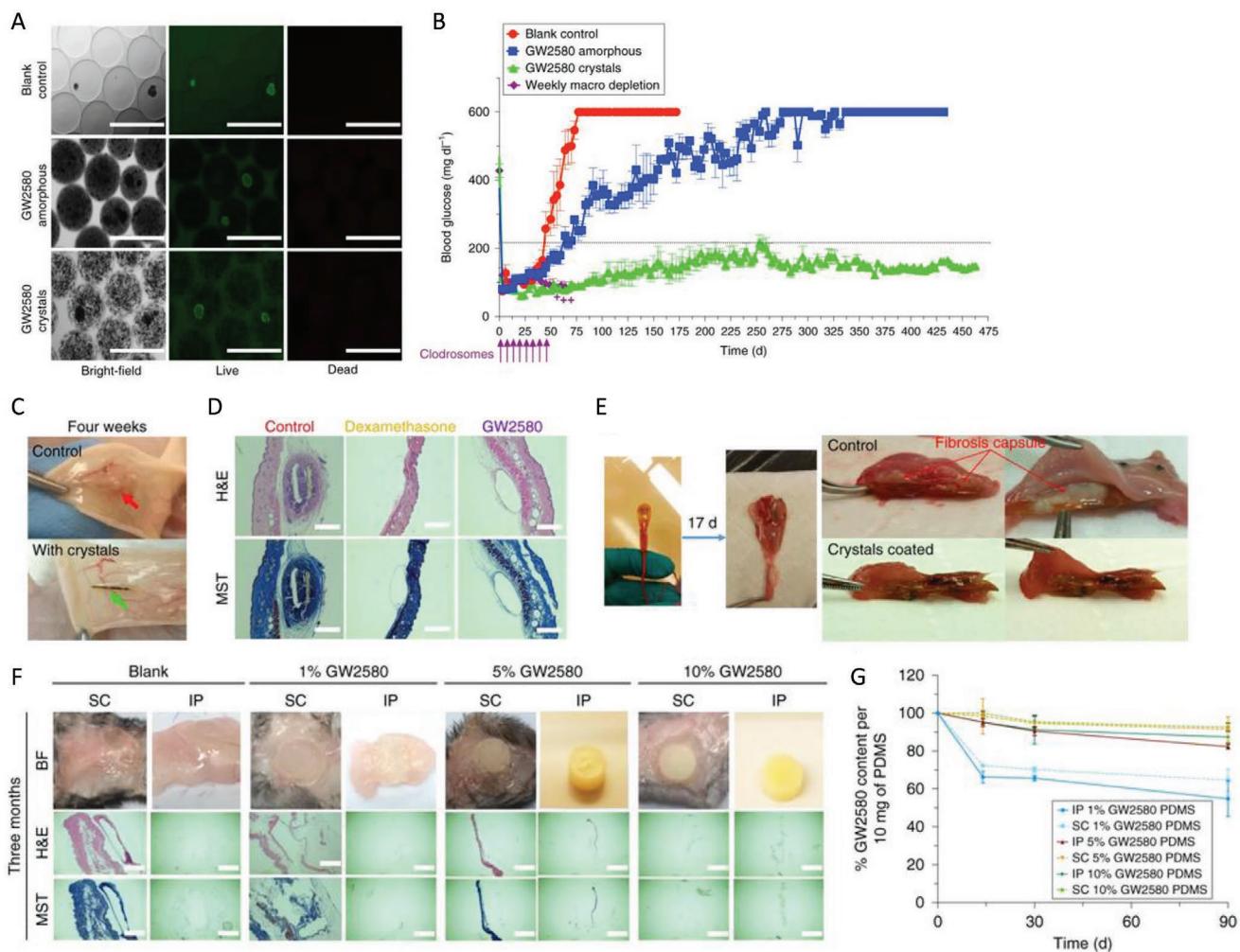
Attention should also be given to the solubility of drugs. Many of the developed drugs are poorly water soluble,<sup>[60,61]</sup> demonstrating low bioavailability that limits the drug performance.<sup>[61]</sup> Another rising issue that rises from low solubility is the requirement of chemicals that are added to enhance the drug solubility.<sup>[61]</sup> In order to improve the poor solubility, many drugs are formulated with organic solvents and solubilizers which may promote toxicity.<sup>[61]</sup> This issue occurred with a known solubilizer and emulsifier named Cremophor EL (CrEL), commonly used with chemotherapeutic agents, such as paclitaxel.<sup>[64]</sup> Researchers found that the CrEL may cause neurotoxicity<sup>[61,65]</sup> and cytotoxicity,<sup>[65]</sup> and may provoke some severe physiological response. This emphasizes the benefit of the crystals' purity, dismissing the need of these solubilizers.

Many of the drug crystals' advantages and their ability to serve as a successful DDS are presented in Farah et al.'s research on crystalline drug administration for treating FBR for devices implantation.<sup>[59]</sup> When implanting medical devices, the device might encounter a severe immune response, leading to a fibrosis reaction in which the device is encapsulated and isolated, as part of its rejection.<sup>[17,59]</sup> The used drug model GW2580 (5-[[3-methoxy-4-[(4-methoxyphenyl)methoxy]phenyl]methyl]-2,4-pyrimidinediamineparylene) is a colony stimulating factor-1 (CSF1) receptor inhibitor, which appears to alter the immune response and prevent the fibrosis.<sup>[17]</sup> The researchers explored three different GW2580 crystallization methods, concluding that the optimal method is solvent/anti-solvent based<sup>[59]</sup> giving the improved thermal stability, also gave a sustained and elongated release among nonhuman primates (NHPs).<sup>[59]</sup> The encapsulated crystals in hydrogel based implant for cellular encapsulation, retain their anti-fibrotic effect for six months,<sup>[59]</sup> presenting very satisfying results and huge potential for establishing a drug administration approach. Also, in mice these crystals protected encapsulated pancreatic beta-cells for up to 1.3 years allowing elongated and fibrosis free protection (**Figure 6A,B**). As discussed in Section 1, FBR to CGM is a known issue of the device. These GW2580 crystals were co-incorporated in

implantable muscle stimulating devices and electrode-based CGMs and shown to enable long-term anti-fibrotic functioning allowing extended devices functionality for 30 days in mice and 17 days in rats (**Figure 6C–E**).

While this research presents a great potential for combining medical device with anti-fibrotic carrier-free drug crystals, it also demonstrates the ability of drug integration through crystalline formulation within a medical device to enhance biocompatibility and elongate significantly the functionality of an implantable device. In addition, the prolonged release profile that was demonstrated as one of the most appealing features of drug crystals, long-term slow localized delivery. The crystals exhibited varied release profiles by changing the device materials, hydrophilicity versus hydrophobicity, finding that crystals in polydimethylsiloxane (PDMS)-based implants exhibit the slowest release profile versus hydrogels- or polyimide-based implants (**Figure 6F,G**). In the same study, they also found that the release profile varying in correspondence to implantation site, where in intraperitoneal (IP) injection in comparison to both intramuscular (IM) and subcutaneous (SC) injection, the crystals were found to release the drug cargo faster. Many therapy approaches include a repeating administration, usually causing an inconvenience for the patients. Using such elongated-release drug might be of great contribution for such conditions, such as immunotherapy, chemotherapy, glucose control, etc.

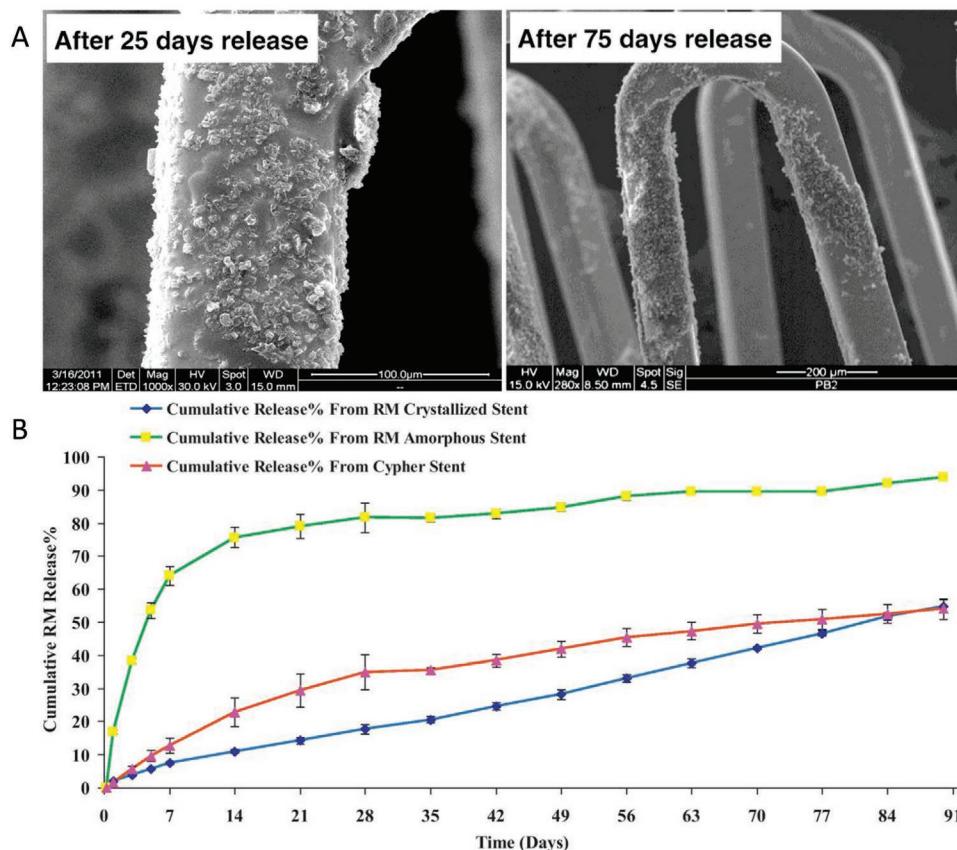
Crystals are also suitable for device coating, as appears in many researches. One such example of coating ability exists in Khan et al.'s work on new approach for drug eluting stent coating with rapamycin.<sup>[66]</sup> Since bare metal stents (BMS) tend to cause restenosis and thrombosis,<sup>[66,67]</sup> drug eluting stents (DES) have become the main treatment device for coronary artery disease.<sup>[67]</sup> The new generation of DES is improved, presenting new features including antiproliferative drugs release<sup>[66,67]</sup> (such as rapamycin, paclitaxel, and more<sup>[67]</sup>). Many of the DES are coated by using spraying or dip coating methods, which provide an unstable coating. This leads to some reported safety issues, due to their effect on thrombosis and neointimal hyperplasia.<sup>[5,66]</sup> In order to develop a robust and uniform method for coating, attempts were made to design a polymeric mixture for drug loading and carrier-free DES.<sup>[66]</sup> In that research, carrier-free DES was produced with a crystalline coating of rapamycin, which are macrocyclic antibiotics with the ability to suppress inflammation, neointimal hyperplasia, protein synthesis, and other restenosis related processes.<sup>[5]</sup> The DES was examined with SEM, presenting an adhesive crystalline coating with no cracking or other defects even after 75 days of drug releasing (**Figure 7A**).<sup>[66]</sup> The coated device was also tested on rats, compared with BMS. The two different stents were subcutaneously implanted and examined 7- and 28-days post implantation. Results showed that the crystalline rapamycin coating was able to prevent tissue proliferation, unlike the BMS that was covered with tissue. Also no severe immune response such as FBR was observed.<sup>[66]</sup> High performance liquid chromatography (HPLC) test also proved that the rapamycin is not released all at once, rather in a controlled and prolonged profile.<sup>[66]</sup> In another in vitro comparison study up to 90 days, release from these crystalline coated stents was found slower than Johnson & Johnson Cypher stent, where



**Figure 6.** Glucose control with encapsulated crystalline GW2580 with islets in diabetic mice. A) Cells staining for viability assay with amorphous and crystalline GW2580, scale bar, 1000  $\mu$ m. B) Glucose levels in mice blood with different GW2580 phases. C) The created fibrosis encapsulation in the control mouse versus the GW2580 crystals treated mouse which showed no fibrotic reaction. D) H&E and Masson's trichrome staining of excised four weeks SC implants, showing reduced fibrosis with crystalline dexamethasone and GW2580, compared with control, scale bar, 400  $\mu$ m ( $\times 10$ ). E) Retrieved MSDs 17 d after suturing to gastrocnemius muscle (IM implantation) in rats. Cross-section images: thick fibrosis for controls ( $>500$   $\mu$ m) versus no significant fibrosis with crystalline GW2580. F) Histology images of tissues after SC and IP polydimethylsiloxane discs implantation with GW2580, loaded with 0 (blank), 1%, 5%, or 10% crystalline GW2580, in C57BL/6 mice, scale bars, 1000  $\mu$ m ( $\times 4$ ). G) The remaining loaded GW2580 in the SC or IP implant after three-month implantation. Adapted with permission. [59] Copyright 2019, Springer Nature.

the drug is incorporated in two nondegradable polymers poly *n*-butyl methacrylate (PBMA) and polyethylene-*co*-vinyl acetate (PEVA) covered with parylene C as top coating (Figure 7B).<sup>[68]</sup> Parylene C is a chlorinated polymer from the xylylene polymers,<sup>[69]</sup> which is considered as a biocompatible material.<sup>[70]</sup> It is commonly used for metal implants coating, specifically for bioelectrodes<sup>[70]</sup> as well as a top layer for drug-eluting stents, thanks to its ability to decrease blood platelet aggregation.<sup>[69]</sup> Also, it is commonly used for assistance in controlling the oxygen transfer in microfluidics systems.<sup>[70]</sup> However, the question regarding the parylene C influence on the FBR to medical implants remains open, as some studies claim that it does not have a significant effect.<sup>[71]</sup> The crystalline coated stent release manner enables to avoid drug toxicity while preserving therapeutic effect of the drug, suggesting an applicable solution for dealing with implants rejection.

Though crystals are stand-alone carrier-free DDS, they can also be combined with carrier-based platform thus impacting their functionality and drug bioavailability. For example, they can be incorporated in liposomes, which are lipidic vesicles that could function as drug carriers.<sup>[20]</sup> Thanks to their biocompatibility, and their ability to provide protection from enzymatic degradation,<sup>[20]</sup> they have become of great interest and widely investigated as DDS.<sup>[20,25,72]</sup> The phase of the entrapped drug has great influence on the releasing profile.<sup>[72]</sup> Research conducted by Li et al. examined the release of crystalline drug release entrapped in liposomes.<sup>[72]</sup> Once the drug is encapsulated in the liposomes, it may stay amorphous or it might crystalize.<sup>[72]</sup> It was previously shown that the anticancer drug DOX form drug crystals within the liposomes, with different morphology when composed of DOX-sulfate and DOX-citrate.<sup>[72]</sup> The drug solubility plays a key factor in controlling its release. As most of the drug molecules



**Figure 7.** A) SEM imaging of the rapamycin (RM) crystalline coating on the stent after 25 days of drug releasing (left), scale bar, 100  $\mu\text{m}$  and after 75 days of drug releasing (right), scale bar, 200  $\mu\text{m}$ . Adapted with permission.<sup>[66]</sup> Copyright 2013, Elsevier. B) The cumulative % release of RM from stent in different phases. Crystalline drug exhibited the most prolonged release profile, while amorphous phase is releasing drug much faster. Adapted with permission.<sup>[68]</sup> Copyright 2013, Elsevier.

are packed in the nanocrystals and not free in the solution, the driving force for DOX release becomes constant, leading to a zero order kinetics for the release profile.<sup>[72]</sup> This provides a proof for the elongated profile release of the crystalline phase, even in combination with carriers, which can even enable reaching even more elongated release.

Crystalline drug formulations are very beneficial for the aforementioned reasons, yet characterizing their release kinetic in a physiological environment remains challenging in the case of drug release under detection limits. This is due to the low and elongated solubility driven by the fact that only dissolved drug molecules can be completely detached from the crystals to be available for therapeutic activity and while the rest are still packed.<sup>[60]</sup> Although separating the solution from the packed crystal seems rational, this action will affect the dissolving kinetics, disrupting the received data.<sup>[60]</sup> Attempts were made to evaluate the kinetics by using TEM, however, the inability to give a live dynamic image limits its ability for a good evaluation. Trying to use the autofluorescence of some of the materials gave good monitoring, yet not all drugs are characterized with autofluorescence, limiting the use of this method.<sup>[60]</sup> In addition to the dividing issue, there is a question of how the physiological environment influences the crystals' dissolution, whether in blood circulation or in the gastrointestinal tract. Given the unique conditions of every tissue, the crystal may be affected by the biological elements.<sup>[60]</sup>

Another interesting feature that drug crystals hold is the ability to create a co-crystal or a hybrid crystal, which is composed of multiple materials, suggesting targeting several elements simultaneously.<sup>[60,73]</sup> One such methodology could be co-crystals, defined by the FDA as following: "crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers ("coformers"), in the same crystal lattice."<sup>[74]</sup> Creating such combination is not an easy task, since the drug might not have the same solubility, and they may not mix well together.<sup>[73]</sup> Hence, a drug hybrid crystal is with great advance to solve these issues: crystalline formulation enhances the solubility, improving the bioavailability, stabilizes the product.<sup>[73]</sup> Former researchers who investigated this administration method have demonstrated the potential for oral, intravenous, transdermal, ocular, and pulmonary administration,<sup>[60]</sup> suggesting a wide range of complex diseases such as cancer or systemic diseases such as diabetes and Crohn's disease that could be treated and managed in a more sophisticated and wide fashion.

### 2.3. Multilayer DDS

Multilayer devices are based on the deposition and absorption of several thin films on top of each other, in a successive

manner.<sup>[75,76]</sup> The commonly used methodology for multilayer devices is a layer-by-layer (LBL) deposition,<sup>[75,77,78]</sup> based on the interaction between the deposited layer, which are mainly attributed to electrostatic interactions,<sup>[75–78]</sup> hydrogen bonds,<sup>[75–77]</sup> covalent bonds,<sup>[75,76]</sup> and hydrophobic interactions.<sup>[76,77]</sup> The common techniques for LBL devices are spraying, immersion, spin coating etc.<sup>[75,76]</sup>

There are encouraging advantages in multilayer devices that could be exploited for implants and DDS development. First, it is considered as a simple and inexpensive methods.<sup>[75]</sup> The variety of materials that could be used is quite wide,<sup>[75,76]</sup> including block copolymer micelles (BCM), graphene oxide (GO), polyelectrolytes (PEs),<sup>[75,77]</sup> polysaccharides, and nanoparticles.<sup>[75]</sup> This enables flexibility in the characteristics, optimizing the materials compatibility for the device purpose. This flexibility and versatility is also contributed by the ability to tailor the device properties by altering the reaction conditions such as solvents and acidity, and also by the number and composition of the layers.<sup>[75,76]</sup>

All of these qualities have amplified the interest among researchers to study this methodology, specifically for DDS development.<sup>[75,76]</sup> Although polymers hold the ability to carry and deliver some drug molecules as many researchers demonstrated, they are still quite limited in their loading capacity, therefore they are not sufficient to perform an improved localized therapy.<sup>[75]</sup> Combining two or more materials in a multilayers construction while tailoring their characteristics holds a promising opportunity to create an improved DDS.

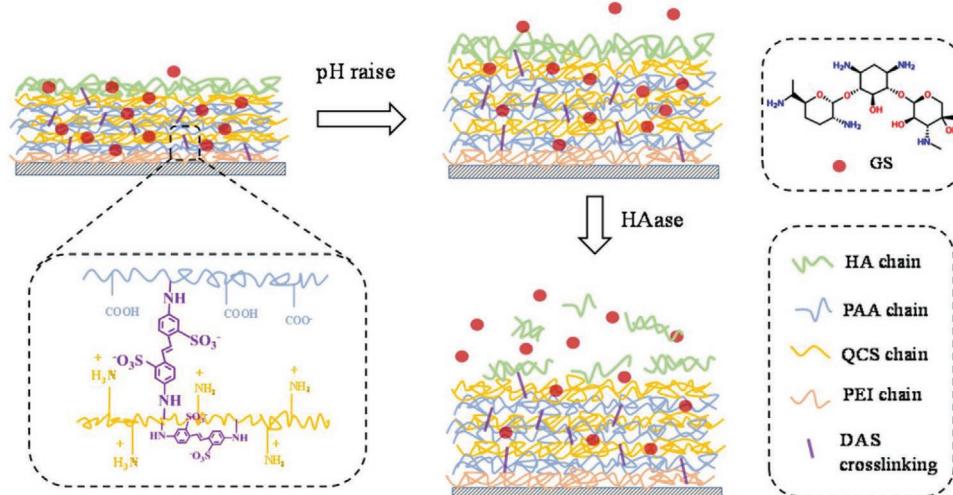
PEs are widely used in multilayer devices, specifically for developing a bioactive surfaces.<sup>[77]</sup> These types of polymers are usually characterized with high molecular weight and charged groups,<sup>[77]</sup> enhancing the interaction between the film's layers and therefore give a good adhesion. PEs are frequently used for theraped carriers, diagnostics, implant's functionalization, and more, and therefore attract a lot of attention in the medical field.<sup>[77]</sup>

Another unique feature of multilayer device is combining several approaches in one device, like a multilayer device which

is made from stimuli-responsive materials. Bacterial infection might also appear with medical implants, as bacteria can colonize and thrive on top of the implant surface, and even generating a biofilm.<sup>[79,80]</sup> Many attempts were made to create an LBL coating for medical devices, to provide an antimicrobial treatment for the implantation site. Yet, all of them posed a repeating problem, which is provoking bacterial resistance. Like many other drug releasing systems, most of the developed platforms release the drug continuously, without the ability to manually change the dosing in the absence of a bacterial threat. Since some of the systems are dosing very low concentration in a sustained manner, the drug concentration might be under the minimum inhibitory concentration (MIC), contributing to the bacterial resistance.<sup>[79]</sup>

Therefore, there is a need to develop a DDS that will allow the release of the drug only around bacterial environment. One such platform was described by Ayaz et al.'s research of a dual responsive multilayer DDS for bacterial infection treatment.<sup>[79]</sup> As infected sites are characterized by lower pH levels, most of the researchers exploited this stimulus alone. Here, it was combined with hyaluronidase (HAase)-responsive together, creating a dual-responsive device with enhanced ability to control the release profile.<sup>[79]</sup> A silicone substrate was initially treated with polyethyleneimine. Later, the bilayer of polyacrylic acid (PAA) and quaternary ammonium salt (QCS) was formed by dip coating five times, creating five bilayers on top of each other.<sup>[79]</sup> Then, the device was immersed in hyaluronic acid (HA) solution three times, following a UV crosslinking. The device was loaded with gentamicin sulfate (GS), which is a known antibiotic. Loading was conducted at pH 5 and 7.4 for 5 h (**Figure 8**).

At a low pH, PAA is neutral, thanks to the carboxyl group protonation, therefore it is more hydrophobic and less absorbing. Yet at higher pH levels, deprotonation occurs, generating more electrostatic interactions that enables increased water absorbing that results in swelling.<sup>[79]</sup> This swelling promotes the release of the positively charged GS, giving the antimicrobial effect. Tests also revealed that the addition of the HA layer slowed the release rate of the GS, in both pH levels. This confirms the role



**Figure 8.** Illustration of the multilayer structure and conformational change under pH shift and with HAase activity. Reproduced with permission.<sup>[79]</sup> Copyright 2020, Elsevier.

of the HA as a barrier. Since the complex is more swelled at pH 7.4, more drug is released. Also, in the presence of HAase the release rate is increased, thanks to the elimination of the HA barrier. Finally, the efficacy of the device was tested on *Staphylococcus aureus* and *Escherichia coli*. The device showed antibacterial activity, which was enhanced in the presence of HAase. Also, the HA layer prevents the bacterial adhesion and plays a role in bacterial adhesion inhibition. To conclude, this device is able to inhibit the contamination. In case the bacteria succeed in growing, the HAase that is produced from the bacteria will degrade the HA, and by that will promote the release on the antimicrobial agent, that will eliminate it. This is a fine demonstration of one of the greatest strengths of multilayer devices that easily combined several properties by combining several materials to one smart platform.

Multilayer devices also have the ability to integrate other known platforms in their layer, suggesting a protection from degradation and the addition of more functionalities. One such usage was demonstrated in the research of Scheffler et al. who investigated the integration of DNA origami nanostructure (DON) in multilayer biopolymers nanocarriers.<sup>[81]</sup> DON are widely explored for DDS purposes, due to their biocompatibility, high solubility, and ability to be designed and tailored according to the need. Also, DON were proved to be uptaken by mammalian cells,<sup>[82]</sup> and also to be responsive for bio-stimuli.<sup>[81]</sup> However, DON have some limitations: the integrity of the nanostructure is hardly maintained under the physiological environment that is rich with enzymes. Second, even if the DON is internalized it is prone to degradation in the lysosomal compartment, not accomplishing its destination.<sup>[81]</sup> But most importantly, although the DNA is a native component to the cell, it still might provoke an immune response, rising serious limitations to the possible usages of DON.<sup>[81]</sup>

One accepted approach is to use a lipid coat that enhances the DON biocompatibility. This research exploited the fact that multilayer could be designed as wanted and integrated with any desired molecules. Researchers created an LBL integrated nanocarrier, composed of two known biocompatible biopolymers: poly-L-arginine (ARG) and dextran sulfate (DXS). As ARG is positively charged and DXS is negatively charged, they are easily assembled onto a silica spherical template. Since DNA is negatively charged, hollow DONs were finely integrated in an internal layer of the ARG.<sup>[81]</sup> Experiments showed that negatively charged particles do not aggregate, so the DON concentration was chosen according to the essential charge for preventing the nanocarriers aggregation. Authors tested the ability of the LBL nanocarriers to maintain the DON integrity with lysosomal content, finding that the internal integration of the DON provides the needed protection from the enzymes and acid environment.<sup>[81]</sup> The LBL nanocarriers interaction with HEK293T/17 cell line was examined, finding that indeed the cells are able to uptake the particles, without harming the cells viability.<sup>[81]</sup>

The ability of the DON to be loaded with cargo was also tested with bovine serum albumin (BSA) as a model, proving that the DON could serve as a smart transporter. DON are very interesting options for drug delivery purposes, yet they are still at the stage of concept due to their drawbacks. Although multilayer devices were proven to be effective for DDS by themselves, the

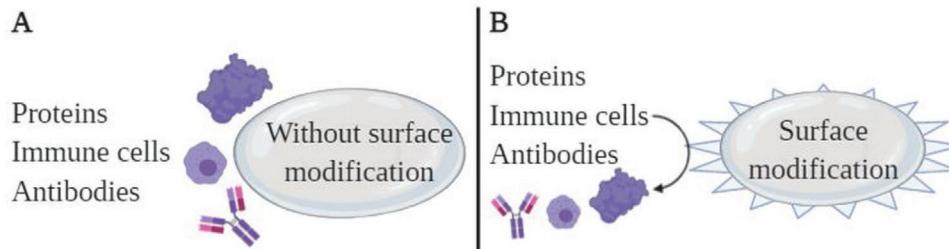
integration of other element such as DON have a great potential to increase their selectivity. As mentioned, it is common to coat the DON with a lipid bilayer in order to enhance their biocompatibility, and allowing functionalization.<sup>[81]</sup> Combining the DON integration in a simple LBL nanocarrier with a lipid bilayer coat could improve and create a smart carrier that will be able to carry cargo efficiently, along with other functionalities that enable selective release of the cargo and smart delivery to the target site.<sup>[81]</sup>

Multilayer based devices suggest a great opportunity for DDS and implantable medical devices design, offering the ability to combine multiple localized immunosuppressive effects in one device. Since the integration is based on simple processes and interaction, the device properties could be easily tailored according to the need. Multilayer devices enable the loading of other structure such as DON and small molecules, providing a protection from physiological elements and conditions. Finally, the functionalization ability also enables to create a smart, programmed device that will serve as an improved treatment platform.

### 3. Surface Modification of Polymers for Biocompatibility Enhancement

Biocompatibility of a device can be improved in two ways. One is by producing a nonfouling surface coating so that the unwanted nonspecific protein and bacteria will not form a layer on the device surface. Second the surrounding immune cells of the implantable device must be given proper cues in order to have a good communication between the surrounding cells and the device.<sup>[1]</sup> Identification of a proper biocompatible material showing low fouling nature is always of great interest in the implantable medical devices research. For biosensors using for affinity applications, it is very important to have an ultralow fouling surface coatings on the surface of such a device along with other biosensing elements.<sup>[83]</sup> Surface modifications to improve the biocompatibility of the implantable medical devices can be possible by various grafting methodologies. These grafting methods can affect the surface properties of the substrate without compromising its mechanical properties.<sup>[84]</sup> Conventional surface modification can be classified into chemical and physical methods. Chemical surface modification is often more advantageous than physical modifications. This method avoids desorption and improves the long-term stability. The grafting surface modifications can be done in three ways such as grafting to, grafting from, and grafting through.<sup>[84]</sup> Along with grafting methods various other surface modification techniques such as physical, chemical, mechanical, and biological methods have been mentioned in the literature.<sup>[85–88]</sup> Figure 9 describes implantable medical devices without and with the surface modification and their effects in developing the FBR and reduced-FBR.

Among the various nonfouling materials for implantable medical devices coating, polyethylene glycols (PEGs) are the most common nonfouling materials for surface decontamination in order to improve the biocompatibility of the implantable devices and enhance functionality.<sup>[89,90]</sup> Self-assembled monolayers (SAMs) based on PEGs have been widely applied as



**Figure 9.** Description of an implant with and without surface modifications. A) The implantable device without surface modifications leads to the adherence of various biomolecules on the surface and elicits FBR. B) The modified surface of a device with nonfouling materials prevents the adherence and repels the biomolecules on the device and reduces the FBR. Created with BioRender.com.

sensors.<sup>[91]</sup> However, when it comes to the exposure of real and complex media, there has been a limitation with the shorter oligo ethylene glycols. Several other strategies based on PEGs and their copolymers have been demonstrated for the non-fouling surface coating for biomedical applications.<sup>[89]</sup> One of the reasons for the excellent performance of PEGs for the non-fouling applications is the length and graft density. Also, PEGs have shown minimal interactions with proteins. The high hydration capacity of PEG chains in water creates extraordinary mobility and they show good conformational flexibility. These important qualities of PEGs made them very good barrier chains in preventing the adsorption of nonspecific proteins.<sup>[92]</sup>

In general, PEGs in their free form do not show any immunogenicity. However, they are extremely immunogenic once anchored to an immunogenic carrier and working similar to a haptan.<sup>[93]</sup> PEG-specific antibodies (Abs) have been found both in animals and humans and showed negative impact in the biomedical treatments causing mortality in the patients.<sup>[94]</sup> Due to this reason, the application of PEG in the biomedical field has become unsafe.<sup>[95,96]</sup>

To overcome the serious concerns of PEG based nonfouling coatings, in the recent times, zwitterionic polymers have been applied as coatings on the surface of the implantable devices to improve the biocompatibility. These coatings possess ultralow fouling capacity.<sup>[97]</sup> The zwitterionic materials have the capacity to hold water by electrostatically induced hydration mechanism.<sup>[98]</sup> This helps in blocking the adhesion of nonspecific proteins and bacteria to the surfaces of the devices and improves the biocompatibility.<sup>[99]</sup> Zwitterions possess both positive and negative charges in equal proportion and are electrically neutral molecules having the strong hydrophilicity.<sup>[100–102]</sup> The charges that present in the zwitterionic polymers are even stronger than the hydration capacity of PEGs, which is highly valuable for the ultralow antifouling capacity of these polymers.<sup>[103]</sup> The unique properties of zwitterionic polymers made them to have a successful in vivo application in minimizing the nonspecific protein interaction with the implanted devices.<sup>[104]</sup>

Various zwitterionic polymers such as poly(2-methacryloyloxyethyl phosphorylcholine), poly(sulfobetaine), poly(carboxy betaine), and recently poly(trimethylamine N-oxide) have been utilized to improve the biocompatibility of medical devices, implants, and DDSs.<sup>[98,105–107]</sup>

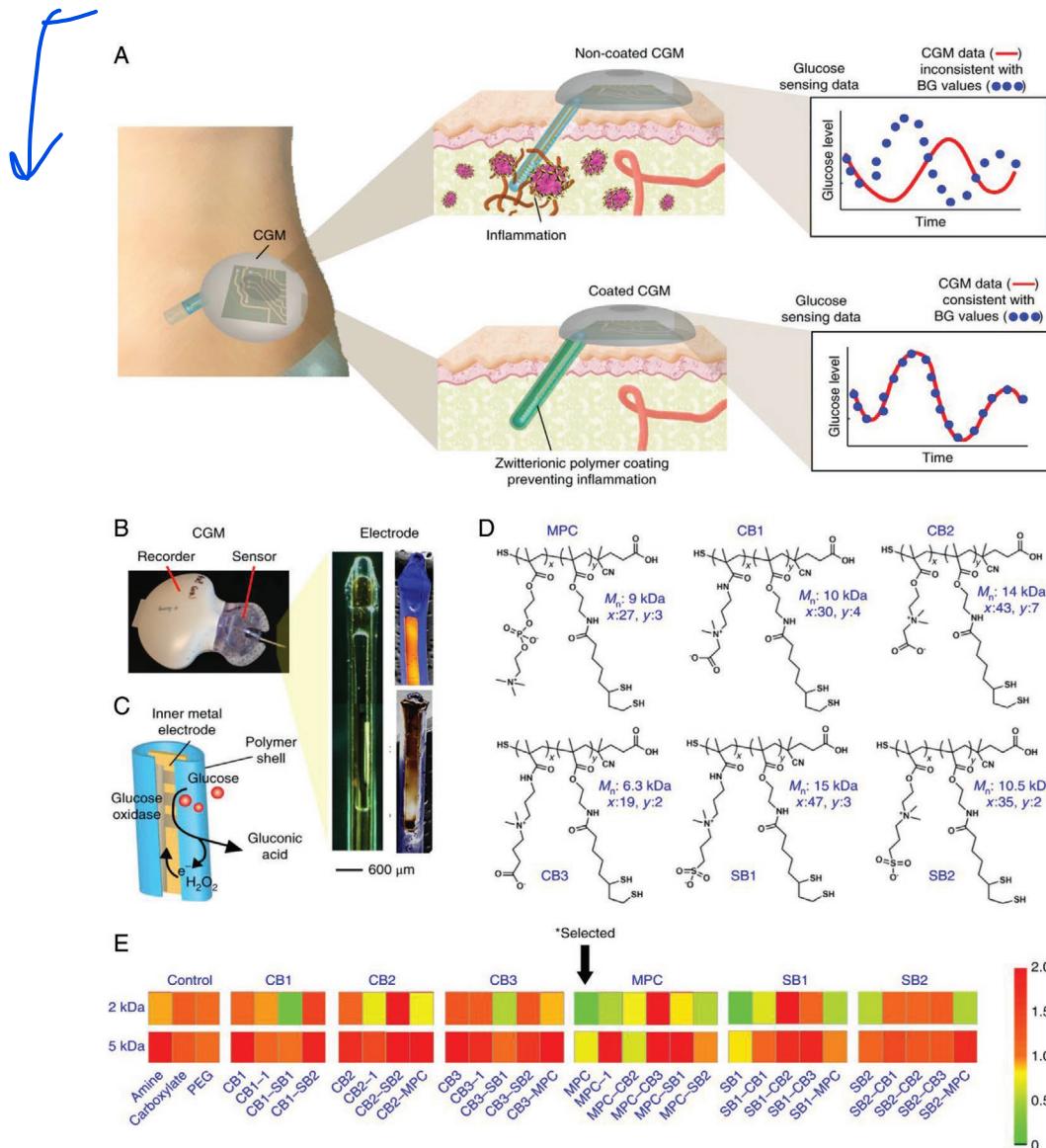
In one example, poly(carboxybetaine) zwitterionic hydrogels were effectively functioning to mitigate the FBR and were strongly resisted the formation of capsules for at least 3 months when implanted in mice, whereas PHEMA showed

inflammatory effect. Carboxybetaine mimics the natural glycine betaine, which is an osmoregulant.<sup>[108]</sup>

In a recent study from the Anderson lab, a library of zwitterionic polymers has been synthesized using combinatorial chemical approach and used for the improvement of biocompatibility of CGM (Figure 10). It is apparent that the FBR induces a substantial noise during the signals generated by the CGM and it is the reason frequent blood glucose recalibration is needed. A substantial progress has been made to overcome this limitation by fabricating the zwitterionic polymer coating on the Medtronic CGM as a model sensor. By applying this coating on the sensor, the ability to reduce signal noise as well as improvement in the biocompatibility of the device has been achieved with accurate glucose levels monitoring in mice model and also in NHPs. In this study, among the three zwitterion types poly(2-methacryloyloxyethyl phosphorylcholine) showed significant anti-inflammatory action compared to carboxybetaines and sulfobetaines.<sup>[105]</sup>

Nonfouling property of zwitterionic polymers and also the hydration capacity increases with the decrease in the intramolecular distances between the positive and negative charges of the head groups of the zwitterions.<sup>[109]</sup> Based on this, naturally occurring small organic osmolyte trimethylamine N-oxide (TMAO) present in the fish has been utilized as a zwitterionic head group for nonfouling applications.<sup>[107]</sup> The charges on this zwitterionic head group are directly connected without having any spacer between them.<sup>[110]</sup> Furthermore, TMAO has showed protein stabilizing ability.<sup>[111]</sup> Due to its protein stabilizing nature along with the superhydrophilic property, the authors have reported the TMAO based polymer as an entirely new class of zwitterionic head group possessing exceptional non-fouling nature both in vitro and in vivo conditions. The reason behind this exceptional nonfouling capacity was attributed to the TMAO extraordinary hydration capacity as studied by molecular dynamics (Figure 11). With this, the fourth zwitterionic moiety was added to the literature along with carboxybetaine, sulfobetaine, and phosphorylcholine which is demonstrated to enrich the arsenal of nonfouling materials.<sup>[107]</sup>

The same group of researchers has added another masterpiece of work in the zwitterionic nonfouling materials: functional zwitterionic polymers. Phosphoserine based functional zwitterionic polymers have been prepared.<sup>[104]</sup> This polymer possesses both immunomodulatory ability and nonfouling nature which was outperforming the available zwitterionic polymers. Uricase conjugation to this polymer has proved to eradicate all unsolicited immune responses (Figure 12).

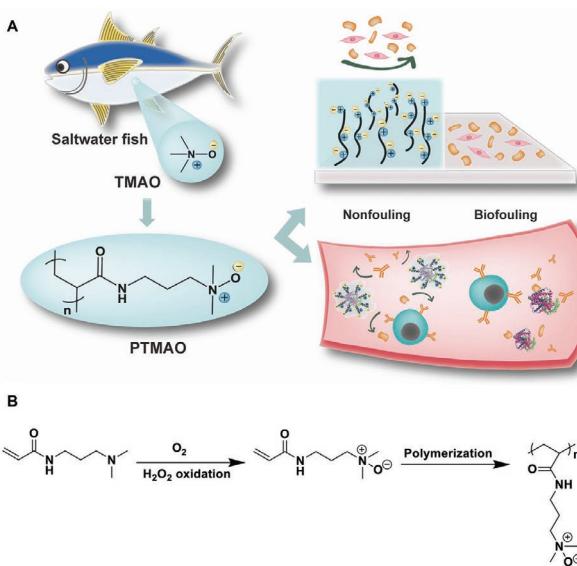


**Figure 10.** A) Noncoated sensor induces inflammatory immune cascade, and the host response causes sensor noise and inaccuracy requiring frequent blood glucose calibrations. The zwitterionic polymer-coated sensor overcomes the hostile *in vivo* environment, eliminating sensor noise and the requirement for BG recalibrations. B) Components of the CGM, including bright-field and scanning electron microscopy images of the CGM electrode. C) Illustration of the enzymatic mechanism of glucose detection by the electrode. D) Examples of different zwitterionic copolymer units utilized for constructing biomaterial combinatorial library. MPC stems from phosphorylcholine, CB1–CB3 stem from carboxybetaine with different spacer lengths, and SB1, SB2 represent slightly different sulfobetaine zwitterionic structures. E) Biocompatibility (inflammation profile) results from the zwitterionic biomaterial library screen. The combinatorial library contained 64 various zwitterionic polymer hydrogels using four-arm PEG polymers (2 or 5 kDa) as crosslinkers. Reproduced with permission.<sup>[105]</sup> Copyright 2018, Springer Nature.

This class of functional zwitterionic nonfouling material possessing immunomodulatory ability has given new insights in the biomaterials field to improve the biocompatibility of implants.

Another interesting polymer that is used as coating on the implants or for medical devices fabrication and is capable to mitigate the FBR and improve the biocompatibility is alginate. Alginate is an anionic biopolymer available from brown seaweed.<sup>[112]</sup> It forms hydrogels in the aqueous solution of dications such as calcium and barium. These hydrogels find numerous applications in the various fields of biology and medicine including implantable sensors.<sup>[113]</sup> The low toxicity and mild

gelation property of this polymer made it one of the popular coating materials particularly in medical implants.<sup>[113,114]</sup> The immune response of alginate microspheres and even increased response in the presence of allogeneic and xenogeneic donor tissue has been reported in the literature.<sup>[115]</sup> In order to identify the alginate materials with low immune response, Anderson's group developed a combinatorial library of alginate hydrogels with various chemical modifications thereby altering the properties to address the FBR.<sup>[116]</sup> The low molecular weight ultrapure alginate was chemically modified to have 774 materials with various functionalities such as amines, azides, alcohols, and alkynes. Among 774 modified alginate materials, 634 materials



**Figure 11.** Scheme illustration of poly(trimethylamine N-oxide) (PTMAO). A) The design of PTMAO is derived from TMAO, a zwitterionic osmolyte in saltwater fishes. The nonfouling property of PTMAO could effectively prevent a surface from biofouling both *in vitro* and *in vivo*. B) Scheme of TMAO monomer and polymer synthesis. Reproduced with permission.<sup>[107]</sup> Copyright 2019, American Association for the Advancement of Science.

showed the capacity to form a gel. Among all the studied class of molecules, triazole functionalities containing alginates (Z2-Y12, Z1-Y15, Z1-Y19) showed reduced FBR (**Figure 13**). In another study by the same group found that the larger size microspheres (>1.5 mm) of alginates showed reduced FBR in mice, indicating the role of implant size in reducing FBR.<sup>[117]</sup> Further, clinical potentials of the triazole functionalities containing alginate polymers have been studied for long term glycemic correction with SC- $\beta$  cells and it was found that the increased sphere size and appropriate chemical modification is important to mitigate the FBR.<sup>[118]</sup> Moreover, the encapsulation of allogeneic cells with Z1-Y15 has achieved long term protection without immunosuppression in NHPs.<sup>[119]</sup>

In another study, zwitterionic moiety sulfobetaine was incorporated covalently into the alginate polysaccharide.<sup>[120]</sup> This modified zwitterionic polysaccharide was utilized to check the therapeutic potential in the type 1 diabetic mouse model with xenogeneic tissue. The xenogeneic tissue cells encapsulated with zwitterionic alginate polysaccharide showed significant reduction in the cellular overgrowth whereas unmodified alginate encapsulated with cells covered by the cellular overgrowth elicited FBR (**Figure 14**).

In summary, **Figure 15** presents the above-mentioned surface modifications with respect to their chemistries. These surface modifications have an important role in the improvement of biocompatibility and longevity of implantable medical devices. Four important characteristic features of a nonfouling coating such as overall neutral surface charge, accepting the hydrogen bonding, lack of hydrogen bonding, and a high hydration capacity are important.<sup>[121]</sup> Based on these characteristic features which are available with the nonfouling surface coating, direct comparison on the performance of the nonfouling

materials presented in this discussion is complicated. However, the hydration capacity is the most relevant feature that is possible with both PEGs and zwitterions. The hydration capacity to form a hydration layer on the zwitterionic surface coating on the device is more efficient compared to PEGs regardless of the coming influx of proteins to have an interaction with the surface coating. This is also highly dependent on a particular study design.<sup>[122]</sup>

## 4. Summary, Perspectives, and Future Outlook

### 4.1. Critical Design Considerations for Biomedical Implants

The host reaction postimplantation could determine the success of the process and the device performance.<sup>[123]</sup> In the perspective of provoking an FBR, there are important considerations that should be taken when designing a biomedical implant:

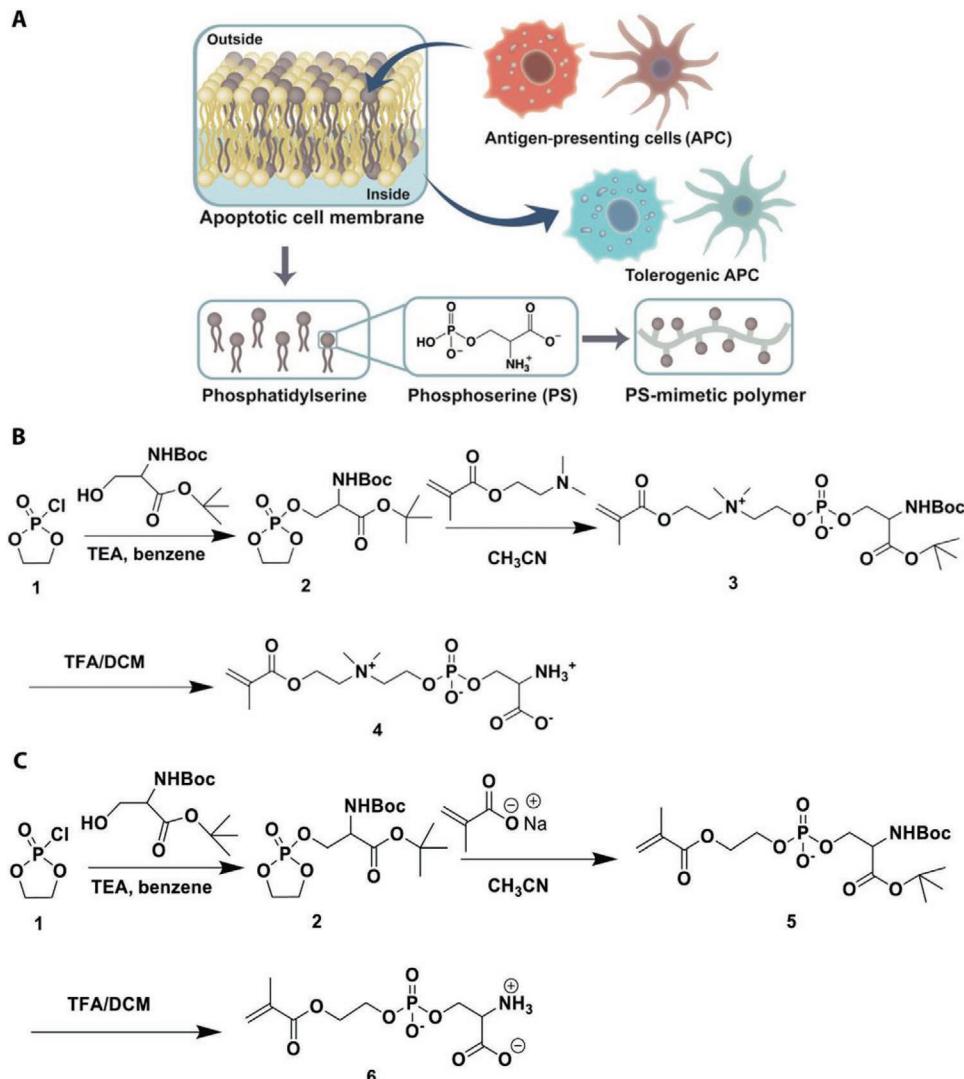
First, the geometry and size of the implant are with great importance.<sup>[2,14,123]</sup> Some shapes were found as more prone to cause a more severe response than others: rods with a circular cross section exhibited a milder reaction compared with rods that had a triangular or pentagonal cross section.

Second, the size of the implanted object is also important. When considering small particles, their size will affect their uptake. Nanometric scale particles tend to be uptake by immune cells, and therefore induce immunogenicity.<sup>[124]</sup> In a research that examined sphere shaped implants with a diameter in a range of 0.3–1.9 mm found that the 1.5 mm demonstrated the mildest reaction.<sup>[2,123,124]</sup> There are additional physical properties that should be considered, like the surface smoothness<sup>[2,123]</sup> and the implant porosity.<sup>[2]</sup>

Third, the mechanical properties of the implant are also important, such as the implant's Young's modulus. Since the body tissue's modulus is in the range of 1–100 kPa, the difference between the implant and the tissues stiffness may encourage the FBR. Therefore, it is important to pay attention to the mechanical properties of the implant during the design process.<sup>[2]</sup>

Fourth, degradability and nondegradability of biomedical implants are also important. When using a biodegradable implant, typically the need for a follow-up invasive surgery is dismissed. As the vast majority of implant provoke an FBR, the uniqueness of a biodegradable material is the shorter and milder reaction that happens.<sup>[2]</sup> When specifically addressing biodegradable implants, one should also pay attention to the degradation products, which also affect the immune reaction. Moreover, the interaction of the implant composite and immune reaction also affects the degradation process. As the degradation occurs, the implant biological microenvironment changes. This causes some changes in the implant surface, which affect the protein layer which is absorbed on top of the implant.<sup>[2]</sup> Therefore, this relationship should be investigated as well.

There are more considerations that should be taken beside the physical properties; for example, the surface chemistry of the implant which plays a key role in setting the immune response level.<sup>[87,123]</sup> This has a direct effect on the absorbance of the plasma protein on top of the implant. The absorbance



**Figure 12.** Illustration of phosphoserine (PS)-mimetic polymers. A) Design of PS-mimetic polymers built from phosphoserine, an immunomodulatory molecule naturally occurring on the outside membranes of apoptotic cells. B) Synthesis of the polymerizable zwitterionic phosphoserine-mimetic monomer. C) Synthesis of the polymerizable nonzwitterionic PS-mimetic polymer monomer. Reproduced with permission.<sup>[104]</sup> Copyright 2020, American Association for the Advancement of Science.

step leads to the recruitment of additional immune factors and proteins and therefore influences the FBR.<sup>[123]</sup> The implant charge and hydrophobicity could also have an effect on the reaction.<sup>[124]</sup> It is also important to remember that in the case of a biodegradable implant, the surface goes through continuous change, which affects the immune response as well.<sup>[2]</sup>

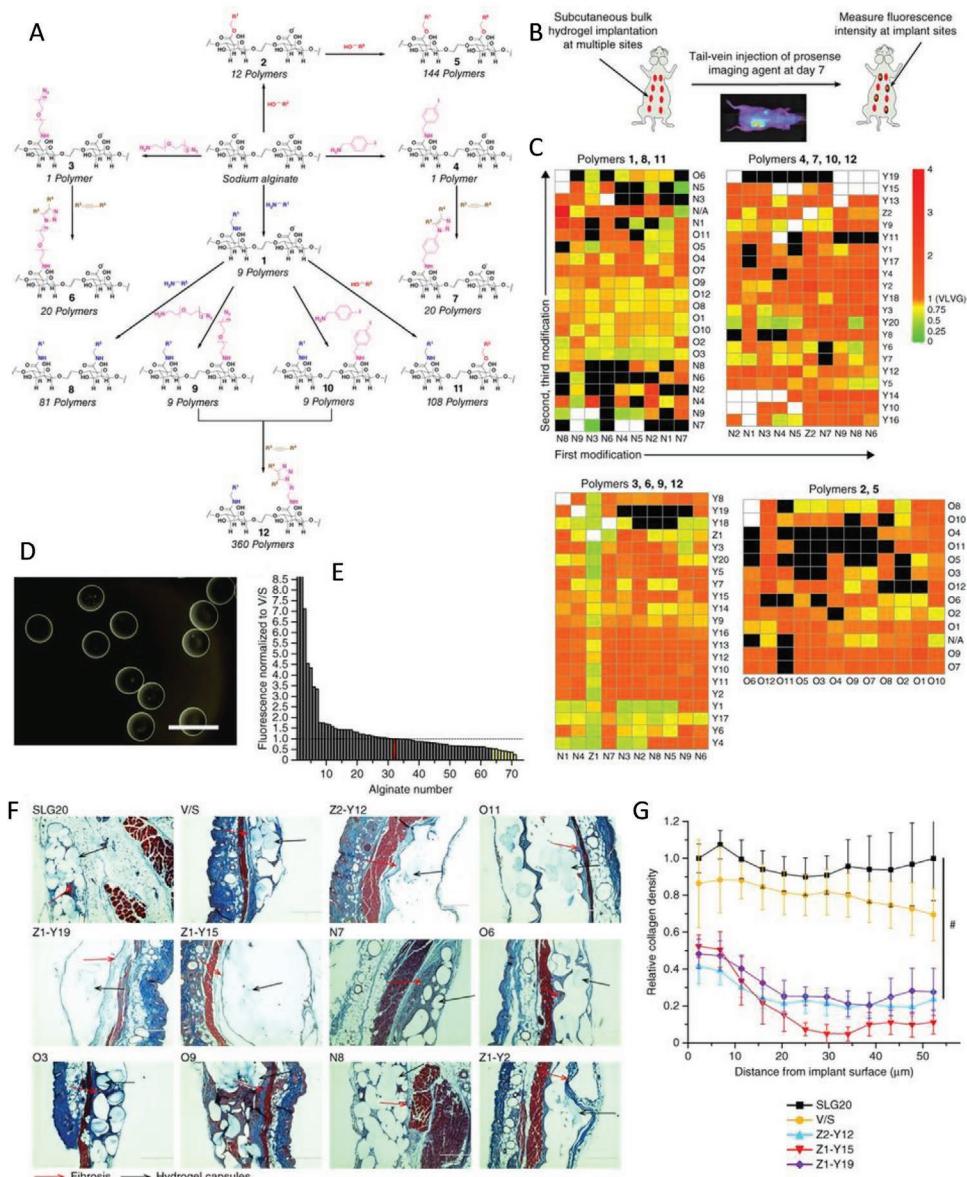
There are also other factors that are not directly related to the implant itself. The implantation site and implant's microenvironment, tissue type and texture, implant mode of action, i.e., static versus dynamic, all together could affect the stability of the implant, degradation kinetic, the implantation procedure, and the patient health condition.<sup>[2]</sup>

It is clear that successful designing of an implant requires the integration of the aforementioned considerations as well as others, regarding both functionality duration and immunogenicity, and thus further studies are needed for each type of implant.

#### 4.2. Comparison between the Two Strategies

One of the main issues with biomedical implants is the host response. As the implantation itself causes a local injury, inflammation occurs. In case of a nondegradable implant, the formed inflammation might eventually cause a fibrotic capsule around the device, leading to its failure. Currently the solution is administrating immunosuppressive drugs, though the potential risk to the patient is high. Therefore, finding a suitable treatment for postimplantation reaction is highly required. Here, we addressed two main approaches to biocompatibility enhancement and elongated functionality, which are controlling the effect of the immunosuppressive drugs by using DDS and surface modifications of the device in order to prevent/decrease the immune response in advance.

The first approach includes stimuli-responsive platforms, which enable the drug release once a defined and known



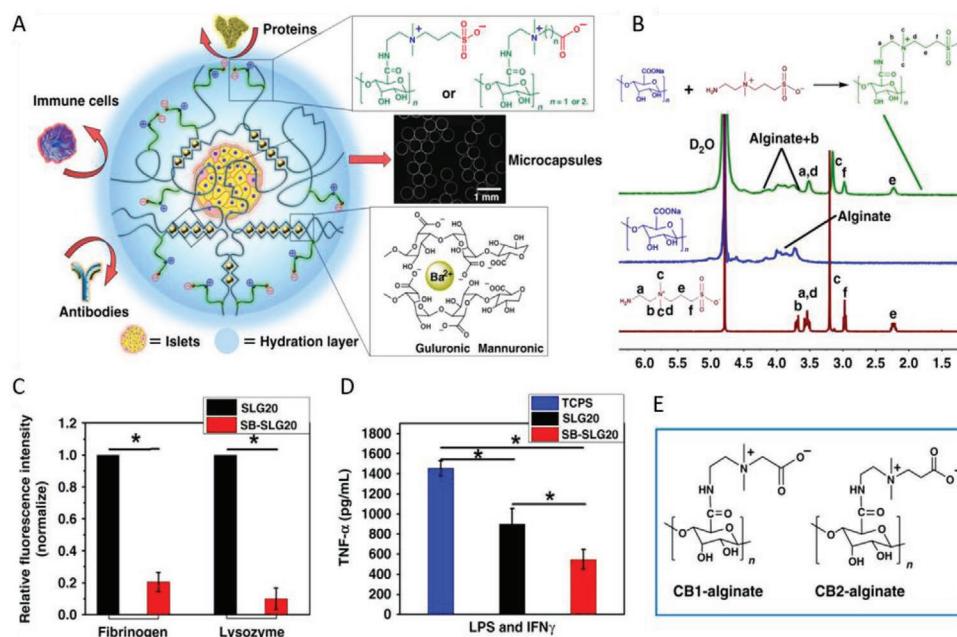
**Figure 13.** A) Synthesis of combinatorial libraries of modified alginates. B) Rapid evaluation of synthesized alginate analogues as bulk hydrogels implanted subcutaneously in the mouse model and the measurement of fluorescence 7 d postimplantation. C) Heat map summarizing gelation and cathepsin evaluation for the entire alginate analog library. D) Microspheres of various alginate analogs and their blends formulated using electrojetting to have good spherical morphology. Scale bar 1000  $\mu\text{m}$ . E) Secondary cathepsin evaluation of top 69 analogs. F) Masson's trichrome (MT) 28-day subcutaneous histology of the top 10 alginate analog microcapsules and the ultrapure control alginate microcapsules, scale bar, 400  $\mu\text{m}$ . G) Quantification of collagen density in the MT-stained histology images of the three lead materials shown in (F). Reproduced with permission.<sup>[116]</sup> Copyright 2016, Springer Nature.

stimulus/stimuli appears. Crystalline form of drug is also of great advantage, suggesting a pure drug dose with prolonged releasing profile. Multilayer devices are easily assembled, suggesting the ability to integrate several approaches, structures, and functionalities.

The concept of localized DDS is revolutionary, solving many issues of the systemic effect caused by most of the known and common treatments. However, it is still in its first steps in becoming feasible and available in the clinic. First, many developments encounter difficulties in becoming a commercialized product. This might be due to several reasons, such

as expensive costs, inability for scale-up, complicated storage requirements, etc. Second, many developments stop after *in vitro* or *in vivo* experiments, not reaching the clinical trials phase. Some of them are even held in the proof of concept phase, which is insufficient. Future development should focus on cheap and easy to manufacture solutions. This will also ease the clinical testing, reaching more progressive phases in the way to become a used product in the clinics.

The second approach includes surface modifications. To mitigate the nonspecific protein adsorption on the implantable devices, various surface nonfouling materials as coatings



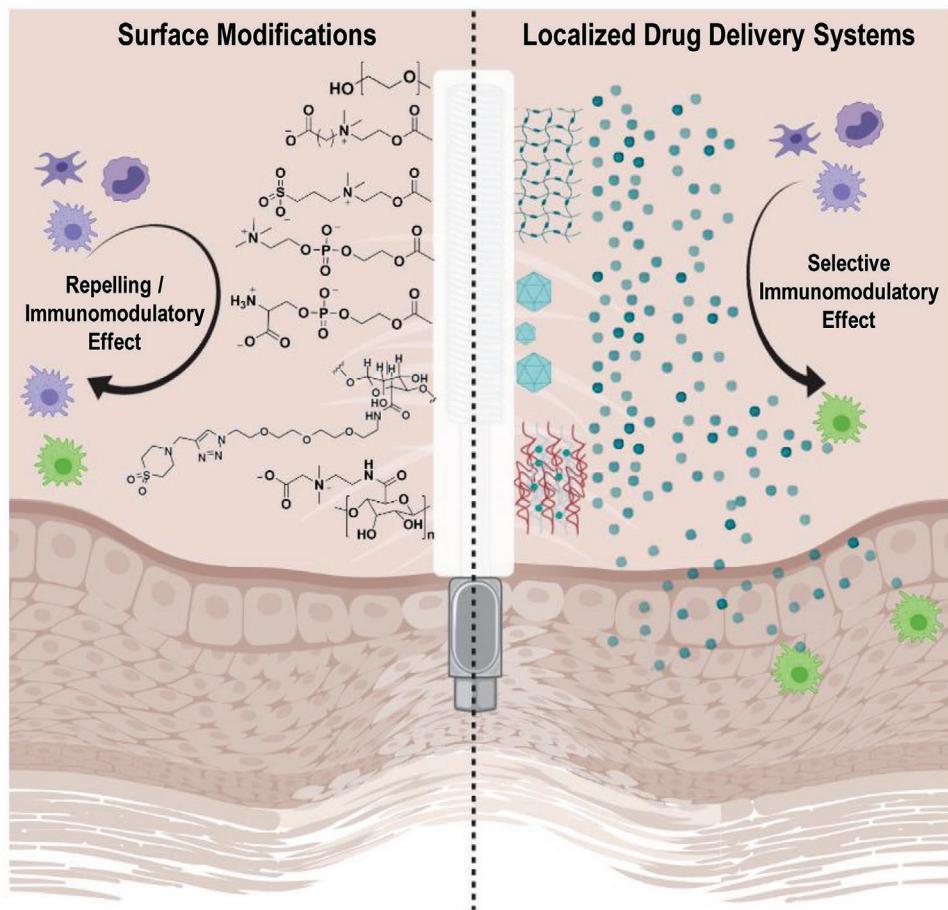
**Figure 14.** Design of zwitterionically modified alginates and their in vitro characterizations. A) Schematic illustration of zwitterionically modified alginate microcapsules encapsulating islets. B) Synthetic pathway and  $^1\text{H}$  NMR characterization of sulfobetaine (SB)-modification of alginate. C) Adsorption of fluorescein isothiocyanate-labeled fibrinogen and lysozyme on the surfaces of different alginate hydrogels quantified by ImageJ. mean $\pm$ SEM;  $n = 6$ ; \* $p < 0.05$ . D) Quantification of TNF- $\alpha$  secretion from macrophages cultured on different surfaces. mean $\pm$ SEM;  $n = 5$ ; \* $p < 0.05$ . E) Chemical structures of CB1-alginate and CB2-alginate conjugates. Reproduced with permission.<sup>[120]</sup> Copyright 2019, Springer Nature.

are applied. Among available nonfouling materials, PEGs are the most common type for nonfouling surfaces of implantable devices. Though PEG as such does not show any immunogenicity, when it is conjugated to an immunogenic carrier it elicits immunogenicity. Also, PEG-specific Abs found both in animals and humans had a negative impact on the health. In the recent times, zwitterionic polymers are promising materials for surface modifications. The structural integrity of zwitterionic materials makes them unique alternative to the conventional PEGs and their derivatives as nonfouling

surface coatings for the improvement of biocompatibility of implantable medical devices. Since zwitterions possess equal amounts of both positive and negative charges, they maintain electrical neutrality and show super hydrophilic nature at the surface. As identified recently, a natural osmolyte TMAO as a zwitterionic material along with other zwitterions based materials such as poly(2-methacryloyloxyethyl phosphorylcholine) and poly(sulfobetaine), poly(carboxybetaine). Together, these zwitterions have been extensively studied for the improvement of biocompatibility and longevity of the implantable medical devices. All these zwitterionic compounds have been mainly working as nonfouling surface coatings for the surface modifications of the implantable medical devices. Functional zwitterionic nonfouling material addition to the existing zwitterions is advantageous in improving the biocompatibility as a surface coating along with suppressing the undesired immune responses. For example, phosphoserine based zwitterionic polymer for the first time ensures both nonfouling and immunomodulatory functions which was never found in a single material. The functional zwitterionic polymers concept has given a new direction in the improvement of biocompatibility as a nonfouling surface coating and also by dropping the nonspecific interactions of biomaterials with complex media. Another interesting biopolymer is alginate, which has been modified chemically via click chemistry with various functionalities, specifically thiomorpholine dioxide, as a surface agent in order to prevent the FBR to improve the biocompatibility.

In comparison, when considering the two aforementioned approaches, one should see the differences between the given effects driven by the mechanism of action (Figure 16).

**Figure 15.** Recent advances in surface modification approaches for improving functionality, biocompatibility, and longevity of implantable medical devices.



**Figure 16.** Illustration of the repelling/immunomodulatory effect made by surface modifications and the selective immunomodulatory effect made by DDS. Left: the local repelling/immunomodulatory effect made by contact with the modified surface. Right: the therapeutic effect made by diffusion of the DDS. Created with BioRender.com.

When using DDS, the immune-modulating drug molecules diffuse in the local microenvironment of the device, so the therapeutic effect is local yet wider, with the possibility to diffuse in the nearby tissue thus impacting immune players in relatively close distance from the implant, including nearby tissues. However, surface modifications give a repelling action, and in some cases are also accompanied with an immunomodulatory effect, both occurring via surface contact. Therefore, surface modifications act more locally, which may limit the wider effectiveness. On the other hand, chemical modifications are supposed to be permanent offering long-term impact. Such a localized long-term impact is also found to be achievable by using well designed localized DDS, such as the reported compact crystals.<sup>[59]</sup>

Choosing the appropriate approach to be followed depends on a variety of factors such as implantable device features, including: size, shape, surface topography, composing materials, complexity of the implant (with or without cellular components), mode of action, purpose (therapeutic, diagnostics, theranostics), as well as other nondevice depending factors such as implantation site and desired duration/course of treatment. While both approaches hold a great potential in boosting implantable devices and deliverable functionality, longevity, as well as enhancing their biocompatibility, still there is no

enough comparison between the two approaches as well as combination studies and thus appropriate research efforts should be allocated for this purpose.

## Acknowledgements

N.K. and K.R.K. contributed equally to this work. The Neubauer Family Foundation is thanked for their generous funding and support. S.F. was supported by MAOF Fellowship from the Council for Higher Education, Israel.

## Conflict of Interest

The authors declare no conflict of interest.

## Keywords

bioactive surfaces, biocompatibility, crystals, drug delivery systems, foreign body response, medical implants, zwitterions

Received: December 19, 2020

Revised: March 6, 2021

Published online: April 15, 2021

- [1] S. R. Meyers, M. W. Grinstaff, *Chem. Rev.* **2012**, *112*, 1615.
- [2] C. Li, C. Guo, V. Fitzpatrick, A. Ibrahim, M. J. Zwierstra, P. Hanna, A. Lechtig, A. Nazarian, S. J. Lin, D. L. Kaplan, *Nat. Rev. Mater.* **2020**, *5*, 61.
- [3] A. J. Domb, W. Khan, *Focal Controlled Drug Delivery*, Springer, Boston, MA **2014**, pp. 33–59.
- [4] J. S. Hanker, B. L. Giammara, *Science* **1988**, *242*, 885.
- [5] W. Khan, S. Farah, A. J. Domb, *J. Controlled Release* **2012**, *161*, 703.
- [6] R. Farra, N. F. Sheppard, L. McCabe, R. M. Neer, J. M. Anderson, J. T. Santini, M. J. Cima, R. Langer, *Sci. Transl. Med.* **2012**, *4*, 122ra21.
- [7] R. Londono, S. F. Badylak, *Host Response to Biomaterials: The Impact of Host Response on Biomaterial Selection*, Elsevier Inc., Amsterdam **2015**, pp. 1–12.
- [8] B. Corradetti, *The Immune Response to Implanted Materials and Devices*, Springer, Berlin **2017**, pp. 1–14.
- [9] O. Veiseh, A. J. Vegas, *Adv. Drug Delivery Rev.* **2019**, *144*, 148.
- [10] A. S. Xue, J. C. Koshy, W. M. Weathers, E. M. Wolfswinkel, Y. Kaufman, S. E. Sharabi, R. H. Brown, M. J. Hicks, L. H. Hollier, *Craniomaxillofac. Trauma Reconstr.* **2014**, *7*, 27.
- [11] M. Rigla, B. Pons, P. Rebasa, A. Luna, F. J. Pozo, A. Caixàs, M. Villaplana, D. Subías, M. R. Bella, N. Combalia, *Diabetes Technol. Ther.* **2018**, *20*, 296.
- [12] N. J. J. O’Malley JT, B. J. Burgess, D. Galler, *Otol. Neurotol.* **2017**, *176*, 100.
- [13] M. J. Foggia, R. V. Quevedo, M. R. Hansen, *Laryngoscope Investig. Otolaryngol.* **2019**, *4*, 678.
- [14] F. Lotti, F. Ranieri, G. Vadalà, L. Zollo, G. Di Pino, *Front. Neurosci.* **2017**, *11*, 1.
- [15] P. M. Rossini, S. Micera, A. Benvenuto, J. Carpaneto, G. Cavallo, L. Citi, C. Cipriani, L. Denaro, V. Denaro, G. Di Pino, F. Ferreri, E. Guglielmelli, K. P. Hoffmann, S. Raspopovic, J. Rigos, L. Rossini, M. Tombini, P. Dario, *Clin. Neurophysiol.* **2010**, *121*, 777.
- [16] J. C. Williams, J. A. Hippenssteel, J. Dilgen, W. Shain, D. R. Kipke, *J. Neural Eng.* **2007**, *4*, 410.
- [17] J. C. Doloff, O. Veiseh, A. J. Vegas, H. H. Tam, S. Farah, M. Ma, J. Li, A. Bader, A. Chiu, A. Sadraei, S. Aresta-Dasilva, M. Griffin, S. Jhunjhunwala, M. Webber, S. Siebert, K. Tang, M. Chen, E. Langan, N. Dholokia, R. Thakrar, M. Qi, J. Oberholzer, D. L. Greiner, R. Langer, D. G. Anderson, *Nat. Mater.* **2017**, *16*, 671.
- [18] M. D. Duncan, D. S. Wilkes, *Proc. Am. Thorac. Soc.* **2005**, *2*, 449.
- [19] W. M. Saltzman, *Drug Delivery: Engineering Principles for Drug Therapy*, Oxford University Press, Oxford **2001**, pp. 3–19.
- [20] T. D. Brown, K. A. Whitehead, S. Mitragotri, *Nat. Rev. Mater.* **2020**, *5*, 127.
- [21] T. Pond, S. M. Tozer, *Clin. Pharmacokinet.* **1984**, *9*, 1.
- [22] W. Poon, B. R. Kingston, B. Ouyang, W. Ngo, W. C. W. Chan, *Nat. Nanotechnol.* **2020**, *15*, 819.
- [23] M. A. C. Stuart, W. T. S. Huck, J. Genzer, M. Müller, C. Ober, M. Stamm, G. B. Sukhorukov, I. Szleifer, V. V. Tsukruk, M. Urban, F. Winnik, S. Zauscher, I. Luzinov, S. Minko, *Nat. Mater.* **2010**, *9*, 101.
- [24] Y. Tao, H. F. Chan, B. Shi, M. Li, K. W. Leong, *Adv. Funct. Mater.* **2020**, *30*, 2005029.
- [25] T. M. Allen, P. R. Cullis, *Science* **2004**, *303*, 1818.
- [26] Y. Lu, A. A. Aimetti, R. Langer, Z. Gu, *Nat. Rev. Mater.* **2016**, *2*, 16075.
- [27] G. Kocak, C. Tuncer, V. Bütün, *Polym. Chem.* **2017**, *8*, 144.
- [28] Y. Liang, X. Zhao, P. X. Ma, B. Guo, Y. Du, X. Han, *J. Colloid Interface Sci.* **2019**, *536*, 224.
- [29] H. L. Pu, W. L. Chiang, B. Maiti, Z. X. Liao, Y. C. Ho, M. S. Shim, E. Y. Chuang, Y. Xia, H. W. Sung, *ACS Nano* **2014**, *8*, 1213.
- [30] P. Sanphui, G. Bolla, *Cryst. Growth Des.* **2018**, *18*, 5690.
- [31] N. Ninan, A. Forget, V. P. Shastri, N. H. Voelcker, A. Blencowe, *ACS Appl. Mater. Interfaces* **2016**, *8*, 28511.
- [32] I. Perelshtain, E. Ruderman, A. Francesko, M. M. Fernandes, T. Tzanov, A. Gedanken, *Ultrason. Sonochem.* **2014**, *21*, 1916.
- [33] Q. Shi, H. Liu, D. Tang, Y. Li, X. J. Li, F. Xu, *NPG Asia Mater.* **2019**, *11*, 1.
- [34] N. Gull, S. M. Khan, S. Khalid, S. Zia, A. Islam, A. Sabir, M. Sultan, F. Hussain, R. U. Khan, M. T. Z. Butt, *Int. J. Biol. Macromol.* **2020**, *164*, 4370.
- [35] A. Basu, K. R. Kunduru, E. Abtew, A. J. Domb, *Bioconjugate Chem.* **2015**, *26*, 1396.
- [36] M. Kitaoka, M. Goto, in *Nanomaterials in Pharmacology* (Eds: Z.-R. Lu, S. Sakuma), Humana Press, New York, NY **2016**, pp. 349–367.
- [37] A. Popat, J. Liu, G. Q. Lu, S. Z. Qiao, *J. Mater. Chem.* **2012**, *22*, 11173.
- [38] K. D. Rainsford, *Inflammopharmacology* **2009**, *17*, 275.
- [39] J. F. H. Jacques, L. van Snick, P. L. Masson, *J. Exp. Med.* **1974**, *140*, 1068.
- [40] J. Qu, X. Zhao, P. X. Ma, B. Guo, *Acta Biomater.* **2017**, *58*, 168.
- [41] S. Daher, M. Massarwa, A. A. Benson, T. Khoury, *J. Clin. Transl. Hepatol.* **2018**, *6*, 1.
- [42] J. Son, G. Yi, J. Yoo, C. Park, H. Koo, H. S. Choi, *Adv. Drug Delivery Rev.* **2019**, *138*, 133.
- [43] M. Nazari, M. Rubio-Martinez, G. Tobias, J. P. Barrio, R. Babarao, F. Nazari, K. Konstas, B. W. Muir, S. F. Collins, A. J. Hill, M. C. Duke, M. R. Hill, *Adv. Funct. Mater.* **2016**, *26*, 3244.
- [44] G. Sinawang, M. Osaki, Y. Takashima, H. Yamaguchi, A. Harada, *Polym. J.* **2020**, *52*, 839.
- [45] S. Kim, H. Jo, M. Jeon, M. G. Choi, S. K. Hahn, S. H. Yun, *Chem. Commun.* **2017**, *53*, 4569.
- [46] Y. Zhao, C. Wei, X. Chen, J. Liu, Q. Yu, Y. Liu, J. Liu, *ACS Appl. Mater. Interfaces* **2019**, *11*, 11587.
- [47] K. De Bosscher, W. Vanden Berghe, G. Haegeman, *J. Neuroimunol.* **2000**, *109*, 16.
- [48] X. Liu, I. De Scheerder, W. Desmet, *Expert Rev. Cardiovasc. Ther.* **2004**, *2*, 653.
- [49] B. Q. Spring, R. B. Sears, L. Z. Zheng, Z. Mai, R. Watanabe, M. E. Sherwood, D. A. Schoenfeld, B. W. Pogue, S. P. Pereira, E. Villa, T. Hasan, *Nat. Nanotechnol.* **2016**, *11*, 378.
- [50] J. G. Croissant, K. S. Butler, J. I. Zink, C. J. Brinker, *Nat. Rev. Mater.* **2020**, *5*, 886.
- [51] Y. T. Chang, P. Y. Liao, H. S. Sheu, Y. J. Tseng, F. Y. Cheng, C. S. Yeh, *Adv. Mater.* **2012**, *24*, 3309.
- [52] A. Ghosh, C. Yoon, F. Ongaro, S. Scheggi, F. M. Selaru, S. Misra, D. H. Gracias, *Front. Mech. Eng.* **2017**, *3*, 1.
- [53] C. K. Yoon, *Nano Convergence* **2019**, *6*, 20.
- [54] H. Li, G. Go, S. Y. Ko, J. O. Park, S. Park, *Smart Mater. Struct.* **2016**, *25*, 027001.
- [55] S. Fusco, M. S. Sakar, S. Kennedy, C. Peters, R. Bottani, F. Starsich, A. Mao, G. A. Sotiriou, S. Pané, S. E. Pratsinis, D. Mooney, B. J. Nelson, *Adv. Mater.* **2014**, *26*, 952.
- [56] J. C. Breger, C. Yoon, R. Xiao, H. R. Kwag, M. O. Wang, J. P. Fisher, T. D. Nguyen, D. H. Gracias, *ACS Appl. Mater. Interfaces* **2015**, *7*, 3398.
- [57] S. Y. Qin, A. Q. Zhang, S. X. Cheng, L. Rong, X. Z. Zhang, *Biomaterials* **2017**, *112*, 234.
- [58] P. Xue, J. Wang, X. Han, Y. Wang, *Colloids Surf., B* **2019**, *180*, 202.
- [59] 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.
- [60] Y. Lu, Y. Lv, T. Li, *Adv. Drug Delivery Rev.* **2019**, *143*, 115.
- [61] L. Gao, G. Liu, J. Ma, X. Wang, L. Zhou, X. Li, *J. Controlled Release* **2012**, *160*, 418.

- [62] R. H. Muller, C. M. Keck, *J. Biotechnol.* **2004**, *113*, 151.
- [63] S. Farah, W. Khan, A. J. Domb, *Int. J. Pharm.* **2013**, *445*, 20.
- [64] J. K. Aronson, *The International Encyclopedia of Adverse Drug Reactions and Interactions*, 16th ed., Elsevier Inc., Amsterdam **2016**.
- [65] H. Gelderblom, J. Verweij, K. Nooter, A. Sparreboom, *Eur. J. Cancer* **2001**, *37*, 1590.
- [66] W. Khan, S. Farah, A. Nyska, A. J. Domb, *J. Controlled Release* **2013**, *168*, 70.
- [67] S. Torii, H. Jinnouchi, A. Sakamoto, M. Kutyna, A. Cornelissen, S. Kuntz, L. Guo, H. Mori, E. Harari, K. H. Paek, R. Fernandez, D. Chahal, M. E. Romero, F. D. Kolodgie, A. Gupta, R. Virmani, A. V. Finn, *Nat. Rev. Cardiol.* **2020**, *17*, 37.
- [68] S. Farah, W. Khan, A. J. Domb, *Int. J. Pharm.* **2013**, *445*, 20.
- [69] M. Kamińska, W. Okrój, W. Szymański, W. Jakubowski, P. Komorowski, A. Nosal, H. Szymanowski, M. Gazicki-Lipman, H. Jerczyńska, Z. Pawłowska, B. Walkowiak, *Acta Bioeng. Biomech.* **2009**, *11*, 19.
- [70] J. Flueckiger, V. Bazargan, B. Stoeber, K. C. Cheung, *Sens. Actuators, B* **2011**, *160*, 864.
- [71] B. D. Winslow, M. B. Christensen, W. K. Yang, F. Solzbacher, P. A. Tresco, *Biomaterials* **2010**, *31*, 9163.
- [72] T. Li, D. Cipolla, T. Rades, B. J. Boyd, *J. Controlled Release* **2018**, *288*, 96.
- [73] R. Thipparaboina, D. Kumar, R. B. Chavan, N. R. Shastri, *Drug Discovery Today* **2016**, *21*, 481.
- [74] The Office of Pharmaceutical Quality in the Center for Drug Evaluation and Administration, *Regulatory Classification of Pharmaceutical Co-Crystals, Guidance for Industry*, **2018**, pp. 1–4.
- [75] U. Han, Y. Seo, J. Hong, *Sci. Rep.* **2016**, *6*, 1.
- [76] K. Park, D. Choi, J. Hong, *Sci. Rep.* **2018**, *8*, 1.
- [77] D. V. Andreeva, in *Advances and Avenues in the Development of Novel Carriers for Bioactives and Biological Agents*, (Eds: M. Rawat Singh, J. R. Kanwar, D. Singh, N. S. Chauhan), Academic Press **2020**, pp. 183–209.
- [78] M. S. Pacheco, G. E. Kano, L. de A. Paulo, P. S. Lopes, M. A. de Moraes, *Int. J. Biol. Macromol.* **2020**, *152*, 803.
- [79] P. Ayaz, B. Xu, X. Zhang, J. Wang, D. Yu, J. Wu, *Appl. Surf. Sci.* **2020**, *527*, 146806.
- [80] W. Wei, J. L. Faubel, H. Selvakumar, D. T. Kovari, J. Tsao, F. Rivas, A. T. Mohabir, M. Krecker, E. Rahbar, A. R. Hall, M. A. Filler, J. L. Washburn, P. H. Weigel, J. E. Curtis, *Nat. Commun.* **2019**, *10*, 5527.
- [81] F. Scheffler, M. Brueckner, J. Ye, R. Seidel, U. Reibetanz, *Adv. Funct. Mater.* **2019**, *29*, 1808116.
- [82] Z. Ge, L. Guo, G. Wu, J. Li, Y. Sun, Y. Hou, J. Shi, S. Song, L. Wang, C. Fan, H. Lu, Q. Li, *Small* **2020**, *16*, 6.
- [83] M. Eisenstein, *Nature* **2006**, *444*, 959.
- [84] W. Sun, W. Liu, Z. Wu, H. Chen, *Macromol. Rapid Commun.* **2020**, *41*, 1900430.
- [85] P. Fabbri, M. Messori, *Modification of Polymer Properties*, Elsevier Inc., Amsterdam **2017**, pp. 109–130.
- [86] O. Neděla, P. Slepčík, V. Švorcák, *Materials* **2017**, *10*, 11115.
- [87] K. Yu, Y. Mei, N. Hadjesfandiari, J. N. Kizhakkedathu, *Colloids Surf., B* **2014**, *124*, 69.
- [88] A. S. Hoffman, *Macromol. Symp.* **1996**, *101*, 443.
- [89] T. M. Blättler, S. Pasche, M. Textor, H. J. Griesser, *Langmuir* **2006**, *22*, 5760.
- [90] S. Pasche, M. Textor, L. Meagher, N. D. Spencer, H. J. Griesser, *Langmuir* **2005**, *21*, 6508.
- [91] H. Vaisocherová, K. Mrkvová, M. Piliarik, P. Jinoch, M. Šteinbachová, J. Hornola, *Biosens. Bioelectron.* **2007**, *22*, 1020.
- [92] P. Kingshott, H. Thissen, H. J. Griesser, *Biomaterials* **2002**, *23*, 2043.
- [93] B. Li, Z. Yuan, H. C. Hung, J. Ma, P. Jain, C. Tsao, J. Xie, P. Zhang, X. Lin, K. Wu, S. Jiang, *Angew. Chem., Int. Ed.* **2018**, *57*, 13873.
- [94] R. P. Garay, R. El-Gewely, J. K. Armstrong, G. Garratty, P. Richette, *Expert Opin. Drug Delivery* **2012**, *9*, 1319.
- [95] Q. Yang, S. K. Lai, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.* **2015**, *7*, 655.
- [96] J. J. F. Verhoef, J. F. Carpenter, T. J. Anchordoquy, H. Schellekens, *Drug Discovery Today* **2014**, *19*, 1945.
- [97] B. Li, J. Xie, Z. Yuan, P. Jain, X. Lin, K. Wu, S. Jiang, *Angew. Chem., Int. Ed.* **2018**, *57*, 4527.
- [98] S. Jiang, Z. Cao, *Adv. Mater.* **2010**, *22*, 920.
- [99] X. Chen, D. Yang, *Biomater. Sci.* **2020**, *8*, 4906.
- [100] L. Mi, S. Jiang, *Angew. Chem., Int. Ed.* **2014**, *53*, 1746.
- [101] L. D. Blackman, P. A. Gunatillake, P. Cass, K. E. S. Locock, *Chem. Soc. Rev.* **2019**, *48*, 757.
- [102] M. E. Schroeder, K. M. Zurick, D. E. McGrath, M. T. Bernards, *Bio-macromolecules* **2013**, *14*, 3112.
- [103] S. Lowe, N. M. O'Brien-Simpson, L. A. Connal, *Polym. Chem.* **2015**, *6*, 198.
- [104] B. Li, B. Li, Z. Yuan, P. Jain, H. C. Hung, Y. He, Y. He, X. Lin, P. McMullen, S. Jiang, S. Jiang, *Sci. Adv.* **2020**, *6*, eaba0754.
- [105] 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.
- [106] J. B. Schlenoff, *Langmuir* **2014**, *30*, 9625.
- [107] B. Li, P. Jain, J. Ma, J. K. Smith, Z. Yuan, H. C. Hung, Y. He, X. Lin, K. Wu, J. Pfaendtner, S. Jiang, *Sci. Adv.* **2019**, *5*, eaaw9562.
- [108] L. Zhang, Z. Cao, T. Bai, L. Carr, J. R. Ella-Menyé, C. Irvin, B. D. Ratner, S. Jiang, *Nat. Biotechnol.* **2013**, *31*, 553.
- [109] Q. Shao, S. Jiang, *J. Phys. Chem. B* **2013**, *117*, 1357.
- [110] J. Hunger, N. Ottosson, K. Mazur, M. Bonn, H. J. Bakker, *Phys. Chem. Chem. Phys.* **2015**, *17*, 298.
- [111] Y. T. Liao, A. C. Manson, M. R. DeLyser, W. G. Noid, P. S. Cremer, *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 2479.
- [112] K. R. Kunduru, A. Basu, A. J. Domb, in *Encyclopedia of Polymer Science and Technology*, John Wiley & Sons Inc. Hoboken, New Jersey **2016**, pp. 1–22.
- [113] K. Y. Lee, D. J. Mooney, *Prog. Polym. Sci.* **2012**, *37*, 106.
- [114] D. An, A. Chiu, J. A. Flanders, W. Song, D. Shou, Y. C. Lu, L. G. Grunnet, L. Winkel, C. Ingvorsen, N. S. Christophersen, J. J. Fels, F. W. Sand, Y. Ji, L. Qi, Y. Pardo, D. Luo, M. Silberstein, J. Fan, M. Ma, *Proc. Natl. Acad. Sci. USA* **2017**, *115*, E263.
- [115] D. W. Scharp, P. Marchetti, *Adv. Drug Delivery Rev.* **2014**, *67*–68, 35.
- [116] A. J. Vegas, O. Veiseh, J. C. Doloff, M. Ma, H. H. Tam, K. Bratlie, J. Li, A. R. Bader, E. Langan, K. Olejnik, P. Fenton, J. W. Kang, J. Hollister-Locke, M. A. Bochenek, A. Chiu, S. Siebert, K. Tang, S. Jhunjhunwala, S. Aresta-Dasilva, N. Dholakia, R. Thakrar, T. Vietti, M. Chen, J. Cohen, K. Siniakowicz, M. Qi, J. McGarrigle, S. Lyle, D. M. Harlan, D. L. Greiner, J. Oberholzer, G. C. Weir, R. Langer, D. G. Anderson, *Nat. Biotechnol.* **2016**, *34*, 345.
- [117] 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-Locke, S. Aresta-Dasilva, M. Bochenek, J. Mendoza-Elias, Y. Wang, M. Qi, D. M. Lavin, M. Chen, N. Dholakia, R. Thakrar, I. Lacik, G. C. Weir, J. Oberholzer, D. L. Greiner, R. Langer, D. G. Anderson, *Nat. Mater.* **2015**, *14*, 643.
- [118] A. J. Vegas, O. Veiseh, M. Görtler, J. R. Millman, F. W. Pagliuca, A. R. Bader, J. C. Doloff, J. Li, M. Chen, K. Olejnik, H. H. Tam, S. Jhunjhunwala, E. Langan, S. Aresta-Dasilva, S. Gandham, J. J. McGarrigle, M. A. Bochenek, J. Hollister-Locke, J. Oberholzer, D. L. Greiner, G. C. Weir, D. A. Melton, R. Langer, D. G. Anderson, *Nat. Med.* **2016**, *22*, 306.
- [119] M. A. Bochenek, O. Veiseh, A. J. Vegas, J. J. McGarrigle, M. Qi, E. Marchese, M. Omami, J. C. Doloff, J. Mendoza-Elias, M. Nourmohammadzadeh, A. Khan, C. C. Yeh, Y. Xing, D. Isa, S. Ghani, J. Li, C. Landry, A. R. Bader, K. Olejnik, M. Chen,

- J. Hollister-Lock, Y. Wang, D. L. Greiner, G. C. Weir, B. L. Strand, A. M. A. Rokstad, I. Lacik, R. Langer, D. G. Anderson, J. Oberholzer, *Nat. Biomed. Eng.* **2018**, *2*, 810.
- [120] Q. Liu, A. Chiu, L. H. Wang, D. An, M. Zhong, A. M. Smink, B. J. de Haan, P. de Vos, K. Keane, A. Vegge, E. Y. Chen, W. Song, W. F. Liu, J. Flanders, C. Rescan, L. G. Grunnet, X. Wang, M. Ma, *Nat. Commun.* **2019**, *10*, 1.
- [121] E. Ostuni, R. G. Chapman, R. E. Holmlin, S. Takayama, G. M. Whitesides, *Langmuir* **2001**, *17*, 5605.
- [122] C. Sanchez-Cano, M. Carril, *Int. J. Mol. Sci.* **2020**, *21*, 1007.
- [123] A. Vishwakarma, N. S. Bhise, M. B. Evangelista, J. Rouwkema, M. R. Dokmeci, A. M. Ghaemmaghami, N. E. Vrana, A. Khademhosseini, *Trends Biotechnol.* **2016**, *34*, 470.
- [124] G. L. Szeto, E. B. Lavik, *J. Mater. Chem. B* **2016**, *4*, 1610.



**Neta Kutner** received her B.Sc. in Biochemical Engineering from Technion - Israel Institute of Technology, Israel. She is currently an M.Sc. student in the Faculty of Chemical Engineering at the Technion at The Laboratory for Advanced Functional/Medicinal Polymers & Smart Drug Delivery Technologies, under the supervision of Neubauer Assistant Professor Shady Farah. Her current research focuses on multicomponent crystalline formulations of antifibrotic drugs for implants rejection prevention.



**Konda Reddy Kunduru** completed his Ph.D. from CSIR, Indian Institute of Chemical Technology, Hyderabad, India. Following Ph.D. completion, he worked as a postdoctoral fellow at the Hebrew University of Jerusalem, Israel and the University of Hyderabad, India. Currently he is postdoctoral research fellow in the lab of Neubauer Assistant Professor Shady Farah at the Faculty of Chemical Engineering, Technion - Israel Institute of Technology, Israel studying multifunctional biopolymers and medical implants fabrication.



**Luna Rizik** received her B.Sc. in Biomedical Engineering and her M.Sc. in environmental engineering from Ben Gurion University of the Negev, Israel. In 2019, she completed her Ph.D. in Biomedical Engineering from Technion - Israel Institute of Technology in Synthetic Biology and Bioelectronics. Currently she is a research associate, focusing on studying biopolymers, biocompatibility of medical implants, and drug delivery systems, plus she manages The Laboratory for Advanced Functional/Medicinal Polymers & Smart Drug Delivery Technologies of Neubauer Assistant Professor Shady Farah at the Faculty of Chemical Engineering, Technion - Israel Institute of Technology, Israel.



**Shady Farah** is a Neubauer assistant professor for medicinal chemistry, drug delivery, and biopolymers at the Wolfson Faculty of Chemical Engineering and RBNI, Technion - Israel Institute of Technology, Israel. He earned Bachelor, Master (Direct-Track) and Ph.D. degrees in Medicinal Chemistry from the School of Pharmacy, Faculty of Medicine, Hebrew University of Jerusalem, Israel under supervisor Prof. Avi J. Domb. In 2014–2019, he did his postdoctoral training at Department of Chemical Engineering, MIT and The David H. Koch Institute for Integrative Cancer Research at MIT & Boston Children's Hospital/Harvard Medical School at Prof. Daniel G. Anderson/Prof. Robert S. Langer Labs, USA. Since 2019, he is heading The Laboratory for Advanced Functional/Medicinal Polymers & Smart Drug Delivery Technologies, Technion. His primary research interests are in biopolymers, controlled drug delivery, implantable devices, cancer therapy, and functional polymers.