# Surface modification of polymers for biocompatibility via exposure to extreme ultraviolet radiation

Inam Ul Ahad,[1,2] Andrzej Bartnik,[1] Henryk Fiedorowicz,[1] Jerzy Kostecki,[1] Barbara Korczyc,[1] Tomasz Ciach,[3] Dermot Brabazon[2]

[1] Institute of Optoelectronics, Military University of Technology, 00–908 Warsaw, Poland

[2] Advanced Processing Technology Research Centre, School of Mechanical and Manufacturing Engineering, Faculty of Engineering and Computing, Dublin City University, Dublin 9, Ireland

[3]Department of Biotechnology and Bioprocess Engineering, Warsaw University of Technology Ul, Wary nskiego 1 , 00–645 Warsaw, Poland

## Abstract

Polymeric biomaterials are being widely used for the treatment of various traumata, diseases and defects in human beings due to ease in their synthesis. As biomaterials have direct interaction with the extracellular environment in the biological world, biocompatibility is a topic of great significance. The introduction or enhancement of biocompatibility in certain polymers is still a challenge to overcome. Polymer biocompatibility can be controlled by surface modification Various physical and chemical methods (e.g., chemical and plasma treatment, ion implantation, and ultraviolet irradiation etc.) are in use or being developed for the modification of polymer surfaces. However an important limitation in their employment is the alteration of bulk material. Different surface and bulk properties of biomaterials are often desirable for biomedical applications. Because extreme ultraviolet (EUV) radiation penetration is quite limited even in low density mediums, it could be possible to use it for surface modification without influencing the bulk material. This article reviews the degree of biocompatibility of different polymeric biomaterials being currently employed in various biomedical applications, the surface properties required to be modified for biocompatibility control, plasma and laser ablation based surface modification techniques, and research studies indicating possible use of EUV for enhancing biocompatibility.

**Key Words**: extreme ultraviolet, polymer processing, biocompatibility, biomaterials, surface modification techniques.

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## INTRODUCTION

The fundamental requirement of a material to be used as biomaterials is its ability to receive an appropriate host response. This response depends on how similar the implant behaves as compared to the real organ. Such requirement is commonly termed as biocompatibility. A material must achieve three fundamental aspects of biocompatibility to be employed as biomaterial in a patient. Biochemical compatibility is the principal aspect which reveals that the foreign material should not induce toxicity, irritation, allergy or carcinogenicity in the host. Second, the material should have a strong bio-adhesive quality. Adhesion of biomaterial

must be specific to a particular type of cells or tissues which depends upon the application. A good adhesive contact between the implant and surrounding tissues must be established so that biomaterial performs efficiently.

Lastly the biomaterial should possess similar biomechanical properties as those of its surrounding tissues and organ for which it is replaced. It is quite worthy to note that all these properties are application dependent. Biomaterials with a low level of biocompatibility readily induce different infections within the patients. Organic polymers are considered as important materials in various biomedical applications ranging from conventional cell growth to the construction of hybrid tissues and artificial organs. Synthetic and naturally occurring polymers have become important elements in new strategies for producing engineered tissues. Several classes of polymers are now employed in biomedical applications, including situations in which the polymer remains in intimate contact with cells and tissues for prolonged periods.[1–4] Control of the degree of biocompatibility in biomaterials is still a challenge to overcome within the health care industry as these polymers very often do not possess the surface properties needed for various applications.

Therefore their surface needs to be refined to the microstructure level to obtain better performance in biomedical applications in terms of biocompatibility.[4] Various chemical and physical methods for modification of the polymer surfaces have been developed and are currently being studied, including chemical and plasma treatment, ion implantation, and UV-irradiation. Yet no surface modification technique is unanimously accepted since these methods are often associated with undesirable side effects. One of them is the degradation of the internal bulk of the material. Biomaterials have very precise requirements that derive from the mechanical performance of the bulk properties. These provisions can be categorized informally into three main groups including mechanical performance, mechanical durability, and physical properties. In total hip replacement surgeries for example, the biomaterial used for constructing a prosthetic implant must be mechanically strong and rigid.

In case of mitral valve replacement, the leaflet of valve must be flexible and tough; otherwise it will cause hindrance in blood flow. Synthetic vascular graft material requires very specific modulus properties in order to behave similar to real vascular soft tissue when implanted within the body such that the walls of the artery or vein pulsate in a similar manner to real tissue. In case of porous membranes (e.g., in dialysis), the membrane material should have high young's modulus and low yield strain though flexible and strong. For articular cartilage substitute the requirements are totally opposite to that of porous membranes. If the bulk material properties are modified inadequately and the material became stiff during UV or other surface modification techniques, then the risk of restenosis or thrombosis originating from these regions became unacceptably high. Similarly surface modification techniques may spoil the refraction and clarity of bulk material of intraocular lens, making them inefficient.

Extreme ultraviolet radiation is high-energy ultraviolet radiation, having photons with energies ranging from about 10 eV up to 124 eV (corresponding to wavelengths of 124– 10 nm, respectively). Degradation of bulk material can be avoided by using short wavelength radiation in the extreme ultraviolet (EUV) range that is absorbed within a very thin (<100 nm) layer of the polymer for surface modification.

The following section, Polymeric Biomaterials and Their Bioincompatibility section, of this article presents important polymeric biomaterials which are used in the health care industry that require biocompatibility control. In Surface Properties for Biocompatibility Control section the important surface properties of biomaterials are discussed. Because

biomaterials and host interact with each other in various ways, different surface properties of biomaterials influence this coexistence. These surface properties are used to determine the qualifications of a material to be used as biomaterial. A number of surface properties along with their contribution in interaction of host and biomaterial are also discussed. In Surface Modification section of this article a review of the plasma and laser ablation based surface modification techniques are discussed. Recently a laser-plasma based EUV source dedicated for polymer processing and surface modification has been built in Institute of Optoelectronics (IOE) at Military University of Technology ( MUT ) Warsaw.[5] Only a few studies have been conducted utilizing this source for surface modification and biocompatibility control. Strong indications of the applicability of this source to be used for polymer processing and surface modification for biocompatibility control are presented.

## POLYMERIC BIOMATERIALS AND THEIR BIO-INCOMPATIBILITY

Biomaterials are specially selected, structured and designed to interact with biological world for treatment of various traumata, diseases, and defects. The most important requirement of a biomaterial is to remain in intimate contact with host tissues without producing any harmful effect (biocompatibility). Biocompatibility is a general term used to describe the suitability of a material for exposure to the body or bodily fluids. It is the ability of a material to perform with an appropriate response in a specific application and it dependents on the particular application or biological conditions. A material will be considered as biocompatible (in a specific application) if it allows the body to function without any complications such as allergic reactions or other adverse side effects. Lack of biocompatibility can result in disruption of the normal healing processes and additional complications like inflammation, cytotoxicity, cell disruption, skin irritation, thrombosis and so forth.

Important polymers used as biomaterials widely in the health care industry are presented below along with their applications and associated problems due to lack of biocompatibility control.

### Polyethylene terephthalate

Polyethylene terephthalate (PET) has a wide range of applications in biomedical engineering. Particularly in tissue engineering, PET is used for vascular grafts and scaffolds for tissue regeneration. Moreover PET is extensively used for tissue replacement surgery.[3,4] Polyamide fabrics are also used for the same applications due to similar characteristics. Nevertheless both polymers exhibit various problems due to lack of integration with the host environment. The most common use of PET grafts is in bypass surgeries. The most common problem encountered by any vascular graft is infection due to lack of antibacterial properties. Most of these polymeric grafts are manufactured in knitted format and often result in occlusion or distal embolization. Because of flow of blood through grafts, erosion into adjacent structures is also common. Infection due to bad host response may also cause formation of true or false aneurysm which may cause sudden death.[6,7] Because of the smooth surface, PET depicts low cell adhesion in a host which results in weak cell attachment. The weakness in cell attachment consequently affects the cell growth, proliferation, and differentiation. Moreover cell loss also occurs under increased shear stress due to decreased roughness. Roughness on surface of PET can be introduced or increased through various procedures, however they also alter the bulk material and the desired mechanical characteristics of PET are ultimately lost. PET demonstrates low water wettability which causes various problems upon contact with blood

plasma (e.g., platelet activation).[8,9] Use of an autologous vein graft may avoid all these complications however they are often not available or sometimes not suitable for the particular case.

**Polytetrafluoroethylene (PTFE)**

In the stenotic arteries bypass autologous vein grafts are preferred to use but in case of unavailability, polytetrafluoroethylene (PTFE) is commonly used. Beside health care applications, PTFE also has various uses in different industries due to its low friction characteristic. In addition to the stenotic arteries vascular grafts, PTFE is also used for general construction of vascular prostheses, tubes for nerve regeneration, subcutaneous augmentation materials, and in maxillofacial surgery.[1,10,11] Various complications and hazards are affiliated with this polymer as its surface is thrombogenic which leads to vascular occlusion.[1,12] To avoid complications, the surfaces of polymers should be attractive for endothelial cells which are not thrombogenic in nature, thus thrombogenicity can be avoided resulting in an increase of biocompatibility of these vascular prostheses. Drug delivery is another important application of polymers in biomedical engineering. Particularly for protein drug delivery, ability to absorb water, open swollen structure and biodegradability is required in polymers so that protein can be efficiently loaded.[13]

**Poly(vinyl pyrrolidone) (PVP)**

For some artificial organs (e.g., artificial heart) nonbiodegradable materials are required with excellent biocompatibility and nonantigenicity.[14] Holding ability to absorb water without dissolving in host environment is crucial for such applications. Hydrogel polymers are prominently used materials which are highly absorbent and can contain huge amounts of water in their composition (99.9%). They possess similar properties as those of soft tissues though in some cases they may be toxic or nonbiocompatible. Beside fabrication of artificial organs, they are also used for scaffold material for tissue engineering, cell encapsulation, and intelligent cell culture substrates. For introducing biocompatibility or optimizing the degree of biocompatibility, polymeric coatings are applied on medical device surfaces.[15] Poly (vinyl pyrrolidone) (PVP) is a common hydrogel coating material for medical devices due to its in-adhesive response towards bacteria. Moreover this polymer provides a smooth surface which has low friction to extracellular fluids. Yet PVP binding with substrate is not stable for long periods of time, thus cannot be used for long term implants. Because of the high level of biocompatibility of PVP, it can be extremely beneficial for long term implants if crosslinking is improved, consequently their stability with substrate will be higher. Different groups have applied various approaches to optimize crosslinking. Though an important limitation exists with stable hydrogel in that they lose the desired mechanical properties which are required for certain applications like heart valves and artificial heart.[16] This limitation is application dependent as for breast implants for example, different mechanical properties compared to those for vascular grafts or heart valves are required. Therefore the requirements of crosslinking density are application dependent.

**Polyurethane ( PU )**

Polyurethane is a synthetic rubber use in diverse biomedical applications including ophthalmological materials, prosthetics and cardiovascular devices.[17] Particularly in prosthetic devices they portray less cell adhesion and may require to have moderate surface

hydrophilicity in order to be compatible for various cell types (e.g., myoblasts, macrophages, etc.).[18]

**Poly(aryl ether ether ketone) ( PEEK )**

Because of the thermoplastic nature, strong mechanical and chemical properties offered by poly(aryl ether ether ketone) (PEEK) makes it valuable for medical implants. The degree of robustness of this polymer is truly exploited in various industries. In biomedical engineering spinal and orthopedic implants are usually constructed by PEEK. They are relatively inert and have been proved to be biocompatible. It is a good replacement of metallic biomaterials in the prosthesis manufacturing. Important concerns in the application of PEEK as a biomaterial include water absorption which reduces polymer crystallinity and inertness of PEEK which affects cell adhesion resulting in limited bone fixation. The versatile nature of PEEK can be extended via surface modification for novel implant applications.[19 , 20]

**Polysulfone and poly(hydroxybutyrate)**

These polymers are used as membranes in various biomedical artificial devices. In principle these polymers exhibit extremely low biocompatibility, yet they are valuable to be used as membranes in the biological world. To increase the biocompatibility, plasma coatings are often deposited on their surfaces.[21]

**Other polymers**

Poly (vinyl chloride) (PVC), nylons polyamides, and silicones polysiloxanes are prominent polymers used for manufacturing of cardiovascular devices (particularly catheters), prosthetic devices and orthodontics materials. Problems associated with these polymers used in the biological worlds include their low biocompatibility in terms of high risk of bacterial infection, inflammatory responses of the body, and adsorption of proteins. High friction coefficient leads to damage of the epithelium or it may result in the excessive mechanical shear stresses. These problems cause various long term side effects such as recurrent infections and kidney inflammation and so forth.

**SURFACE PROPERTIES FOR BIOCOMPATIBILITY CONTROL** The basic factors that govern the biocompatibility of biomaterials are incompletely understood. No single test is sufficient to characterize the material on the basis of the biocompatibility. A variety of tests are necessary to determine the degree of the biocompatibility. These tests depend on the surface property to be investigated, implant class, application, and most importantly the host cell type to be in contact with the biomaterial. The response between the host and the biomaterial is not unidirectional. It is important to note that the routine of this mechanism is not unique even for any particular application. A range of natural phenomena occur due to interaction of the host and the biomaterial. Therefore a range of in vitro and in vivo tests, which characterize the surface properties and the chemical structure of the polymers that influence their biocompatibility have been developed and are routinely implanted.

In this section, most important surface characteristics of the polymers are discussed which can be modified in order to gain the control over the degree of the biocompatibility.

**Surface morphology**

The surface morphology of biomaterials determines the interactions occurring at the interface site of the host and biomaterial. Crystallinity is a major morphological characteristic of materials that influence host response. Moreover low dielectric constant, low refractive index, and high optical transparency along with good mechanical and thermal stability are the important properties required in bio-MEMS, blood-contact devices and cell culture substrates.

**Chemical structure and functional groups**

The harmful response by the host, like damaged cells or irritants which cause inflammation and homogenization can be avoided by making the biomaterial attractive for endothelial cells (improved endothelialization).[6,22,23] Similarly for various applications, proliferation and cell adhesion towards a particular host cell types are required. To make the polymer surface attractive for the particular cell type, polymeric biomaterials surfaces are often functionalized through various modification techniques by trapping or dopping reactive substances on the surface.[23,24] The chemical composition is therefore important to recognize the presence of externally introduced functional groups for particular applications and also to determine the presence of any toxic substance (element or compound) that may be present within the material.

**Interfacial free energy**

For biologically and mechanically stable solid (biomaterial)liquid (blood/extracellular fluid) interface a low solid–biological fluid interfacial free energy of the order 1–3 dyne $cm^{21}$ is required.[25] Although the interfacial free energy primarily depends upon the interface layer thickness, it also depend on certain variables such as temperature, friction, and pressure of the biological fluids. These variables in the biological environment are ever-changing within a specific range.[24] This thermodynamic quantity contributes to the adsorption of blood components onto the guest biomaterial.

The blood component adsorption thus can be control by interfacial free energy.

**Wettability**

It is evident that polymeric surfaces possess quite low wettability.[26] The wetting of a surface by a liquid is affected by the roughness of the surface. In practice it is shown that both the chemical properties (heterogeneity) and the physical properties (surface roughness, shape, and particle size) of the surface influence its wetting behavior.[27] Wettability of the biomaterials can be optimized to limit the contact friction between the host and the implant.[28] Regulating the wettability influences the protein adsorption and biocontact properties.[29] Wettability is also related to surface energy. Low surface energy polymers depict poor wettability.[30] Good wettability is required in some biomaterials for deposition of functional groups onto the surface. Such modified polymers can be used as a substrate material used for cell

cultures.26 , 31

**Hydrophobicity**

Particularly for biodegradable applications, the biomaterials to be used should have increased hydrophobicity so that they may dissolve in water. For tissue repairing scaffolds, biodegradable biomaterials are preferred in research projects for special experiments. Such

biomaterials are now employed in recent commercial applications. The proliferation and differentiation of cells can be biologically altered by control of the surface hydrophobicity and charge of culture substrates.[32]

### Hydrophilicity

Protein fouling has been a major problem for biomaterials in general often making them nonbiocompatible. The aggregation of proteins results in their adsorption onto the surface of the biomaterials. Ultimately thrombus formation due to protein fouling causes not only resistance in the extracellular fluid flow but also the surface chemistry of the host alters. Particularly in the membrane surfaces, increased hydrophilicity helps to suppress protein fouling.[33 – 35]

### Cytotoxicity

Toxic behavior investigation is mandatory in order to assess any material to be used in biomedical engineering applications. The cytotoxicity experiments determine whether the material depicts toxic behavior while in contact with the general or particular cell lines. The test is generally done in a laboratory using standard/relevant cell lines and the cells are seeded on the materials. As far as the experimental evaluation of biocompatibility is concerned, the cytotoxicity tests are widely cited as the primary assessment of biocompatibility.

### Adhesion

For the design of biomaterials, adhesion is an important factor to be optimized for the compatible cell–material interactions. Therefore it is important to control the cell growth on implant surfaces in order to characterize the biomaterials for biocompatibility.[36–38] In the biological world, "Bioadhesion" represents both bacterial and cell adhesion. Bacterial adhesion on biomaterial surfaces could be fatal as it results in evasion or inhibition of immune response of the host. However the requirement of cell adhesion on implant is both application dependent and cell-type dependent. Typically in vascular grafts, increased adhesion is desirable for better cell attachment, proliferation, and spreading.[39] Moreover metallization of polymers requires strong adhesion between the polymer and the metal for medical applications.[26] As an indirect paradigm, for vascular prostheses, the inner surface is in direct exposure to the endothelial cells and therefore it must be attractive to such cells. This is achieved by a protein coating on the polymer surfaces. However strong adhesion is required to hold the protein coating onto the polymer surfaces.[11]

On the contrary for some applications platelet adhesion with polymeric implant has to be minimized in order to avoid thrombus formation.[22,40,41] In the artificial heart valves, thromboembolism is the prominent complication which hosts experience, eventually leading to blockage in the blood flow.[42,43] To increase the uptime of such prosthetics, the implants should be treated to minimize thrombous regeneration.

## SURFACE MODIFICATION

Surface modification to alter a wide range of characteristics of surfaces is an expanding field enchanting the researchers and industries equally. Particularly for biomedical engineering applications the assorted mechanisms of host and biomaterial interaction require explicit surface characteristics in order to avoid any deleterious effects. Employment of polymers as biomaterials in the healthcare industry is well established due to the ease in the production of

versatile polymers which hold required physical and chemical properties. Because surface properties of polymers determine their biological performance during interaction with the host, biocompatibility control through surface modification is an inevitable step in the production process. Different bulk and surface properties are crucial for biomaterials in the biomedical engineering applications. It is however not possible to well define these properties during a single stage fabrication process. The common practice is to provide a special treatment following the fabrication of the biomaterials to modify surface properties to the desired level. Eventually decoupled bulk and surface properties are attained. A combination of two or more physical and/or chemical treatments can assure such modifications. In the following section a brief overview of plasma based and laser ablation based surface modification techniques used to control the degree of the biocompatibility are presented. Thenceforth initial research studies regarding a new technique of surface modification by extreme ultraviolet ( EUV ) are discussed with indications of possible application in the control of the degree of biocompatibility.

**Plasma-enhanced chemical vapor deposition**

Plasma-enhanced chemical vapor deposition (PECVD) is a chemical process in which gas vapors from plasma deposit on the surface of the sample being treated. Plasma deposition is quite often used in manufacturing of semiconductor devices particularly those with temperature sensitive structures. PECVD has vast applications ranging from semiconductor technology,[44–47] molecular sieve membranes for gas separation[48] and packaging barrier films.[49,50] However surface modification by PECVD for biomedical engineering applications is limited to silicon based membranes and substrates,[51] steel,[52] and alloys.[53,54] Polymer processing for biocompatibility control by PECVD is quite restricted due to non-uniformity and formation of by-products. Nevertheless a few studies demonstrated preparation of diamond-like carbon (DLC) coated films by PECVD with an improved degree of biocompatibility.[55 – 57]

**Reactive ion etching**

Reactive-ion etching (RIE) is the main plasma etching technology used for fabrication of microstructures. The etching mechanism in RIE is a result of chemical etching which takes place due to chemical reaction between the sample (wafer or film) and gas atoms forming a molecule to be removed from the substrate. Negligible amount of physical etching is also involved. RIE is primarily used in the semiconductor industry for the fabrication of the integrated circuits (IC).[58] As RIE is typically used for pattern transfer, prominent applications in biomedical engineering can be found in the fabrication of membranes, microelectrode arrays (MEA), and microelectromechanical systems ( MEMS ) for biosensors and lab-on-a-chip (LOC). Ultrananocrystalline diamond (UNCD) membranes with 100 and 200 nm diameter pores (high porosity [50%]) were fabricated using reactive ion etching.[59] Such membranes mimic natural filtration system thus can be used for wide applications in biomedical engineering. Micro-patterns are introduced in poly (dimethylsiloxane) (PDMS) silicone elastomer using customized RIE technique for fabrication of elastic multielectrode array for surface stimulation of the spinal cord.[60] However there are associated undesirable RIE effects which influence the micropatterning. Most prominent is the implantation of impurities during the chemical process of etching such as hydrogen diffusion. There is risk of

pattern damage due to the presence of the energetic ions or radiation. Because of the chemical interactions loss of the doping agent which is aimed to be inserted into the sample is another major problem. Most undesirable factors can be eliminated or limited but post processing is required. [58]

**Plasma immersion ion implantation**

Plasma immersion ion implantation (PIII) is used to insert impurity into the substrate by extracting accelerated ions from the plasma and directing them towards the sample. PIII has been used to improve antibacterial properties of polymers. Polyvinyl chloride (PVC) which is one of the most produced plastic has been coated with triclosan and bronopol and doped with argon using plasma treatment. Improvement in antibacterial properties against S. aureus and E. coli is demonstrated by biocompatibility tests though such surface modification.[61] Argon and oxygen immersed on surfaces of polycarbonate and polytetrafluoroethylene using PIII respectively. Oxygen enrichment resulted in hydrophocitiy of surface which offer higher affinity for human cell attachment.[62] PIII used to treat polyethylene terephthalate surface by acetylene to control the degree of hemocompatibility with pronounced effect on bacteria adhesion.[62] PIII can also be successfully employed for surface modification of the bio-implant alloys with the doping of nitrogen and phosphorus.[63] Nevertheless in the long run, the antibacterial property introduced or enhanced by PIII is reduced significantly due to interactions in the biological world.[62]

**Ultraviolet radiation surface modification**

The ultraviolet radiation in the range from 126 to 222 nm wavelength can be well absorbed by organic materials. The ultraviolet laser light from excimer lamps can be used to irradiate the sample with enough energy to disrupt the molecular bonds on the surface. The disruption of molecular bonds causes a number of photo-physical, thermal and photochemical processes.[64–68] This influence is not limited only to surface layer of the material but it also alters the bulk properties. The use of the excimer laser for surface modification to provide enhanced biocompatibility is quite an old technique.[66,69–71] Laurens et al. irradiated polycarbonate (PC) and polyether-etherketone (PEEK) with different UV wavelengths even below the ablation threshold and demonstrate increased wettability after treatment.[31]

Because different types of cell from the host (the patient) interact with the polymer surface, it is quite beneficial to introduce particular functional (reactive) groups on the interface site of the biomaterial. Such type of material functionalization adjusts the surface characteristics of the biomaterial and can provide attractive sites for the attachment of the particular cell types. In this way, the biomaterial can be designed with favorable adhesive properties for particular tissues. Consequently inflammatory and toxic responses can be avoided. Tidwell et al. tabulated the effect of different functional groups on the proliferation of bovine aortic endothelial cells. It has been demonstrated in the study that the growth rate of these cells significantly improved in the presence of different chemical functionalities.[72] Functional groups deposition onto the polymer surfaces is quite a delicate process as the polymer surfaces are treated in a way to remain nontoxic while in contact with particular cell types. Therefore no toxic materials should be induced during the modification process.

UV surface modification has been considered to control the degree of biocompatibility for various polymers. Heitz et al. irradiated polytetrafluoroethylene (PTFE) with UV light of a Xe2-excimer lamp at 172 nm wavelength. The polymer was treated in an ammonia

atmosphere. Some samples were grafted with amino acid alanine after being treated by UV. It was observed in the study that UV irradiated PTFE foils depict higher optical absorbance, exhibit strong fluorescence and increased wettability. Consequently rat aortic smooth muscle cells (SMC), mouse fibroblasts (3T3 cells) and human umbilical vein endothelial cells adhere more to such UV irradiated polymer samples as compare to untreated samples and exhibit good proliferation.[73] Gumpenberger from the same group performed further investigations on UV irradiated PTFE and observed formation of new chemical groups on treated polymer surfaces and demonstrated statistically higher proliferation rates and elevated adhesion on smooth muscle cells and fibroblasts.[11] Prolonged process timings (up to 30 min UV irradiation) were used in these studies. Uchida et al. confirmed increased hydrophilicity of poly(ethylene terephthalate) (PET) film upon UV treatment.[9] Doi et al. introduced microporosity in polyurethane (PU)-based vascular prosthesis through computer-aided excimer laser (KrF) ablation technique. This small caliber graft was expected to exhibit enhanced in vivo transmural tissue proliferation.[74] This anticipation is further confirmed by the same group for polyurethane grafts.[75] UV light was used to enhance the interaction between DNA molecules and the plasma polymer chains.[76] Several other biocompatibility control studies through UV irradiation can be found elsewhere.[3,29] Surface functionalization of amorphous carbon films can be used for various biomedical engineering applications. UV laser assisted micro-structuring of hydrogenated amorphous carbon thin films result in formation of carboxyl groups at the surface which leads to improved wettability of water, polar and dispersive liquids.[77] It is quite worthy to note that rather than polymers, UV micro-patterning is more suitable for control of the degree of biocompatibility of metallic alloys.78 – 80

**Extreme ultraviolet (EUV) radiation surface modification**

A basic requirement for a technique to be acceptable for the surface modification to provide control over the degree of the biocompatibility is that the bulk properties are retained during treatment. Photo (chemical) processes employed conventionally use short wavelength radiation (UV) with photon energies sufficient to break the chemical bonds on the polymer surface. These photons are capable of penetrating deep inside the polymer. In some cases penetration depth of these radiations is up to 500 mm which ultimately alter bulk properties.[81] Similarly in the case of plasma based techniques, degradation of sample lattice and bulk material was reported. Yet for application of polymers in biomedical engineering, surface and bulk properties must be decoupled as nearly for all applications in the biomedical domain, different surface and bulk properties of biomaterials are required.

Extreme ultraviolet (EUV) radiation is high-energy ultraviolet radiation, having photons with energies from about 10 eV up to 124 eV (corresponding to wavelengths from 124 to 10 nm, respectively). Two important factors encourage the employment of EUV for surface modification of polymers. The most significant is the corresponding photon energy which is capable of breaking more molecular bonds at the upper polymeric surface as compared to excimer lamps or excimer lasers. Smooth ablation of polymers by a laser plasma based EUV source is well established.[82] Second since the EUV radiations are highly absorbable even in low dense medium, their penetration depth is very limited (<100 nm in the upper layer of polymers).[83] The range of wavelength and penetration depth offered by EUV photons make them possible to write small patterns on the surface layers of polymers.

The EUV radiation may produce by plasma based sources or by synchrotron sources. In plasma based sources, EUV can be produced either by laser irradiation or by gas discharges. In synchrotron sources (SR), ultrarelativistic charge particles accelerated through magnets emits EUV radiation. In the laser-plasma based sources, a hightemperature plasma is generated by the interaction of high power laser pulses with a solid target. However, production of debris during laser interaction with matter target is a huge limitation. This problem has been solved by introducing gas target instead of a solid target.

Laser ablation leans on the nature of the material and its ability to absorb energy. Therefore the wavelength of the ablation laser should have a minimum absorption depth. Laser ablation rate hence primarily depends upon the laser wavelength and the pulse length. Therefore the ablation rate relies upon amount of total energy delivered in one shot and optimal spectral distribution. These two factors cause the main reason of the huge difference between the ablation rate of SR sources and laser-plasma based sources. SR sources have long pulse length and have low-peak-power while high energy laser-plasma sources are able to produce ultra-short pulses with high peak-power. As a matter of fact, single photon from both sources carries enough energy to break any chemical bond for direct photo-etching. However the photons from two sources interact with material distinctively due to following factors:

***Total energy in one shot***. As the peak intensity (PI) is calculated by peak-power in a given unit area (focal spot), low peak power SR source produce low-peak-intensity irradiation. As a result of this irradiation only a small area (focal spot) with a very thin surface layer obtain energy for quite a slow ablation process. On the contrary, in case of laserplasma source, high peak intensity irradiation causes a huge number of simultaneously occurring radiation induced photoetching proceedings. The absorption length of the radiation is relatively long in this case as compare to a SR source. The energy which is absorbed in the surface layer is also able to overheat the material. The evaporated (or sublimated) materials blow off into the vacuum. In this way fast ablation rate is achieved by a compact laser-plasma source which results in the construction of microstructures up to few microns in depth at material surface.

*Optimal spectral distribution.* As explained above, laser ablation depends upon the ability of a material to absorb energy. This means that the absorption length of the radiation in the materials should be comparable to the thickness of the material being desorbed. Strictly speaking, for a given radiation energy range (power density) there must be an optimal spectral distribution for efficient photo-etching. With specific critical energy and wavelength, SR sources do not fit in this criterion. However studies by single shot highpeak-power laser-plasma source demonstrated the optimal spectral distribution.

Considering these two factors, a compact laser plasma source demonstrates fast laser ablation rate as that of synchrotron sources. Moreover due to the limited number of SR sources and high cost of such facilities, various laser-plasma based EUV sources by various groups have been proposed and considered for various applications in science and technology. A laser-plasma based EUV source is specially built which is dedicated to polymer processing and surface modification at MUT, Warsaw.[5] Recent studies from this EUV source show that EUV micro-patterning produce micro- and nano-structures on polymer surfaces and consequently the surface properties of polymeric biomaterials modified in order to attain control over the degree of the biocompatibility. Moreover photochemical processes (by introducing extra gas during EUV irradiation on the sample) result in the formation of

specific functional groups at the polymer surface which could be useful to get good adhesion and proliferation of particular cell types.

Our group has been involved in the treatment of inorganic and organic materials by laser plasma based EUV source to identify ablation and micro structuring for a long period.[84–89] Polytetrafluoroethylene (PTFE) surface has been modified with this technique to produce a surface with a high aspect ratio cross sectional profile which indicates that this method can be used as a polymer surface modification technique for biomedical applications. Scanning electron microscopy (SEM) has been employed for investigation the effects of EUV micro-patterning on different polymers using this source.[82,90] Surfaces of poly ( methyl methacrylate) (PMMA) and fluorinated ethylene propylene (FEP) were modified in two EUV spectral ranges (using Zr and Al filters). This study provided an understanding about the effect of EUV intensity on the surface modification. It was observed that irradiating filtered EUV produced different surface alterations on the macro- and nanoscale.[91]

Changes in surface morphology and chemical structure by EUV irradiation were investigated in detail on polyethylene terephthalate (PET).[92] EUV radiation in the wavelength range of 9–70 nm was exposed for duration of 1–120 s at 10 Hz repetition rate. With increased number of irradiating pulses, it was observed that a ripple like microstructure changed to a wall-like pattern which is similar to pattern attain by UV laser PET ablation as demonstrated by Arenholz et al. in 1991.[93] Although UV and EUV photons interact with polymers in quite different ways, the resemblance between the wall type micropatterns induced by the UV and EUV irradiation is highly significant as it establishes ground to explore the EUV surface modification technique for the biocompatibility control. To further investigate the patterns of structures which appeared on the polymer surfaces upon EUV exposure, polycarbonate (PC) foils were treated in a similar way as PET foils by our group using a 10-Hz laser plasma EUV source. This EUV source is unique in the world as it possess auxiliary gas puff valve which enables the user to introduce extra gas during EUV exposure within the interaction region.

The additional supplied gas can be excited and ionized by EUV and can result in further refinement of control over the photon energy deposition onto the sample near-surface and hence influencing the morphological changes on the treated sample surface. Various experimental schemes were employed for polymer irradiation depending upon laser pulses. The samples were also irradiated with increasing number of pulses to visualize the effect of EUV intensity on morphological alterations. The number of pulses depends upon the sensitivity of polymer towards EUV radiation. The experimental setup details have been reported previously.[92]

EUV treated and pure polycarbonate (PC) surface areas were investigated by Scanning Electron Microscopy ( SEM ). Figure 1 shows SEM image of PC foil sample irradiated with 100, 200, 300, and 600 pulses. EUV modified and pure foil areas can be easily distinguished at 503 magnification.

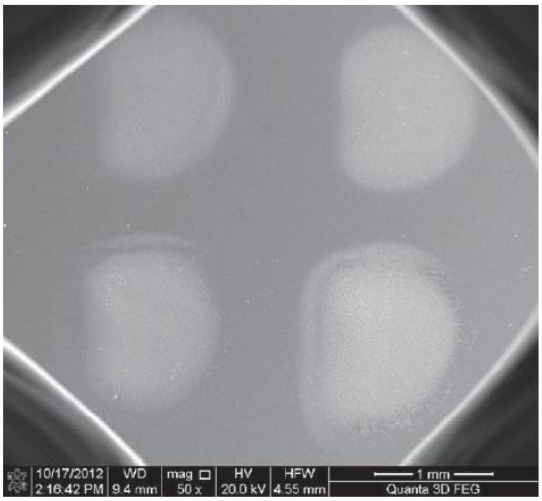


**FIGURE 1.** SEM image of PC foil irradiate with 100, 200, 300, and 600 EUV pulses.

The EUV irradiated PC foil areas were closely investigated at 50,0003 and 100,0003 magnification which showed interesting microstructures that emerged after EUV irradiation. No micropatterning can be seen on untreated areas [Fig. 2(a)]. Coarse microstructures with less detail were observed after 200 EUV pulses [Fig. 2(b,e)]

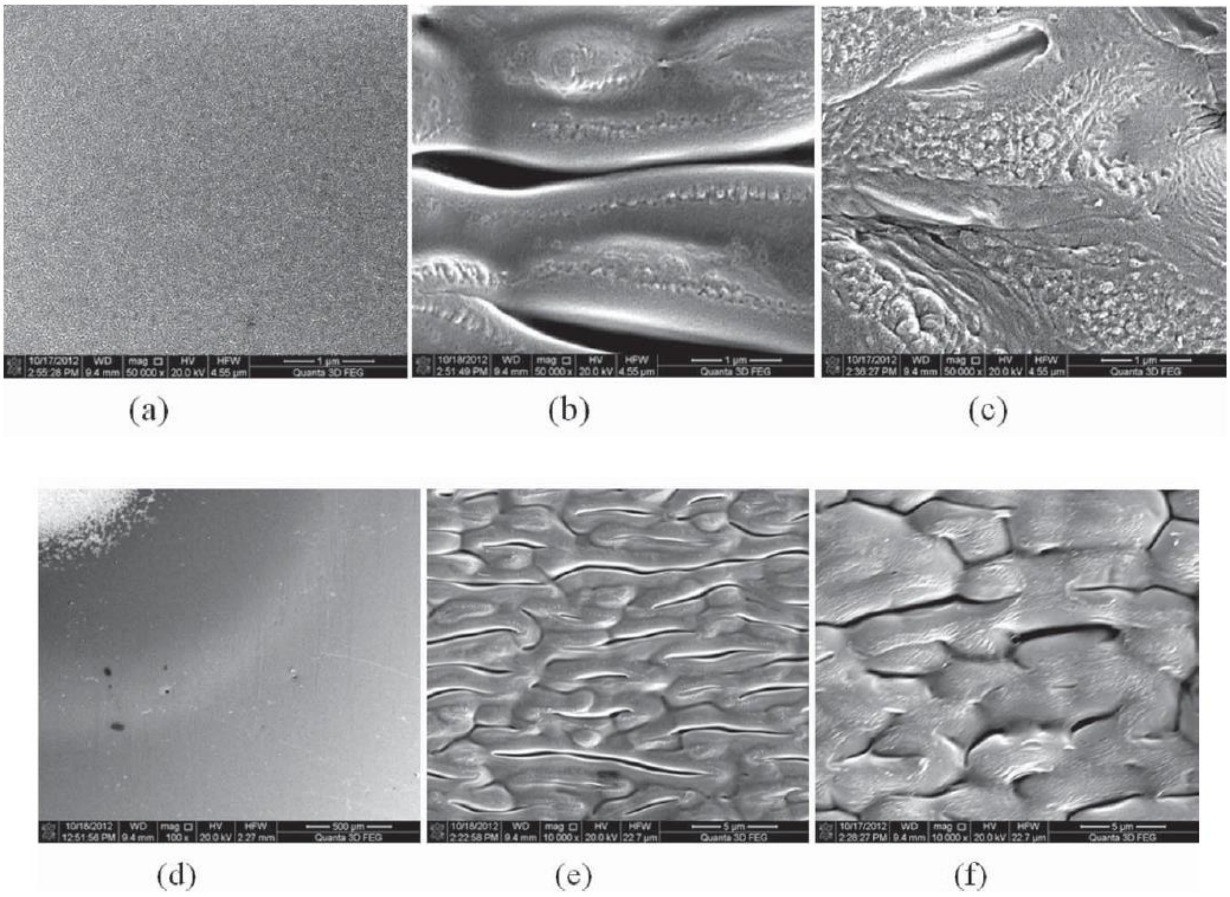


**FIGURE 2.** SEM images of EUV irradiated polycarbonate samples: (a) pristine sample, (b) Mag. 50Kx I 200 EUV shots, (c) Mag. 50Kx I 600 EUV shots, (d) Mag. 100x Icircular ring around 600 EUV shots exposed area, (e) Mag. 10Kx I 200 EUV shots, (f) Mag. 10Kx I 600 EUV shots.

however more refined and detailed wall-like structures were observed in areas irradiated by 600 EUV pulses [Fig. 2( c,f )]. An interesting ring structure was also found to surround the EUV exposed area as shown in Figure 2( d ).

As described earlier, modifications in chemical structure and the presence of functional groups on the polymer surfaces change the behavior of the polymeric biomaterial in activities like cell adhesion, cell growth, and toxicity. Therefore it is crucial to determine the alterations in chemical structure and composition of polymer surfaces treated by EUV. X-ray photoelectron spectroscopy (XPS) is a wellknown technique to characterize the chemical structure and composition of the surface of the materials. Our group has characterized changes in EUV modified PET sample surface by XPS.[92] Figure 3 shows the results from this experiment, including the XPS spectrum of EUV treated and pristine PET samples. Because of ablation of polymer samples by EUV irradiation, the concentration of oxygen decreases. Because the sample was irradiated in a vacuum, no additional component was added into the EUV treated sample surface.

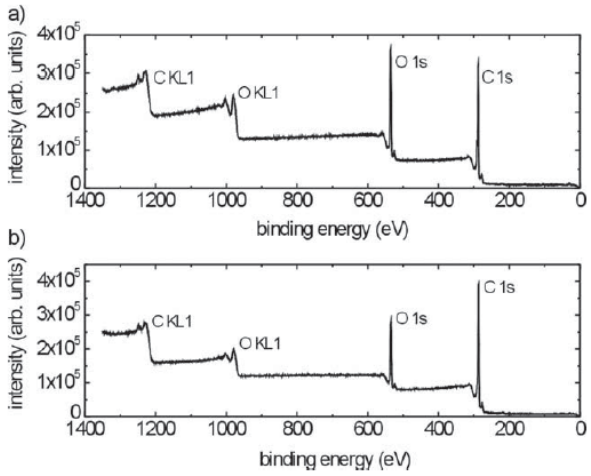


**FIGURE 3.** XPS spectra of PET foils (a) pure sample, and (b) EUV irradiated sample.

Incorporation of functional groups on the polymer surfaces changes the course of both therapeutic and toxic processes during the biomaterial tenure within the biological environment. Various studies demonstrate enhanced growth, adsorption, adhesion, and activation of particular cell types by substituting functional groups on the polymer surface. As described earlier, the EUV source developed by our group facilitates the sample irradiation in a reactive atmosphere by introducing extra gas within the EUV-sample interaction region using an auxiliary gas-puff valve. Polyvinylidene fluoride (PVDF) is a highly nonreactive polymer which makes it suitable for manufacturing of vascular sutures and surgical meshes with minimum tissue reaction at the interface site.[94,95]

To demonstrate photochemical surface modification by EUV treatment, our group modified PVDF surface by EUV irradiation in a reactive environment.[96] Nitrogen was introduced in the interaction region, thus ionized and excited by EUV radiations. Incorporation of nitrogen atoms in the molecular structure of PVDF was demonstrated by the experimental results as shown in Figure 4.

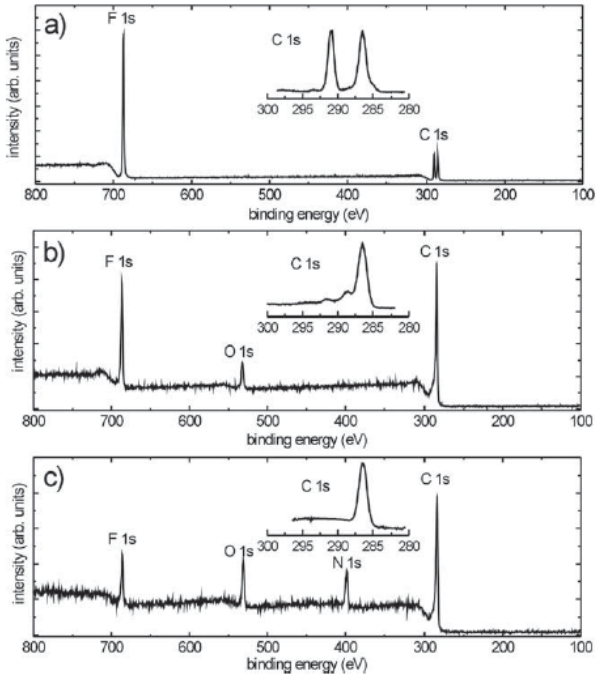


**FIGURE 4.** XPS survey spectra of PVDF surface: (a) pristine sample, (b) sample irradiated with 150 EUV pulses, (c) sample irradiated with 150 EUV pulses in the presence of nitrogen. Subimages show the high-resolution XPS spectra of C1s.

Three XPS spectra were obtained in that study presenting pristine sample [Fig. 4(a)], EUV irradiated sample in vacuum [Fig. 4(b)], and EUV irradiated sample in a reactive environment ( ionized nitrogen) [Fig. 4(c)]. Each spectra exhibit two main peaks which are characteristic of fluorine (F1s) and carbon ( C1s ). For pristine sample, F1s peak is very high as compared to C1s, however in the second case; C1s peak is much higher than F1s peak. In the last case, the C1s peak is much higher than F1s peak and the N1s peak appeared confirming the incorporation of nitrogen during treatment. Moreover an additional oxygen characteristic O1s peak was present within the EUV irradiated sample spectra as this sample was exposed to air after irradiation resulting in oxygen incorporation on the sample surface. Detailed analysis of these spectra can be found in the related publication however incorporation of additional elements and modification of the chemical composition of polymer surface through photochemical processing using EUV radiation has been demonstrated successfully.[96]

The first experiments of EUV surface modification for the biocompatibility control were performed on PET.[7] The biocompatibility tests including adhesion and alignment of biological cells (Chinese hamster ovary (CHO) cells) were performed for characterizing the EUV-treated polymer surfaces. This study revealed that EUV treated PET samples exhibited good adhesion of CHO cells. Moreover CHO cells seeded on EUV treated PET sample exhibit better alignment than those found on the UV-laser treated sample surface.

Polymers with wide range of applications in biomedical engineering described above along with affiliated problems in the health care industry and respective surface properties which are needed to be modified are summarized in Table I.

The problems and corresponding surface properties which are foreseen to be useful to modify and examine over the coming couple of years by EUV treatment are included.

**TABLE I. Materials and Surface Properties That May be Altered Successfully by EUV Treatment for the Biocompatibility Control**

| Polymer | Applications | Associated Problems | Surface Property to be Modified |
|---|---|---|---|
| Polyethylene terephthalate (PET) | Vascular grafts, scaffolds, and tissue replacement surgery | Infection/inflammation. Low cell adhesion. Low cell growth. Low proliferation. Cell lost under shear stress. Platelet activation | Roughness. Wettability. Cell adhesion |
| Polytetrafluoroethylene (PTFE) | Vascular grafts/prostheses, tubes for nerve, regeneration. Subcutaneous and augmentation materials, maxillofacial surgery, and drug delivery | Thrombogenicity, vascular occlusion, infection/ inflammation, hydrophobicity, and cell lost under shear stress | Thrombogenic surface (modify to be attractive for endothelial cells). Wettability. Hydrophilicity. Cell adhesion |
| Poly(vinyl pyrrolidone) (PVP) | Coating material for medical devices | Poor cross linking | Bonding with substrate material. Wettability |
| Polyurethane | Ophthalmological materials, prosthetic and cardiovascular devices | Less cell adhesion (e.g., for myoblasts, macrophages, etc.) | Cell adhesion. Hydrophilicity |
| Poly(aryl ether ether ketone) (PEEK) | Spinal and orthopedic implants | Reduce polymer crystallinity overtime, Inertness of PEEK which effect cell adhesion. Limited bone fixation | Cell adhesion. Wettability |
| Polysulfone and poly(hydroxybutyrate) | Membranes for artificial devices | Infection/inflammation, thrombogenicity | Plasma coating |
| Poly (vinyl chloride) (PVC), nylons polyamides, silicones polysiloxanes | Cardiovascular devices (particularly catheters), prosthetic devices and orthodontics materials. | High risk of bacterial infection, inflammatory responses of the body, or adsorption of proteins), high friction coefficient (could damage Epithelium, mechanical stress recurrent infections, kidney infections, etc. | Thrombogenic surface (modify to be attractive for endothelial cells), protein adsorption |
| Polyvinylidene fluoride (PVDF) | Vascular sutures. Surgical meshes. Membrane material | Hydrophobic membrane surface and nonspecific adhesion of biomolecules | Adhesion of biomolecules. Hydrophobicity |

Beside numerous advantages and strong indications of efficient surface modification technique, EUV polymer processing also has some disadvantages. First and foremost is unavailability of EUV radiation source. Only in recent years, laboratory based compact EUV sources are available for processing of polymers. The source at MUT, Warsaw is now being used for fundamental research in polymer processing for biocompatibility control. EUV sources are still in progress towards miniaturization. Degradation of laser optics is another prime aspect in the health care industry and respective surface properties which are needed to be modified are summarized in Table I. The problems and corresponding surface properties which are foreseen to be useful to modify and examine over the coming couple of years by EUV treatment are included.

Beside numerous advantages and strong indications of efficient surface modification technique, EUV polymer processing also has some disadvantages. First and foremost is unavailability of EUV radiation source. Only in recent years, laboratory based compact EUV sources are available for processing of polymers. The source at MUT, Warsaw is now being used for fundamental research in polymer processing for biocompatibility control. EUV sources are still in progress towards miniaturization. Degradation of laser optics is another prime aspect in terms of efficiency of EUV source. An ellipsoidal grazing incidence mirror which is used for collection of EUV source for interaction chamber in tabletop EUV source works on the principle of total external reflection.[5] Such type of mirrors currently employed in various applications with optimal thermal resistance and reflectivity. Damage threshold investigations about the grazing incidence mirror in EUV source are currently in progress by

some groups.[97] Damaged grazing incidence mirror result in uncontrolled EUV flux ultimately influencing EUV ablation process and micro-structuring of treated polymers.[97]

## CONCLUSION

Despite being a multi-billion dollar industry, control over the degree of biocompatibility is still an important research and development challenge facing the biomaterials research and industrial communities. To overcome this challenge it is required that the processes which occur at the interface site between the biomaterial and the host do not induce any deleterious effects such as chronic inflammatory response or formation of unusual tissues. Therefore the importance of biomaterials with appropriate surface properties is evident. At the same time, specific bulk properties are essential, particularly mechanical properties for biomaterials in order to perform particular tasks in the biological world. It is evident that designing of biomaterials which fulfill both needs is quite difficult. A common approach is to fabricate biomaterials with adequate bulk properties, followed by modification of surface properties through various treatments. This procedure leads to development of a final material with decoupled bulk and surface properties. However there is no surface modification technique unanimously accepted to control the degree of the biocompatibility for polymers. Plasma and laser ablation techniques have been employed for surface modification of polymers however they induce alterations in bulk material due to deep penetration in to the material.

To avoid such problems, extreme ultraviolet (EUV) radiation has been successfully employed for surface modifications with a few polymer types. Most importantly EUV micro-patterning produced similar wall-like structures on polymer surfaces as those created by the UV irradiation. The discovery of this breakthrough sets up new trails for the exploitation of EUV micro-patterning to allow the control over the degree of biocompatibility. The changes in the physical structure of the surface provide for appropriate physical properties for the interface site between host and biomaterial. Moreover crosslinking of functional groups by introducing extra gas during EUV exposure to the polymers could significantly improve biocompatibility for particular biological cell types. To date only a few studies carried out for surface modification of polymers by EUV irradiation. In only one study biocompatibility tests were performed on EUV-treated polymers. These studies yield promising indications towards employment of EUV radiation for enhanced biocompatibility in polymers. Exploitation of specific wavelengths within the EUV spectrum for biomedical engineering applications is a vast vacant area belongs to polymer physics, chemistry, and biotechnology yet to be explored. Such studies however require multidisciplinary teams from medicine, engineering, and material science.

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