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# Advanced Smart Biomaterials and Constructs and their Applications

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**ABSTRACT:** Smart biomaterials have the ability to respond to changes in physiological parameters and exogenous stimuli and continue to impact many aspects of modern medicine. Smart materials can promote promising therapies and improve treatment of debilitating diseases. Smart biomaterials and constructs refer to biomaterials and constructs that possess instructive/inductive or triggering/stimulating effects on cells and tissues by engineering the material's responsiveness to internal or external stimuli or have intelligently tailored properties and functions that can promote tissue repair and regeneration. The smart material-based approaches include smart scaffolds and stem cell constructs for bone tissue engineering; smart drug delivery systems to enhance bone regeneration; smart dental resins that respond to pH to protect tooth structures; smart pH-sensitive dental materials to selectively inhibit acid-producing bacteria; smart polymers to modulate biofilm species away from a pathogenic composition and shift towards a healthy composition; and smart materials to suppress biofilms and avoid drug resistance. These smart biomaterials can not only deliver and guide stem cells to improve tissue regeneration and deliver drugs and bioactive agents with spatially and temporarily controlled releases but can also modulate/suppress biofilms and combat infections in wound sites. The new generation of smart biomaterials provides exciting potential and is a promising opportunity to substantially enhance hard tissue engineering and regenerative medicine efficacy.

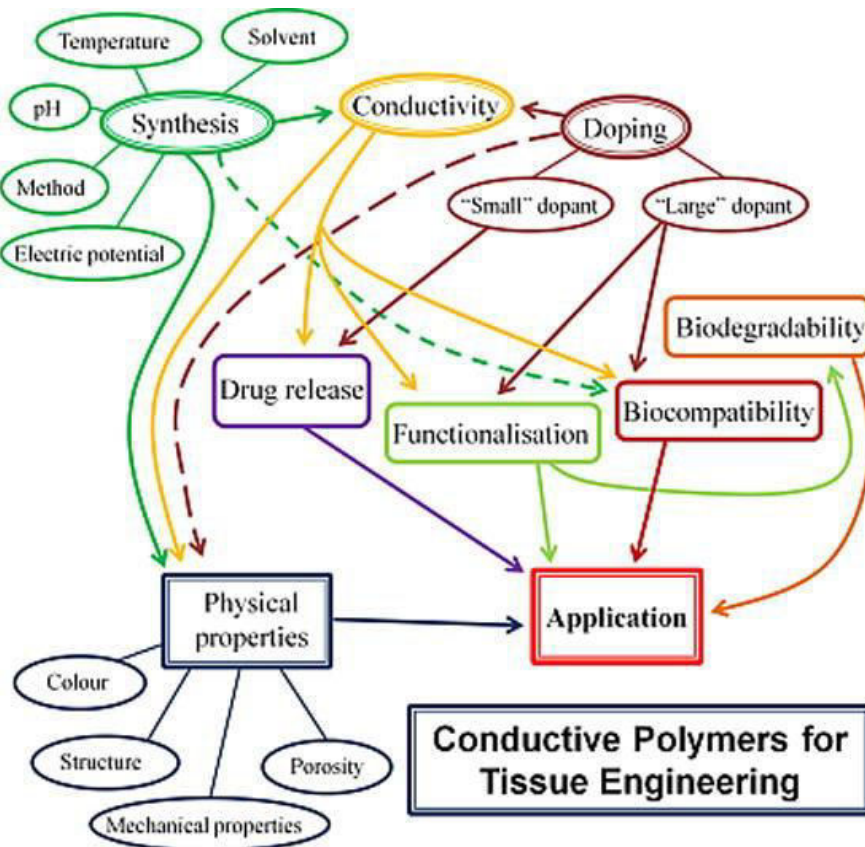
**KEYWORDS:** smart biomaterials, advanced, applications, medicine, engineering

## I. INTRODUCTION

The emergence of smart biomaterials has significantly developed the boundaries of modern medicine. This class of biomaterials can operate as an 'on-off' switch for multiple applications from nanometer to micrometer scales because of their unique characteristics responsive to the environmental changes. They can also self-fold or self-unfold to encapsulate and release cells or drugs in a controlled fashion, leading to a smart drug delivery system. Besides, the combination of stimuli-responsive biomaterials with additive manufacturing introduces smart constructs that may closely resemble natural tissues. Therefore, progress in smart biomaterials can trigger significant changes in the field of biomedical engineering. Developing stimulus-responsive biomaterials with easy-to-tailor properties is a highly desired goal of the tissue engineering community.[1,2] A novel type of electroactive biomaterial, the conductive polymer, promises to become one such material. Conductive polymers are already used in fuel cells, computer displays and microsurgical tools, and are now finding applications in the field of biomaterials. These versatile polymers can be synthesised alone, as hydrogels, combined into composites or electrospun into microfibres. They can be created to be biocompatible and biodegradable. Their physical properties can easily be optimized for a specific application through binding biologically important molecules into the polymer using one of the many available methods for their functionalization. Their conductive nature allows cells or tissue cultured upon them to be stimulated, the polymers' own physical properties to be influenced post-synthesis and the drugs bound in them released, through the application of an electrical signal. It is thus little wonder that these polymers are becoming very important materials for biosensors, neural implants, drug delivery devices and tissue engineering scaffolds. [3,4]

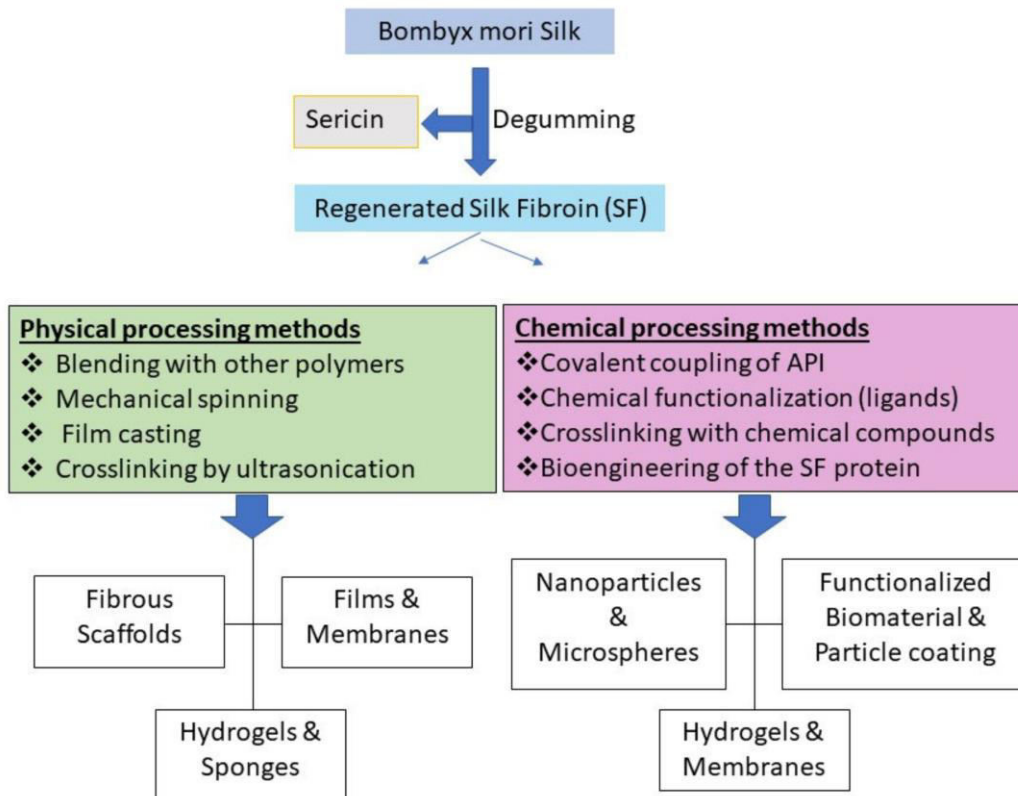
Most biomaterials fail from the start because improper blood supply leads to cell death at the implant site prompted by scarceness of nutrients (including O<sub>2</sub>), accumulation of waste products, impaired biochemical signalling and abnormal cell recruitment, resulting in an overall poor host integration. These problems can be circumvented by improving vascularisation in the local environment of the implant, and many efforts have been directed to clarify or solve the problem, mostly employing prevascularised or endothelialised constructs. An alternative possibility implies the use of proangiogenic smart biomaterials able to recruit cells that actively participate in angiogenesis in vivo, such as endothelial progenitor cells (EPCs). This would greatly simplify the preparation of the biomaterial previous to implantation, but more importantly, would facilitate vascularisation to proceed as in vivo, that is, coordinated with the host's healing response. In the case of bone, matrix formation starts with osteoblast-mediated collagen I deposition to form osteoid with angiogenesis occurring almost simultaneously. The matrix is gradually mineralised acquiring

properties of mature bone. These bone healing sites consist of a complex mixture of mechanical signals determined by the matrix stiffness, and biochemical cues (growth factors, cytokines and ions). Together, these components establish a highly specific microenvironment that directs cell fate and tissue maturation. Initially, matrix elasticity properties of the bone healing microenvironment are mainly dictated by collagen I. Osteoid has an initial stiffness in the 30- 40 kPa range and increases as mineral deposition takes place .Mechanical forces exerted by the cells alter their shape and function through focal adhesions and actomyosin contraction, which lead to activation of intracellular signalling pathways . The process has been shown to be dependent on a non-muscle myosin II-dependent pathway that can be decoupled with the use of blebbistatin (a specific myosin inhibitor). A role for mechanosensing has been observed in endothelial cells, in which matrix elasticity dictates VEGFR-2 expression changes .This mechanism enhances angiogenesis in matrices with elastic properties similar to those of blood vessel extracellular matrix (ECM).[5,6]



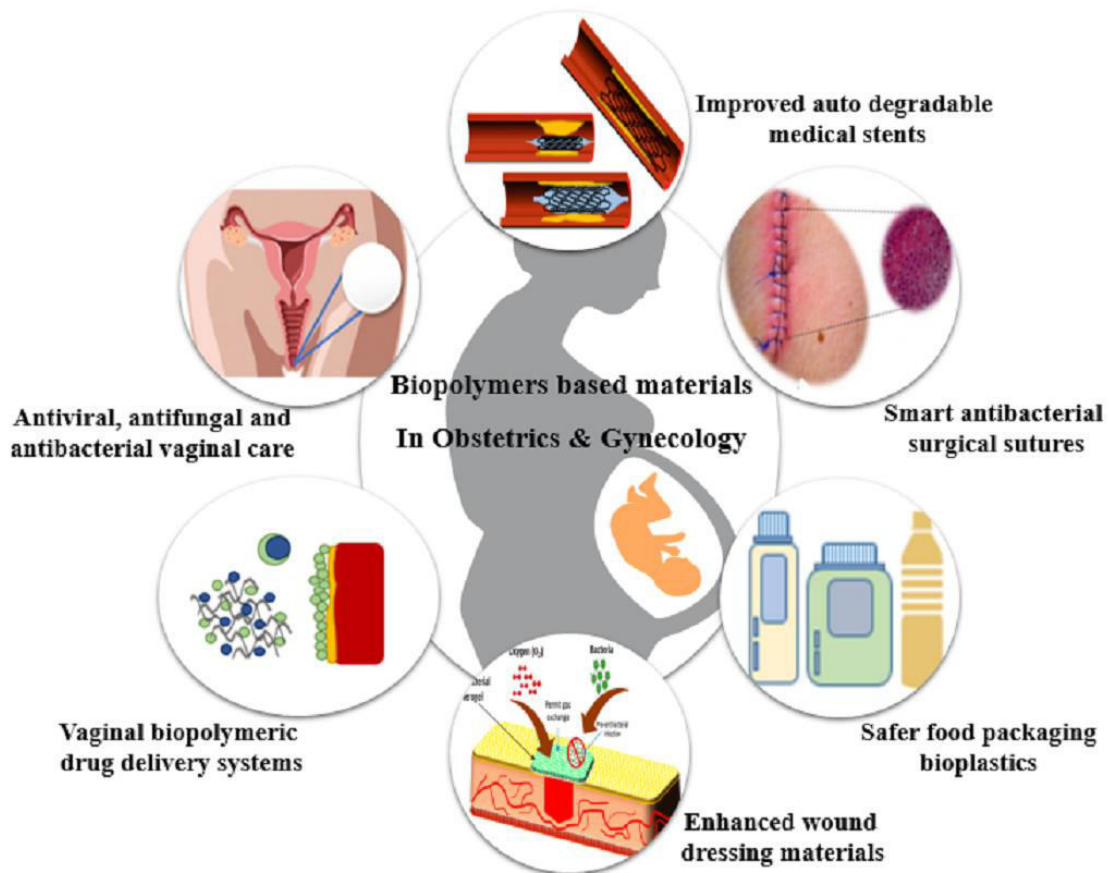
With the advancement of chemical and polymer sciences, the various strategies have been grown up for the development of novel Nanotherapeutics. Controlled Release Drug Delivery strategy has also been utilized by the novel Nanoformulations to alter the pharmacokinetic and pharmacodynamic property of drugs as well as to target the drug at different sites inside the body. Drug carrier materials play a significant role in the delivery of drugs. These carriers are processed into different drug controlled release systems. As the time passed the preference for biodegradable smart biomaterials have been increasing day by day. The biomaterial is those substances that have been engineered to interact with biological systems for therapeutic or diagnostic purposes. Smart Biomaterials are mainly derived from natural materials but are can also be synthesized in the laboratory. Silk fibroin (SF) is a natural protein polymer that has been approved as a smart biomaterial by the US Food and Drug Administration (FDA). Silk fibroin based materials have a great biocompatibility profile due to their cytocompatibility and relatively lower or similar immunogenic potential compared to other common degradable polymers. SF has many unique characteristics, including appropriate mechanical properties, versatile process ability in an aqueous environment, biocompatibility, and a controlled degradation rate that make it an excellent candidate for drug delivery applications. So far silk-based nanoparticles have been developed to target lung, tumor and ocular disease for the delivery of proteins, small molecules, and anticancer drugs.[7,8]





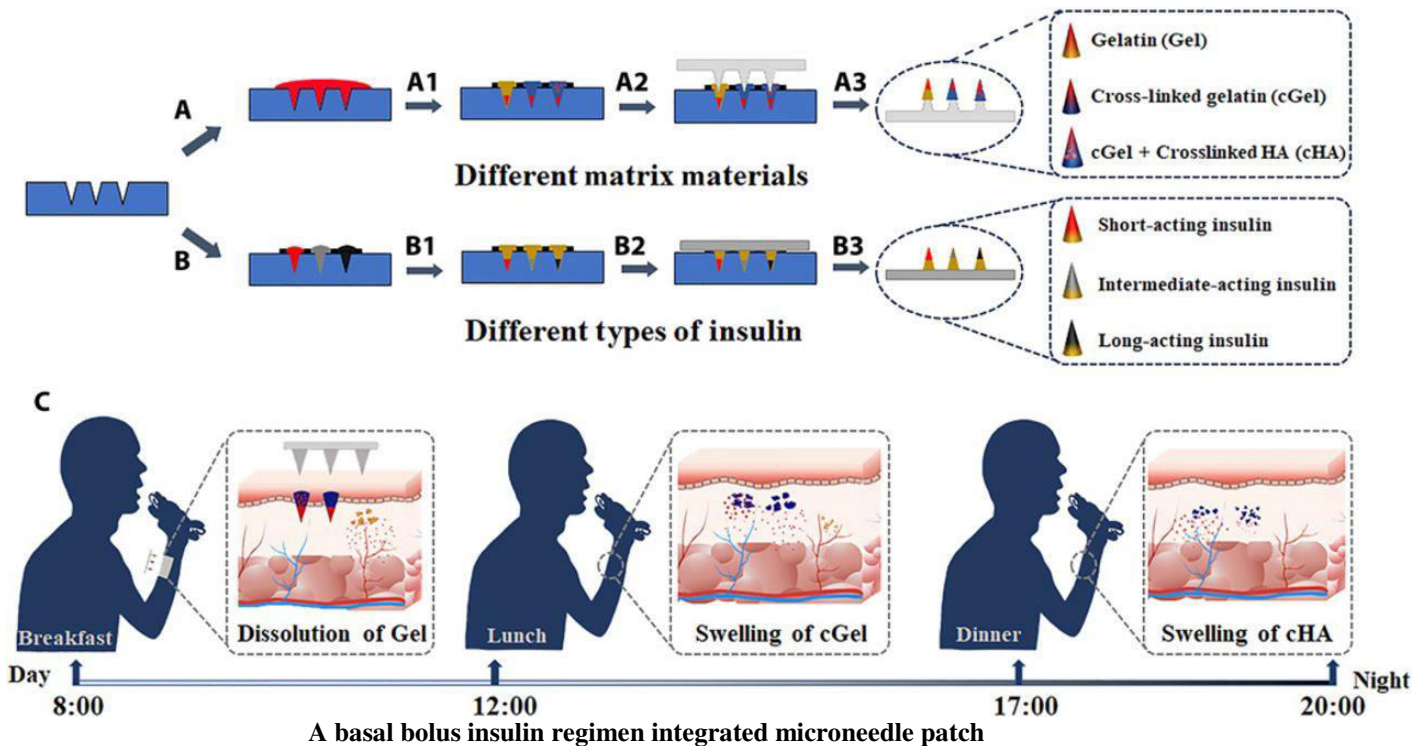
## II. OBSERVATIONS

There are a selected class of polymeric hydrogels, such as superabsorbent hybrid nanohydrogels, conducting polymer hydrogels, polysaccharide-based or protein-based hydrogels, or gels based on synthetic polymers. In this way, some of the fascinating properties and applications of polymeric hydrogels: they are three-dimensional, hydrophilic, polymeric networks that can absorb, swell and retain large quantities of water or aqueous fluids. In combination with metal nanoparticles, nanofibrils or nanowhiskers, which may be embedded in the gels, they find widespread applications, ranging from agriculture, and waste water treatment, over electronics, to pharmaceutical and biomedical applications. Applications include electro sensors, capacitors, electromechanical actuators, and even artificial muscles.[9,10]



One of the most popular applications of pH-sensitive polymers is the fabrication of insulin delivery systems for the treatment of diabetic patients. Delivering insulin is different from delivering other drugs, since insulin has to be delivered in an exact amount at the exact time of need. Many devices have been developed for this purpose and all of them have a glucose sensor built into the system. In a glucose-rich environment, such as the bloodstream after a meal, the oxidation of glucose to gluconic acid catalysed by glucose oxidase (GluOx) can lower the pH to approximately 5.8. This enzyme is probably the most widely used in glucose sensing, and makes possible to apply different types of pH-sensitive hydrogels for modulated insulin delivery

Low glucose concentrations allow contraction of the hydrogel inhibiting release of insulin. Further glucose-responsive mechanisms have been incorporated into hydrogels in order to achieve a mechanism that closely mimics the normal physiological glucose-monitoring and insulin-releasing functions of a human pancreas.[11,12]



### III. DISCUSSION

Electric current can be used as an environmental signal to induce responses of hydrogels. Those that are sensitive to electric current are usually made of polyelectrolytes and undergo shrinking or swelling in the presence of an applied electric field. Electro-sensitive hydrogels have been applied in controlled drug delivery.

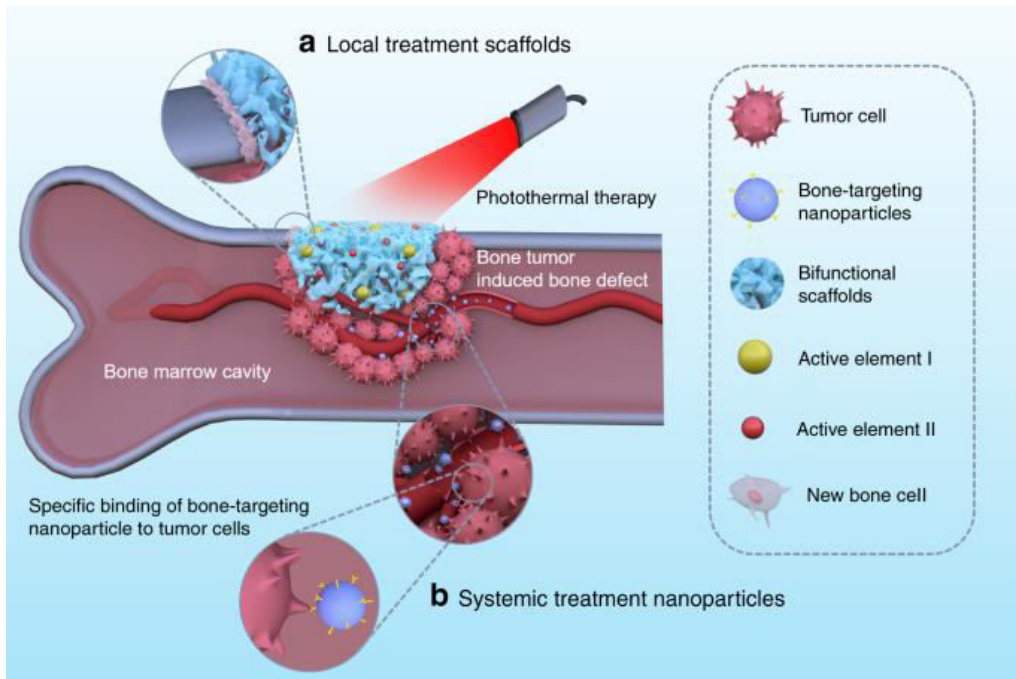
Chemomechanical shrinking and swelling of poly(methacrylic acid) hydrogels under an electric field have been developed and investigated for the pulsatile delivery of pilocarpine and raffinose. Also microparticles of polyacrylic acid hydrogel have demonstrated rapid and sharp shrinkage with the application of electric current and recover their original size when the electric field is turned off. The electric field-induced alterations in size of the microparticles results in an “on-off” release profile.

Extracellular microenvironments (eg, pH, temperature, dissolved oxygen concentration, enzymes, etc) can be greatly affected by disease progression. Tumours, for example, are a region that is more acidic (approximately pH 6.5) than blood (approximately pH 7.4) due to the anaerobic production of lactic acid and adenosine triphosphate hydrolysis in an energy-deficient environment.[13,14]

A non-viral gene delivery nanoparticulate system consisting of DNA, polyethylenimine (PEI) and poly(methacryloyl sulfadimethoxine) (PSD)-block-PEG demonstrated high transfection and cytotoxicity at pH 6.6 when the PSD-block-PEG becomes detached and there is direct interaction of PEI with the cells. At pH 7.4, the nanoparticles had low transfection (the process of deliberately introducing nucleic acids into cells) due to shielding of the PEI by the PSD-block-PEG.

The hyperthermic conditions found at a tumour site have also been exploited with the use of thermo-responsive copolymers that are tuneable between 37 and 42C.

Condensed DNA form small, neutrally charged polyplexes which aggregate and result in a two-fold increase in transfection efficiency when the temperature is increased from 37 to 42C. Upon intravenous administration in mice, these thermo-responsive polyplexes accumulated in the hyperthermic region of the neoplastoma, subsequently resulting in increased DNA transfection in vivo.



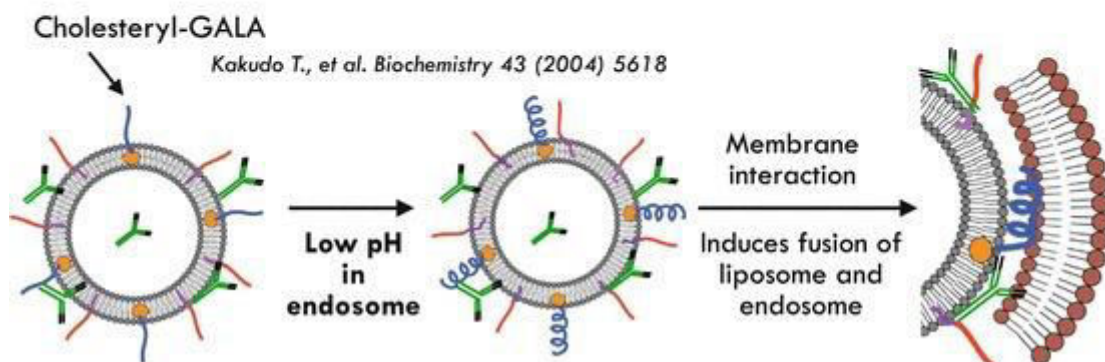
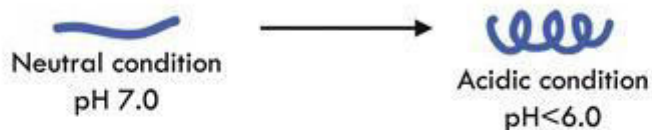
#### IV. RESULTS

Extracellular enzyme-triggered dePEGylation has been investigated to achieve efficient gene delivery by overcoming poor adhesion to the cell surface and entry. A multifunctional envelope-type nanodevice (MEND) consisting of a lipid linked via matrix metalloproteinase (MMP)-cleavable peptide was developed for delivery of small interfering RNA (siRNA).

Also, pH-sensitive fusogenic GALA peptide was integrated into the MEND to enhance endosomal escape resulting in an MMP-dePEGylable, fusogenic MEND that demonstrates effectively improved siRNA delivery both in vitro and in vivo.

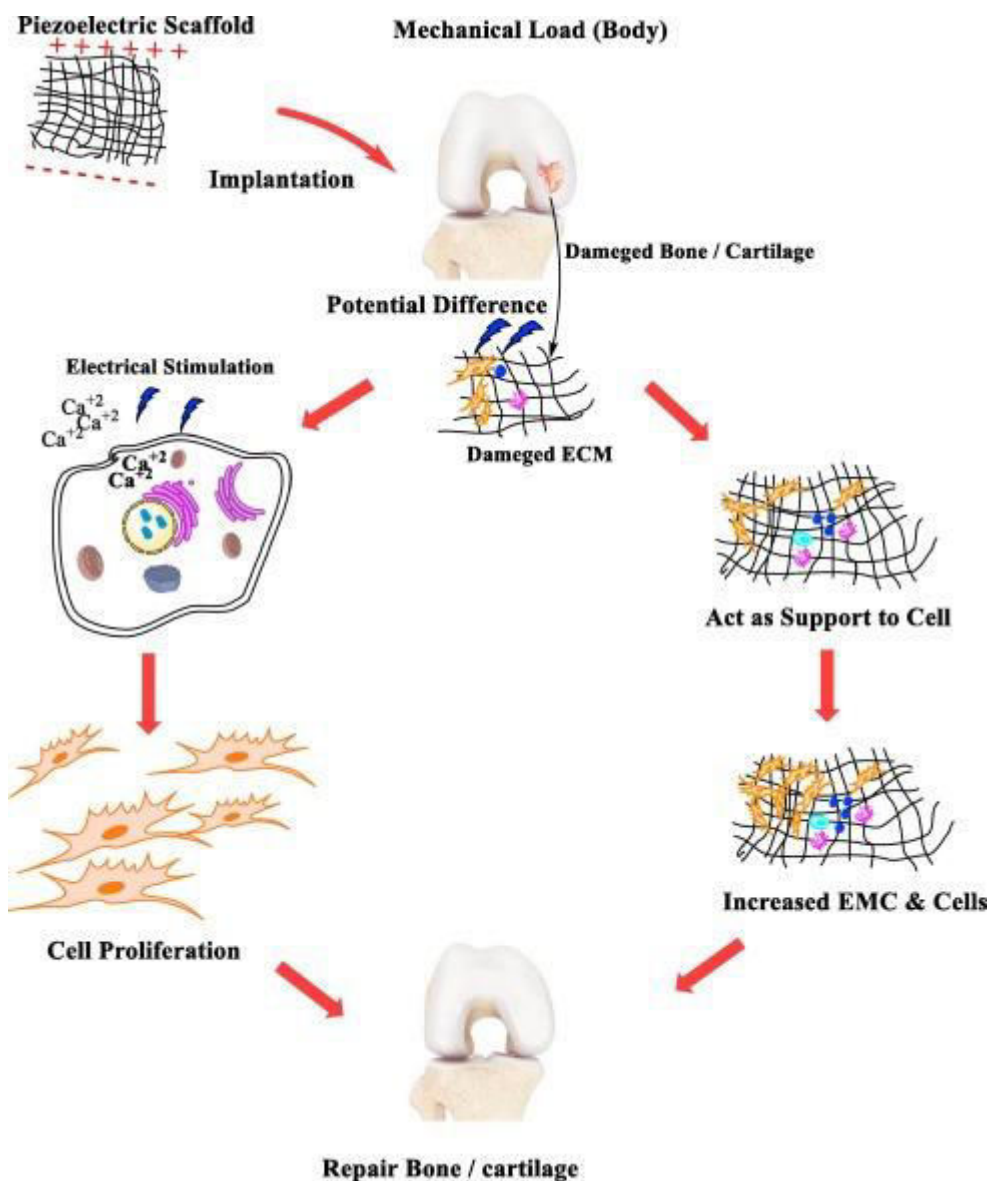
### GALA: pH sensitive fusogenic peptide

GALA: WEAAAEALAEALAEHLAEALAEALEALAA





Conventional therapies include pharmacological treatments such as, estrogens and selective estrogen receptor modulator (e.g. tamoxifen, raloxifen and nafoxidine) , biphosphonates (e.g. alendronate, zoledronate and pomidronate) , anti-inflammatory molcules (e.g. NSAID, indomethacine and aspirin) . However, major limitation of the pharmacological therapies are disease dependent, less effective in case of critical degeneration, lack of site specificity and drug associated toxicity . Surgical intervention is an important treatment choice; the major practices are autograft, allograft, xenograft, bone marrow stimulation, mosacoplsty and autologous chondrocyte implantation. The surgical practices have success rate up to some extent, the major limitations come from; donor site morbidity, due to secondary surgery associated with autograft and allograft. Furthermore, immunogenic rejection and disease transmission as consequence of allograft and xenograft practices . Bone marrow stimulation has poor regenerative capacity and the regenerated cartilage has low biomechanical integrity , the donor site morbidity also associated with mosiacplasty . The autologous chondrocyte implantation is a costly practice and complicated process, it is not recommended for osteoarthritis .[15]



Piezoelectric material for bone cartilage regeneration

## V. CONCLUSIONS AND FUTURE SCOPE

Healthcare is one the largest and most rapidly expanding needs of modern society, and smart approaches and materials are required to extend the boundaries required to improve the field. In this era of modern technology a series of



biomaterials and strategies that have emerged over the last decade. In particular, focus has been driven around the nanorealm. Some of the diverse arenas surrounding the nanodomain and applications include drug screening technologies, biocompatibility, emerging approaches and biomimetics. In a wider front, intelligent materials are which would prove a boon to mankind and would help millions of sufferers. It would make painless therapies with easy routes for human beings and create betterment for survival.[16]

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