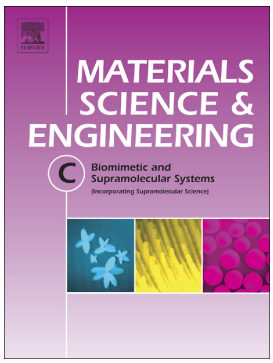

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Recent Exploration of Bio-Mimetic Nanomaterial for Potential Biomedical Applications

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Abstract

Bio-inspired materials with the multiscale skeleton show intrinsic multifunctional integration. This special biological characteristic is designed and developed to encourage scientists and engineers to multiobjective artificial physicals with multiscale frameworks. This review focuses on some recent development in the areas of classical biomaterials including lotus leaves, butterfly wings, red rose petals, spider silks and the associated multiscale frameworks acquiring function coalescence. We have also addressed some queries and standpoints for bio-inspired form of drug delivery using pathogens, which sheds light on delivery of proteins, small interfering RNA and other therapeutic agents.

Keywords: biomimetics; nanomaterials; drug delivery system; biosensor

1. Introduction

The most promising areas of research within the array of biological materials science and engineering nowadays are bioinspired, biomimetic and nanobiomaterials. The technological significance of this area is immensely used for applications such as drug delivery systems to bio-mimicked sensors, tissue engineering and optical devices [1]. The research and refinement of basics activities found in biological systems are involved in the study of bio-inspiration and biomimetic which has evolved through development. Applying the knowledge involves production of unique and exciting basic technologies and also this has modern methods for resolving various scientific issues [2].

For example, particles of polymer and lipid are used as synthetic carriers, which often struggle to meet clinical expectations. Therefore natural particulates ranging from pathogens to mammalian cells are worth examining in further depth, due to their highly optimized *in vivo* activity and convincing features that are often desired in drug delivery carriers [1, 3]. Having clear understanding of these biological systems, researchers attempt to use natural particulates for multiple applications in the delivery of proteins, small interfering RNA (siRNA) and other therapeutic agents. The natural drug delivery carrier boosts up the thirst for new drug delivery systems, which has been reviewed here.

1.1 Interpretation, concepts and fields of biomimetics

1.1.1 Interpretation of biomimetics

The term "biomimetics" originates from the Greek words "bios" (life) and "mimesis" (to imitate), yet its definition is not as simple as just those two words. Biomimetics is the understanding of nature and natural phenomena to study the principles of underlying mechanisms, to obtain ideas from nature, and to apply concepts that may benefit science, engineering, and medicine [1]. In terms of Chemistry it is defined as 'a field that creates synthetic chemicals which act like biological molecules'. In the field Molecular biology it is defined as 'the development of synthetic systems based on information from biological systems'. In Technology it is referred as 'the formal study of biological processes and systems as a model for creating synthetic structures similar to those produced in nature' [1].

1.1.2 Concepts of biomimetics

The study of biomimetics is not a recent trend, but for a long time it was a practice for researcher to use the idea of looking into nature and take the inspiration from it and make something new and conceptual. The idea mostly focused on the fact there is no model better than nature for developing something innovative, which has excellent productivity and function. It has been called by different names such as "intellectual structure" in Japan and "smart material" in the USA. This idea reduced research expenses and as well as gaining realistic result by eliminating waste [1, 2].

1.1.3 Field of biomimetics

Biomimetics can help to avoid the extensive industrialization and resource extraction done by human. On the basis of innovating new products, the biomimetics can go beyond just applying natural properties. Such products can be designed to play a part in general industry as well as to provide human convenience in the fields of chemistry, biology, architecture, engineering, medicine, and biomedical engineering (**Fig. 1**a) [2, 3].

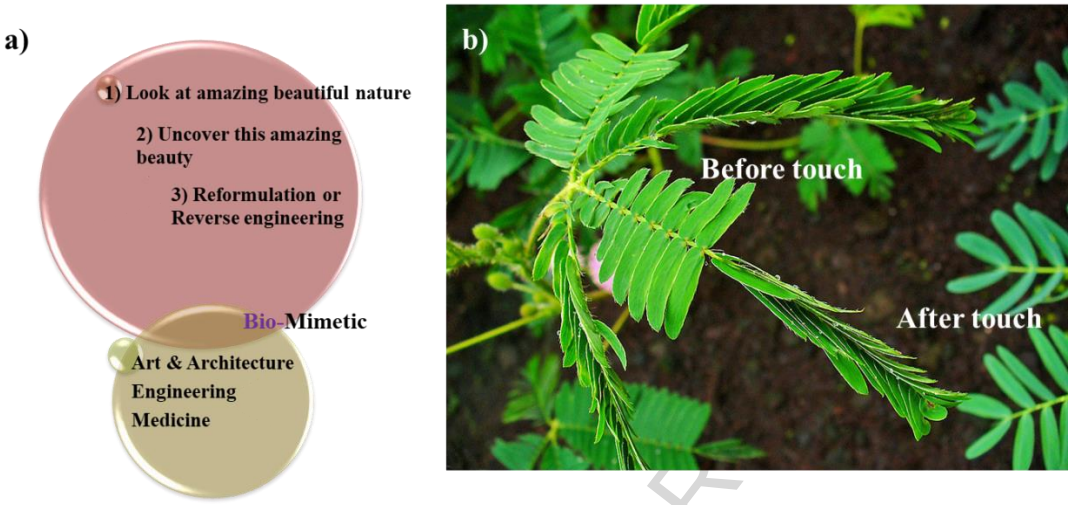

Figure 1. a) The exploration and areas of application in biomimetic or bio-inspired research. b) The natural beauty (leaves of the sensitive plant *mimosa pudica*) is a potential source to learn from nature.

Many human creations and innovations were inspired by biological systems. This program focuses on the intrinsic functions of biological molecules to direct 1) nanomaterial synthesis, 2) molecular recognition and 3) self-assembly processes to develop next generation bioinspired materials and devices that are multifunctional and sustainable [1, 3]. Collaboration with engineers, biologists and clinical investigators have solved interdisciplinary biological problems and translate these technologies into commercial products for biomedical applications in sensing, imaging, drug screening, delivery and theranostics.

1.2 History of biomimetics and research methods

1.2.1 The history of biomimetics

Biomimetics is a broad field with a long history which will be found easily in everyday life and no knowledge will be needed to use this. From knives and axes inspired by the dental structures of currently extinct animals to the strongest cutting-edge carbon nanomaterials, bioengineering has always evolved along with human history [4, 5]. Furthermore, the natural beauty of plant origin like *mimosa pudica* plant inspired us to learn more lessons from nature (Fig. 1b). These

type brand new biomimetics lesson can possible to use to solve different critical question in biomedical sciences.

Leonardo da Vinci's (1452–1519) work is a fundamental example of biomimicry was a "flying machine" designed by him that was inspired by a bird [6]. In the Far East; the turtleship was built by General Yi Sun-sin, which was modelled after a turtle, to fight Japanese raiders during invasions [7]. The Wright brothers (1867–1948) took note of the wings of eagles and made a powered airplane that succeeded in human flight for the first time in 1903. Over the next century, the airplane became faster, more stable, and more aerodynamic [8, 9]. Schmitt was the first to coin the term biomimetics in 1957, and he announced a turning point for biology and technology [10]. Jack E Steele of NASA, who coined the word bionics in 1960, was also the first to use the word biomimetics in a paper in 1969, which led to the addition of the term to the dictionary in 1974. In 1997, Janine M Benyus published her book Biomimicry, which emphasizes that biomimicry is leading the path to a new age of technological development by taking lessons from nature as the groundwork for products, rather than just using it for raw materials [1]. Janine Benyus and others stepped further to organize a social enterprise called Biomimicry to share ideas and concepts of biomimicry and biomimetics as well as to connect interdisciplinary researchers, scientists, artists, engineers, business leaders, and stakeholders [5, 10].

1.2.2 Research methods for biomimetics

There are six steps for basic research method for biomimetics, which can be used to apply biomimetics to design, product, service, and agriculture [4]. Like the sticky substance found in mussel byssal and spider silk (**Fig. 2**) [5, 11, 12].

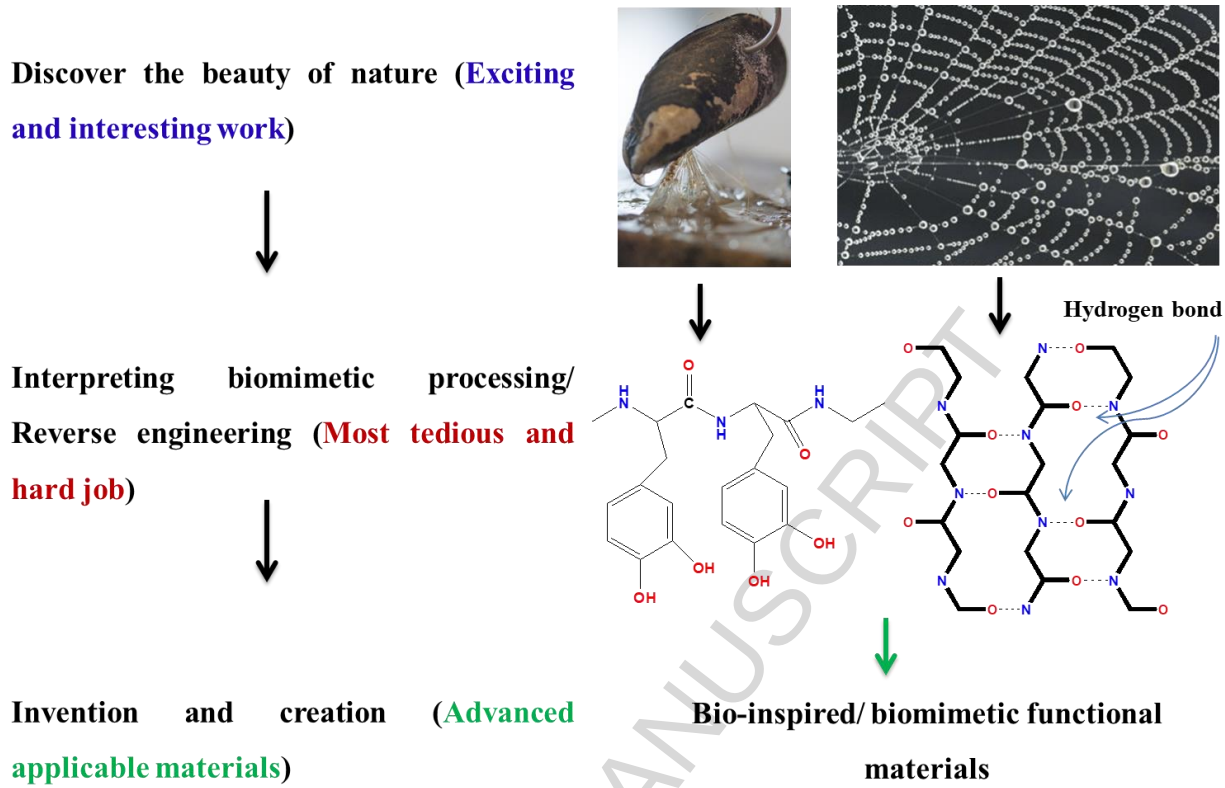

Figure 2. Development of bio-inspired functional materials by using discovery, interpreting/translating, and invention. First in the discovery, natural materials are copied as the source of inspiration (mussel byssal and spider silk, etc). Next, interpreting the natural beauty through a logical experimental ways and reverse engineering the experimental outcome comply with bio-inspiration (Mussel adhesion dopamine, silk fiber with hydrogen bonding). Finally, the interpreted knowledge from nature is used to develop different multifunctional materials [5, 11, 12].

Step 1: The functional possibilities of biologically should not be just applied as it is used by the organism, it must be researched to make an inspired design. Although the discovery or fusion is crucial for an increased profit was to make innovative technology, the idea was to make a simple creative design which can provide greater convenience for human life.

Step 2: The relationship between the function of the organism and the principles under which that function is achieved must be established. Through research and database compilation

knowledge and application of various materials need to be accumulated. The relationship between structure and function can be observed by a scanning through electron microscopy technique which usually comes from the surface structure. These fine structures play an important role in the organism and are said to be the first step for biomimetics. The US researchers are using the Biomimicry Taxonomy as a practical database.

Step 3: The greatest challenge faced by biomimetics is to find their relationship with the organism and the environment to determine how nano- and microstructures function, especially if these have not been fully explored yet [4]. Finding substantial examples through the integration of biology, natural history, and materials science is the next step in biomimetic research.

Step 4: The next research frontier is to identify various functional and environmental adaptation mechanisms of organisms and their energy-minimizing design [4]. A successful example of this is the antireflective coating that was inspired by the 200 nm structures reflecting visible light rays from a moth's eye [4, 14, 15]. The nature of new biomimetic materials is to remodel hierarchical structures and their corresponding functions, and utilize them into something important.

Step 5: The combination of newly discovered materials with biomimetics research will be a key to understanding their applications and limitations [4]. Along with the pros and cons of biomimetics, the morphological and functional uses of the new material must first be understood as well, and the results from their combination have to be unravelled. Active research is going on these fronts, but making progress in these areas is realistically a difficult approach.

Step 6: The determined biological material's structure and the function is the source of innovation for the development of other materials as well as for a new material [4]. The tests and assessments that took place for the structure and function were for known materials, which then helps them to morph and evolve into new materials. By combining them with current advancements in medicine, chemistry, and nanotechnology, we may find novel utilities that may benefit human life.

2. Moving smaller and going natural in medical equipment and drug discovery

After billions of years of evolution, creatures in nature still acquire almost perfect frameworks and functions [16]. Biological materials which are characterized for multiscale structures ranging from nano, micro to macro have performed important role in achieving structural and functional integrity. A huge number of natural structures have been scrutinized by scientists and engineers in the last few decades for their multidisciplinary fields. The natural multiscale framework of biological structures was found to be multifunctional not unifunctional, i.e., it possess functions more than one. Therefore the practical coalescence, such as lotus leaves, butterfly wings, red rose petals, mussel byssal and spider silks was found to design useful materials. Apparently, the multifunctional properties are presented to their corresponding biomimetic materials. This may be lead to inspiration of collaborating professionals of material science, chemistry, physics, biology, engineering, etc., which is required for the further exploration of additional function of biological materials and judicious outline and the coherent edifice of bio-inspired multi objective materials [16].

2.1 Biomimetic materials of lotus leaves

It was seen for over millions of years that there are many plants in nature whose leaves demonstrate special wet-ability. Out of which the lotus (*Nelumbo nucifera*) leaf, which commonly known as water lily, is one of the most inspiring. For over 2000 years, asian religious people took lotus as sacred flower that was referred as sybol of purity. It also has dirt resistant properties which was always praised and investigated, for a long time, by the scientists [26-28]. Lotus leaf surfaces are made up of micropapillae randomly distributed (5-9 mm in diameter) which is enveloped by magnificent branch-like nanostructures (Fig. 3b). The concurrence confers high water contact angle and small sliding angle due to multiscale surface and hydrophobic epicuticle wax, inducing super-hydrophobic and low-adhesion functions. They also have self-cleaning effect which is again known as lotus effect, because dirt particles get easily picked up by the spherical water droplets which roll across the lotus leaf easily cleaning its surface (**Fig. 3**) [26-28].

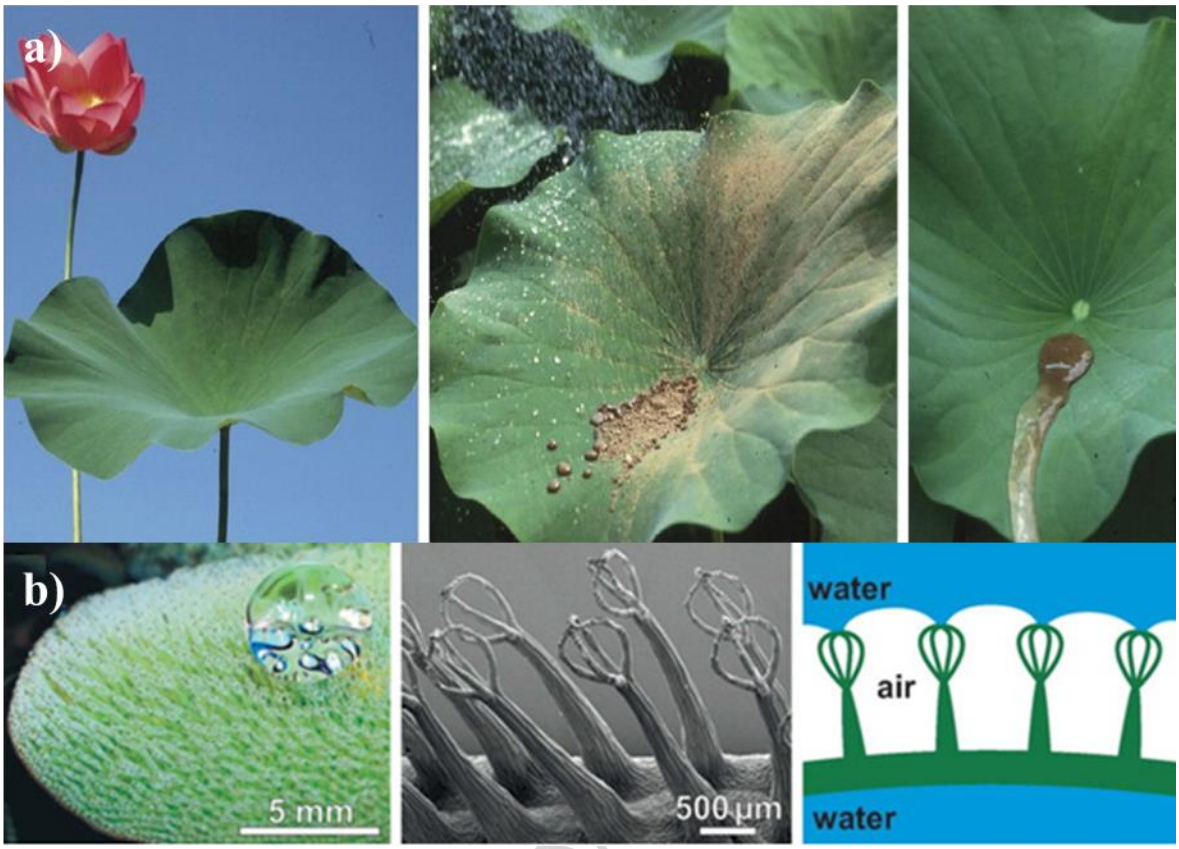

Figure 3. (a) Dirt particles gets easily picked up the water droplets which roll across by the lotus leaf easily. (b) Showing super-hydrophobicity of *Salvinia molesta* at different magnifications. [23] Copyright © 2015 The Authors. Published by Elsevier Ltd.

Many different composite approach have been developed which was inspired by lotus leaves, this included constructing super-hydrophobic self-cleaning surface along with less water adherence by creating multiscale structural surface [29-32]. An elementary and cheap mechanism was developed by mimicking the lotus leaf, which leads to the preparation of a super-hydrophobic coating using isotactic polypropylene (i-PP) surface [22]. The resulting coating with a water contact angle of 160◦ was a gel-like porous which exhibited super-hydrophobicity. Other than glass slides, a wide variety of substrates, including aluminum foil, stainless steel, teflon, high density polyethylene, and polypropylene could be used to give coatings made of super-hydrophobic. For producing micro-to nanoscale fibers or particles, the electro-hydrodynamics (EHD) technique is a versatile and effective method [25]. Making use of

the EHD method, a lotus-leaf-like microspheres and nanofibers has been prepared with super-hydrophobic porous composite structure [23]. The porous microsphere increases surface roughness contributing to the superhydrophobicity and a three-dimensional (3D) network which is formed by interweaving nanofibers to reinforce the composite film.

The special wettability of lotus leaves, large area, flexible and super-hydrophobic films inspired to fabricate thermal dispersing of silver nanoparticles on the designed flexible hemispheres arrangement and modifying it with 1-dodecanethiol [24]. The stratification of the obtained biomimic film is quite similar to the natural lotus leaves which consist of hierarchical micro/nano structures (Fig. 3b). A high water contact angle and a low sliding angle gave remarkable super-hydrophobicity and good flexibility of this kind of biomimic polymer film.

2.2 Biomimetic materials of butterfly wings

Since the 17th century Hooke, Newton, Lord Rayleigh everyone got amazed by the dazzling and diversity of colors produced by a wide variety of creatures in nature, which created interest for researching of some scientific giants. Colors are naturally created by complexion, structural color (iridescence), or a combination of both complexion and structural color [18]. The structural color results from the interaction between light with highly rigid and refined architectures, these has different characteristics which are not possible using complexion. Butterfly wings and peacock feathers are taken as a perfect example. An example of a bright insect is the Morpho butterfly (**Fig. 4**), which can be found in Central and South America, are famous for their dazzling blue iridescent colors. The shiny colors arise from nanometer, micrometer, to millimetre of multiscale photonic structures which reside on their wing scales [34-36]. In addition to the dazzling iridescent blue colors, the butterfly wing scales have super-hydrophobicity, self-cleaning capabilities [17-21]. Furthermore the wing consists of two types of scales. The ground scales are needed for their structural color, while the superhydrophobic and self-cleaning properties are found in the cover scales which are quite similar to the lotus leaves [21]. Further researches showed that the highly ordered photonic and multiscale framework of Morpho butterfly wing show various optical response to different individual vapors (such as water, methanol, ethanol, and isomers of dichloroethylene) [19]. The existing nano-engineered is going on photonic sensors which was inspired by iridescent scales of the butterfly because their selectivity on vapor response. The layout of diverse vapor detection applications was highly acute chemical sensors

and promising route for the researcher. For the African swallowtail (Papilio) butterflies the scales are made of pigement-infused 2D photonic crystal which provides fluorescence those are intensely directed and directionally intensified by the distributed Bragg reflectors [20].

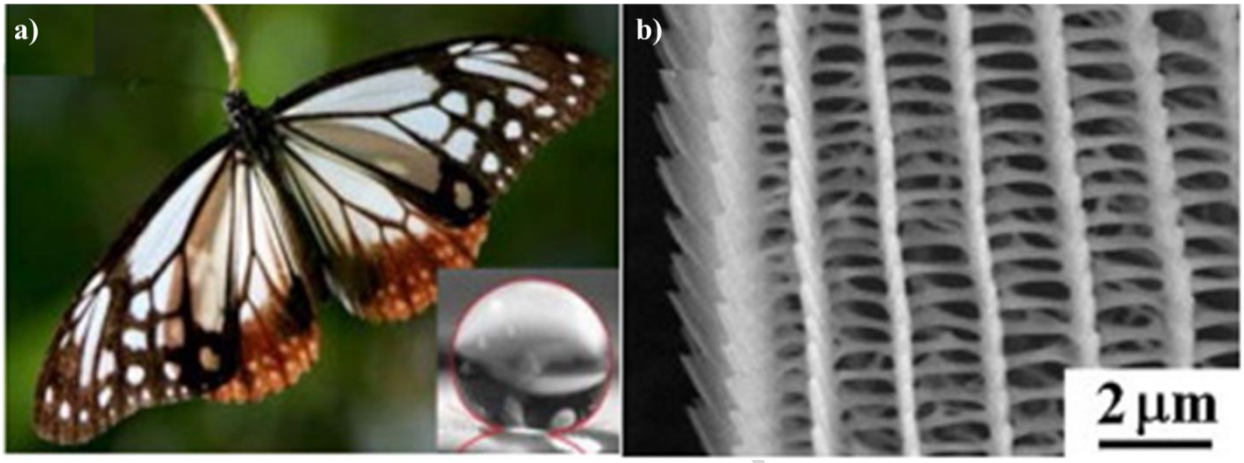

Figure 4. a) *Parantica sita* and b) SEM images and cross-section of a ground scale of the butterfly. [23] Copyright © 2015 The Authors. Published by Elsevier Ltd.

The multifunctional properties of the butterfly wing scales are determined by multiscale framework, these inspire to design biomimetic multiscale materials by scientists and engineers for function integration. An inverse opal film construct by mimicking the Morpho butterfly wings that includes self-assembly of polystyrene spheres and silica nanoparticles. As a result, the opal film shows both superhydrophobicity and structural color [23, 37, 38]. Moreover stratified structures which are photonic can be completely replicated by a coating of alumina with a process of low-temperature atomic layer deposition to form micro and nanometer scale that was also mimic the natural butterfly wings as the templates [23, 39]. Furthermore, the alumina replicas with a 3D structure can be served as a beam splitters, optical waveguides, and building blocks of other photonic integrated circuits (Fig. 4) [40].

In recent times, a high-resolution multi-colored arrangement strategy has been developed to resolve fabricated structural color. This biomimic strategy was inspired by the structural color from the special stratified structures found in butterfly wings and peacock feathers, and within

seconds this takes place by using only one material and flexible photonic crystal, where the color can be magnetically tune able and lithographically fixable [41].

2.2.1 Butterfly-inspired design enables low-cost thermal imaging

Based on the principles of high gas selectivity of the wing scales of Morpho butterflies, a new gas sensor has been fabricated. These new sensors can detect different type of gases as well as can quantify gases in mixtures. These new class bio-inspired nanostructures would enable broader application of thermal imaging which will improve the manufacturability, image resolution, sensitivity and response time. Next goal of this gas sensors are to be made in a cost-effective manner and will be offered to the market as new attractive sensing solutions [39].

At the same time, the sensors will take over all classical and micro-fabricated instruments based on gas chromatography and mass spectrometry which have limited in field use by power, cost, size, carrier gas or vacuum demands. Applications such as industrial inspection, home health care, wearable units for workplace monitoring, and monitoring in harsh environments could be improved and maintained at low cost [39]. Also gas leak detection can be easier with this highly selective colorimetric sensor. The following are examples where gas sensors can be easily applicable -

a. Thermal imaging for advanced medical diagnosis-to better visualize inflammation in the body and understand changes in a patient's health earlier

b. Advanced thermal vision - to see things at night and during the day in much greater detail than what is possible today

c. Fire thermal imaging - to aid firefighters with new handheld devices to enhance firefighter safety in operational situations

d. Thermal security surveillance - to improve public safety and homeland protection

e. Thermal characterization of wound infections - to facilitate early diagnosis

2.3 Biomimetic materials of spider silks

Spider can construct stable, impenetrable, and incompetent orb-webs for prey grasping, this is one of the biology's best ''manufacturing engineers'' [40-45]. For different purposes spiders produce different types of silks maintaining ambient temperature and pressure from an aqueous solution, which can resist wind, rain and sunlight. Multiscale structures is present in the spider silk which possess a range from nano to macroscale, thus it includes the density of electrons at the silk fibrils, Angstrom scale, β-sheet nanocrystals, β-strands, etc. (**Fig. 5**) [40, 46]. In carrying out the particular mechanical, physical, and chemical properties of spider silks the stratified assembling of the nano- and microscale plays a pivotal role [47-51]. A huge number of researches have been operated due to the remarkable properties of spider silk to resolve the development mechanism of spider silk [52-54]. Biomaterial science and the synthesis of biomimetic spider silk needed to have deeper perceptive on how the networking of the various spider silk constituents transcribes into the final thread inheritance with multifunctional properties [55].

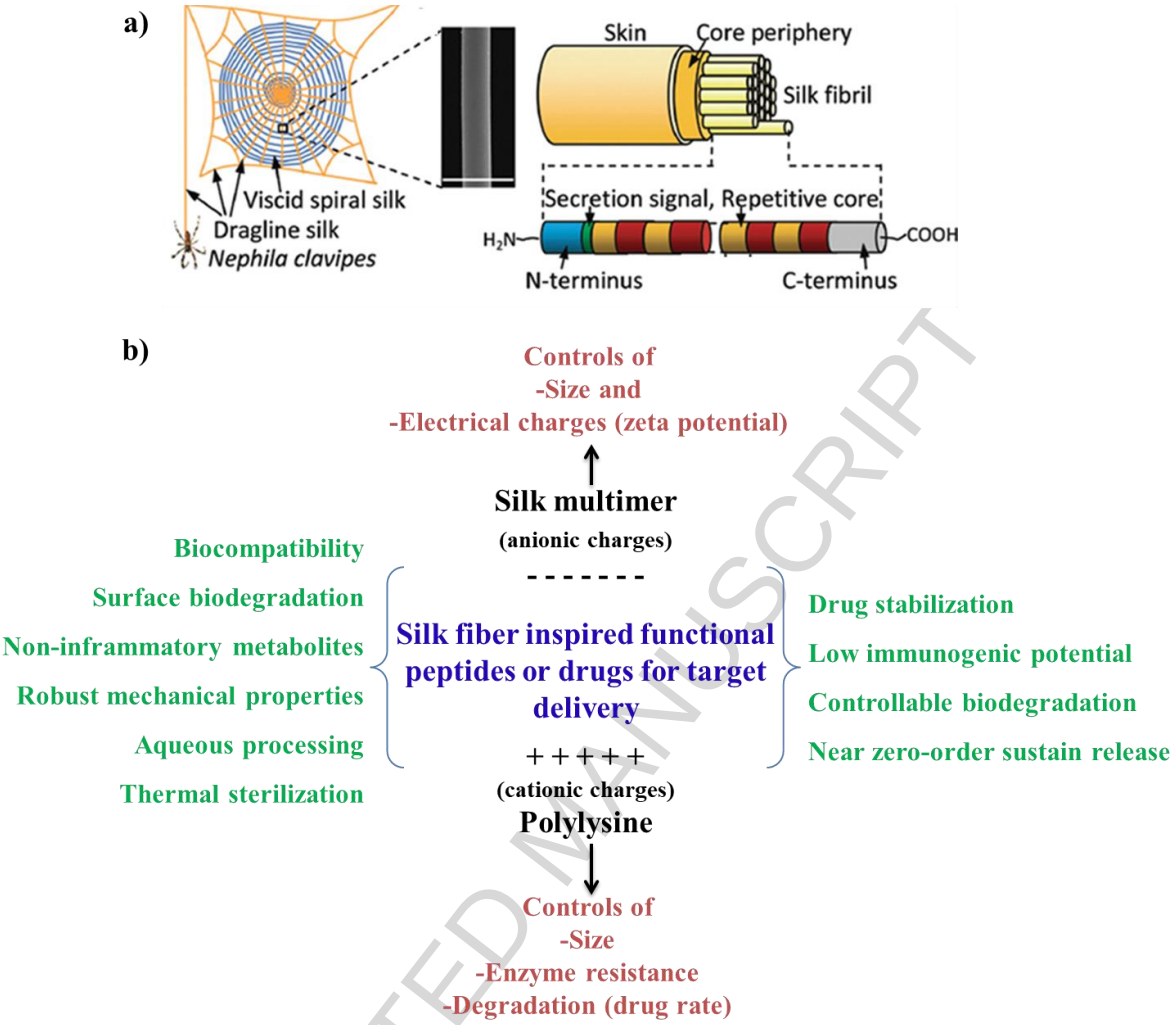

Figure 5. Schematic presentation of primary structure of silk-based block copolymer and functions of each module of the copolymer.

The most extensively studied biological fibers are the spider dragline silks, show stunning mechanical properties (robustness and toughness) that are preferable to almost all innate and man-made high-performance materials [40, 55]. Wetting-induced super contraction of spider dragline silk was shown, their mechanical properties results in an expansion in diameter and reduction in length [56-60]. To modernize the hardness of the silk in the spider's web this process is very important, because by this mechanical properties of fiber materials can provide an avenue to adjust performance, which develops 50 times greater work than the identical mass

of human muscle. The torsional shape memory is another remarkable characteristic of spider dragline silk, which show stopping of spider twisting and swinging by an exceptional torsional qualities [61].

Artificial dragline spider silk has been constructed by mimicking the spider, which was made by rotating dissolve recombinant dragline silk proteins (ADF-3 (Araneus Diadematus Fibroin-3); 60 kDa) originated in mammalian cells under moderate shear and coagulation circumstances [62]. Correlating to those of natural spider dragline silks, the recovered spun fibers had a fine diameter (10-40 mm) with water insolubility and also showed toughness and modulus values [40]. A variety of potential applications of these strong and lightweight fibers are being compatible for tendons and ligaments, biodegradable ophthalmic sutures, and high-strength fishing line.

Nanotubes made up of carbon are one-dimensional nanomaterials; their strength is extremely high with steep stiffness, low density, and chemical stabile. Due to these preferable resources of carbon nanotubes it is possible to assemble spider silk like super-tough fibers. Single-walled carbon nanotubes (SWNTs)-PVA composite fibers was constructed by spinning to get 100-metre-long tougher spider silk and any other innate or fabricated organic fiber proclaimed previously [62]. The preferable toughness of SWNTs-PVA composite fibers shows the combination of high toughness and high elasticity, which is associated due to the existence of PVA between SWNTs and between individual slippage nanotubes within bundles [63-64]. Moreover, at the atomic level the mechanical property of the material can be altered by infusing metals, where spider dragline silks can be strengthened into their protein structure and intensify the durability and toughness [65]. This facility can be a model for a more generic access, such as collagen membranes from eggs.

Capture silk, which is five times as elastic as dragline, is the viscous spiral in the webs of orb-weaving spiders, determining notable elasticity. To consume exceptional amounts of energy orb-weaving, the spiders depend on viscous capture silks and also absorb prey long abundant to be placed and attacked. Thus, spider capture silk can be said to have multi-functional physical maintaining high toughness, elasticity, and stickiness [66-68]. Recently, the ability to collect directional water from moist air was found as another fascinating property of the spider capture silk [69]. Due to the special hierarchical fiber structures the water-collecting ability of the spider

capture silk takes place, research indicated that the wet-rebuilt fibers acquire periodic spindle-knots which are made up of irregular nano-fibrils detached by joints made of regulated nano-fibrils. A slant of exterior energy on the fibrils and the axis outline of the knots act to generate forces together which directs the water droplets towards the knots. Multifunctional features of the spider silk have more yet to resolve to the scientific world.

3. Biomimetic drug delivery system

3.1 Spider silk-based biomimetic strategies

3.1.1 From reconstituted spider silk based proteins

The spider *Araneus diadematus* dragline silk protein was reconstituted to prepare microcapsules for drug delivery which go under self-assemble of the proteins at an emulsion interface. These microcapsules were useful to encapsulate small active ingredients, that does not provides the active ingredient to impede the adsorption of the silk [70]. ADF4 is derived from *A. diadematus* to make microspheres of bioengineered spider silks by using dialysis and micro-mixing [71]. Spider silk microspheres may offer potential for the development of targeted drug delivery systems taking in consideration of their material strength, biocompatibility and the possibility of functionalization using recombinant protein techniques. For example, macromolecular drugs like proteins loaded on recombinant spider silk protein eADF4(C16) has been shown to be a promising biomaterial for the use as drug delivery system [72].

3.1.2 From spider silk based polycation block copolymers

For gene delivery, a silk-based block copolymer was generated by repeating poly (l-lysine) which was combined with spider silk. Poly (l-lysine) is a cationic polymer, which assemble into polyelectrolyte complexes by interacting with DNA through electrostatic interactions, thus it is degraded in cells and has been used for the delivery of DNA into cells as an alternative to recombinant viruses (Fig. 5). Ion complexes were formed using the silk-based block copolymers with DNA, and the sizes were controllable based on the polymer/DNA ratio or molecular weight of poly (l-lysine) bioengineered into the designs [73]. Copolymer/DNA ratio was prepared depending on the sizes of DNA complexes prepared at 10 ranged from 310 to 590 nm. Also, no

cytotoxicity was seen by the DNA complexes of silk-based block copolymers with less than 30 lysines toward human embryonic kidney (HEK) cells.

3.1.3 From spider silk based polycation-functional peptide multiblock copolymers

For non-viral gene vector silk-based block copolymers are potentially useful candidates because of their various functional peptides such as cell binding motifs (RGD), cell penetrating peptides, signal peptides of virus, and/or tumour-homing peptides, which can be added as ligands through recombinant DNA techniques to take advantage of recombinant silk proteins over liposomes and synthetic polymers as gene delivery [74-77]. The molecular design for specific target delivery along with regulating sizes, drug releasing rates and zeta potentials are based on silk-based block copolymers which form complexes of the copolymer and bioactive molecules.

Tumour vasculature is a target for anticancer therapy, which plays an important role in cancer, however, most carriers for gene or drugs are relatively poor at specific delivery to specific cells. Using several tumour-homing peptides, selective targeting to tumour cells has been reported. Peptides which include antibodies that recognize tumour-specific vascular signature *in vivo* the screening was done to identify phage libraries, revealed extensive heterogeneity in tumour blood vessels and lymphatics [78-80].

Cell-penetrating peptides (CPPs) are able to efficiently penetrate cellular lipid bilayers or destabilize cellular membrane and can be defined as short peptides. Therefore, for new non-viral vectors of oligonucleotides, (short hairpin) shRNA, double strand and plasmid DNA, CPPs are useful candidates. A dimer of ppTG1 of the recombinant silk protein showed higher transfection efficiency, which was almost identical to lipofectamine 2000, in comparison with the other silk-based gene vectors [81]. Thus, to enhance transfection efficiency significant improvements are anticipated upon addition of such peptides as an approach.

Signal peptides and capsid proteins are virus-derived peptides, which have been studied for gene delivery. Adenovirus infection is mediated predominantly by the penton and fiber capsid proteins. These proteins interact to get permission for the passage of viral particles in cell with cellular factors to coordinate key events and subsequently to the nuclear periphery for gene transfer [81]. The outer protein coat or capsid is the key to infection efficiency [82]. High levels of receptor binding was seen after utilizing polylysine for DNA transport, but showed relatively

low transgene expression. In the absence of viral gene expression, the viral capsid itself promotes cytosolic entry. The development of gene and drug transport systems with silks for improved delivery can be taken into consideration using the functions of signal peptides and capsid proteins.

3.2 Pathogen-based biomimetic strategies

3.2.1 Pathogen-mimicking vaccines

The development structure and/or composition of microbes aroused from the poor immunogenicity of soluble antigens in a reductionist fashion [83]. A process which is known as cross presentation where internalisation of the particle-associated protein processes the antigens for presentation to CD8+ T cells, this is a nature of pathogens which has an important role in their recognition by immune cells: professional antigen-presenting cells (APCs). As a result the APCs undergoes up to 1,000-fold more efficiently than if the same extracellular proteins are internalized in a soluble form [84, 85]. In addition, it triggers improved T cell after antigen presentation to CD4+ T cells is amplified, which assistance for CD8+ T cell and antibody responses [83, 84]. Consequently, the continuous release of antigens within APCs was developed using polymer particles such as poly (lactic-co-glycolic acid) (PLGA) micro- and nanoparticles, which might sustain T cell priming *in vivo* [85].

In vivo, the dissemination is also by the size of pathogens; through the extracellular matrix the viral particles can easily diffuse freely as they are small enough to be drained rapidly from the peripheral tissue sites to lymph nodes, where primary immune responses are generated [84]. Synthetic polymer particles that carry antigens and are <100 nm in size have been shown efficient transport to lymph nodes by mimicking this size-dependent transport process, following their injection into the skin, thereby yielding more efficient immune responses [86, 87].

The generation of potent immune responses by natural pathogens can be dictated by the internalization of antigens in a particulate form which represents only one of the many factors. Conserved molecular designs in the structure of microbes (example such as, unmethylated cytosine-guanine units (CpG DNA), double-stranded RNA, and so on) are the signals which are recognized by immune cells, and they engage receptors such as Toll-like receptors (TLRs). Mimicking the coexistence of both antigens and stimulatory signals that are present in pathogens

promotes both antibody and cellular immune responses by incorporating defined TLR agonists or other molecular danger signals into antigen-carrying particles.

Key mechanisms by which APCs can easily distinguish harmless environmental antigens from genuine pathogenic threats are co-delivered of danger signals and antigens to a common phagosomal compartment by antigen-carrying particles [88]. Via encapsulation or surface immobilization in synthetic particulate vaccines the pathogen-derived danger signals have been incorporated into them. Furthermore the complementary antigen-carrying particles can also be designed to trigger components of the host response [88]. Pathogens may be sensed by intracellular sensors of cellular damage and/or stress which trigger the activation of pattern recognition receptors. By the disruption of phagosomes and/or endosomes by pathogens might induce a complex intracellular signaling network which is known as the inflammasome. The classic adjuvant alum and degradable PLGA particles are synthetic particles which includes the potential to activate this pathway, thus providing a previously unappreciated mechanism for the design of effective vaccine carriers [89].

3.2.2 Virus-mimicking particles, including effects of shape

Researcher were motivated by an increased understanding of the mechanisms of viral infection, which helps in adapting viral structures and functions towards the design of synthetic drug carriers. Mimicking viral structures self-assembled liposomes have developed as tumour-targeted gene delivery carriers. Using lipids, transferrin and DNA, nanostructures were highly yield fabricating liposomes, with uniform size distribution (50-90 nm); the yielded nanostructures are characterized through a multicentre lamellar core structure and a transferrin-coated membrane, thus developing in mimicking the architecture of envelope viruses such as influenza virus and herpes virus. For example, the efficacy of the delivery of the gene is enhanced by mimicking transferrin nanostructures, which *in vivo* encodes the cellular tumor antigen p53 into human prostate cancer tumors [90].

The structural and functional traits of a virus have also been developed which was used to develop a pH-sensitive nanogel system [91-97]. This virus-mimetic nanogel is made up of a hydrophobic core and two layers of hydrophilic shells along with tumour-targeting ligands (**Fig. 6**). The hydrophobic core of nanogel facilitated to load hydrophobic anticancer drug like

doxorubicin. To mimic the capsid-like structure, PEG inner shell core polymer was linked to the outer shell bovine serum albumin (BSA). Reversible swelling of the nanogel was induced by these virus-mimicking particles, as they were pH-sensitive such that a pH reduction from a physiological (pH 7.4) to endosomal (pH 6.4) level may cause an increase in size from 55 nm to 340 nm; thus it facilitated endosomal escape and the release of doxorubicin into the cytosol. The nanogels moved to the neighboring cells, once the cells are killed by doxorubicin and disintegrated and they repeat the same cycle, thus replicating the infection cycle of viruses [91-97].

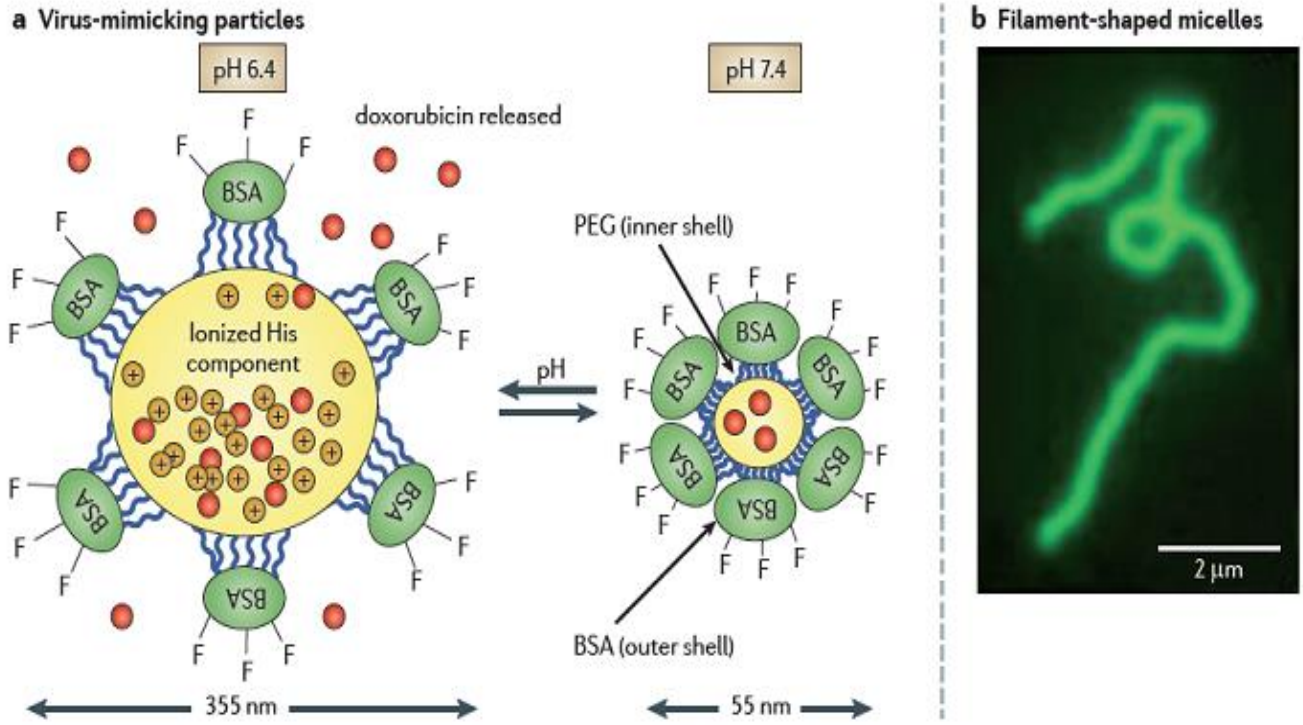

Figure 6. Virus-mimicking synthetic drug carriers. a) Virus-mimicking nanogels b) Filomicelles. [97] Copyright © 2011, Rights Managed by Nature Publishing Group.

Many of the viruses are filamentous, 'filomicelles' - have been synthesized to take advantage of the morphological features of viruses because of their wormlike filamentous micelles (Fig. 6b) [91-97]. The reticulo-endothelial system (RES) is evaded by the long and flexible filomicelles that are composed of self-assembling amphiphilic block copolymers, which

results in remarkably long blood circulation times (approximately 1 week). Interestingly, filomicelles optimal length is similar to that of the ~8 μm diameter of circulating RBCs. Moreover longer filomicelles rapidly gets fragmented to this size, whereas shorter filomicelles were cleared more quickly. Filomicelles are potential candidate to shrink tumours when they were loaded with the widely prescribed anticancer drug paclitaxel, which is more effective than either the free drug or spherical nanocarriers.

The circulation and targeting ability which depends on the effect of shape and flexibility of filomicelles is very promising. The ability of pH-sensitive nanogels to infect the adjacent just like virus and to escape from endosomes is also promising. Overall, the advanced engineering supports these strategies beyond simple surface modification of synthetic drug delivery carriers from viruses, and they broaden the applications of these virus-mimicking particles in targeted drug delivery. However, these studies are in early stages and it is not still proven about their utilization in the clinic

3.3 Cell-based biomimetic strategies

3.3.1 RBC-mimicking particles

Biocompatible polymeric particles that mimic RBC have been studied (**Fig. 7**) [92–97]. Using layer-by-layer building onto a PLGA template that mimic RBCs are resembles of natural RBCs (Fig. 7). These polymeric particles were used to encapsulate various compounds, which includes drugs and imaging agents. Haghgooie *et al.,* synthesized PEG particles were capable of passing through thin capillary channels that mimic various aspects of the size, shape and flexibility of RBCs (Fig. 7). Merkel *et al.,* in another study designed RBC-like hydrogel micro particles which consists of tunable elasticity and found to have great circulation which increases with tuning of the modulus these particles to that of RBCs (Fig. 7) [92–97].

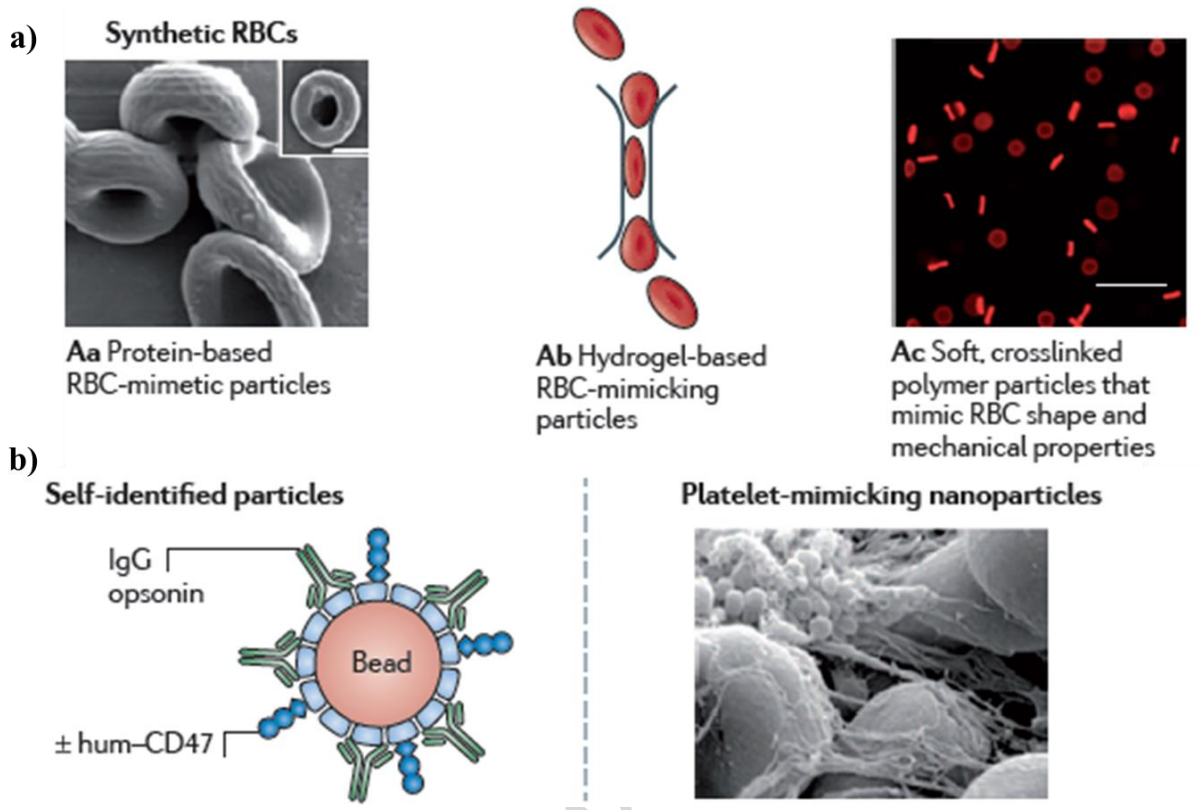

Figure 7. Cell-mimicking synthetic drug particles. a) Synthetic red blood cells (RBCs) and protein-based RBC-mimetic particles. b) Self-identified particles of platelet-mimicking nanoparticles. [97] Copyright © 2011, Rights Managed by Nature Publishing Group.

In addition there is a key factor that contributes to the exceptionally long circulation time of RBCs (~120 days) to the size, shape and mechanical flexibility of RBCs, a 'marker of self' recognition system has been considered. CD47 is a membrane protein, shows signal inhibition of the phagocytic activity of macrophages also present on all cells. For example, *Tsai et al.*, attached polystyrene particles to control recombinant version of the immunoglobulin-like domain of CD47 to *in vitro* phagocytosis (Fig. 7a). The studied showed uptake of these particles to that CD47 inhibited phagocytosis by human macrophages and monocytes in a dose-dependent manner. Generally *in vivo* immune-comparability is improved by incorporating a 'marker of self' into RBC-mimicking systems and many other particles [92–97].

3.3.2 Platelet-mimicking particles

Platelet-mimicking nanoparticles have also been developed for promoting haemostasis [93]. Synthetic platelets were conjugated to PEG and functionalized by RGD (Arg-Gly-Asp) peptides which consist of poly-L-lysine conjugated to PLGA (PLGA–PLL) block copolymers, which have a specific binding affinity for activated platelets. The *in vitro* and *in vivo* studies shows the synthetic platelets are able to stop bleeding successfully by adhering to the activated platelets [93].

3.3.3 Particles that mimic compartmental cellular architecture

Within spatially defined compartments, the complex chemistry and function of living cells are facilitated by the organization of the cellular machinery. At a simple level of initial studies of hierarchical drug carrier structures that mimic the eukaryotic cells have the compartmental organization. This spatially defined compartment motivating to design advanced drug delivery systems that are capable of sequestering diverse compounds within a single particulate carrier [96-97]

Kisak *et al.*, developed multiple internal bilayer-enclosed compartments, termed 'vesosomes' by exploiting a reversible vesicle-to-bilayer sheet transition (Fig. 7b). In vesosomes, each of which may have distinct membrane compositions that encapsulate drugs cargos to diffuse into the cytosol of the vesosome through the internal vesicle wall. Thereof they can easily permeate through the external bilayer, which results in a sustained release profile (over ~10 hours) [97].

For distinct release kinetics, hybrid lipid and/or polymer 'nano-cells' have been devised which help to co-deliver two anti-tumour drugs, these are based on the encapsulation of biodegradable polymer nanoparticles within lipid vesicles (Fig. 7b). An anti-angiogenesis agent, combrestatin, was trapped within the surrounding lipid bilayer compartment where the nanoparticles were formed from a doxorubicin–PLGA conjugate. For rapid release of the anti-angiogenesis agent this design was aimed from the outer compartment, trapping the nano cells within the tumour environment irreversibly helps in accumulating in tumours and stimulate the collapse of blood vessels within the tumours by intravenously injecting the particles. By a steady release of the cytotoxic doxorubicin cargo remaining tumour cells were killed with the help of

nuclear compartment of the nano cell. Compared to the single-drug treatment controls this two-pronged strategy greatly decelerated tumour growth. Therefore, this approach could be extended to several potential treatment synergy or known chemotherapeutic drug combinations.

Multicompartmental micelles are formed by multiple distinct block chemistries, designing block copolymers, which assemble to form stable structures in water [98]. These structures can be used to discrete nanoscale zones of individual micelles to sequester multiple drug cargos of distinct physical properties. On the micrometre scale, core-shell structures are well defined which are prepared using microfluidic reactors as well as emulsion spray-drying strategies, which provide concentric compartments for drug loading [99].

Electro-hydrodynamic spray-drying strategies can be used to access more complex morphologies, in which complex multicompartmental particle structures are fabricated using controlled phase separation in polymer solutions [98]. Using techniques such as continuous- and stop-flow lithography approaches which involve the fabrication of hydrogel particles with defined internal compartments of varying composition and chemistry; thus these approaches permit the synthesis of well-defined internal structures of monodispersed micro-particles [97, 101].

The importance of carrier properties (such as size, shape, mechanical flexibility, surface property and internal architecture) for drug delivery has been revealed in particle-cell interactions, thus more complex particles have been developed and showed advancement in engineering technologies. Researchers have therefore started to mimic the key properties of the cells and also take advantage of the morphologies and functions. For example, the internal structure and CD47, a pivotal maker for surface recognition, of RBCs did not combined into a single particle but the size, shape and mechanical properties of RBCs have been combined into biocompatible particles. Combination of a single synthetic particle with desirable properties of different cell or pathogens can be used to tailor drug delivery carriers which is designed and optimized for specific purposes. For future drug delivery carrier systems key cellular properties can be expanded and mimicked synthetic particle systems which have great potential.

3.4 Hydrogels-based biomimetic strategies

Hydrogels are hydrophilic natural or synthetic polymeric materials. They are capable of swelling by absorption of water and biological fluid owing to chemical and physical cross-linking properties of polymer chains. Their softness, flexibility, tunable porosity and biocompatibility have made them promising candidate to develop stimulus (such as pH, temperature, and ionic strength) responsive drug delivery carriers [102]. Moreover, by means of biomimetic modification of the hydrogel matrix could create specific properties for biocompatible delivery like; arginine-glycine-aspartic acid (RGD) within alginate polymer chains inspired bioactive cell-hydrogel and extra cellular matrix (ECM) mimic elastin-like polypeptide (ELP) derived hydrogel [103].

3.5 Liposomes-based biomimetic strategies

The cell membrane mimic of lipid bilayer inspire liposomes have considered another potential candidate for drug delivery applications [102]. Liposomes have hydrophobic as well as hydrophilic properties which could be synthesized by self-assembly of cholesterol and natural phospholipids in an aqueous medium. The typical non-toxic, biocompatible and biodegradable liposomes could carry both hydrophobic and hydrophilic drugs and gene therapeutic agent to promote the intracellular transportation through cellular barriers [104].

3.6 Polymeric carriers-based biomimetic strategies

The polymer carriers are easy of synthesizing and modification for drug delivery applications. The biomimetic polymers are produced by mimic cellular interactions mechanism with the cellular micro environments. Moreover, the integration of biological active moieties of these polymers allowed loading and delivery of drug in target diseased cells [102]. For example, the negative surface charge of biomimetic zwitterioni poly(amido amine)s (PAAs) have minimum toxicity effect on living cells in comparison with positive surface polymeric carriers [105].

3.7 Nanotubes-based biomimetic strategies

The walls of nanotubes have produced by the layer-by-layer method with various organic/inorganic components such as polyelectrolytes, inorganic nanoparticles, dendrimers, peptides, DNA, and enzymes [102]. The calcium-carbonate biomimetic synthesis of nanotubes provides the metastable outer shell that could be controlled release in drug delivery. Moreover,

biomiemtic multi-walled carbon nanotubes (MWCNTs) have inherent antiproliferation and migration effects on cells. This translocation effects made it possible to use against cancer cells [106].

3.8 Nanoparticles-based biomimetic strategies

The advantages of biomimetic fabrications of organic and inorganic composite nanoparticles as drug carriers have the capacity of loading drugs as well as cellular uptake [102]. The biomimetic collagen (CL) and poly vinyl alcohol (PVA) mediated hydroxyapatite (HA) nanocrystal are considered similar to the ECM for targeted drug delivery. The mussel-inspired fabrications of grapheme oxide (GO) crosslinked hyaluronic acid (HA) gel matrix are of another potential candidate to enhance drug loading and target delivery [106-107].

4. Sensor-based biomimetic strategies

4.1 Biomimetic strategies for sensing biological species

The word "sensor" comes from the Latin word "sentire" which originally means 'to identify' anything. By hearing the word sensor, the concept springs our five basic senses of human being. A sensor, which contain specific reacting site, would respond to a specific analyte in the medium. An electrical signal is initiated by the analyte/stimulus due to chemical interaction which takes place at the site. This electrical signal is then transmitted into another unit, which is a processing unit for carrying out the detection response [108]. A typical sensor is composed of two parts i.e., receptor and transducer. Electrical energy information is received by receptor which gets converted from the physical/chemical stimulus, while transducer converts this to valuable analytical signal that is further analyzed and then presented in an electronic form.

Figure 8. Biomimetic based typical components of a biosensor.

Biosensors, is a class of a sensor, which is recently described and analysed due to its hybrid physical and chemical sensing technique. In principle (**Fig. 8**), the biophysical or biochemical property of the medium can be interpreted by biosensors, which are receptor-transducer based tool. Moreover, the presence of biological/organic recognition element is the most intriguing character that sets this type of sensors apart from others, which enables the detection of particular biological molecules in the medium [111]. A new era of advancement in science was brought leading to the development of biosensors. This phenomenon withholds set of techniques which had access to detection signal of interaction between biological molecules (such as a domain of protein and another molecule or analyte of interest like any other small molecule, another protein or an enzymatic activity). Thus we can say the device which enables sensing of the molecular interactions is named as biosensors [112]. Due to its versatility in different area, such as, interdisciplinary technology and involves the collaborative efforts of engineering, microbiology, physics, chemistry, biology, biotechnology and so on, researcher are fascinated to lot of study and development on this [113]. Lot of biosensors are developed, which are in use now days. They are including -

a. Calorimetric/ thermal detection biosensors

b. Ion sensitive biosensors

c. Optical biosensors

d. Piezoelectric biosensors

e. Electrochemical biosensors

f. Immuno-biosensors

There are wide ranges of biosensors which have importance uses in different scientific disciplines due to their outstanding results. Biosensors can be used in medical for accurate and precise detection of tumours, pathogens, elevated blood glucose levels in diabetic patients and other toxins. In the basics fields of agriculture, biomedicine, food and environmental studies, the most recent developments and improvements of this biosensing discipline are studied. The one that will be discussed in this review are the glucose and hydrogen peroxide.

4.1.1 Biomimetic glucose sensors

Every year a good number of individuals is diagnosed with diabetes mellitus, thus the demand for using glucose sensing technologies has also grown. The two enzymes which are utilized for large scale of glucose detection are glucose oxidases (G-ox) and glucose dehydrogenases [114]. The methods of the preparing graphene-(G-ox) bio-composite which displayed excellent sensitivity of 1.85 μAmM^{-1} cm^{-2} over the glucose concentration range of 0.1-27 mM. The potential bio-application of the engineered biosensor was studied over human serum, which showed high precision result for evaluating the blood glucose level [114].

Another successful penetration in the field was the use of nanoparticles (Nps) as a sensing medium, where immobilized gold Nps and G-ox composite were used for acquiring the same aforementioned purpose. This membrane based composite was utilized as biosensor, which was wrapped over the oxygen electrode. Advanced glucose sensor can quantify the level of glucose from 0.5 μM up to the level of 34 mM. The core-shell assembly, which contains polypyrrole Nps, are utilized and incorporate it over magnetically active carbon electrode to acquire the sensor. The two basics appeals of this core-shell based biosensor were high economical response time of 6s and good stability [115].

4.1.2 Biomimetic hydrogen peroxide (H_2O_2) sensors

In tissue engineering, measuring the H_2O_2 content with accuracy and reproducibility is most important. In humans, oxidative stress faced by cell or hypoxic conditions of tissues is a direct indicative of its present. Various analytic techniques such as titration, electrochemistry and photocatalysis could be employed for H_2O_2 recognition [116]. If this highly unstable species is present in any biological system in high concentration, and it is highly injurious and also causes cytotoxicity in humans and also to a large variety of plants, animals as well as bacteria.

Due to several difficulties (poor detection, low sensitivity, less portability and applicability issues on the organic system) the user, engineering generally described that methods for H_2O_2 quantification are mostly electrochemical in nature. Biosensors which are mostly enzymes based showed high stability and accuracy. Interest in this type of biosensing material could be attributed for the manufacturing of steady sensor which assembles fully functionalized binding sites of the pertinacious enzyme even after its deposition over some rigid

electrode/surface [116]. For example Suarez *et al.* explored the extracellular detection of H_2O_2 released by phytoplanktonic cells in response to Cd(II)-induced oxidative stress using the MPA-cytc/Au biosensor [117]. Thereof, increases understanding of the actual biological species have a substantial scientific interest to generate different strategies for biomimetic sensors.

Although most of the biomimetic studies were done on the applications of the energy materials and structural materials, the rapid progress in the biomimetic researches could also promote the successful development of drug delivery system. In one biomimetic studies of butterflies and beetles, the wet-ability and photonic properties of material have been enhanced [17-18]. In other review, the biomimetic stabilizing silk proteins and carbon nanotubes have shown to provide super-tough fiber materials which can work 50 times more than the identical mass of human muscle [40, 51, 60-61]. On the basis of sensing application, the ability of H_2O_2, H_2S and NO sensing profile inside cells have been promoted significantly, in another biomimetic review [101, 115-116]. Therefore biomimetic studies have also a great potential to lead the advanced drug delivery systems where loading of drug in carriers can improve, cells can efficiently uptake the drug carriers, and sustained release of drugs within target cells.

Over the past decade, the better understanding of natural and biological systems has emerged to explore environment friendly sustainable biomimetic materials. These types of material have intelligent and adaptable properties, self-sensing and self-repairing structures without external intervention. It is evident but important to look closely at nanostructures gift in nature to mimic them within the laboratory. This was solely created by the event of varied microscopic and chemical analysis tools for applied science. To achieve this transformation, collaboration of different research area is required for truly biomimetic responses in materials and structures. The potential application areas will shape the slicing strands in an effort to combine the technologies, direct the work toward sensible and relevant situations and directly engage the multi disciplinary research within the studies. Furthermore the novel characteristics of biomimetic materials have shaped our future in very promising way and research works have expanded from the lab scale to bulk production for practical applications.

5. Future scopes

In brief, the bio-inspired multiscale framework of biological material has become an interesting topic for research, which would be appropriate for the better responsive of multiscale design laws, intepretation of framework multifunction material relationship, abstraction of useful engineering assumption, and variation of models for practical functions inspired by natural material. Although in the last few years different properties of biological materials have been demonstrated, some more properties are yet to be resolved. Bio-inspired materials are not only being used in medical needs, their use has also been expanded in the areas of engineering, architecture and art as well. They have great potential to be used in biomimicked sensors, tissue engineering and optical devices as mentioned in this review. In future the research will be growing in various fields, such as to extend the function through modification with functional molecules of different bio-inspired multiscale structures or by fabricating the novel multiscale materials by two or more biological materials for their functional integration. The research of biomimetic and bio-inspired is still in its nonage, however, it is a rapid growing ground which holds huge promise for multidimensional use in future.

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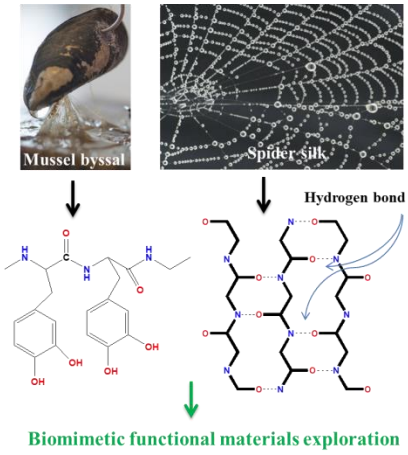
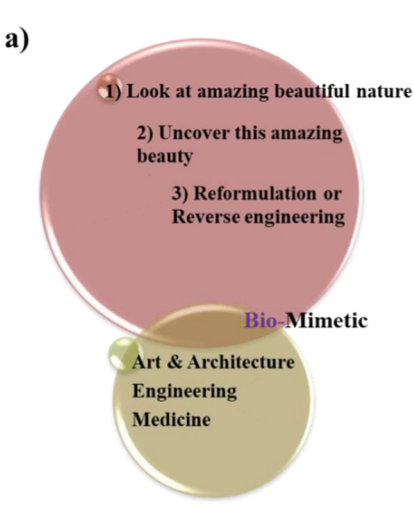
Graphical abstract



Highlights

- The development of bio-inspired functional materials by using discovery, interpreting/translating, and invention.
- The discovery, natural materials are copied as the source of inspiration.
- The interpreting natural beauty through a logical experimental ways and reverse engineering the experimental outcome comply with bio-inspiration
- The interpreted knowledge from nature is used to develop different multifunctional healthcare materials.


a)
1) Look at amazing beautiful nature
2) Uncover this amazing beauty
3) Reformulation or Reverse engineering
Bio-Mimetic
Art & Architecture
Engineering
Medicine

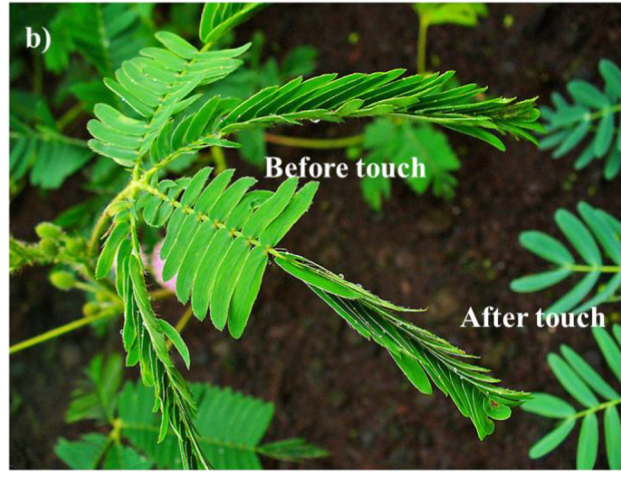
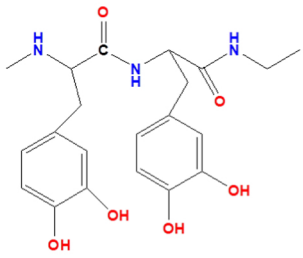

b)
Before touch
After touch

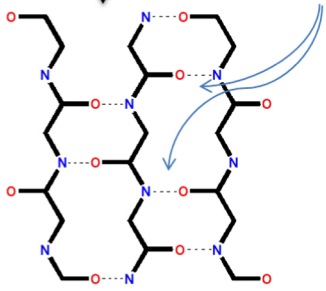
Figure 1

Discover the beauty of nature (Exciting and interesting work)

Interpreting biomimetic processing/ Reverse engineering (Most tedious and hard job)



Hydrogen bond



Invention and creation (Advanced applicable materials)

Bio-inspired/ biomimetic functional materials

Figure 2

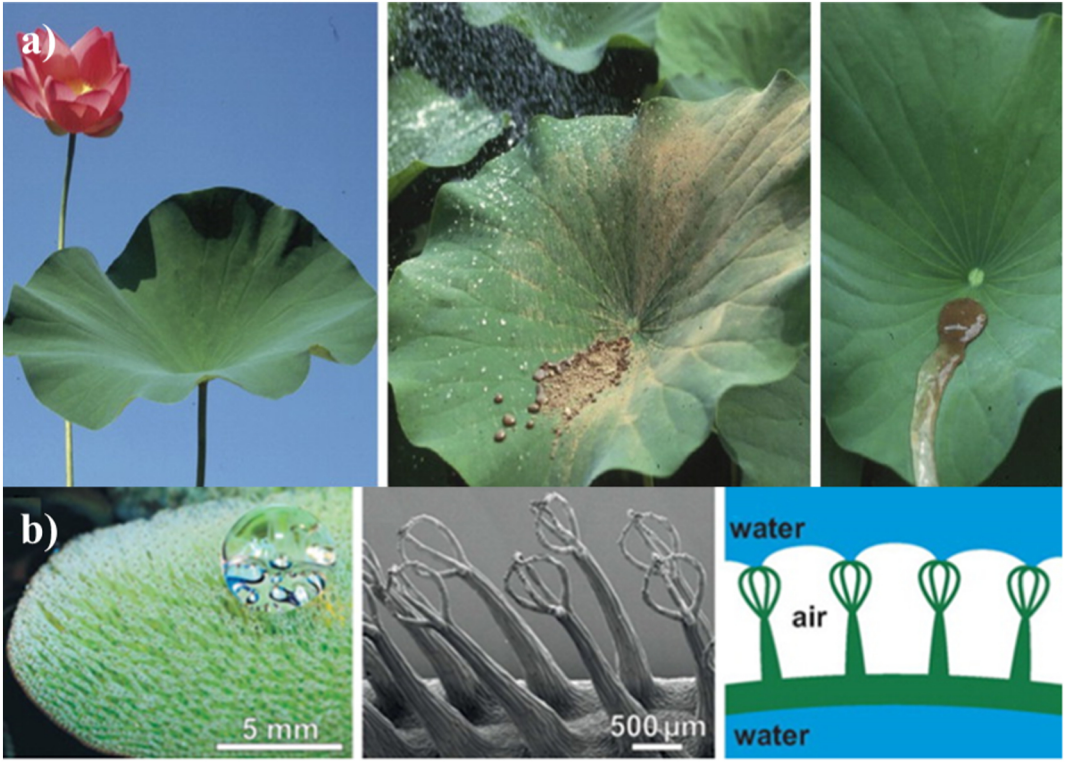


Figure 3

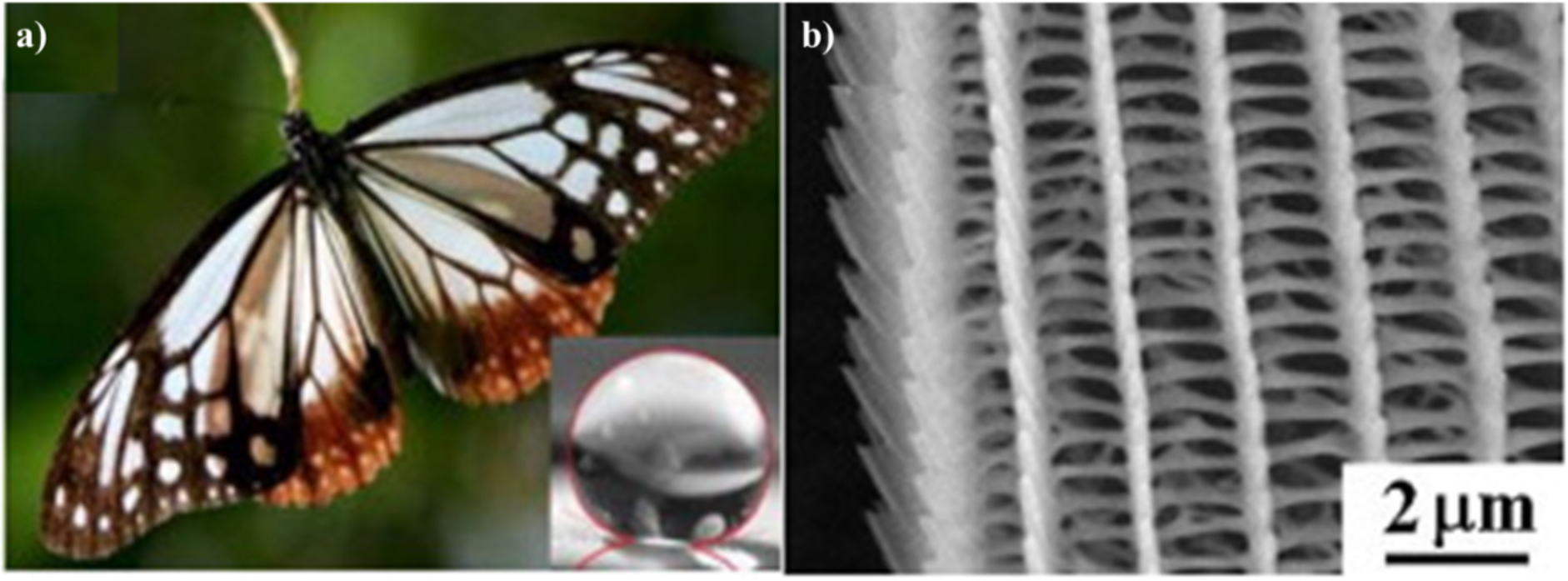
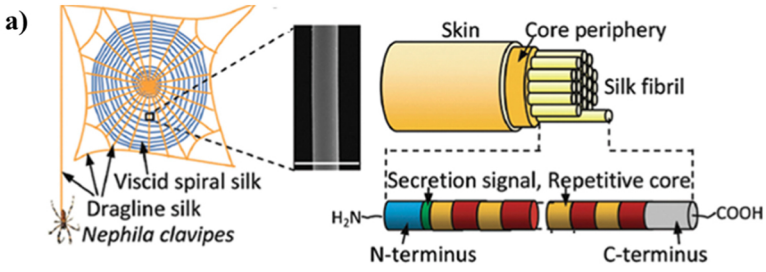


Figure 4


a)
Viscid spiral silk
Dragline silk
Nephila clavipes
Skin
Core periphery
Silk fibril
Secretion signal, Repetitive core
H2N
COOH
N-terminus
C-terminus

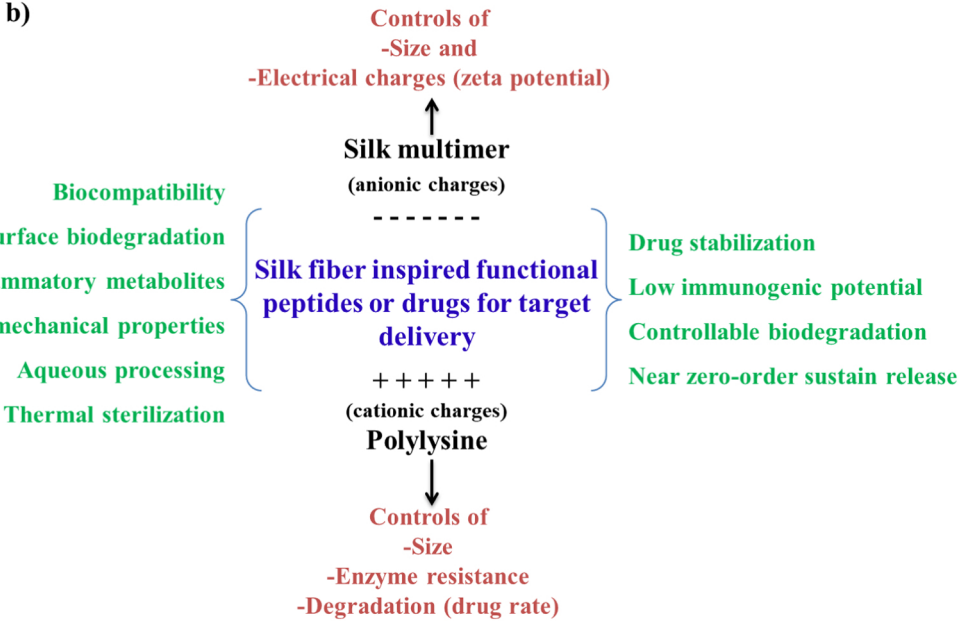

b)
Controls of
-Size and
-Electrical charges (zeta potential)
Silk multimer
(anionic charges)
Biocompatibility
Surface biodegradation
Non-inframmatory metabolites
Robust mechanical properties
Aqueous processing
Thermal sterilization
Silk fiber inspired functional peptides or drugs for target delivery
Drug stabilization
Low immunogenic potential
Controllable biodegradation
Near zero-order sustain release
(cationic charges)
Polylysine
Controls of
-Size
-Enzyme resistance
-Degradation (drug rate)

Figure 5

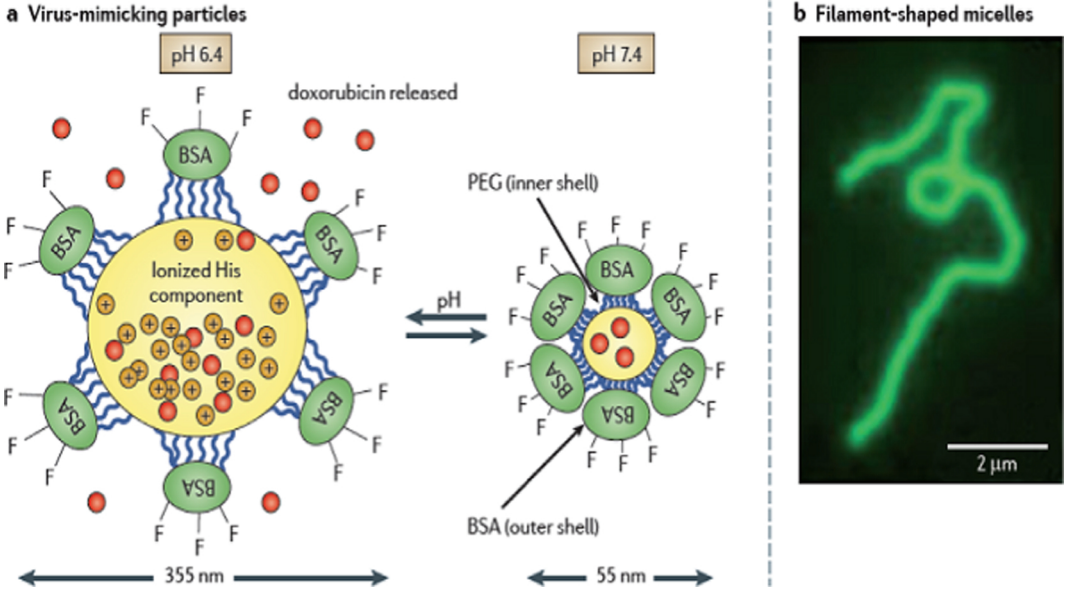

a Virus-mimicking particles
pH 6.4
pH 7.4
doxorubicin released
BSA
F
Ionized His component
pH
PEG (inner shell)
BSA (outer shell)
355 nm
55 nm
b Filament-shaped micelles
2 μm

Figure 6

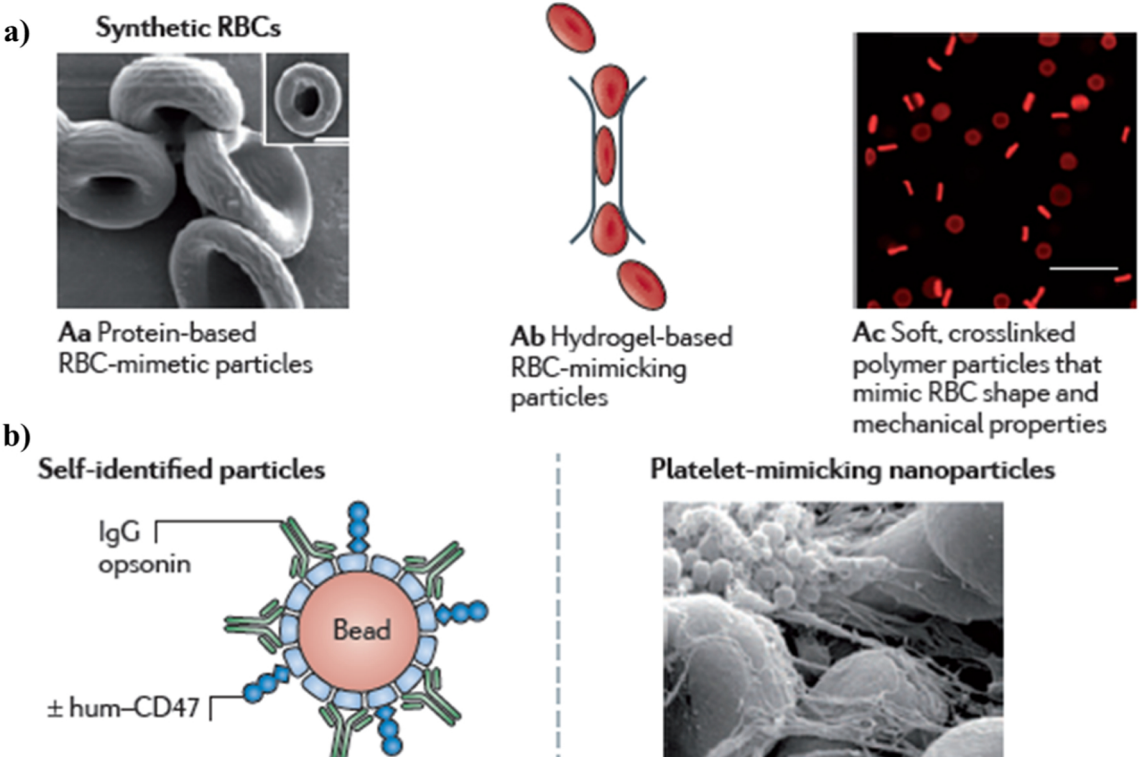

a)
Synthetic RBCs
Aa Protein-based RBC-mimetic particles
Ab Hydrogel-based RBC-mimicking particles
Ac Soft, crosslinked polymer particles that mimic RBC shape and mechanical properties
b)
Self-identified particles
IgG opsonin
Bead
± hum–CD47
Platelet-mimicking nanoparticles

Figure 7


Targets
Bio-recognition molecules
(Surface chemistry)
Optical transducers
Signal processing
Virus
Toxins
Heavy metal
Antibody
Enzyme
Cells
Fluorescence
Light absorption
Refractive index
Signal conversion, amplification & display

Figure 8