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Biomedical applications of polymers in biosensors, cancer vaccines and drug delivery systems

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Aim. To analyze the substantial development of biomedical polymers in a number of potential biomedical domains, including the disease diagnosis and therapy. **Results.** The relationship between material's properties and functions for matching biomedical applications is thoroughly elucidated in this paper, along with a rundown of current advancements in the production and appliance of biomedical polymers. The peptide, biomembrane, microbe and cell-based biomedical polymers are presented and highlighted as new biomaterials for the tumor precision treatment. Additionally, the prospects and difficulties of creating the future biomedical polymers, which are healthier, safer, and more effective, are appraised. **Conclusions.** This systematic and in-depth analysis of the most recent advancements in the biomedical polymers development is intended to inspire and promote new discoveries in the basic science and clinical application.

K e y w o r d s: biomedical polymers, synthesis, properties and applications

Introduction

According to the origin, biomedical polymers can be divided into synthetic and naturally generated types. These two types of polymers differ mostly in their structures. The basic structures of many naturally occurring polymers, such as proteins and polysaccharides, which in turn dictate their biological functions, typically spontaneously fold into compact forms in complex way. The majority of synthetic polymers (such as polyesters, poly(ethylene glycol), and polycarbonates) have more straightforward, haphazard topologies [1]. Additionally, naturally derived polymers are frequently biodegradable and interact favorably with biological objects (such as cells and tissues), but they have such drawbacks as poor mechanical properties, uncontrolled degradation, and potential immunogenicity, which severely restricts their *in vivo* application [2].

Numerous biomedical spheres, including smart drug delivery, illness detection/diagnosis, biosensing, regenerative medicine, and disease therapy, have benefited from the vast development of biomedical polymers. For instance, polymer-based carriers offer significant improvements in therapeutic results and bioavailability at spatiotemporal drug delivery, considerably enhancing the treatment of diseases including cancer, organ transplantation, and infections. The adaptable nature of polymer-based theranostic systems allows them not only to target diseased body regions but, when necessary, to report on the severity of the disease and its response to treatment [3].

The most recent developments in the manufacture and use of biomedical polymers are thoroughly summarized in this review (Fig. 1). The use of biomedical polymers in a wide range of applications, including drug transport, bioimaging, biosensing and theranostic, anti-infection, regenerative medicine, and cancer therapy, is explored in detail. The use of biomedical polymers for vaccine-based immunotherapy, cytokine therapy, and adoptive T cell therapy are a few more cutting-edge approaches that are covered. It is underlined that bioactive polymers, such as peptide, biomembrane, microbe and cell-based biomedical polymers, are the clever nanotherapeutics for the cancer

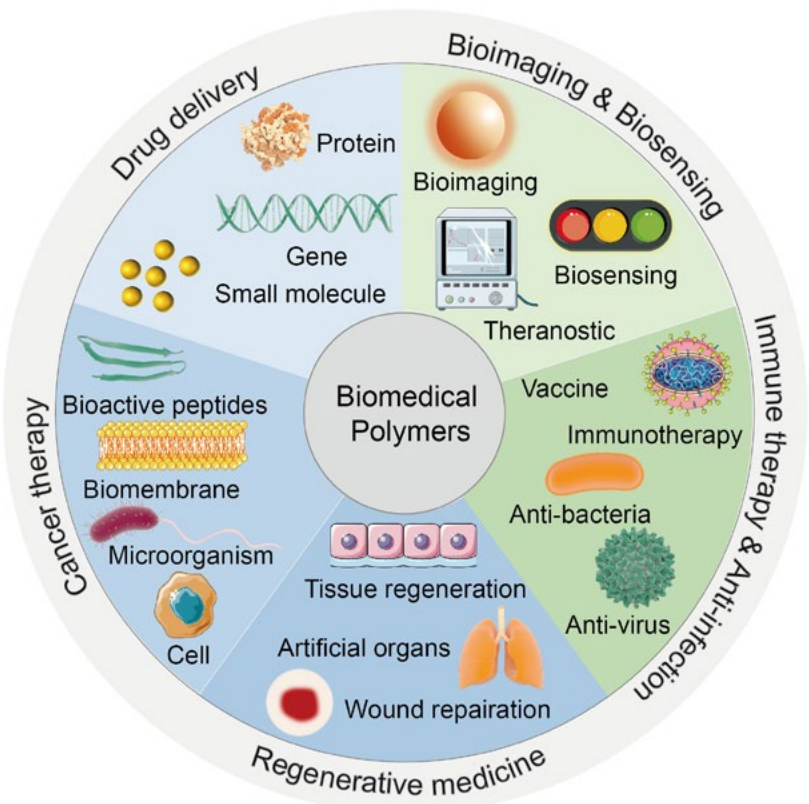

Fig. 1. Smart polymers for biomedical applications are illustrated schematically.

precision therapy. The final section includes a detailed discussion of certain important issues and the future prospects for applications of biomedical polymers [4].

The Synthesis of Biodegradable Biomedical Polymers

Both manufactured and natural polymers are considered to be biomedical polymers. Proteins and polysaccharides are the examples of naturally occurring polymers that have biodegradability and connections with cells and tissues but also have restricted mechanical qualities, unpredictable degradation, and potential immunogenicity. Synthetic polymers, in contrast, are typically deficient in intrinsic bioactivities but exhibit good controllability in composition, structure, mechanical characteristics, and degrading behaviors [5]. Synthetic biomedical polymers can also be divided into biodegradable and nonbiodegradable synthetic polymers depending on their biodegradability *in vivo*. Numerous of these polymers are examined and employed as long-term implanted prosthesis to partially or entirely replace the functions of damaged organs due to their nonbiodegradability and bioinert nature *in vivo* [6]. It is desirable that the polymers to be used in cancer vaccines and drug delivery systems have the nanoscale size (<100 nm) in order to address the biocompatibility requirements, while the polymers to be used in biosensors may be of the microscale.

The polymers for biomedical application should be provided with an amphiphilic structure of the molecule consisting of two parts — having polar hydrophilic groups and having hydrophobic hydrocarbon groups. Such a structure is necessary for micelle formation and immobilization of water-insoluble molecules that are characteristic for most drugs.

Aliphatic Polyesters

One of the most studied types of biodegradable polymers for biomedical applications is synthetic aliphatic polyester, which is commonly made of poly(lactic acid), poly(glycolic acid), poly(lactic acid-co-glycolic acid), and poly(-caprolactone). Polycaprolactone (PCL) exhibits an evidently longer hydrolytic breakdown period for over 2 years when compared to the polyesters indicated above. A monofilament suture that is sold in stores is made from a copolymer of GA and -caprolactone (-CL). The PHA poly(3-hydroxybutyrate) (P3HB) has received the most research attention and has been developed commercially as biodegradable polymers [7]. By incorporating additional hydroxyalkanoate units, the crystallinity and breakdown rate can be adjusted. In addition to the microbiological source, a chemical pathway through the ROP of -butyrolactone monomer for the production of P3HB has also been discovered. The FDA's clearance of an absorbable suture made of poly(4-hydroxybutyrate) (P4HB) for clinical use encourages researchers to implement PHAs for biomedical applications. It is noteworthy that endotoxin levels in PHAs generated from bacteria must be rigorously regulated for clinical usage [8].

Aliphatic Polycarbonates

A carbonyl bond joins two ether bonds in cyclic carbonates. Due to the simple methods for obtaining functionalized cyclic carbonates through the interactions between diol-containing compounds and triphosgene or ethyl chloroformate, aliphatic PCs exhibit the remark-

able benefits in the integration of functional moieties as compared to the aliphatic polyesters. Although aliphatic PCs are generally hydrolytically stable, the presence of enzymes can hasten their deterioration. Due to its exceptional flexibility and lack of an acidic microenvironment brought on by degradation byproducts, Poly(trimethylene carbonate, or PTMC), a typical aliphatic PC, has been studied for soft tissue regeneration and drug delivery systems [8].

Polypeptides

Poly(amino acid)s, another name for synthetic polypeptides, are made up of amino acid residues connected by peptide bonds. By employing solid phase peptide synthesis or ring opening polymerization (ROP) of amino acid N-carboxyanhydrides (NCAs) with amine-containing initiators, polypeptides can be chemically produced. It is simple to produce polypeptides with reasonably high molecular weights using the ROP of amino acid, NCAs. Polypeptides have been thoroughly studied for biomedical applications due to their excellent biocompatibility, enzymatic degradability, and distinctive secondary structures akin to endogenous peptides [9]. Polypeptides break down into amino acids, which are nontoxic, nonimmunogenic, and are metabolized in the presence of proteinases. Clinical trials in phases I, II, and III have assessed a number of ROP-derived polypeptides [10].

Poly(ortho esters)

Three hydrolyzable and acid-sensitive geminal ether linkages can be found in the backbones of poly(ortho esters, or POE). There are four POE families that have been looked into. For instance, POE II is created by reacting of diol with a diketene acetal while utilizing a small amount of an acidic catalyst. By controlling this reaction, the molecular weight of the polymerization products can be effectively managed [11]. During the preparation procedure akin to that of POE II, oligo(lactide)s or oligo(glycolide)s are typically inserted into the polymer backbone to alter the degradation rate at neutral environments. This results in the creation of POE IV, which has entered Phase I of clinical trial and has received more attention for possible biomedical use than other forms of POE in recent decades. Depending on the composition, POE IV can be hydrolyzed over a period of days to months, producing biocompatible products such pentaerythritol, diol, propanoic acid, and lactic acid (or glycolic acid) [12].

Poly(ester amide)s

A polymers known as poly(ester amides, or PEAs) have backbones that contain both ester and amide linkages. The combination of the thermomechanical capabilities of polyamides with the biodegradability of polyesters has made this family of polymers very appealing for biomedical applications. PEAs can be made using a variety of processes, including passerini reactions, polycondensation reactions based on monomers containing diamide (or bis(amino acids)) and diester moieties [13].

Poly(amidoamine)s

Synthetic polymers called poly(amidoamines) have amide bridges and tertiary amino groups in their backbones. As a result of their biocompatibility, biodegradability, and electrostatic interactions with genes and other biomacro-

molecules, poly(amidoamine)s have been researched for a variety of biomedical applications. Similar to PBAEs, stepwise Michael addition reactions between primary or secondary amines and bisacrylamides are generally used to create linear poly (amidoamines). By substituting bisacrylamides for diacrylate-containing monomers, poly(amidoamine)s are made more hydrolytically stable than PBAEs [14].

Polyanhydrides

A group of biodegradable polymers known as polyanhydrides have anhydride connections in their backbones. Because the anhydride links are water-sensitive, polyanhydrides show faster hydrolytic breakdown than polyesters and PCs. In addition to the precise methods of the polymers' ROP synthesis, the condensation polymerization is frequently used to create polyanhydrides, which can result in polydispersity indices that are relatively broad. The FDA has authorized and commercialized an absorbable implant based on PCPP-SA for controlled release of carmustine (Gliadel®) for the treatment of brain tumors [15].

Poly(ester urethanes)

Due to their high biocompatibility, hydrolytic stability, and superior mechanical qualities, polyurethanes (PUs) with microphase-separated soft and hard segments have received extensive research as long-term implants. PUs are frequently created by polycondensing monomers containing diisocyanates with diols or polyols. Poly(ester urethanes) have been created by adding biodegradable polyester diols or triols as the soft segments in the PU backbones in order to modify the biodegradability of PUs. By changing the polyester segment's structure, the degradation rate can be regulated [16].

Poly(organo)phosphazenes

Inorganic-organic hybrid polymers known as poly(organo)phosphazenes have two organic dangling groups attached to the phosphorus atom in addition to an alternating phosphorus-nitrogen backbone [17]. The ROP of hexachlorocyclotriphosphazene or live cationic polymerization of a phosphoranimine utilizing phosphorus pentachloride as a catalyst are often the bases for the production of poly(dichlorophosphazene), the precursor to polymers. After that, poly(dichlorophosphazene) is substituted with monofunctional, occasionally protected nucleophiles like amino acid ester derivatives, sodium salts of glycolate or lactate ester, and sodium salts of protected D-glucose to produce biodegradable poly(organo) phosphazenes [18].

Biomedical polymers for drug delivery systems

Biomedical Polymers used for Small Molecule Drug Delivery

Molecular imaging is essential for the early and precise diagnosis of disease because it enables real-time, non-invasive observation of physiological or pathological processes occurring at the cellular or molecular level in living systems. Small molecular probes frequently have issues with their water solubility, photobleaching speed. Depending on the polymer configuration, there are two ways to obtain such biomedical polymer-based probes. The first kind of polymer-based probes is cre-

ated by covalently bonding probes to hydrophilic polymers. Hydrophilic polymers provide probes with better water solubility. The probes of second kind are physically incorporated into micelles of amphiphilic polymer. This section provides a summary of current developments in the creation of biomedical polymer-based probes with imaging capabilities for *in vivo* bioimaging, including fluorescence, photoacoustic, and other imaging modalities [19].

Biomedical Polymers used for Biosensing

The biomarkers can be established *in vitro* on the surface of the body, and *in vivo* using electrical, optical, and other methods. Due to their real-time and precise detection at the desired position, the implanted biosensors have drawn more and more attention. Long-term stable monitoring typically depends on a strong contact between implanted biosensor and surrounding tissues, presuming it has good biocompatibility, is miniature, and has a mechanical fit with the tissues in flexibility [20]. Traditional biosensors, on the other hand, are built on stiff silicon substrates and metal electrodes and are capable of causing significant inflammation when used for long-term monitoring *in vivo*. As a result, flexible thin-film and fiber biosensors are created using other polymers that have moduli that are many orders of magnitude lower, enabling long-term stable monitoring *in vivo*. For a variety of purposes, including substrates, insulating layers, electrodes, active materials, surface modifications, and aided implantations, polymers with various characteristics have been incorporated into biosensors [21].

Polymer-Based Electrodes

For mechanical fit with tissues and quick transit of electron impulses, the electrodes must be flexible and conductible. The process procedures typically need to be adjusted in order to balance the materials' flexibility and conductivity. Another successful approach for the polymer electrodes is to combine flexible nonconductive polymers with conductive nanomaterials, such as carbon nanotubes and graphene, which gives designers more freedom in the material choices and fabrication methods they can use. Assembling aligned carbon nanotubes into macroscopic hierarchical fibers or threading them on polymer fibers represents another innovative and successful technique created in recent years that offers great electrical conductivity while maintaining flexibility [22].

Biomedical Polymers used for Theranostics

The concepts "therapeutics" and "diagnostics" are combined to form the term "theranostics". In essence, it represents a multifunctional system that allows simultaneous monitoring of the treatment response, diagnosis, and therapy. This method may also enable one to avoid some of the unpleasant side effects that may otherwise occur when these tactics are applied independently [23]. Theranostic systems based on polymers which can target sick regions of the body without harming healthy organs or tissues. Theranostic systems may provide details on the severity of a disease and, if applicable, provide the disease response to therapy once the location of interest has been identified. This section provides an overview of theranostics applications for biomedical polymers using the imaging modalities of op-

tical, ultrasound, photoacoustic, nuclear, and MRI [24].

Advanced biomedical polymers for immune and anti-infection therapy

Biomedical Polymers used for Vaccines and Immunotherapy

By utilizing the patient's coordinated and adaptive immune system, immunotherapy has emerged as a potent method for treating and even curing some forms of cancer in the clinic. In cancer immunotherapy, medicinal agents are employed to stimulate the immune system so that it can target cancer cells naturally. Immunotherapy has several advantages over conventional chemotherapy, radiation, and other treatments that destroy cancer cells directly because of its special quality. Immunotherapy may encounter difficulties with both efficacy and safety, limiting its practical adoption despite its many benefits. For instance, the majority of patients use different escape mechanisms to avoid immune checkpoint blockade (ICB) inhibitors, which has a limited therapeutic effect [25]. Additionally, immune-related adverse events (IRAEs), such as renal dysfunction, liver dysfunction, colitis, interstitial pneumonia, fever, and other potentially fatal side effects, frequently happen during immunotherapy. Therefore, it is still urgent to create new methods for successfully and safely promoting immunotherapy to a larger variety of patients [26].

Biomedical Polymers Used for Cancer Vaccines

The vaccination technique stimulates a specific immune response against a particular infection. The adjuvants and right antigens are typically used in the cancer vaccines to stimulate powerful immune responses. Cancer vaccinations not only treat pre-existing cancers but also work to stop a particular cancer from developing. In order for the cancer vaccines to be effective, antigens and adjuvants must be successfully delivered to APCs so that T cells can be stimulated to exert cytotoxic antitumor effects during maturation. Because of this, many biomedical polymers have been researched for the creation of vaccines [27].

Biomedical Polymers Used for Immune Checkpoint Blockade (ICB)

Ineffective immune responses persist because of immunological resistance, despite the fact that using biomedical polymers to improve cancer immunotherapy has mostly focused on cancer vaccines by effectively delivering antigens and adjuvants. A popular method of immunological resistance called immune checkpoint treatment is crucial in defending healthy tissues from immune system assault [28]. By suppressing regulatory signals expressed on immune cells or tumor cells, ICB therapy has shown exceptional therapeutic effects in the treatment of numerous types of malignancies. The current ICB still faces several difficulties, such as enhancing efficacy and lowering immune-related adverse effects, despite the fact that some of the ICB inhibitors have demonstrated exceptional therapeutic results. Consequently, numerous methods based on biomedical polymers have been created to increase ICB effectiveness while minimizing its negative effects [29].

Biomedical Polymers for Adoptive T Cell Therapy

Adoptive T cell treatment is a type of passive immunotherapy in which patients get T cells that have undergone extra multiplication and alteration. Biomedical polymer-based methods to increase adoptive T cells effectiveness are now being researched in light of the complex processes and high costs involved in their production [30]. One of the more effective methods is to adhere drug-loaded T cell membrane particles. For instance, the Irvine's team [31] effectively expanded T cells within the tumor by loading cytokines into nanoparticles and conjugating them to T cells. Using such a method, additional chemicals that support Tcell activation may be delivered. In a second study, they additionally coupled tumor-specific T cells to nanoparticles loaded with NSC-87877 to greatly increase T cell growth in the tumor. A 'backpack' of PEG-b-PLL and disulfide-crosslinked cytokine nanogels (NGs) was recently attached to T cells by Tang *et al.* [32] They discovered that activated T cells had more free thiols than normal on their surfaces, which could cause antigens to release cytokines inside the tumor and result in the tumor-specific proliferation of T cells with little off-target damage **[**33].

Biomedical Polymers used for Anti-Bacteria

Human health and life safety are being threatened by bacterial infections. The World Health Organization estimated that there are around 80 billion person-years worth of infectious diseases, resulting in 10 million fatalities [34]. Drug resistance, which lowers the effectiveness of antibacterial medications, is a severe issue brought on by the misuse of antibiotics. As a result, numerous antibacterial materials are being thoroughly researched on a global scale to combat bacterial illnesses. Polymers have drawn more attention recently because of their tremendous flexibility and diversity [35].

Biomedical Polymers used for Anti-Virus

The novel coronavirus pneumonia outbreak caused by the SARSCoV-2 has nearly completely spread around the world and caused significant harm to human society. Roughly 20% of all deaths worldwide each year are attributable to the infectious diseases, and roughly one-third of these deaths are brought on by viral infections [36]. Accurate and prompt identification, good disinfection, or cooperative protective equipment, and early and effective medicines are all crucial for controlling the spread of viruses, necessitating multidisciplinary solutions. Chemistry, material science, and associated technologies have made amazing advancements in recent years. New chemical processes, chemicals, and materials with distinctive features have been created and used in everyday life by people. These chemical compounds and materials, which have lately been classified as biosafety chemistry and biosafety materials, can be utilized to address biosafety issues such as pathogen detection and disintegration, among others [37].

Biomedical Polymers for Detection and Diagnosis of Viruses

The first issue in preventing the devastation of human society brought on by infectious diseases is to identify an undiscovered pathogen that resembles an epidemic and can manifest itself in several ways [38, 39]. Traditional im-

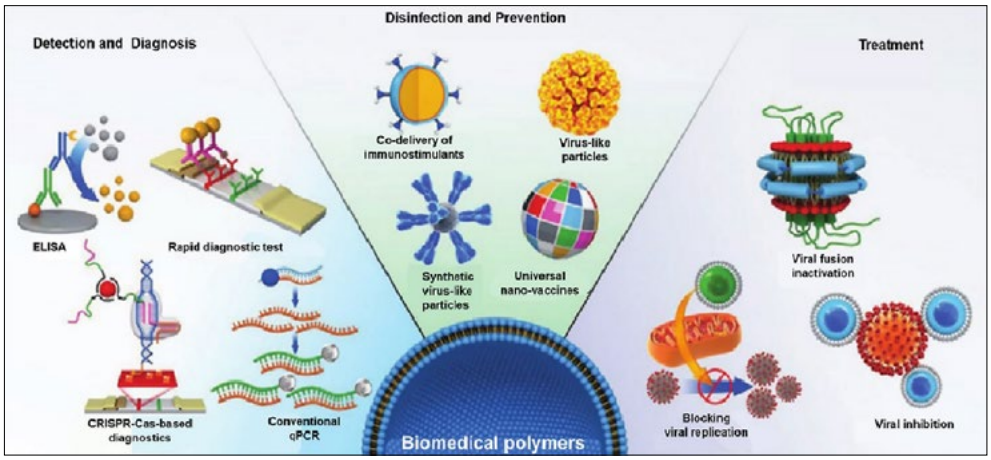

Fig. 2. Biomedical polymers for virus detection, diagnosis, disinfection, and drugs for prevention and treatment.

munoassays, such ELISA are less sensitive to viruses and can result in false-positive results that can be hard to discern from genuine positive samples. To get around these restrictions, optical immunosensors including colorimetry, fluorescence, and surface plasmon resonance have been created (Fig. 2) [40]. For instance, polydiacetylene (PDA), a conjugated polymer, exhibits distinct chromatic properties. The PDA color will change from blue to red as soon as the particular antigen-antibody interaction causes a conformational change and shortens the — conjugated bonds on the molecular skeleton. As the color shift can be clearly seen by unaided eyes, this good characteristic can be exploited to design PDA as optical immunosensors used for the effective virus detection [41].

Conclusion

Due to their unique properties, biomedical polymers are currently used widely in the tissue engineering, regenerative medicine, precise nanomedicine therapeutics, diagnostics, and theranostics, with some significant advances. However, the significant obstacles still exist in developing and using practical animal models, even with large animals like pigs and monkeys, such as patient-derived xenograft (PDX), for precisely guiding and indicating clinical translation potentials. Additionally, two essential qualities for their task-specific biomedical use are the biocompatibility and biodegradability of biomedical polymers. The polymer-based drug delivery systems must have good biocompatibility to minimize adverse effects *in vivo* and increase applicability. The clinical translation experts believe that the biodegradability of biomedical polymers is more important because it helps to reduce potential safety risks like immunogenicity, long-term toxicity, and metabolic toxicity. Additionally, the biomedical polymers' safety is a requirement that should be guaranteed for their clinical use. Besides, it is essential to overcome challenges related to the quality control and large-scale fabrication when developing biomedical polymers. Although these

aspects are not considered as extremely important in clinical research, they still should be carefully taken into account when designing polymers for the biomedical applications. Due to these difficulties and not realized opportunities, there is still much to learn about the practical usage of biomedical polymers for disease detection, biosensing and disease treatment. We hope that the most recent advancements and successes highlighted in this review will encourage even more fruitful research and clinical application of biomedical polymers.

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Біомедичне застосування полімерів у біосенсорах, вакцинах проти раку та системах доставки ліків

П. Селвакумар

Мета. Проаналізувати суттєвий розвиток біомедичних полімерів у ряді потенційних біомедичних областей, включаючи діагностику та терапію захворювань. **Результати.** У цій статті детально висвітлено взаємозв'язок між властивостями та функціями матеріалу для відповідних біомедичних застосувань разом із викладом поточних досягнень у виробництві та застосуванні біомедичних полімерів. Пептиди, біомембрани, мікроби та клітинні біомедичні полімери представлені та виділені як нові біоматеріали для точного лікування пухлин. Крім того, оцінюються перспективи та труднощі створення майбутніх біомедичних полімерів, які будуть здоровішими, безпечнішими та ефективнішими. **Висновки.** Цей систематичний і поглиблений аналіз останніх досягнень у розробці біомедичних полімерів має на меті надихнути та сприяти новим відкриттям у фундаментальній науці та клінічному застосуванні.

Ключові слова: біомедичні полімери, синтез, властивості та застосування

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