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Review article

Clinically advancing and promising polymer-based therapeutics

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ABSTRACT

In this review article, we will examine the history of polymers and their evolution from provisional World War II materials to medical therapeutics. To provide a comprehensive look at the current state of polymer-based therapeutics, we will classify technologies according to targeted areas of interest, including central nervous system-based and intraocular-, gastrointestinal-, cardiovascular-, dermal-, reproductive-, skeletal-, and neoplastic-based systems. Within each of these areas, we will consider several examples of novel, clinically available polymer-based therapeutics; in addition, this review will also include a discussion of developing therapies, ranging from the *in vivo* to clinical trial stage, for each targeted area of treatment. Finally, we will emphasize areas of patient care in need of more effective, accessible, and targeted treatment approaches where polymer-based therapeutics may offer potential solutions.

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1. Introduction

In less than a century, the medical device industry has been transformed by the discoveries and developments of polymer-based therapeutics. In order to understand the current and future directions of polymer-based therapeutics, it is necessary to first consider the historical context and background of the industry. The advent of polymers in medicine would likely not have occurred without two historical events: (1) World War II, which established a pressing need for biocompatible medical devices and therapeutics for thousands of injured soldiers, and (2) the surge of the chemical industry in the middle of the nineteenth century, which fueled the quest for biomaterials by providing a repertoire of materials to choose from [1,2].

During World War II, almost 15,000 service personnel returned home to the U.S. as amputees, nearly quadruple the number of amputee U.S. soldiers from World War I [3]. This sudden inundation of amputees was coupled with the advent of synthetic polymers, such as nylon, poly(vinyl chloride), polyethylene terephthalate, poly(urethanes), and poly(methyl methacrylate) (PMMA) (Plexiglas®), owing to the extensive growth and investment in the chemical industry to support the war effort [4–9]. These materials were not applied to the realm of biomaterials, however, until Dr. Harold Ridley, a British ophthalmologist, first

Table 1
Milestones for the field of polymer-based therapeutics and highlights of U.S. regulations of drug products.

1820	U.S. Pharmacopeia is established [22]
1862	President Lincoln appoints Dr. Charles M. Wetherill to serve in the Agricultural Department [22]
1872	Polyvinyl chloride (PVC) is invented by Dr. Eugene Baumann [6]
1902	The Biologics Control Act is established [22]
1906	The U.S. FDA is created under President Roosevelt [22]
1908	Cellophane® is invented by Mr. Jacques Brandenberger [6]
1909	Bakelite, the first fully synthetic plastic product, is invented by Dr. Leo Baekeland [6]
1934	Dr. Willem J. Kolff invents the first artificial kidney using cellophane [13]
1936	PMMA is invented [6]
1937	The Elixir of Sulfanilamide establishes the need for drug safety after causing 107 deaths [22]
1938	Teflon™ is invented by Dr. Roy Plunkett [6]
1938	The Federal Food, Drug, and Cosmetic Act is passed by Congress and signed into law [22]
1938	Dr. Belding H. Scribner develops the Scribner Shunt using Teflon™ [14]
1944	The Public Health Service Act was passed to help regulate biological products [22]
1945	Captain H. Bloom uses cellophane as a wound treatment for POWs during WWII (*Lancet*) [16]
1948	Modern gas permeable contact lenses are invented by Kevin Touhy using PMMA [23]
1948	Dr. William H. Sewell creates the first artificial heart using a glass pumping chamber and rubber bladder [24]
1949	Dr. Harold Ridley uses PMMA to develop the first plastic IOL [12]
1949	The U.S. FDA first publishes guidance to industry regarding toxicity of chemicals in food (“black book”) [22]
1952	Dr. Charles Hufnagel invents the first successful long-term prosthetic heart valve using Plexiglas™ [25]
1955	The Division of Biologics Control separates from the NIH after a polio vaccine was improperly inactivated [22]
1956	DuPont patents poly(ethylene-co-vinyl acetate)
1958	The first list of substances (~200) generally recognized as safe (GRAS) is established [22]
1960	The Starr-Edwards Heart Valve is implanted in the first human patient [25]
1960	The first thermoplastic IUD, Perma-Spiral/Gynecoil®, is introduced by Ortho Pharmaceuticals [26]
1961	Dr. Jack Lippes develops the trapezoidal-shaped Lippes Loop IUD [26]
1962	Thalidomide tragedy lead to greater drug regulation support and the Kefauver-Harris Drug Amendment, requiring proof of effectiveness before marketing; in 1966, 4,000 drugs were re-evaluated which were previously approved based on safety alone from 1938 to 1962 [22]
1965	Dr. Marshall Urist discovers BMP, revolutionizing methods of bone repair [27]
1967	Davis & Geck, Cyanamid Co. patents poly(lactic-co-glycolic acid) (PLGA) [28]
1968	Dr. Alex Zaffaroni founds ALZA [17]
1968	Dr. Charles Sparks pioneers the Sparks' mandril graft method for revascularization [29]
	Late 1960's: Dr. Frank Davis introduces the concept of PEGylation [17]
1974	Vicryl®, the first PLGA suture product, is developed by Ethicon [28]
1975	Dr. James Reinwald and Dr. Howard Green demonstrate human keratinocytes can be grown *in vitro* [30]
1976	The Medical Device Amendment is passed [22]
1976	Drs. Robert Langer and Judah Folkman demonstrate polymers can deliver proteins and macromolec. (*Nature*) [17]
1977	Bioresearch Monitoring Program: ensures data integrity and human subject protection in clinical trials [22]
1978	PEEK is invented by Imperial Chemical Industries [31]
1979	*Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* is published [22]
1984	Dr. Hiroshi Maeda discovers the EPR effect [17]
1984	The Drug Price Competition and Patent Term Restoration Act is established to 1) approve applications of generic drugs without repeating research to excessive extents and 2) allow companies to make up lost time of patent protection while going through the U.S. FDA approval process [22]
1986	DebioPharma launches the first clinically-approved, injectable PLGA microparticles (Decapeptyl®) [17]
1990	The Safe Medical Devices Act is passed to require reports of incidents related to medical devices and to require manufacturers to conduct post-market surveillance for specific permanently implanted devices [22]
1995	Doxil®, the first liposomal-based drug, is approved by the U.S. FDA [32]
2000	Mirena®, the first LNG IUS, is approved by the U.S. FDA [33]
2001	NuvaRing® becomes the first monthly contraceptive ring to be approved by the U.S. FDA [34]
2002	Medical Device User Fee and Modernization Act: enables the U.S. FDA to meet performance goals [22]
2002	The current good manufacturing practice (cGMP) initiative is established [22]
2002	The Office of Combination Products is formed to oversee products that spread across jurisdiction lines [22]
2005	Retisert® is the first approved intravitreal drug implant for treating chronic, noninfectious posterior uveitis [35]
2007	Integra® Flowable Wound Matrix: U.S. FDA approved flowable collagen matrix for treating tunneled lesions [36]
2014	Iluvien®: U.S. FDA approval for the first DME treatment to provide up to three years of continuous treatment [37]
2016	Epicel® is granted HDE status by the U.S. FDA, making it the first and only commercially available CEA [38]
2016	The AMPLATZER® PFO Occluder becomes the first PFO closure device with U.S. FDA approval [39]
2016	MACI®: first U.S. FDA-approved cellularized scaffold for symptomatic, full-thickness cartilage defects [40]

observed that PMMA aircraft fragments embedded inside pilots were generally well-tolerated by the body and did not induce adverse bodily reactions [1,10]. In 1949, following this realization, Dr. Ridley adapted PMMA for use in the first plastic intraocular lens, which remains one of the standard materials used in lenses today, in addition to other silicone, acrylic-, and collagen-based materials (i.e. Collamer®) (Table 1) [11]. Opthamology was not the only area to benefit from these early polymers; in 1943, Dr. Willem J. Kolff developed the first artificial kidney using cellophane, a semi-permeable material invented by Mr. Jacques E. Brandenberger in 1908, which allowed for urea to be filtered from the blood (Table 1) [6,12,13]. Later, in 1964, Dr. Belding H. Scribner built off of Dr. Kolff's findings, using polytetrafluoroethylene (Teflon®), a plastic invented in 1938, to develop the Scribner Shunt (Table 1) [14,15]. Early application of polymers to medicine also extended to improvements in wound care, when, during World War II, Captain H. Bloom developed an alternative to treating second-degree burns using cellophane in 1945, which was found to both greatly reduce pain and promote wound healing (Table 1) [16].

As the polymer-based medical device industry began to expand, work done in the mid-1960s by two independent researchers, Dr. Judah Folkman and Dr. Alex Zaffaroni, led to the development of zero-order drug delivery [17,18]. Early controlled drug delivery products were made of poly(ethylene-co-vinyl acetate) (PEVA), a polymer patented by DuPont in 1956 (Table 1) [17,19]. In the mid-1970 s, Dr. Folkman and Dr. Robert Langer discovered that protein drugs could be released from nondegradable polymer matrices, a finding that led to the beginnings of biodegradable microparticle drug release systems (Table 1) [17,19]. Later developments include half-life manipulation through PEGylation, the evolution of protein- and polysaccharide-based polymers, and the use of active targeting to control delivery of nanotherapeutics (Table 1) [17,20,21].

Over the past eighty years, the polymer-based medical industry has rapidly evolved from an offshoot of the chemical industry to its own distinct and innovative field. This review paper presents a broad yet comprehensive perspective of several notable polymer-based therapeutics, categorized by the area of application (Table 2). It is important to emphasize that this review is not intended to serve as an all-inclusive listing of currently available and developing technologies but rather as a survey of the past, present, and future of polymer-based therapeutics. For this reason, each section also includes references to additional clinically available and developing therapeutics for readers who are interested in deeper study of a particular area. Additionally, for the purposes of this review, polymer-based therapeutics is defined to include, but is not limited to, implants and medical devices, macromolecular drugs, polymer-drug and polymer-protein conjugates, and polymeric micelles containing covalently bound drug or polyplexes. Although the scope of polymer-based therapeutics spans across all organ systems, not all organ systems are included in this review because of the lack of clinically advanced therapeutics currently available for the omitted system. While emphasizing polymer-based therapeutics that have been clinically translated, this review paper will also discuss polymer-based therapeutics that are possibly nearing clinical translation.

2. Central Nervous System-Based Therapeutics

Collectively, neurodegenerative central nervous system (CNS) disorders make up one of the leading causes of death and disability today [41]. Specifically, in 2010, brain and other CNS cancers were reported to have a prevalence rate of 221.8 per 100,000 worldwide, with an estimated five-year survival rate of 34.7% in the U.S. alone

Table 2
Applications of select polymer-based technologies.

Central Nervous System-based Therapeutics	Intraocular-based Therapeutics	Gastrointestinal-based Therapeutics	Cardiovascular-based Therapeutics	Dermal-based Therapeutics	Reproductive-based Therapeutics	Skeletal-based Therapeutics	Neoplastic-based Therapeutics
Gliadel® Wafers (Arbor Pharmaceuticals): Grade III or grade IV glioma and recurrent GBM treatment, *Approved in 1996*	Retisert® (Bausch & Lomb): Implant for treating chronic noninfectious posterior uveitis, *Approved in 2005*	TheraSphere® (BTG Interventional Medicine): HUD for unresectable HCC, *Approved in 1997*	AMPLATZER™ PFO Occluder® (St. Jude Medical):PFO closure device, *Approved in 2016*	Integra® Flowable Wound Matrix (Integra LifeSciences Corp): Tunneled lesions treatment, *Approved in 2007*	Mirena® (Bayer HealthCare): Intrauterine contraceptive, *Approved in 2000*	i-FACTOR™ Peptide Enhanced Bone Graft (Cerapedics, Inc.): ACDF treatment, *Approved in 2015*	Doxil® (PEGylated) (Alza Corporation): Treatment for AIDS-related Kaposi's Sarcoma, ovarian cancer, and multiple myeloma (PEGylated), *Approved in 1995*
Integra™ CSF Reservoir (Integra LifeSciences Corporation): Access to CSF and for delivery of chemotherapy, *Approved in 2016*	Iluvien® (Alimera Sciences): Implant for treating DME, *Approved in 2014*	Veltassa® (Relypsa): Hyperkalemia treatment, *Approved in 2015*	Catapres-TTS® (Boehringer Ingelheim): Mild to moderate hypertension treatment, *Approved in 1984*	Apligraf® (Organogenesis): Treatment for DFUs and chronic venous leg ulcers, *Approved in 2000*	ParaGard® (Teva Pharmaceutical Industries): Intrauterine contraceptive, *Approved in 1984*	Cortoss® Bone Augmentation Material (Stryker): VCF treatment, *Approved in 2009*	Abraxane® (Celgene): Treatment for metastatic breast cancer, non-small cell lung cancer and pancreatic adenocarcinoma, *Approved in 2005*
C-Plus™ PEEK VBR/IBF System (Pioneer Surgical Technology): IBF and VBR device, *Approved in 2014*	AzaSite® (InSite Vision): Bacterial conjunctivitis treatment, *Approved in 2007*		TAXUS® stent (Boston Scientific): Restenosis treatment, *Approved in 2004*	Epicel® (Vericel Corporation): Treatment for deep dermal or full thickness burns greater than or equal to 30% of body surface area, *Approved in 2007*	NuvaRing® (NV Organon): Intravaginal combination hormonal contraception, *Approved in 2001*	Matrix Induced Autologous Implantation® (MACI®) (Vericel Corporation): Treatment for symptomatic, full-thickness cartilage defects, *Approved in 2016*	

[42]. The relatively low number of currently available polymer-based therapeutics targeting CNS diseases, however, does not reflect the frequency and severity of these diseases. One of the primary obstacles of treating CNS diseases is the presence of the blood-brain barrier (BBB). The BBB is a tightly regulated membrane that separates the extracellular fluid within the tissue of the brain from the cerebrospinal fluid (CSF) and also limits the capacity of drug transport to the brain [43]. Several commercially available technologies have addressed this challenge by developing interstitial glioma treatments or mechanisms that allow for drugs to be transported directly into the brain. While some of these technologies are included in the discussion below, the relatively short length of this section reflects the overall lack of polymer-based CNS treatments available today. However, as will be discussed later, many promising technologies are currently being investigated to address this pressing need. For additional discussion of other clinically translated and developing technologies, the interested reader is encouraged to refer to the additional references provided [44–49].

Serving as a prime example of a treatment that effectively circumvents the BBB, Gliadel® Wafers (Arbor Pharmaceuticals, Atlanta, Georgia, USA) were developed as an adjunctive therapy for recently diagnosed Grade III or Grade IV glioma and recurrent glioblastoma multiforme (GBM) (Fig. 1**A**) [50]. Gliadel® Wafers are the product of a collaboration between Dr. Robert Langer and Dr. Henry Brem, who teamed up in 1985 to develop an interstitial chemotherapeutic for treating brain cancer [50]. Unlike a systemic chemotherapeutic, Gliadel® Wafers deliver chemotherapeutic agents locally via surgical implantation, thereby avoiding the challenge of drug transport across the BBB [50]. Following removal of the tumor, it is recommended for no more than eight Wafers to be implanted in the resection cavity [51]. Each Gliadel® Wafer contains 7.7 mgs of carmustine (3.85% of the wafer by mass), a chemotherapeutic agent, and 192.3 mgs of polifeprosan 20, a biodegradable copolymer of poly (bis(p-carboxyphenoxy)) propane and sebacic acid, which acts to moderate the release of carmustine [51]. Carmustine is released gradually over a period of 2–3 weeks as the anhydride bonds of polifeprosan 20 are hydrolyzed [51]. One of the limitations of Gliadel® Wafers, however, is the short half-life of carmustine, which limits the overall effectiveness of the treatment [51]. With that said, Gliadel® Wafers have been shown to significantly improve survival rates for both GBM and malignant glioma patients [51]. Since receiving U.S. FDA approval in 1996, Gliadel® is available in thirty countries worldwide as of 2013 [52].

Polymer-based CNS therapeutics not only serve as solutions to BBB drug transport but also act as spinal implant devices. The C-Plus™ PEEK VBR/IBF System (Pioneer Surgical Technology, Alachua, FL, USA) is a spinal implant that functions as both an intervertebral body fusion (IBF) and vertebral body replacement (VBR) device that was introduced to U.S. markets in 2014 following FDA 510 (k) approval (Fig. 1**B**) [53,54]. In 2016, the System expanded its indication to include use with both allograft and autograft [53]. In conjunction with these grafts, the C-Plus™ PEEK VBR/IBF System functions to replace or repair spinal bony segments that are either absent or damaged [54]. The IBF/VBR system is made of PEEK-OPTIMA® (Invibio® Biomaterial Solutions, Lancashire, UK), a polymer first developed by the U.S. aerospace industry in the 1970s that was later modified by Invibio® Biomaterial Solutions [55]. PEEK is noted for its longevity and durability under high temperature and pressure, making it an ideal material for load-bearing applications such as the C-Plus™ PEEK VBR/IBF System [56].

CSF reservoirs offer another method for effectively bypassing drug transport across the BBB. The history of CSF reservoirs originates with the Ommaya Reservoir, which was introduced in 1963 for treating fungal meningitis [57]. Similar to the Ommaya Reservoir, the Integra™ CSF Reservoir (Integra LifeSciences Corporation, Plainsboro, NJ, USA) offers the same functionality with updated technology (Fig. 1**C**). Specifically, the Integra™ CSF Reservoir is designed to provide access to the lateral ventricles for both sampling of CSF and chemotherapy treatment [58]. Access to the brain and/or CSF can be achieved using a 25-gauge or smaller needle, which is inserted directly through the reservoir dome [58]. Additionally, the convertible form of the reservoir can be used in hydrocephalic patients for shunting CSF from the lateral ventricles to the right atrium of the heart or peritoneum as part of a larger shunting system [59]. All of the available models are made of flexible silicone elastomer and include a suture flange that facilitates attachment to the periosteum [58].

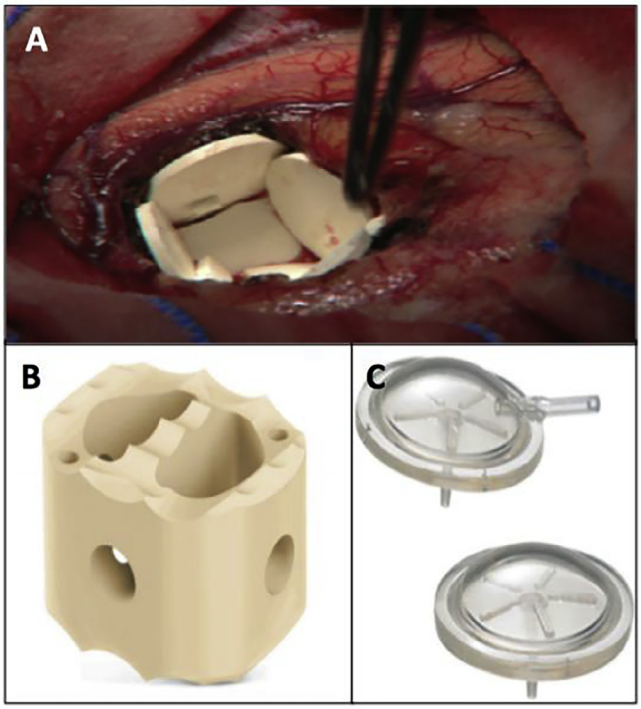

Fig. 1. CNS-based Therapeutics. **A.** Gliadel® wafers embedded in a resection cavity [60]; **B.** C-Plus™ PEEK VBR/IBF System [53]; C. Integra™ CSF Reservoir [61].

2.1. Future Trends of Central Nervous System-Based Therapeutics

As mentioned before, the BBB acts as the primary obstacle to developing effective CNS disease treatments. Unlike the capillaries of other body tissues, brain and spinal cord capillaries are lined with endothelial cells instead of pores, making it challenging for lipid-insoluble compounds to enter [43]. If a drug does manage to pass through the BBB, it is further subjected to the blood-cerebrospinal fluid barrier (BCB), which is formed by the tight junctions between the choroid plexus and the arachnoid membrane [43]. In addition to the blockade imposed by these junctions, an organic acid transporter within the BCB acts to transport "CSF-derived organic acids" into the systemic circulation, thereby limiting delivery of organic acid therapeutics (i.e., penicillin) to the brain [43]. For delivery of chemotherapeutics, this process is further complicated by the blood-tumor barrier (BTB) [43]. Due to the irregular vasculature of tumors, the BTB causes drug to be unevenly distributed across the tumor, resulting in compromised drug delivery and reduced treatment efficacy [43]. This section will discuss several technologies that are currently being developed to

address the challenges posed by the BBB, BCB, and BTB. Moreover, this section will also report on a developing spinal cord injury (SCI) treatment that could potentially offer new hope for patients suffering from SCIs.

In 2012, Shao et al. showed that Amphotericin B (AmB), an antibiotic commonly used in treating intracerebral fungal infections, could be formulated as a polymeric micellar system to improve treatment efficacy while also lowering toxicity [62]. Current commercially available formulations of AmB have poor penetration into the CNS and face limited effectiveness as a result [62]; the authors compared angiopep-2 modified AmB incorporated 1, 2-Distearoyl-*sn*-glycero-3-phosphoethanolamine-N-(methoxy(polyethylene glycol)-2000) (PE-PEG)-based polymeric micelles (Angiopep-PEG-PE/AmB) against commercial formulations of AmB to determine whether incorporation of P-glycoprotein (P-gp), an efflux transporter in the extracellular membrane of brain endothelial cells, improved AmB permeability into the brain [62]. The results showed that a majority of the polymeric micelles were internalized in murine brain tissue cells compared to AmB commercial formulations, thus suggesting that this system might be able to effectively deliver AmB in patients [62]. Although the precise mechanism that accounts for the increased CNS penetration of the micellar system is not yet known, the delivery system shows potential for treating intracerebral fungal infection in humans [62].

The Neuro-Spinal Scaffold™ is a novel SCI treatment currently being developed by InVivo Therapeutics (Cambridge, MA, USA) [63]. In April 2013, the Neuro-Spinal Scaffold™ was designated as a Humanitarian Use Device (HUD) by the U.S. FDA and is currently undergoing an open-label clinical pilot study, which is expected to finish in 2017 [63]. A HUD is a device which benefits no more than 8000 people within the U.S. per year. The scaffold consists of two biodegradable polymers, poly(lactic-co-glycolic acid) (PLGA) and poly-L-lysine (PLL), which allow for structural support and facilitate cell-adhesion during the healing process [63]. The scaffold is designed for insertion within the first 96 h after injury and can be sized to fit the injury site [63]. Following implantation, the Neuro-Spinal Scaffold™ is seeded with neural stem cells (NSC)s, which have the ability to differentiate into astrocytes, oligodendrocytes, and neurons, the main cell types of the CNS [64]. InVivo Therapeutics is also developing an approach to deliver these NSCs to the Neuro-Spinal Scaffold™. Referred to as Bioengineered Neural Trails™, the injectable scaffold creates longitudinal conduits for cells, which facilitates uniform cell delivery and connectivity as opposed to a perpendicular bolus injection, which would not direct the cells as well in the intended direction [64]. While Bioengineered Neural Trails™ has not yet undergone clinical studies, *in vivo* studies using rat spinal cord cells demonstrated cell viability and homogeneous cell conduits [64]. In the U.S. alone, the Neuro-Spinal Scaffold™ could potentially impact as many as 17,000 people per year, based off the number of SCIs that occur annually [65].

3. Intraocular-Based Therapeutics

Beginning with the development of PMMA-based contact lenses during the 1940s, the field of intraocular therapeutics was one of the first to take advantage of the therapeutic applications of polymers [66]. In 1949, Dr. Harold Ridley established PMMA as the standard intraocular lens material in cataract extraction procedures; later, PMMA came to be used as an intracorneal lens implant for correcting myopia and hyperopia [66]. During the 1970s, Ocusert® (Alza Corporation, Mountain View, CA, USA) was introduced as the first ocular sustained-release drug delivery system, paving the path for later innovations in intraocular drug delivery [67]. Recently, polymers such as silicones and hydrogels have been adopted as the base material for scleral buckling for treating retinal detachments [66]. The following discussion will detail several of these polymer-based intraocular therapies, with a focus on the most recently translated devices. For additional discussion on clinically-translated and developing intraocular-based therapeutics, the reader is referred to the following articles [68–78].

Retisert® (Bausch & Lomb, Rochester, NY, USA) is a non-biodegradable intraocular implant indicated for treating chronic noninfectious posterior uveitis that was developed by pSivida Corp. (Watertown, MA, USA) (Fig. 2**A**) [79]. Approved by the U.S. FDA in 2005, Retisert® was noted as the first intravitreal drug

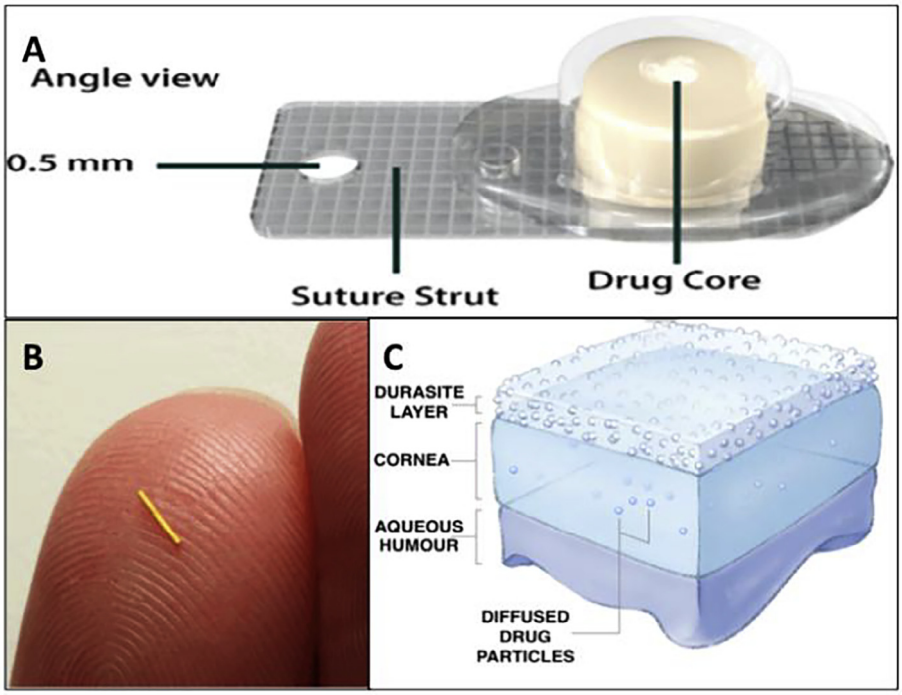

Fig. 2. Intraocular Therapeutics. **A.** Retisert® implant [84]; **B.** Iluvien® implant [85]; **C.** DuraSite® technology mechanism of action [86].

implant for treating this type of uveitis [35]. Retisert® is designed to release fluocinolone acetonide (FA), a corticosteroid commonly used in treating inflammation, directly into the posterior segment of the eye at a controlled rate for over 30 months [80]. The FA-containing tablet is encased by a polyvinyl alcohol (PVA) membrane, which is further surrounded by a silicone elastomer cup containing a release orifice [80]. FA exits through the orifice at a rate of 0.6 μgs/day during the first month, followed by a sustained rate of 0.3–0.4 μgs/day for the remaining months of treatment [80]. To facilitate surgical implantation, Retisert® also includes a silicone elastomer suture strut, which is intended to attach to the sclera [80]. Although Retisert® has been shown to cause complications such as cataract, increased intraocular pressure (IOP), and pain, it has been shown to reduce infection recurrence and improve visual acuity compared to traditional posterior uveitis treatments, such as topical corticosteroids or intravitreal injections [79].

Similar to Retisert®, Iluvien® (Alimera Sciences Limited, Aldershot, UK) is a nonbiodegradable, FA-containing implant also developed by pSivida using Medidur™ technology (Fig. 2**B**) [81]. Iluvien® is indicated for treating diabetic macular edema (DME) in patients who have been previously treated with corticosteroids without success [37]. Approved by the U.S. FDA in 2014, Iluvien® is the first commercially available DME treatment to provide up to 36 months of continuous corticosteroid release from a single dose [37]. Unlike Retisert®, however, Iluvien® instead functions as an injectable capsule, avoiding the need for surgery [37]. The capsule itself is made from polyimide and surrounds a PVA matrix containing 0.19 mgs of FA [82]. Membrane caps on both ends of the capsule moderate the rate of FA release [82]. While many nondegradable, polymeric capsule devices have been associated with fibrosis, the authors were not able to find, to the extent possible, reports of such a response in patients treated with Iluvien®. Iluvien® is, however, associated with the risk of cataract, IOP, and myodesopsia, in addition to other less common reactions [37]. As of 2017, Iluvien® is also available for sale in Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Spain, Sweden and the United Kingdom [37].

While the antibiotic azithromycin (AZM) has shown success in treating intraocular infections when taken orally, AZM is associated with a range of systemic side effects [83]. AzaSite® (InSite Vision, Alameda, CA, USA) overcomes this challenge using DuraSite® technology, a cross-linked polyacrylic acid polymer-based vehicle (Fig. 2**C**) [83]. AzaSite®, the only FDA-approved topical drug to contain AZM, is indicated for treating bacterial conjunctivitis; however, InSite Vision is also exploring the potential of DuraSite® for drug delivery to the ear, nose, skin, and throat [83]. Following the administration of AzaSite® as an eye drop, AZM diffuses from the polymer matrix into the tear film and site of conjunctivitis [83]. AzaSite® delivers AZM for up to 6 h, compared to conventional eye drops, which require application every 1–2 h [83]. In clinical studies, AzaSite® was shown to resolve clinical symptoms of bacterial conjunctivitis in 63.1% of patients, compared to 49.7% of patients who received the vehicle treatment [83].

3.1. Future Trends of Intraocular Therapeutics

Despite the abundance of commercially available intraocular therapies, the World Health Organization (WHO) estimates that, of the 285 million people worldwide who suffer from visual impairments, 20 million people were blinded as a result of cataracts in 2010 [87]. Moreover, glaucoma, which is treatable if diagnosed early, is estimated to account for 12% of global blindness [87]. Because the greatest burden of blindness is in developing countries lacking medical infrastructure, developing more accessible therapies for treatable diseases such as glaucoma and cataracts would significantly reduce the toll of visual impairment. The following discussion will highlight some current advances in polymer-based intraocular therapeutics that could potentially better address this global health crisis.

In the United States, cataract removal is the most commonly performed surgery, with almost 4 million surgeries having taken place in 2014 alone [88]. A common post-surgical complication from cataract removal surgery is failure of the patient to follow the prescribed eye-drop dosing schedule, which can result in a compromised healing process [88]. To address this challenge, both IVMED-10 and IVMED-20 (iVeena Pharmaceuticals, Salt Lake City, UT, USA) are currently being developed as an alternative to postoperative cataract anti-inflammatory eye drops [88]. IVMED-10 and IVMED-20 are bioerodible dexamethasone (DXM) implants (BDI) that are implanted in the lens capsule during cataract surgery, allowing for DXM to be delivered to both the posterior and anterior sub-portions of the eye [88]. As the PLGA matrix of the BDI is hydrolyzed, DXM is released either over a period of 2 weeks (IVMED-10) or 6 weeks (IVMED-20), depending on whether the patient has pre-existing conditions that require additional anti-inflammation treatment [88]. Proof-of-concept studies published in 2013 showed that DXM release exhibited near zero-order release kinetics during the 42 days of observation [89]. iVeena Delivery Systems is also developing new approaches for treating wet age-related macular degeneration (IVMED-50 and IVMED-55), diabetic retinopathy (IVMED-60), and glaucoma (IVMED-70), although these products are still in the proof-of-concept phase [88].

Secondary to cataract complications, photoreceptor death from degenerative retinal diseases makes up one of the leading causes of blindness worldwide [90]. NeuroTech Pharmaceuticals, Inc. (Cumberland, RI, USA) is currently developing a treatment for degenerative retinal diseases using its proprietary Encapsulated Cell Therapy (ECT) technology [91]. NT-501 ECT is furthest along in NeuroTech's pipeline and is currently being tested in a phase II study in subjects with macular telangiectasia (MacTel) and phase I study for glaucoma treatment [91]. The ECT platform is an implantable device containing ciliary neurotrophic factor (CNTF)-secreting cells from the NTC-200 cell line, a genetically engineered line derived from healthy human retinal pigment epithelia cells [91]. CNTF, an endogenous protein expressed by neurons, has been shown to exhibit a neuroprotective effect on photoreceptors in animal models, inspiring the basis behind NT-501 ECT [91]. The NTC-200 cells are encapsulated within a proprietary polymer-based semi-permeable outer membrane and supported by a polyethylene terephthalate scaffold, which allows for CNTF to be secreted over a period of at least two years [92]. By injecting CNTF-secreting cells directly into the vitreous cavity, the challenge of crossing the blood-retina barrier can be avoided [91]. In addition, because the cell line secreting CNTF is immortalized, NT-501 ECT offers the convenience of a single injection [91]. NeuroTech Pharmaceuticals, Inc. is also exploring the use of ECT and the NTC-200 cell for additional intraocular treatments by secreting therapeutics such as antibodies, fusion proteins, and growth factors.

4. Gastrointestinal-Based Therapeutics

In the U.S. alone, gastrointestinal (GI) diseases are estimated to affect 60–70 million people annually [93]. In a recent study investigating the burden of GI diseases in the U.S., Peery et al. concluded that 10% of all mortalities in the US during 2009 were caused by a GI-related problem [93]. The burden of GI diseases is also reflected worldwide. On the global scale, colorectal cancer (CRC), the third most common form of cancer, is associated with a 40% mortality

rate [94]. Moreover, *Helicobacter pylori*, a species of bacteria associated with stomach ulcers and a risk of stomach cancer, is estimated to affect 50% of the global population [94]. The prevalence and associated mortality of GI diseases such as these highlights the need for effective and widely accessible treatments. The following discussion will consider advances in commercially available polymer-based treatments that have helped to not only address this need but also utilize the GI tract as an effective drug delivery route. For further discussion on polymer-based therapeutics applied to the GI system, readers are encouraged to refer to the following references [95–99].

In 2015, the U.S. FDA approved Veltassa® (Relypsa, Redwood City, CA, USA) for the treatment of hyperkalemia, a metabolic condition marked by high potassium ion levels in human serum as a result of kidney dysfunction (Fig. 3) [100]. While the disease is estimated to affect only 2–3% of the general population, as many as 50% of patients with chronic kidney disease suffer from hyperkalemia [101]. If left untreated, hyperkalemia can lead to cardiac dysrhythmia or fatality [102]. Veltassa® is administered orally as a powder dissolved in water and contains patiromer sorbitex calcium, a cross-linked polymer of calcium 2-fluoroprop-2-enoate with diethenylbenzene and octa-1,7-diene, as an active ingredient [103]. When Veltassa® enters the GI tract, patiromer sorbitex calcium complex binds to potassium ions in exchange for calcium, which is then excreted normally [103]. Veltassa® is the first new hyperkalemia treatment to be FDA-approved since Kayexalate™ was introduced over 50 years [100]. Compared to Kayexalate™, Veltassa® has been shown to cause fewer side effects [104].

4.1. Future Directions of Gastrointestinal-Based Therapeutics

Despite the successes of treatments that both address and utilize the physiology of the GI system, the field of polymer-based GI therapeutics remains largely uncharted compared to other areas. In the following section, we will consider early-stage polymer-based GI therapeutics currently under investigation. In addition, we will also discuss a GI-based drug delivery platform that takes advantage of the unique physiological conditions of the GI tract to promote long-term drug release. While the following section serves to provide an overview of the current state of developing GI therapeutics, it is also meant to highlight the need for novel GI therapies and promote further research in the field.

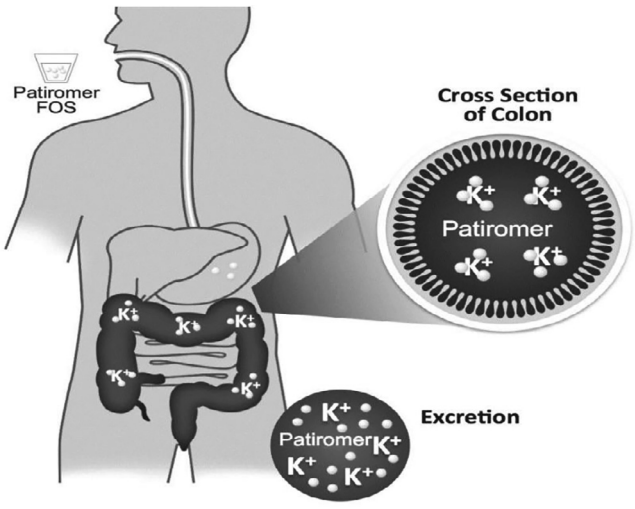

Fig. 3. Gastrointestinal-based Therapeutics: Summary of Veltassa® treatment [105].

4.1.1. Non-Oral Delivery

Nippon Kayaku (Tokyo, Japan) is currently investigating NK911, a pancreatic and colorectal cancer treatment, in phase II clinical trials [106]. NK911 is a polymeric micelle (PM) carrier system that was developed in the early 2000s using a block copolymer of poly(ethylene glycol)-b-poly(α,β-aspartic acid) [106]. NK911 is specially designed for targeting solid tumors and contains two forms of DOX, incorporated and conjugated [106]. Conjugated DOX is covalently bound to 50% of carboxylic groups of the polyaspartate block (PEG-b-p(Asp-DOX)), which prevents it from affecting tumors; instead, conjugated DOX allows for micelle stabilization and prolongs the release of incorporated DOX, which is loaded freely into the PM [106]. Preclinical studies demonstrated that NK911 accumulates 3.4 times more in tumor tissue than free DOX due to the enhanced permeability and retention (EPR) effect [106]. Moreover, because NK911 is made with PEG, the PMs can effectively evade the reticuloendothelial system, thus improving circulation time [106]. There is currently no public information regarding when Nippon Kayaku expects to officially launch NK911.

4.1.2. Oral Delivery

The development of a versatile drug delivery platform that can provide long-term drug dosing for a myriad of diseases and conditions remains a coveted goal in pharmaceutical engineering research. One such GI-based platform is currently being developed by Lyndra, Inc. (Watertown, MA, USA) [107]. The platform is intended to prolong drug release over a week or month for medications that would otherwise require daily dosing [107]. The Lyndra platform encapsulates drug within a poly(ε-caprolactone) drug release matrix, which undergoes a pH-triggered shape transformation upon reaching the stomach, thereby preventing the capsule from entering the GI tract [108]. The capsule remains in the stomach until the linker molecules holding the expanded structure dissolve, allowing the capsule to leave the stomach and progress through the GI tract [108]. A notable property of this platform is its versatility and potential for use as a multi-drug platform for treating diseases such as malaria, Alzheimer's disease, diabetes, and epilepsy [109]. Lyndra, Inc. is currently seeking FDA approval to test the device in humans [109].

Patients with inflammatory bowel disease (IBD), an idiopathic condition that is estimated to affect between 1 and 1.3 million people in the United States alone, are often treated with intravenous corticosteroids; in cases where patients are nonresponsive to corticosteroids, cyclosporine-A (CYA), an immunosuppressant, may be used as an alternative [110,111]. CYA, however, is associated with serious side effects, including neurological toxicity, renal dysfunction, and nephrotoxicity [110]. In a study published in 2017, researchers demonstrated that orally administered PLGA NPs incorporated with CYA could potentially be used as a method of not only lowering the effective CYA dosage but also reducing systemic exposure. In the study, CYA-NPs and CYA-MPs were prepared using the nano spray drying method and then orally administered in a dextran sulfate sodium (DSS)-induced IBD mouse model [110]. The results from the CYA-NP and CYA-MP treatments were also compared to groups receiving Sandimmune Neoral®, an existing commercial formulation of CYA, and drug-free NPs and MPs [110]. The results indicated that the 25 mg/kg CYA-NP formulation was the most promising, in terms of both its effectiveness in treatment and bioavailability [110]. While this data suggests that CYA-NPs may be an effective new alternative for treating IBD, further analysis must be done to address the limitations associated with the DSS-induced mouse model, in addition to investigating the long-term toxicity of the formulation [110].

While traditionally used for treating *H. pylori* infections, amoxicillin is often limited in use because of its poor ability to maintain an effective concentration at the infection site [112]. In a study

published in 2016, Su et al. showed that delivery of amoxicillin to the site of *H. pylori* infection could be improved using poly(γ-glutamic acid)-g-arginine (γ-PGA-g-Arg) polypeptide colloidal nanoparticles modified with chitosan-arginine conjugate (CS-N-Arg) [112]. Because *H. pylori* infection sites in the gastric mucosa are characterized by having a pH greater than 5.0, the sensitivity of the drug carrier to pH can be manipulated as a way of improving amoxicillin delivery [112]. By complexing γ-PGA-g-Arg polypeptide with CS-N-Arg, the researchers demonstrated that the stability of the nanoparticles can be modified from a pH range of 2.0–3.0 to 2.0–6.0, thereby enabling rapid, pH-triggered release at the infection site [112]. In addition, the researchers showed that amoxicillin-loaded CS-N-Arg/γ-PGA-g-Arg NPs were most effective at inhibiting *H. pylori* growth compared to both γ-PGA-g-Arg NPs and free amoxicillin as a result of the antibacterial activity of chitosan in acidic conditions [112]. The researchers concluded that the pH-responsive CS-N-Arg/γ-PGA-g-Arg NPs can serve as a potential method for effectively delivering amoxicillin orally, although further experimentation is needed [112].

Another potential CRC treatment is currently being explored by Chaurasia et al. In 2015, the researchers demonstrated the anticancer efficacy of curcumin (CUR)-containing polymeric NPs in treating CRC using an *in vivo* murine model [113]. While known for its free radical scavenging and anticarcinogenic effects, CUR poses a challenge for researchers due to its low oral bioavailability and poor aqueous solubility [114]. To address these limitations, the researchers loaded CUR into Eudragit® E100 (EE100) copolymer using the emulsification-diffusion-evaporation method [113]. The CUR-loaded EE100 NPs (CENP)s were shown to boost the oral bioavailability of CUR; in addition, the particles were shown to decrease tumor size in a colon carcinoma tumor-bearing mouse model following 30 days of daily oral administration [113]. CENPs are larger than free CUR but sufficiently small to still bypass renal clearance (glomerular filtration cutoff is near 5–6 nm), thereby allowing the particles to accumulate at tumor sites by the EPR effect, while limiting the risk of harming healthy tissues [113].

5. Cardiovascular-Based Therapeutics

Cardiovascular therapeutics have long been linked to polymers, beginning with the invention of the first synthetic heart valve [115]. In 1952, Dr. Charles Hufnagel's PMMA-based ball valve became the first heart valve to be surgically implanted in a human (Table 1) [25]. Later, during the 1960s, Dr. Hufnagel's design was modified by Dr. Albert Starr, a surgeon, and Mr. Lowell Edwards, an electrical engineer, to improve survival rates in mitral valve replacement patients (Table 1) [25]. Referred to as the Starr-Edwards heart valve, the improved design enclosed a heat-cured silicone-rubber ball within a Lucite (PMMA) cage, which later evolved into a stellite (cobalt-chromium alloy) metal cage for improved durability [25,116]. Beyond heart valves, polymers have also played key roles as vascular grafts. Spark's mandril, one of the earliest fibrocollagenous tissue-tube vascular grafts, was made using polyethylene terephthalate and polycarbonate (Table 1) [117]. Today, polymers are used in cardiovascular therapeutics for purposes ranging from occluders, drug delivery systems, and stent coatings. The following discussion will consider several novel polymer-based cardiovascular therapeutic devices available today. For additional information on the history and future direction of polymer-based cardiovascular applications, we recommend the following sources for further study [118–124].

The AMPLATZER™ PFO Occluder® (St. Jude Medical, Saint Paul, MN, USA) is the first heart occluder device to be FDA-approved for closing patent foramen ovale (PFO) malformities (Fig. 4**A**) [39]. Because a PFO allows blood to leak from the right atrium to the left atrium, blood clots that would otherwise be filtered by the lungs risk travelling to the brain stem, resulting in a potentially life-threatening cerebrovascular accident (CVA) [125]. In fact, it is estimated that as many as 40–70% of patients who have suffered an idiopathic CVA also have PFO malformities [125]. Because PFOs are typically not treated until after a CVA occurs, surgical closure of PFOs offers a way to significantly reduce the risk of recurrent complications in at-risk patients [125,126]. Studies have shown that patients treated with both anticoagulant medication and the AMPLATZER™ PFO Occluder® experienced a 50% reduction in the rate of CVAs, in comparison to patients who took only blood-thinning medication [39]. During percutaneous closure surgery, the AMPLATZER™ PFO Occluder® is guided to the heart using a catheter or sheath [127]. To facilitate its closing ability, the AMPLATZER™ PFO Occluder® is made from nitinol, a superelastic shape memory nickel titanium alloy, which is shaped into two discs containing polyester fabric connected to each disc by polyester thread [127]. While the AMPLATZER™ PFO Occluder® was originally marketed as a HUD in 2002, the device was later withdrawn from the market after the U.S. FDA concluded that the device targeted more than 8000 patients and had to be approved as a medical device [127,128]. After receiving U.S. FDA approval, the AMPLATZER PFO Occluder® returned to the market in October 2016 [127].

Furthermore, many polymer applications in cardiovascular therapeutics are associated with sustained drug release properties. Catapres-TTS® (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is a transdermal drug delivery system indicated for treating mild to moderate hypertension (Fig. 4**B**) [129]. The clonidine-delivering Transdermal Therapeutic System (TTS) was U.S. FDA approved in 1984 as an alternative to oral clonidine, which is associated with side effects such as dry mouth and dizziness [130]. Catapres-TTS® is the first adhesive patch that releases clonidine at a nearly constant rate for over seven days [129]. Because of the difference in clonidine concentrations between the skin and patch, clonidine naturally exits the drug reservoir and enters the body transdermally [129]. A microporous polypropylene membrane, which is situated between the drug reservoir and the point of skin contact, regulates the release of clonidine over time [129]. A colloidal suspension of silicon dioxide is used both as a filler within the drug reservoir as well as an adhesive component [131]. Clonidine itself functions as a hypotensive agent and is thought to reduce blood pressure by triggering α_2 adrenoceptors in the brain [130]. In clinical studies, Catapres-TTS® was proven to be equivalent or superior to oral clonidine treatments for controlling blood pressure [130,132].

While both balloon angioplasty and coronary artery stents offer potential treatments for coronary artery disease, both are associated with failure due to elastic recoiling of blood vessels hyperplasia [133]. It is estimated that 30–50% of patients receiving a balloon angioplasty experience restenosis, compared to 10–30% of patients treated with coronary artery stents [133]. In 2004, the TAXUS® stent (Boston Scientific, Marlborough, MA, USA) was approved by the U.S. FDA for treating restenosis as a result of balloon angioplasty or coronary artery stents (Fig. 4**C**) [134]. In 2012, the indications for the TAXUS® stent expanded to include patients who have suffered an acute myocardial infarction (AMI), making it the first U.S. FDA-approved drug-eluting stent for treating AMI patients [135]. The TAXUS® stent, similar to regular stents, is made of metal, but differs in that it contains a layer of PTX and Translute™ polymer, a proprietary compound also referred to as poly(styrene-b-isobutylene-b-styrene) [133]. Unlike a bare metal stent, the TAXUS® stent allows for the local delivery of PTX to the arterial wall, which inhibits hyperplasia while minimizing its release into the bloodstream [133].

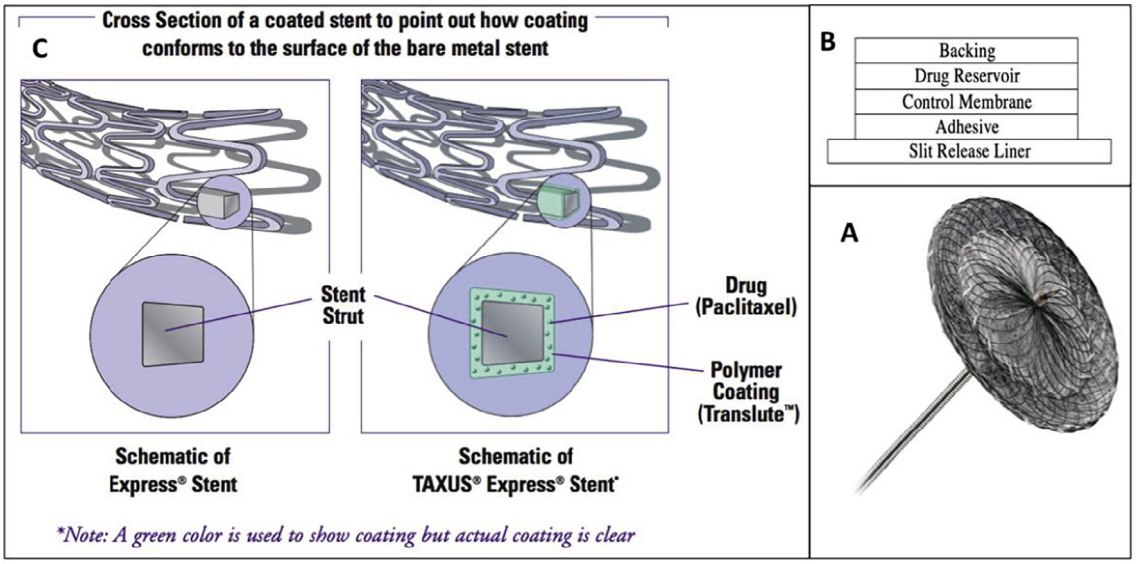

Fig. 4. Cardiovascular Therapeutics. **A.** AMPLATZER™ PFO Occluder® [127]; **B.** Cross section of Catapres-TTS® [129]; **C.** Comparison of paclitaxel-coated and non-paclitaxel coated Express® Stents [133].(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5.1. Future Direction of Cardiovascular-Based Therapeutics

Despite the advances made in cardiovascular therapeutics over the past decade, cardiovascular diseases (CVD)s remain the leading causes of death globally [136]. In 2015, the WHO reported that 31% of all deaths were due to CVDs [136]. In the U.S., the CDC estimates that 1 in 4 deaths are caused by CVDs [137]. Collectively, this data highlights the need for improved and novel treatments that address CVDs. The following discussion will consider two promising polymer-based therapies that aim to target this global public health crisis.

Shape Memory Medical Inc. (Santa Clara, CA, USA) is currently developing a novel peripheral and neurovascular embolization system for treating aneurysms using shape-memory polymer (SMP) foams [138]. Founded in 2009, Shape Memory Medical Inc. is the product of collaboration between Texas A&M University and Lawrence Livermore National Laboratory [138]. The SMP foams are formulated using polyurethane and offer an alternative to platinum embolization coils and plugs, which can degrade over time and pose health risks for the patient [139]. Polyurethane-based SMP foams have shape-changing properties that allow them to change from a crimped shape, ideal for catheter insertion, to an expanded shape upon reaching the aneurysm site [139]. Compared to traditional embolization devices, the polyurethane-based SMP foams have both a larger volume and surface area, allowing for improved aneurysm healing [139]. In addition, the foams have been shown to more successfully promote growth of collagen compared to other embolization systems, indicating that the SMP foams may in fact reduce the risk of aneurysm recurrence [139]. Shape Memory Medical Inc. expects to begin human trials in 2018 [139].

Novel treatments for atherosclerosis, one of the leading causes of CVD, remain largely in early development stages. In 2015, Sanchez-Gayton et al. demonstrated one such treatment by showing that synthetic high-density lipoproteins (HDL) modified with PLGA exhibited similar biological functions to endogenous HDL [140]. Because HDL has a natural affinity for atherosclerotic plaques, it offers potential not only for treating atherosclerosis but also other diseases, including sepsis. By modifying synthetic HDL with PLGA, synthetic HDL can be used for controlled release of drug at the site of atherosclerotic lesions [140]. In this study, the HDL-mimetic PLGA NPs were formed using microfluidic-based technology previously developed by the same laboratory [140]. The NPs were then tested to see whether they shared the same biological functions as endogenous HDL [140]. The results of the study showed that the HDL-mimetic PLGA NPs could also function as cholesterol acceptors and retained the atherosclerotic plaque-targeting abilities of natural HDL, thus demonstrating the potential for using synthetic PLGA-modified HDL as a theranostic platform [140].

6. Dermal-Based Therapeutics

Non-healing wounds are considered by some to be a "silent epidemic" because of their relatively unknown impact compared to big-name diseases such as cancer and CVD [141]. By 2025, it is estimated that over 400 million people will be diagnosed with diabetes, 25% of whom will develop diabetic foot ulcers (DFU)s [142]. The frequency of non-healing wounds is even greater in populations living in remote areas or developing countries lacking medical infrastructure [142]. In recent years, however, novel developments in dermal-based therapeutics have offered a solution for curbing the non-healing wounds epidemic. In the following discussion, we will consider several commercially available products that aim to address this plight. For further discussion of emerging trends and challenges of the field, readers are recommended to refer to the following sources [143–151].

The Integra® Flowable Wound Matrix (Integra LifeSciences Corp, Plainsboro, NJ, USA) is an injectable collagen matrix for treating tunneled lesions that was approved by the U.S. FDA in 2007 (Fig. 5**A**) [36]. Granulated cross-linked bovine tendon collagen and glycosaminoglycans enable the matrix to mold to the injury site upon injection, which then acts as a scaffold to support cell and capillary growth [152]. One of the most notable benefits of the Integra® Flowable Wound Matrix is that it provides a minimally invasive treatment while still promoting complete coverage of the wound [152]. In a pilot study published in 2015, the efficacy of the Integra® Flowable Wound Matrix when combined with percutaneous cannula scar release was tested in patients with post-burn hand malfunction [153]. The authors of the study concluded that use of the Integra® Flowable Wound Matrix demonstrated gains in various measures, such as active range of motion and disabilities of the arm, shoulder, and hand score, though the results

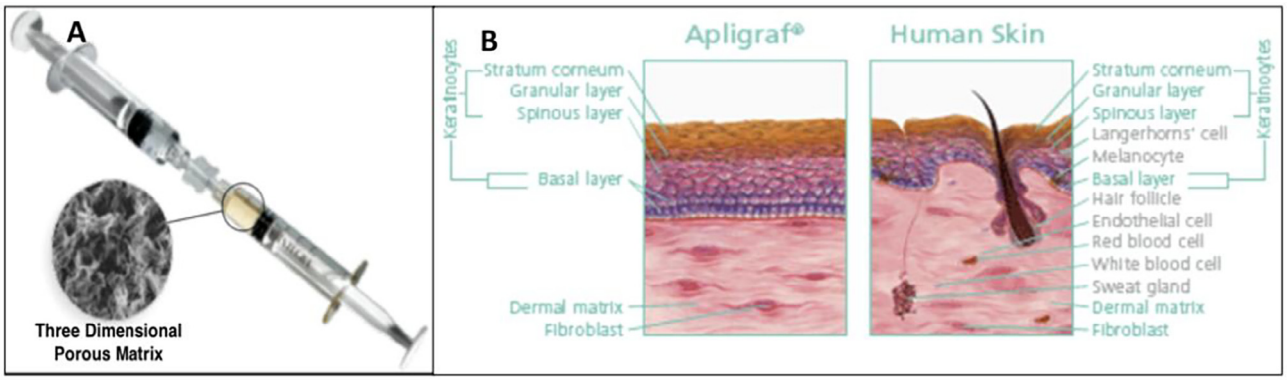

Fig. 5. Dermal Therapeutics. **A.** Integra® Flowable Wound Matrix [157]; **B.** Comparison between Apligraf® and human skin [154].

were not statistically significant, possibly because of the small study size [153].

Skin grafts offer an alternative method for treating DFUs. Apligraf® (Organogenesis Inc., Canton, MA, USA) is the only FDA-approved, living, bi-layered skin graft indicated for treatment of chronic venous leg ulcers and DFUs (Fig. 5**B**) [154]. Similar to living skin, Apligraf® contains both an epidermal and dermal layer, which serves to provide a defense against infection and promote wound closure [155]. Apligraf® differs from human skin, however, because it lacks melanocytes, Langerhans' cells, macrophages, lymphocytes, and structures such as blood vessels, hair follicles, and sweat glands [154]. The graft is prepared over a 31-day period, beginning with the collection of fibroblasts and keratinocytes from donated neonatal foreskins [154]. Following decontamination and culturing of the cells, the fibroblasts are seeded onto a bovine type I collagen lattice to form the dermis, followed by keratinocyte seeding [154]. As the cells continue to grow and mature, the epidermal and dermal layers differentiate [154]. In clinical trials, 57% of patients treated with Apligraf® for venous leg ulcers demonstrated complete wound closure, compared to only 40% of patients who received the control treatment [154]. Similarly, 56% of patients receiving Apligraf® for treatment of DFUs experienced complete wound closure, as compared to 36% of patients receiving the control [154].

In addition to DFUs and chronic venous leg ulcers, burns also account for a significant portion of the chronic wound epidemic. Epicel® (Vericel Corporation, Cambridge, MA, USA) is a cultured epidermal autograft (CEA) indicated for treating deep dermal or full thickness burns covering greater than or equal to 30% of the body [38]. Epicel® is the product of work done by Drs. James Reinwald and Howard Green, who were the first to demonstrate that human keratinocytes could be grown *in vitro* using irradiated mouse fibroblasts (Table 1) [30]. Following its HDE approval in 2016, Epicel® became the first and only CEA to be FDA-approved [38]. The process used to manufacture Epicel® today is the same process Dr. Reinwald and Dr. Green first used in 1975 [38]. After a sample of the patient's healthy skin is sent to the Vericel facility in Cambridge, Massachusetts, the keratinocytes are extracted and grown ex vivo using proliferation-arrested, murine fibroblasts on a benzyl esterified hyaluronic acid matrix [38,156]. Each graft is manufactured to be 50 square centimeters and can cover an entire body in 3–4 week [38]. Since Epicel® was introduced in 1988, it has been used to treat over 1500 patients [38].

6.1. Future Direction of Dermal-Based Therapeutics

In developing countries that lack access to medical infrastructure and healthcare, patient compliance to medication regimes is often poor, and monitoring patient adherence is a challenge. Long-term subcutaneous drug implants could offer a solution, which would remove the need for continual or bolus-based (i.e., for vaccine development) administrations of the drug of interest and improve patient outcomes. In developed countries, such technologies can also be helpful in terms of patient compliance, as well as providing a convenience factor. In the case of vaccine development, periodic boluses help avoid T cell anergy issues. The concept of a multi-dose, single injection vaccine has been met with formidable challenges, including antigen stability. Such sophisticated delivery systems could also help elucidate what the optimal antigen release kinetics are for vaccine development. The following will consider two subcutaneous drug implant systems currently in development.

The Medici Drug Delivery System™ (Intarcia Therapeutics, Inc., Boston, MA, USA) is a platform that enables small molecules, such as proteins, peptides, and antibody fragments, to be delivered subcutaneously at a constant rate for up to a year [158]. Water from extracellular fluid enters the device through a semipermeable membrane and drives the system, allowing for drug to be released at a constant rate [158]. Intarcia Therapeutics, Inc. is currently preparing to launch ITCA 650, a treatment for type 2 diabetes that utilizes the Medici Drug Delivery System™ to release exenatide, a natural, amino acid-based polymer and glucagon-like peptide-1 (GLP-1) receptor agonist (RA) [159]. Existing treatments using GLP-1 RAs require daily or weekly injections, which can result in less than optimal treatment outcomes due to poor patient compliance [159]. In contrast, ITCA 650 promotes virtually 100% therapy compliance and allows for continuous, zero-order exenatide release for up to a year [160]. In February 2017, following completion of phase III clinical trials for the device, the U.S. FDA accepted the New Drug Application for ITCA 650 [158]. Intarcia Therapeutics, Inc. is also currently funded by the Bill & Melinda Gates Foundation to develop a prophylactic treatment for HIV using the Medici Drug Delivery System™ [158]. The implantable treatment will target populations most at-risk for HIV infection and will be the first anti-HIV prophylactic treatment of its kind [158].

Microchips Biotech, Inc. (Bedford, MA, USA) is also currently developing a subcutaneous implant solution for providing long-term drug dosing. Microchips Biotech, Inc. has had 113 patents granted so far, with over 30 patent applications currently pending [161]. The microchip implants are designed to store hundreds of 1-mg doses, which can be activated and deactivated using wireless signals, or triggered by physiological conditions [161]. The technology is specifically targeted to diseases and conditions requiring long-term dosing, such as osteoporosis, multiple sclerosis, diabetes, and pain management [161]. In addition to programmable, electronic microchips, the Microchips Biotech pipeline also includes resorbable, non-electronic polymer-based microchips made of poly(L-lactic acid) with PLGA membrane-covered reservoirs [162]. In 2012, Farra et al. conducted the first-in-human test-

ing of the electronic microchip design using human parathyroid hormone fragment (1–34) (hPTH(1–34)) to treat patients with osteoporosis and osteopenia [163]. The results of the study demonstrated that the drug and device combination were well-tolerated; in addition, the pharmacokinetic profile of hPTH(1–34) in patients treated with the drug and device was shown to be similar to that of patients receiving only subcutaneous injections [163]. Microchips Biotech, Inc. is also working with the Gates Foundation to develop a contraceptive implant utilizing the microchip-based implant design that allows for up to 16 years of reversible birth control [161].

7. Reproductive-Based Therapeutics

The first example of polymeric-based contraception could arguably be the use of aromatic hydrocarbons in honey mixed with unripe acacia fruit in the 16th century BCE [164,165]. While the history of intrauterine devices (IUD)s dates to the early 20th century, polymer-based IUDs were not introduced until the 1960s [26]. These early IUDs, such as the Perma-Spiral/Gynecoil® in 1960 and the Lippes Loop in 1961, took advantage of the shape memory properties of thermoplastics, increasing the ease of insertion and removal (Table 1) [26]. Later, in 1970, the first contraceptive vaginal ring was developed using silicone rubber combined with medroxyprogesterone acetate (Table 1) [166]. Over time, advances in the development of polymer-based IUDs and vaginal rings have allowed for expanded indications, such as hormonal therapy. While IUDs are the most commonly used contraception method, both IUDs and vaginal rings offer distinct advantages and disadvantages, such as the duration of use and indication [167]. In the following discussion, we will evaluate three commercially available polymer-based IUDs and vaginal rings. Readers interested in further discussion of clinically translated and developing reproductive-based therapeutics are encouraged to refer to the provided references [168–174]. In addition, readers interested in a more thorough history and discussion on the evolution of IUDs and vaginal rings are recommended to refer to the provided sources [166,175].

Mirena® (Bayer HealthCare, Berlin, Germany) is a levonorgestrel intrauterine system (LNG IUS) indicated for up to 5 years of intrauterine contraception, in addition to managing idiopathic menorrhagia, dysmenorrhea, adenomyosis, and endometrial hyperplasia (Fig. 6**A**) [176]. Originally developed by Schering, Mirena® was first licensed in Finland in 1990 and later approved by the U.S. FDA in 2000 as the first LNG IUS [33]. Mirena® is made of a polyethylene T-shaped frame and vertical drug reservoir, which contains a blend of silicone and LNG [177]. For the first month following insertion, LNG is released topically at a rate of 20 μgs per day; over a period of 5 years, the rate decreases to 10 μgs per day [177]. The failure rate of Mirena® by the Pearl Index is 0.14 pregnancies per 100 women, with an overall cumulative efficacy of 99.3% over 5 years [176]. Today, Mirena® is available in over 120 countries worldwide, although its high price tag limits its accessibility for many [178].

In comparison to LNG IUSs, copper-containing IUDs offer a non-hormonal solution to contraception. ParaGard® T 380A Intrauterine Copper Contraceptive, or ParaGard®, (Teva Pharmaceutical Industries, Petah Tikva, Israel) is currently the only copper-containing IUD approved for use in the U.S. (Fig. 6**B**) [179]. In studies, ParaGard® has been shown to be nearly as effective as male or female sterilization; unlike sterilization, however, ParaGard® allows for reversible fertility [179]. Similar to other IUDs such as Mirena® and Fibroplant®, ParaGard® shares the same polyethylene T-shaped frame design; unlike LNG IUDs, however, ParaGard® contains 380 square millimeters of copper wire wrapped around its stem [179]. The copper ions act to reduce sperm mobility, consequently inhibiting fertilization [179]. While ParaGard® has a slightly lower success rate compared to Mirena® and other LNG IUDs (specifically, 0.6/100 accidental pregnancies, compared to 0.5/100), it is noted for its longer protection time of up to 12 years and hormone-free properties [180].

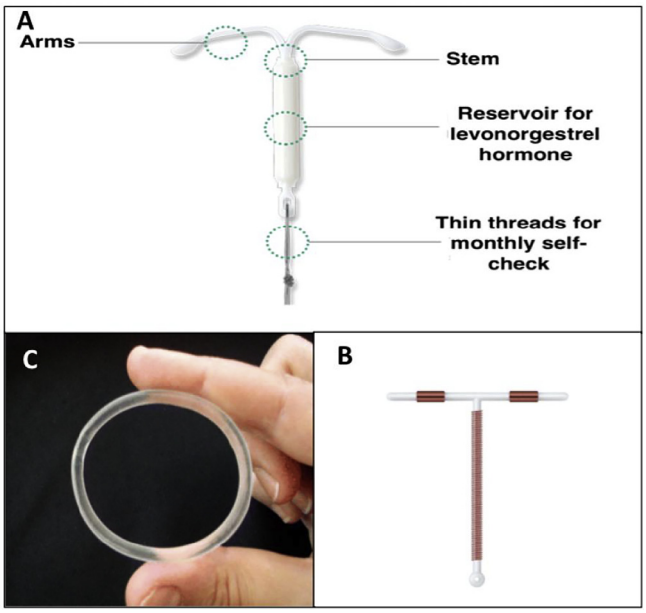

Fig. 6. Reproductive-based Therapeutics. **A.** Labeled components of Mirena® [186]; **B.** ParaGard® [187]; **C.** NuvaRing® [188].

While not as widely used as IUDs, vaginal rings such as NuvaRing® (Merck, Darmstadt, Germany) offer an alternative contraceptive method (Fig. 6**C**). In addition to being approved by the U.S. FDA in 2001 as an estrogen/progestin combination hormonal contraceptive, NuvaRing® is licensed for sale in Russia, Canada, and several other European countries [34]. NuvaRing® releases 120 μgs of etonogestrel and 15 μgs of ethinyl estradiol (EE) daily. These hormones function by suppressing gonadotropins, thereby inhibiting ovulation, increasing cervical mucus levels, and causing changes in the endometrium [181]. The ring has an outer diameter of 54 mms and is made from poly(ethylene–vinyl acetate) (PEVA) and magnesium stearate [182]. The core contains etonogestrel and EE, which is surrounded by a sheath layer of PEVA [183]. One ring is used per cycle, with a 1-week ring-free period between uses [181]. NuvaRing® has a Pearl Index of 1.18 (number of pregnancies per 100 woman years) and overall efficacy of 99.1% [182]. One of the advantages of contraceptive vaginal rings over oral medication is that the steroid concentration remains uniform throughout the day [183]. In addition, because the contraceptive is administered topically, a lower dose of the steroid can be used since administration avoids the hepatic first-pass and gastrointestinal interference [183]. NuvaRing®, however, is allegedly associated with causing 83 wrongful deaths, in addition to resulting in side effects such as blood clots, strokes, heart attacks, and cancer [184]. Today, NuvaRing® is sold in over 50 countries worldwide, and it is estimated that over 44 million prescriptions have been filled in the U.S. alone since 2002 [185].

7.1. Future Direction of Reproductive-Based Therapeutics

The HIV/AIDS pandemic is one of our generation's most severe health threats. In 2015 alone, the WHO estimated that 36.7 million people were living with HIV, with a total of 2.1 million new infections and 1.1 million deaths resulting from AIDS-related problems

[189]. While much work has been done to develop an HIV vaccine, a highly effective candidate remains to be identified [190]. For this reason, many researchers have turned to HIV microbicides as the future of prophylactic treatment. In particular, microbicide-based vaginal rings offer advantages over other HIV prevention methods, such as condoms, by providing discreetness and female control [190]. While a microbicide-based vaginal ring has yet to become commercially available, current efforts show promising results. The following discussion will highlight two such vaginal rings that are currently in development.

In 2004, the International Partnership for Microbicides (IPM) began developing the first vaginal ring capable of delivering a prophylactic HIV-1 antiretroviral (ARV) drug [191]. Because the majority of individuals infected with HIV-1 are women, developing a preventive treatment specifically geared toward women would significantly aid in lowering infection rates [192]. The ring is formulated from silicone and contains 25 mgs of dapivirine (Janseen Sciences Ireland UC, Cork, Ireland), a non-nucleoside reverse-transcriptase inhibitor (NNRTI) ARV drug, which is released over a month-long period [192]. Since the dapivirine ring acts locally, potential side effects resulting from dapivirine are minimized, while also providing a discreet and convenient treatment [192]. In a phase III study conducted by IPM, researchers found that consistent use of the dapivirine ring reduced HIV risk by at least 56% [191]. Approval for the ring is expected in late 2018 or 2019 [191]. Moreover, a dapivirine-contraceptive ring that also contains levonorgestrel is currently being investigated in an ongoing phase I trial [193].

Another microbicide vaginal ring currently in development is the VersaRing® technology platform (Auritec Pharmaceuticals, Santa Monica, CA, USA). Studies have demonstrated that herpes simplex virus type 2 (HSV-2) infection increases the risk of contracting HIV-1, suggesting that a dual HIV-1 and HSV-2 prophylactic treatment could effectively lower infection rates for both diseases [194]. This novel platform design allows for prevention against both HSV-2 and HIV-1 using a pod intravaginal ring (IVR) system, which allows for multiple polymer-coated drug cores (or "pods") to be positioned within a nonmedicated, silicone elastomer ring [195]. *In vivo* studies performed in both sheep and rabbits demonstrated that topical, sustained-release of both tenofovir, an NNRTI used in HIV-1 prevention and treatment, and acyclovir, an antiviral commonly used in treating HSV-2, from poly-DL-lactide-coated pods could be achieved using the platform [195]. Because the release rate of each drug is determined by factors such as the cross sectional area of the pod and number of delivery channels, up to ten drug dosages can be released at different rates [195]. Auritec Pharmaceuticals expects VersaRing® to launch in 2022 and is currently designing five different IVR formulations [195].

8. Skeletal System-Based Therapeutics

The history of musculoskeletal therapeutics can be traced back to the seventeenth century, when Dr. Job van Meekeren became the first documented person to successfully perform a bone graft in 1668 [196]. During the 1960s, the development of the demineralized bone matrix and bone morphogenetic protein by Dr. Marshall Urist revolutionized bone repair methods (Table 1) [27]. With the advent of polymers in the twentieth century, bone graft substitutes expanded to include both degradable and nondegradable polymers in products such as CORTOSS®, OPLA®, and IMMIX®, to name a few [197]. The following paragraphs will discuss three recently approved polymer-based bone grafts. Readers interested in further discussion of skeletal system-based therapeutics, including dental applications, are encouraged to refer to the provided references [198–209].

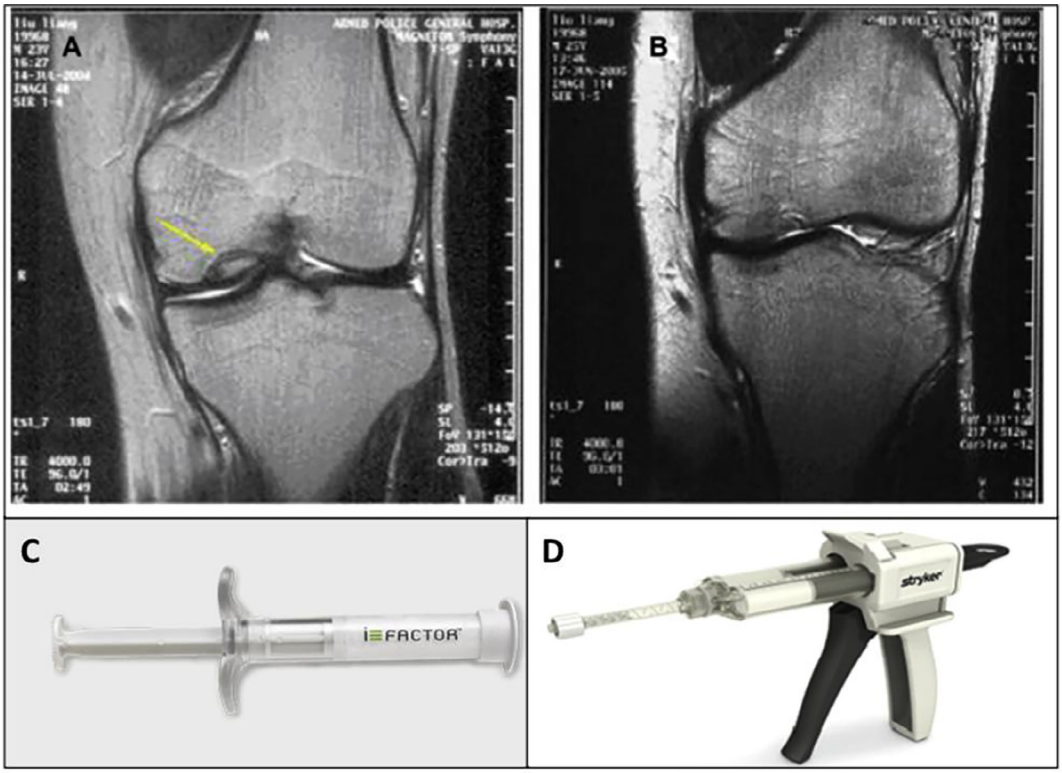

Fig. 7. Skeletal Therapeutics. **A.** The yellow arrow indicates the cartilage defect before surgical intervention [218]; **B.** Image of the same defect area shown in Fig. 7A six months following the MACI® procedure; **C.** i-Factor™ Peptide Enhanced Bone Graft [210]; **D.** Cortoss® Bone Augmentation Material [219]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Matrix-Induced Autologous Chondrocyte Implantation® (MACI®) (Vericel Corporation, Cambridge, MA, USA) is the first cellularized scaffold of its kind to be approved by the U.S. FDA for treating symptomatic, full-thickness cartilage defects (Fig. 7**A, B**) [40]. Each implant is manufactured using a biopsy of the patient's own healthy chondrocytes, which is then grown onto a Type I/III porcine collagen membrane scaffold [40]. Each implant contains at least 500,000 cells per square centimeter and can be trimmed by the surgeon to fit the precise size and shape of the defect site [40]. All patients undergoing the MACI® procedure must also adhere to a rehabilitation program following surgery [40]. Within 9–12 months following surgery, patients can resume their normal activities [40]. In a two-year prospective randomized trial comparing patient treatment outcomes from treatment with either MACI® or traditional microfracture (MFX) surgery, it was found that MACI® performed both clinically and statistically significantly better than MFX in treating cartilage defects [217].

i-FACTOR™ Peptide Enhanced Bone Graft (Cerapedics, Inc., Westminster, CO, USA), also referred to as i-FACTOR™ Bone Graft and i-FACTOR™ Putty, is the first and only bone graft to be FDA-approved for anterior cervical discectomy and fusion (ACDF) surgery (Fig. 7**C**) [210]. i-FACTOR™ Putty is composed of P-15, a synthetically derived protein found in human collagen, bovine anorganic bone material (ABM), and a hydrogel component containing glycerin, water, and sodium carboxymethylcellulose, which accounts for 41.8% of the putty [210]. Upon placement within the allograft ring, the P-15/ABM complex recruits both mesenchymal stem cells and other progenitor cells [210]. The recruited cells are then able to activate integrin signaling, resulting in osteoblast proliferation [210]. In a study comparing the efficacy of i-FACTOR™ Putty and autografts, patients treated with i-FACTOR™ Putty showed an overall statistically significant success rate of 68.75%, compared to a success rate of 56.94% in patients treated with a traditional autograft procedure [211].

Beyond serving as bone graft materials, polymers are also noted for their use as bone strengthening agents. Cortoss® Bone Augmentation Material (Stryker®, Malvern, PA, USA) is a bioactive microglass cement containing an amorphous calcium phosphate polymer ceramic that functions as a vertebral augmentation treatment (Fig. 7**D**) [212–215]. Cortoss® was FDA-approved for the treatment of vertebral compression fractures (VCF)s in 2009, making it the first approved alternative to PMMA [212,213,216]. Because Cortoss® is associated with a low viscosity, it disperses upon injection, allowing the cement to diffuse into microfractures [212,213]. Within 15 mins, Cortoss® can reach 75% of the compressive strength of normal cortical bone [123]. The bioactive properties of Cortoss® allow for the deposition of hydroxyapatite onto the cement, promoting redevelopment of host bone at the site of treatment [214]. In comparison to PMMA, Cortoss® has been shown to reduce pain faster and improve spinal function in less time [214]. In a two-year clinical study, patients receiving Cortoss® demonstrated an Oswestry Disability Index success rate of 96.7% at 24 months, while patients treated with PMMA had a success rate of 88.4% [216].

8.1. Future Direction of Skeletal System-Based Therapeutics

As previously discussed, polymer-based bone grafts, strengthening agents, and cell-based implants have helped improve treatment outcomes and restore mobility for many patients. With that said, the field of skeletal therapeutics still falls short in providing effective therapies for diseases such as osteoporosis, osteomyelitis, Rickets, and acromegaly, to name a few. It is estimated that between 1990 and 2010 the number of disabilities resulting from musculoskeletal diseases rose by 45%, due in part to the growing global population of seniors [220]. We will next consider two potential polymer-based therapies that could potentially fill some of these unaddressed needs.

In 2015, Cong et al. reported on the development of a potential polymer-based osteomyelitis treatment using vancomycin-loaded NPs prepared from micelle-forming PLGA-block-PEG-alendronate copolymer [221]. Current osteomyelitis treatments involve surgical intervention, which can lead to additional infection, or long-term antibiotic dosing, which may result in undesirable side effects (i.e., unfavorably modifying the gut biome) and possible drug resistance [221]. Inspired by these limitations, the PLGA-PEG micelles developed in this study offer a potentially noninvasive treatment for osteomyelitis with a reduced side effects profile [221]. Alendronate (ALN) is a bisphosphonate that binds to the calcium ions of hydroxyapatite (HA), the principal inorganic component of bone (ALN has been known to cause bone to be excessively brittle in some cases, however) [221]. Conjugating ALN onto the surface of the micelles allows the NPs to overcome the blood-bone marrow barrier and effectively deliver antibiotics directly to the infection site [221]. From the *in vivo* study results, the researchers concluded that the NPs inhibited the growth of *Staphylococcus aureus*, the more prevalent pathogen found in osteomyelitis, without causing cytotoxicity [221]. Moreover, the micelles also demonstrated their affinity to HA and showed potential as a targeted osteomyelitis treatment, although these results have yet to be confirmed *in vivo* [221].

Polymeric drug delivery systems are also being explored for treating osteoporosis. Takeuchi et al. recently published a paper describing a PLGA-based iontophoretic transdermal delivery system [222]. Designed to address the limitations of oral 17β-estradiol (E2) administration, a drug commonly used in hormone replacement therapy for treating postmenopausal osteoporosis, this polymer-based system uses NPs to avoid the hepatic first-pass effect, which is unavoidable via the oral route [222]. To improve skin permeability of the E2-loaded NPs via iontophoresis, the particles were given a high surface charge density [222]. In this study, both bare NPs and PVA-coated NPs loaded with E2 were prepared using antisolvent diffusion methods and preferential solvation [222]. The results from this study showed that NPs with a high surface charge number density allowed for better transdermal iontophoresis, in addition to increasing both cancellous and cortical bone mineral density [222]. In conclusion, the researchers determined that the iontophoretic transdermal delivery system developed in this study could serve as a potentially clinically translatable therapy for osteoporosis [222].

9. Neoplasm-Based Therapeutics

Since the 1960s, polymers have been recognized as attractive cancer therapeutic vehicles because of their selective-targeting and controlled-release properties [223]. Many polymers since have been modified through a variety of methodologies (i.e., functionalization, bioconjugation) to achieve increasingly more optimal targeting and drug release profiles. Despite the fact that approximately 9,000 papers discussing polymer-based cancer treatments have been published over the past eighty years, only 95 (or 1%) of these potential treatments have entered clinical trials [223]. Moreover, it is of note that other nanocarriers, such as monoclonal antibodies and liposomes, also demonstrate a similarly disappointing trend in clinical translation, further exemplifying the challenge of developing successful cancer nanotherapeutics [223]. Despite the obstacles associated with this field, however, several of these therapies have been successfully translated, as we will explore in the following discussion. For further discussion of developing technologies and future directions of the field, readers can refer to the following citations [224–235].

Doxil® (Alza Corporation, Mountain View, CA, USA), which is marketed as Caelyx® in Europe, became the first commercially available liposomal-based drug in 1995, following its U.S. FDA approval for treatment of AIDS-related Kaposi's Sarcoma (Fig. 8**A**) [32]. Today, Doxil® indications have expanded to both ovarian cancer and multiple myeloma [236]. The current formulation of Doxil® contains doxorubicin hydrochloride, an anthracycline topoisomerase II inhibitor, within a sterically stabilized, or STEALTH®, liposome [236]. The STEALTH® liposomes are coated with PEG, which allow for improved stability and circulation time, in turn reducing side effects such as cardiotoxicity, myelosuppression, alopecia, and nausea [237,238]. Compared to free DOX, which distributes systemically, Doxil® is targeted to tumors by the EPR effect and released only after the liposome degrades [239]. It is also thought that Doxil® is metabolized through a different mechanism than free DOX, which may also account for its comparative effectiveness [239]. Similar to Doxil®, a number of PEGylated drugs have been clinically translated, including Adagen®, PegIntron®, Mircera®, and Cimzia® [240].

Abraxane® (Celgene, Summit, NJ, USA) offers another example of a polymer-based chemotherapeutic (Fig. 8**B**). Initially approved by the U.S. FDA in 2005 for treating metastatic breast cancer, Abraxane® has since expanded its use for treating both non-small cell lung cancer and pancreatic adenocarcinoma [241]. For the purposes of this review, Abraxane® can be considered a natural polymer because of the presence of human serum albumin. Because PTX is poorly soluble in water, traditional PTX formulations use lipid-based solvents, such as Cremophor EL®, to improve solubility; however, these formulations are limited by their potentially severe toxicities, which can result in conditions such as anaphylaxis, hyperlipidemia, and irreversible neuropathy [242]. Abraxane® addresses the limitations of lipid-based solvent formulations by binding PTX with human serum albumin, a protein carrier of hydrophobic molecules in the blood plasma [242]. With annual sales in 2013 reaching $649 million, Abraxane® is one of the most common chemotherapeutic drugs used in treating metastatic breast cancer [243]. Also encouraging is a PTX-loaded recombinant polypeptide nanoparticle that outperforms Abraxane® in murine cancer models, which was published in 2015 [244].

9.1. Future Directions of Neoplasm-Based Therapeutics

One reason explaining why potential cancer nanomedicines have such a low rate of clinical translation is that formulations are often excessively complex with many desired functionalities to the point that seeking FDA approval is an arduous process, stifling clinical translation. As increasingly complex nanomedicines receive approval and researchers are able to demonstrate substantial equivalence to previously FDA-approved technologies, nanomedicine formulations with a great deal of functionality will be able to undergo the approval process in a more timely fashion. A thorough investigation of how clinical translation in a burgeoning field is stifled, due to the inability to demonstrate equivalence to previously translated technologies (i.e., 510(k) clearance), would be worthwhile. For these reasons, much of the work currently being done in cancer therapeutics remains largely in the preclinical and early clinical stages. In the following discussion, we will highlight several notable and promising multi-targeting cancer technologies currently in early stages of development.

Nanospectra Biosciences, Inc. (Houston, TX, USA) is currently developing a hyperthermia treatment using specially designed NPs that have been engineered to have a surface plasmon resonance capable of absorbing infrared (IR) light and subsequently converting the energy to heat [247]. NPs that absorb in the IR or near-IR (NIR) wavelengths are desirable because biological tissues attenuate electromagnetic radiation to a lesser degree in this region, thereby enabling crosstalk with the NPs through tissue on demand via light on the order of a few centimeters [248]. Termed as AuroShell® particles, these NPs are about 150 nms in diameter and consist of a 120 nm silica core surrounded by approximately 15 nms of gold, providing the AuroShell® particles with their unique optical extinction properties [247]. To improve circulation time, the AuroShell® particles are made with PEG [247,249]. Following accumulation at the tumor site by the EPR effect, which occurs approximately 12–24 h after administration, NIR laser energy is applied at the tumor site using an interstitial fiber optic probe, as the tumor is often deeper than a few centimeters in tissue [249]. *In vitro* and *in vivo* studies showed no indications of toxicity [249]. Currently, Nanospectra Biosciences, Inc. is conducting clinical studies of AuroLase® Therapy in both refractory and recurrent head and neck cancer and prostate cancer; other cancer indications are still in development [247]. For metastatic cancer, NIR therapy is further limited since all tumor locations must be identified prior to NIR application. While obstacles such as these complicate NIR use as a broad-spectrum cancer therapy, NIR still demonstrates potential as a cancer therapeutic for non-metastatic cancers located close to the skin.

As discussed previously, an emerging trend in cancer nanomedicine is using the selective-targeting properties of polymers as an alternative to systemic chemotherapy and radiation. Branching off of this idea, Cantu et al. showed that using conductive polymer-based NPs as photothermal therapy (PTT) agents may potentially offer a safer, more effective alternative to radiation and chemotherapy [250]. Because PTT relies on NIR light to excite agents that convert light into heat, it can be targeted specifically to cancer cells,

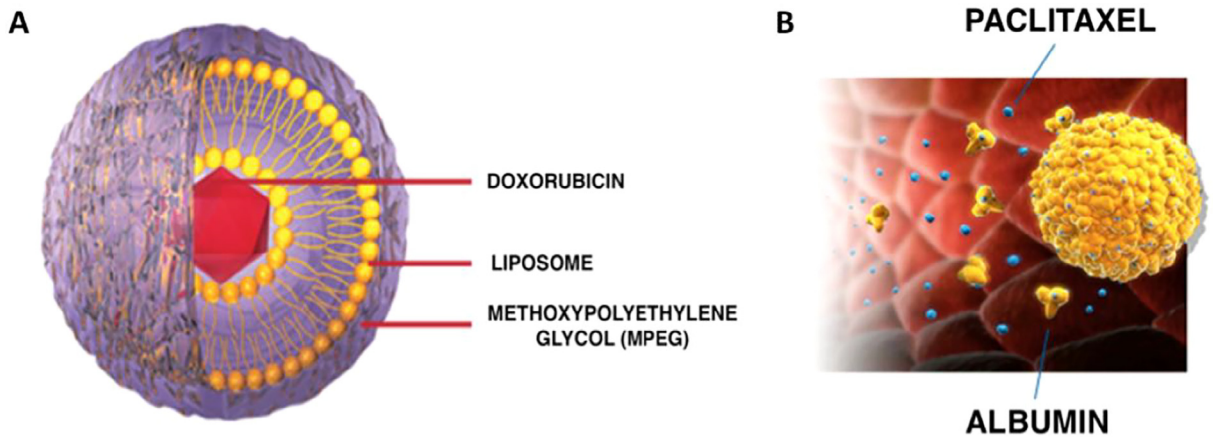

Fig. 8. Neoplastic Therapeutics. **A.** Doxil® [245]; **B.** Representation of Abraxane® in the bloodstream [246].

while minimizing the risk of harming healthy tissue [250]. The reason why cancer cells are more susceptible to cell death via PTT is because tumors are generally not as well-vascularized (hence their hypoxic tendencies) which is the main mechanism that regulates tissue temperatures. In this particular study, the researchers tested whether conductive polymeric NPs (CPNP)s made of poly(diethyl-4,4′-{[2,5-bis(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-1,4-phenylene] bis(oxy)}dibutanoate) and poly(3,4-ethylenedioxythiophene) stabilized with 4-dodecylbenzenesulfonic acid and poly (4-styrenesulfonic acid-co-maleic acid) had greater conversion efficiencies than gold-based PTT agents using an MDA-MB-231 *in vitro* cancer model [250]. CPNPs can be modified to absorb NIR light by a variety of ways, including manipulation of the polymer chain backbone [250]. Previous studies have not investigated CPNPs as PTT agents because of the NPs' inability to dissolve in aqueous solutions; however, this study used oxidative-emulsion polymerization to overcome the challenge of insolubility [250]. Because the CPNPs tested in this study demonstrated conversion efficiencies greater than both gold nanorods and gold NPs, the researchers concluded CPNPs could potentially be used as PTT agents [250].

In the past several years, theranostic nanomedicine has become a growing research interest. Recently, Jia et al. reported on the development of a theranostic photodynamic therapy (PDT) treatment that showed promising *in vivo* results [251]. PDT offers a less-invasive cancer treatment option than surgery or radiation; for this reason, it is often used in treating early-stage cancers and pre-cancers [252]. However, current PDT treatments are limited by the hydrophobicity of most photosensitizer molecules, which can cause aggregation in aqueous solutions, in addition to poor tumor selectivity [251]. To address these limitations, the researchers developed a nanoparticle system by conjugating protoporphyrin IX (PpIX) and methoxy-PEG using a glycol chitosan (GC) linker [251]. Referred to as GC-PEG-PpIX NPs, the NPs self-assemble in aqueous solutions and then accumulate at the tumor site by the EPR effect, after which the particles undergo adsorption onto the cell membranes [251]. Upon irradiation, PpIX fluoresces and produces singlet oxygen radical molecules, disrupting the cell membrane and allowing PpIX influxion into the cell, causing cell death by way of disrupting the cell membrane [251]. The researchers of this study concluded that the results from the *in vivo* studies demonstrated potential for clinical use, although further experiments are necessary [251].

In addition to the exciting developments taking place in preclinical chemotherapeutics research, encouraging results can also be seen in clinical studies. Cerulean Pharma (Waltham, MA, USA) is currently developing CRLX101 (formerly known as IT-101), a nanoparticle-drug conjugate containing camptothecin (CPT), a powerful chemotherapeutic limited in use by its high toxicity and poor water solubility [253,254]. In CRLX101, CPT is conjugated to cyclodextrin-PEG copolymer by linker molecules, enabling CPT delivery to be localized at the tumor site [253]. In human studies, CRLX101 was shown to accumulate in biopsied gastric tumors, as opposed to adjacent, healthy tissue, suggesting that CRLX101 acts through the EPR effect [253]. While CRLX101 was shown to be safe in treating metastatic renal cell carcinoma (RCC) during phase I clinical trials, results from phase II clinical trials in 2016 reported that there was no statistically significant difference in median progression free survival rates in RCC patients treated with co-administration of CRLX101 and Avastin® versus patients who received standard of care therapy [255]. CRLX101 is also currently being investigated in a phase I/II trial in patients with relapsed/refractory small cell lung cancer [256].

Similar to CRLX101, BIND-014 is another chemotherapeutic nanoparticle also currently in the clinical trial phase. BIND-014 is a novel targeted nanoparticle treatment being developed by BIND Therapeutics (Cambridge, MA, USA) consisting of polylactic acid polymer and docetaxel, a cancer drug already approved for use in treating several solid tumor cancers [257]. The outer surface of BIND-014 is coated with PEG and contains ligands that target prostate-specific membrane antigen (PSMA), a surface protein expressed by both prostate cancer cells and developing cancer vasculature in most nonprostate solid tumors, allowing BIND-014 to selectively target cancer cells [258]. In preclinical studies, higher levels of docetaxel were shown to accumulate intratumorally following BIND-014 administration compared to that resulting from equal dosages of docetaxel [257]. Results from the phase I clinical trials reported not only the safety of BIND-014 but also confirmed these same preclinical results [257]. BIND-014 is currently undergoing a phase II clinical trial in patients with solid tumors [259].

10. Conclusion

Polymer-based therapeutics have not only expanded the impact of modern medicine but have also enhanced the accessibility of patient care. The adoption of polymers in both the medical device and pharmaceutical industries further speaks to their unparalleled properties as biomaterials. With the emerging field of sustained release drug delivery, therapeutics can be better tailored for application in areas lacking access to permanent medical infrastructure. On the other side of the spectrum, polymer-based medical devices, such as the TAXUS® Stent, Iluvien®, and C-Plus™ PEEK IBF System, have broadened the capabilities and efficacy of disease treatment. However, despite the success and promise of polymers in medicine, the global toll of disease remains a growing concern today. According to the WHO, in 2015 alone, ischemic heart disease and stroke made up the leading causes of death worldwide [260]. In this same year, lower respiratory infections, chronic obstructive pulmonary disease, and cancers of the trachea, bronchus, and lung caused over 8 million deaths [260]. Data such as this underscores the need for new and innovative approaches for disease treatment. To better target the global burden of disease, we suggest that polymers may offer a novel approach to combatting these diseases, while also continuing to expand the accessibility of medical care worldwide.

Acronyms

γ-PGA-g-Arg: poly(γ-glutamic acid)-g-arginine; ABM: anorganic bone material; ACDF: anterior cervical discectomy and fusion; ALN: alendronate; AmB: amphotericin B; AMI: acute myocardial infarction; ARV: antiretroviral; AZM: azithromycin; BBB: blood-brain barrier; BCB: blood-cerebrospinal fluid barrier; BDI: bioerodible dexamethasone implant; BTB: blood-tumor barrier; CEA: cultured epidermal autograft; CENP: curcumin-loaded Eudragit® E100 nanoparticle; CNS: central nervous system; CNTF: ciliary neurotrophic factor; CPNP: conductive polymeric nanoparticles; CPT: camptothecin; CRC: colorectal cancer; CSF: cerebrospinal fluid; CS-N-Arg: chitosan-arginine conjugate; CUR: curcumin; CVA: cerebrovascular accident; CVD: cardiovascular disease; CYA: cyclosporine-A; DFU: diabetic foot ulcer; DME: diabetic macular edema; DOX: doxorubicin; DSS: dextran sulfate sodium; DXM: dexamethasone; ECT: Encapsulated Cell Therapy; E2: 17 β-estradoil; EE: ethinyl estradiol;EE100: Eudragit® E100; EPR: enhanced permeability and retention; FA: fluocinolone acetonide; GBM: glioblastoma multiforme; GC: glycol chitosan. GI: gastrointestinal; GLP-1: glucagon-like peptide-1; HA: hydroxyapatite; HCC: hepatocellular carcinoma; HDL: high-density lipoprotein; hPTH(1-34): human parathyroid hormone fragment (1–34); HSV-2: herpes simplex virus type 2; HUD: humanitarian use device; IBF: intervertebral body fusion; IOP: intraocular pressure; IBD: inflammatory bowel disease; IPM: International Partnership for

Microbicides; IUD: intrauterine device; IUS: intrauterine system; IVR: intravaginal ring; LNG: levonorgestrel; MACI®: Matrix-Induced Autologous Chondrocyte Implantation®; MacTel: macular telangiectasia; MFX: microfracture; MNP: magnetic nanoparticle; MSN: magnetic silica nanoparticle; NIR: near infrared; NNRTI: non-nucleoside reverse transcriptase inhibitor; NP: nanoparticle; NSC: neural stem cell; PDT: photodynamic therapy; PEG: polyethylene glycol; PE-PEG: 1, 2-Distearoyl-*sn*-glycero-3-phosphoethanolamine-N-(methoxy(polyethylene glycol)-2000); PEVA: poly(ethylene vinyl acetate); PFO: patent foramen ovale; PLGA: poly(lactic-co-glycolic) acid; PLL: poly-l-lysine; PM: polymeric micelle; PMMA: poly(methyl methacrylate); PpIX: protoporphyrin IX; PTT: photothermal therapy; PTX: paclitaxel; PVA: polyvinyl alcohol; RA: receptor agonist; RCC: renal cell carcinoma; VBR: vertebral body replacement; VCF: vertebral compression fracture; SCI: spinal cord injury; SMP: shape-memory polymer; TTS: Transdermal Therapeutic System.

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