Expert Opinion

Using liposomes to target infection and inflammation induced by foreign body injuries or medical implants

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Importance of the field: Foreign body (FB) injuries occur under many circumstances: at work, when practising a hobby, in car accidents, or in violence-afflicted zones. Owing to the nature of these injuries, they are not restricted to a certain part of the body and may affect several organs simultaneously. In general, an FB will be surgically removed when it is a cause of pain or infection or when jeopardizing a critical biological function. However, in many cases removing the FB is not possible owing to risk of harming adjacent delicate tissue. Furthermore, often when surgically removing the FB, microscopic fragments or debris remain at the site of invasion, becoming a cause of pain and recurring infection and inflammation. FB-related complications can also originate from micro- or nanoparticles released by degradation of medical implants. The use of advanced drug delivery technologies to target the tissue surrounding the FB, or the FB itself, may be of therapeutic benefit. Liposomes, vesicles with an aqueous core entrapped in one or more lipid bilayers, are widely used as drug delivery systems. Previous studies show that nanoliposomes can effectively target infected and inflamed tissue. The working hypothesis of this paper is that nanoliposomes, of specific lipid composition, may be used to target FB under conditions of inflammation.

Areas covered in this review: A comprehensive literature review regarding the use of liposomes for targeting and treating infection and inflammation, as well as a prospective on conjugates that can improve FB targeting *in vivo.*

What the reader will gain: The article aims to assess whether nanoliposomes loaded with a therapeutic compound may be advantageous for treating FB-related pathologies.

Take home message: Nanoliposomes are promising candidates for targeting FB-induced infection and inflammation. Certain properties, related to the micro-anatomy and physiology of inflammation as well as to the liposome physicochemical properties, make possible 'passive' targeting of the FB region. Conjugating specific ligands to the surface of the liposomes can improve their efficacy by adding an element of 'active' targeting. Despite the great clinical need, the use of nano-based technologies to target and treat FB-induced infection, inflammation and pain has not been exploited yet. The use of drug-loaded nanoliposomes for this application seems to be most promising and should be evaluated with high priority.

Keywords: antibiotics, dexamethasone, foreign body, infection, inflammation, liposome, medical device, nanotechnology, steroid

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Article highlights.

- FB injuries are highly prevalent at work places and in violence-afflicted zones, inducing inflammation, infection and pain.
- The ability of liposomes to target a single or multiple sites of infection and inflammation, as well as to be stable carriers for a wide range of therapeutic agents, points to their high potential for treatment of FB-induced medical complications.
- Targeted delivery systems have been shown to reduce long-term indirect costs associated with complications and side effects of conventional treatments.
- Treating FB injuries with advanced delivery technologies has been under-researched, leaving a large area for innovation and patenting.
- Platform technologies, which have been successful in treating diseases that share similar biological features, may prove successful in treating this medical condition.

This box summarizes key points contained in the article.

1. Foreign bodies

1.1 Foreign body injuries

Foreign body (FB) injuries can occur while practising almost any daily activity at work or home. Examples include injuries that require minimal medical attention: penetration of splinters when grasping a banister and climbing stairs, opening a box, or handling wood. However, FB injuries can also be serious, causing severe pain, infection and inflammation, thus requiring professional medical attention. The aim of this report is to describe common FB injuries that require medical attention, their treatments, and the possibility of using liposome-based technologies to improve the treatment of these injuries. FB injuries associated with obstruction of airways [1] or of the gastrointestinal tract [2] are not addressed.

1.2 Common causes of foreign body injuries

Foreign body wounds that require medical attention exceed 150,000 cases annually in the US alone [3-5]. Although non-fatal, these injuries caused increased morbidity, with 62% of the patients missing 5 days of work and > 25% missing up to 30 days of work (the remainder missed longer periods of time) [3]. FB injuries are the second most prevalent occupational injury among teenage employees (ages 15 – 19 years), after lacerations, with a similar prevalence as sprains and strains [6,7]. Naturally, these injuries occur more often among workers whose responsibilities involve physical tasks [8-10].

Fifty-nine per cent of eye injuries occurring at work are induced by an FB [11-13]. By comparison, among eye injuries occurring at home or recreation, FB injuries account for only 20% of all eye injuries [14]. Malik *et al.* [15] reported that in nearly 20% of eye injuries occurring at workplaces in Delhi, India, the perforating FB was retained in the eye.

Car accidents are another common cause of FB injuries, caused mainly by penetration of glass or by other propelled objects during the collision [16,17]. Locating and removing all the glass particles is extremely complicated and may cause more damage than benefit [18-20]; therefore, in many cases the FB remains undetected in the body until it starts to induce secondary discomfort and/or inflammation [19,20].

Foreign body injuries are highly prevalent in violence-afflicted zones, affecting both civilians and combat forces. Injuries can be caused by shrapnel [21,22], firearms [23] and other objects propelled by blasts (including even body parts of a suicide bomber) [22,24]. These injuries affect various parts of the body (see **Figure 1**). In the continuing wars in Iraq and Afghanistan, most injuries to combat soldiers are caused by FBs spread by improvised explosive devices [25].

A previous study [26], dealing with blast injuries, demonstrated that the extent of injury depends mainly on the explosive power, the distance of the injured patient from the site of detonation, the nature of the space in which the explosion occurred (closed or open) and the nature of the shrapnel within the bomb. Penetrating injuries are often accompanied by other morbidities such as burns, cuts and fractures [26]. Thus, the FB may be discovered long after the injury, mostly owing to patients' discomfort [27].

In general, shrapnel is inert owing to the high temperature at which it enters the body, and it rarely causes an immediate systemic inflammatory response [28]. Some metals have biological activity. Tungsten alloys, for example, which are used to strengthen hand grenades and bullets, can cause systemic inflammation and have been shown to propagate rhabdomyosarcoma [29]. Injuries from reactive metals warrant early removal. However, most other FBs are removed by surgery only when endangering neurovascular bodies or joints, or when they induce systemic toxicity or local tissue complications (e.g., abscess, FB granuloma) [22,30].

Foreign body injuries in the eye are very common in violence-afflicted zones [31,32]. Mines *et al.* [32] showed that people at distances of up to ~ 100 m from a bomb detonation suffered from severe ocular injuries, including lid/brow lacerations, open globe injuries, orbital fractures, retinal detachment, and others. Objects propelled by the blast accounted for most of the injuries (also referred to as secondary blast injuries). Thach *et al.* [31], studying the characteristics of intraocular FB injuries (IOFB) among soldiers participating in Operation Iraqi Freedom, found that there were on average 1.7 FBs per injured eye; these were made of metal (68%), glass (14%), stone/cement (14%), or other materials. Most of the soldiers were operated on after 20 days or more for FB removal. Such injuries are usually associated with other FB injuries to the upper extremity, face, lower extremity, and neck [31]. The use of ocular protection (i.e., specialized glasses for combat use) has been shown to decrease both severity and occurrence of such injuries [33].

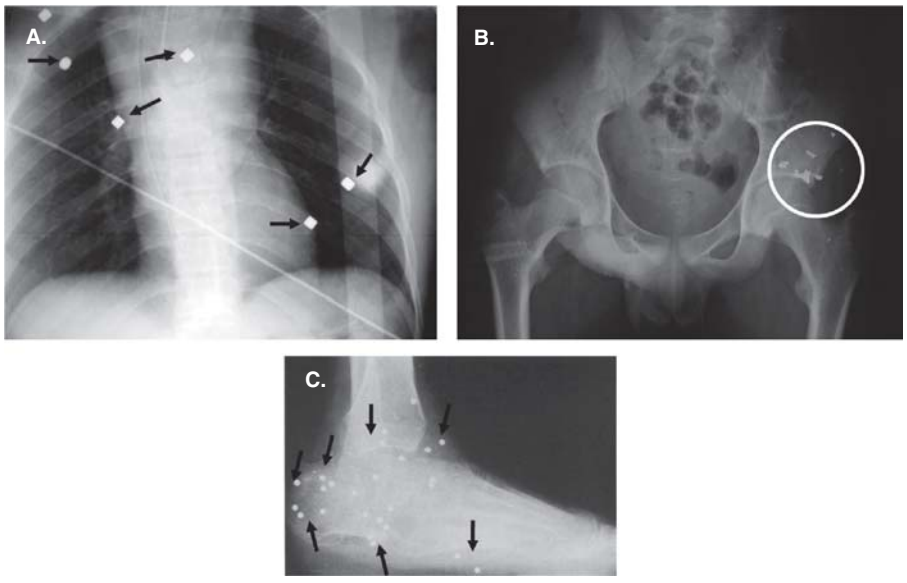

Figure 1. Shrapnel wounds are highly prevalent in violence afflicted regions, affecting different organs and tissues. The characteristics of the penetrating foreign body can be of different material, size and structure. X-ray images of shrapnel wounds in the **(A)** chest cavity, axilla and mediastinum, **(B)** iliac bone, adjacent to the hip joint and **(C)** the ankle and foot.

1.3 Foreign body reaction

Foreign body reaction is a nonspecific multicomponent immune system reaction that involves cellular, humeral and complement pathways [34]. This process is evoked when a foreign material (FB injury or implanted medical device) enters the body. When the FB penetrates the body a wound occurs. Although it takes several days/weeks for the wound to heal, the surface of the penetrating FB is covered by a layer of adhering proteins within several hours [34-36]. Surface chemistry, structure and charge play an important role in the type and extent of protein adhesion [34,36]. In the next step cells anchor to the proteins and coat the FB [36]. This initial reaction is part of an acute inflammatory response to the FB, leading, in some cases, to chronic inflammation [36].

As part of the immune response to the FB penetration, pro-inflammatory cytokines are released, increasing the permeability of blood vessels near the site of the FB invasion. This enables platelets and white blood cells to migrate to the site of the FB and release inflammatory mediators and angiogenesis factors [34]. Coagulation occurs around the FB, in which fibrinogen is hydrolyzed to fibrin by thrombin. This leads to the formation of a dense fibrin network and a non-degradable capsule around the FB [34]. The mediators released by the coagulation and by the migrating cells further trigger the migration of neutrophils and macrophages to the site of injury, increasing the biologic response to the FB. Over several days, the zone in which the FB resides becomes a site for leukocyte, phagocyte and fibroblast activity, releasing pro-inflammatory cytokines. Furthermore, adsorption of antibodies or of complement components (e.g., C3b proteins) to the FB leads to activation of the classical or alternative complement pathways [34]. Throughout this process new 'leaky' vasculature is formed at the site of the FB invasion as a consequence of the angiogenic factors released at the site of inflammation [34,36]. This compromised and leaky vasculature can be utilized to target passively the FB using drug delivery systems such as nanoliposomes or other nanoparticles.

The adsorbed antibodies, complement factors and fibrin promote phagocytosis of the FB. As the FB is too large for phagocytosis by macrophages, these cells fuse to form multinucleated giant cells [34], being of either round (Langhans type, in the case that < 20 cells fuse) or of irregular configuration (FB type, in the case that > 20 cells fuse) [34,37]. This process causes a chronic inflammation that can lead to the formation of a granuloma or absorption of native surrounding tissue [38].

1.4 Foreign body reaction to implanted medical devices and aesthetic implants

It is estimated that ~ 8 – 10% of all Americans have an implanted medical device (IMD) [39]. FB reaction to an IMD may occur for several reasons, including a reaction to the device itself or to degradation products of the IMD [40]. Bostman and co-workers [41,42], studying patients with implanted orthopedic devices (made of polyglycolide, polylactide, or glycolide-lactide copolymers), found that 6.1% suffered from an inflammatory FB reaction to the implants, which resulted in osteoarthritis in a small number of these patients. In a different scenario, residuals of packing materials remaining on the surface of biologically inert medical devices

caused an FB reaction [43]. Klinge *et al.* [44], ranking the inflammatory potential of meshes used to repair abdominal wall defects, found that polypropylene induces the least inflammation and adjacent connective tissue formation, followed by polyester; whereas implants made of polytetrafluoroethene (PTFE) induced most inflammation and connective tissue formation. In many cases, the inflammatory process persisted for many years, even after removing the meshes.

This inflammatory process was also seen in the first generation of silicone cochlear implants [45]. In this case the inflammation passed after removing the implant, thus suggesting that the inflammation was induced by the device itself, not by degradation products of the implant.

The use of injectable aesthetic micro-implants is extremely common. In some cases these implants induce FB granulomas [46-48]. Kawamura *et al.* [49] reported a case of FB reaction to a polyacrylamide-based skin filler; this was most probably due to the chemical composition of the product.

The FB reaction to implanted medical devices is especially problematic, as they are needed for everyday use by the patient and may even be necessary for the patient's survival (e.g., defibrillators or pacemakers). Therefore, a long-term treatment to manage FB reactions is warranted, with an advantage for localized and targeted drug delivery over systemic treatments.

2. Imaging the foreign body

Determining the exact location of an FB is not an easy task, as it may be made of radiolucent materials. In other cases, despite the fact that the FB is made of detectable materials, it may not be large enough to generate a sufficient contrast in an imaging device [50]. Not all imaging technologies may be used for detecting an FB; for example, MRI cannot be used in cases where the FB is suspected to be of magnetic-metallic composition.

Foreign bodies residing in the lungs can be diagnosed by X-ray or by CT of the chest, or, if large enough, by selective intralobular measuring of blood oxidation levels [26]. In brain injuries, CT examination, especially three-dimensional CT reconstruction of the skull, conveys a good understanding of the mechanism of injury and the location of the FB [26].

In most other areas of the body, FBs can be detected by combining X-rays and CT scans or by the use of ultrasound [51,52]. The use of positron-emission tomography-CT (PET-CT) showing sites of biological activity can be highly useful for detecting a small concealed FB [53].

This combination gives the treating team an understanding of the nature of the material of the FB, its location, the immune response, and any organs that are endangered by the FB, thus allowing planning of the best medical interventions needed to treat the patient.

3. Treating foreign body injuries

The surface of the skin, through which the FB enters, is not sterile; therefore, patients are usually administered prophylactic antibiotic therapy for several days using broad-spectrum cephalosporins [26]. Shrapnel is removed when needed and whenever its surgical removal will not endanger nearby delicate tissue, such as nerves or blood vessels. If the FB affects the proper function of a vital organ or circulation it must be removed immediately. **Figure 2** presents the compromised blood flow through an artery in the axila resulting from pressure imposed by an invading FB. This shrapnel was removed and the blood flow was restored.

Shrapnel fragments can migrate to other locations in the body, usually by means of the blood or lymphatic vessels [26]. This migration risk does not always mandate excision; for example, Gasparovic *et al.* [54], treating a poly-traumatized child, decided not to remove an intra-cardiac shrapnel fragment, instead using three-dimensional CT to monitor the state and exact location of the fragment. A similar approach was described by Symbas *et al.* [55], showing that patients with intra-cardiac missile shrapnel tolerated the object well for a 15-year follow-up period.

In orthopedic injuries, when fractures are involved (including open or closed fractures), penetrating injuries can become infected, requiring repeated debridement and therapy with long-term local and systemic antibiotics [26].

In ocular invasion, several studies have shown that delaying the removal of intraocular foreign bodies for > 24 h after penetration results in increased inflammation and damage to vision [56,57]. Knox *et al.* [58] showed that direct administration of antibiotics to the eye, before the removal of intraocular foreign bodies, helps preserve the eye and prevent harmful infection. In some cases, eye injuries that are thought to be minor by the patient, and are therefore neglected, can result in long-term inflammation and eye damage [59]. This fear has dictated the use of topical and systemic administration of antibiotics to injured personnel in the war in Iraq, decreasing long-term damage to the eye [60].

Even in cases where the FB is removed, especially in cases of an FB made of organic materials, minor fragments may remain in the injured location, thereby inducing recurring inflammation [59]. Using advanced delivery vehicles to target accurately the diseased site and then release drugs in a therapeutically effective manner would improve the outcome of the treatment.

4. Using liposomes to target infection and inflammation

Liposomes have been studied over the past 40 years as delivery vehicles for a broad spectrum of drugs and biological agents, including small molecules, peptides, proteins, nucleic acids and vaccine antigens. The attractiveness of liposomes as drug carriers stems from: their good biocompatibility (low toxicity, biodegradability, low immunogenicity); high drug loading levels; versatility in choice of the liposome lipid composition, size and lamellarity as well as methods of fabrication; and availability of good manufacturing practice (GMP)-grade

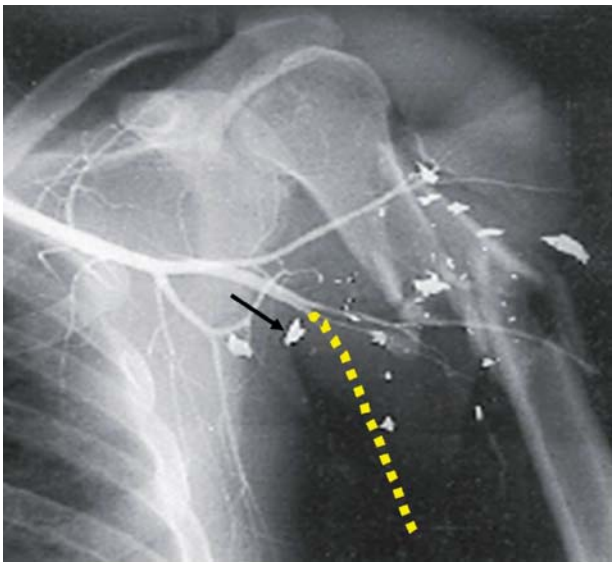

Figure 2. Foreign body injuries can induce different types of tissue damage. In this case a shrapnel fragment (marked with arrow) imposed pressure and blocked blood flow to a neurovascular vessel (dotted yellow line). In such cases the foreign body must be removed immediately to restore flow and prevent irreversible damage.

lipids – all making them good candidates for delivery of a broad spectrum of drugs, as is evident from the > 10 FDA-approved liposomal drugs [61,62]. One of the major breakthroughs in the evolution of liposomal formulations was the development of sterically stabilized liposomes (SSL) by including lipopolymers in the liposome membrane. Lipopolymers are anchored into the bilayer with the lipid portion of the molecule, and the polymeric portion of the molecule (such as PEG of molecular mass > 750 Da) extends out of the liposome, thereby 'coating' its surface [63,64]. Such PEGylation results in a long circulation time [65], a decrease in liposome uptake by macrophages of the reticuloendothelial system, and increased accumulation in sites of tumors, infection and inflammation [66,67].

Once the first liposomal product, the anticancer nano-drug Doxil™ (liposomal doxorubicin, produced by Johnson & Johnson, Mountain View, CA, USA), was approved by the FDA, the possibility of using drug delivery systems for site-specific drug delivery was demonstrated [68], thus paving the way to other nanoliposomal formulations.

4.1 Treatment of inflammation with liposomes

Inflammation is a vital physiological response, necessary for the survival of the organism. However, excessive or chronic inflammation incites tissue destruction and disease [69]. The inflammatory process is composed of three main phases: acute inflammation, immune response and chronic inflammation.

Owing to the damage inflammation can cause, there is a need to stop the inflammatory process from progressing into chronic inflammation. The obvious initial treatment is, when possible, clearing the noxious agent either by surgery or by eliminating the pathogen with drugs (e.g., antibiotics, fungicides). In chronic inflammatory pathologies there is no possibility of clearing the noxious agent. Therefore, the only solution is either immunosuppression or suppressing the inflammatory response [70-73]. Glucocorticosteroids (GC) are the drugs of choice in many diseases with inflammatory components. However, in most cases these drugs have unfavorable pharmacokinetics and biodistribution affecting their efficacy [74]. In fact, most of the drug that is administered systemically localizes in healthy (non-target) tissues if not rapidly excreted from the body. This implies that to reach pharmacologically active drug levels at the site of inflammation, high and frequent doses must be administered.

The great interest in nanoliposomal systems stems from their ability to accumulate in sites of increased vascular permeability. **Figure 3** presents a schematic representation of the compromised vasculature in inflamed tissue [67], enabling the extravasation of liposomes. This phenomenon is usually referred to as 'passive targeting'. Retention of liposomes at these sites corresponds to localized elevated drug concentrations [75,76].

Liposomes have been widely used as drug carriers, intrinsic lung surfactants [77,78], cartilage lubricants [79] and other applications, facilitating improved intracellular delivery [78] and reducing the toxicity of incorporated drugs [80]. In the lungs, selective targeting of glucocorticoids to alveolar macrophages, which play a key role in the inflammatory response, offers efficacious pharmacological intervention with few side effects. A 2008 study in an endotoxin-induced lung inflammation model [81] demonstrated that dexamethasone-palmitate incorporated into mannosylated liposomes, administered intratracheally, reduced pro-inflammatory cytokines, suppressed neutrophil infiltration and downregulated NF-κB and p38MAPK signaling. This suggests that inhaled drug-loaded liposomes are effective for the delivery of anti-inflammatory drugs to alveolar macrophages.

Glucocorticosteroids can also inhibit solid tumor growth by means of downregulation of tumor-associated inflammation/angiogenesis. Banciu *et al.* [82] reviewed the possible mechanisms of GC action in tumor growth inhibition. In addition to anti-inflammatory activity, preclinical studies have shown that high and frequent dosing of GC is a prerequisite for obtaining antitumor activity [83-87]. Non-encapsulated GC are rapidly cleared from circulation, and accumulate at the tumor site only to a very limited extent. Encapsulating GC in long-circulating liposomes can improve tumor-targeted delivery [82].

Administration of high doses of GC in a pulsed mode is the most common treatment protocol of acute relapses in multiple sclerosis (MS). Several studies have shown that using high doses of GC (> 500 mg/day) decreases the number of brain lesions while maintaining a functional blood–brain barrier [88,89]. Liposomal GC and especially methylprednisolone formulations display an enhanced efficacy not only in acute inflammatory, but also in chronic demyelinating models of MS and confer long-term protection from relapses [90,91].

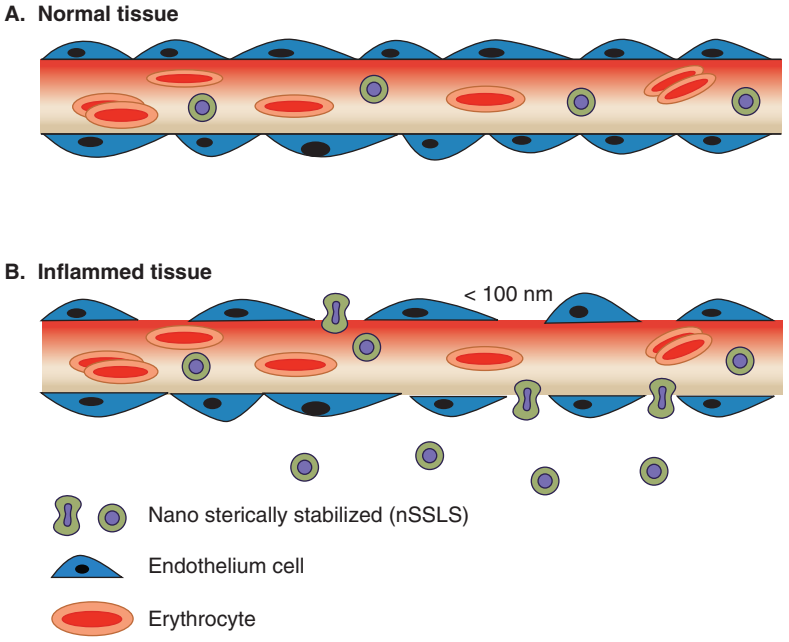

Figure 3. Extravasation of nanoliposomes from highly permeable blood vessels into regions of inflammation.

Glucocorticosteroid treatment is widely used in the treatment of rheumatoid arthritis (RA) as well as other inflammatory joint diseases because of its anti-inflammatory and immunosuppressive features [92,93]. Targeted delivery to inflamed joints using long-circulating PEGylated liposomes, < 100 nm in diameter, has been shown to be more effective than treatment with the free drug [76,91].

Long-circulating PEGylated liposomes encapsulating methylprednisolone or betamethasone were also used to treat Lewis rats with adjuvant-induced arthritis (AIA) both at early (before clinical signs appear) and late (at the peak of the disease) stages of the disease [94]. A single injection of 10 mg drug/kg (body weight) resulted in complete remission of the inflammatory response for almost a week. By contrast, the same dose of free (non-encapsulated) drug did not reduce inflammation. This is explained by enhanced liposome localization in the inflamed joints and the prolonged profile of drug release at the target site.

These all point to the ability to target and treat inflammation induced by FB injuries or medical implants using sterically stabilized nanoliposomes.

4.1.1 Liposomes as drug delivery systems for the treatment of inflammatory bowel disease

Inflammatory bowel disease (IBD) encompasses several chronic inflammatory conditions of the gastrointestinal tract that can impact the small or large bowel. The best known subtypes of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Conventional drugs for the treatment of IBD include aminosalicylates, corticosteroids, antibiotics and immunosuppressive agents. Most of the current agents act by downregulating chronic inflammation in the intestinal mucosa and cannot cure the disease.

Oral or rectal pathways have been the common routes of drug administration for treating these disorders. In the oral route, which is generally preferred owing to its high compliance, only a small fraction of the active components actually reaches the inflamed intestinal mucosa [95-97]. Advanced drug delivery systems can be programmed to release a drug in a specific region within the digestive tract by intrinsically measuring local pH levels [98,99], the transit time from administration [100], enzymatic activity of colonic microflora [101], or intraluminal pressure [102].

Newer developments include liposomal formulations, cyclodextrins, micro- or nanoparticles, and gene therapy approaches (reviewed in [103]). It has been shown that liposomes introduced intravenously tend to accumulate in the inflamed colonic tissue of IBD [103]. Furthermore, cationic liposomes tend to adhere better to healthy colonic mucosa, wheras anionic liposomes adhere better to inflamed mucosa [104], indicating that the latter is suitable for delivery of drugs to sites of inflammation.

4.2 Treatment of infection with liposomal antibiotics

Systemic antibiotics are usually satisfactory in the treatment of uncomplicated infections. However, in certain circumstances, such as in the presence of an FB, necrotic tissue, an overwhelming introduction of bacteria, or in cases of poor vascular supply, systemic antibiotics fail [105,106].

Antibiotics can be designed to target or, conversely, avoid phagocytic cells of the mononuclear phagocyte system [107-113]. Encapsulating antibiotics in drug delivery systems can modify

their pharmacokinetics by increasing serum half-life and decreasing the apparent volume of distribution, thereby allowing an increase in the maximum tolerated dose of the drug [114]. The development of long-circulating formulations that avoid macrophages will improve biodistribution and overcome the translocation of intracellular pathogens.

Numerous studies have shown that resistance to antibacterial agents is increasing, especially when bacteria stick to, and embed in, the glycocalyx matrix. To eliminate persisting bacteria, either in an inaccessible site or in a state of dormancy, new combating strategies must be developed [114].

Bakker-Woudenberg *et al.* [115] showed that SSL co-encapsulating ceftazidime and gentamicin were highly effective in treating pneumonia caused by *Klebsiella pneumoniae* and that the SSL localized at the infectious focus. The synergistic interaction of the two drugs was strong enough to overcome infection with a resistant *K. pneumoniae*. Similarly, SSL loaded with antibiotics were used for treating complex infections induced by *Mycobacterium avium* in the liver, spleen, lungs and lymph nodes. This approach has led to the development of liposomal amikacin [116]. The aim in this drug trail is to improve the efficacy of aminoglycosides by increasing their concentration at the site of infection.

The efficacy of SSL carrying antiviral agents was investigated in various *in vitro* models. In these cases, large or non-PEGylated liposomes were more effective than < 100 nm SSL [117,118]. However, the ability of SSL to localize in lymph nodes or other deep tissue macrophages, where high virus replication takes place, may be of advantage.

The ability of nano-sized SSL passively to target sites of infection and inflammation has great clinical importance not only for treatment, but also for diagnostics, as SSL carrying contrast agents can be used to image these diseased tissues.

4.3 Improved imaging of infection and inflammation using liposomes

Radiology plays an important role in visualizing FB. Imaging devices include X-ray, CT and ultrasound for both metallic and non-metallic FB and MRI for non-metallic particles. In cases where the FB is small or composed of a low-contrast material it may be very difficult to detect.

Utilizing the ability of liposomes to accumulate at sites of infection and inflammation has been suggested previously for imaging applications [119]. Oyen *et al.* [120] used ^{99m}Tc-labeled PEGylated liposomes, ~ 90 nm in diameter, introduced intravenously, to target infections induced by *Staphylococcus aureus* and *Escherichia coli* or inflammation induced by turpentine. They found that liposomes accumulated at the infectious and inflammatory foci over a 24-h period, starting 1 h post-administration. In another study [121], that group compared the uptake of In-111 and ^{99m}Tc-labeled stealth liposomes with the uptake of white blood cells (WBC) in an infection model and found that the stealth liposomes had similar post-injection abscess uptake as the WBC.

Boerman *et al.* [122] found that liposomes ~ 90 nm in diameter were optimal for imaging infection induced by *S. aureus* owing to their high accumulation in the abscess and low spleen accumulation. Including 1 mol% of the anionic lipid phosphatidylserine in the liposome lipid bilayer enhanced abscess accumulation; however, the negative charge induced rapid clearance of the liposomes from circulation.

In a similar scenario, Laverman *et al.* [123] showed that small (< 100 nm in diameter) radiolabeled (Tc-99m or In-111) PEGylated liposomes were effective in targeting bacterial infections, sterile inflammation, arthritis, infected lungs, colitis and osteomyelitis, and that nanoliposomes are more effective in avoiding spleen uptake in comparison with larger ones.

Dams *et al.* [124] showed clinically that ^{99m}Tc-PEG liposomes are at least as effective as ^{111}In-IgG scintigraphy in detecting an inflammatory disease or site of infection.

All of the above further support the use of long-circulating nanoliposomes for targeting sites of infection and inflammation.

4.4 A summary of liposomal targeting approaches

Three major approaches for using liposomes to treat infection and inflammation have been described in the literature (reviewed in [125]).

(1) *Local application of large multilamellar liposomes* provides a reservoir (**Figure 4**) from which the encapsulated drug can be released slowly, thereby prolonging the drug concentrations at the site of administration [63,64,70-72,74,75,126].

(2) *Targeting of (relatively) short circulating conventional liposomes to the cells of the mononuclear phagocyte system (MPS) for treating intracellular bacterial infections.* The rate at which liposomes are taken up by the MPS can be manipulated by controlling the liposome dose, but also by variation of liposomal characteristics such as charge, size and lipid composition. Generally, large, charged liposomes composed of fluid lipid bilayers tend to accumulate in the MPS more rapidly than small, neutral, rigid liposomes [76,127]. Despite the aforementioned, the plasma half-lifes of intravenously administered conventional liposome-encapsulated aminoglycosides are prolonged in comparison with that of free drug [128-134]. This may be owing to continuous release of drug into the circulation even after their uptake by MPS cells [128-134]. Without exception, all studies showed a substantial reduction in acute toxicity for the liposome-encapsulated drug in comparison with the free drug [111,135,136].

(3) *Targeting of long-circulating liposomes to infectious foci localized outside the MPS.* To target liposomes to infectious sites outside the major MPS organs (liver and spleen), it is necessary to decrease the rate of uptake of liposomes by the phagocytic cells. One way to achieve this is by preparing small (< 100 nm in diameter [137]) and neutral vesicles with a rigid bilayer. Using this approach, NeXstar

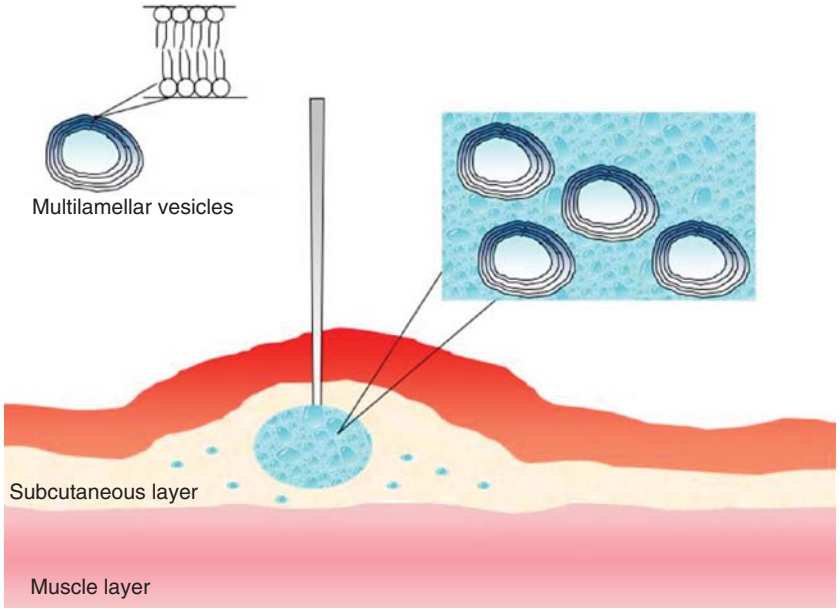

Figure 4. Subcutaneous administration of large multilamellar vesicles loaded with a drug have been shown to be effective in treating local inflammation.

Pharmaceuticals (now Gilead Sciences) developed MiKasome, a small (50 nm) unilamellar liposome formulation containing amikacin [138]. Another approach to prolong the circulation time of liposomes is to use 'sterically stabilized' (PEGylated) liposomes. When sufficient amounts of PEG-lipids are introduced to the lipid bilayer [62], low MPS uptake of the SSLs is independent of liposome *lipid* composition. This is an important advantage when tuning the liposome lipid composition for optimal targeting, retention and release [139,140]. This unique approach proved itself for the anticancer liposomal nano-drug Doxil [141].

5. Using liposomes to target invading foreign bodies or medical implants

Previously [142], the authors examined the potential of nanoliposomes to target the site of an invading FB (**Figure 5**). SJL mice were surgically implanted with either a needle (simulating an implanted medical device) or a thorn (simulating an FB injury) in a hind limb. Two to three weeks after implanting the FB, radiolabeled liposomes loaded with an anti-inflammatory drug were administered intravenously by the tail vein. Twenty-four hours after administering the liposomes animals were killed, and the tissue surrounding the FB, as well as corresponding non-implanted tissue, were extracted and quantified for levels of liposome accumulation. Liposomes accumulated in the FB-injured tissue at significantly higher levels in comparison with the control, healthy, tissue. This study exemplifies that nanoliposomes, loaded with a drug, can be used to target FB injuries or implanted devices.

5.1 Targeting medical implants

Medical devices and medical implants are aimed at performing within the body. However, in many cases these implants can be a source of constant infection and inflammation. **Figure 6** presents a hip view X-ray of a patient after a total hip replacement. This X-ray visualizes changes that are indicative of microparticles and debris shed from the device, causing wear and osteolysis (i.e., resorption of the bone matrix by osteoclasts).

Several studies used liposomal formulations to treat infection and inflammation induced by medical implants. Danenberg *et al.* [143] tested whether bisphosphonates encapsulated in liposomes can inhibit in-stent neointimal formation by depleting monocytes and macrophages. For this, rabbits that underwent bilateral iliac artery balloon denudation and stent deployment were treated with liposomal alendronate. They found that the treatment reduced significantly the intimal area, monocyte count and arterial stenosis. Reduction in neointimal formation was also associated with reduced macrophage infiltration and proliferation, thereby showing that a single injection of liposomal bisphosphonates can transiently deplete the population of monocytes and macrophages.

Koromila *et al.* [144] coated polymer-covered stents with heparin-encapsulating liposomes to improve their hemocompatibility. They found that the recalcification time of the liposome-coated stents increased significantly. Interestingly, the liposomes also remained on the surface of the stent under

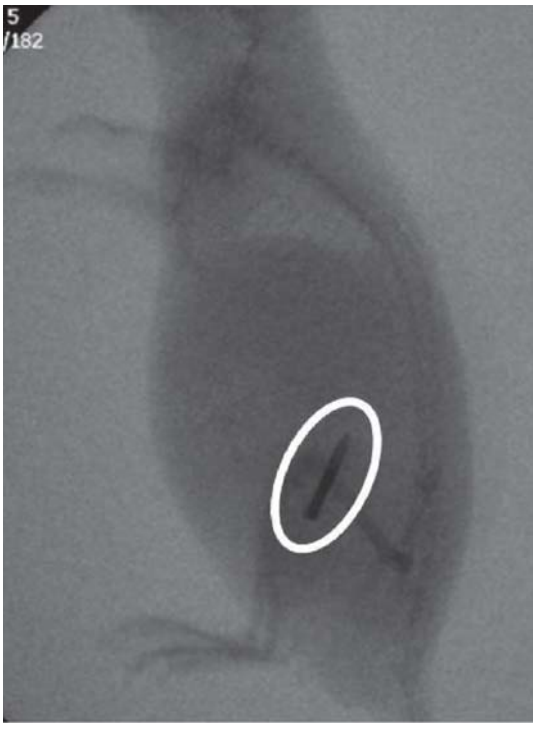

Figure 5. PEGylated nanoliposomes were injected intravenously to SJL mice with an implanted 1-cm-long 19G needle tip (in this X-ray image) or *Lycium europaeum* bush thorn. In both cases, 24 h after administration, the level of liposomes in the tissue surrounding the implants was significantly higher than the level of liposomes in the other, non-implanted hind leg.

extensive flow conditions. Similar results using stents coated with drug-loaded liposomes were described by Antimisiaris and co-workers [145,146]. Kallinteri *et al.* [147] and Antimisiaris *et al.* [146] coated PET-covered metallic stents with liposomal dexamethasone in order to release the drug locally. Both studies found that the liposomes remained on the surface of the stent for several days despite flow, releasing the drug in the near vicinity of the stent [146]. Joner *et al.* [148] showed that this approach reduced in-stent restenosis in a rabbit model. Huang *et al.* [149] used RGD peptides, conjugated to liposomes, to improve liposomal binding to activated platelets. Platelet adhesion, activation and fibrinogen-mediated aggregation are primary events in vascular thrombosis and occlusion.

Rossetti *et al.* [150] found that liposomes containing phosphatidylserine form supported phospholipid bilayers (SPBs) on titanium dioxide surfaces, thereby suggesting its potential to improve the biocompatibility of TiO_2-based medical devices.

The approaches mentioned above assume that the liposomes are inserted into the body together with the device. However, liposomes may be injected independently of the implanted device in order to target the sites of inflammation, regardless of the specific type of material or device used. This would provide a broad treatment platform to inflammatory responses induced by implanted medical devices. Taking this approach another step would allow targeting of medical devices even without an inflammatory event. Such targeting could be governed by properties of the device and of the liposomes, for example, the targeting of a medical device (having magnetic properties) using magnetic liposomes [151]. Targeting using a material property of the implanted medical device is not trivial, as many characteristics, such as surface properties, are masked by rapid adhesion of proteins and cells to the surface of the device.

6. Conclusion

The ability of liposomes to target a single or multiple sites of infection and inflammation, as well as to be stable carriers for a wide range of therapeutic agents, points to their high potential for treatment of FB-induced medical complications.

Strong existing patents on leading liposome formulations and liposome drug loading approaches as well as relatively low cost of nonspecific generic drugs may have slowed down the development of targeted delivery systems. However, many of these patents have recently expired or will expire soon. In addition, there is increasing understanding that passive targeting to inflamed sites is a feasible option, and that such targeted treatments can improve the efficacy, tolerability and patients' quality of life. Furthermore, targeted delivery systems have been shown to reduce long-term indirect costs associated with complications and side effects of conventional treatments.

7. Expert opinion

Foreign body complications are highly prevalent among people with trauma injuries. At times, the FB cannot be removed surgically, thereby becoming a source of recurring infection, inflammation and pain. These injuries are not confined to a single organ, and in many cases a patient may suffer simultaneously multiple FB injuries in different parts of the body. Current treatments include systemic or local administration of drugs to alleviate symptoms; however, new therapeutic approaches are warranted to improve the treatment of this medical condition. The integration of nanotechnology with drug delivery systems has significantly improved the ability to target therapeutics to specific tissue within the body. The authors propose that this approach can be expanded also for targeting invading foreign bodies or implanted medical devices. In some cases, biological characteristics, such as utilizing the enhanced permeability and retention (EPR) effect in sites of inflammation or specific biological markers, can assist targeting. In other cases, material-specific properties, such as magnetism or unique surface chemistry, may be utilized.

Despite the great need for a growing number of patients, this field seems to have been under-researched in academic

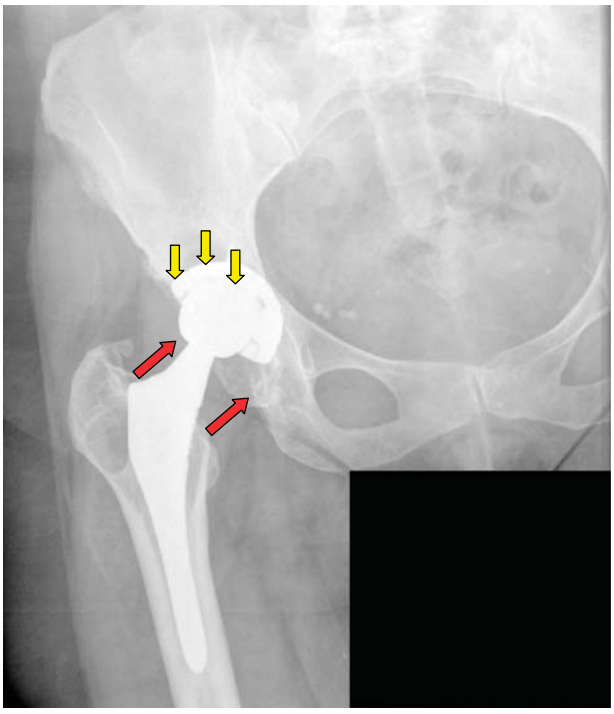

Figure 6. Implanted medical devices are in some cases a constant source of microparticles and debris that are shed from the device. The image presents a hip view X-ray of a patient after a total hip replacement. This X-ray visualizes changes that are constant with microparticles and debris shed from the device, demonstrating both wear and osteolysis (i.e., resorption of the bone matrix by osteoclasts). The prosthetic femur head is not centered within the prosthetic acetabulum, as indicated by the red arrows, secondary to the polyethylene liner wear. The yellow arrows indicate bone resorption around the acetabulum resulting from osteolysis.

institutions, leaving a large space for innovation and patenting. Furthermore, platform technologies, which have been successful in addressing diseases that share similar biological features, may prove successful in treating this medical condition.

Declaration of interest

Barenholz is a co-inventor of Doxil, and declares no *other* conflict of interest. The authors have received no payment in preparation of this manuscript.

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