A fully functional drug-eluting joint implant

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Despite advances in orthopaedic materials, the development of drug-eluting bone and joint implants that can sustain the delivery of the drug and maintain the necessary mechanical strength to withstand loading has remained elusive. Here, we demonstrate that modifying the eccentricity of drug clusters and the percolation threshold in ultra-high molecular weight polyethylene (UHMWPE) results in maximized drug elution and the retention of mechanical strength. The optimized UHMWPE eluted antibiotic at a higher concentration for longer than the clinical gold standard antibiotic-eluting bone cement, while retaining the mechanical and wear properties of clinically used UHMWPE joint prostheses. Treatment of lapine knees infected with Staphylococcus aureus with the antibiotic-eluting UHMWPE led to complete bacterial eradication and the absence of detectable systemic effects. We argue that the antibiotic-eluting UHMWPE joint implant is a promising candidate for clinical trials.

More than one million joint replacements are performed annually in the United States.¹ Five to ten percent of joint replacements are revised within seven years,² with prosthetic joint infection (PJI) being one of the most common reasons for revision (Fig. KT29 in ref. ³). PJI is an increasing healthcare burden with a recurrence rate of 16% (ref. ⁴) and a mortality rate of 2.5% (ref. ⁵). End-stage treatments are severely morbid, including multiple revisions, resection arthroplasty, arthrodesis and amputation.⁶

Antibiotic penetration into the joint space and bone from systemic administration is limited because of poor blood supply to the infected area.⁷ A strategy to address this is to deliver antibiotics locally by incorporating them into orthopaedic implant materials.⁸,⁹. The current treatments incorporate antibiotics into poly methyl-methacrylate bone cement,⁹ ceramic bone graft substitutes,¹⁰ or resorbable polymeric systems.¹¹ The gold standard in treating PJI involves two-stage surgery, where removal of all components of the infected implants is followed by a minimum of 6–8 weeks of antibiotic-eluting bone cement spacer placement, during which patients have limited mobility and function (Fig. 1).¹² This period is followed by the placement of new implant components; however, in cases where the temporary spacers are used for long-term weight bearing without the placement of new implants, bone cement spacers have shown a complication rate of 26–60% within 49–54 months,¹³ mainly due to dislocation (11–17%) and fracture (10–14%). The primary use of bone cement in joint implants is fixation of the bone–implant interface; however, bone cement has low tensile strength and impact toughness and is unsuitable for use in continuous load and articulation.¹⁴,¹⁵

The high incidence of bone cement fractures (Fig. 1)¹⁴ is also due to the decrease in mechanical properties caused by incorporated antibiotics.¹⁶ In addition, although drug elution into the peri-prosthetic space is desired for 3–8 weeks, the elution from antibiotic-eluting bone cement spacers often falls below the minimum inhibitory concentration (MIC) of common PJI bacterial contaminants within 1 week.¹⁷ Low antibiotic concentration without the complete eradication of bacteria has the potential of increasing antibiotic resistance.¹⁸ The antibiotic concentration in bone cement is limited by the minimum allowed mechanical properties, but results in low interconnectivity of drug clusters (Fig. 1)². In fact, for drug-eluting polymers with spherical drug clusters, 40–60% (w/w) drug content is required to reach complete interconnectivity. Our goal was to develop load-bearing joint implant materials with efficient antibiotic release for at least 3 weeks, and high mechanical strength and wear resistance within that of clinically used UHMWPE (Supplementary Discussion), to allow direct replacement of infected prosthetics with a new implant (Fig. 1) without the complications and morbidity associated with a two-stage procedure.

Drug cluster interconnectivity was studied using percolation theory, which showed that drug elution increased sharply as the percolation threshold was reached, whereas mechanical strength decreased with total drug content.²³ Computational simulation showed that increasing eccentricity of the drug cluster shape and increasing polymer particle to drug cluster size ratio may increase drug cluster interconnectivity. We hypothesized that by increasing the eccentricity of the drug clusters and increasing the polymer particle to drug cluster size ratio in a drug-incorporated polymer matrix, interconnectivity of drug clusters could be reached at lower drug content, thus improving the mechanical properties of the polymer matrix. We demonstrate application of this concept to UHMWPE to develop a load-bearing implant for the treatment of PJI.

Effect of cluster eccentricity on elution and strength

A comparison of drug elution rate and tensile mechanical properties was made for low density polyethylene (LDPE), which could be prepared using solvent casting, resulting in conventional spherical drug clusters (Fig. 2a,g; continuous) and compression moulding, resulting in highly eccentric drug clusters (Fig. 2a,g; highly eccentric). Variation in the content of the antibiotic drug vancomycin (2, 6 and 10 wt%) and the LDPE/vancomycin particle size ratio (6:1, 16:1, and 40:1) showed that the polymer with the highly eccentric drug clusters had a higher elution rate than the one with spherical drug clusters for 6 and 10 wt% drug loading (Fig. 2d–f). This

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was because the percolation threshold was reached at this loading, a much lower concentration than for the conventional spherical cluster system. The elongation at break (Fig. 2b) and the ultimate tensile strength (UTS; Fig. 2c) were highest at a polymer/drug particle size ratio of 4:1.

Highly eccentric drug clusters in UHMWPE
Antibiotic-eluting UHMWPE displaying highly eccentric drug clusters was prepared using compression moulding. Although drug loading at the studied levels increased porosity linearly, the percolation threshold was reached at a drug loading between 4 and 6 wt% (Supplementary Figs 1 and 2), which was corroborated by a sharp increase in drug elution around 6 wt% (Fig. 3a). However, the UTS decreased linearly from 0 to 10 wt% drug loading (Fig. 3b).

We created and utilized an optimization equation to maximize the UTS, impact strength (IS), and drug elution rate (equation (1)). Because UTS, impact strength and elution rate were variable at different scales, their contributions to the optimization were normalized with their respective maximum values (UTS\textsubscript{n}, IS\textsubscript{n}, and Rate\textsubscript{n}; UTS and impact strength at 0% drug loading and elution rate by 14% drug loading). In equation (1), C is the drug concentration and t is time.

\[
\text{Max} \left(0.5 \times \text{UTS}_n (C) + 0.5 \times \text{IS}_n (C) + (\text{Rate}_n (C, t)) \right)
\]

Solving for this equation showed that the optimum drug loading was 7 wt% (Fig. 3c). Above this concentration, the additional gain in drug elution rate was offset by the decrease in the mechanical properties, while below this concentration the drug elution rate was not sustained at an effective level for treating PJI.

We compared the drug elution of our optimized polymer system with 11 wt% vancomycin in bone cement, which is the highest drug content that can still maintain the industry standard of 70 MPa for compressive strength.\textsuperscript{28} The vancomycin elution rate and antibacterial activity of 7 wt% vancomycin-loaded UHMWPE (VPE) was similar to that of 11 wt% vancomycin in bone cement (Fig. 3d and Supplementary Fig. 3), supporting our hypothesis that the highly eccentric drug clusters resulted in more efficient drug release. Vancomycin elution of VPE and bone cement in synovial fluid did not show any statistically significant difference compared with elution in phosphate-buffered saline (PBS) (Supplementary Fig. 4).

The mechanical properties (yield strength, UTS, impact strength and elongation at break) and wear rate of VPE were all within the

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**Figure 1 | Highly eccentric drug-eluting polyethylene.** The current gold standard of treatment for PJI is two-stage surgery, which involves replacement of the infected prosthesis with antibiotic-eluting PMMA bone cement and intravenous antibiotics (stage 1), then removal of PMMA bone cement and replacement with a new joint prosthesis after bacterial cultures confirm clearance of infection (stage 2). Because of its spherical drug cluster morphology (scanning electron microscopy image, top right), PMMA bone cement requires high drug loading for sufficient drug elution and has weak mechanical strength. Drug-eluting polyethylene with highly eccentric drug clusters allowed much lower drug loading for efficient drug elution, high mechanical strength and a favourable wear rate. Drug-eluting PMMA had spherical drug clusters, which require 30–40% drug content to reach percolation. The high drug loading needed to achieve sufficient drug elution significantly reduces its mechanical strength to the point of insufficient strength for full load bearing. However, drug-eluting UHMWPE with highly eccentric drug clusters (scanning electron microscopy images, bottom right) reached percolation at 6–8 wt% drug content, allowing sufficient drug elution to be reached at a lower content than the antibiotic-eluting bone cement. As a result, the mechanical strength necessary for a fully functional drug-eluting joint prosthesis was maintained and the direct replacement of infected prosthetic joints with new prosthetic joints without immobilization of patients is possible. Scale bars, 100 μm; VPE, 7 wt% vancomycin in UHMWPE; RVPE, 7 wt% vancomycin + 3 wt% rifampin in UHMWPE (red) with underlying non-antibiotic-eluting (unmodified) UHMWPE (white).
limit of clinically used UHMWPE\textsuperscript{29} (Fig. 3e,f and Supplementary Figs 5–7) and were superior to those of 11\% vancomycin-loaded bone cement (Fig. 3e,f).

**Drug type and elution rate relationship**

We tested nine different antimicrobials (ciprofloxacin hydrochloride (HCl), tobramycin, tetracycline HCl, gentamicin, vancomycin HCl, rifampin, teicoplanin, ceftriaxone and fusidic acid) that spanned different polar surface areas (PSA; 72–663 $\text{Å}^2$) and molecular volumes (MV; 282–1600 $\text{Å}^3$) (ref. \textsuperscript{30}). The ratios of these values (PSA/MV) were used to normalize polarity by molecular size. In UHMWPE with highly eccentric drug clusters (Supplementary Fig. 8), more polar compounds (PSA/MV > 0.3) had higher early elution rates, but these dropped more rapidly over time, compared with non-polar compounds (PSA/MV < 0.3) (Supplementary Fig. 9). Therefore, drugs with a large polar surface area or small molecular volume (low PSA/MV) can be advantageous in applications that require a potent, short-term release of medication, such as local anaesthetics (bupivacaine, lidocaine, ropivacaine) and antifibrinolytics (tranexamic acid). However, drugs with a smaller polar surface area or larger molecular volume (high PSA/MV) can be advantageous in applications that require a less potent initial release, but sustained elution. For example, pertinent to PJI treatment, rifampin is an antimicrobial that is highly effective at the time-dependent eradication of \textit{Staphylococcus aureus} biofilm\textsuperscript{31}, but is also hepatotoxic at high concentrations. Therefore, sustained and lower concentration drug release can be beneficial for bacterial eradication, while minimizing the side effects.

**Irradiated VPE enhances antibacterial properties**

Most clinically used prosthetic joints are irradiated either for sterilization (25–40 kilogray (kGy); ref. \textsuperscript{32}) or for cross-linking (>50 kGy; ref. \textsuperscript{33}). Sterilization dose (~25 kGy) did not affect the UTS, impact strength, elution profile or wear rate (Supplementary Fig. 6), compared with those of unirradiated VPE. High dose irradiation (100 kGy) decreased the UTS, impact strength and wear rate (5.4 mg per million cycles (mg MC$^{-1}$)), but did not affect the elution rate (Supplementary Fig. 10).

After vancomycin was eluted for six months and no further elution of vancomycin could be detected by liquid chromatography (detection limit = 0.1 $\mu$g ml$^{-1}$), 25- and 100-kGy irradiated VPEs showed less bacterial adherence than unirradiated VPE (Fig. 3g). Immunofluorescence staining of vancomycin showed fluorescence on the surfaces of the irradiated VPEs, but not on unirradiated VPE (Fig. 3h and Supplementary Fig. 11), indicating the presence of vancomycin on the surfaces of the VPE after all elutable drug was released. This suggested that some vancomycin was immobilized in the UHMWPE as a result of irradiation, presumably by grafting through its phenolic hydroxyl group\textsuperscript{34}.  

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**Figure 2** | Highly eccentric drug cluster morphology influences the mechanical and elution properties of the implant material. a, Schematic view of the process for creating highly eccentric drug clusters in LDPE. Vancomycin crystals are interspersed between LDPE particles. Subsequent casting or moulding under minimum flow forms highly eccentric drug clusters. b, c, UTS (b) and elongation to break (c) of compression-moulded LDPE (highly eccentric drug clusters) at various LDPE/vancomycin particle size ratios (PDr; 40:1, 16:1 and 4:1) and solvent-cast LDPE (traditional spherical drug clusters, control) at different initial drug loading levels (2, 6 and 10 wt\%). d–f, Vancomycin elution rates from both LDPEs at different drug contents (2 wt\% (d), 6 wt\% (e) and 10 wt\% (f)). g, Scanning electron micrograph images of vancomycin-eluting LDPE at various initial drug contents (2 and 10 wt\%) under different PDr values (40:1, 16:1 and 4:1) or with vancomycin-eluting LDPE made by solvent casting (control). Scale bars, 100 $\mu$m. Drugs were pre-eluted before imaging. For b–f, data are derived from n = 5 per group. Data shown are the means ± s.d.; *P< 0.05.
VPE eradicates planktonic *S. aureus*

An intra-articular PJI model was created by implanting osteochondral plugs of VPE, non-antibiotic containing UHMWPE and a commonly used bone cement spacer formulation (containing 8.3 wt% tobramycin sulfate and 2.3 wt% vancomycin HCl; VTBC) in the femoral trochlear groove, and a titanium plug with a porous surface (radiation sterilized VPE) for the duration of the study (Supplementary Fig. 14). These results confirmed the efficacy of vancomycin eluted from radiation sterilized VPE *in vivo*.

**Drug-eluting UHMWPE against biofilm**

In PJI, the bacterial biofilm is often localized at the bone–implant interface, which is difficult to eradicate due to limited antibiotic penetration administered systemically. The combination of rifampin and vancomycin is the state-of-the-art treatment used against bacterial biofilm, and can synergistically act against both Gram-positive and Gram-negative bacteria. The synergy reduces the MIC for vancomycin and can hinder the rapid bacterial resistance associated with rifampin alone, by tailoring the concentration ratios of vancomycin to rifampin such that the concentration of vancomycin is higher for the duration of the release.

Kidney function byproducts (creatinine and body urea nitrogen) and liver function enzymes (alanine aminotransferase and alkaline phosphatase) remained within normal limits for all rabbits in the VPE group for the duration of the study (Supplementary Fig. 14). These results confirmed the efficacy of vancomycin eluted from radiation sterilized VPE *in vivo*.

**Figure 3** | Influence of the highly eccentric morphology of modified UHMWPE on its drug elution and mechanical properties. a, Response surface of vancomycin elution rate, elution time and initial vancomycin content of highly eccentric morphology in vancomycin-eluting UHMWPE. b, Relationship between UTS and initial drug content (n = 5). c, Response surface optimization of equation (1) for drug content in UHMWPE and elution time. d, Elution rate of rifampin and vancomycin from RVPE and that of vancomycin from VPE and bone cement (11 wt% vancomycin loading, bone cement) (n = 5).

VPE was determined. No vancomycin was detected systemically in any of the rabbits at any time point (detection limit 10 ng mL⁻¹).}

Based on clinical guidelines for vancomycin/rifampin concentration ratios for the treatment of PJI (Supplementary Table 1), incorporation of a 2.5:1 vancomycin/rifampin ratio allowed long-term maintenance of a vancomycin/rifampin elution rate ratio closest to the clinically desired trough ratio (Supplementary Fig. 15). The vancomycin elution rate was consistently higher than the rifampin elution rate for UHMWPE incorporated with 3 wt% rifampin in addition to 7 wt% vancomycin (RVPE; Fig. 3d) and the vancomycin elution rate from RVPE was significantly higher than that from VPE and bone cement (Fig. 3d). Rifampin and vancomycin elution of VPE and bone cement in synovial fluid was not significantly different than elution in PBS (Supplementary Fig. 4). Pre-eluting
the RVPE for one year and then exposing it to a liquid culture of *S. aureus* still prevented the bacteria from growing, indicating that the antibiotics eluted from RVPE were still above the MIC for this microorganism in biofilm form. Mechanical strength (UTS and impact strength) and wear rate were within the limit of clinically used UHMWPE (Fig. 3f and Supplementary Figs 5–7).

RVPE with a total drug concentration of 10 wt% was localized only in the surface, unloaded regions\(^1\), to minimize the effect of the increased drug concentration on the mechanical properties of the potential implant (Fig. 1). Our previous work in spatially controlling the morphological properties of UHMWPE, by layering different compositions of UHMWPE during compression moulding, showed integrity at the interface\(^1\). An *in vitro* simulation of biofilm formation at the bone–implant interface of a joint implant was done by sandwiching bone, titanium and UHMWPE (Fig. 5a). A bioluminescent *S. aureus* (Xen 29, PerkinElmer) biofilm was grown on the porous surface of titanium discs for 48 h. The surfaces were clamped together, with the biofilm-laden porous titanium surface in contact with the bone and the non-porous surface in contact with UHMWPE (Fig. 5b). The average synovial fluid volume and the size of the femoral component of a knee implant were used to scale down the size of the RVPE, the volume of media and the bone–titanium interface, respectively (Supplementary Table 2). The average biofilm thickness was 25.5 ± 2.2 μm, in agreement with previous reports\(^2\). The biofilm was completely eradicated in the sandwiches with RVPE by 48 h (Fig. 5c). Two-photon live/dead fluorescence excitation imaging of the titanium beads revealed >95% biofilm eradication in the RVPE group within 96 h, while the bacteria viability in the controls remained consistently elevated for 2 weeks (Fig. 5d,e). These results suggested that the antibiotics eluted from the UHMWPE implant surfaces could reach therapeutic levels at the bone–implant interface.

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In an adaptation of the PJI model for acute infections with planktonic bacteria above, all rabbits received a titanium rod with fully grown bioluminescent *S. aureus* biofilms in the tibial canal (Fig. 6a). There was no statistically significant difference in bioluminescence between the three groups (control, VTBC and RVPE) before implantation (Fig. 6b). None of the rabbits received any systemic antibiotics for the duration of the study (3 weeks). All control rabbits and 80% of rabbits receiving VTBC expired, whereas all rabbits in the RVPE group survived for 3 weeks (Fig. 6f). Because live bacteria were found in the joints during the postmortem analysis (Fig. 6c,d), we suspect that some of the bacteria spread hematogenously and caused sepsis. Immediately post-surgery, no difference in gait and joint movement was observed between control and RVPE groups. However, after several days, the infected knees in the control and VTBC rabbits were more swollen, retracted and passive than those in the RVPE rabbits. No mechanical failure, including deformation, fracture, delamination or pitting was observed in the retrieved implants. No live bacteria were observed in the RVPE...
We report a new method of making a drug-eluting polymer with
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compared with conventional polymers with spherical drug clusters
(Fig. 1). The method was applied to both low- and high-melt flow
index polymers (for example, UHMWPE and LDPE, respectively).
There is the possibility of applying this technique to other commonly
used drug-eluting polymer systems, such as poly(lactic-co-glycolic
acid). In addition, the effects of drug chemistry and structure have
been studied, while maintaining the highly eccentric morphology
(Supplementary Fig. 4), to evaluate the possibility of using this
morphology for other drug–polymer combinations to treat various
diseases. Due to higher interconnectivity, the highly eccentric drug
clusters in polyethylene enabled the reduction of the drug percola
tion threshold from very high drug loading (40–60 wt%) (ref. 23) to
6–8 wt% (Supplementary Figs 1 and 2 and Fig. 3a). The intercon-
ected morphology also resulted in drug elution that was sustained for
a longer duration (Fig. 2d–f) and had a higher mechanical strength
(Fig. 2h,c), compared with drug-eluting polyethylene with
spherical drug clusters. Lower initial drug loading may also imply
a higher safety margin in adverse scenarios, where incorporated
drugs may be unintentionally released.

Polymeric matrices can be effective local delivery devices
because they enable more effective drug delivery than through
systemic administration; they can also enhance the efficacy of the
incorporated drugs by targeting the required location of treatment44.
Common strategies involve injectable, drug-eluting polymers in
the form of microspheres45 or micelles46, but degradation products
can be toxic47, drug elution rates can fall below effective levels48,
and drug release can have low efficacy49. The gold standard for
drug-incorporated polymers in treating PJI is antibiotic-eluting
bone cement made of polymethylmethacrylate (PMMA)50, which

Discussion
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Figure 5 | In vitro evaluation of RVPE. a. Schematic of ‘sandwich’ experiment to treat bacterial biofilm between bone and titanium using either non-
antibiotic-eluting UHMWPE (control) or RVPE. Bacterial biofilm was often found between titanium and bone surfaces in patients with chronic PJI.
Bioluminescence was measured for all 21 constructs. At predefined time points (6 h, 24 h, 48 h, 96 h, 120 h, 1 week and 2 weeks; n = 3 each for each
time point), bone and titanium were live/dead stained and imaged with two-photon fluorescence microscopy. b, c. Bioluminescent imaging (b) and its
quantiﬁcation (c) at the titanium–bone interface after 24 h and 48 h with RVPE or control treatment (n = 3, ***P < 0.001). d, Two-photon live/dead imaging
of the bacteria that adhered to the surface of titanium at 6 h and 2 weeks after treatment with the control or RVPE. Scale bars, 200 μm. e, Percent live/dead
as a function of time of exposure in the control and RVPE treatments. Data are means ± s.d.
can only be used in limited load-bearing applications\(^a\). A fully load-bearing permanent implant using UHMWPE can address the shortcomings of other drug-eluting polymers in joint replacement. The reported highly eccentric drug clusters combined with our spatially controlled consolidation technology can enable the sustained delivery of state-of-the-art antibiotic combinations, without sacrificing the required mechanical properties of the implant. The long track record of safety and efficacy of UHMWPEs\(^a\), combined with well-known antibiotics such as vancomycin and rifampin, has the potential of eliminating the use of antibiotic-eluting spacers and reducing the gold standard two-stage treatment surgeries for PJI to a single surgery. Based on the effects of increasing antibiotic concentration on the mechanical properties of UHMWPE and the contact stresses of the joint\(^a\), we proposed several implant designs (Supplementary Table 4). All of the designs provided have mechanical strengths and wear rates within the range of clinically used UHMWPE (conventional UHMWPE and highly cross-linked UHMWPE (HXLPE); Supplementary Table 3). The uniform vancomycin-containing UHMWPE (7 wt%; VPE) and VPE with a surface layer of rifampin and vancomycin-containing UHMWPE (10 wt%; RVPE) are intended for temporary (6–8 weeks) usage or for longer term usage in patients with low activity, because the wear rates were closer to conventional UHMWPE than HXLPE. Virgin UHMWPE with a surface layer of rifampin and vancomycin-containing UHMWPE (10 wt%; RVPE) can be used for long-term applications (years), because its articulating surface is composed of HXLPE with the lowest wear rate.

In addition to the risk of mechanical failure during weight bearing, antibiotic-eluting PMMA bone cements showed bacterial adhesion\(^b\) even during antimicrobial elution\(^b\). However, radiation sterilized VPE significantly reduced bacterial adherence through surface-bonded vancomycin (Fig. 3g,h). This is in agreement with previous reports on vancomycin grafting on titanium, which prevented biofilm formation on its surface\(^c\). Reduction of bacterial adherence reduced the infection rate\(^c\). Surface-bound vancomycin eradicated bacteria by making the peptidoglycan layer that is essential to biofilm formation less rigid and more permeable. As a result, the osmotic pressure can cause bacterial death\(^d\). In addition to sustaining effective concentrations of antibiotic elution for bacterial eradication, grafting of the antibiotic by irradiation may further hinder bacterial attachment in antibiotic-eluting UHMWPE in the longer term.

VPE and RVPE outperformed clinically used antibiotic-eluting bone cement VTBC in planktonic and biofilm PJI models, respectively. The ability of VTBC to control the bacterial concentration was better in the planktonic model than in the biofilm model, presumably because bacterial susceptibility to vancomycin and tobramycin decreased by at least 1,000-fold in biofilm form\(^d\). While...
similar survival rates were observed for animals treated with VPE and VTBC, VPE (but not VTBC) completely eradicated all the bacteria in the joint. This may be partly due to the higher susceptibility of Xen29 to vancomycin\(^1\) than to tobramycin\(^2\).

Usage of antibiotics intravenously, orally, in the form of antibiotic-eluting bone cement, VPE and RVPE, all come with a risk of developing resistant bacteria. Even when bacteria were exposed to 200 times their MIC, they could develop resistance within 10 h (ref. \(^{13}\)). This suggests that our previous understanding that bacterial resistance is directly related to being exposed to below-MIC concentrations of antibiotics\(^5\) may be incomplete. Nevertheless, by matching the vancomycin elution of VPE to clinically used vancomycin-eluting bone cement (Fig. 3d), we expect VPE to pose no extra risk in bacterial resistance development to antibiotic-eluting bone cement. In the case of RVPE, by creating elution of vancomycin that exceeds the antibiotic-eluting bone cement (Fig. 3d) and by ensuring that vancomycin elution is always higher than that of rifampin to prevent sole exposure of bacteria to rifampin, we also expect that RVPE will not pose any extra risk of bacterial resistance development to antibiotic-eluting bone cement.

Loading UHMWPE with therapeutic agents using highly eccentric drug clusters could potentially address problems, such as pain, osteolysis, osteoporosis and infection, in joint arthroplasty and other orthopaedic fields, such as trauma and spine. In addition, the application of this morphology to other drug–polymer matrices could benefit treatment in other applications where both drug elution and mechanical strength are crucial for the success of implants.

### Methods

#### General experimental approaches.

No samples, rabbit or data points were excluded from the analyses. Samples were not randomized to experimental groups unless specified. Lapine experiments and analyses were not performed in a blinded fashion.

#### Solvent casting of vancomycin-eluting LDPE with spherical drug clusters.

LDPE was dissolved slowly in boiling xylene (138 °C) to reach a concentration of 60 mg ml\(^{-1}\). After all the LDPE had dissolved, the resulting solution was then cooled to 110 °C. Under mechanical stirring, vancomycin crystals, size <75 μm, were added to reach the desired weight percent with respect to the LDPE content (0–10 wt%) and kept at 110 °C for 30 minutes to further remove the solvent. The resulting viscous solution was transferred to a stainless steel rectangular mould (50 mm × 85 mm) and put in a vacuum oven, with a vacuum pressure of ~0.1 MPa, at 90 °C to further remove the solvents.

#### Manufacture of vancomycin-eluting LDPE with highly eccentric drug clusters.

LDPE pellets were cryomilled and then sieved to the appropriate desired particle size range. Vancomycin HCl was crushed with a mortar and pestle and then passed through a 75 μm sieve. To create vancomycin-eluting LDPE with 7 wt% drug loading, 0.7 g of the sieved vancomycin powder was mechanically mixed with 9.3 g of the cryomilled LDPE powder for 30 min at room temperature. The resulting mixture was transferred to a rectangular mould (50 mm × 85 mm) and compressed at 25 °C for 1 min at 10 MPa. The compressed solid mixture was subsequently heated at ~0.1 MPa and 190 °C for 30 min and then compression moulded at 10 MPa for 1 min before being cooled to 25 °C at a rate of 10°C min\(^{-1}\).

#### Manufacture of optimized vancomycin-eluting UHMWPE with highly eccentric drug clusters (VPE).

Vancomycin HCl (1.75 g) was crushed with a mortar and pestle and then passed through a 75 μm sieve. The vancomycin powder was mechanically mixed with GUR1020 UHMWPE powder (Celanese, 23.25 g) for 30 min at room temperature to obtain a 7 wt% vancomycin-blended UHMWPE and poured into a circular mould (10.5 cm inner diameter). The vancomycin-UHMWPE mixture was then consolidated by compression moulding at 170 °C and 20 MPa, for 5 min. The resulting consolidated VPE was cooled, at a rate of 10°C min\(^{-1}\), to room temperature to yield approximately 3-mm-thick and 10.5-cm-diameter vancomycin-blended UHMWPE.

#### Manufacture of optimized rifampin-vancomycin-eluting UHMWPE with highly eccentric drug clusters (RVPE).

Rifampin (0.4 g) was crushed with a mortar and pestle and passed through a 75 μm sieve. Vancomycin HCl (0.8 g) was crushed with a mortar and pestle and passed through a 75 μm sieve. The rifampin and vancomycin HCl powders were then mechanically mixed for 30 min at room temperature. GUR1020 UHMWPE (12 g) was added to the rifampin and vancomycin HCl mixture, which was then mechanically mixed/blended for 30 min at room temperature, to obtain a 3 wt% rifampin and 7 wt% vancomycin-blended UHMWPE. The resulting rifampin and vancomycin-blended UHMWPE (10 g) was transferred and spread evenly onto a circular stainless steel mould (11 cm inner diameter). GUR1020 UHMWPE without additives (25 g) was then added and spread evenly on top of the rifampin and vancomycin-blended UHMWPE. The resulting constructs were consolidated by compression moulding at 170 °C and 20 MPa, for 5 min, before being cooled at a rate of 10°C min\(^{-1}\) to room temperature.

#### Manufacture of vancomycin-eluting PMMA bone cement.

Vancomycin HCl (5 g) powder that had been crushed with a mortar and pestle and passed through a 75 μm sieve was mechanically mixed with PMMA powder (27 g; Simplex P, Stryker) for 30 min at room temperature. After thorough mixing, the cement's liquid monomer was added and then mixed thoroughly with spatula. The vancomycin-cement dough was poured into a stainless steel mould to form its final shape. After about 15 min, the hardened vancomycin-eluting PMMA bone cement was removed from the mould.

#### Manufacture of clinically relevant PMMA bone cement spacer (VTBC).

Tobramycin-sulfate (3.6 g) and vancomycin HCl (1 g) that had been crushed with a mortar and pestle and passed through a 75 μm sieve was mechanically mixed with PMMA powder (30 g) for 30 min at room temperature. After thorough mixing, the cement's liquid monomer was added and then mixed thoroughly with spatula. The antibiotic-containing cement dough was poured into a stainless steel mould to form its final shape. After about 15 min, the hardened VTBC was removed from the mould. VTBC samples were ethylene oxide sterilized before implantation.

#### In vitro drug release from drug-eluting UHMWPE and drug-eluting PMMA bone cement.

For drug-eluting UHMWPE, blocks (5 mm × 5 mm × 20 mm; n = 6) were cut from the consolidated samples. For drug-eluting PMMA bone cement, vancomycin-cement dough was poured into a stainless steel mould to form 25 mm × 5 mm × 20 mm blocks. Each block was immersed in 1 ml PBS at 37 °C; after 6 h, 24 h, every 24 h for 1 week, and then once every week up to 12 months, the blocks were washed with PBS and placed in new PBS (1 ml). Concentrations of vancomycin and rifampin were determined using ultraviolet–visible spectroscopy (UV–Vis Cary100, Varian) at 280 nm (vancomycin) and 450 nm (rifampin). The rate of drug release was calculated by dividing the measured concentration by the duration that the sample had been in contact with PBS.

#### Scanning electron microscopy.

All LDPE, UHMWPE and PMMA bone cement samples were sputter coated with a thin layer of gold/palladium and imaged on a Zeiss Supra55VP microscope. Both Everhart–Thorley and Inlens detectors were used to acquire the images.

#### Structural analysis of drug-eluting UHMWPE with highly eccentric drug clusters using micro-computed tomography (micro-CT).

Tomograms of cylindrical pins (9 mm diameter, 5 mm long) were acquired and three-dimensional (3D) reconstruction was performed using a cone-beam X-ray scanner (μCT 40, Scanco Medical) with a voxel resolution of ~10 μm. Porosity analysis and pore accessibility were analysed using the iMorph software package (version 3.1; www.imorph.fr)\(^4\). The resulting tomogram was then thresholded to partition between the pores and the polymeric matrix. Porosity was calculated by dividing the volume belonging to the pores to the total volume of the samples. The accessible porosity module implanted in iMorph allowed quantification of the pore volume accessible from one side of the sample by a particle depending on its size.

#### Tensile strength measurement.

Type V samples (n = 5 for each group) were stamped out of 3.2-mm-thin sections of the materials mentioned above according to ASTM-D638. These samples were tested in tension (Insight) with a crosshead speed of 10 mm min\(^{-1}\). The stress and strain were recorded at 100 Hz and the gauge length was monitored using a laser extensometer. The engineering stress–strain curves were calculated using the crosshead displacement. The UTS, yield strength, elongation at break, work to failure, and Young's modulus (E) were calculated.

#### Fracture toughness measurement.

Samples (63.5 mm × 12.7 mm × 6.35 mm\(^2\); n = 5) were double notched according to ASTM-D256 and were impacted fractured with a hammer (CEAST Instron). The energy loss of the pendulum after impact was recorded as the impact strength of the samples.

#### Determination of wear rate by bidirectional pin-on-disc test.

Cylindrical pins (9 mm diameter, 13 mm long; n = 3 for each group) were machined using a computer numerical control (CNC) mill (ShopBot) from the materials prepared above. The pins were wear tested with a rectangular pattern (5 mm × 10 mm) against polished cobalt–chromium (CoCr) discs at 2 Hz in undiluted, preserved bovine serum as a lubricant. The pins were cleaned and weighed before testing and at 0, 0.5, 1, 3, 6 and 12 months after the first 0.5 MC up to 1.2 MC. The wear rate was determined by a linear regression of the weight loss as a function of the number of cycles from 0.5 to 1.2 MC.
Antibacterial activity of VPE and vancomycin-eluting PMMA bone cement. Relative antibacterial activity of VPE and bone cement was assessed using a protocol modified from ref. 40. Cylindrical discs (8 mm diameter, 3 mm thick) of VPE and vancomycin-eluting PMMA bone cement were sterilized using ethylene oxide. Test organisms (S. aureus, ATCC 29213 and Staphylococcus epidermidis, ATCC 35984) were cultured in tryptic soy broth at 37 °C for 24 h and subsequently plated to Mueller–Hinton II agar at 37 °C for 18 h. Three to five colonies were then selected and suspended in Mueller–Hinton II broth and the inoculum concentration was diluted to 0.5 McFarland turbidity standards. The surface of a new Mueller–Hinton II agar plate was then covered uniformly with bacterial suspension using a sterile swab. Samples were placed on the surface of the Mueller–Hinton II agar plates that had been seeded with either the S. aureus or S. epidermidis strains and further incubated at 37 °C for 24 h. Pictures of the back of the plates were taken to calculate the inhibition (that is, the clear area with no sign of bacterial growth) was measured using Image J software (version 1.5). When bacteria grew to the immediate 24 h for 3 weeks.

Determination of vancomycin grafting on gamma-beam-irradiated UHMWPE. VPE, RPMVE and UHMWPE with no antibiotics (the control) were incubated in PBS for 12 months; the PBS was replaced every week until the end of the study. At 12 months, no vancomycin and rifampin was detected by either UV–vis or HPLC. Samples were washed twice with PBS and blocked for 30 min using 10% fetal bovine serum in PBS. Antigen–antibody complex was detected using Syto9 and propidium iodide. A two-photon fluorescence microscopy (Nikon Eclipse TE2000). 488-coupled goat anti-mouse IgM (A-21042, Thermo Fisher) diluted 1:300 in PBS. Species were visualized using an inverted fluorescence microscope (Nikon Eclipse TE2000).

Antibacterial activity of surface-bonded vancomycin-irradiated UHMWPE. VPE, RPMVE and UHMWPE with no antibiotics (the control) were incubated in PBS for 12 months; the PBS was replaced every week until the end of the study. At 12 months, no vancomycin and rifampin was detected by either UV–vis or HPLC. Samples were washed in PBS and sterilized with ethylene oxide before incubation in 1 ml of 1% dextrose/PBS. S. aureus was cultured in trypticase soy broth for 12 h. The culture was pelleted by centrifugation at 3,200 × g for 5 min and then resuspended in Mueller–Hinton II broth to create 1.5×10⁶ cfu ml⁻¹ using 0.5 McFarland standard. The bacterial suspension (2µl) was added to each well and the cultures were incubated at 37 °C for 24 h. Samples were then washed twice with PBS to remove planktonic bacteria. Samples were stained using a Live/Dead BacLight Viability kit (Molecular Probes) that contained Syto 9 and propidium iodide. Samples were imaged using an inverted fluorescence microscope, where live bacteria fluoresced green and dead bacteria fluoresced red.

Two-photon fluorescence microscopy. For quantification of antibacterial activity, a home-built, two-photon fluorescence microscope was employed to image the samples stained with the Live/Dead BacLight Viability kits. The system included a mode-locked titanium–sapphire laser (MaiTai DeepSee eHP, Newport), which provided light at ~150 fs pulse width at a 80 MHz repetition rate. The emitted fluorescence was detected using a mode-locked titanium–sapphire laser (MaiTai DeepSee eHP, Newport), which provided light at ~150 fs pulse width at a 80 MHz repetition rate. The emitted fluorescence was detected using a two-photon fluorescence microscope (Nikon Eclipse Ti-U). Samples were imaged using an inverted microscope. Percent red fluorescence, corresponding to percent cell death, was calculated using Matlab (r2015b; www.mathworks.com/products/matlab.html) by dividing the number of red pixels by the total number of fluorescent pixels.

Lapine planktonic bacteria PJI model. Study approval was granted from Pine Acres Research Facility Institutional Animal Care and Use Committee (protocol 15-06). Based on the pilot in vivo mouse study, the standard deviation in total flux from bioluminescence was 200,000 pps⁻¹. Taking type I error of 5% and 80% power to detect the mean difference of the total flux in control and treatment groups of 370,000 pps⁻¹, a sample size of at least 4.6 was needed per group. In total, ten fully immune-competent, skeletal mature male New Zealand rabbits aged 12 months were used. Animals were randomly assigned to control (non-antibiotic-eluating UHMWPE) or VPE (70% vancomycin-bonded UHMWPE) groups. Each rabbit had one of the following implants: UHMWPE-only implants (3 mm diameter, 6 mm height) in the patellofemoral groove, and one beaded titanium rod in the tibial canal (4 mm diameter, 12 mm length). Each rabbit in the VPE group received two VPE implants (same dimensions as control) in the patellofemoral groove and one beaded titanium rod in the tibial canal (same dimensions as control).

Antimicrobial activity of surface-bonded vancomycin-irradiated UHMWPE. VPE, RPMVE and UHMWPE with no antibiotics (the control) were incubated in PBS for 12 months; the PBS was replaced every week until the end of the study. At 12 months, no vancomycin and rifampin was detected by either UV–vis or HPLC. Samples were washed in PBS and sterilized with ethylene oxide before incubation in 1 ml of 1% dextrose/PBS. S. aureus was cultured in trypticase soy broth for 12 h. The culture was pelleted by centrifugation at 3,200 × g for 5 min and then resuspended in Mueller–Hinton II broth to create 1.5×10⁶ cfu ml⁻¹ using 0.5 McFarland standard. The bacterial suspension (2µl) was added to each well and the cultures were incubated at 37 °C for 24 h. Samples were then washed twice with PBS to remove planktonic bacteria. Samples were stained using a Live/Dead BacLight Viability kit (Molecular Probes) that contained Syto 9 and propidium iodide. Samples were imaged using an inverted fluorescence microscope, where live bacteria fluoresced green and dead bacteria fluoresced red.

Two-photon fluorescence microscopy. For quantification of antibacterial activity, a home-built, two-photon fluorescence microscope was employed to image the samples stained with the Live/Dead BacLight Viability kits. The system included a mode-locked titanium–sapphire laser (MaiTai DeepSee eHP, Newport), which provided light at ~150 fs pulse width at a 80 MHz repetition rate. The emitted light was detected by two photomultiplier tubes through appropriate dichroic and bandpass filters for Syto9 and propidium iodide. A×10, 0.3 numerical aperture objective (Leica) was used for visualization of multiple beads in one field-of-view (FOV; at ×10 this was approximately 600 × 600 µm²), while a×0.6, 0.6 numerical aperture objective (Nikon) was used for quantification of live/dead bacteria fluorescence. At least five images were randomly selected across each sample for data quantification.

Antibacterial activity of RVPE on biofilm between the bone–titanium interface. RVPE was machined into discs (5 mm diameter). The following were also used: (1) a 4 mm-thick consolidated UHMWPE without additives (control), which was prepared using the same conditioning conditions; (2) titanium discs containing one side with titanium beads (10 mm diameter, 5 mm thickness, bead diameter 100 µm; manufactured by Orchid Orthopedics); and (3) bovine cortical bone discs (10 mm diameter, 3 mm thickness; the bovine cortical bone was machined from bovine tibia obtained from Animal Technology). All samples were sterilized with ethylene oxide gas. Fresh overnight liquid culture of bioluminescent S. aureus was diluted to 2×10⁶ cfu ml⁻¹ and 50 µl of the liquid culture was added on top of the bead surface of the titanium discs to simulate an infection at an orthopaedic implant–bone interface. Cortical bone was added on top of the titanium discs seeded with bacteria and held together with a circular clamp (McMaster–Carr). The constructs were immersed in 5 ml of fresh Mueller–Hinton II broth and then incubated at 37 °C for 24 h. Pre-emptive analgesia was administered 30 min before the procedure started (buprenorphine 0.02–0.05 mg kg⁻¹ subcutaneously (SC)). No pre- or post-operative antibiotics were administered. The rabbits were placed in the supine position and the right or left leg was freshly prepared and draped in a sterile fashion (randomization of operated leg was established using www.random.org). A parapatellar incision was performed, the joint capsule was incised, the patella was displaced and two osteochondral defects were created in the trochlear groove (2.9 mm diameter, 6 mm depth). No antibiotic polyethylene (control branch) or VPE (VPE branches) implants were press-fitted into the defects. For the titanium island, the tibial plateau was accessed and a defect was created by drilling distally into the marrow, creating a 3.9-mm-diameter and 12-mm-depth defect. Bioluminescent S. aureus (5×10⁶ cfu in 50 µl 0.9% saline) was injected into the tibial defect, followed by press-fitting the titanium implant to seal the bacteria in situ. The patella was then relocated onto the trochlear groove and soft tissues were approximated using interrupted sutures. An additional dose of 50 µl of bioluminescent S. aureus in 50 µl 0.9% saline was injected into the knee. All animals received buprenorphine 0.02–0.05 mg kg⁻¹ SC every 12 hours throughout the study. After recovering from anaesthesia, rabbits were housed individually in cages (~58.8 cm x 63.5 cm x 66.6 cm). Load bearing on implants was allowed immediately after surgery, as no postoperative limiting motion device was utilized. Twice a day, rabbits were removed from their cages and placed in an open space to visually inspect the operated joint and gait. All animals were monitored at least twice throughout the study. Complete blood count and chemistry (vancomycin, creatinine, body-urea nitrogen, alanine aminotransferase and alkaline phosphatase) were assessed before surgery and postoperatively on day 3, day 7, day 14 and day 21.

Two-photon bioluminescence imaging was performed on all operated knees (a midline incision was performed on the knee and the joint capsule was opened to expose the joint space). Bioluminescence signal was measured whenever the rabbits expired or when the study endpoint was reached (day 21). After imaging, the knees were dissected to aseptically isolate the femur, quadriceps tendon (including patella and patellar tendon), tibia, titanium and UHMWPE implants. The titanium rods were stained with BacLight Bacterial Live/Dead Stain and imaged using two-photon fluorescence microscopy to detect presence of live bacteria. The femur, quadriceps tendon, tibia and UHMWPE implants were separately sonicated in sterile saline; saline was then cultured in Mueller–Hinton II broth at 37°C for 24 h to detect live bacteria.
To create the S. aureus biofilm covered titanium rod, fresh overnight liquid culture of bioluminescent S. aureus was diluted to 5 × 10^6 cfu ml⁻¹. The liquid culture (50μl) was added to 2 ml of Mueller–Hinton II broth. A sterile titanium rod was then immersed in the bacterial suspension and incubated at 37°C for 48h. Titanium rods were washed with PBS twice and then imaged with bioluminescent imaging to ensure uniform biofilm formation on all of the samples. One titanium rod was sacrificed for measurement of the biofilm thickness. The samples for use were then stained using a Live/Dead BacLight Viability kit that contained Cyto 9 and propidium iodide and imaged using two-photon fluorescence microscopy.

Anaesthesia was achieved using intramuscular ketamine-xylazine (40mg kg⁻¹−5mg kg⁻¹) and inhaled isoflurane (1.5–2.5%) supplemented with oxygen (1.21min⁻¹). Pre-emptive analgesia was administered before the procedure started (buprenorphine 0.02mg kg⁻¹). No pre- or post-operative antibiotics were administered. The rabbits were placed in the supine position and the right or left leg was prepped and draped in a sterile fashion (randomization of operated leg established using www.random.org). A parapatellar incision was performed, the joint capsule was incised, the patella was displaced and a 12-mm-depth defect was created in the trochlear groove (2.9 mm diameter, 6 mm depth). Control (for control branches) or VPE (for VPE branches) implants were press-fitted into the defects. For the titanium implant, the tibial plateau was accessed and a defect was created by drilling distally into the marrow cavity, creating a 3.9-mm-long and 12-mm-depth defect. The biofilm-laden titanium implant was then press-fitted into the tibial canal. Load bearing on implants was allowed immediately after surgery, as no postoperative limiting motion device was utilized. Twice a day, rabbits were removed from their cages and placed in an open space to visually inspect the operated joint and gait. All animals were monitored at least twice per day for 3 days following surgery and at least once per day for the remainder of the study. Complete blood count and chemistry (vancomycin, creatinine, body urea nitrogen, alanine aminotransferase and alkaline phosphatase) were assessed before surgery and postoperatively on day 3, day 7, day 14 and day 21.

Postmortem bioluminescence imaging, tissues and implant sonication were performed as described in ‘Lapine planktonic bacteria PJI model’.

Murine osseointegration model. Based on the pilot in vivo rat study, the standard deviation in BV/TV was 15%. Taking type I error of 5% and 80% power to detect a mean difference of BV/TV between the control and treatment groups of 23%, a sample size of at least four rats was needed per group. Eight Sprague–Dawley rats aged 8 weeks were randomly assigned into either control (non-antibiotic-eluting UHMWPE) or VPE (layered 6.7 wt% vancomycin and 3.3 wt% rifampin in UHMWPE and non-antibiotic UHMWPE) groups. Each rat in the control group received an UHMWPE implant without antibiotics. Each rat in the antibiotic-eluting UHMWPE) or RVPE (layered 6.7 wt% vancomycin and 3.3 wt% rifampin in UHMWPE and non-antibiotic UHMWPE) groups. Each rat in the control group received an UHMWPE implant without antibiotics (3 mm diameter, 4 mm length) transcondylarly in the medial distal femur and one stainless steel screw (3.5 mm diameter, 5 mm length) in the patellofemoral groove and one beaded titanium implant covered with micro-CT to give 8

3 days following surgery and at least once per day for the remainder of the study.

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Author contributions
V.J.S., D.A.B., E.O., O.K.M., H.R., A.A.E., H.M., S.I.J.K. and S.H.Y. designed the experiments. V.J.S., D.A.B. and S.I.J.K. performed the experiments. All authors were involved in the analyses and interpretation of the data. V.J.S., D.A.B., S.I.J.K., E.O. and O.K.M. wrote the paper, with the help of the co-authors.

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Competing interests
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