Dynamic actuation enhances transport and extends therapeutic lifespan in an implantable drug delivery platform

Our immune system has evolved to acquire a robust defence mechanism against foreign body invasion. In the presence of a ‘foreign object’, neutrophil infiltration initiates a cascade of inflammatory and wound healing processes, which precipitates the formation of a dense, encapsulating fibrous capsule (FC)\(^1\). The foreign body response (FBR) minimises exposure to potential toxins and is often advantageous; for example, soldiers with bullet wounds rarely develop clinical symptoms of lead poisoning\(^4\). This protective response, however, is detrimental to the long-term durability of implantable biomedical devices such as breast implants\(^5\), heart valves\(^6\), and pacemakers\(^7\). These devices have transformed modern patient care, but the immune infiltration and fibrotic

Fibrous capsule (FC) formation, secondary to the foreign body response (FBR), impedes molecular transport and is detrimental to the long-term efficacy of implantable drug delivery devices, especially when tunable, temporal control is necessary. We report the development of an implantable mechanotherapeutic drug delivery platform to mitigate and overcome this host immune response using two distinct, yet synergistic soft robotic strategies. Firstly, daily intermittent actuation (cycling at 1 Hz for 5 minutes every 12 hours) preserves long-term, rapid delivery of a model drug (insulin) over 8 weeks of implantation, by mediating local immunomodulation of the cellular FBR and inducing multiphasic temporal FC changes. Secondly, actuation-mediated rapid release of therapy can enhance mass transport and therapeutic effect with tunable, temporal control. In a step towards clinical translation, we utilise a minimally invasive percutaneous approach to implant a scaled-up device in a human cadaveric model. Our soft actutable platform has potential clinical utility for a variety of indications where transport is affected by fibrosis, such as the management of type 1 diabetes.
response can negate device function over time, necessitating painful revision or replacement surgery. This fibrous barrier is particularly deleterious for biosensors, such as continuous glucose monitors, and controlled drug release devices, such as insulin pumps, which rely on interactive communication with their local tissue environment\textsuperscript{31}. In such cases, the formation of a hypopermeable capsule can impede transport of molecules, both to\textsuperscript{40} and from\textsuperscript{32} the implant, and lead to therapy failure.

One pertinent example is the management of type 1 diabetes, a chronic disease affecting 18 million people worldwide, with an annual economic burden of greater than $90 billion USD (Study: Disease-Modifying Therapies Needed to Offset Costs of Type 1 Diabetes - Juvenile Diabetes Research Foundation). Successful implementation and clinical adoption of an artificial pancreas combining continuous glucose monitoring with the rapid, responsive, release of insulin (or glucagon) would vastly improve outcomes and quality of life for this patient population. The development of a fully automated closed loop insulin delivery system would reduce user burden, remove the need for multiple daily injections, and increase time spent in the optimal blood glucose range, which is imperative for the prevention of long-term diabetic complications. Unfortunately, current efforts at developing such a device have been hindered by the dynamic and unpredictable FBR, leading to glucose sensing inaccuracy, inhibition of insulin release, and gradual loss of functionality in the weeks to months following implantation\textsuperscript{43,17}. Looking towards the future, living implants containing stem cell-derived pancreatic β-cells represent a potential cure for diabetes. However, the attenuation of oxygen and molecular transport due to the FC barrier still constitutes a major hurdle to successful clinical translation of these implants\textsuperscript{30,31,38,39}. It is evident that a method to (i) mitigate the FBR or (ii) improve transport across the FC could transform the management of this pervasive disease. Furthermore, such a method could have broader implications for a range of diseases and device-based treatments affected by the FBR.

Conventional strategies to mitigate the FBR have focused on changing the attributes of the implant material itself, such as its size, shape, topography and surface coating\textsuperscript{30,38}, or involved the concomitant delivery of FBR modifying drugs, such as steroidal anti-inflammatory, anti-fibrotic, and anti-proliferative agents\textsuperscript{32}. While these strategies have shown promise, they have not succeeded in completely disarming the FBR and possess several limitations. Firstly, materials are generally pre-designed to target only one component or timepoint of an immune response that is multifaceted and temporally dynamic. Historically, studies have observed biomechanical stress as a pro-fibrotic or regenerative stimulus\textsuperscript{1}, demonstrating that application of stretch\textsuperscript{36,40} fluid flow\textsuperscript{42,44} or compression\textsuperscript{43} to cells can lead to increased deposition of collagenous matrix. Accordingly, many anti-FBR strategies have focused on minimising the mechanical mismatch, interfacial stress, and movement between the implant and local tissue. One such approach seeks to challenge this status quo and reveals the potential for a dynamic mechanotherapeutic that uses low-magnitude, atraumatic, tissue strain and convective flow as a defence mechanism against the invading cellular FBR. Interestingly, some studies have observed that small magnitude, dynamic loading has anti-inflammatory and pro-regenerative effects. Previous work applying dynamic loading to tissue has used daily mechanical, pneumatic, or magnetic stimuli, either internally or externally, to apply cyclic loads, inducing strains ranging from 4 to 50%, with each cycle lasting between 1 s and 10 min\textsuperscript{44,45}. These studies have demonstrated beneficial effects in terms of vascularisation\textsuperscript{44,45,50}, functional tissue regeneration\textsuperscript{46,49,51}, and anti-inflammatory gene expression\textsuperscript{52}. These prior works on mechanical loading have indicated the presence of a therapeutic threshold, beyond which tissue damage and inflammation occurs\textsuperscript{47,49}.

Our lab previously demonstrated the fibrotic attenuating potential of a dynamic device during the initial stages of the FBR (2 weeks)\textsuperscript{34}. Based on this foundational work, we propose that application of intermittent, cyclical, low amplitude actuation can act as an oscillating shield against the invading, multiphasic FBR, induce local immunomodulatory effects, and create a favourable environment for the rapid long term transport of macromolecular drug therapy (Fig. 1a). To test this hypothesis, we first designed a reservoir suitable for long-term tissue implantation and the precise repetitive delivery of both drug and actuation therapy. Figure 1b shows the multi-layered composition of STAR, with a low-profile design that minimises the presence of sharp angles or edges which may exacerbate the FBR\textsuperscript{41,53}. A therapeutic chamber lies in direct contact with underlying tissue and is separated by a membrane with an array of 10 μm pores (Supplementary Fig 1). A connected indwelling catheter line allows for delivery of drug therapy with temporal control (Fig. 1b, c). Superimposed on the therapeutic chamber is an actuation chamber that can be pressurised to elicit controlled oscillation of the porous, tissue-contacting membrane (Fig. 1c, d; Supplementary Movie 1). Imbalances between the mechanical properties of the implant and the surrounding tissue are also known to exacerbate FC formation, with stiffer implants eliciting a heightened immune response\textsuperscript{52}. For this reason, STAR was manufactured from thermoplastic polyurethane (TPU) with an elastic modulus of ~15 MPA (Fig. 1d), similar to that of extracellular matrix\textsuperscript{13,14}. STAR can easily be scaled between animal models using 3D printed moulds and a simple thermoforming/heat-sealing process (Supplementary Fig 2).
As part of device design and optimisation, we performed finite element (FE) simulations to understand the biomechanical changes mediated by actuation, particularly the relationships between membrane deflection, convective flow, and tissue strain (Fig. 1e, f; Supplementary Fig 3). Based on recently reported results⁴⁹, we designed our soft robotic actuation strategy to induce tissue strain that would fall within the atraumatic range (<40%), and hypothesise that this regimen would mitigate the FBR by creating convective flow disruptive to the cellular immune response.

Insulin transport test (ITT): a longitudinal, in vivo method to study the effect of the FBR on therapy transport
Following STAR design and manufacture, we next developed a method to longitudinally monitor the detrimental and progressive effect of the FBR on therapy transport (Fig. 2a). Insulin was chosen as our model macromolecular drug to allow for a real-time, dose-dependent measurement of functional response as insulin crosses the FC and enters the bloodstream.

First, we implanted static STAR devices (without IA) on the subcutaneous dorsal aspect of C57BL/6 mice (Supplementary Fig 4). Next, we injected short-acting human insulin into the device and monitored diffusion-based release across the FC into the systemic circulation via serial blood glucose measurements at day 3 (baseline, BL), 2 weeks, and 3 weeks post implantation (Fig. 2b).

The functional efficacy of an equivalent dose of insulin decreased with implantation time and with progression of the FBR, as indicated by the maximum blood glucose (BG) drop (Fig. 2c) and the area under the BG curve (AUC; Supplementary Fig 5a, b). To corroborate these results, we analysed FC thickness longitudinally using 2D micro-computed tomography (µCT; Fig. 2d) and related it to these functional results. As expected, thickness of the capsule increased with time (Fig. 2e). Importantly, we observed an inverse linear relationship ($r = -0.929$) between FC thickness and insulin efficacy metrics (Fig. 2f, Supplementary Fig 5c).

In a final validation step, we examined the effect of FC thickness on therapy release using a multiphysics computational diffusion model. Our simulations corroborate our experimental results, also indicating that increasing FC thickness has a pronounced effect on drug transport (Fig. 2g), introducing a time lag for the desired therapeutic concentration to cross the capsule and elicit a functional effect (Fig. 2h).

In summary, this data demonstrate the development and validation of a pre-clinical model that can detect real-time changes in FC formation via its effect on macromolecular transport and track these changes over time.
Dynamic intermittent actuation (IA) extends therapeutic lifespan of STAR

Following device and in vivo model development, we designed an 8-week longitudinal preclinical study to test the ability of STAR to modulate the FBR and improve macromolecular delivery across the formed FC.

We implanted STAR devices (without drug) on the dorsal subcutaneous aspect of three groups of mice (Fig. 3a). In two experimental groups, we performed STAR-enabled IA with cyclic pressure input of 2 psi at 1 Hz for 5 min every 12 h using a custom-made pneumatic control system (Supplementary Fig 6). One group (8W IA) was intermittently actuated for the total study duration of 8 weeks, while the second group (3W IA) received 3 weeks of IA followed by no actuation for the remainder of the study. A third group that did not receive IA served as the control. We then injected short-acting human insulin (2 IU/kg) into the device at various time points post-implantation: 2, 3, 4, 5 and 8 weeks as well as day 3, which served as a BL. We monitored passive, diffusion-based transport across the formed FC and into the tissue.

![Fig. 2](https://example.com/fig2.png)

**Fig. 2** Development of a pre-clinical model to monitor the effect of FBR on therapy transport longitudinally. 

- **a** Schematic demonstrating detrimental effect of fibrous capsule (FC) formation on therapy delivery with time.
- **b** Blood glucose (BG) response to human insulin delivered via STAR, measured over 120 min at baseline (BL, day 3), week 2 and week 3. *n* = 5 mice at each time point.
- **c** Temporal evolution of the maximum BG % drop (denoting functional effect), calculated from b. 
- **d** Representative 2D µCT slice of STAR with fibrous encapsulation. Scale bar is 1 mm.
- **e** Average FC thickness encapsulating STAR at baseline (day 3), week 2 and week 3 following implantation. *n* = 3 mice at baseline and 2 weeks, 5 mice at 3 weeks. Data are means ± standard error of mean.
- **f** Relationship between FC thickness and maximum effect of insulin measured by reduction in blood glucose level.
- **g** COMSOL Multiphysics simulations showing spatial drug diffusion through FCs of varying thicknesses.
- **h** Temporal evolution of drug release percentage for varying FC thicknesses.
bloodstream via serial blood glucose measurements at these timepoints.

At baseline, insulin administration produced a similar drop in blood glucose in both IA and control groups (Fig. 3b, Supplementary Note 1). Over 8 weeks, the blood glucose curves separate, with decreased insulin responsiveness in the control and 3W IA groups, compared to the 8W IA group. Impressively, the 8W IA group maintained its rapid drop in blood glucose over the entire study duration.
Multiphasic temporal effects of intermittent actuation

Following the completion of our pre-clinical study, we next set out to analyse differences in FC composition at evolving timepoints to better understand the multiphasic cellular changes and key drivers of enhanced drug transport caused by IA (Fig. 4a). First, we investigated the initial, acute phase of the inflammatory FBR. Using immunofluorescent Ly-6G+ staining, we examined the pericapsular region for the presence of neutrophils, the first responders of the immune defence. We found that IA significantly reduces the presence of neutrophils at day 5 in comparison to the control (Fig. 4b, c). This result indicates that the application of IA can mediate a localised immunomodulatory effect.

We next assessed the activation of matrix-producing cells into a myofibroblast phenotype, a key contractile cell in fibrosis progression. The IA group exhibited a significant reduction in αSMA expression when compared to the control at 2 weeks (Fig. 4d, e). Despite observing differences in individual cell populations (neutrophils, myofibroblasts), we did not detect differences in overall cell number at equivalent timepoints (Fig. 4f, g).

Next, we investigated the macroscale capsular changes responsible for improved therapy transport. We examined evolving capsule thickness with longer periods of STAR implantation. IA mitigated capsule growth in the first 2 weeks following implantation, with a significant reduction in thickness observed w.r.t. the control at 2 weeks (Fig. 4h, i). This result aligns with the enhanced blood glucose responsiveness of the IA group at early timepoints (Fig. 3) and suggests that FC thickness is an important contributor to initial improvements in macromolecular transport.

By 8 weeks, however, capsule thickness had equalised between the IA and control groups (Fig. 4i). This result suggests that additional mechanisms are responsible for the sustained improvement in functional response to insulin in the IA group at later timepoints (Fig. 3). To investigate this further, we examined capsule vascularity, density, and the maturity of the collagen fibres. However, we did not observe differences that would account for improvements in macromolecular transport and functional effect (Supplementary Fig 7, Supplementary Note 1). By optical coherence analysis of polarised light microscopy images, we found that collagen fibres exhibited higher alignment in the IA group compared to control at week 9 (Fig. 4j, k). IA appeared to increase collagen alignment over time from 2 weeks to 8 weeks, whereas there was no temporal change in alignment observed in the control group (Fig. 4k). We posit that the lower degree of alignment, and therefore greater degree of fibre entanglement, in the control group creates steric hindrance which potentially slows or immobilises transport of macromolecules through the collagenous matrix.

Finally, we examined the ability of IA to protect against cellular invasion and blockage of the porous membrane of STAR. Scanning electron microscopy demonstrated clear differences in cellular infiltration between the control and IA group at the same week timepoint (Fig. 4i). This effect could be attributed to convective flow generated by STAR upon actuation (Supplementary Fig 3g). These capsular analyses reveal the pleiotropic role of IA in modulating the FBR and highlight cellular and structural changes that lead to improved transport of macromolecular therapy.

On-demand, actuation-mediated rapid release of drug using STAR

In addition to intermittent immunomodulatory actuation, we demonstrate another soft robotic actuation-based mechanism of augmenting drug transport. Actuation-mediated RR of a drug-loaded STAR device consists of a few (~1–5) cycles of on-demand actuation at the same magnitude as IA (2 psi, 1Hz). This strategy can accelerate mass transport of drug from the device reservoir (Fig. 5a, Supplementary Movie 2) into surrounding tissue (Fig. 5b, Supplementary Movie 3). Using this on-demand, convective flow-based approach, we investigated if RR could overcome a diffusion-limiting FC barrier by inducing higher concentration and pressure gradients (Fig. 5c, d).

First, we developed a multiphysics computational model comparing passive diffusion-based transport to RR (Fig. 5d–f). RR enhances drug transport across the capsule and thus higher concentrations can reach the therapeutic target in a temporally controlled manner (Fig. 5d, e). Furthermore, multiple actuation cycles can increase transcapillary transport in comparison to a single cycle, and thus dosing can be adapted to the specific clinical scenario (Fig. 5f). Péclét number (Pe) calculations’ estimate Pe = 2.35 for passive diffusion and Pe = 70.18 for actuation-mediated RR, suggesting that for a given dose of drug, the time required for passive drug delivery through a diffusion dominated process far exceeds that of actuation-mediated drug delivery, which is convection dominated.

To substantiate these simulations, we next investigated the utility of RR in vivo, following long-term implantation and development of a FC. We implanted two STAR devices in a Sprague Dawley rat model to evaluate the spatial distribution of drug with and without RR. On day 24 following implantation, we monitored the distribution area of a fluorescent small molecule drug analogue (Genhance 750) using an in vivo imaging system (IVIS) (Fig. 5g). While passive diffusion of Genhance was slow, RR led to a sharp increase (~7 fold) in drug distribution, despite presence of a FC (Fig. 5h).

In a final example, we demonstrated enhanced mass transport and downstream functional effect using RR in our ITT model at 2 weeks.
Fig. 4 | Multiphasic temporal effects of intermittent actuation (IA). a Timeline of multiphasic cellular and fibrous capsule (FC) changes induced by IA. b Representative fluorescent images of the FC stained with Ly-6G + (green) and DAPI (blue). Scale bars are 20 µm. c Quantification of neutrophils present within FC +/− IA at day 3 and 5. d Representative fluorescent images of the FC stained with α-SMA (green) and CD31 (red). Scale bars are 50 µm. e Quantification of myofibroblasts present within FC +/− IA at 2 weeks. f Representative histologic images of the FC stained with haematoxylin and eosin. Scale bars are 20 µm. g Quantification of total cells/capsular area +/− IA at day 3, day 5, and 2 weeks. h Representative topographical reconstructions of µCT images showing the differences in FC thickness +/− IA at 2 weeks. i Average FC thickness of the control and actuated groups at day 3, day 5, 2 weeks, and 8 weeks with two measurements taken per animal. j Representative polarised light microscopy images of the FC obtained after picrosirius red staining at 8 weeks. Scale bars are 100 µm. k Quantification of the FC collagen fibre orientation by optical coherency with 60 ROIs per animal. l Representative SEM images demonstrating reduced cellular invasion with actuation at the 8-week timepoint. Scale bars are 500 µm. n = 2–6 animals per group; data are means ± standard error of mean; *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. See Supplementary Note 1 for detailed statistical analyses.
after STAR implantation (Fig. 5i). Passive diffusion of insulin led to a drop in blood glucose over 120 min in all animals. At this point, food was given to one group to allow recovery of blood glucose levels towards baseline. At 150 min, this group was subjected to 5 cycles of actuation (with the same parameters of 2 psi at 1 Hz). No additional insulin was administered after the initial dose given at the start of the ITT. Despite a reduced insulin concentration gradient across the device and attenuated insulin sensitivity in the post-prandial animals, actuation-mediated RR led to a significant reduction in blood glucose levels over 15 min due to augmented release of insulin from STAR (Fig. 5i).

These results support the development of an on-demand actuation-based method to enhance transport across a diffusion limiting FC.

**Minimally invasive surgical implantation and vision for clinical translation**

We demonstrate in a human cadaver model that the soft and foldable characteristics of STAR lend themselves to minimally invasive implantation, establishing feasibility of clinical translation. Our choice of material (TPU) enables scalability to clinically relevant dimensions (80 mm × 120 mm) and integration of additional elements such as deployment and adhesive channels, without changing the
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IA is the first element in STAR's armamentarium. By inducing strain at the tissue-contacting membrane and perturbing peri-device fluid flow, STAR acts as an oscillating mechanical shield against the invading cellular FBR. These localised mechanical effects create a favourable environment for the long-term transport of macromolecules. IA is able to preserve the functional effect of STAR over the repeated, non-invasive measurements enable longitudinal studies of complex, multiphasic phenomena with the ability to track individual animals and treatment groups over time.

### Discussion

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We demonstrated that IA produces a localised immunomodulatory effect by clearing neutrophils from the pericapsular site (Fig. 4b, c). The infiltration of neutrophils is an important first step in the FBR, initiating and propagating the inflammatory process, which causes the subsequent recruitment of cell populations known to develop the FC (e.g., macrophages). Early modulation of the neutrophil response may have important long-term consequences on the FBR. Indeed, we observed a trend towards better functional effect in the 3W IA group compared to control even after stopping actuation. Though this effect did not reach statistical significance, there may be some long-term benefits in therapy transport even with initial periods of actuation; however, it is clear that maximal anti-inflammatory benefit comes with continued actuation (Fig. 3D). A recent study by Seo et al.86, corroborates the mechanosensitive nature of neutrophil cell populations following dynamic loading for skeletal muscle regeneration. The authors postulated that mechanical flushing of chemoattractants was responsible for the reported decrease in neutrophils49. In this context, our work motivates further study on the effect of IA on pro-inflammatory chemoattractant gradients such as interleukin 1, 6 and 8 compared with direct mechanical effects on cell attachment, orientation, and function.

We noted a significant decrease in myofibroblast cell number with IA compared to control (Fig. 4d, e). The activation of matrix-producing cells into a myofibroblast phenotype, characterised by αSMA expression, is a critical step in fibrosis progression. Increased expression leads to heightened contractile activity, formation of stress fibres, and synthesis of extra-cellular matrix. Furthermore, activated fibrogenic cells can produce cytokines responsible for additional cell recruitment and propagation of the deleterious fibrotic response35. It is becoming increasingly evident that stiffness precedes, or is an important contributor to fibrosis.48. Thus, reducing myofibroblast expression and its effect on matrix stiffness may be a key strategy to modifying this self-perpetuating fibrotic effect.

In addition to multiphasic cellular changes with time, we also observed multiphasic differences in macro-capsular architectural evolution, with distinct differences between the IA and control groups. At early timepoints (2 weeks) following implantation, we observed differences in capsule thickness between groups (Fig. 4h, i), which aligns well with improved diffusion-based transport at these timepoints (Fig. 3b, f). FC thickness equalises between groups after 8 weeks of implantation, indicating that other mechanisms are responsible for the improved transport at later timepoints. We rejected several relevant hypotheses for improved transport in the IA group including vasculature, capsule density, and collagen maturity (Supplementary Fig. 7). However, we noted differences in collagen architecture and cellular infiltration into the device reservoir which may contribute to late differences in transport and functional effects between the groups (Fig. 4h–i). Further study will be necessary to fully elucidate and understand the multiple mechanisms at play. Note that 2 out of 6 mice in the control group had to be withdrawn from the study at later time points due to self-inflicted damage to their dorsal tissue and subcutaneous implant. Interestingly, this did not occur in any IA group mice. Capsular contracture mediated by excessive FBR is a painful condition87 that could rationalise this group difference, and future work could investigate this observation further.

In addition to IA, STAR possesses a second transport-augmenting strategy of RR. Actuation of a drug-loaded STAR can induce higher concentration and pressure gradients37,38, and thus improve drug transport across a formed FC with temporal control (Fig. 5). RR can be particularly advantageous for potent drugs where accurate dosing and a rapid time to functional effect are important, or macro-drugs such as proteins, where convective flow enhances diffusion-based flux, principally governed by molecular weight and concentration gradient114. Convection-enhanced delivery has been successfully used to improve distribution of chemotherapy in deep brain tumour targets, albeit with modest clinical outcomes125,126,132,133.

We envision several clinical use scenarios for IA and RR technologies demonstrated in this work. RR could be used independently of IA, such as for the rapid, on-demand delivery of therapeutics in response to a clinical emergency. Some relevant examples include the delivery of adrenaline for the treatment of anaphylaxis or glucagon for the treatment of hypoglycaemic coma. In both cases, impedance of delivery due to FC formation would have grave consequences.

An optimal FC mitigating strategy could also combine both IA and RR. For example, short daily bursts of IA (without drug) could attenuate the FBR to extend device lifespan and improve performance in long-term implantation. A temporally controlled and modular RR actuation regime could then be used to make rapid, precise dosage adjustments in accordance with the patient-specific clinical scenario and/or FBR severity. IA and RR are complementary strategies that elegantly make use of a single device design and pump, making STAR well suited to a variety of clinical scenarios.

The management of type 1 diabetes is one relevant clinical area where STAR could provide synergistic benefit. For example, IA could be applied to extend the lifespan of an artificial pancreas49, preventing unnecessary FBR-mediated blockages, linked hyperglycaemic events, and ultimately simplifying the dosing regimen and patient experience. In synergy, actuation-mediated RR could make rapid insulin adjustments and maintain blood glucose levels in the narrow window necessary to prevent long-term complications66. Looking further into the future, application of STAR could enable translation of next-generation bioartificial technologies utilising human-derived insulin-producing islet cells by modifying the transport-limiting FC, which has been a major barrier to the viability of cell-based therapeutics66,68,118.

Considering the need for daily IA for long-term efficacy, it is likely that embodiments will require a wearable pump, similar to those used in existing insulin pumps60.

STAR’s soft material endows it with biocompatibility advantages over rigid implantable drug delivery systems60, and lends itself to minimally invasive catheter implantation. In a step towards clinical translation, we scaled up the STAR device and developed a bespoke delivery tool as well as a minimally invasive procedure that is congruent with conventional interventional radiology techniques (Fig. 6). We demonstrated delivery of STAR to a clinically accessible intermuscular space in the anterior abdominal wall in a human cadaver model. This approach allowed for a short procedure time (∼20 min) for implantation of a human-scale device through a modified sheath using ultrasound guidance in the hands of an experienced interventional radiologist. Additional design features demonstrated correct deployment and adhesive delivery to maintain device position in the tissue plane. Thus, STAR can be quickly implanted by interventionalists in an outpatient setting under local anaesthesia using an established imaging modality.

Though we have demonstrated robust preclinical results in a long-term mouse model, there are several limitations and barriers to clinical translation. Our findings from implantation in the dorsal subcutaneous space of mice may not directly predict similar results in humans at different anatomical locations (e.g., abdominal intermuscular space), and further work is needed to understand how these anatomic and microenvironmental differences impact the effects of STAR. Although rodent models have been extensively used to study the FBR10,10, rodents have been shown to have different tissue collagen content in the subcutaneous space surrounding an implant and different metabolites in the interstitial fluid at implant interfaces, as compared to humans51. Moreover, differences in rodent skin, fur, and behaviours may subject implanted devices to different biomechanical forces than in humans111. Encouragingly, thus far, we have observed similar FBR mitigating effects with an IA regimen that is agnostic of species and device design4. In addition to this, the presence of conserved inflammatory pathways in FC formation across species22 suggests that STAR may have a similar benefit in prolonging implant lifespan in humans.
Although there have been a number of prior studies that examine the effect of mechanical loading on inflammation and tissue regeneration, there is significant heterogeneity with regards to actuation methods, regimens, resulting deformations, target tissues, and animal models used\(^{44,45}\). Only a few studies have attempted to address the effect of varying tissue strain\(^{46,47}\) and loading frequency\(^{48}\); therefore, significant work is needed to define the optimal loading parameters that maximise the anti-inflammatory effects of mechanical actuation, which may differ with the type of tissue and mechanical stimulus.

We can draw six conclusions from this study: (1) The ITT represents a robust, longitudinal method to monitor macromolecular therapy transport across a developing FC in vivo. (2) The FBR can negate insulin transport over time from a static STAR device until complete implant isolation and therapy failure. (3) Intermittent actuation can preserve therapy transport at baseline levels and extend the therapeutic lifespan of STAR, even with long-term implantation. (4) IA can mediate immunomodulatory changes in the neutrophil inflammatory response and elicit downstream multiphasic temporal changes in cellular infiltration and capsule formation. (5) Actuation-mediated RR of a drug-loaded STAR device can synergistically enhance mass transport and therapeutic effect with tunable, temporal control, despite the presence of a FC. (6) Minimally invasive catheter implantation of STAR was possible in a human cadaver model, showing clinical translatability of our approach.

In summary, the STAR platform represents a new mechanotherapeutic approach to both mitigate and overcome the FBR, extending the lifespan and efficacy of implantable drug delivery devices. It holds vast clinical utility for a variety of indications where transport is affected by fibrosis, such as the management of type 1 diabetes.

Methods

Device manufacture for pre-clinical mouse model

One and two-channel positive, and corresponding negative moulds were 3D printed using VeroBlue resin (Stratasys Object30) (Supplementary Fig 2a). Thermoplastic urethane (TPU; 0.3 mm, XG0035, QING GEN) was vacuum thermoformed (Yescom Dental) over the positive two-channel mould (Supplementary Fig 2b). This process was then repeated with the positive one-channel using a thinner TPU (0.076 mm, HTM-8001-M, polyether, American Polyfilm) (Supplementary Fig 2b). Pores with 10 \(\mu\)m diameter were laser cut in a TPU membrane (0.076 mm, HTM-8001-M, polyether, American Polyfilm) using a UV Nanosecond laser (National Centre for Laser Applications, National University of Ireland Galway).

The thermoformed and laser-cut membranes were assembled in a negative mould (Supplementary Fig 2c). Mandrels of outer diameter 0.21 mm were inserted into the channels to retain patency. The assembly was heat sealed together using a heat transfer machine (330QXAI, PowerPress). The mandrel was removed and a TPU catheter tubing (0.037\(\times\)0.023\(\mu\)m, MRE037, Micro-Renathane, BrainTree Scientific) was inserted and heat sealed to the device using heat shrink tubing. The final assembled devices measured 15 mm (width) \(\times\)18 mm (length) \(\times\)2 mm (height) and consisted of two chambers—the larger measuring 12 \(\times\)6 mm and the smaller measuring 3 \(\times\)12 mm (Supplementary Fig 3a, b).

Device manufacture for pre-clinical rat model

Rat scale devices were produced as previously described\(^{34}\). Final devices measured 12 mm in length with the hemispherical reservoir measuring 3.9 mm in height and 3.5 mm in diameter, with variable lengths of 3Fr TPU catheter tubing.

Device manufacture for human-scale prototype

Human scale devices measuring 120 \(\times\)80 mm were produced as previously described (Supplementary Fig. 8)\(^{34}\). An additional deployment channel and actuation chamber were included to allow for minimally invasive delivery through a sheath and dynamic actuation following implantation (Supplementary Fig. 9).

Electropneumatic actuation and control system

A custom-made electropneumatic system to deliver actuation to the implanted device was developed as described in Supplementary Fig 6. The system consisted of pre-programmed electrical signalling to control pneumatic power sources. Pneumatic components included a positive pressure and vacuum generator, a pressure regulator, and electropneumatic (solenoid) valves. A programmable microcontroller board (Arduino Uno) along with a power source were used to establish an open loop control of the pneumatic power. Positive pressure was guided through an electropneumatic pressure regulator (ITV1030; SMC Inc.) which was controlled via the microcontroller board to adjust the precise actuation pressure. Actuation of the implanted device was then achieved by alternating the positive pressure for device expansion and negative pressure for device deflation. The delivery of this pneumatic actuation pattern was ensured by two electropneumatic solenoid valves (NVKF333; SMC Inc.) for positive and negative pressure which were controlled using the same microcontroller and two MOS-FETs coupled to the electrical supply power (Supplementary Fig. 6a). A manifolds was used to actuate multiple devices in separate animals simultaneously, ensuring that the set pressure level was consistently achieved on all the manifold channels (Supplementary Fig. 6b, c).

STAR membrane deflection characterisation

STAR devices were manufactured and placed in a custom-made 3D printed holder (Object30 Prime, Stratasys). Devices were pneumatically inflated from 1 to 9 psi using the electropneumatic actuation and control system described above. Images of membrane deflection were captured using a digital camera (Nikon DLSR) and tripod positioned in the side view. Deflection magnitude was subsequently analysed using ImageJ. Based on this strategy, a bi-chambered configuration was selected to investigate the effect of two distinct deflection magnitudes (0.58 and 1.3 mm) in our pre-clinical mouse model. It should be noted that the lower deflection magnitude was closely matched to our previous work.

STAR membrane pore characterisation

5 mm \(\times\)5 mm pieces of laser-cut porous TPU membranes were characterised by scanning electron microscopy (SEM) using a Hitachi S2400 microscope operating at 20 kV electron accelerating potential in backscatter electron imaging mode and a sample working distance between 8 and 10 mm. After imaging, pore diameters were measured from the images using the Hough circle transform function in Fiji 2.0.0 (ImageJ) (Supplementary Fig. 1).

Computational modelling

 Fluid-structure interaction (FSI) simulations using smoothed particle hydrodynamic (SPH) method were conducted to investigate the peri-implant fluid flow and the dynamics of drug transport under active delivery. All FSI simulations were created using Abaqus/Explicit 2018 (Dassault Systemes, Vélizy-Villacoublay, France). The device was modelled as a 3D surface geometry and meshed with 14,636 four-node shell elements (Abaqus node type S4R). A Dirichlet boundary condition, where nodal displacement in all directions were fixed to zero, was applied on the edge of the bottom porous membrane to prevent rigid body motion. A pressure loading which linearly ramped up to 2 psi in 500 ms and ramped down to 0 psi in the next 500 ms was applied to the internal surface of the outer and middle membranes. The membranes were modelled using an Ogden 3rd order hyperelastic material with parameters, \(\mu_1 = -8.31\text{MPa}, \mu_2 = -0.36\text{MPa}, \mu_3 = 17.89\text{MPa}, \alpha_1 = 0.46, \alpha_2 = -3.62, \alpha_3 = -3.10\). The fluid domains, drug and outer fluid, were meshed with linear tetrahedral elements and each element was
A structural finite element (FE) model was constructed to investigate the deformation of the tissue underneath the device. The device was modelled with same geometry and material model as the FSI simulations. To model the skin constraint when the device is implanted subcutaneously, a dome shape shell structure with a linear elastic property ($E = 1$ MPa) was added on top of the device. The tissue was also modelled as a linear elastic material ($E = 15$ kPa). In terms of boundary conditions, the edge of the skin and the bottom face of the tissue were both fixed in all directions. Tie constraints were used to model the suture attachments between the device and the tissue. A general contact with friction coefficient of 0.5 was applied throughout the entire model. The inner chamber of the device was subjected to different linearly increasing pressure loadings (1 psi, 2 psi and 3 psi). From the FE simulations, strain contour plots and downward displacement contour plots of the tissue were extracted. The average strain and deflection were calculated at the interface between the device and the tissue.

FE simulations were conducted using COMSOL Multiphysics software version 5.6 (COMSOL, Burlington, MA). The 2D model contains three domains: the drug reservoir, the FC, and the outer fluid domain representing the body. The FC is a thin layer surrounding the device with thickness ranging from 50 μm to 200 μm. The outer fluid domain is a rectangular region with height and width of 5 mm and 20 mm, respectively. Mass transport was modelled using the transient diffusion-convection equation in the 'Transport of Diluted Species' module in COMSOL. Diffusivity in the reservoir and outer fluid domain was given as $855 \mu$m$^2$/s and the diffusivity in the FC was given as $50 \mu$m$^2$/s. Initial concentration of 1 mol/mm$^2$ was applied in the drug reservoir domain. Fluid velocity between pure fluid domain and porous media was calculated using the Brinkman Equations in COMSOL. The drug reservoir and the outer fluid domain were modelled as pure fluid domain with density of 997 kg/m$^3$ and viscosity of 0.01 Pa·s. The FC was modelled as porous media with permeability of 8.9E-16 m$^2$. A mass transport model was constructed to investigate the diffusion of the drug from the reservoir to the outer fluid domain. The model shows that the maximum device membrane deformation is 0.2 mm under the applied pressure.

Péclet number calculations

The Péclet number for mass transfer, for a characteristic length $L$, is defined as $Pe = uL/D$, where $u$ is the local flow velocity and $D$ is the diffusivity. For representative calculations, $L = 1$ mm was assumed. This assumption is based on experimental and computational data showing that the maximum device membrane deflection is ~1.5 mm and the estimated tissue deflection is ~0.73 mm (Supplementary Fig. 3). A diffusivity of $D = 0.855 \mu$m$^2$/s, which is the same value used in the COMSOL Multiphysics models above, was used. For the passive diffusion scenario, a reasonable estimate for $u$ is the velocity of interstitial fluid, which has been reported widely to be in the range $0.1$–$2 \mu$m/s. A flow velocity of 0.06 mm/s adjacent to the porous membrane immediately following actuation was calculated from the COMSOL simulations above.

Pre-clinical studies

Animal procedures were reviewed and approved according to ethical regulations by the Institutional Animal Care and Use Committee at Massachusetts Institute of Technology. Animals were housed in a facility with 12 h on/off light cycle, at 20–22 °C with a relative humidity ranging between 30 and 70%. Animals were singly housed with standard bedding and food for the duration of the study. All devices were sterilised using ethylene oxide before implantation.

Mouse pre-clinical surgery. Male C57BL/6 mice (25–30 g) were placed under anaesthesia using inhalable isoflurane (1–3%). A single dose of sustained-release buprenorphine (Bup-SR, 1 mg/kg) was administered subcutaneously to control pain. A STAR device was implanted subcutaneously in the mouse as depicted in Supplementary Fig. 4. To prepare the surgical site, the hair on the back of the mouse was removed using a clipper and topical depilatory cream, and the site was sterilised with three washes of Povidone-iodine and 70% ethanol. Medial dorsal incisions were made at the base of the neck and 1 cm from the tail (Supplementary Fig. 4a). A blunt dissection was made at the incision sites, and a curved haemostat was used to tunnel subcutaneously from the superior to the inferior sites. A transcutaneous self-sealing port available from Instech laboratories (VABM2B/22R22) was connected to the dorsal end of the therapy and actuation catheter of each STAR device. The 15 × 18 × 2 mm STAR device (Supplementary Fig. 3a, b) was then inserted under the skin via the superior incision site and tunnelled inferiorly into position. The device was secured to the underlying fascia with one suture at either side (7-0 monofilament). The port was then inserted under the skin via the superior incision site and connected using a PNP3M connecter (Instech) (Supplementary Fig. 4d). The tail was warmed using a HotHand warmer for 10 s prior to blood sampling. The area was then disinfected with a Kimwipe soaked in 70% ethanol. Finally, a sterile dressing was applied and the incision was sutured.

Insulin transport test (ITT). A kinetic measure of insulin release from STAR devices and subsequent effect on blood glucose levels was measured through an ITT. The mouse was weighed and a solution containing a dose of 1 IU/kg/150 μL was prepared from a stock solution of Humulin R U-100 short-acting human insulin. Animals were fasted for 4 h prior to the start of the ITT, and were kept in a clean cage without food and bedding for the duration of the test. An initial blood glucose measurement was taken to establish a baseline. An insulin preparation at a total dose of 2 IU/kg was then administered into the device via the transcutaneous self-sealing port available from Instech laboratories (VABM2B/22R22) at time = 0 min. A PNP3M connected to a 1 mL Luer Lock disposable syringe (BD) was used to administer the dose (Supplementary Fig 4e). Following administration, blood was sampled from the lateral tail vein of the mouse and serial blood glucose measurements were performed over 120 min using a Bayer Contour Next Blood Glucose Monitoring System at time = 15, 30, 45, 60, 75, 90, and 120 min. The animal was restrained using a commercial restrainer (TV-RED 150-STD, Braintree Scientific). The tail was warmed using a HotHand warmer for 10 s prior to blood sampling. The area was then disinfected with a Kimwipe soaked in 70% ethanol. Finally, venepuncture was performed using a 27-gauge needle (BD) and the measurement was recorded.

Intermittent actuation. Intermittent actuation was performed by connecting a custom-made electropneumatic actuation and control system (described above) to the self-sealing transcutaneous actuation port using a PNP3M connecter (Instech) (Supplementary Fig. 4d). The device was then cycled actuated at a controlled input pressure of 2 psi at 1 Hz for 5 min every 12 h as previously described. No drug was present in the device during IA throughout the study.

Long-term mouse preclinical study. Devices were implanted into male C57BL/6 mice as described above. ITTs as described above were performed in all mice at 2, 3, 4, 5 and 8 weeks following transplantation.
device implantation, after which point animals were euthanized by CO₂. Six devices were static controls, and ten devices were dynamically actuated for 5 min every 12 h. The actuation group was split at 3 weeks post-actuation, with one group (n = 5) stopping actuation and remaining passive thereafter, and another group (n = 5) continuing dynamic actuation for the entire 8-week study period (Fig. 3a).

**Actuation-mediated rapid release of insulin.** At 2 weeks following implantation, serial blood glucose measurements were performed over 120 min after insulin injection as described above. Food was given to the RR group at 120 min to allow recovery of blood glucose levels. Actuation-mediated RR was then performed by actuating the STAR device at 150 min. Note that no additional insulin was administered after the initial dose given at time = 0 min. The STAR actuation reservoir was connected to a custom-made pneumatic control unit, via the transcutaneous self-sealing access port, using a PNPSM connector (Instech) and pneumatically activated for 5 cycles of 2 psi cyclical pressure at 1 Hz. The duration of activation and evacuation were equivalent. Blood glucose levels were measured by tail vein sampling at four additional 15 min increments in 4 mice per group.

**Rat pre-clinical study.** Two female Sprague Dawley rats (250–300 g) were placed under anaesthesia using inhalable isoflurane (1–3%). Bup- SR (1 mg/kg) was administered subcutaneously to control pain. To prepare the surgical site, the hair on the back of the rats was removed, and the sites were sterilised with three washes of Betadine and 70% ethanol. A superior incision was made at the base of the neck for the port, and two inferior incisions were made 9 cm from the original incision along the back of the rat and 1 cm lateral of the spine. A blunt dissection was made at all incisions, and a pair of forceps was used to tunnel subcutaneously from the anterior to the posterior sites. A transcutaneous self-sealing port available from Instech laboratories (VABM2B/22R22) was connected to the dorsal end of the therapy cartridge (Supplementary Fig 9). The delivery sheath and STAR delivery device were split at 3 weeks post-actuation, with one group (n = 5) continuing passive thereafter, and another group (n = 5) continuing dynamic actuation for the entire 8-week study period (Fig. 3a).

**Human cadaveric studies.** The protocol for this study was approved by the National University of Ireland Galway (NUI Galway) Research Ethics Committee. All cadaveric material was bequeathed to the Medical School, NUI Galway, for further advancement of medical knowledge. Informed consent was obtained from next of kin as part of the bequeathment process. This is covered by legislation governing the practice of Anatomy in the Republic of Ireland (Medical Practitioners Act 2007). Whole adult male human cadavers were fixed with embalming fluid containing 21% methanol, 21% glycerine, 5.6% phenol and 3.1% formaldehyde. A Sel-dinger technique was used to access the transversus abdominis plane under ultrasound guidance⁶. The delivery system consisted of a delivery sheath, a space-creating balloon and the STAR delivery cartridge (Supplementary Fig 9). The delivery sheath and STAR delivery cartridge were directly 3D printed (Form2, Formlabs, Somerville, MA). The space-creating balloon consisted of a 3D printed shaft connected to a TPU balloon. A 4–14 MHz linear ultrasound transducer (Clarius) was used to visualise the muscular layers of the anterior abdominal wall in the cadaver. An 18-gauge needle was advanced into the transversus abdominis plane and physiological saline as injected to separate the muscle planes with hydro-dissection. The needle was exchanged over a 5 Fr, 10 cm sheath, and a 1 cm skin incision was made using a scalpel. An 0.035” Amplatz Super Stiff wire (Boston Scientific) was then advanced into the space, and the serial dilation was performed using an Amplatz-type renal dilator set (Boston Scientific), followed by the advancement of the custom-made delivery sheath into the tissue plane. The space-creating balloon was used to fully separate the tissue planes, and then exchanged for the delivery cartridge. STAR was then deployed using the cartridge into the intermuscular space. The cartridge and delivery sheath were removed, and reservoir filling was demonstrated with infusion of an ultrasound contrast agent (Sonovue) and visualised under ultrasound. Proper deployment of the device and positioning was confirmed with dissection.

**Histology and immunohistochemistry.** After euthanizing the animals with CO₂, each device and the immediate surrounding tissue were extracted. Tissues were fixed for 24 h using 10% formalin (pH 7.4). The tissue was then washed and stored in PBS. Fixed tissue samples were transected in half, oriented, and embedded in paraffin wax blocks for histological and immunohistochemical analyses. Each block was assigned a code for randomisation and blinding purposes. Sections of 7 μm were cut, deparaffinized in xylene, and rehydrated through a series of graded alcohols. For assessment of FC collagen maturity and arrangement, sections were stained in 0.1%
Fast Green and then in 0.1% Sirius red in saturated picric acid. Slides were then dehydrated through graded alcohols and cleared in two changes of xylene. The slides were cover slipped using DPX mounting medium and left to dry. Slides were imaged using Ocular 2.0 Imaging Software on an Olympus BX4 polarised light microscope (Mason Technology Ltd, Dublin, Ireland) at 20× magnification. Slides were imaged using Ocular 2.0 Imaging Software on an Olympus microscope (Mason Technology Ltd, Dublin, Ireland) at 40× magnification. For immuno-histochemical analysis, primary antibodies of CD3 (1:200; Ab182981, Abcam) and αSMA (1:500; ab7817, Abcam) were incubated for 1h at 37°C. Secondary antibodies of Alexa Fluor 594 goat anti-mouse immunoglobulin G (IgG; 1:200 Thermo Fisher Scientific), Alexa Fluor 594 goat anti-rabbit IgG (1:200; Thermo Fisher Scientific), and Alexa Fluor 488 goat anti-mouse IgG (1:200; Thermo Fisher Scientific) were incubated for 1h at room temperature, respectively. Primary antibody Ly-6G (1:100; Biologend 127602) was incubated for 1h at 37 °C after Tris-EDTA (pH 9) antigen retrieval. A ready probes mouse-on-mouse (Invitrogen, R37621) blocking solution was performed to block endogenous binding. Secondary antibody Alexa Fluor 488 goat anti-rat 488 (1:100; Thermo Fisher Scientific) was incubated for 1h at room temperature. Sections were stained with Hoechst and cover slipped using fluoromount. Immunofluorescence-stained slides were observed using a spinning disc inverted confocal microscope (CSU22, Yokagawa) combined with Andor iQ 2.3 software. For blood vessel analysis, CD31–HRP (DAB) staining of the FC was performed using a previously reported technique. From DAB stained slides, five random fields of view were acquired from two sections using light microscopy. Images were cropped to ensure only the capsule was included in the analysis. Sections were converted to 8-bit images and nuclei were manually thre-   e. 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groups. Unpaired, two-tailed, two-sample t-tests were used to assess the histological, immunohistochemical, vascularity, and radiodensity differences between the control and IA groups. Before performing t-tests, equality of variances was verified between groups using Levene’s test. The analyses were performed in OriginPro 2018b (OriginLab Corp.) and the same software was used to generate all plots. Data are represented as mean ± standard error of mean. Between-group differences were evaluated at a significance level of 95% (α = 0.05). The Bonferroni correction was applied for multiple comparisons by dividing α by m, where m is the number of comparisons, p was deemed significant at p < α/m. Exact p values for all statistical comparisons are presented in Supplementary Note 1.

Reporting summary
Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability
All data supporting the findings of this study are available within the article and the Supplementary Information. Data is available from the corresponding author(s) upon request.

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Acknowledgements

W.W., S.T.R., R.B., and G.P.D. acknowledge support from Science Foundation Ireland under grant SFI/12/RC/2278, Advanced Materials and Bioengineering Research (AMBER) Centre, Royal College of Surgeons in Ireland, National University of Ireland Galway, and Trinity College Dublin, Ireland. W.W., E.B.D., and E.T.R. acknowledge a Pilot and Feasibility Grant from the Juvenile Diabetes Research Fund (1-PNF-2019-778-S-B). N.A.W. and E.B.D. acknowledge funding from the Science Foundation Ireland Royal Society University Research Fellowship (URF/R1/191335). S.X.W. acknowledges funding from the National Institutes of Health training grant T32 HL007734. S.T.R. has received funding from the European Union’s Horizon 2020 research and innovation program under the Marie Skłodowska-Curie Actions Grant Agreement No. 713567. D.S.M. acknowledges funding from the Irish Research Council Government of Ireland Postgraduate Scholarship (GOIPG/2017/927) and a Fulbright Enterprise Ireland Award. E.B.D. and G.P.D. acknowledge the DRIVE project which has received funding from the European Union’s Horizon 2020 Framework Programme under Grant Agreement No. 645991. E.T.R. acknowledges departmental funding from the Institute for Medical Engineering and Science and the Mechanical Engineering Department at the Massachusetts Institute of Technology and funding from NSF EFRI grant 1935291. We thank the Centre for Microscopy and Imaging (NUI Galway) and Ciarán Weldon for assistance with SEM imaging. We thank Dr. Bo Ri Seo for providing the staining protocol for the neutrophil immune response.

Author contributions

W.W., D.G., S.X.W., G.P.D., E.B.D., and E.T.R. designed the study. W.W., D.G., S.X.W., N.A.W., R.E.L., R.B., S.T.R., D.S., R.O.C., D.S.M., K.L.M., C.E.V., M.A.H., J.O.D., and A.S.R. performed the experiments. Y.F. performed computational modelling. W.W., D.G., S.X.W., Y.F., N.A.W., R.E.L., R.B., L.T., D.A.D.-L, R.W., and E.B.D. analysed and reviewed the data. W.W., D.G., S.X.W., Y.F., N.A.W., R.E.L., S.T.R., G.P.D., E.B.D., and E.T.R. wrote the paper. All authors reviewed and edited the paper.

Competing interests

W.W., S.T.R., K.L.M., C.E.V., G.P.D., E.B.D., and E.T.R. are inventors on a pending patent application related to the device described here. The other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-022-32147-w.

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Peer review information Nature Communications thanks David Grainger and the anonymous reviewers for their contribution to the peer review of this work. Peer reviewer reports are available.

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