Biodegradable Untethered Magnetic Hydrogel Milli-Grippers

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Small-scale magnetic soft-bodied robots based on biocompatible and biodegradable materials are essential for their potential high-impact minimally invasive medical applications inside the human body. Therefore, a strategy for fully biodegradable untethered soft millirobots with encoded 3D magnetic anisotropy for their static or dynamic shape programming is presented. Such a robot body is comprised of a porcine extracellular matrix-derived collagen-based hydrogel network with embedded superparamagnetic iron oxide nanoparticles (SPIONs). 3D magnetization programming inside the hydrogel body is achieved by directionally self-assembled SPION chains using an external permanent magnet. As a proof-of-concept demonstration, a hydrogel milligripper that can undergo flexible and reversible shape deformations inside glycerol and biologically relevant liquid media is presented. The gripper can perform cargo grabbing, transportation by rolling, and release by controlling magnetic field inputs. These milli-grippers can be completely degraded by the matrix metalloproteinase-2 enzyme in physiologically relevant concentrations. Furthermore, biocompatibility tests using human umbilical cord vein endothelial cells with the degradation products of the grippers demonstrate no acute toxicity. The approach offers a facile fabrication strategy for designing biocompatible and biodegradable soft robots using nanocomposite materials with programmable 3D magnetic anisotropy toward future medical applications.

1. Introduction

Untethered small-scale soft robots, that is, wireless robots with a few millimeters or smaller size, have the potential to be disruptive in diverse applications, such as targeted cargo delivery[1–3] environmental remediation,[4,5] biotechnology,[6] and minimally invasive medicine.[7–12] Their small size and remotely controlled mobility can enable access to small, dangerous, and hard-to-reach spaces. Recent progress on such field has resulted in various forms of soft robotic designs that have combined different actuation methods, materials, and fabrication strategies based on the specific requirements of the desired application.[12–15] Remote magnetic actuation[16–22] is a prominent and robust way of actuating small-scale untethered soft robots compared to thermal,[23–25] optical,[26] electrical,[27] and acoustic methods,[28,29] due to its ease of use, fast response time and safe penetration of magnetic fields in biological environments. As a result, small-scale soft robotics has been rapidly evolving around magnetic soft robot designs where they fully benefit from the compliance of soft robots as well as their small size and remote control.[30] Also, encoding morphing information in the soft robot body with a programmed 3D magnetization profile enables shape programming capability with high spatial resolution. To date, a few examples of soft robots with a programmed magnetization have been developed to achieve multimodal locomotion and execute their multiple functions in complex environments toward medical applications.[31,32–33]

Biocompatibility and biodegradability are critical aspects of small-scale medical robot designs for medical applications inside the human body in order not to create any adverse effects such as immune response.[14] However, the magnetic soft robots developed so far are limited to exhibit their potentials in vivo applications due to the choice of non-degradable polymer materials and toxic magnetic micro/nanoparticles. For example, commonly used polymeric materials to build the backbone of the soft robots are non-biodegradable, such as polyvinyl alcohol,[35] Irogran PS455-203,[36] a thermoplastic polyurethane,[37] polydimethylsiloxane (PDMS),[38] poly(ethylene glycol) diacrylate (PEGDA),[39] and silicone rubber (Ecoflex).[31,33] Also, hard magnetic materials, such as neodymium–iron–boron (NdFeB),[16,20,31–33] barium hexaferrite microparticles,[40] chromium dioxide (CrO2) microparticles,[41] and cobalt nanoparticles,[42] used to actuate the soft milli/microrobots leach[43] in physiologically relevant environments. A soft millirobot made of such materials can lead to serious acute and chronic toxicities, which could cause many detrimental side effects.

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Hence, choosing the right material composition is of utmost importance to develop medical robots that can fulfill the requirements of safe in vivo use. Recently, we have demonstrated that 3D-microprinted nanocomposite magnetic hydrogels derived from natural macromolecules can be used to make non-toxic biodegradable microswimmers.\cite{1,44} However, these microswimmers lacked a 3D magnetization profile and thus are not able to achieve 3D body deformations under low magnetic fields. However, 3D body deformations require 3D magnetic profiles and higher magnetization magnitudes.

Here, we present a design and fabrication strategy for biocompatible and completely biodegradable untethered millimeter-scale soft robots that demonstrate compliant body motions enabled by programmed 3D magnetic anisotropy. The soft body is mainly comprised of porcine extracellular matrix-derived photocrosslinkable collagen and superparamagnetic iron oxide nanoparticles (SPIONs) of 10 nm diameter\cite{45} together dispersed homogeneously in an aqueous precursor solution. The polymer precursor solution in the form of a hydrogel milli-gripper is then exposed to an external inhomogeneous magnetic field to create a 3D magnetization profile. The application of gradient magnetic fields drives the self-assembly of SPIONs into chains and photopolymerization fixes the assembled state in the hydrogel network. To demonstrate the capability, we present a hydrogel milli-gripper that can undergo flexible, complex, and reversible shape deformations upon an applied external magnetic field. The direction of the programmed magnetization axis in each arm of the gripper differs and thus, enables the fabricated hydrogel milli-grippers to exhibit high-order shape deformations inside glycerol and biologically relevant liquid media. The gripper can perform cargo grabbing and transportation tasks via rolling and grasping locomotion modes under the controlled magnetic fields. These milli-grippers can be completely degraded by the matrix metalloproteinase-2 (MMP-2) enzyme without leaving any toxic residue demonstrated in human umbilical vein endothelial cells (HUVECs). This strategy allows designing soft small-scale robots that can undergo predetermined complex shape deformations with enhanced biocompatibility for future medical applications.

2. Results and Discussion

2.1. Design and Fabrication of the Hydrogel Milli-Grippers with 3D Magnetic Anisotropy

Hydrogels are 3D crosslinked networks of water-soluble polymers. Their major compositional fraction is water; thus, they are soft and their porosity permits the loading of nanoparticles and drug molecules into their matrix. Also, their tunable mechanical properties enable encoding complex deformation schemes to soft robots. Therefore, we formulate a nanocomposite hydrogel precursor to realize the biodegradable soft milli-grippers, which are capable of demonstrating predetermined shape deformations upon an applied magnetic field. In this sense, gelatin methacryloyl is an appealing hydrogel material with biodegradable properties.\cite{31,46} Gelatin is a semi-synthetic material derived from the hydrolysis of porcine skin collagen and bears enzyme-sensitive sequences in its backbone, therefore biologically degradable. Also, the methacryloyl groups on the gelatin enable covalent crosslinking by the free-radical polymerization in the presence of a photoinitiator and ultraviolet (UV) light leading to the formation of a 3D porous network (Figure 1a). Our formulation of hydrogel precursor is comprised of gelatin methacryloyl (10% w/v), lithium phenyl (2,4,6-trimethylbenzoyl) phosphinate (80 mg mL\(^{-1}\)) and superparamagnetic iron oxide nanoparticles in the form of water-based ferrofluid (2.9% v/v). The saturation magnetization of SPIONs is 7.5 emu cc\(^{-1}\) at a given 2.9% volume fraction (Figure S1, Supporting Information). To fabricate the milli-gripper, the gripper design is initially printed on a silicon substrate using a commercial IP-Q resin by two-photon polymerization (Figure 1b). Then, the printed structures are used as a template for PDMS molding. The solidified PDMS presents an excellent replication of the gripper pattern. Next, photopolymerization is employed to fabricate the milli-gripper from the nanocomposite hydrogel precursor filled in the PDMS mold by global UV curing (Figure 1b).

Magnetic nanoparticle distribution within the hydrogel milli-gripper is the critical element paving the way for the complex and controlled shape deformations in response to an applied magnetic field. Random distribution of the nanoparticles should be avoided to have predetermined shape change and actuation. In the absence of an external magnetic field, superparamagnetic nanoparticles are randomly dispersed in the hydrogel precursor and their magnetic moment randomly changes due to thermal fluctuations. Therefore, to encode programmed 3D magnetic anisotropy within the hydrogel network, the magnetic field is applied perpendicular (along positive Z-axis or negative Z-axis direction) to the nanocomposite via a permanent magnet during the fabrication process. The applied magnetic field induces alignments of SPION chains along with a magnetic flux profile due to attractive dipolar interactions as shown in Figure 1c. The chains are formed by induced dipolar coupling between the particles and the assembled state in the form of chains is fixed in the gel matrix by photopolymerization. Thereby, a programmed 3D magnetic anisotropy is imparted to the gripper as shown in numerical simulation and experiments in Figure 2a. Although superparamagnetic nanoparticles have no net magnetic moment under zero magnetic field, the assembled state in each arm of the gripper has a preserved magnetization axis, which leads to differential response to the applied magnetic field. Also, the cooperative response of chains is more sensitive to the applied magnetic fields compared to individual particles.\cite{47} Hence, the use of biocompatible\cite{48,49} superparamagnetic nanoparticles, which are normally weaker than ferromagnetic particles but capable of inducing enough torque and force for the execution of a given task in the form of chains, is a viable strategy to build biologically safe small-scale robot designs.

Previously, magnetic actuators with flexible joints were developed by the assembly of magnetic nanoparticles within the PEGDA polymeric network for preprogrammed complex motion under a homogeneous magnetic field.\cite{39} That method relied on a sequential process to program the direction of the magnetic easy axis differently to discrete parts of the
multicomponent actuator. Instead, here we provide a one-step strategy to program a 3D magnetization profile for the fabrication of soft deformable matter with self-assembled magnetic nanoparticle chains. Also, compared to the fabrication strategy of bilayer-based soft grippers and self-folded actuators, which have a soft and stiff layer with heterogeneous swelling degrees to fold into 3D shape, our method avoids further alignment processes of secondary materials.\cite{50,51} From the materials point-of-view, compared to the previously presented actuators, including polyurethane-based elastomeric films embedded with SPION chains,\cite{97} our hydrogel milli-gripper is composed of fully biodegradable material, which addresses one of the main challenges of small-scale untethered magnetic robots toward the pursuit of clinical relevance.

Figure 1. Design and fabrication of the biodegradable soft hydrogel milli-gripper with a programmed 3D magnetic profile. a) Chemical structure of gelatin methacryloyl and the crosslinked network upon UV photopolymerization. b) Illustration of the fabrication process and the formation of the 3D magnetic anisotropy/profile (directionally self-assembled superparamagnetic iron oxide nanoparticle (SPION) chains) via the non-uniform fields generated by the external permanent magnet. c) Schematic representation of the inner structure of the soft body with directionally self-assembled SPION chains.
2.2. Magnetically Induced Shape Deformation and Actuation of the Hydrogel Milli-Gripper

The programmed 3D anisotropic SPION chains inside the hydrogel milli-gripper induce magnetic torques under an applied magnetic field, which collectively create the shape deformation of the gripper. In general, SPION chains act as magnetic dipoles. Hence, under the magnetic gradients or uniform magnetic fields, the gripper arms bend either upward or downward based on the dipole moment direction in the programmed 3D magnetization profile (Figure 2b and Figure S2, Supporting Information). In addition, the anisotropic SPION chain distribution inside the hydrogel gripper also creates local mechanical anisotropy. The potential of this dual anisotropy could benefit the deformation behavior of the milli-gripper. The increase in the bending angle of the gripper arms is observed with an increment of the applied magnetic field strength as shown in Figure 2c. When the magnetic field strength is 5.5 mT, the gripper arms bend only 3.8°, whereas the bending angle increases to 58.3° when the magnetic field strength is 25.2 mT. A larger bending angle is important to have a better cargo gripping. When the applied field is off, the gripper transforms back to its original state. Note that the as-fabricated gripper has small deviations from the perfectly planar shape, because of the stress generated in the soft hydrogel during the peel-off process, which could be further reduced by the optimization of the fabrication method. The resting angle of the as-fabricated gripper is 14.7°, which is subtracted from the bending angles at magnetically actuated states.

To actuate the hydrogel milli-gripper, both a rotating magnetic field and a magnetic field gradient, which enable reconfigurable locomotion modes, are applied. Under the rotating magnetic field, the gripper undergoes time-varying shape deformations which induce rolling locomotion (Figure S3, Supporting Information). This type of motion enables the gripper to wrap around cargo and roll on the surface to the desired location (Figure 3a). To demonstrate the cargo delivery capability through rolling motion, the cargo is positioned above the planar gripper prior to the application of the magnetic field. The gripper wraps the cargo by bending of the arms following the application of the magnetic field. Then, the torque exerted by the rotating magnetic field with a strength of 25 mT and a frequency of 0.5 Hz induces the rolling of the milli-gripper with the cargo (Figure 3b and Movie S1, Supporting Information).

However, this locomotion is limited to environments where there are no obstacles on the way to the target location. Thus, we also show another locomotion mode, pulling the gripper in 3D, which is achieved by using the 3D magnetic field gradients generated from a permanent magnet, as shown in Figure 3c,d (Movie S2, Supporting Information). The movement of the gripper toward the cargo is achieved by performing up and down control of the permanent magnet manually.
within 5–25 mT range. Thus, the gripper can reconfigure its body between its original state and actuated state during its navigation. When the gripper reaches the position of the cargo, the arms of the gripper apply the pinching force, so that they can grasp the cargo. Further, we can gradually tune the magnetic field gradients to allow the gripper to cross the obstacle. When the gripper passed over the obstacle, we removed the applied magnetic field to release the cargo. Further, we have tested the cargo grasping capability of the gripper by the applied magnetic field gradients, where the cargo weights are 5.7, 9.5, and 11.7 mg, respectively. We have observed that the cargoes up to a maximum payload of 9.5 mg can be grasped and transported to another location (Figure S4a,b, Supporting Information). However, the gripper cannot grasp and lift the cargo with a weight of 11.7 mg as shown in Figure S4c, Supporting Information due to the limited maximum magnetic field gradient of around 900 mT m\(^{-1}\) and maximum magnetic field strength of around 25 mT. Herewith, we demonstrate the successful grasping, delivery, and release of the cargo by magnetic manipulation of the hydrogel gripper. Although all results presented above are in the glycerol medium, similar shape deformations are observed in biologically relevant environments, such as phosphate-buffered saline (PBS) and fetal bovine serum (FBS) as shown in Figure S5, Supporting Information.

Unlike the bilayer-based self-folding grippers that actuate in response to temperature and pH by differential swelling of the individual layers, magnetic grippers are advantageous in terms of mobility and steering control, and faster response time on the order of milliseconds.\(^{50,52–55}\) Also, self-folding gripper materials are limited to the ones that are responsive to physiological temperature and pH because it is not easy to create local variations in temperature and pH in the physiological environment. Poly(N-isopropylacrylamide) is one of such commonly utilized materials that is responsive to physiological temperature, yet is not biodegradable contrary to gelatin. Thus, its use in medical applications is limited.

2.3. Biocompatibility and Biodegradability of the Magnetic Hydrogel Grippers

As a hydrolysis product of collagen, gelatin exhibits enzymatic degradation properties due to having unaltered enzyme-sensitive amino acid sequences in its backbone,\(^{56}\) which makes them an appealing material to build biodegradable robots across different length scales.\(^{46}\) MMP-2 with its collagenolytic activity is one such enzyme used to degrade gelatin-based hydrogels. Matrix metalloproteinases are critical

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**Figure 3.** Magnetic actuation of the untethered hydrogel milli-gripper for a proof-of-concept cargo grasping, transport and release demonstration. 
(a) Schematic representation of cargo delivery via surface rolling motion. 
(b) Snapshots of cargo delivery via rolling locomotion under rotating magnetic fields of 25 mT. 
(c) Schematic representation of the cargo grasping, transport, and release steps. 
(d) Crossing over the obstacle while gripping the cargo to fulfill the cargo transport and release tasks under the magnetic field gradients generated by a permanent magnet.
remodeling enzymes that operate in an extracellular matrix of tissues with various concentrations depending on the pathophysiological state of the tissue.\textsuperscript{[57]} The activity of these enzymes is responsible for the remodeling of the matrix components as well as the degradation of implanted or administrated biodegradable hydrogels and materials. To assess the enzyme-mediated degradability of our soft hydrogel grippers, the grippers are treated with MMP-2 containing enzymatic cocktail for 9 days at 37 °C and the degradation is assessed both macroscopically and microscopically. The degradation time is defined as the time required for the complete disappearance of the magnetic milli-gripper macroscopically. As depicted in Figure 4a, the start of the degradation and release of the nanoparticles into the environment is observed within 4 h at an elevated MMP-2 concentration of 3.3 µg mL\textsuperscript{-1} and complete degradation after 192 h. It is important to note that the degradation cocktail also contains proteolytic acutase enzyme, which also contributes to the breakage of the polymeric network.\textsuperscript{[58]} Since the kinetics of degradation depends on the initial concentration of the enzymes, we anticipate having a longer degradation period at more realistic concentrations of the MMP-2 and different degradation times depending on the enzyme concentration at the target region. Also, degradation kinetics can be fine-tuned by changing the crosslinking density of the network. However, as a showcase, the accelerated degradation of the grippers is demonstrated by using a high concentration of proteases.

Mechanistically, biodegradation of the grippers proceeds substantially by bulk degradation, in which water and enzymes diffuse into the network and, thus start to degrade the polymer chains of the grippers uniformly across the body, leading to the release of nanoparticles into the environment (Figure 4a). Therefore, we observe the pieces of gripper body instead of a gradual reduction in its size, as in the case of surface-mediated degradation mechanism. However, due to the unequal distribution of the nanoparticles in the gripper, the spatial degradation profile over the material could also be expected. The parts with the higher nanoparticle density are more amenable for the erosion because the polymer amount is lesser. As the degradation proceeds, the polymer segments dissolve inside the water with an evident loss of mass and released nanoparticles. At this elevated enzymatic concentration, locomotion of the gripper could be limited due to the apparent change in its morphology after 4 h. However, we anticipate a longer duration, several weeks to months, for full degradation of the gripper in the biological environment due to the lower concentration of enzymes (e.g., almost 12-fold less) present in physiological conditions compared to our experimental one. Therefore, the time window for the locomotion of the gripper is also expected to be much longer in future in vivo conditions.
After biodegradation of the gripper, the in vitro biocompatibility of the degradation products using human umbilical cord vein endothelial cells is investigated. HUVECs are treated with the degradation products for 24 h and stained with LIVE/DEAD assay for the assessment of the viability (Figure 4a–c, Supporting Information). No significant difference is found between the viability of the treated and control cells (Figure 4d). The results show that the degradation products of the magnetic hydrogel gripper did not have any adverse effect on the growth of HUVECs. Although no acute toxicity is observed at 24 h, further investigation is needed for long-term toxicity evaluation.

3. Conclusion

Small-scale soft robots offer a great opportunity to perform minimally invasive medical interventions once the challenges in material design, biocompatibility, performance, and function coupled with medical imaging modalities are overcome. In this regard, soft hydrogel materials allow complex deformation of robotic designs and are suitable for safe operation in a biological environment for performing delicate tasks with reduced possibility of collateral injury during in vivo use. When coupled with biocompatibility and biodegradability, they can fulfill the desired material properties to ensure the safety of the medical robotic platforms. Therefore, adoption of existing materials and/or developing new smart materials, which allows integration of control and actuation elements, such as biocompatible and biodegradable magnetic nanoparticles, is critical to alleviating the potential leap toward realistic applications. The present study proposes a unifying design and fabrication strategy to develop soft biodegradable small-scale robots with a 3D anisotropic magnetic profile to execute cargo delivery tasks by different locomotion modes. We show a proof-of-concept milli-gripper fabrication by the proposed method and impart the anisotropic magnetization profile to the grippers by inducing the self-assembly of SPION chains and fixing them in the hydrogel matrix. We demonstrate the 3D magnetization profile patterning for the directional bending and deformation of the gripper arms based on the dipole moment direction in the profile, upon the magnetic field is applied. The bending of the gripper is also used to perform cargo grabbing and transportation tasks via rolling locomotion under the external rotating magnetic fields. Alternatively, we show that gripper can grasp the cargo and cross it over an obstacle by gradual tuning of the magnetic field gradients. Cargo delivery and release tasks achieved through both rotating magnetic fields and magnetic field gradients show the versatility of our design strategy. Furthermore, we show the complete degradation of the hydrogel milli-gripper after all assigned tasks are completed. The degradation process leaves no toxic residue behind. Overall, biocompatibility and biodegradation as the critical assets that a potential medical robot should carry, is implemented by the material design in a magnetically deformable gripper. This fabrication strategy we show herein can be extended to design micro-scale soft robots, which is a significant next step to pave the way for their leap toward the minimally invasive medical operations.

4. Experimental Section

All chemicals were purchased from Sigma-Aldrich and used as received unless otherwise mentioned.

Preparation of Superparamagnetic Hydrogel Nanocomposite and Characterization: 100 mg mL\(^{-1}\) gelatin methacryloyl (40% substitution), 100 mg mL\(^{-1}\) lithium phenyl (2,4,6-trimethylbenzoyl) phosphinate, 2.9% vol. EMG 700 SP ferrofluid, containing iron oxide nanoparticles with 10 nm hydrodynamic size (Ferrotec, USA), were mixed in ultrapure water with vortex mixing and ultrasound sonication. The resulting suspension was dropped on a PDMS mold with a thickness of 1.5 mm, fabricated by a commercially available Direct Laser Writing system (Photonic Professional, Nanostructure GmbH, Germany). Magnetic profiling was achieved by placing a 1 mm NdFeB disc magnet (Suppermagnete, Germany) for 30 seconds under the center of mold to induce the assembly of nanoparticle chains. The gelatin methacryloyl nanocomposite solution was polymerized into a hydrogel network by UV illumination at room temperature for 50 min using OmniCure S2000 Spot UV Curing System, which has mercury lamp source with a built-in 320–500 nm standard filter (Polytex, Germany).

The magnetic properties of ferrofluid were measured (2.9% v/v) using vibrating sample magnetometry (MicroSense EZ2, USA). The magnetic profile in the gripper was predicted by a numerical simulation of the permanent magnet implemented using COMSOL Multiphysics 5.5 Software. Self-assembled nanoparticle chains and the magnetization profile images of milli-gripper were taken by an inverted optical microscope (Zeiss Axio Imager. M2, Germany).

Magnetic Actuation of the Gripper: Rolling locomotion of the gripper was achieved by generating external magnetic fields through a custom-made electromagnetic coil setup. The setup can produce fields up to 40 mT in the presence of iron cores. The input currents and fields were controlled by LabVIEW (National Instruments). The motion of the gripper was observed by a video camera. Cargo grasping, transportation, and release tasks were performed with the help of gradient magnetic fields generated by the permanent magnet (50 mm × 50 mm × 25 mm NdFeB cuboid magnet, Maqna GmbH, Germany). The magnetic field measured at the center of the magnet surface was 500 mT. The magnetic fields were controlled manually. Rolling and grasping of the grippers were tested in glycerol and water mixture with a volume (mL) ratio of 2:25 and 1× PBS and FBS.

Biodegradation Tests: To investigate the biodegradation of the hydrogel grippers, grippers were immersed in the degradation solution, composed of 1:15 diluted 50 μg mL\(^{-1}\) MMP-2 in Accutase solution and kept at 37 °C. Degradation cocktail was replenished every 48 h for 9 days. Images of grippers were acquired every 24 h to determine the degradation status of the grippers. After complete degradation of the system, degradation products were collected and the enzymatic cocktail was deactivated by diluting 1 to 1 with the growth medium of HUVECs. Degradation products were sterilized under UV for 1 h before the treatment of the cells.

HUVECs (DSMZ, Germany) were cultured in growth medium (EBM-2, Lonza) supplemented with 10% fetal bovine serum (FBS, Gibco), penicillin (50 UI mL\(^{-1}\)) and streptomycin (50 μg mL\(^{-1}\)). Cells were grown at 37 °C and 5% CO\(_2\) in a humidified environment and subcultured before confluence using a trypsin/EDTA solution. In order to investigate the toxicity of the degradation products, the viability of HUVECs was tested by the LIVE/DEAD Cell Imaging Kit (Invitrogen) after 24 h of treatment with degradation products. Live and dead cells were observed under a fluorescent microscope (Nikon Eclipse Ti-E) using FITC and TRITC filters. Fluorescence microscopy images were analyzed with ImageJ (NIH) to calculate the number of live and dead cells. Cells with no treatment were taken as control.

Statistical Analysis: All experiments were repeated independently at least three times. The error bars represent the mean ± standard deviation. The viability data were analyzed with GraphPad Prism 6 (GraphPad Inc., San Diego, CA) and a Student’s t-test was performed to assess the statistical significance of the collected data.
Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest
The authors declare no conflict of interest.

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