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Previews

Robotic pills for gastrointestinal-tract-targeted oral mRNA delivery

Wei Tao[1,*] and Nicholas A. Peppas[2,3,4,5,6,*]

mRNA has become a new class of therapeutics and vaccines that possess high efficacy for the treatment and prevention of a variety of diseases. Recently, a team led by Professors Traverso and Langer, pioneers and leaders in the field of drug delivery and biomedical devices, reported the design and use of robotic pills for gastrointestinal-tract-targeted oral mRNA delivery, opening up a new avenue for the oral mRNA medicines.

Nucleic-acid-based medicines, especially mRNA-based therapeutics and vaccines, have been shown to exhibit high efficacy in the treatment and prevention of a variety of diseases. The pivotal role of mRNA vaccines in controlling the COVID-19 pandemic highlights the great potential of mRNA-based medicines.[1] This has stimulated the rapid development of various mRNA-based biomedical applications including vaccines, immunotherapy, gene editing, and functional protein restoration in tackling different diseases. Compared to conventional vaccines, mRNA vaccines have extraordinarily high efficacy and a much shorter development cycle, which is crucial for quickly slowing down the spread of highly contagious viruses such as SARS-CoV-2, which originally caused the COVID-19 pandemic. While the current mRNA medicines are predominantly administrated via intravenous or subcutaneous injection, novel mRNA medicines that can be administrated to patients by oral dosage forms are very much preferred.[1]

Recently, Abramson et al. demonstrated the possibility of the direct delivery of mRNA-loaded polymeric nanoparticles into the gastric submucosa via orally administrated robotic pills (Figure 1).[2] To facilitate the cellular uptake of mRNA, they first screened a library of hybrid branched poly(β-amino esters) (PBAE) nanoparticles for the encapsulation and cellular delivery of mRNA. The top-performing mRNA-loaded PBAE nanoparticles were then lyophilized, concentrated, and filled into the robotic pill called Self-Orienting Millimeter-Scale Applicator (SOMA). Upon oral administration, the robotic pills quickly entered the stomach, where they could self-orient to allow the direct injection of mRNA nanoparticles into the stomach submucosa for robust mRNA expression, bypassing the natural barriers existing in the gastrointestinal (GI) tract. This study has led to a novel GI-tract-targeted oral delivery system for mRNA, holding great promise to promote the development of more convenient and patient-preferred oral mRNA therapeutics and vaccines.

In addition to the oral delivery of mRNA, the SOMA robotic pills can also be used for the oral delivery of other macromolecules. The oral delivery strategy has the advantages of superior convenience and patient compliance.[3–5] For example, Abramson et al. previously described the oral delivery of insulins using the SOMA robotic pills.[6] In this study, the authors demonstrated the novel and creative design of the ingestible self-orienting system-SOMA robotic pills, which were inspired by the leopard tortoise's ability to passively reorient. Thus, orally administrated robotic pills could rapidly reach the stomach and enable self-orientation to the preferred upright position, allowing the injection of insulin-loaded tips into the mucosa within 1 min, which was triggered by the dissolution of caramelized sucrose. The insulin loads were then released to the mucosa within 1 h of the dissolution of the tips. To expand the applications of the SOMA robotic pill system, Traverso, Langer, and their groups have implemented the oral delivery of systemic monoclonal antibodies, peptides, and small molecules using a new version of the SOMA robotic pills.[7] The new robotic pills could not only enable the oral delivery of drugs whose size range from small molecules to monoclonal antibodies but also achieve a maximum drug plasma concentration that is similar to the standard-of-care subcutaneous injection within 30 min after the oral administration.

Besides the SOMA robotic pill system, Traverso and associates have also

[1]Center for Nanomedicine and Department of Anesthesiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

[2]McKetta Department of Chemical Engineering, The University of Texas at Austin, Austin, TX 78712, USA

[3]Institute for Biomaterials, Drug Delivery, and Regenerative Medicine, The University of Texas at Austin, Austin, TX 78712, USA

[4]Department of Biomedical Engineering, The University of Texas at Austin, Austin, TX 78712, USA

[5]Division of Molecular Pharmaceutics and Drug Delivery, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, USA

[6]Department of Surgery and Perioperative Care and Department of Pediatrics, Dell Medical School, The University of Texas at Austin, Austin, TX 78712, USA

*Correspondence:
wtao@bwh.harvard.edu (W.T.),
peppas@che.utexas.edu (N.A.P.)

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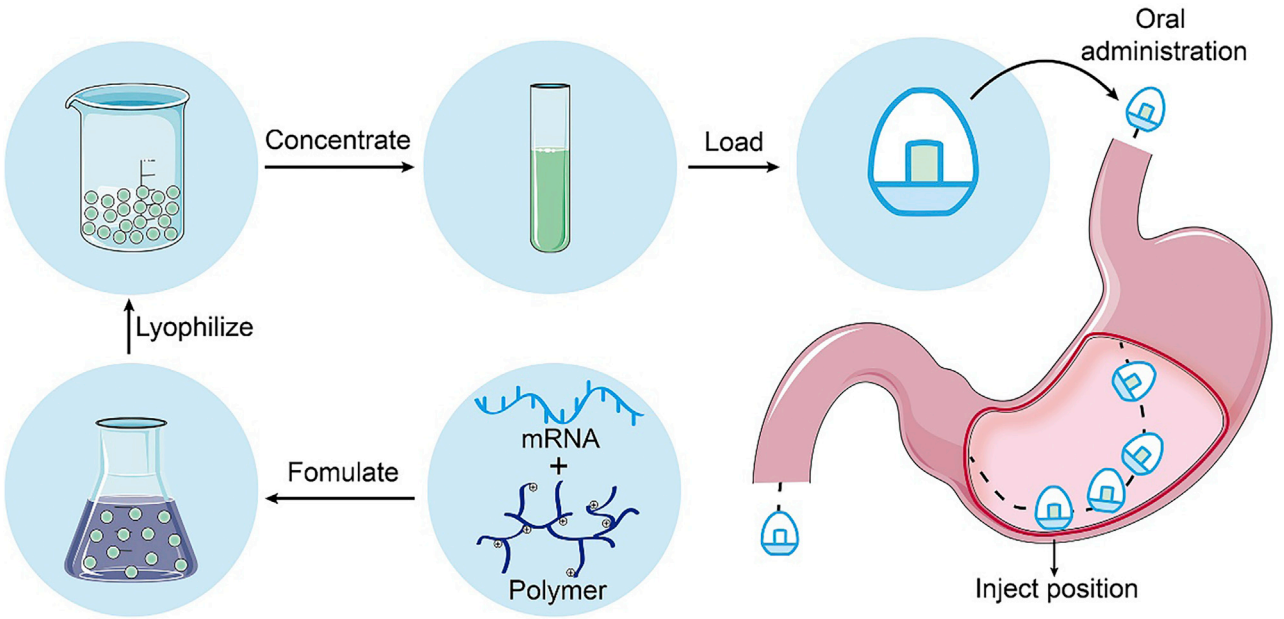

Figure 1. The preparation of mRNA-loaded robotic pills, which are administrated orally to bypass the natural barriers existing in the gastrointestinal tract

developed many other smart biomedical devices for the oral delivery of biologic drugs.[8] Instead of delivering the therapeutics to the stomach tissues, a new robotic pill system called luminal unfolding microneedle injector (LUMI), utilizing the tube-like geometry of the small intestine to provide plenty of points of contact with the tissues, was invented to deliver therapeutics to the intestinal tissues.[9] Upon oral administration, the elegant design of this robotic pill allows the rapid propelling of dissolvable drug-loaded microneedles, located on three unfolding arms, into intestinal tissues. In another study, they designed a kirigami-inspired stent for the sustained delivery of therapeutics to the GI tract with maximal local drug efficacy and minimal potential systemic side effects.[10]

Therefore, a well-designed robotic pill system enables the oral delivery of mRNA to the GI tract, providing a simple and non-invasive approach for mRNA delivery, and might eventually benefit the rapid development of novel mRNA therapeutics and vaccines.

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DECLARATION OF INTERESTS

W.T. and N.A.P. are on the *Matter* scientific advisory board.

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Origami-inspired heart pouch for minimally invasive cell delivery

Mine Altunbek[1] and Gulden Camci-Unal[1,2,*]

Cardiac therapy is hampered by the poor retention of cells or therapeutic agents at the pathological site of the heart. Mei et al. developed a heart pouch system with a unique origami design for effective, repeated, and localized administration of cells through minimally invasive surgery.

Studies for pre-clinical cardiac therapy have demonstrated the successful application of stem cells, growth factors, or drug deliveries to the pathological site of the heart to restore cardiac function.[1–4] Stem cells are particularly useful because they secrete and deliver cytokines and growth factors locally to damaged tissue. However, the rapid *in vivo* clearance and poor cell survival limit the application of cell therapy. Localized stem cell delivery strategies, including repeated administration of cells and implantation of cardiac patches as delivery vehicles for cells, have shown enhancement of retention and survival of the cells. However, difficulties arise during the re-administration of cells and implantation of patches due to the continuous pulsation of the heart. In addition, the invasive nature of these procedures limits their use in the treatment of mild-to-moderate patients.[5]

A replenishable therapeutic reservoir system was developed to keep the delivered cells localized and provide repeated administration of stem cells for cardiac repair.[6] This therapeutic device was comprised of a highly porous methacrylated gelatin cryogel (GelMA) or a commercially available gelatin sponge (Gelfoam), which is encapsulated between an impermeable thermoplastic polyurethane (TPU) polyether film and a semi-permeable polycarbonate membrane with 0.4 μm pore size. This device was directly sutured onto the epicardium via an invasive open chest surgery. The porous structures supported the retention of the delivered therapeutic cargo (cells and/or biomolecules) inside the reservoir, while the semi-permeable membrane surface was placed in direct contact with the epicardial tissue for the local diffusion of therapeutic cargo. A reservoir was connected to a subcutaneous port with an integrated ambulatory setting, enabling refills to the system with cells or biomolecules utilizing a 14G needle or 1.6 mm diameter catheter. Although this system enabled repeated administration and sustained delivery of the therapeutic agents to the pathological site of the heart, the implantation procedure remained invasive.

Origami-inspired approaches prove to be promising for various biomedical applications.[7,8] Particularly, the principles of origami are advantageous for the development of reconfigurable and minimally invasive therapeutic devices. Flexible origami structures with shape-shifting capability can facilitate changes from voluminous to compact deployment and minimize the invasiveness of device insertion.[8,9] In a recent study, Mei et al. (2021) presented a replenishable system with a unique origami-inspired design enabling the placement of the device with minimal invasion.[10] A compressible solid skeletal origami structure was sealed into a pouch with an impermeable cover membrane from one side (TPU) and a semi-permeable membrane (0.4 μm pore size, Whatman) on the opposing side (Figure 1A). The compressible structure enabled the 5 × 5 mm device to fold into 5 × 1 mm dimensions (Figure 1B). The folded structure was able to expand with the administration of the mesenchymal stem cells (MSCs) from a tube attached to the heart pouch system.

[1]Department of Chemical Engineering, University of Massachusetts, Lowell, MA 01854, USA

[2]Department of Surgery, University of Massachusetts Medical School, Worcester, MA 01605, USA

*Correspondence: Gulden_CamciUnal@uml.edu

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