CTL CENTER FOR TECHNOLOGY LICENSING AT CORNELL UNIVERSITY

Minglin Ma Lab

Technologies for Cell Therapy Delivery: Type 1 Diabetes And Other Chronic Conditions

Cell Therapy Delivery Technologies

"**Cell replacement therapies** hold tremendous promise for **type 1 diabetes**, hemophilia, lysosomal storage diseases and others. We developed technologies for **safe and functional delivery** of cell therapies **ready for pre-clinical development.** Most of our recent work, ranging from material synthesis and device fabrication to cell engineering and process integration, has been centered around the goal of successfully delivering safely insulin producing cells with long-term function for T1D patients"

Minglin Ma, PhD, Biomaterials and Cell Therapy Laboratory

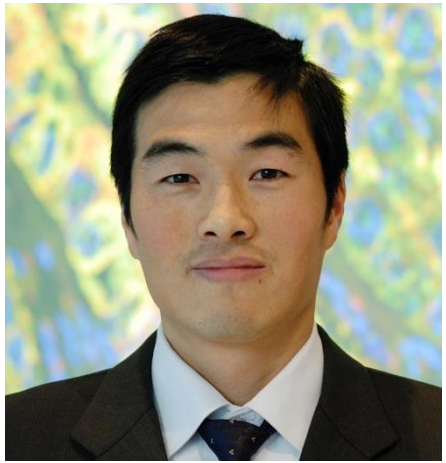
Advantages

- **Immune protection** without systemic immune suppression
- **Supply of oxygen** and nutrients to implanted cells
- **Safety**
- **Easy retrieval** & replacement
- **Clinically relevant** cell loading capacity

Applications

- **Type 1 diabetes**
- Hemophilias
- Liver diseases
- Cancer
- Chronic pain
- Lysosomal storage diseases
- Hormone deficiency disorders
- Medical device implants
- Implantable drug capsules

Minglin Ma Lab



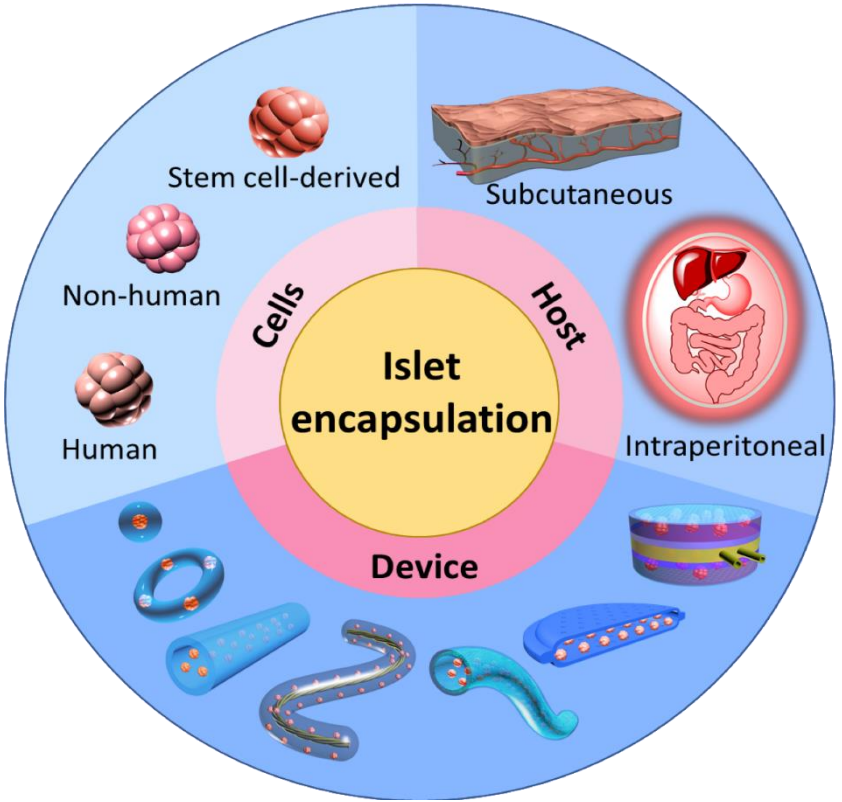
- Associate Professor, Department for Biological and Environmental Engineering, Cornell
- PhD and Postdoc, MIT
- **Cell packaging** for life sciences

The Biomaterials and Cell Therapy Laboratory

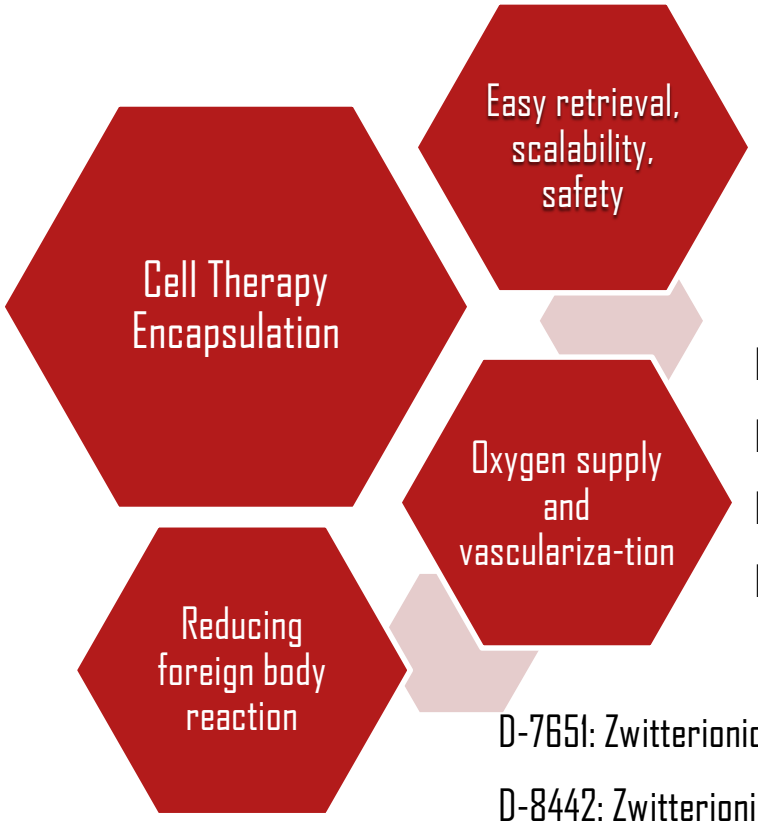
Department of Biological and Environmental Engineering

The Ma Lab @Cornell develops novel biomaterials and engineering approaches for **cell therapy delivery**

- Immunoprotective cell encapsulation materials
- Vascularization and oxygen supplementation strategies
- Scalable, replaceable, safe cell delivery devices
- For type I diabetes, hemophilia, other chronic conditions



Cell Therapy Encapsulation Portfolio



D-6480: String-based therapeutic delivery system

D-9313: Nanofiber membrane design

D-9365: Nanofibrous skin encapsulation

D-9204: Atmosphere-breathing device

D-9508: Inverse-breathing device

D-9728: Scaffold for rapid oxygenation

D-8402: Guiding pillar substrate transferrable vasculature

D-7651: Zwitterionically modified alginates

D-8442: Zwitterionically modified polyurethanes & nylons

D-6480: String-based therapeutic delivery system for cell therapies

Technology Overview

- Host recognition and subsequent foreign body response can cause the failure of transplanted cell therapies even when encapsulated in a relatively biocompatible material.
- "TRAFFIC" (thread-reinforced alginate fiber for islet encapsulation) is a therapeutic delivery system for cell therapies.
- TRAFFIC system combines an immuno-protective hydrogel fiber featuring high surface area for mass transfer with a "beads-on-a-thread' design which imparts mechanical strength and enables easy handling, implantation, and retrieval.
- **Proof of concept:** rat islets encapsulated in TRAFFIC device cured chemically-induced diabetes in mice (n=5) for at least 1 month. Upon device removal, the mice returned to their diabetic state.
- To demonstrate clinical feasibility for diabetes treatment, the system was scaled up, implanted and subsequently retrieved with minimally invasive laparoscopic procedures in a dog model.

Technology Advantages

- Increased surface area combined with shorter diffusion distance is beneficial for therapy delivery and glucose responsiveness
- Immunoprotective and biocompatible
- Easy non-invasive implantation, retrieval, and replacement
- Clinically convenient and controllable device sizes
- Thin, flexible, yet mechanically robust and leakage-proof

Technology Applications

- Encapsulation of cell therapies for type I diabetes
- Implantation of cell therapies and drugs for hemophilia, lysosomal storage disorders, and other chronic diseases

Supporting Data / Figures

Figure 1: Schematic illustration of "beads-on-strand" design.

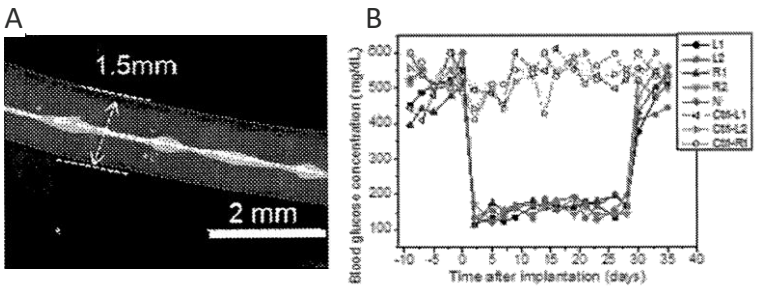


Figure 2. A: Representative optical microscope image of the implantable delivery system. **B:** Blood glucose levels of diabetic mice with and without transplanted TRAFFIC system containing rat islets; the devices were retrieved after 4 weeks of implantation.

Inventors:

Minglin Ma
James Flanders
Duo An

Patents:

US Patent
2017/0258852A1

Cornell Reference:

D-6480

D-9313: Nanofiber membrane encapsulation devices for type 1 diabetes cell therapies

Technology Overview

- In order to facilitate longevity and function of implanted cell therapies for chronic diseases, encapsulation devices need to simultaneously enable nutrient and oxygen supply, vascularization, protection against inflammation and fibrosis, and easy retrieval.
- Devices described in this technology achieve these goals by combining porous nanofiber membranes with alginate hydrogels.
- Zwitterionically modified coating hydrogels create an immune invisible surface.
- Novel designs and precise fabrication methods enable clinically relevant cell loading capacity in a small form factor.

Technology Applications

- Encapsulation of cell therapies for Type 1 Diabetes
- Implantation of cell therapies and drugs for hemophilia, lysosomal storage disorders, and other chronic diseases

Technology Advantages

- Device protects implanted cells from escaping and immune attack, enables nutrient and oxygen supply and long-term cell survival
- Novel fabrication, coating, loading, and sealing methods enable various clinically relevant form factors and designs
- Device can be implanted intraperitoneally or subcutaneously and can be easily retrieved or replaced

Supporting Data / Figures

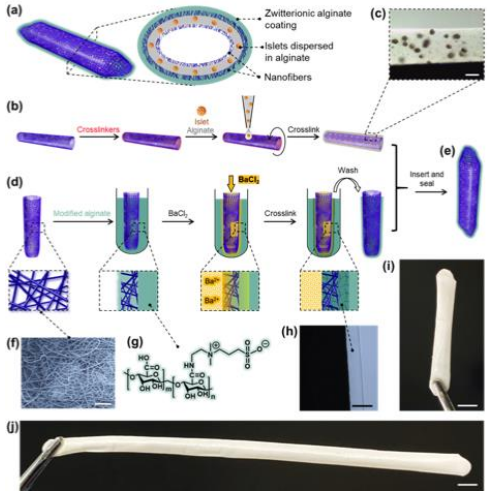


Figure 1: Design and Fabrication of the SHIELD (Safe, Hypo-immunoreactive, Islet Encapsulation, Long-term-functional Device) device.

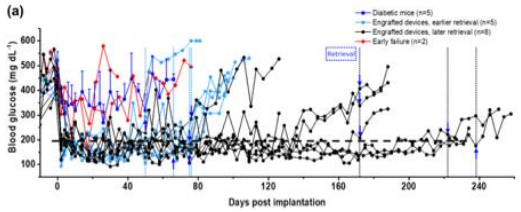


Figure 2: SHIELD device loaded with human stem cell derived beta cells reverses hyperglycemia in diabetic mice as measured by blood glucose levels.

Inventors:

Wanjun Liu
Minglin Ma
James Flanders
Longhai Wang
Daniel Bowers

Patents:

Filed

Cornell Reference:

D-9313

Note: SHIELD was originally referred to as "NEED v2.0" (Nanofiber-Enabled Encapsulation Devices) in publications.

D-9365: Nanofibrous skin-based encapsulation device for safe delivery of insulin-producing cells to treat type 1 diabetes

Technology Overview

- Transplantation of insulin-producing stem cells (a promising diabetes treatment) without immunosuppression and in a safe, functional, and retrievable device remains a challenge.
- Scientists at Cornell developed a nanofibrous-skin, hydrogel-core encapsulation device for safe delivery of cell therapies.
- The soft yet tough device is made by electrospinning a medical grade thermoplastic silicone-polycarbonate-urethane.
- Imaging confirmed containment of cells for up to 5 months.
- Loaded with allogeneic or xenogeneic rodent islets, the device corrected chemically induced diabetes in mice and remained functional for up to 200 days until device retrieval.

Technology Applications

- Encapsulation device for stem cell therapies for Type 1 Diabetes
- Delivery of cell-based therapies for hormone deficiency diseases, liver diseases and hemophilia

Technology Advantages

- Device ensures safety by preventing cell escape or penetration
- Nanofibrous skin provides superb transfer of nutrients and secretory products to and from the transplanted cells
- Alginate hydrogel material has immunoprotective properties and supports islet survival with high hydration
- The low complexity design enables easy fabrication

Supporting Data / Figures

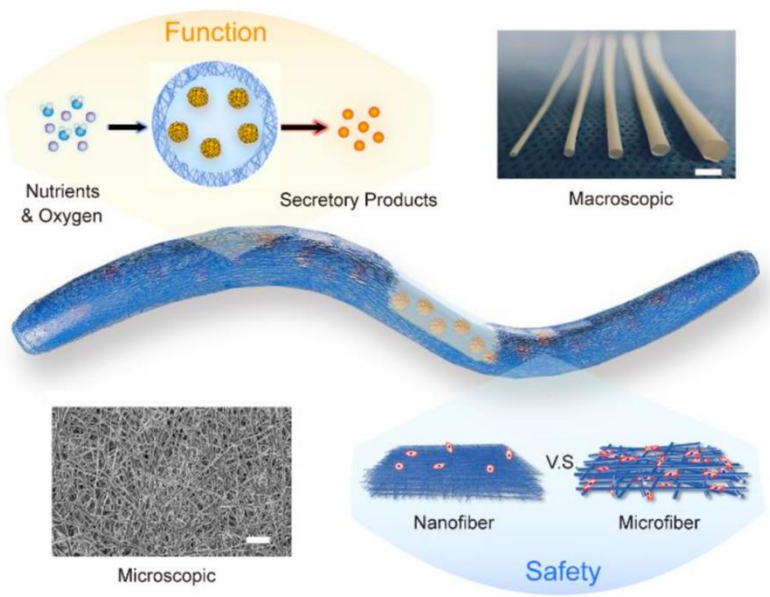


Figure 1: Device schematics showing the hydrogel core with islets surrounded by the nanofibrous skin that prevents cell escape and allows nutrient supply. Upper right: photo of nanofibrous tubes with different diameters. Lower left: a scanning electron microscope image of the nanofibers.

Inventors:

James Flanders
Minglin Ma
Xi Wang

Patents:

Filed

Publications:

Wang et al. Sci Transl Med 2021

Cornell Reference:

D-9365

D-9204: Atmosphere-breathing refillable device for cell replacement therapy

Technology Overview

- In cell replacement therapy, low oxygen levels at transplantation sites limit survival of cells and often lead to graft failure. Graft oxygenation is further impaired by fibrotic tissue formation.
- There is an unmet need for a device which can enable long-term oxygenation and survival of encapsulated cells with minimally invasive refilling.
- This novel modular cell encapsulation device provides enhanced and unlimited oxygen supply by direct contact with the atmosphere and enables surgery-free cell replacement.
- Device was tested in a diabetes mouse model and showed robust cell survival and diabetes correction in vivo.

Technology Applications

- Delivery of insulin producing islets for Type 1 diabetes
- Cell replacement therapy for endocrine, hormone deficiency, and chronic diseases including bleeding disorders, lysosomal storage disorder, kidney failure, chronic pain, and cancer

Technology Advantages

- Unlimited oxygenation is provided by direct contact with the atmosphere, without the need for interventions
- Modular design enables non-surgical replacement or replenishment of cells
- Device design facilitates transplanted cell growth and survival

Supporting Data / Figures

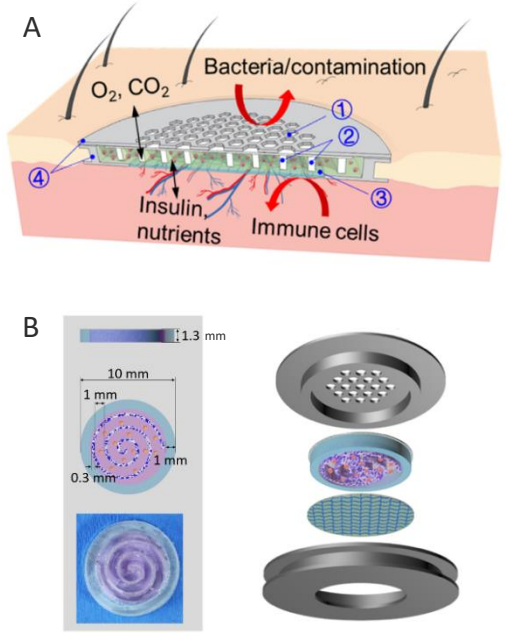


Figure 1. Illustration of device functions (A) and components (B).

Inventors:

Duo An
Alexander Ernst
James Flanders
Minglin Ma
Longhai Wang

Patents:

US Patent 2021/0170072A1

Publications:

An et al. Adv Mater 2019

Cornell Reference:

D-9204

D-9508: Inverse-breathing encapsulation for oxygen-dependent cell therapies

Technology Overview

- Cell therapies like islet transplantation for Diabetes face critically low oxygen (O_2) levels in poorly oxygenated transplantation sites.
- Hypoxia exacerbated by fibrosis impairs the islets' metabolic function and may precipitate immunogenicity and graft failure.
- This novel encapsulation system generates O_2 by using lithium peroxide to recycle cells' own waste product, carbon dioxide.
- O_2 release can last for months with one implantation and may be extended through refilling.
- The system achieved diabetes reversal in immunocompetent diabetic mice for over 3 months, 10 times longer than the non-oxygenated control.

Technology Applications

- Cell replacement therapies for Type 1 Diabetes and other hormone deficient endocrine disorders
- Oxygen generation for bioengineered tissues

Technology Advantages

- Long-term continuous self-regulated O_2 generation and release
- Physical separation of O_2 generation from encapsulated cells protects them from potential harmful impact
- Device design allows for easy lithium peroxide refilling and rapid O_2 diffusion

Supporting Data / Figures

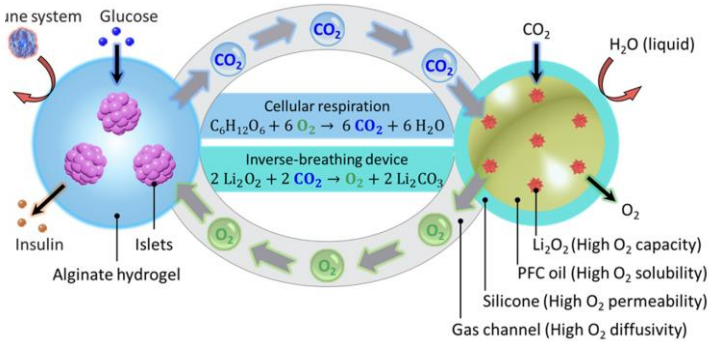


Figure 1. A: Schematic representation of the inverse-breathing system.

Figure 2. The inverse Breathing Encapsulation Device (iBED) device.

Inventors:

Minglin Ma
Longhai Wang
Alexander Ernst
James Flanders

Patents:

Filed

Publications:

Wang et al. Science Advances 2021

Cornell Reference:

D-9508

D-9728: A bioinspired scaffold provides rapid oxygenation of cell encapsulation systems

Technology Overview

- Cell encapsulation devices protect cell therapies such those for type I diabetes from the immune rejection but remain isolated from the bloodstream after transplantation.
- As the result, inadequate oxygenation requires islets to be within a few hundred micrometers of the blood stream, necessitating exceedingly thin devices impractical for clinically relevant doses.
- Inspired by insects' tracheal oxygen (O_2) delivery system, this biomimetic scaffold device features internal continuous air channels with high O_2 diffusivity and facilitates rapid O_2 transport to cells several millimeters away from the host vasculature.
- The device loaded with rat insulin-producing islets corrected diabetes in vivo in immunocompetent mice for over 6 months.

Technology Applications

- Cell encapsulation for insulin-producing islets to treat diabetes
- Cell therapies for other chronic diseases including hormone deficiency diseases, liver diseases and hemophilias
- Encapsulation of other transplanted biomaterials

Technology Advantages

- Adequate oxygenation regardless of proximity to O_2 source
- Effective O_2 permeability enables transplanted cell viability and functionality in thick encapsulation devices
- The scaffold can be 3D printed in various scales and designs, including multiple layers and spiral geometry

Supporting Figures

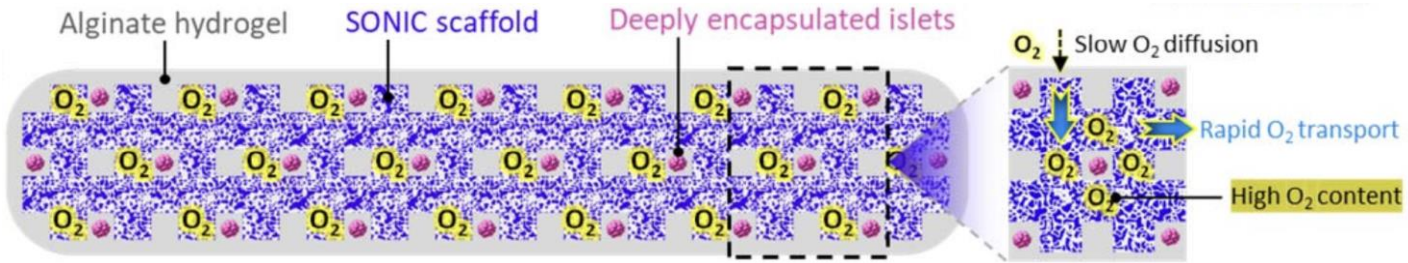


Figure 1. A schematic illustrating O_2 delivery inside a cell encapsulation system through a tracheal ladder network-like SONIC scaffold.

Inventors:

Alexander Ernst
Minglin Ma
Longhai Wang

Patents:

Filed

Publications:

Wang et al. Nat Commun (In Press)

Cornell Reference:

D-9728

D-8402: Transferrable vasculature network for improved survival of cells encapsulated in implantable devices

Technology Overview

- The success of engineered cell or tissue implants depends on vascular regeneration to meet adequate metabolic requirements.
- This technology describes a pre-vascularization strategy using a Guiding Pillar Substrate (GPS) that supports a rapid assembly of endothelial cells into vascular-like networks.
- These networks can be co-implanted with any cell encapsulation device and promote rapid anastomosis and vascularization in vivo.
- This approach was validated in a diabetes mouse model with encapsulated islets pre-vascularized with GPS-derived endothelial networks (See Fig. 2 B, C). Upon examination, devices exhibited well-vascularized cell networks and presence of islets that were intact and viable.

Technology Applications

- Pre-vascularization of therapeutic cells for type I diabetes treatment
- Cell therapy encapsulation for inflammation and other chronic diseases

Technology Advantages

- Rapid and effective assembly
- Better control of the structure organization
- Retrievable and replaceable
- Stackable

Supporting Data / Figures

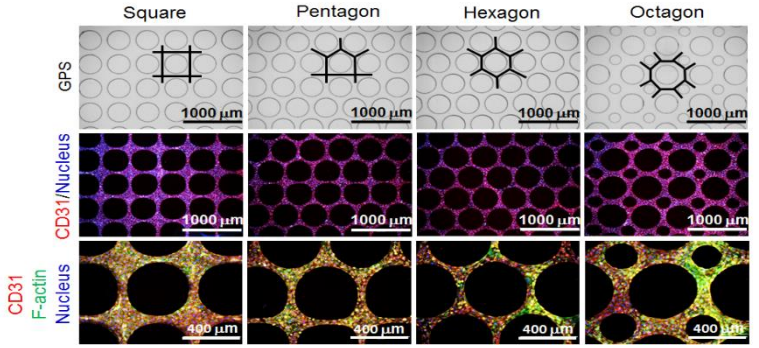


Figure 1. Arrangement and different sizes of pillars on GPS control endothelial cell assembly into square, pentagon, hexagon, and octagon networks.

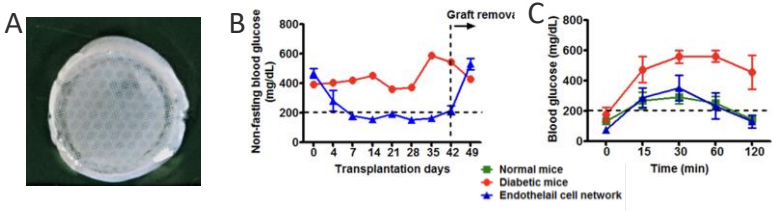


Figure 2. A: Endothelial cell network on encapsulation device. **B:** Non-fasting blood glucose tests showed that diabetic mice displayed diabetes correction after device implantation but became diabetic again after devices were retrieved. **C:** Glucose tolerance test results in diabetic mice with the cell network device are similar to those of healthy mice.

Inventors:

Minglin Ma
Wei Song
Alan Chiu

Patents:

Filed

Publications:

Song et al. Nat Commun 2019

Cornell Reference:

D-8402

D-7651: Zwitterionically modified alginates as biocompatible materials for encapsulating cell therapies

Technology Overview

- Implanted biomaterials including cell therapies often invoke the foreign body response (FBR), a process involving nonspecific protein adsorption and triggering a host immune response.
- The resulting cellular overgrowth (CO) and fibrosis cut off nutrient and oxygen supply to implanted cells and lead to graft failure.
- This technology describes novel super-biocompatible coating polymers with zwitterionic modifications that prevent protein adsorption, suppress FBR, and can significantly improve cell therapy effectiveness.
- These materials reproducibly reduced CO for up to 6 months in mice, dogs, and pigs and when used to encapsulate insulin-producing rat islets in diabetic mice, achieved better long-term glycemic control (up to 200 days).

Technology Applications

- Mitigation of FBR and cell overgrowth on implanted cell therapies for type I diabetes and other hormone deficiency diseases
- Coating for drug delivery capsules, medical devices, biosensors, and other biomaterials

Technology Advantages

- Super bio-compatible and non-toxic materials with anti-inflammatory effect
- Simpler, less expensive and less damaging to encapsulated cells than other cell overgrowth-mitigating chemical modifications

Supporting Data / Figures

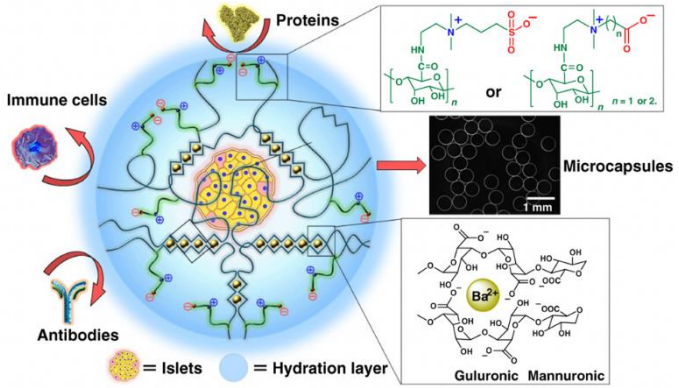


Figure 1. Illustration of zwitterionically modified alginate microcapsules encapsulating islets.

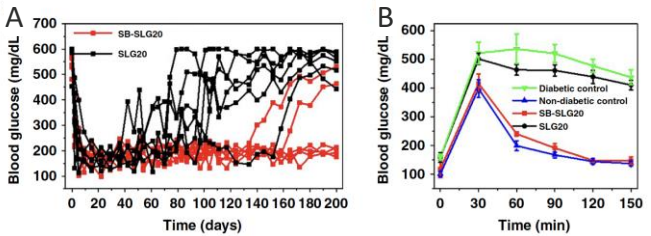


Figure 2. SB-SLG20 microcapsules improve diabetes correction in mice in a 200-day study. **A:** Blood glucose concentrations (n =6 mice per treatment group). **B:** Intraperitoneal glucose tolerance test before retrieval (n = 3).

Inventors:

Minglin Ma

Qingsheng Liu

Patents:

US Patent 2019/0389979A1

Publications:

Liu et al. Nat Commun 2019

Cornell Reference:

D-7651

D-8442: Zwitterionically modified polyurethanes and nylons for biomedical applications

Technology Overview

- Implanted cell therapies often trigger an innate immune response involving cell adhesion and fibrosis, which limits the graft success and the health of the implanted islets.
- Implanted medical devices such as contact lenses or artificial joints are prone to bacterial accumulation and subsequent formation of biofilm, affecting implant durability and the patient's quality of life.
- These novel functionalizable and biocompatible nylons and polyurethanes incorporate zwitterionic moieties endowing them with long-term antifouling and antimicrobial properties.
- Materials can be electrospun into nanofiber tubes for cell encapsulation, protecting implanted cells from escaping and immune response while allowing the flow of oxygen and nutrients.
- In vitro and in vivo experiments showed that these materials prevent cell adhesion, mitigate fibrosis, and are easily retrievable.
- An in vivo experiment in diabetic mice demonstrated that implanted rat islets encapsulated in these materials retained healthy morphology and functionality, and mice remained normoglycemic for 8 weeks until the devices were retrieved.

Technology Applications

- Encapsulation of cell therapies for type I diabetes and regenerative medicine
- Catheter, artificial joint, and other medical device implants

Technology Advantages

- Robust antifouling and antimicrobial properties preventing cell and bacterial adhesion and foreign body response
- Excellent mechanical properties and durability
- Ease of retrieval
- Versatility in fabrication of nanoscale implantation devices including nanofiber tubes well suited for cell therapy

Supporting Data / Figures

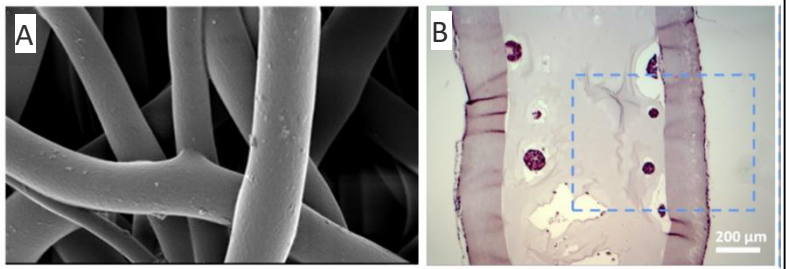


Figure 1. **A**: Scanning electron microscope (SEM) image of a Zwitterion-based polyurethane (ZPU) nanofibrous tube. **B**: H&E staining of retrieved rat islets encapsulated in ZPU tubes shows unchanged islet cell morphology.

Inventors:

Minglin Ma
Qingsheng Liu
Xi Wang
Alan Chiu

Patents:

Filed

Publications:

Liu et al. Adv Mater (In press)

Cornell Reference:

D-8442

Ma Lab Publications

A bioinspired scaffold for rapid oxygenation of cell encapsulation systems. Nature Communications (In Press).

A nanofibrous encapsulation device for safe delivery of insulin-producing cells to treat type 1 diabetes. Science Translational Medicine (2021).

A zwitterionic polyurethane nanoporous device with low foreign body response for islet encapsulation. Advanced Materials (In Press).

An inverse-breathing encapsulation system for cell delivery. Science Advances (2021).

Developing mechanically robust, triazole-zwitterionic hydrogels to mitigate foreign body response (FBR) for islet encapsulation Biomaterials (2020).

An Atmosphere-Breathing Refillable Biphasic Device for Cell Replacement Therapy. Advanced Materials (2019).

Zwitterionically modified alginates mitigate cellular overgrowth for cell encapsulation. Nature Communications (2019).

Engineering transferrable microvascular meshes for subcutaneous islet transplantation. Nature Communications (2019).

Engineering the vasculature for islet transplantation. Acta Biomaterialia (2019).

Conformal Hydrogel Coatings on Catheters to Reduce Biofouling. Langmuir (2019).

Islet Encapsulation. Journal of Material Chemistry (2018).

Designing a Retrievable and Scalable Cell Encapsulation Device for Potential Treatment of Type 1 Diabetes. PNAS (2018).

High-water-content and Resilient PEG-containing Hydrogels with Low Fibrotic Response. Acta Biomaterialia (2017).

Drug-Eluting Conformal Coatings on Individual Cells. Cellular and Molecular Bioengineering (2016).

Combinatorial hydrogel library enables identification of materials that mitigate the foreign body response in primates. Nature Biotechnology (2016).

Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates. Nature Materials (2015).

Designing Compartmentalized Hydrogel Microparticles for Cell Encapsulation and Scalable 3D Cell Culture. Journal of Materials Chemistry (2015).

Developing Robust, Hydrogel-based, Nanofiber-Enabled Encapsulation Devices (NEEDs) for Cell Therapies. Biomaterials (2015).

Core-shell hydrogel microcapsules for improved islets encapsulation. Advanced Healthcare Materials (2013). *(Back Cover)*

Enhanced function of immuno-isolated islets in diabetes therapy by co-encapsulation with an anti-inflammatory drug. Biomaterials (2013).

CTL CENTER FOR TECHNOLOGY LICENSING AT CORNELL UNIVERSITY

For more information, please contact:

Aris Despo

Senior Licensing and Business Development Officer

add74@cornell.edu

(607) 254 4460