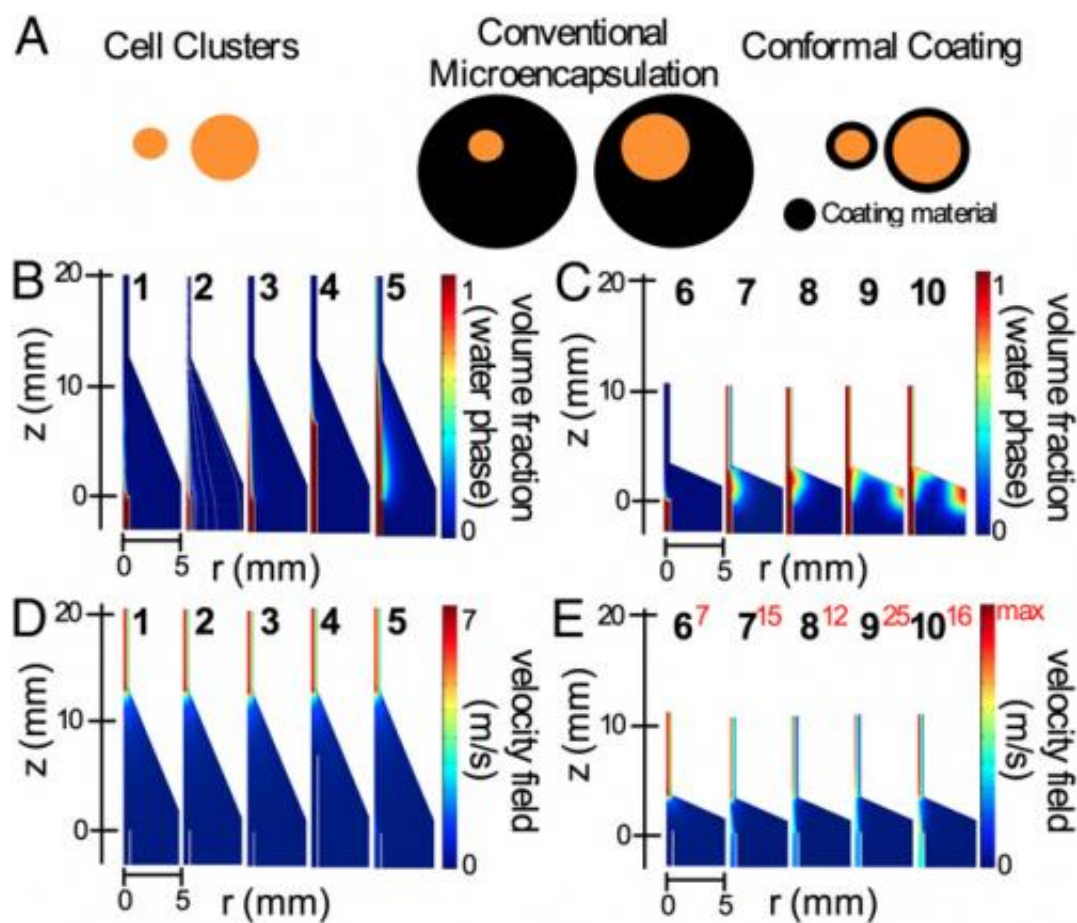


Fit to a T-cell: Conformal hydrogel coating could lead to immunosuppression-free islets of Langerhans transplantation

August 12 2014, by Stuart Mason Dambrot



Computational model of the conformal coating procedure for optimization of the fluid dynamic conditions and the design of the encapsulation device. (A) Schematic of conformal coating encapsulation of islets compared with conventional microencapsulation. Consol plots of the water-phase volume fraction for models 1–5 (B; “less focusing”) and 6–10 (C; “more focusing”) and the velocity field for models 1–5 (D) and 6–10 (E) as a function of the z axis and

r radius are shown. Credit: Copyright © PNAS, doi:10.1073/pnas.1402216111

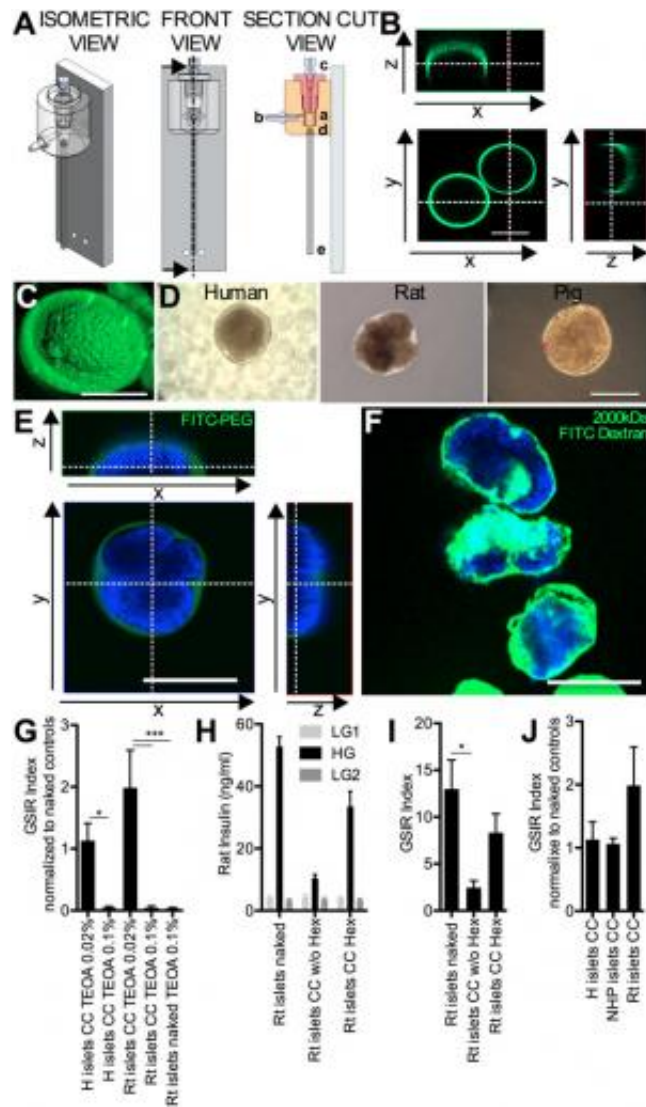
(Medical Xpress)—Type 1 diabetes is a chronic autoimmune disease in which viral infection^{1,2}, genetics and environmental factors conspire to impact the immune system's T-cells, which then attack and destroy the pancreatic insulin-producing islets of Langerhans (also known as beta cells). There is no vaccine or cure, only management – and while a successful islet or pancreas transplant may address Type I diabetes and its associated long-term complications, the procedure requires a lifelong regimen of immunosuppressive drugs that may be only partially efficacious, have a negative impact on the islets themselves and create an increased risk of infection and cancer. Given these caveats, research has long focused on encapsulating islets in a manner that obviates the need for post-transplantation immunosuppression. That being said, current microencapsulation techniques have been shown to interfere with various islet functions, such as cellular hypoxia (lack of oxygen), delayed GSIR (glucose-stimulated insulin release), and transplant site size limitations. Recently, however, scientists at the Diabetes Research Institute, University of Miami Miller School of Medicine have designed and optimized a conformal encapsulation technique based on biocompatible permeable hydrogels, resulting in thin, complete, uniform coatings on islets of various sizes in which the coating conforms to each islet's individual shape. Moreover, syngeneic (genetically identical or sufficiently identical, and thereby immunologically compatible) diabetic mice receiving transplanted conformally coated islets achieved and maintained euglycemia – that is, normal blood glucose levels – for over 100 days without foreign body response to the encapsulating material or abnormal revascularization.

Dr. Alice A. Tomei discussed the paper that she and her co-authors published in *Proceedings of the National Academy of Sciences*. "Our

motivation and long-term goal is making islet encapsulation successful to allow islet transplantation with no or minimal immunosuppression, which is not completely effective and is the leading cause of adverse events associated with the procedure," Tomei tells *Medical Xpress*.

"Based on a critical review of the literature and on Dr. Hubbell's previous promising conformal encapsulation efforts⁶, we hypothesized that failure of traditional islet encapsulation efforts is partially due to the large size of traditional capsules, which causes impaired oxygen/nutrient diffusion and delays in insulin secretion in response to glucose challenge. Further, large capsules limit the transplantation site to the peritoneal cavity, which may not be ideal for islet transplantation due to the poor oxygen tension."

Tomei adds that their goal for the current study was to design a method for minimizing islet capsule thickness to a few tens of microns. "Since islet size ranges from 50 to 350 μ m, we decided to design a method that was based on shrink-wrapping the cells *within* the hydrogel material rather than incorporating islets within droplets of the hydrogel material with a constant diameter – the technology currently used for islet encapsulation." Furthermore, she continues, the scientists decided to avoid any direct binding of hydrogel components to the islet surface because it can prevent islet remodeling and damage the islet basal membrane, the latter being critical for protecting the islets against autoimmunity⁵.



Design of the flow chamber and optimization of conformal coating encapsulation of model beads and pancreatic islets with PEG-VS cross-linked with DTT. (A) computer-aided design (CAD) drawings of the encapsulation chamber in isometric, front, and section cut views. Orthogonal projections (B) and a 3D surface plot (C) of islet model beads conformally coated with FITC-labeled PEG. (Scale bar, 200 μm .) (D) Phase-contrast images of conformally coated human, rat, and pig islets. (Scale bar, 100 μm .) Orthogonal projections (E) and maximum projection on the z axis (F) of rat islets conformally coated with FITC-labeled PEG (E) or with a solution of PEG containing 1 mg/mL 2,000-kDa FITC dextran (F). (Scale bars, 200 μm .) (G) Effect of different percentages of TEOA in the PPG oil outer bath on GSIR function of conformally coated (CC) human and rat islets. (H and I) Effect of hexane (Hex)

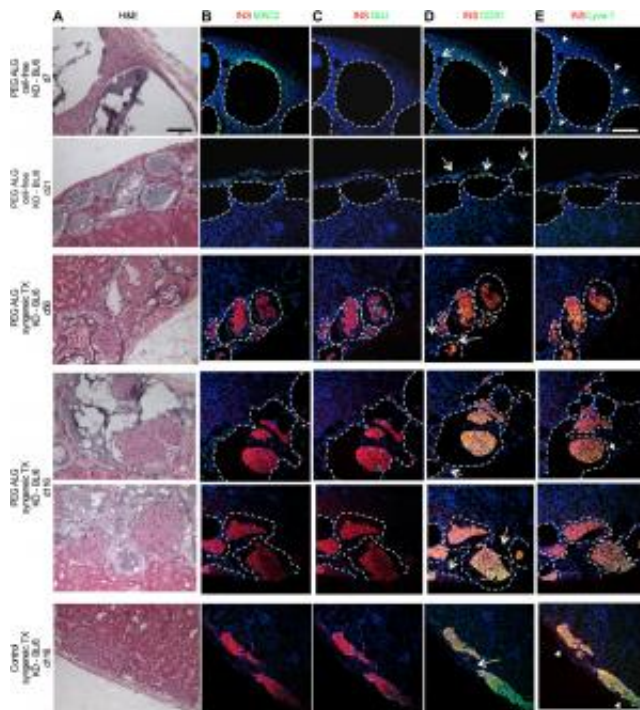
purification of CC rat islets on GSIR function. (J) GSIR index (normalized to naked controls) of human (H), nonhuman primate (NHP), and rat (Rt) islets CC with 0.02% TEOA and purified with hexane. Low glucose (LG) = 2.2 mM and high glucose (HG) = 16.7 mM. Shown are mean \pm SD with $n = 3$ for each value. *P

"We based our islet shrink-wrapping microfluidic system design on previous work for generation of coaxial jets^{3,4,8,9}, as well as on conformal coating of single cells⁵," she explains. "Four key design challenges we encountered were defining the right combination of fluid dynamic parameters that allows conformal coating of particulates rather than generation of droplets with constant diameters; devising the process to allow PEG gel precursor polymerization *after* capsule formation, rather than before encapsulation within the microfluidic device; tailoring the process to islets, which are very sensitive to manipulations; and adjusting PEG hydrogel composition to maximize enclosed islet viability and function."

Tomei notes that future translational studies are needed to treat Type 1 diabetes in humans – and such studies are already in the planning stages. "In our *PNAS* study, we've shown that conformal coating does not compromise islet viability and function after encapsulation in syngeneic islet transplant settings in mice – and therapeutically, we've proven that conformal coating shows real potential for autologous transplants." The next steps, she continues, are to evaluate whether conformal coating provides efficient immunoisolation against allojection and autoimmunity – studies the researchers are currently performing in small animal models with the support of *the Diabetes Research Institute Foundation, the Juvenile Diabetes Research Foundation and the Leona M. and Harry B. Helmsley charitable trust (Grant 17-2012-361), and BioRep Technologies*. "Additionally, we need to prove that conformal coating encapsulation is safe and efficacious in large animal models – so in parallel with efficacy and safety studies, we're scaling up procedures and devices." Tomei adds that they are also exploring novel and more effective ways to achieve local (rather than systemic) modulation of immune responses needed to prevent rejection of transplanted islets. The scientists are also investigating ways of counteracting autoimmunity by re-establishing tolerance towards beta cell autoantigens – normal tissue constituents which the immune system targets by producing autoantibodies that trigger

autoimmune destruction and Type 1 diabetes.

Regarding how the intrinsic lack of size-limiting factors enabled the scientists to transplant conformally-coated islets at curative doses in sites not accessible with standard microencapsulation methods, Tomei tells *Medical Xpress* that standard microencapsulation methods are based on incorporating islets within droplets of the hydrogel material with a constant diameter – and in order to be able to enclose even large islets (up to 500 μ m in diameter), droplets need to be in the range of 600-1000 μ m. What happens, she explains, is that small islets – as small as 50 μ m – will be enclosed in a large volume of inert polymeric material. During post-implantation revascularization, blood vessels that carry oxygen and nutrients and allow glucose-sensing the insulin-secreting processes in islets will grow on the capsule surface – but the thick polymeric wall between the blood vessels and the islets form a barrier for oxygen, nutrient and glucose transport into the islets and of insulin and waste products from the islets to the blood vessels.



Biocompatibility, islet morphology, and revascularization of cell-free PEG alginate (ALG) (at day 7 and day 21 posttransplantation) and conformally coated syngeneic murine islet grafts (at day 56 and day 116 posttransplantation) transplanted in streptozotocin diabetic C57BL/6 (BL/6) mice under the kidney capsule (KD). Formalin-

fixed, paraffin-embedded 5- μm thick tissue sections have been processed. Biocompatibility was assessed by H&E staining (A) and MAC2+ macrophage immunofluorescence (B; green); islet morphology was assessed by insulin (INS, red) and glucagon (GLU, green) immunofluorescence (C); and islet revascularization was assessed by insulin (INS, red) and CD31 (green, arrows) (D) or Lyve-1 (E; green, arrowheads) immunofluorescence. Capsules are outlined. (Scale bars, 50 μm .) Credit: Copyright © PNAS, doi:10.1073/pnas.1402216111

"Such a large transport barrier causes the center of the islets to suffer from hypoxia and central necrosis, or cell death, as well as a delayed insulin secretion in response to glucose" Tomei explains. "Additionally, since 500,000 to 1,000,000 islets need to be transplanted in humans to reverse hyperglycemia and cure diabetes, if islets are enclosed in 600 μm -1000 μm diameter capsules, a large volume of encapsulated material will need to be transplanted, taking up hundreds of milliliters of space. Such large volumes can only be placed in the peritoneal cavity and cannot be transplanted within engineered organs like the DRI [BioHub](#) bioartificial pancreas. On the other hand," she continues, "conformal coating does *not* greatly increase islet volume relative to non-encapsulated, or naked, islets. Therefore, conformally coated islets can be transplanted in the same site and engineered organs where naked [islets](#) can be placed – and as mentioned, conformal coating minimizes central necrosis by not creating a barrier to the blood vessels transporting oxygen, nutrients, waste, glucose, and insulin to and from the encapsulated islet."

Given that the conformal coating thickness is determined by the geometry, viscosity ratios, interfacial tension, and flow rate ratios of the process, Tomei points out that other areas of research might benefit from their study. "The conformal coating process can be adapted to different types of cells and cell clusters, including other differentiated primary cells like neurons or renal epithelial cells, tumor and embryonic/stem cells, and different types of degradable and permanent hydrogel coating materials that will allow providing capsule performances tailored to the specific application."

More information: Device design and materials optimization of conformal coating for islets of Langerhans, *Proceedings of the National Academy of*

Sciences, Published online before print June 30, 2014,
[doi:10.1073/pnas.1402216111](https://doi.org/10.1073/pnas.1402216111)

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⁷[The peri-islet basement membrane, a barrier to infiltrating leukocytes in type 1 diabetes in mouse and human](#), *Diabetes* (2013) 62(2):531-542

⁸[Drop and Spray Formation From a Liquid Jet](#), *Annual Review of Fluid Mechanics* (1998) 30(1):85-105

⁹[Tip streaming from a liquid drop forming from a tube in a co-flowing outer fluid](#), *Physics of Fluids* (2006) 18(8)

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